Voor Neal

TREATMENT OUTCOMES IN CHRONIC RHINOSINUSITIS

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ISBN: 978-94-6522-065-9

Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Layout and design: Hans Schaapherder, persoonlijkproefschrift.nl
Artwork cover and chapterpages: Kay Hooijmans

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 9 april 2025, te 11.00 uur

door Evelijne Suzanne Lourijsen
geboren te Heemstede

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CHAPTER 1

GENERAL INTRODUCTION

Chronic rhinosinusitis (CRS)

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nose and paranasal sinuses. For a few decades, there is international consensus that CRS is defined as an inflammation of the nasal mucosa and sinuses for at least 12 weeks (1, 2). Symptoms are either nasal obstruction or purulent rhinorrhoea, with or without reduction or a loss of smell and facial pain or pressure. Clinical signs of disease should be present with nasal endoscopy or visible on CT-scan. These signs include either oedema of the mucosa, mucopurulent discharge, nasal polyps, or additional changes of mucosa within the ostiomeatal complex ascertained on CT-sinus. Recently, the division between primary versus secondary CRS was introduced (1). Primary CRS separates in different phenotypes and endotypes (types of inflammation). Major clinical phenotypes are CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). Nasal polyps are oedematous benign swellings of the nasal mucosa, predominantly originating from within the ostiomeatal complex (3).

The prevalence of CRS is established to be 5-12% based on epidemiological research with questionnaires (4-7). Consequently, the diagnosis is symptom-based and can be highly variable within countries (1). The prevalence of CRSwNP is estimated to be between 0.5-6%; the exact percentage is difficult to determine since the need for endoscopic evaluation for the diagnosis (8-11). CRSwNP is most frequently seen in men, increases with older age (≥40), is associated with higher BMI, and patients more frequently smoke cigarettes (12). Furthermore, it is frequently paired with adult-onset asthma (13).

Multiple studies suggest a prominent role for a T helper cell (Th) 2-mediated inflammation in the pathogenesis of CRSwNP (1). In approximately 85% of patients with CRSwNP this type-2 inflammatory response is the pathophysiological endotype (8, 14). This endotype is characterised by elevated levels of eosinophils and multiple interleukins, such as interleukin (IL)-4, IL-5, and IL-13 (15, 16). Eosinophils play a key role in the pathogenesis of CRSwNP, but recent insights highlight the value of IL-5, a cytokine activating eosinophils, as equally important (17).

Burden of CRS

CRS can present with various symptoms on the sinonasal, auricular, sleep and emotional level. Sinonasal symptoms (nasal obstruction, nasal discharge, loss of smell and facial pain) are considered the cardinal symptoms of the disease. These symptoms are most frequently reported and more severe compared to symptoms on the other domains. Patients with CRSwNP more often have altered or loss of smell compared to CRSsNP. Sleeping problems are also frequently reported, mainly feeling fatigued and waking up tired (18). It is well-described that the symptoms that are associated with the disease have a major influence on a patient's general and disease-specific quality of life (QoL), reportedly bigger than ischemic chest pain or chronic respiratory disease (19). The loss of QoL paired with the high prevalence of the disease brings a substantial financial societal cost (20). Not only extensive medical resources, such as various doctor visits, medication, and surgery contribute to this burden, also other costs due to absence from work or reduced productivity contribute. In the United States direct

costs for CRS are estimated to be $10-15 billion yearly and costs are still increasing (5, 21). Yet, the main costs of CRS are attributable to indirect costs and were estimated to be $20 billion yearly in the United States (5, 22, 23). In several non-European studies, it was demonstrated that CRSwNP has higher costs than CRSsNP (20, 24).

Comorbidities in CRS

CRS joins with other upper and lower airway diseases, such as allergic and non-allergic rhinitis, asthma, and hypersensitivity for non-steroidal anti-inflammatory drug (NSAIDS). The prevalence of allergy in CRS varies and is probably normal to that in the general population, however there are indicators that it depends on CRS phenotype (2, 25). There are contradictory results in controlled studies for CRSwNP, demonstrating associations and no associations despite clear eosinophilic inflammation in both diseases. There are no controlled studies for CRSsNP.

A strong association exists between asthma and CRS (26, 27). They share the same immunologic environment, expressing equal signs of inflammation and remodelling (28-30). About 20-45% of patients with CRS have asthma (8,9, 31, 32). On the other hand, only 7% of patients with asthma have CRS(wNP), but this percentage is still higher than the general population of 4% (33-35). Patients with both asthma and sinonasal disease frequently have more severe symptoms and express lower QoL (36, 37). Therefore, treatment of CRS is also attempted to decrease asthma severity.

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is associated with CRSwNP and was formerly known as Samter's triad (38). This disease is a combination of CRSwNP, asthma and intolerance for aspirin. N-ERD patients usually have more extensive respiratory symptoms and quicker recurrence of nasal polyps after surgery than patients without aspirin intolerance (39). The prevalence of N-ERD is between 0.5-2.5% in the general population, and this increases to 4-10% in patients with CRSwNP (8, 40, 41).

Medical treatment of CRS

Nasal saline

Nasal saline spray or saline rinsing is internationally a well-integrated treatment modality in patients with CRS, mostly as first step-medication and additive to other topical treatments. Nasal rinsing or irrigating is a procedure to flush the nasal cavity with isotonic or hypertonic saline solution. Its exact mechanism of action is unknown, but it is thought to positively influence nasal mucosal function by removing nasal crusts and mucus, antigens, biofilms and enhances ciliary functioning with consequent adequate mucus clearance (42). Moreover, it is a cheap, safe, and immediately available treatment option. Nasal irrigation has been shown to be more effective in distributing saline solution to the sinuses compared to spray, however it is probably not more effective in reducing symptoms and clinical signs of CRS (1). Low-quality evidence, based on one randomised controlled trial, concluded that large-volume (150 ml) saline irrigation with a hypertonic solution (2%) was better in improving disease-

specific and general health-related QoL compared to placebo (43, 44). Nonetheless, in studies comparing hypertonic with isotonic saline solution more nasal irritation or burning of the nose was described (45, 46). Several additives can be used in the saline water. Xylitol is one of the proven useful additives, disrupting the bacterial biofilm in CRS (47).

Corticosteroids

Alongside nasal saline, one of the most common first-step treatment options for CRS are topical or intranasal corticosteroid sprays or drops (ICS) (48). This is not remarkable considering the inflammatory nature of the disease. ICS have been available since the 1970's (49). Glucocorticoids act by binding to specific glucocorticoid alpha receptors, present in most cells of the body, including nasal mucosa and nasal polyp tissue, consequently mediating the anti-inflammatory and immunosuppressive effect by promoting or depressing gene transcription processes (50).

Topical corticosteroids have proven to be effective in many placebo-controlled trials. They effectively reduce CRS symptoms and improve disease-specific QoL when used on a daily basis. Furthermore, they reduce polyp size and prevent polyp recurrence (48). Their main function is to suppress the inflammatory process by reducing tissue eosinophils, eosinophil cationic protein (ECP) and IL-5 (51). Treatment is often supplied for at least 12 weeks; however, there is no evidence that shorter or longer duration influences the symptom burden. There are many different classes or brands of ICS, for which none has proven to be more effective than the other (26). The topical method of choice may influence the amount of the medicine that comes in contact with the nasal mucosa (52). Nasal irrigation provides a better delivery to the sinuses, however there is insufficient evidence that irrigation with ICS improves disease severity, nasal endoscopy, or opacification on imaging modalities in contrast to spray (52-54). A higher dose seems to have a more positive influence on symptom severity and polyp size (55).

Although ICS are crucial in the treatment of CRS, not every patient will experience progress as much as they would like. Oral corticosteroids (SCS) are considered a common treatment option for more severe disease after failure of first-step treatment in CRSwNP (56). SCS show an improvement in QoL and improve symptoms in CRSwNP, as well as a reduction in nasal polyp size (56, 57). SCS are most effective in patients with eosinophilic disease and less in patients with neutrophilic disease, in which some patients are refractory to treatment with SCS (58).

In airway diseases, short courses between seven and twenty-one days are common based on asthma management schemes, either with a fixed dose or reducing dose over time (1, 59). The optimal dosage, duration, and prescription frequency of SCS has not been studied extensively in CRSwNP or other upper respiratory airway diseases (1, 56, 57, 60). Apart from the anti-inflammatory properties, SCS can cause adverse effects that range from slight discomfort to life threatening. Fat metabolism disturbance, glucose intolerance, gastrointestinal problems, neuropsychiatric disturbances, hypothalamic-pituitary-adrenal-axis dysfunction, and musculoskeletal problems, such as osteoporosis, are reported (61-63).

Antibiotics

Despite the high utilisation of antibiotics in primary and secondary care no substantial evidence is present that supports the use of short-term antibiotics in CRSwNP. Short-term antibiotics were only compared to placebo in two randomised controlled trials (RCT) in patients with CRSwNP (64, 65). Sabino *et al.* compared a fourteen-day course of amoxicillin-clavulanate to placebo in CRSsNP (N=12) and CRSwNP (N=20). Nasal endoscopy, symptom scores, and disease-specific QoL showed no between-group differences. Van Zele *et al.* compared a 3-week course of doxycycline to methylprednisolone and placebo. The study showed a reduction in postnasal drip after two weeks, a reduction in nasal polyp size up to 3 months, however no difference was seen in patient-reported other nasal symptoms or Peak Nasal Inspiratory Flow score. Another RCT compared antibiotics to placebo in patients that underwent endoscopic sinus surgery and found no influence on nasal polyp size, symptoms and QoL (66). To date there are no studies evaluating long-term treatment with non-macrolide antibiotics in CRSwNP. Long-term macrolide treatment was evaluated mainly in cohort studies (level 2B evidence) and in just one RCT in patients that underwent endoscopic sinus surgery. Macrolides (most studied was Claritromycin) seem to reduce nasal polyp size, improve symptoms and disease-specific QoL (67). It is unknown if the benefits outweigh the potential harm from antibiotics (diarrhoea and abdominal pain), the cardiovascular risk and antibiotic-resistance (68, 69).

Alternative medical treatments

Aspirin Treatment after desensitisation (ATAD)

When patients with CRSwNP and aspirin hypersensitivity (N-ERD) are refractory to any common medical or surgical treatment there is need for alternative strategies to optimise a postoperative result and minimize recurrence or exacerbations.

Aspirin desensitisation therapy involves repeated administration of small doses of aspirin at fixed time intervals. To maintain desensitisation, patients can be treated with a long-term maintenance dose, aspirin-treatment after desensitisation (ATAD), with a range of 300 mg to 1300 mg per day in one or two doses (70). Several controlled studies have been performed, which reported positive results on QoL, symptoms and need for revision surgery or the use of SCS (71-74).

Biologicals

The use of biologicals in CRSwNP has evolved over the past years. An extensive amount of studies has been performed in CRSwNP, which all show beneficial clinical results and acceptable side effects. Mepolizumab (anti-IL-5) and Dupilumab (anti-IL-4) are currently used as treatment for CRSwNP (1, 75, 76). From 2019, Dupilumab is the solitary monoclonal antibody officially registered as a medicine for diffuse bilateral type-2 CRSwNP. Omalizumab (anti-IgE) has been examined in low-sample sized studies and is currently under investigation in larger trials. Treatment with monoclonal antibodies is started only after fulfilling patient criteria such as clear evidence for type-2 inflammatory disease and received previous sinus surgery (77).

Surgical treatment of CRS

After failing of appropriate medical therapy (AMT) and confirmed presence of disease on CT-scan of the sinuses, surgery is currently one of the most common options for removing polyp tissue and restoring airway ventilation and adequate drainage of mucus (1). Functional endoscopic sinus surgery (ESS) is the technique widely used, removing polyps and damaged tissue, and sparing the normal nasal mucosa. Usually, the surgery is aimed at the anterior ethmoids and maxillary sinuses at a minimum, opening and improving the function of the ostiomeatal complex.

Since the beginning of performing ESS there is an ongoing debate what constitutes unsuccessful appropriate medical therapy (AMT) and this definition varies across continents, nations and within nations, resulting in a variety of surgical rates. Not many studies that concentrate on outcomes after ESS report on previous medical therapy, which makes it difficult to interpret outcomes after surgery in light of pre-medication (78). Attempts have been made to understand what is judged as an 'indication for surgery', but no comprehensive guideline has been developed. Pre-operative symptom scores could be used to predict success rates after surgery and CT-sinus Lund-Mackay scores (which tells the amount of opacification for each sinus), however approximately 8% of patients with CRSwNP have values comparable to the general population (79-81).

Most guidelines advise nasal saline irrigations and nasal corticosteroids as AMT before surgery, since their effectiveness has been proven (43, 48). Others choose to try an additional course of SCS before considering surgery. Evidence from cohort studies suggest that a prompt surgery within 12 months after diagnosis of CRS contributes to more improvement and maintenance of improvement over 5 years compared to later surgery. These studies also suggest that earlier ESS after diagnosis of CRS contributes to a lower incidence of asthma (82, 83).

Nowadays, success of ESS is appraised by using patient-reported outcome measures (PROMs) with corresponding minimal clinically important difference (MCID). MCID is the smallest change in a particular outcome that a patient perceives as an actual change. For CRS, the Sinonasal Outcome Test-22 (SNOT-22) is a validated PROM with a MCID of 9.0 points (84).

The efficacy of ESS has been demonstrated in various prospective studies, showing improvement in QoL and clinical outcomes (81, 85-87). Also, asthma severity decreases, reduced frequency of asthma exacerbations and need for inhaled corticosteroids is expected (88-90). Nonetheless, surgical revision rates are between 15-30%, which necessitates a type of postoperative medical treatment to have a clean surgical cavity and adequate patient follow-up on the one hand, and on the other hand a good management of doctor and patient expectations (81, 85, 86, 91).

Studies performed over the last decade show that eosinophilia and increased levels of IL-5 are associated with a higher risk of recurrence of nasal polyps (92-95).

One thing that must not be overlooked is that a success of ESS can only be achieved with adequate surgical circumstances. Therefore, bleeding should be minimized in order to be able to complete surgery to an acceptable result without complications.

AIM AND OUTLINE OF THE THESIS

This thesis presents prospective studies and systematic reviews- all with the aim to evaluate the impact/ burden of primary bilateral chronic rhinosinusitis (CRS) and specifically CRS with nasal polyps (CRSwNP) on society and to appraise both medical and surgical management options to be able to make evidence-based choices.

As previously mentioned, chronic rhinosinusitis (CRS) affects 5-12% of the general population, based on epidemiological research (1). The prevalence of the diagnosis is based on symptoms, rather than validation by radiology or physical examination and could be overestimated due to its symptomatic overlap with acute rhinosinusitis, and non-allergic or allergic rhinitis. In **chapter 2** we explored the prevalence of CRS using a combination of symptom-based CRS with opacification of the sinuses on imaging jointly.

CRS has a well-described substantial impact on QoL (1, 4-8). The relatively high prevalence of the disease and the chronicity leads to high costs for society (1, 2, 9). CRSwNP in particular has high direct costs on a yearly basis compared to CRSsNP or no diagnosis of CRS (12, 13). In Europe, there are hardly any data on these costs. In **chapter 3** we describe the results of a cross-sectional study aimed to define the total economic burden of CRSwNP in a Dutch cohort of patients including both direct and indirect costs.

To the most current revised European guideline, treatment of CRS depends primarily on which type of CRS a patient is diagnosed with. In contrast to the common division of CRS in CRSwNP or CRSsNP, the current guideline differentiates between primary or secondary CRS nature and can be further subdivided into a localized or diffuse disease, depending on the anatomic distribution of disease. Considering primary diffuse CRS, two endotypes are dominant and form an important cornerstone in the treatment; either type-2 or non-type 2 disease. At the moment a combination of the phenotype of the disease, a patient's response to SCS and markers in the blood (e.g. eosinophils, IgE) could indicate the correct endotype and consequently predict a response to treatment.

In addition to the main treatment with ICS and saline rinsing for diffuse bilateral CRSwNP, other treatment depends on the specific endotype. For type-2 disease, a short-term course of SCS or a longer tapering course could be offered. Glucocorticosteroids are widely used as anti-inflammatory therapy. They play a key role in the treatment of immunologic, allergic, and chronic upper and lower airway inflammatory disorders (96, 97). Unfortunately, glucocorticosteroids come with a wide range of potential unwanted side effects on the short- and long term. The association between long-term SCS use and development of adverse effects has been proven

in a variety of inflammatory conditions in non-CRS and non-asthmatic patient populations (98). It is doubtful if the risks of adverse effects as demonstrated in other inflammatory diseases can always be generalised to patients with CRSwNP or other airway diseases. The difficulty to generalize these established risks arise from diversity in patient disease severity, patient activity level, nutritional status, and the use of concomitant medications. Furthermore, CRSwNP patients or patients with asthma are usually treated with multiple short courses of SCS each year, instead of maintenance therapy with SCS. In **chapter 4** we performed a systematic review of the current evidence for beneficial as well as harmful effects of SCS in distinct upper airway diseases and we aimed to provide recommendations about their use in airway disease.

If patients do not tolerate SCS or respond substandard on SCS, without reaching an acceptable state of control of disease, the option of endoscopic sinus surgery (ESS) could be discussed, to create better conditions for local treatment. Despite previously proven efficacy of ESS in cohort and observational studies revision rates are high. There is a clear need for a dependable insight in the efficacy of ESS in addition to medical therapy after failure of AMT. Therefore, in **chapter 5** we first present a study protocol of the first large Dutch multicentre randomised controlled trial comparing ESS in addition to medical therapy versus medical therapy in patients with CRSwNP. In **chapter 6** we present the accompanying statistical analysis plan. In **chapter 7** we present the final results on the efficacy of ESS in addition to medical therapy in the treatment of CRSwNP. We determined the generic- and disease-specific QoL in both treatment groups one year after the treatment, evaluated symptom scores, disease control and polyp recurrence.

A clear visibility of the surgical field is very important for the ability to complete ESS, as well as for the safety of the patient with respect to anatomical landmarks. To improve or maintain field visibility peri-operatively, surgeons can source induced hypotension and vasoconstrictive or anaesthetic agents (1). Tranexamic acid (TXA; trans-4 amino methyl-cyclohexane carboxylic acid) is a synthetic lysine analogue that binds to the lysine binding site of plasminogen, inhibiting the interaction between plasminogen and fibrin (99). The antifibrinolytic properties of TXA are used as a topical or intravenous agent to reduce bleeding. In ENT-practice, its use is mainly investigated and known for epistaxis and tonsillectomy (100, 101). It is of high clinical benefit to have other safe interventions that reduce blood loss during ESS with subsequent improvement of surgical field visibility. In **chapter 8** we performed a systematic review and meta-analysis of randomized controlled trials to assess the effects of TXA. We determined whether TXA improves bleeding score, intra-operative blood loss and duration of surgery and we evaluate serious or non-serious side-effects.

Patients with CRSwNP usually have comorbidities, such as asthma, allergies, or hypersensitivity for non-steroidal anti-inflammatory drug (NSAIDS). NSAID-exacerbated respiratory disease (N-ERD) is the coexistence of hypersensitivity to NSAIDs with underlying inflammatory disease of the upper and lower airways, including asthma or CRS. Cyclooxygenase 1 (COX-1) becomes inhibited, which is an important enzyme in the lipoxygenase pathway of arachidonic acid metabolism. The inhibition triggers respiratory symptoms due to deprivation of the protective

prostaglandin E2 expression and upregulation of LTC4 synthase enzymes genes (70). These patients will need to strictly avoid all COX-1 inhibitors, e.g. aspirin, naproxen, ibuprofen. However, another management option is desensitisation, performed by repeated administration of small doses of aspirin. To maintain desensitisation, patients can be treated with a long-term maintenance dose, so-called treatment after aspirin desensitisation (ATAD). For patients that have uncontrolled CRSwNP or asthma despite appropriate medical therapy or ESS, ATAD can improve symptoms and is an alternative treatment strategy (70, 102). In **chapter 9** we performed a systematic review and meta-analysis of randomised controlled trials to assess the effectiveness of oral or intranasal aspirin desensitisation. We determined if ATAD effects health-related QoL, control of asthma and we look into significant serious or non-serious side-effects.

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CHAPTER 2

PREVALENCE OF CHRONIC RHINOSINUSITIS IN THE GENERAL POPULATION BASED ON SINUS RADIOLOGY AND SYMPTOMATOLOGY

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J Allergy Clin Immunol. 2019 Mar;143(3):1207-1214

ABSTRACT

Background
The prevalence of Chronic Rhinosinusitis (CRS) measured in epidemiological studies is 5-12%. This might be an overestimation because of overlap with other diseases like allergic rhinitis.

Objective
We aimed to calculate the prevalence of CRS using a combination of epidemiologically based CRS according to EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) together with sino-nasal opacification on imaging.

Methods
Subjects who underwent a CT or MRI scan of the head for any nonrhinologic indication were asked to fill in the GA2LEN survey containing the EPOS symptom criteria. The scans were evaluated according to the Lund-Mackay (LM) scoring system. Epidemiologically based CRS is based on nasal symptoms according to EPOS, clinically based CRS also encompasses endoscopy and/or CT scan.

Results
834 subjects were included. 107 subjects (12,8%) had epidemiologically based CRS according to EPOS. Of these subjects, 50% had a LM score of 0; 26% had a LM score of 1-3 and 23% had a LM score of ≥4. Twenty-five subjects (3.0%) had clinically based CRS (based on LM score ≥4) and 53 subjects (6.4%) had clinically based CRS (based on LM score ›0). Allergic rhinitis was reported by 167 subjects (20%). In subjects that did not report upper airway symptoms, 57% had a LM score of 0: 30% had a LM score 1-3 and 12% had a LM score ≥4.

Conclusion
We found a prevalence of 3.0 – 6.4% of clinically based CRS (depending on LM cut-off point, LM≥4 or LM›0 respectively) in a relatively randomly selected group of subjects.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a significant health problem and affects 5-12% of the general population (1). CRS is characterized by at least nasal blockage/obstruction/congestion or nasal discharge with facial pain and/or reduction of smell. Reliable epidemiologic research is extremely important in addressing this major social healthcare issue to get a clear understanding of the quantitative impact of the disease.

EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) provides two definitions of CRS: a clinical diagnosis based on symptoms, supported by signs of mucosal inflammation found on imaging or with nasal endoscopy, and a symptom-based definition to be used in epidemiologic research, without radiologic imaging or endoscopic examination (1).

CRS is a clinically challenging disease; as in asthmatic patients, symptoms lack good correlation with objective measurements, because of the lack of a gold standard(2, 3). This might be caused by an underlying variation of endotypes leading to a common phenotype (4) and results in a discrepancy of estimates of prevalence based on either symptoms or objective measures(5). Current data on prevalence of CRS based on the EPOS symptom-based definition show a prevalence of 5,5% in Brazil (6), 8% in China (7), 11% in Europe (8) and Korea (9) and 12% in the USA (10). These numbers might be an overestimation due to the overlap of symptoms between CRS, acute rhinosinusitis (ARS) and (non-)allergic rhinitis (NAR / AR); up to 10% of responders had symptoms of all three diagnoses (11, 12).

Earlier, we evaluated the value of nasal endoscopy in the epidemiologically based diagnosis of CRS(12). In this Global Allergy and Asthma European Network (GA2LEN) follow up study, a sample of subjects with CRS, asthma, asthma and CRS, and 'no asthma or CRS' were invited to undergo nasal endoscopy, blinded for symptom status and found to have a sensitivity of nasal endoscopy of 62% in a population with symptom-based CRS. This might imply a one-third overestimation of 'true' or 'clinical' CRS in patients when using a symptom-based diagnosis of CRS.

To gain more insight in the prevalence of clinically based prevalence of CRS based on imaging, we would ideally scan a selection of the prior named GA2LEN study population with known sinonasal symptoms; however, this is both ethically unacceptable because of radiation exposure and too expensive because of the need for hundreds of Magnetic Resonance Imaging (MRI)-scans.

Previous epidemiologic studies found 20-40% Computed Tomography (CT)- scan abnormalities in symptom negative populations(13-15). Also common cold has been shown to give sinus abnormalities on imaging in a majority of otherwise healthy subjects, usually clearing in a few weeks(16). In patients with allergic rhinitis, opacification of the sinuses is infrequent and only minimal during natural seasonal exposure (17), with an average Lund-Mackay (LM) score comparable to a normal population(18). In a population without sinusitis, a LM score from 0 to 5 has been described (19).

In this study, we primarily describe the prevalence of epidemiologically (symptom-) based versus clinically (imaging-) based CRS in a population with nonrhinologic indications. Furthermore, we analyse the alignment of imaging abnormalities with symptom scores to test the feasibility of the imaging-based CRS diagnosis as a solid construct. The influence of other factors on imaging abnormalities is also considered (e.g., patient demographics and comorbidities such as asthma). Moreover, we investigate whether it would make any difference if we used the definition of CRS (containing 3 months of symptoms in the last year) or current symptoms of CRS (defined as CRS in the last three months) because it might reflect a difference in LM-scores at the time of imaging. Furthermore, we investigate what symptoms and findings are associated with the outcome of clinically relevant opacification on imaging and whether we were able to predict no abnormalities at the time of CT scan (LM score=0).

MATERIALS & METHODS

Study design

We conducted a cross-sectional survey of consecutive subjects referred to our radiology department for imaging of the head for nonrhinologic indications. All consecutive subjects that underwent CT or MRI of the head (patients undergoing CT-sinus were excluded) were asked to fill in the GA2LEN questionnaire on upper and lower airway symptoms (supplementary table 1). The questionnaire was sent 1 week before the radiology appointment, and patients were asked to fill in the questionnaire during their imaging appointment.

Indications for imaging included stroke, seizures, head injury, or suspected skull-base, intracranial or intra-orbital pathology.

Exclusion criteria were inability to fill-in the questionnaire because of confusion, aphasia, or severe illness, incomplete imaging or artefacts of the nasal sinus prohibiting complete Lund-Mackay scoring, history of transsphenoidal pituitary surgery, history of radiotherapy in sinonasal area, or if the interval between imaging and completion of the questionnaire exceeded 3 months. All dedicated sinus sequences were also excluded from this study.

Data were obtained between January 2012 and December 2013. The study was approved by the medical ethical committee of the Academic Medical Centre Amsterdam.

Measurements

The GA2LEN survey is a survey developed by The Global Allergy and Asthma Network of Excellence (GA2LEN) and funded by the European Union, and was based on validated questions from the European Community Respiratory Health Survey (ECRHS) (20-22) and EPOS (12, 23). The GA2LEN questionnaire was previously used in epidemiologic research on the prevalence of allergy, asthma, and upper airway symptoms (8, 24). Subjects were asked for symptoms of CRS, ARS, asthma and AR in the last 3 months and in the last year. For the full survey, see supplementary table 1.

Imaging was scored by a radiologist specialized in otolaryngology and skull-base imaging (N.J.M.F.) according to LM scoring system (25). Opacification on imaging was classified into: LM score of 0 (LM0), LM score of 1 to 3, LM score of 1 and greater, and LM score of 4 and greater. For the full scoring system, see supplementary table 2.

Definitions used

Epidemiologically based CRS: Continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell for more than 12 weeks during the last year (see supplementary table 3).

Epidemiologically based current CRS: Continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell in the last three months.

Clinically based CRS: Continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell for more than 12 weeks during the last year, together with a LM score of greater than 0 or 4 or greater.

Clinically based current CRS: Continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell for the last twelve weeks, together with a Lund-Mackay score of 4 or greater.

Acute Rhinosinusitis (ARS): Presence of an acute episode of blocked nose, coloured nasal discharge and facial pressure or pain during at least at least 10 days.

Allergic rhinitis (AR): Positive answer to the following question: ''Do you have nasal allergies including hay fever?''.

Current AR: Allergic Rhinitis (self-reported hay fever) with current nasal obstruction, rhinorrhoea or both.

No nasal symptoms: A negative response to questions on any nasal symptom and on the questions for hay fever symptoms in the last year, and doctor-diagnosed CRS.

Asthma: Positive answer to the following question ''Do you have asthma?''.

History of smoking: Positive answer to the following question ''Have you ever smoked during at least a year?''.

Current smoker: Positive answer to the question ''Have you ever smoked during at least a year?'' in combination with a positive answer to the question 'Have you smoked the last month?'.

Former smoker: Positive answer to the question ''Have you ever smoked during at least a year?'' in combination with a negative answer to the question ''Have you smoked the last month?''.

Statistical analysis

Data were collected in a predesigned Microsoft Access 2010 database. Analysis of data was performed using IBM SPSS Statistics 24 (Armonk, New York, US).

The primary question (i.e. ''What is the prevalence of clinically based CRS?'') was answered by describing the prevalence of epidemiologically based CRS and clinically based CRS, both using cut-off points of a LM score of greater than 0 and LM scores of 4 or greater and calculating prevalence of current CRS. Similarly, the prevalence of current CRS (both epidemiologically and clinically based) was determined as was its overlap with (epidemiologically and clinically based) CRS and AR.

We constructed a contingency table of the five main categories of indications for imaging (neurovascular, cerebral tumors, orbital, mastoid, and other) and the epidemiological CRS diagnosis, and tested whether both variables were independent (Pearson's chi-squared-test of independence).

Variables associated with opacification on imaging

The secondary research question (i.e. ''What symptoms and findings are associated with opacification on imaging?'') was analysed in three ways: (1) by analysing predictors of having a LM score of 4 or greater, which is the characteristic that bridges the epidemiologic and clinical diagnosis of CRS; (2) by analysing predictors of total LM score; and (3) by analysing predictors of having a LM score of 0.

With around 850 included subjects, and a prevalence of 12-14% (based on epidemiological data available), the smallest group would be around 100-120 respondents. This provided room for multivariate analyses with around 10-12 factors. (8, 10)

Variables associated with a positive LM score (LM ≥4)

Univariate logistic regression models were used for models to study the association of a selection of relevant symptoms and descriptive factors (see Table 4), and the outcome variable. Odds ratios (ORs), 95% confidence intervals and *P*-values of all univariate test were reported. Additionally, multivariable regression analysis was conducted.

The goal of the first model was to determine which predictors were of additional predictive value for a LM of 4 or greater compared with the 4 EPOS symptoms alone. Based on the total number of subjects with LM scores of 4 or greater (n =119), we could include approximately 12 variables in a multivariable logistic regression analysis. The multivariable model for LM score of 4 or greater was built in two steps. In the first step, all 4 EPOS symptoms (nasal obstruction, rhinorrhoea / postnasal drip, loss of smell and facial pain or pressure) were included. In the

second step, other potentially relevant factors (operationalized as factors with P-levels of less than .10) from the univariate analysis were included. We applied a backward selection (significance level to stay in the model: $P \leq .05$, based on a likelihood ratio test ($P \leq .05$)) on the predictors that were added in the second step. After both steps, OR's, 95% CI's, *P*-values, the Nagelkerke R^2 values and the area under the curve were reported.

Variables associated with total LM score

To identify variables that are significantly associated with the total LM-score (model 2), we conducted negative binominal regression analyses with a log link. The distribution of the LM-score in this specific sample was very much like a count score (heavily left-skewed and bound at zero), which allowed us to model the actual LM-score also in a negative binomial regression model rather than dichotomizing the LM-score, as we did with models 1 and 3. The same procedures were conducted as for the dichotomous variable of a LM-score of 4 or greater: run univariate models, run a multivariable model with EPOS symptoms only, and run a series of multivariable models that included EPOS symptoms and other factors. Effects (the natural logs of regression coefficients B) are quantified as expected count ratios (ECRs), which displays the multiplicative effect of a variable or the presence of a symptom on the LM-score. Predictive count ratios with 95% CI's and *P*-values of all univariate tests and the final multivariable model were reported.

Variables associated with having no opacification (LM score = 0)

The goal of model 3, predicting a LM-score of 0, was to determine which factors could help to rule out any opacification. We used the same variables as for model 1 for univariate logistic regressions. The multivariable model for LM score of 0 was built by applying backward selection ($P \leq .05$) on the variables that had *P*-values of less than .1 in the univariate regressions. The final model after the backward selection procedure was rerun to include subjects with missing data on any of the deselected variables. ORs, 95% CI's, *P*-values, the Nagelkerke R^2 and the area under the curve were reported.

Analysis of season influence

We performed Mann-Witney *U* tests to analyse the influence of seasons on the LM-scores. We used 2 distinctions: May to July compared with the rest of the year ("pollen1"), and June to September ("pollen2") compared with the rest of the year. Additionally, we checked how many participants who reported to have loss of smell also had an epidemiological CRS diagnosis.

Table 1. Subjects' Characteristics

	n/total n[a]	% or mean (SD)
Age (years)	834/834	53 (16)[b]
Female sex	525/834	62.9%
CRS (EPOS, 12mo)	107/828	12.9 %
Current CRS	67/747	9.0 %
Asthma	83/829	10.0%
AR	167/830	20.1%
CRS and AR	57/824	6.9%
No CRS, no AR	612/824	74.3%
Current AR	50/761	6.6%
No symptoms	508/826	61.5%
Smoke		
Never	410/833	49%
Ever	423/833	51%
Current	167/418[c]	40%
Former	251/418[c]	60%
Pack-years smoking		
Ever	204 /423	17.4
Current	16/167	11.2
Former	185/251	17.7
Self-reported doctor diagnosed CRS	38/834	4.6%
Ethnicity		
White	748/834	89.7%
African	28/834	3.4%
Asian	20/834	2.4%
Mediterranean	17/834	2.0%
Other	21/834	2.5%

AR: Allergic Rhinitis (self-reported hay fever), Current AR: Allergic Rhinitis (self-reported hay fever) with current nasal obstruction and/or rhinorrhoea, CRS: Chronic Rhinosinusitis, Current CRS: Chronic rhinosinusitis in the past three months, Asthma: Self-reported Asthma, Pack-years: number of packs of cigarettes smoked per day x the number of years the subject has smoked, 12mo: in the last 12 months.

[a] Total number of subjects is maximal 834 but sometimes less because some data were missing.

[b] Median age: 54 years; inter quartile range: 42-64 years, range: 8-89 years.

[c] Five participants who stated they had smoked for at least a year, did not answer whether they had smoked the last month.

RESULTS

Participants

In total 2051 subjects were invited to participate, 1003 of whom responded. Of these, 169 subjects refused participation or had incomplete imaging. One thousand forty-eight subjects did not respond at all. Age and sex of the responders and non-responders were comparable, but the subjects who did not respond or actively refused more often had brain damage, very serious disease, or both, rendering them unable to answer or probably too ill to care.

In total, 834 subjects were included, with a mean age of 53 years (SD: 16, range 8-89). Sixty-three percent were female and 37% were male. The subject characteristics are specified in Table 1.

Subjects had imaging for a number of neurological (e.g. neurovascular or aneurysm evaluation, evaluation of intracranial tumors, including pituitary tumors), ophthalmological (e.g. intra-orbital tumors, graves, and trauma), and otological (e.g. evaluation of cholesteatoma and internal auditory canal) reasons. For details see Table 2. No association was found between the type of indication and having an epidemiologic CRS diagnosis (X^2 [4] = 4.27, P = 0.37).

Table 2. Indications for imaging (n=834)

		n	%	Prevalence of epidemiological CRS (%)
Neurovascular	Stroke/CVA/Aneurysm	322	38.6	36/321 (11.2%)
Cerebral Tumor	Endocranial / metastasis	109	13.1	30/219 (13.7%)
	Pituitary	46	5.5	
	Meningeoma	65	7.8	
Orbital	Graves	37	4.4	19/104 (18.3%)
	Tumor	53	6.4	
	Trauma / visual loss	14	1.7	
Mastoid	Cholesteatoma	18	2.2	9/89 (10.1%)
	Pre-CI / Vertigo	8	1.0	
	Vestibular schwannoma	66	7.9	
Other	Headache	46	5.5	13/95 (13.7%)
	Parkinson	21	2.5	
	Psychiatry	15	1.8	
	Pre-deep brain stimulation	5	0.6	
	Salivary glands / facial tumors	9	1.1	
Total		**834**	**100**	**107/828 (12.9%)**

CVA: cerebrovascular accident, Pre-CI: pre-Cochlear implant.

Prevalence of CRS

One hundred and seven subjects (12.8%) had epidemiologically based CRS. Of these subjects, 50% had a LM score of greater than 0 and 23% had a LM score of 4 or greater (Table 3). The prevalence of clinically based CRS in this study was 3.0% or 6.4%, depending on which cut off point is used (LM score of 4 or greater or greater than 0). In subjects with abnormalities on imaging (LM score ≥4), only 21% had epidemiologically based CRS. In subjects who denied nasal symptoms, 57% had a LM score of 0 and 12% had a LM4 score of 4 or greater.

Of 107 participants who reported loss of smell in the last 12 months, 56 satisfy the epidemiological criteria for CRS.

Table 3. Findings on imaging in CRS and AR

	LM score = 0	LM score = 1-3	LM score ≥4
Total (n=834)	464 (56%)	251 (30%)	119 (14%)
CRS (n=107)	54 (50%)	28 (26%)	25 (23%)
Current CRS (n=67)	37 (55%)	19 (28%)	11 (16%)
AR (n=167)	76 (46%)	58 (35%)	33 (20%)
Current AR (n=50)	25 (50%)	16 (32%)	9 (18%)
CRS and AR (n=57)	24 (42%)	19 (33%)	14 (25%)
No symptoms (n=508)	292 (57%)	154 (30%)	62 (12%)

AR: Allergic Rhinitis (self-reported hay fever), Current AR: Allergic Rhinitis (self-reported hay fever) with current nasal obstruction and/or rhinorrhoea, CRS: Chronic Rhinosinusitis, Current CRS: Chronic rhinosinusitis in the past three months, LM score =0: No opacifications on imaging, No symptoms: no nasal symptoms

Prevalence of current CRS

We asked ourselves whether it would make any difference if we used the definition of CRS (containing 3 months of symptoms in the last year) or current symptoms of CRS (defined as CRS in the last three months). It did not make any difference; 67 (7.7%) subjects reported current CRS. Of these subjects, 45% had a LM score of greater than 0 and 17% had a LM score of greater than 4 (see Table 3).

LM score in other groups

Furthermore, we investigated whether having AR would influence the LM scores in subjects with CRS. AR was reported by 167 (20%) subjects, 54% of whom had LM scores of greater than 0 and 20% of whom had LM scores of 4 or greater. Fifty-seven subjects (6.9%) had epidemiologically based CRS and AR, 58% of whom had LM scores of greater than 0 and 25% of whom had a LM score of 4 or greater.

We also analysed to what extent season influenced opacification, using two definitions. When comparing the LM scores of scans made in May to July (the grass pollen season in

the Netherlands) with those that were made in the rest of the year, no difference was found ($N_{pollen1}$ = 22, N_{other1} = 812, U = 9,139.5, *P* =.84). When shifting this period to June to September to account for time of AR to induce CRS symptoms (arbitrarily taken as 1 month) and for symptoms to cure/heal, a very small difference in the opposite direction of what was expected was seen: the scans made in this period had slightly lower LM scores compared with those made in the rest of the year. Medians were zero in both groups; mean LM scores were 1.1 and 1.4 respectively ($N_{pollen2}$ = 99, N_{other2} = 735, U = 32,241.5, *P* = .04).

Variables associated with positive LM scores (LM ≥4)

To investigate which symptoms were associated with a LM score of 4 or greater, we conducted univariate logistic regression. Table 4 shows that male sex (OR = .55, *P* =.002), history of smoking (OR = 1.79, *P* =.004), AR (OR = 1.65, *P* =.026), waking-up short of breath in the last 12 months (OR = 1.72, *P* =.048), nasal obstruction (OR = 2.10, *P* =.002), rhinorrhoea/postnasal drip (OR = 1.84, *P* =.031) and loss of smell (OR = 1.75, *P* =.034) were associated with increased odds of having a LM score of 4 or greater. Table 5 shows association of the EPOS symptoms with LM scores of 4 or greater. This model has a Nagelkerke R^2 value of .023. The area under the curve was .579, which indicated that EPOS symptoms are incapable of predicting LM scores of 4 or greater. Several prognostic factors were significantly associated with LM scores of 4 or greater (Table 6) in a multivariable regression model that also included all 4 EPOS symptoms: male sex and history of smoking were associated with increased odds for having a LM score of 4 or greater. The model had a R^2 value of 0.061. The area under the curve was 0.625.

Table 4. Univariate Logistic regression: Odds ratio on LM scores of 4 or greater

Variable	Odds ratio	*P*-value	95% CI
Obstruction	2.10	.002	1.31 – 3.36
Facial pain/ pressure	1.24	.37	0.78 – 1.94
Rhinorrhoea / PND	1.84	.031	1.06 – 3.19
Loss of smell	1.75	.034	1.04 – 2.94
Female sex	0.55	.002	0.37 - 0.81
Smoking	1.79	.004	1.20 – 2.68
AR	1.65	.026	1.06 – 2.57
Woke up short of breath 12mo	1.72	.048	1.01 – 2.94
Wheezing 12mo	1.20	.53	0.68 – 2.14
Woke up with chest tightness	1.37	.25	0.80 – 2.35
Woke up coughing	0.92	.73	0.59 – 1.45
Coughing up sputum on most days ›3months/y	0.84	.60	0.44 – 1.59
Ever asthma	1.49	.18	0.83 – 2.67

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Table 4. *[continued]*

Variable	Odds ratio	*P*-value	95% CI
Admitted to hospital because of asthma	0.99	.99	0.22 – 4.50
Exacerbation of asthma in last 3 months	1.61	.40	0.53 – 4.94
Current asthma medication	1.39	.42	0.63 – 3.08
Episode of ARS in last year	1.33	.23	0.83 – 2.13
Itchy rashes	1.07	.80	0.64 – 1.78
Eczema	0.83	.38	0.54 – 1.27
NSAID-intolerance	2.02	.23	0.64 – 6.36
Current smoker	1.16	.52	0.73 – 1.85
Occupation in healthcare	0.93	.88	0.35 – 2.43
Occupation in cleaning	0.59	.48	0.14 – 2.55

AR: Positive answer to question on 'hay fever', NSAID: nonsteroidal anti-inflammatory drug, PND: Postnasal drip, Smoking: History of smoking, 12mo: in the last 12 months.

Table 5. Multivariable Logistic regression: Prediction model for EPOS symptoms with a LM score of 4 or greater (Nagelkerke R^2: .023).

EPOS symptoms	OR	*P*-value	95% CI
Obstruction	1.91	.026	1.08 - 3.39
Facial pain/ pressure	0.84	.52	0.49 - 1.44
Rhinorrhoea / PND	1.26	.49	0.65 - 2.45
Loss of smell	1.35	.31	0.76 - 2.40

PND: Postnasal drip. (>12 weeks in the last 12 months).

Table 6. Multivariable Logistic regression: Prediction model for a LM score of 4 or greater (Nagelkerke R^2: .061)

Variable	OR	*P*-value	95% CI
Obstruction	2.08	.014	1.16-3.70
Facial pain/ pressure	0.84	.53	0.48-1.46
Rhinorrhoea / PND	1.35	.38	0.69-2.65
Loss of smell	1.31	.38	0.72-2.37
Female sex	0.57	.005	0.38-0.85
Smoking (ever)	1.69	.029	1.13-2.55

PND: Postnasal drip, Smoke: History of smoking.

Variables associated with total LM score

To avoid dichotomisation of the LM score, we also investigated the association of the symptoms and descriptive factors with the total LM score by conducting negative binomial logistic regression (Table 7). From the EPOS symptoms, nasal obstruction (ECR = 2.01; $P < .001$), rhinorrhoea (ECR = 1.81; $P = .002$) and loss of smell (ECR = 1.75; $P = .002$) were associated with higher LM scores. Additionally, male sex, history of smoking, asthma, AR, ARS, itchy rashes, and occupation in cleaning were associated with higher LM scores. Table 8 shows the model with EPOS symptoms only. In a model that includes all 4 EPOS symptoms, male sex, history of smoking, itchy rashes and occupation in cleaning are significantly associated with higher LM scores (Table 9).

Variables associated with LM scores of 0

To investigate also whether it was possible to predict a LM score of zero, we conducted logistic regression. It was again not possible to produce a model that reliably predicted LM scores of 0 (Table 10 and 11).

Table 7. Univariate Generalized Linear Model Analysis: Effect of variable on increase of LM score.

Variable	Expected count ratio (ECR)	*P*-value	95% CI
Obstruction	2.01	.000	1.46 – 2.78
Facial pain / pressure	1.21	.24	.88 – 1.67
Rhinorrhoea / PND	1.81	.002	1.24 – 2.66
Loss of smell	1.75	.002	1.22 – 2.49
$\text{Sex}_{(\text{female} = 1)}$	.63	.000	.49 - .80
Smoking	1.39	.01	1.08 – 1.78
Asthma	1.50	.05	.99 – 2.25
AR	1.46	.007	1.11 – 1.93
AR in last 12 months	1.34	.06	.99 – 1.81
Episode of ARS in last year	1.46	.01	1.05 – 1.97
Itchy rashes	.73	.06	.52 – 1.01
Occupation in cleaning	.48	.06	.23 – 1.03
ARS	1.46	.01	1.05 – 1.97
Current asthma medication	1.60	.09	.93 – 2.75
Age	1.00	.36	.99 – 1.00
Wheezing in last 12 months	1.08	.68	.75 – 1.56
Woke up with chest tightness	1.08	.64	.78 – 1.50

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Table 7. *[continued]*

Variable	Expected count ratio (ECR)	*P*-value	95% CI
Woke up short of breath	1.25	.19	.90 – 1.75
Woke up coughing	.89	.44	.67 – 1.19
Coughing up sputum on most days ›3 months/y	.80	.21	.56 – 1.14
Admitted to hospital due to asthma	.73	.56	.25 – 2.14
Exacerbation of asthma last 3 months	1.69	.16	.81 – 3.50
Eczema	.89	.38	.67 – 1.16
NSAID-intolerance	1.49	.27	.74 – 3.03
Current smoker	1.19	.26	.88 – 1.60
Occupation in healthcare	1.17	.68	.57 – 2.41

The expected count ratio (exp(B)) means that the expected number of opacified sinus (LM score) is multiplied by a factor of, for example, 2.014 when a certain symptom is present, or the independent variable increases by one unit. AR: Positive answer on question about 'hay fever', ARS: Acute Rhinosinusitis, Itchy rashes: itching skin in the last 12 months, NSAID: nonsteroidal anti-inflammatory drug, PND: Postnasal drip, Smoking: History of more than one year of smoking.

Table 8. Multivariate Generalized Linear Model Analysis: Effect of EPOS symptoms on increase in LM score

Variable	Expected count ratio	*P*-value	95% CI
Obstruction	1.53	.03	1.04 – 2.39
Rhinorrhoea / PND	1.23	.36	.79 – 1.91
Loss of smell	1.20	.39	.79 – 1.82
Facial pain/ pressure	.83	.30	.58 – 1.18

PND: Postnasal drip

Table 9. Multivariate Generalized Linear Model Analysis: Effect of variable on increase in LM score

Variable	Expected count ratio	*P*-value	95% CI
Obstruction	1.53	.03	1.04 – 2.39
Rhinorrhoea / PND	1.23	.36	.79 – 1.91
Loss of smell	1.20	.39	.79 – 1.82
Facial pain/ pressure	.83	.30	.58 – 1.18
Sex $_{(female = 1)}$	.67	.002	.52 - .86
Smoking	1.37	.02	1.06 – 1.79
Itchy rashes	.67	.01	.49 - .92

PND: Postnasal drip, Smoking: History of more than one year of smoking.

Table 10. Univariate logistic regression: OR on LM scores of 0

Variable	OR	*P*-value	95% CI
Obstruction	0.86	.43	0.59 – 1.26
Facial pain/ pressure	1.11	.56	0.79 – 1.56
Rhinorrhoea / PND	0.78	.27	0.50 – 1.21
Loss of smell	0.71	.10	0.47 – 1.07
Female sex	1.87	‹ .001	1.40 – 2.48
Smoking	0.76	.05	0.58 – 1.00
AR 12mo	0.60	.006	0.41 – 0.86
Woke up short of breath 12mo	0.76	.21	0.50 – 1.17
Wheezing 12mo	1.09	.68	0.72 – 1.67
Woke up with chest tightness 12mo	0.96	.85	0.64 – 1.45
Woke up coughing 12mo	1.03	.85	0.75 – 1.41
Coughing up sputum on most days ›3months/y	1.08	.72	0.70 – 1.66
Ever asthma	0.58	.02	0.37 – 0.92
Admitted to hospital because of asthma	1.45	.51	0.48 – 4.37
Exacerbation of asthma 12mo	0.72	.47	0.29 – 1.78
Current asthma medication	0.51	.03	0.27 – 0.95
Episode of ARS in last year	0.91	.58	0.64 – 1.29
Itchy rashes	1.16	.44	0.80 – 1.70
Eczema	1.06	.68	0.79 – 1.43
NSAID-intolerance	0.62	.34	0.23 – 1.67
Current smoker	0.72	.07	0.51 – 1.02
Occupation in healthcare	1.06	.86	0.55 – 2.06
Occupation in cleaning	1.75	.23	0.71 – 4.33

PND: Postnasal drip, Smoking: History of smoking, AR: Positive answer on question on 'hay fever', 12mo: in the last 12 months. Note: Odds ratios below 1 reflect increased odds for having opacifications.

Table 11. Multivariable logistic regression: OR on LM score of 0

Variable	OR	*P*-value	95% CI
Female sex	2.06	‹.001	1.49 – 2.85
AR 12mo	0.58	.004	0.40 – 0.84

AR 12mo: Positive answer on 'hay fever' and on the question 'Have you been troubled by nasal allergies in the last 12 months?'.
Note: results after backward selection (P_{out}= .05) of a multivariable model that included 7 predictors: loss of smell, sex, AR in the last 12 months, asthma (ever), current medication for asthma, ever smoked, and current smoker. We reran this model to also include cases with missing values of the deselected variables. This model predicted 118 (57%) false positives, so 118 out of 326 patients for whom a LM score of 0 was predicted, in fact had a LM score of greater than 0. Area under the curve = .607.

DISCUSSION

We set out to find the prevalence of clinically based CRS based on CT scans in a (rather) healthy population, which was 3.0% or 6.4%, depending on which cut off point is used (LM scores of 4 or greater or greater than 0). This value is in the same range as studies using nasal endoscopy (1.2 - 5.7) (12) and percentages found in the Korean National Health and Nutrition Examination Survey (KNHANES) (CRS with nasal polyps 2.6%; CRS without nasal polyps 5.8%),(26) but greater than those in the earlier version of the (KNHANES) (1.2%) found by Kim et al. in South Korea(9). The prevalence of epidemiologically based CRS found in this study (12%) compares well with these studies (both ±11%), with our previous studies using the GA2LEN questionnaire (14 to 16%),(8, 24), and to other existing literature where it is found to be 5 to 12 % with significant variation between countries (6, 7, 10, 27).

Although the role of allergy in CRS with nasal polyps and CRS without nasal polyps continues to be controversial, AR might be a potential relevant factor influencing LM scores in the current population (28). Seasonal variation has been described with a paradoxical improvement of LM scores in season (18). In the current data, an improvement (although very slight and based on small numbers) in LM scores was seen but only when the period July to September was analyzed. From the current data, we cannot find a good explanation for this phenomenon.

For CRS *per se*, no seasonal influence is to be expected. Moreover, the time between complaints and imaging does not explain their poor alignment, because the subjects with current CRS (complaints in the past three months) show the exact same distribution as those with epidemiologic CRS (complaints for 3 months somewhere in the past year; Table 3). The CRS symptom most strongly associated with CT abnormalities in the paranasal sinuses is nasal obstruction. Other symptoms that constitute epidemiologic CRS have a smaller influence in the models; facial pain or pressure did not reach significance in any of them. This might be due to the study population in which headache (usually without sinonasal disease) is slightly overrepresented (5.5%).

In the end, the key question remains how CRS can be diagnosed correctly and reliably. Although this study was not primarily set up to answer this question, some interesting points can be made from the current data. Having nasal symptoms is a common finding; 58% of the subjects reported any form of nasal complaint and 12% fulfil the EPOS criteria for CRS. Conversely, having abnormalities on imaging is also a common finding: 44% of the subjects had a LM score of greater than 0, of whom roughly one third had a score of 4 or greater. Combining both modalities will lead to reduction of the prevalence (eliminate false-positive results), while at the same time inducing false-negative results. For example: the prevalence of clinically based CRS is found to be 3.0 % when taking a LM score of 4 or greater (a cut-off that is well in line with other studies)(19, 29-32). This eliminates three-quarters of the patients with epidemiologically based CRS, half of whom had no CT abnormalities, and a quarter of whom did have LM scores of between 1 and 3. Other studies have shown that the same trade-off is true when combining

the epidemiologic diagnosis with findings on nasal endoscopy (9, 12). To make matters worse, there is only moderate agreement between nasal endoscopy and radiologic data (33-36). We wondered whether it was possible to exclude the diagnosis clinically based CRS with these questions. Unfortunately, just like it was not possible to predict CRS, it was also not possible to exclude (data not shown).

In the end, the multivariate models we demonstrate here, based largely on the epidemiologic CRS symptoms, have poor model fits. Using other techniques for variable selection (such as the lasso technique) did not improve this (data not shown). As such, predicting clinically based CRS from questionnaires remains difficult. In other words, the construct for the diagnosis of CRS requires careful further consideration because there is room for improvement to align the data from history with objective outcomes (imaging / nasal endoscopy). An interesting recent development in this field is the identification of symptom clustering within factors (e.g. nasal obstruction and discharge) depending on severity and frequency of these symptoms(37).

This study had several limitations. Because the study population underwent imaging of the head mainly for neurological evaluation (Table 2), the mean age (53 years) was greater than that in the general population in the Netherlands (39 years) (38, 39). Because the prevalence of CRS is lower in the elderly, we performed a sub-analysis excluding all subjects older than 70 years. This did not lead to any remarkable change in the overall epidemiologically based CRS prevalence or in the distribution of the LM scores (data not shown). Therefore, there are no clear indications that the current study population should differ significantly from the general population.

Our choice to exclude all dedicated sinus sequences (CT-sinus) from the study might also have induced bias. Because we have a large national tertiary center treating many patients with CRS, including the dedicated sinus sequences would probably have increased the prevalence of CRS disproportionally. On the other hand, excluding all of them might lower the prevalence.

Finally, the number of questions in the QA2LEN questionnaire about CRS and AR are limited, and we did not perform skin prick tests. Ideally, we could have used more extensive questionnaires like the Sino-Nasal Outcome Test-22 (40, 41). However, these more extensive quality-of-life questionnaires have not been shown to be correlated to CT scan abnormalities in otorhinolaryngologic patients (40).

In conclusion, the clinically based prevalence of CRS in the Dutch population based on radiological examination is 3.0%. There is a poor alignment of reported symptoms and objective findings, which urges us to reconsider the construct of a CRS diagnosis.

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SUPPLEMENTARY DATA

Supplementary table 1. the GA2LEN survey

Number	Question	Answering options
1	Have you had wheezing or whistling in your chest at any time in the last 12 months?	Yes/No If no, go to 2
1.1	Have you been at all breathless when the wheezing noise was present?	Yes/No
1.2	Have you had this wheezing or whistling when you did not have a cold?	Yes/No
2	Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	Yes/No
3	Have you been woken by an attack of shortness of breath at any time in the last 12 months?	Yes/No
4	Have you been woken by an attack of coughing at any time in the last 12 months?	Yes/No
5	Do you bring up phlegm from your chest on most days for as much as three months each year?	Yes/No
6	Have you ever had asthma?	Yes/No If no, go to 7
6.1	How old were you when you had your first attack of asthma? (If unsure, give your best guess!)	Number
6.2	Have you ever been hospitalised with asthma?	Yes/No
6.3	Have you had an attack of asthma in the last 12 months?	Yes/No
6.4	Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?	Yes/No
7	Do you have any nasal allergies including hay fever?	Yes/No If no, go to 8
7.1	Have you been troubled by nasal allergies in the last 12 months?	Yes/No
7.2	Have you ever been troubled by nasal allergies for more than 4 days in any one week?	Yes/No
7.3	If yes did this happen for more than 4 weeks continuously?	Yes/No
8	Has your nose been blocked for more than 12 weeks during the last 12 months?	Yes/No
9	Have you had pain or pressure around the forehead, nose or eyes for more than 12 weeks during the last 12 months?	Yes/No
10	Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat for more than 12 weeks during the last 12 months?	Yes/No
11	Has your sense of smell been reduced or absent for more than 12 weeks during the last 12 months?	Yes/No

[continued on next page]

Supplementary table 1. *[continued]*

Number	Question	Answering options
12	Has a doctor ever told you that you have chronic sinusitis?	Yes/No
12A	In the past 12 months, have you had at least one episode of at least ten days where you had a blocked nose, discoloured nasal discharge (snot) and pain or pressure over the sinuses?	Yes/No If no, go to 13
12A.1	How many of these episodes of at least 10 days where you had a blocked nose, discoloured nasal discharge (snot) and pain or pressure over the sinuses did you have in the past 12 months?	1, 2, 3, 4, >4
12A.2	Have you visited a doctor for one of these episodes?	Yes/No
12A.3	Have you received antibiotics for one of these episodes?	Yes/No
12A.4	Have you received a corticosteroid nose spray for one of these episodes?	Yes/No
13	Have you ever had an itchy rash that was coming and going for at least 6 months?	Yes/No If no, go to 14
13.1	Have you had this itchy rash in the last 12 months?	Yes/No
13.2	Does this affect only your hands?	Yes/No
14	Have you ever had eczema or any kind of skin allergy?	Yes/No
15	Have you ever had any difficulty with your breathing within 3 hours after taking a pain killer?	Yes/No If no, go to 16
15.1	Please write the name of the tablet?	Open
16	Have you ever smoked for as long as a year?	Yes/No If no, go to 17
16.1	How old were you when you started smoking?	Number
16.2	Have you smoked at all in the last month?	Yes/No If yes, go to 16.3
16.2.1	How old were you when you stopped smoking?	Number
16.3	On average how much do you (or did you) smoke?	Number
17	Are you currently: a. employed b. self-employed c. unemployed d. not working because of poor health e. full-time house person f. full-time student g. retired h. other	Select one option
18A	Are you currently working as a health care worker (e.g. as a nurse, medical technician, doctor, paramedic or similar)?	Yes/No

[continued on next page]

Supplementary table 1. *[continued]*

Number	Question	Answering options
18B	Are you currently working in a job that is mainly involved with any sort of cleaning?	Yes/No
19.1	Do you understand the language in which this questionnaire is composed?	Yes/No
19.2	Which language do you speak most when you're at home?	Open
19.3	Which language do you speak most when you're away from home?	Open
20.1	In which country were you born?	Open
20.2	In which country was your father born?	Open
20.3	In which country was your mother born?	Open
20.4	What is your ethnicity? a. Caucasian/white b. Asian c. African/Creole d. Latin-American e. Hindustani f. Mediterranean g. Other (please specify):	Select one option
20.5	How many years have you been living in the Netherlands	Number
21	What is your date of birth?	Date
22	What is today's date?	Date
23	Are you male or female?	Male/Female
24	What is your postal code?	Postal code

Supplementary table 2. the Lund-Mackay score

Sinus / location	Score left side	Score right side
Frontal	0 / 1 / 2	0 / 1 / 2
Anterior ethmoid	0 / 1 / 2	0 / 1 / 2
Posterior ethmoid	0 / 1 / 2	0 / 1 / 2
Sphenoid	0 / 1 / 2	0 / 1 / 2
Ostiomeatal complex	0 / 2	0 / 2
Maxillary	0 / 1 / 2	0 / 1 / 2

0 = no abnormality / 1 = partially opacification / 2 = complete opacification
The ostiomeatal complex is assigned a score of either 0 (not obstructed) or 2 (obstructed).
The maximum score is 24.

Supplementary table 3. EPOS symptoms defining chronic rhinosinusitis

Primary symptoms	Secondary symptoms	Objective findings	Duration
Nasal obstruction	Loss of smell	Nasal endoscopy	‹12 weeks
Rhinorrhoea (anterior or posterior)	Pressure over the sinuses	Radiology	≥12 weeks

Epidemiologically based chronic rhinosinusitis is defined as two or more nasal symptoms, at least one of them from the 'primary symptoms', and a duration of 12 weeks or more. Clinically based chronic rhinosinusitis is defined in the same way, but also requires abnormalities on endoscopic or radiologic examination.

CHAPTER 3

DIRECT AND INDIRECT COSTS OF ADULT PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

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Rhinology. 2020 Jun 1;58(3):213-217

ABSTRACT

Background
European direct and indirect cost data is missing for patients with chronic rhinosinusitis with nasal polyps (CRSwNP). This study was aimed to establish the economic burden of CRSwNP based on a Dutch cohort of patients.

Methods
A cross-sectional study was performed in adult patients with CRSwNP (N=115) to calculate mean annual direct medical costs and indirect costs per patient with CRSwNP. Outpatient visits, general practitioner visits, first aid visits, hospitalisation and patient travel expenses were measured with the iMTA medical consumption questionnaire. Missed workdays (absenteeism) and decreased productivity during paid work (presenteeism) or during daily life were measured with the and the iMTA productivity cost questionnaire.

Results
Total direct costs were €1501 per patient/year, primarily due to outpatient department visits and hospitalisation. Indirect costs were €5659 per patient/year, with productivity losses as major cost expense.

Conclusion
Adult patients with CRSwNP have higher indirect costs than direct costs and this forms a substantial burden to society. Total annual costs of patients with CRSwNP are estimated to be 1,9 billion/year in the Netherlands.

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nose and the paranasal sinuses characterized by nasal blockage or nasal discharge with or without facial pressure/pain or reduction of smell (1). CRS is a highly common disease in Europe affecting about 11% of people based on epidemiologic data only (1,2). However, when combining epidemiologic CRS with clinically based CRS (depending on a CT-scan Lund-Mackay cut-off point) the 'real life' prevalence in the general population is lower, between 3.0-6.4% (3). Treatment consists of local or systemic therapy and endoscopic sinus surgery in case where medical treatment has failed. A substantial impact on most aspects of quality of life is well recognized as well as a decrease in work productivity (1, 4-8). The relatively high prevalence and the chronicity of the disease lead to high costs, due to healthcare resource use (direct costs) and due to less productivity at work (presenteeism) or absenteeism (indirect costs) (1,2,9). Evidence shows that the main costs are attributable to these indirect costs (10). Indirect costs are very important to understand from a socioeconomic point of view, since most patients with CRS are of working age (between 30-50 years of age) (1). Recent data suggests that costs of CRS are increasing in the US; the latest report in 2017 estimated indirect costs to be about $20 billion for CRS in general (11). However, also the total direct costs of CRS in the US are increasing and are estimated to be between $10 and $13 billion annually (11). CRS with nasal polyps (CRSwNP) has a significant incremental increase in direct costs on a yearly basis compared to without nasal polyps (CRSsNP) or no diagnosis of CRS (12,13). In Europe, there are hardly any data on costs of CRS. We are aware of two studies evaluating direct costs of CRSsNP (4,14). We are not aware of any European data on indirect cost of CRSwNP. To define the importance of CRSwNP as a burdensome diagnosis, the relative economic impact of CRSwNP to a population needs to be clear, including indirect costs. This study was aimed to establish the total economic burden of CRSwNP based on a Dutch cohort of patients.

MATERIAL AND METHODS

Study design and sample population

A cross-sectional study was designed with inclusion of adult patients with CRSwNP from three academic hospitals and 11 local hospitals in the Netherlands. Inclusion criteria were patients older than 17 years of age with diagnosed CRSwNP. Exclusion criteria were comorbid vasculitis, cystic fibrosis, sarcoidosis, sinonasal malignancy or known immunodeficiency. Data on age, gender, smoking status, diagnosed asthma or diagnosed NSAID-exacerbated respiratory disease (N-ERD) and any previous sinus surgery were recorded. Ethical approval was obtained from the Medical Ethics Committee located in the Amsterdam UMC, location Academic Medical Centre (Amsterdam, The Netherlands). All patients signed written informed consent.

Table 1. Baseline characteristics of CRSwNP study population (N=115).

Baseline characteristic	N	%
Male	65	56.5
Female	50	43.5
Payed worker	83	72
Current smoker	16	13.9
Former smoker	51	44.3
Asthma	68	59.1
N-ERD	24	20.9
Previous sinus surgery	79	68.7

N-ERD= NSAID-exacerbated respiratory disease.

Outcome measures

Outcome parameters were direct and indirect costs. Direct costs of interest were outpatient visits, general practitioner visits, first aid visits, hospitalisation, endoscopic sinus surgery, use of at least one course of antibiotics or systemic corticosteroids in the previous year (specifically for CRSwNP) and patient travel expenses. Indirect costs were composed of missed workdays (absenteeism) and decreased productivity during paid work (presenteeism) or during daily life (unpaid work). Two patient-reported outcome measurements were used to measure the direct and indirect costs: the medical consumption questionnaire (iMCQ) and the productivity cost questionnaire (iPCQ). The Institute for Medical Technology Assessment (iMTA), an independent scientific committee that performs health economic research in the Netherlands, developed these questionnaires. Patients were able to complete the questionnaires online with a personal token (16,17). The iMCQ questions about individual healthcare resource use over the past three months and the iPCQ about any productivity losses in the past 4 weeks. Local nasal steroid sprays or drops were not included in the current evaluation since this parameter was not included in the iMCQ. Total yearly estimates were calculated after extrapolation of the iMCQ (3 months) and iPCQ (1 month) to 12 months. Yearly data on endoscopic sinus surgery, antibiotic and systemic corticosteroid use were retrieved from the electronic patient medical record.

Cost calculations

The friction cost method was used for presenteeism and absenteeism, in accordance with the current guidelines on performing health economic evaluations, which prefers the friction cost method above the human capital approach (18). All costs are expressed in euros (€) and are based on 2014 reference prices if available (18). Prices of endoscopic sinus surgery for CRS were derived from the Dutch website of the 'Nederlandse Zorgautoriteit' (2018 data, www.opendisdata.nl/msz/zorgproduct/109799004). Medication costs were calculated using the Dutch website https://www.medicijnkosten.nl (18). Costs due to prescriptions of short courses of systemic corticosteroids were calculated by applying 'Prednison' 30 mg for 10

days as standard course and costs due to prescriptions of antibiotics by applying 'Augmentin' 500/125 mg for 7 days. Both chosen prescriptions are frequently used in the Netherlands for an exacerbation of CRSwNP.

Statistical analysis

Descriptive analyses were conducted and frequencies or means with SD were reported for direct and indirect outcome measures. Statistical analyses were performed using IBM SPSS Statistics, version 25.0.

RESULTS

In total 115 patients (56.5% males and 43.5% females) with CRSwNP were enrolled with a mean age of 50.8 (SD 12.7) years. The characteristics are outlined in Table 1. In total 44.3% of patients were former smokers, 59.1% had comorbid asthma and 20.9% had NSAID-exacerbated respiratory disease (N-ERD). Previous endoscopic sinus surgery was performed in 68.7% of patients.

Direct costs

Annual direct costs were € 1501,20 per individual patient with CRSwNP. The largest contributors to these costs were outpatient department visits, endoscopic sinus surgery and hospitalisation. An overview of expenditures is presented in Table 2. Patient travel expenses to hospitals covered a mean € 33.80 (SD 109,4) yearly per patient. Additional yearly parking costs were € 14.53 per patient (SD 84,5).

Table 2. Average annual direct expenditures with accompanying total costs per individual with CRSwNP in € (N= 115)

Expenditure	Mean (SD)	Direct costs (€)
ENT outpatient department visits	4.59 (1.8)	417.81 (161.7)
Total outpatient department visits	7.89 (7.0)	718.50 (636.8)
General practitioner visits	3.48 (4.4)	114.78 (146.8)
First aid visits	0.24 (0.9)	63.06 (248.8)
Days of hospitalisation	0.66 (3.7)	314.57 (1726.7)
No. of endoscopic sinus surgeries	0.087 (0.3)	240.43 (782.5)
Course of antibiotics	0.31 (0.4)	0.95 (1.1)
Short course of systemic corticosteroids for CRSwNP	0.42 (0.5)	0.64 (0.96)

ENT= Ear-, Nose- Throat; CRSwNP= Chronic Rhinosinusitis with Nasal Polyps

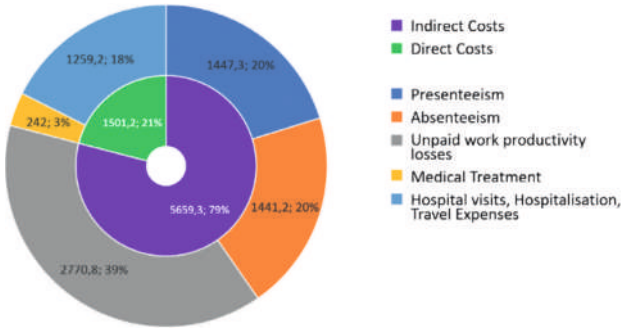

Figure 1. Division of total annual costs per patient into subcategories. ean € and percentage of total costs are presented. Total costs per patient: € 7160.

Indirect costs

Total indirect costs were at least € 5659,28 per patient/year due to productivity losses and absenteeism. In Table 3 annual indirect costs and total days of absence and productivity losses are shown for patients with paid work and without paid work.

Patients were absent from work for a mean 10,55 (SD 44,4) days/ year). Short-term absence (less than four consecutive weeks) costed a mean € 644,41 (SD 2777,8) per patient/year (N=115). In addition, some patients also experienced long-term absence from work (longer than four consecutive weeks). Long-term absence costed an additional € 796,77 (5617,0) yearly per patient (N=115). A reduction in effectiveness of work was experienced by 34,9% of patients with a mean overall productivity of 7,48 (SD 2.09, Likert scale 0-10, in which 10 indicates normal productivity). Presenteeism costs were € 1447,28 (5078,1) per patient/ year (N=115).

Total costs

Direct and indirect costs are € 7160,54 yearly per patient. The division of costs is illustrated in Figure 1. We used the ~2% prevalence of CRSwNP and the current Dutch adult population of 13,4 million people to calculate estimates of total annual costs; direct costs would be €402 million/year and indirect costs would be at least €1.5 billion/year.

Table 3. Average annual days of absence and productivity losses with accompanying total indirect costs in Euros per patient with CRSwNP

Expenditure	Paid work (N=83)	Costs in €	No paid work (N=32)	Costs in €	Total (N=115)	Costs in €
Absence (days, SD)	10.55 (44.4)	1996.82 (7212.9)	NA	NA	NA	1441.18 (6183.1)
Work-related lost productivity (days, SD)	30.36 (65.9)	2005.27 (5892.2)	NA	NA	NA	1447.28 (5078.1)
Unpaid work lost productivity (days, SD)	15.90 (66.0)	1877.77 (11555.0)	43.88 (98.7)	5087.18 (21718.7)	23.69 (77.1)	2770.83 (15046.4)
Total no. of days (SD)	56.82 (124.9)	5879.85 (18155.2)	43.88 (98.7)	5078.18 (21718.7)	23.69 (77.1)	5659.28 (19117.6)

DISCUSSION

This evaluation of the economic burden of CRSwNP found a large cost difference between direct medical costs and indirect costs. Mean direct medical costs were at least €1501 and mean indirect costs were at least €5659 annually per patient. Larger indirect costs were expected based on the figures from the Unites States (11).

Annual direct and indirect costs of CRS on an individual patient level have been evaluated before (4,12,13,19-22), however there are no studies that evaluated CRSsNP and CRSwNP as separate disease phenotypes for indirect costs. Moreover, not many European cost evaluations are available to compare with (4,14). Bhattacharyya demonstrated in 20039 that patients with CRS (N=322) in the United States were absent for 4,8 days annually (23). A follow-up study in 2009 using data from the National Health Interview Survey reported that patients with any form of sinusitis missed 5.7 days annually (21). CRSsNP patients in the United States were absent for 5,8 days annually (21). Our absence rate of 10,6 days for CRSwNP is significantly higher. Rudmik et al. showed that patients with recalcitrant CRS (N=55) had mean annual presenteeism and absenteeism rates of 25-39 days/year, with costs $10,000 per patient / year (~ €9000). Apart from severity, the type of CRS symptoms is also of influence on indirect costs (24). The current study did not evaluate the influence of severity and symptoms on costs in patients with CRSwNP. The Dutch Central Bureau of Statistics published data of absenteeism rates in the general population (2018). Compared to their reported average 7,6 days absence/year, our finding of 10,6 days/year is significantly higher than what would be expected as normal. When these additional ~ 3 workdays would be multiplied with 2% (prevalence of CRS 1-4%) of 13,4 million adults, this would generate 1 million lost workdays/year (25). Some caution is warranted with this estimate given this is a cross-sectional study. However, our findings generally support the available evidence that absenteeism forms a large expenditure. The main costs of patients with CRSwNP were due to productivity losses in both paid and unpaid patients. Since 72% of patients had paid work, we felt that we could divide total costs among all included patients to provide an estimate of mean annual indirect costs per patient independent of working status. Higher productivity losses in unpaid patients during unpaid work were found. An explanation could be older age (50% of patients were retired, N=16).

Direct costs formed only 21% of total costs and main contributors were outpatient department visits and hospitalisation. Murphy et al. (19) showed higher direct costs (~€2400) of CRS patients in the United States compared to controls, mainly due to non-urgent outpatient visits (~€920) and drug treatment (~€320). A good comparison could not be made since our study did not include full pharmacy costs. Van Agthoven calculated direct costs of severe CRS patients to be €1792/year (N=35) (4). This study also included costs of medical treatment but seems to compare well to our current direct cost value of €1501. The cost estimates of this study are reflections of CRSwNP burden in the Netherlands measured by the iMCQ and iPCQ. Although the prevalence of CRSwNP can be similar between countries, costs do not necessarily have to be so. A generalisation cannot be made directly due to country-level differences in medical costs, reference prices used and mean income per individual.

This study has some limitations: 1. This was a cross-sectional study design with extrapolation of data. Care must be taken with cost estimates since the moment of assessment of questionnaires is not guaranteed to be representative. We feel that the sample size is large enough to provide reliable cost figures; 2. Self-reported data in questionnaires are subject to recall bias and so the results must be interpreted with caution; however, these questionnaires are validated to such an extent that recall bias is limited; 3. Intranasal (mainstay) therapy for CRSwNP was not included in our analysis and consequently annual direct costs will most likely be an underestimation of total costs.

The focus of this study was to evaluate direct and indirect costs per patient with CRSwNP in general, rather than to make a comparison with objective findings of disease or severity of disease based on validated patient reported outcome measurements for CRSwNP, such as the SNOT-22 (26). It would be very helpful in future studies to relate healthcare utilization costs and costs of lost productivity or absenteeism to the severity of sinonasal symptoms measured by the SNOT-22, total symptom scores or a more objective measurement such as nasal endoscopy. Our findings show a skewed distribution of costs in Dutch patients with CRSwNP indicating that indirect costs, particularly productivity losses, form the main part of the large annual costs found. Future interventions should be directed to lowering absence rates and improve productivity at work and at home.

More (European) research should be performed on the extent of productivity losses in patient with CRSwNP and the influence of treatment on productivity.

CONCLUSION

We showed the economic burden of CRSwNP to be at least €1501 per patient/year for direct medical costs and €5659 per patient/year due to productivity losses and absenteeism. The high indirect costs produce a significant burden to the Dutch economy, to companies and to patients. In current times, healthcare policy makers become more interested in costs of illness and the effect of the applied interventions on these costs, which further justify any procedure or medical intervention for CRSwNP. Therefore, awareness must be created among ENT-specialists that indirect costs form the biggest cost expense.

Authorship contribution

As per ICMJE recommendations: 1) Contributions to conception and design of, or acquisition of data and analysis and interpretation of data; 2) drafting the article of revising it critically for important intellectual content; 3) final approval of the version to be published: EL 1,2,3; WJF: 1,2,3; SR 2,3

Conflict of interest

None.

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CHAPTER 4

BENEFITS AND HARM OF SYSTEMIC STEROIDS FOR SHORT- AND LONG-TERM USE IN RHINITIS AND RHINOSINUSITIS: AN EAACI POSITION PAPER

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Clin Transl Allergy. 2020 Jan 3; 10:1

ABSTRACT

Because of the inflammatory mechanisms of most chronic upper airway diseases such as rhinitis and chronic rhinosinusitis, systemic steroids have been used for their treatment for decades. However, it has been very well documented that—potentially severe—side-effects can occur with the accumulation of systemic steroid courses over the years. A consensus document summarizing the benefits of systemic steroids for each upper airway disease type, as well as highlighting the potential harms of this treatment is currently lacking. Therefore, a panel of international experts in the field of Rhinology reviewed the available literature with the aim of providing recommendations for the use of systemic steroids in treating upper airway disease.

INTRODUCTION

Chronic upper airway inflammation is one of the most prevalent chronic disease entities in the world with rhinitis being the most common presentation form affecting 30% of the Western population (1).

Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. Allergic rhinitis (AR) is the best-known form of non-infectious rhinitis and is associated with an IgE-mediated immune response against allergens(1).However, a substantial group of rhinitis patients has no known allergy and they form a very heterogeneous non-allergic rhinitis (NAR) patient population suffering from drug-induced rhinitis, occupational rhinitis, irritant-induced rhinitis, hormonally linked rhinitis and idiopathic rhinitis (2,3). When inflammation of the nasal mucosa extends to the mucosa of the paranasal sinuses, the consensus term of rhinosinusitis is used. Rhinosinusitis has been shown to affect about 10% of the Western population (4). In addition to rhinitis symptoms, rhinosinusitis is characterized by postnasal drip, facial pressure and reduction or loss of smell (5). Acute rhinosinusitis (ARS) is a very common condition and mostly of viral origin (5). About 0.5–2% of the viral ARS are complicated by a bacterial infection (5).

Chronic rhinosinusitis (CRS) is defined as the presence of two or more nasal symptoms, one of which should be either nasal blockage or nasal discharge, and/ or smell problems, and/ or facial pain for more than 12 weeks, in combination with inflammatory signs confirmed by nasal endoscopy and/or CT scan. CRS can either present with nasal polyps (CRSwNP) or without (CRSsNP). Additionally, chronic upper airway disease often coexists with lower airway problems, most frequently asthma, but also a link with chronic obstructive pulmonary disease (COPD) and bronchiectasis has been reported (6).

Glucocorticosteroids (GCS) are the oldest and most widely used anti-inflammatory therapy. Since their introduction in the 1950s, GCS have played a key role in the treatment of various inflammatory, allergic, and immunologic disorders. Consequently, they are known as a very effective drug for treating chronic airway inflammatory diseases involving both lower as well as upper airways (1,4,7). GCS can be administered topical or systemically. If possible topical GCS are preferred over systemic GCS treatment as it is well known that this systemic GCS treatment is linked to an extensive range of potential adverse effects (AE's) that have been well-described in the literature and vary from uncomfortable to life-threatening (8). Notably, reports on AE and/or toxicity of systemic GCS cover a heterogeneous group of GCS-treated diseases, which complicates the interpretation of the actual risk for the rhinitis/rhinosinusitis patients.

Therefore, the risk–benefit ratio of treating non-life-threatening upper airway diseases with systemic GCS remains debatable and needs clarification.

This document summarizes the current evidence for beneficial as well as harmful effects of administration of systemic GCS in the different types of upper airway disease and aims at providing recommendations about its use in rhinitis and rhinosinusitis based on the current evidence. For each topic 2 experts in the field were appointed to review the literature and topics that were appropriate for clinical recommendations were considered as evidence-based reviews with recommendations. The experts then provided a recommendation based upon the guidelines of the American Academy of Pediatrics (following the recommendation strategy used by the International Consensus on Allergy and Rhinology (9)). Table 1 summarizes the recommendation development based on the combination between levels of evidence and the benefit/harm balance. Generally, the search was focused on adults. Two experts reviewed the literature specifically for the pediatric population.

The search was performed in the MEDLINE (Ovid 1946—current; and PubMed 1966—current) and Cochrane databases. The search strategy was based on a combination of MeSH-terms and free text words. Search terms are listed in Additional file 1.

Table 1. American Academy of Pediatrics defined strategy for recommendation development (9)

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit
A. Well-designed RCTs	*Strong recommendation*	*Option*	*Strong recommendation against*
B. RCT's with minor limitations; overwhelming consistent evidence from observational studies	*Recommendation*		
C. Observational studies (case-control and cohort design)			*Recommendation against*
D. Expert opinion; Case reports; Reasoning from first principles	*Option*	*No recommendation*	

RCT: randomized controlled trial.

Mechanisms and actions of GCS

Corticosteroids, which are produced by the adrenal glands, can be classified as glucocorticoids and mineralocorticoids. Cortisol is the endogenous glucocorticoid in humans, naturally derived from cholesterol metabolism upon stimulation by the hypothalamic–pituitary–adrenal axis (Fig. 1), which is regulated initially by the circadian rhythm, but also by negative feedback by glucocorticoids and glucocorticoid increment induced by stressors such as pain, inflammation or infections (10).

GCS are involved in several physiologic functions. They control the metabolism of carbohydrates, proteins and lipids, as well as the balance of calcium (11,12). However, the most explored effects of GCS are the anti-inflammatory and immune-suppressive functions. GCS inhibit the activation and survival of inflammatory cells and modulate the activity of structural cells

(13,14). The main anti-inflammatory effects of GCS are based on their ability to reduce the synthesis of several cytokines (IL-1, -2, -3,-4, -5, -6, -8, TNF-α, IFN-γ, GM-CSF) from many cells (macrophages, monocytes, lymphocytes, fibroblasts, and epithelial and endothelial cells). This affects recruitment, localization, protein synthesis, and survival of inflammatory cells such as eosinophils (15). The recruitment of inflammatory cells is also diminished by an inhibited expression of adhesion molecules such as ICAM-1 and VCAM-1 (16), which affects the influx of basophils and mast cells in the epithelial layers of nasal mucosa. Finally, GCS are involved in the pathological wound repair mechanism called remodelling. Remodelled tissue such as the stroma of nasal polyps contains abundant infiltration of inflammatory cells, increased fibroblasts numbers and increased extra-cellular matrix deposition. However, GCS appear to be minimally effective in reversing the structural changes resulting from remodelling (17).

All these effects are exerted by intracellular activation of the glucocorticoid receptor (GR) (18). The GR belongs to the superfamily of ligand regulated nuclear receptors (19) and alternative splicing of the GR primary transcript generates two receptor isoforms, named GRα and GRβ. GRα has a widespread distribution in cells and tissues (20), including healthy and diseased upper airway mucosa. Inactive GRα is found primarily in the cytoplasm of cells as part of a large multi-protein complex (21). Glucocorticoids diffuse across the cell membrane and bind to GRα resulting in a nuclear entry (Fig. 2) (22) where GRβ modulates either positively or negatively the expression of target genes. GRβ has a very low level of expression compared to GRα (20) and acts mainly as a negative inhibitor of GRα-mediated gene modulation (23).

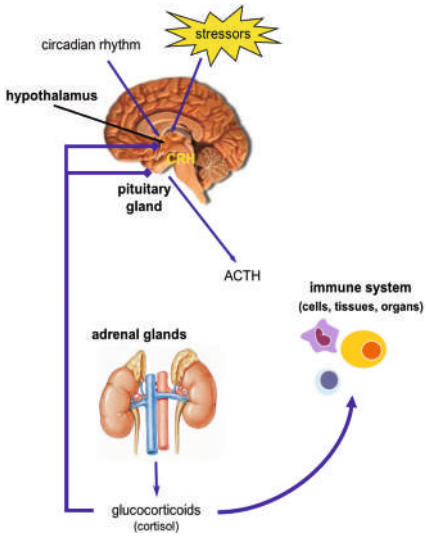

Figure 1. The hypothalamic–pituitary–adrenal axis. Stress stimuli induce the production of CRH by the hypothalamus. CRH induces the production of ACTH by the pituitary gland which stimulates the production of glucocorticoids (cortisol) in the adrenal gland cortex. Cortisol acts on many cells, tissues, and organs including the immune system. The excessive release of cortisol as well as proinflammatory cytokines have a negative feedback on the central nervous system by inhibiting this circadian cycle. *CRH* corticotrophin releasing hormone, *ACTH* adrenocorticotrophin hormone

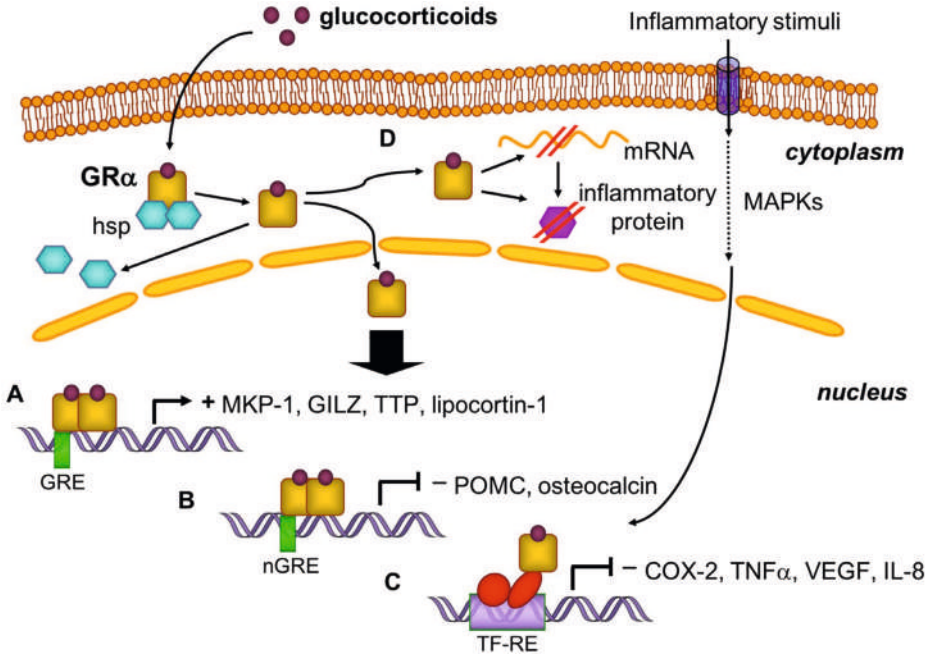

Figure 2. Molecular mechanisms of glucocorticoid action. After crossing the cell membrane by passive diffusion, glucocorticoids bind to GRα, associated heat-shock proteins (HSP) are released, and the ligand bound receptor translocates into the nucleus. Through the activation of MAP kinase (MAPKs) intracellular cascade, inflammatory stimuli induce the production of transcription factors. A GRα dimer can bind glucocorticoid responsive elements (GRE) on the promoter region of target genes and activate anti-inflammatory gene (MKP-1, GILZ, TTP, lipocortin-1) transcription. B Binding of GRα to a negative GRE (nGRE) leads to gene (POMC, osteocalcin) repression. C Protein–protein interactions between GRα and transcription factors (AP-1, NF-κB) repress the transcription of pro-inflammatory genes (COX-2, TNF-α, VEGF, IL-8). D GRα can alter mRNA or protein stability of inflammatory mediators

The anti-inflammatory effects of GCS are explained by three broad molecular mechanisms: the decreased expression of pro-inflammatory genes (trans-repression), the increased expression of anti-inflammatory genes (trans-activation), and non-genomic mechanisms. Trans repression is thought to be mainly due to direct interactions between GRα and pro-inflammatory transcription factors such as the activator protein-1 (AP-1) and NF-κB (24). Transactivation is explained by the interaction of GRα to specific target DNA sequences, named glucocorticoid-responsive elements (GRE). Among the genes activated by GRα through GRE with anti-inflammatory functions, there are the mitogen activated protein kinase phosphatase-1, the glucocorticoid inducible leucine zip- per and tristetraprolin. In addition, the activated GRα can also reduce inflammation at the post-transcriptional (altering mRNA stability), translational (affecting protein synthesis) and post-translational levels (altering protein processing, modification or degradation) (Fig.2). For example, the expression of cyclooxygenase-2, TNF-α and GM-CSF are regulated by one or more of these post- genomic mechanisms (25).

Increased expression of GRβ has been reported in different inflammatory diseases, including asthma, and nasal polyposis and has been proposed as one of the potential mechanisms explaining GC resistance (26). The expression of GRβ is higher in nasal polyps than in nasal mucosa epithelial cells and correlates with increased infiltration of inflammatory cells (27). Although downregulation of GRα after treatment with glucocorticoids has been reported (28) and could account for secondary steroid resistance, a recent study in patients in patients with nasal polyps has shown that this effect does not occur in vivo (29).

Evidence for efficacy of systemic GCS in different inflammatory upper airway diseases

1. Allergic rhinitis

AR is the most prevalent presentation form of all allergic diseases and the most common chronic disorder in children. It is considered a risk factor for the development of asthma and a major public health problem, due to its prevalence and impact on patients' quality of life, work/ school performance, and economic burden (30).

Intranasal GCS and oral/topical antihistamines are the most effective symptomatic treatment for AR and should be the first-line therapy for mild to moderate disease (30,31). Moderate to severe disease not responsive to intranasal GCS, should be treated with additional pharmaco- logical therapies (including cromolyns and leukotriene receptor antagonists), allergen immunotherapy (AIT) and non-pharmacologic therapies (such as nasal irrigation) (30,31). Usually, a combination of intranasal GCS and a topical or oral antihistamine is used for moderate to severe AR.

Regarding the use of systemic GCS in AR, the current evidence is scarce. Three studies compared the effect of systemic GCS in adult patients (› 15-year-old) with AR (Table 2).

The first randomized controlled trial (RCT) from 1987 showed a beneficial effect of a depot injection of 80 mg methylprednisolone (MP) vs. placebo on nasal obstruction and eye symptoms in 48 AR patients, which lasted for 4 weeks (32). The second study by Brooks et al. (33) investigated the efficacy of different doses of oral MP and placebo in patients not treated with other medications. Thirty-one patients were randomized to receive 0, 6, 12, or 24 mg MP. Oral GCS produced dose-related reduction in all symptoms. The difference between placebo and 24 mg MP was significant for all the symptoms monitored, except itching, which benefited marginally. With 6 mg MP, congestion, drainage, and eye symptoms showed significant drug-placebo differences, but itching, running/blowing, and sneezing did not. The third study by Laursen et al. (34) compared prednisone 7.5 mg for 3 weeks with a single intramuscular injection of betamethasone dipropionate also in patients not treated with other medications. This study showed a therapeutic index in favour of the depot injection versus oral treatment in AR (33).

Table 2. Summary of the evidence for 'Efficacy of systemic steroids in allergic rhinitis in adults'

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Borum P et al.	1987	1b	RCT	1) 80 mg MP (n=12 adults with AR) vs placebo early in the season (n=12 adults with AR) 2) 80 mg MP (n=12) vs placebo late in the season (n=12)	1) Nasal and ocular symptoms 2) Number of sneezings and nose blowing/day	The effect of MP on nasal blockage is marked and last for 4 weeks. MP administration before the pollen season is effective but not recommended in clinical practice to avoid too widespread use
Laursen et al.	1987	1b	RCT	1) 10 mg betamethasone dipropionate IM single dose and oral placebo (n=17 adults with AR) x 3 weeks 2) 7.5 mg oral prednisolone x 3 weeks and IM placebo (n=19 adults with AR)	1) Nasal and ocular symptoms 2) Blood eosinophils	Both treatments equally controlled hay fever symptoms Reduction of blood eosinophils with both drugs
Brooks CD et al.	1993	1b	RCT	1) Placebo (n=7 adults with AR) 2) 6 mg MP (n=8 adults with AR) 3) 12 mg MP (n=8 adults with AR) 4) 24 mg MP (n=8 adults with AR)	1) Nasal and ocular symptoms 2) Dose-response effect 3) Minimal effective dose 4) Relative effectiveness against various symptoms	MP produced dose-related reduction in all symptoms. 24 mg MP reduced significantly all symptoms except nasal itching. 6 mg MP reduced significantly nasal congestion, drainage, and eye symptoms. Not all rhinitis symptoms responded equally to corticoid treatment. Those that responded least could reflect histamine effect, which was not effectively suppressed by low-dose, short-term corticoid treatment.

RCT: randomized controlled trial. MP: methylprednisolone. AR: allergic rhinitis. IM: intramuscular

Despite the therapeutic benefits of systemic GCS in the treatment of AR that were shown in these studies, their use is strongly recommended against in view of the AE's GCS that are discussed below, and a short course of systemic GCS is only indicated in rare cases. These cases include patients with severe symptoms who do not respond to other drugs, or those who are intolerant to intranasal drugs (1,35). Systemic GCS should never be considered as a first line of treatment for AR (1). Consequently, oral GCS can be used for a few days as in carefully selected cases when other medical treatment options have failed.

- Evidence level: B.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value, except for patients suffering from very severe and therapy-resistant symptoms.
- Recommendation: Strong recommendation against. Option in patients suffering from very severe and therapy-resistant symptoms.

2. Non-allergic rhinitis

Although, the prevalence of NAR among the chronic rhinitis patients ranges from 20 to 50% (36), their disease mechanisms and treatment options are much less studied than their allergic peers. NAR comprises a heterogeneous group of chronic rhinitis subtypes, such as drug-induced rhinitis, hormonal-induced rhinitis, some forms of occupational rhinitis and rhinitis linked to systemic diseases (37). However, in about 50% of the NAR patients, no specific causal factor can be found and this is addressed as idiopathic rhinitis (IR) (37). Up till now, no studies are available that investigate the effectiveness of systemic steroids in NAR or IR patients. However, since it is believed that in IR neurogenic pathways are involved, rather than classical inflammatory pathways (38), systemic GCS are not the therapy of choice. Of note, all IR patients included in a recent study investigating the effect of capsaicin in IR, reported lack of clinical response to intranasal GCS (38). By extrapolation, there is a low likelihood of oral GCS being effective in this patient population, unless more than one etiologic or inflammatory mechanism underlies the development of rhinitis.

Only in selected cases of other subtypes of NAR, such as rhinitis linked to vasculitic or systemic diseases, oral GCS might play a role in the treatment strategy (see below) (39). Although oral GCS are often prescribed in patients suffering from rhinitis medicamentosa to overcome the withdrawal period of topical decongestants, there are no valuable studies supporting this clinical practice.

- Evidence level: D.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value.
- Recommendation: Recommendation against.

Table 3. Summary of the evidence for 'Efficacy of systemic steroids in acute rhinosinusitis in adults'.

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Cannoni et al.	1990	1b	RCT	1) Adults with (sub)acute, non-allergic sinusitis with antibiotics and prednisolone 40-60 mg/day for 7 days 2) Adults with (sub)acute, non-allergic sinusitis with antibiotics and NSAID for 7 days	1) Therapeutic success defined as combination of resolution of pain and absence of nasal discharge clinically and endoscopically at day 7	Beneficial effect of prednisolone in combination with antibiotics
Gehanno et al.	2000	1b	RCT	1) Adults with acute sinusitis treated with antibiotics and methylprednisolone 8 mg; 3x/day for 5 days 2) Adults with acute sinusitis treated with antibiotics and placebo for 5 days	1) Clinical recovery on day 14 2) course of symptoms on day 4 3) Symptoms and radiological signs on day 30	Significant pain relief in combination with antibiotics compared to antibiotics in monotherapy, no additional effect on nasal discharge
Klossek et al.	2004	1b	RCT	1) Adults with acute maxillary sinusitis treated with antibiotics and prednisone 0.8-1.2 mg/kg/day for 3 days 2) Adults with acute maxillary sinusitis treated with antibiotics and placebo for 3 days	1) Difference in VAS for pain at baseline and day 3 2) Differences in VAS for nasal obstruction 3) Time to pain relief 4) Administration of paracetamol 5) Global subjective effect of treatment on day 3 6) Global subjective effect of treatment on day 10-12	Benefit of short course treatment of prednisone in combination with antibiotics vs. antibiotics with placebo.

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Table 3. *[continued]*

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Ratau et al.	2004	1b	RCT	1) Adults with acute sinusitis treated with antibiotics and betamethasone 1mg/d for 5 days 2) Adults with acute sinusitis treated with antibiotics and placebo for 5 days	1) improvement of symptoms between day 0 and day 6 2) percentage of participants with physical signs present or absent on day 0 and day 6 3) number of paracetamol tablets taken	Benefit of steroids treatment in combination with antibiotics vs. antibiotics with placebo
Venekamp et al.	2012	1b	RCT	1) Adults with acute sinusitis treated with prednisolone 30 mg/d for 7 days 2) Adults with acute sinusitis treated with placebo for 7 days	1) Resolution of facial pain/pressure at day 7 2) Resolution of other clinically relevant symptoms on day 7 3) Time to resolution of total symptoms 4) Median duration of symptoms 5) Quality of life 6) Resumption of daily activities	No clinically beneficial effects of systemic corticosteroid monotherapy

RCT: randomized controlled trial. MP: methylprednisolone. NSAID: non-steroidal anti-inflammatory drug

3. Acute rhinosinusitis

Compared to the literature on effectiveness of systemic GCS in CRS, data on acute rhinosinusitis (ARS) are scarce. In 2014 an update of a Cochrane review was published (40) concluding that systemic GCS as a monotherapy are ineffective compared to placebo in ARS patients, but might have a beneficial effect on short-term symptom relief when used as an adjunctive therapy to antibiotics. Up to date, five randomized, placebo-controlled trials investigating the effect of oral GCS in adults with ARS are available and included in the Cochrane meta-analysis (Table 3).

From those, only one focused on systemic GCS as a monotherapy (41). In this high-quality second-line clinical trial, patients with clinically diagnosed ARS were randomized to receive either prednisolone 30 mg/day or placebo for 7 days. In the 174 patients who completed the trial, no clinically relevant benefit of prednisolone over placebo was found regarding facial pain or pressure, other nasal symptoms or quality of life.

Four other RCTs investigated the adjunctive effect of systemic GCS to oral antibiotics in ARS. Gehanno et al. (42) reported the adjuvant effect of 5 days of 3 × 8 mg MP/day to amoxicillin–clavulanate in 417 patients. On day four, patients showed significantly less pain in the steroid group whereas nasal discharge did not significantly improve. The use of additional medication was not reported.

In 2004, two similar studies were published; a French study (43) showed a beneficial effect on pain with oral prednisone as an add-on therapy to cefpodoxime in 291 ARS patients. Also, Ratau et al. (44) reported a significant benefit of 1 mg of oral betamethasone per day as adjunct to amoxicillin–clavulanate in 42 patients. In 1990 Cannoni already published similar findings showing a better symptom resolution in ARS patients treated with 40 mg prednisolone/day in combination with antibiotics, compared to patients receiving a non- steroidal anti-inflammatory drug (NSAID) with antibiotics (45).

Altogether, these limited data suggest that systemic GCS as a monotherapy appear to be ineffective in ARS patients. However, oral GCS in combination with antibiotics may be modestly beneficial for short-time symptom relief in adults suffering from ARS, compared to antibiotics alone, with a number needed to treat of seven (40). Due to the small number of included studies (n = 5) and their methodological bias, a definite conclusion would only be justified if large, controlled trials would be available. Given the self-limiting nature of ARS, the relatively small additional clinical benefit of adding GCS to antibiotics, and the potential AE's, GCS should not be used routinely, but may be considered an option after informed discussion and shared decision making with the patient in the setting of severe pain.

- Evidence level: B.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value in mild and moderate disease.

- Recommendation: Strong recommendation against when only mild to moderate symptoms. Option in patients suffering from severe headaches/symptoms when combined with antibiotics.

4. Chronic rhinosinusitis without nasal polyps

For clinical purposes, the definition of CRS includes nasal polyposis (NP) and currently it is still unclear why some CRS patients develop NP and others do not. CRSsNP is characterized by basement membrane thickening, goblet cell hyperplasia, fibrosis, subepithelial oedema and influx of inflammatory cells that are mainly of the neutrophilic subtype with a cytokine pattern deviated towards the Th1 subtype (5).

Based on available data, medical therapy for CRS should begin with daily application of intranasal

steroids in conjunction with saline irrigation and subsequent therapies are based on the patient's severity of symptoms and/or quality of life impairment (4).There is limited data showing efficacy of oral GCS in CRSsNP and a systematic review analysed the available literature in 2011(46).

No RCT investigated the effects of oral GCS in CRSsNP and only two retrospective case series in adults are available (47,48) that both considered CRSwNP and CRSsNP patients, but subgroup analysis allowed an evaluation specific to CRSsNP (Table 4). Both retrospective studies investigated the effects of oral prednisone in conjunction with 1 month of oral antibiotics added to intranasal steroids and irrigations. Improved subjective and objective outcomes were seen after multimodality treatment schemes in both studies for CRSsNP. The study of Subramamian et al. (48) pooled both CRSwNP and CRSsNP patients and found that the CRSsNP patients had better outcomes than CRSwNP patients. Lal et al. (47) demonstrated that the CRSsNP patients showed total symptom resolution 2 months after treatment of 54.9% compared to 51% for the total CRS group. There are no studies available that investigated the benefits of systemic GCS in monotherapy in treating CRSsNP.

Because of a lack of RCTs or even prospective studies, evidence for clinical efficacy of oral GCS therapy in CRSsNP is Level 4 or 5 and in view of the AE discussed later on, not recommended for the management of CRSsNP.

- Evidence level: C.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value.
- Recommendation: Recommendation against.

Table 4. Summary of the evidence for 'Efficacy of systemic steroids in Chronic Rhinosinusitis without nasal polyps in adults'.

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Subramanian et al.	2002	4	Retrospective	CRS patients (23 CRSsNP and 17 CRSwNP) treated with 1 month antibiotics + intranasal steroids + prednisone tapered over 10d (20mg 2x/day for 5 days, 20mg 1x/day for 5 days). Mostly adult patients (2 patients under 18).	Change in CT scores, symptom scores post-treatment. Time to relapse.	Beneficial effect of multimodal therapy on scoring of CT, symptoms or both in 90% of all CRS patients, no specific subanalysis for CRSsNP. Beneficial effect continued beyond 8 weeks in 60% of patients. No subanalysis made for CRSsNP
Lal et al.	2009	4	Retrospective	Adult CRS patients (23 CRSsNP and 17 CRSwNP) treated with antibiotics + intranasal steroids + intranasal decongestants + prednisone tapered over 12 days (60, 40, 20, 10 mg for 3 days each)	Complete endoscopic and symptomatic resolution of symptoms 2 months after start of treatment	Beneficial effect of treatment in 54.9% of CRSsNP

CRS: chronic rhinosinusitis. CRSsNP: chronic rhinosinusitis without nasal polyps. CRSwNP: chronic rhinosinusitis with nasal polyps.

5. Chronic rhinosinusitis with nasal polyps

CRSwNP is different from CRSsNP by the presence of nasal polyps consisting of a large quantity of extracellular oedema with the presence of a dense inflammatory cell infiltrate (49,50), which is characterized in about 80% of the Caucasian CRSwNP patients, by activated eosinophils (51,52) and is associated with a predominant Th2 cytokine profile (IL-4, IL-5, IL-10, eotaxin) (53,54).

A recent suite of Cochrane Reviews has considered the efficacy of interventions for CRSwNP. Two reviews were performed with respect to short-term oral GCS; one comparing oral GCS alone versus placebo or other treatment (55), and a second comparing oral GCS used as an adjunct to other treatments, versus control (56).

For oral GCS alone, 8 trials with a total of 474 participants, all of whom were adult patients CRSwNP, were identified (57-64). All studies followed up patients to the end of the treatment course, and 3 followed patients for 3 to 6 months after completion. Patients receiving oral GCS achieved better quality of life (standardized mean difference (SMD) of – 1.24 95% CI – 1.92 to – 0.56, measured with RSOM-31), lower nasal symptom scores (SMD – 2.84, 95% CI – 4.09 to – 1.59) and greater polyp reduction (SMD – 1.21) than control groups at the end of the course of treatment. However, there was no difference between groups at 3 to 6 months after the course of treatment.

Treatment doses utilized in included studies included prednisone at 30 mg and reduced over 14 days, prednisolone at 60 mg reducing over 17 days, or at constant dosage of 50 mg or 25 mg for 14 days or reducing dosages of MP over 20 days. Of the three studies that followed patients beyond the course of treatment, 2 prescribed ongoing intranasal GCS after completion of the systemic dose to both groups while one did not (58,62,63).

Included trials were considered to be at low risk of bias, but overall the quality of evidence was rated as low due to the small numbers of participants, heterogeneity of outcome measures and limited follow-up time in most studies.

Another trial considered oral GCS versus placebo as an adjunct to treatment with intranasal GCS in CRSwNP patients (65). This study recruited 30 participants and was considered at high risk of bias because of lack of blinding and lack of information on randomization. It reported greater reduction in polyp size in the active treatment arm (MD – 0.46, 95% CI – 0.87 to – 0.05).

One trial included in the Cochrane review of oral GCS as an adjunctive treatment recruited children (66) and is therefore considered later in this document. Table 5 summarizes the evidence of these studies and provides a recommendation for the treatment of CRSwNP by systemic GCS. There is good evidence that systemic GCS are effective in the management of CRSwNP, at least in the short-term. However, considering the evolving understanding of CRSwNP and the chronicity of this condition, the short-lived benefits of systemic GCS therapy need to be balanced with the long- term potential AE's which are discussed below.

Table 5. Summary of the evidence for 'Efficacy of systemic steroids in Chronic Rhinosinusitis with nasal polyps'.

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Alobid et al.	2014	1b	Prospective non-blinded RCT	Adult CRSwNP patients treated with intranasal budesonide 800 µg daily for 2 weeks in combination with oral prednisone (30 mg daily for 4 days followed by a 2-day reduction of 5 mg) (n=67) or nothing (n=22)	1. Polyp grade measured by CT 2. Nasal congestion 3. Loss of sense of smell 3. Polyp tissue eosinophils 4. Nasal nitric oxide	Combined oral and intranasal corticosteroids improve smell and nasal congestion, decrease tissue eosinophilia and increased detection of nNO.
Benitez et al.	2006	1b	Prospective non-blinded RCT	Adult CRSwNP patients treated with oral prednisone, 30 mg for 4 days and a 2-day reduction of 5 mg for a total duration 14 days followed by intranasal budesonide for 12 weeks (n=63) or no treatment (n=21)	1. Disease individual symptom scoring of nasal obstruction, loss of sense of smell, rhinorrhoea and sneezing 2. Polyp size measured by endoscopy 3. Nasal flow measurements	14 days of oral steroids improved all nasal symptoms, polyp size, and nasal flow, which is maintained by intranasal steroid.
Ecevit et al.	2015	1b	Prospective double-blind RCT	Adult CRSwNP patients treated with oral prednisolone, 60mg/day (6 tablets per day) for 7 days, then reduced to 10 mg (1 tablet) taken every other day, stopping on day 17 (n=11) or placebo (n=10)	1. Visual analogue scale for sense of smell, nasal discharge, nasal obstruction and pressure over the sinuses 2. Smell testing 3. Peak nasal inspiratory peak flow	The improvement in the corticosteroid group in the VAS scores, smell tests and PNIF values showed statistically significant differences compared to the placebo group.
Hissaria et al.	2006	1b	Prospective double-blind RCT	Adult CRSwNP patients treated with prednisolone, 50 mg/day for 14 days (n=20) or placebo (n=21)	1. Health-related quality of life (RSOM-31) 2. physician assessment of nasal symptoms (congestion, hyposmia, rhinorrhoea, sneezing, postnasal drip and itch) 3. Polyps size measured by endoscopy 4. MRI of the paranasal sinuses	The prednisolone-treated group showed significant improvement in nasal symptoms. The RSOM-31 improved in both groups, but the prednisolone-treated group had significantly greater improvement than the placebo group. There was significant reduction in polyp size, as noted with nasendoscopy ($P < .001$) and MRI ($P < .001$), only in the prednisolone-treated group.
Kapucu et al.	2012	2b	Prospective unblinded RCT	Adult CRSwNP patients treated with oral methylprednisolone 1 mg/kg/day. The dose was applied for 3 days and tapered gradually, with a reduction rate of 8 mg/3 days (n=12) or no medication (n=12)	Apoptotic Index.	Statistically significant differences in apoptotic index were found between each steroid-medicated group and the control group

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Table 5. *[continued]*

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Kirtsreesakul et al.	2012	1b	Prospective double-blind RCT	Adult CRSwNP patients treated with oral prednisolone 50 mg daily for 14 days (n=67) or placebo (n-47)	1. Symptom scoring for blocked nose, runny nose, sneezing, nasal itching, hyposmia, postnasal drip, cough and sinonasal pain. 2. Nasal polyp size measured by endoscopy	The prednisolone-treated group showed significantly greater improvements in all nasal symptoms, nasal flow and polyp size than the placebo-treated group.
Vaidyanathan et al.	2011	1b	Prospective double-blind RCT	Adult CRSwNP patients treated with prednisolone tablets, 25 mg/day, 2 weeks (n=30) or placebo (n=30) in patients on intranasal steroids.	1. Juniper mini Rhinoconjunctivitis Quality of Life Questionnaire 2. total nasal symptoms score 3. sense of smell 4. nasal polyp score by endoscopy 5. Peak nasal inspiratory flow rate 6. Serum eosinophil-derived neurotoxin 7. High-sensitivity C-reactive protein levels	Short oral steroid therapy followed by topical steroid therapy is significantly more effective over 6 months than topical steroid therapy alone in decreasing polyp size and improving olfaction in CRSwNP patients with at least moderate nasal polyps.
Van Zele et al.	2010	1b	Prospective double-blind RCT	Adult CRSwNP patients treated with oral methylprednisolone (32 mg/day on days 1 to 5; 16 mg/day on days 6 to 10; 8 mg/day on days 11 to 20) (n=14) or placebo (n=19)	1. Polyps size measured by endoscopy 2. Nasal peak inspiratory flow 3. Blood analysis for eosinophils, eosinophilic cationic protein and soluble IL-5 receptor _ 4. Nasal secretion analysis for eosinophilic cationic protein, IL-5, IgE, matrix metalloprotease-9, myeloperoxidase 5. Need for rescue surgery and need for rescue nasal steroids	Methylprednisolone significantly decreased nasal polyp size compared with placebo. The effect was maximal at week 3 and lasted until week 8. Methylprednisolone significantly reduced levels of ECP, IL-5, and IgE in nasal secretions.

RCT: randomized controlled trial. CRS: chronic rhinosinusitis. CRSwNP: chronic rhinosinusitis with nasal polyps.

Table 6. Summary of the evidence for 'Efficacy of systemic steroids before endoscopic sinus surgery in Chronic Rhinosinusitis with nasal polyps'.

Study	Year	LOE (1a to 5)	Study Design	Study groups	Clinical Endpoints efficacy	Conclusion
Ecevit et al.	2015	1b	Prospective double-blind RCT	Adults with CRSwNP with surgical indication receiving either oral prednisolone, 60mg/days for 7 days, then reduced to 10 mg (1 tablet) taken every other day, stopping on day 17 (n=11) or placebo (n=10)	1. Perioperative bleeding 2. Visibility of the operative field 3. Operative time 4. Hospital stay	Perioperative bleeding, operative time and hospital stay were significantly reduced in patients who received oral steroids. Visibility of the operative field was significantly better after receiving steroids.
Wright et al.	2007	1b	Prospective double-blind RCT	26 adult CRSwNP patients with surgical indication receiving either 30mg of prednisone for 5 days preoperatively or placebo.	1. Difficulty of surgery 2. Operative time 3. Per-operative blood loss	Surgeons rated the surgery in the placebo-treated group as more difficult than the steroid-treated group. No differences were noted in operative duration and blood loss.
Günel et al.	2015	1b	Prospective double-blind RCT	65 adult CRSwNP patients with surgical indication receiving either oral prednisolone (1 mg/kg for 2 days and then tapered down, with treatment completed on the day 10) or placebo	1. Intraoperative blood loss 2. Quality of surgical field	No difference in intraoperative blood loos when patients received oral steroids preoperatively Non-significant improvement of quality of surgical field after oral steroids
Fraire et al.	2013	3b	Prospective non-randomized CT	Adult CRS patients with surgical indication (CRSsNP and CSRwNP) receiving either 2x/day 30 mg methylprednisolone On 5 consecutive days prior to surgery (n=27) vs. no treatment (n= 27)	1. Intraoperative bleeding 2. Surgical time 3. Quality of surgical field	Operative bleeding was significantly reduced in CRSwNP patients who received oral steroids preoperatively. No significance obtained in quality of operating field. No difference in surgical time
Sieskiewicz	2006	1b	RCT	36 adult CRSwNP patients with surgical indication receiving either prednisone (30 mg/day for 5 consecutive days directly before the surgery) or no preoperative treatment	1. Intraoperative bleeding 2. Surgical time 3. Quality of surgical field	Quality of the operating field and surgical time were significantly improved in CRSwNP patients who received oral steroids preoperatively. No significance obtained in total blood loss.

RCT: randomized controlled trial. CRS: chronic rhinosinusitis. CRSwNP: chronic rhinosinusitis with nasal polyps.

Therefore, systemic GCS should not be considered as a first line of treatment for CRSwNP. They can be used in a short course during 2–3 weeks as a last resort of treatment when combinations of other medications are ineffective.

- Evidence level: A.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value in the long- term, except in patients with severe symptomatology.
- Recommendation: Strong recommendation against. Option for a short-term course in patients with severe symptoms and therapy-resistance.

A separate indication, for which oral GCS have been prescribed in CRSwNP patients, is the preoperative setting, in order to reduce perioperative bleeding and improve surgical conditions for the surgeon during endoscopic sinus surgery (ESS). Of the five studies that have been performed studying this topic in adults (Table 6), four are RCTs, however, their outcomes are not conclusive. The study from Ecevit demonstrated a significant improvement on all perioperative variables studied (perioperative bleeding, visibility of the operative field, operative time, hospital stay) after a preoperative course of GCS in CRSwNP patients (59). However, while some other studies confirm a significant improvement of intra-operative bleeding time (67) or quality of the operating field (68) and surgical time (69), these differences were not found to be significant by their colleagues (67-70). A recent meta-analysis reported on a significant reduction in operating time, perioperative blood loss and improved surgical field quality when patients were given preoperative steroid treatment, however, the result was mainly based on a large RCT reporting on intranasal GCS (71).

Therefore, the use of oral GCS is currently not recommended in the preoperative setting of CRSwNP patients.

- Evidence level: B.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value.
- Recommendation: Strong recommendation against.

6. Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a form of a non- invasive fungal rhinosinusitis and although it is not characterized by a specific phenotype, it seems to be an immunologically distinct subtype of CRS (72). The diagnosis is based on the criteria proposed by Bent and Kuhn: (1) production of eosinophilic mucin without fungal invasion into sinonasal tissue; (2) positive fungal stain of sinus contents; (3) nasal polyposis; (4) characteristic radiographic findings; and (5) allergy to fungi (73). In view of the locally aggressive character of the disease, the corner- stone of AFRS treatment is surgery (74). However, a lot of uncertainty remains concerning the medical options and postoperative therapy. Although no RCTs are available, we found four smaller studies that investigated the role of GCS in the management of AFRS mostly in adults (Table 7).

Table 7. Summary of the evidence for 'Efficacy of systemic steroids in Allergic Fungal Rhinosinusitis'.

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Woodworth et al.	2004	3b	Prospective case control study	Adults with CRSwNP from which 8 AFRS and 6 eosinophilic mucin rhinosinusitis were treated with oral prednisone (60mg for 3 days, 40mg for 3 days, 30mg for 3 days, 20mg for 12 days)	1. SNOT-20 2. Nasal endoscopy score 3. Mucosal IL-5, IL-13, eotaxin, MCP-4	Significant reduction in nasal endoscopy scores and inflammatory markers, non-significant reduction in SNOT-20 scores
Landsberg et al.	2007	3b	Prospective case control study	Adult AFRS and CRSwNP patients received 1 mg/kg prednisone for 10 days	1. CT Lund Mackay scores 2. Nasal endoscopy score, but no scoring system used	CT score changes were significantly greater in AFRS patients compared to CRSwNP.
Kupferberg et al.	1997	4	Retrospective case control study	Adult and adolescent AFRS patients (13-69 yr) that underwent surgery and receiving: 1. No treatment; 2. Oral steroids (4 days 40mg, then 4 days 30mg, then 20mg/day until 1 month postop); 3. Oral steroids and oral antifungals; 4. Oral antifungals	1. Nasal endoscopy score 2. Symptom scoring	Postoperative treatment with oral steroids alone improved 90% of the patients, however, disease recurrence was seen after cessation of steroids.
Kuhn and Javer.	2000	4	Case series	Postoperative steroids in adult AFRS patients (0.4mg/kg/day for 4 days, then 0.3 mg/kg/day for 4 days, then 0.2mg/kg/day maintenance dose)	Nasal Endoscopy score	Endoscopic stage 0 maintained if oral steroid was maintained for an average of 4.5 months

CRS: chronic rhinosinusitis. CRSwNP: chronic rhinosinusitis with nasal polyps. AFRS: allergic fungal rhinosinusitis. IL: interleukin. MCP: monocyte chemotactic protein.

Two prospective non-controlled studies examined the effects of GCS in a small number of AFRS patients without surgery (75,76). Woodworth showed a significant reduction in nasal endoscopy scores and inflammatory markers in the AFRS group after 18 days of prednisone (76). Landsberg (75) showed a more significant reduction in radiologic and mucosal scoring in AFRS patients compared to CRSwNP patients after 10 days of prednisolone. An older retrospective study from Kupferberg (77) in 26 AFRS patients, found that patients who received postoperative GCS showed more symptom improvement and less endoscopic disease com- pared to treatment with oral antifungals or no treatment. However, disease recurrence was noted after cessation of GCS. Similar findings were seen in a non-controlled retrospective study from Kuhn and Javer (78) who showed a maintenance of low endoscopic scores in AFRS patients, only after long-term GCS use. No AE's were reported in any of the four studies. It has to be noted that all of these studies have a high risk of bias and the level of evidence for the use of oral GCS in AFRS patients remains at level C.

- Evidence level: C.
- Benefits–harm assessment: Balance of harm and benefit in patients with severe disease.
- Recommendation: Option in patients with severe AFRS (severe symptoms and/or locally invasive dis- ease) in conjunction with ESS.

7. Nasal manifestations of auto-immune disease

Many auto-immune disorders can involve the nose: thyroid auto-immunity, various vasculitis, Sjogren's syndrome and sarcoidosis are the most frequently encountered, but other connective tissue diseases, such as systemic lupus erythematosus, polyarteritis nodosa, scleroderma and relapsing polychondritis can also have nasal symptoms (39).

GCS have been the major therapeutic option for some of these diseases as an immune suppressant for the past decades, probably being most effective where eosinophils, which are exquisitely steroid-sensitive, are involved (79). However, the quality of the evidence for their efficacy is poor, with studies mostly being reviews or open pilots, even in seminal trials such as those of Fauci for Wegener's granulomatosis (80-82). The reasons for this include not only time-hallowed use, but also difficulty in undertaking placebo-controlled trials in severe diseases, differences in the manifestations and their intensity between individual patients, disease complexity and plasticity and probably lack of interest in funding. This situation is now changing with the advent of newer therapies, particularly monoclonal antibodies, which are being trialled against older therapies including GCS (83).

Churg–Strauss syndrome, now called eosinophilic granulomatosis with polyangiitis (EGPA), is classically considered a Th2-mediated disease and affects sinonasal mucosa in › 80% of the patients. Treatment must be tailored according to prognostic factors identified by the French Vasculitis Study Group (84). GCS alone are used for mild disease, high-dose GCS and cyclophosphamide is still the gold standard for severe cases (85), but biological agents such as rituximab or anti-IL-5 biologicals are promising, though costly, alternatives (86).

The hallmark of granulomatosis with polyangiitis (GPA; previously known as Wegener's disease) is the coexistence of vasculitis and granuloma and again over 80% of patients show sinonasal involvement (87). GCS alone are insufficiently effective: the induction treatment for severe GPA comprises GCS combined with another immunosuppressant, cyclophosphamide or rituximab. Once remission is achieved, maintenance strategy following cyclophosphamide-based induction relies on less toxic agents such as azathioprine or methotrexate.

GCS decrease the frequency, duration, and severity of flares in relapsing polychondritis, but do not stop disease progression in severe cases (88).

The presence of sinonasal disease is associated with more severe sarcoidosis and the need for systemic GCS therapy (89).

Treatment for systemic lupus erythematosus (SLE) by various organ systems is not evidence-based beyond the usual first- or second-line treatment, however a recent meeting achieved consensus in several scenarios, including anti-phospholipid syndrome (90).

GCS, often combined with NSAIDs, are used in Sjogren's syndrome to treat associated interstitial lung disease and/or sensorineural hearing loss (91).

Table 8 shows the evidence available for auto-immune disorders for which GCS are frequently used.

- Evidence level: D.
- Benefits–harm assessment: Depending on other organ involvement and severity.
- Recommendation: Following the recommendation for the management of the specific auto-immune disease.

8. Sinonasal pathology and concomitant asthma

Asthma is a chronic inflammatory disease of the lower airways involving inflammation of the bronchial mucosa, and variable obstruction of bronchi due to intrinsic/extrinsic stimuli, and leading to symptoms such as episodic breathlessness and wheezing with airway hyperresponsiveness to environmental stimuli (92). Since the introduction of the "United Airway Disease" concept (1), a large series of scientific publications from clinical epidemiology, pathophysiology, histology, and treatment outcomes has correlated asthma and upper airway disease. AR and asthma often coexist, and AR is regarded as a risk factor for the development of asthma. Uncontrolled rhinitis impacts asthma control. Asthmatic patients have a higher CRS severity score than non-asthmatic patients, and more nasal polyps, indicative of a strong relationship between CRS severity and asthma (93). It has been reported that 20–60% of patients with CRSwNP have asthma (94,95).

Table 8. Summary of the evidence for efficacy of systemic steroids in the treatment of auto-immune disease.

Auto- immune disease + Study	Year	LOE	Study Design	Study Groups	Conclusion
EGPA. Moosig et al.	2013	3	A retrospective cohort study at a vasculitis referral centre	150 fulfilled the inclusion criteria. Of those, 104 had more than one follow-up visit. Severe organ manifestations: heart (46%), kidney (18%) and lungs (10%). Cyclophosphamide was used in 107 patients (71%). The prednisolone-doses of all patients were within the targeted range (i.e. ≤7.5 mg) in 69% of the total follow-up time; the median dose at end of follow-up was 5mg/day.	10-year survival rate was 89%, mortality comparable to the general population (SMR 1.29). Patients with cardiac failure had increased mortality (SMR 3.06)
GPA WGET Research Group	2005	1b	180-patient multicentre, , placebo-controlled RCT examining the efficacy of etanercept in WGCT	Severe disease received cyclophosphamide and corticosteroids; limited disease received methotrexate and corticosteroids Etanercept (25 mg twice weekly) or placebo was added to conventional therapy	Addition of etanercept did not lead to more sustained remissions; lower levels of disease activity; reduction in time to remission nor the number or relative risk of flares; nor fewer severe or life-threatening adverse events or deaths
Relapsing polychondritis McAdam et al.	1976	3	Review	159 reported cases,23 those of the authors	Three-fourths of our patients required chronic corticosteroid therapy with an average dose of 25 mg per day of prednisone. Corticosteroids decrease the frequency, duration, and severity of flares, but do not stop disease progression in severe cases. Mortality rate 30 percent in our series and 22 percent in the other 136 reported cases
EGPARibi C et al.	2008	2	RCT	72 patients with newly diagnosed EGPA (FFS of 0) treated with CS alone. At treatment failure or relapse, patients were randomized to receive 6 months of oral AZA or 6 pulses of CYC.	93% achieved remission with CS alone, 35% relapsed, mainly during the first year of treatment. Among the 19 patients randomized to additional immunosuppression, 5 of 10 receiving AZA and 7 of 9 receiving pulse CYC achieved remission, p=NS. Survival rates in all patients at 1 and 5 years were 100% and 97%, respectively. At the end of follow-up, 79% of the patients whose disease was in remission required low-dose CS therapy, mainly to control respiratory disease. CS-related adverse events were observed in 31% of the 72 patients.

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Table 8. *[continued]*

Auto- immune disease + Study	Year	LOE	Study Design	Study Groups	Conclusion
GPA Hoffman et al.	1992	3	An open-label pilot study of weekly low-dose methotrexate (MTX) plus glucocorticoids (GC) for treatment of patients with WG	Weekly administration of MTX (at a mean stable dosage of 20 mg) and GC in 29 WG patients	Marked improvement in 76%. Remission achieved in 69%. 7% improved but had intermittent smoldering disease that precluded total withdrawal of GC, and 17% had progressive disease within 2-6 months of starting the study treatment. Two patients who initially achieved remission later relapsed after GC discontinued. Of those who remain in remission (mean follow-up time 14.5 months), 72% have not required GC for a mean period of 10 months.
Sarcoidosis Aubart FC et al.	2006	3	Retrospective single-center study	Twenty patients with histologically proven SNS (men/women, 7/13; mean age, 32 +/- 9 year) were compared with control patients with sarcoid but without sinonasal (SN) involvement. Each patient was matched with 2 controls for the date of admittance in our institution.	SNS had significantly more frequent and severe involvement of vital organs than controls, had a longer history of sarcoidosis, and required systemic treatment more frequently (100% vs. 57.7%, p < 0.001) and for a longer time (78 +/- 42 months vs. 29 +/- 18 months, p < 0.0001). Corticosteroids maintenance dosage was high (10.5 +/- 6 mg daily) and mainly depended on SN involvement.
GPA Guillevin et al.	1997	2	Prospective multi-centre RCT	50 newly diagnosed WG patients. Every patient received a daily injection of methylprednisolone for 3 days, followed by daily oral prednisone (1 mg/kg/day) and a 0.7-gm/m2 pulse of CYC. Patients were then randomly assigned to prednisone plus intravenous pulse CYC (group A), n=27 or prednisone plus oral CYC (group B) n=23 as first-line treatment.	Pulse CYC was as effective as oral CYC in achieving initial remission of WG with fewer side effects and lower mortality. However, in the long term, treatment with pulse CYC does not maintain remission or prevent relapses as well as oral CYC.

EGPA: Eosinophilic granulomatosis with polyangiitis. GPA: granulomatosis with polyangiitis. AZA: azythromycine. CYC: cyclophosphamide

The first use of GCS to treat acute asthma exacerbation was in 1956 (96). Development of GCS that have less mineralocorticoid activity, like prednisone, and later those that have no mineralocorticoid activity, like dexamethasone, made steroid use more attractive therapies to use in asthma. Prescribing a short course of oral GCS following the treatment of acute asthma exacerbations was found to reduce the rate of relapse (97). However, courses longer than 5 days were not found to provide any additional benefit (98).

As described above, systemic GCS should not be considered as a treatment for AR. We could not identify any systematic review, randomized trial, or controlled study that evaluated the use of systemic GCS in patients with AR with concomitant asthma not responding to other therapy. When analysing the evidence of oral GCS for patients with CRS and coexisting asthma there are a few randomized controlled trials and uncontrolled prospective interventional studies that evaluated the efficacy of different treatments (Table 9) of which only one looked at systemic GCS use. This study was carried out in adults by Ikeda et al. (99) and included 21 CRS patients with concomitant asthma. Fifteen patients underwent ESS, and 6 other patients remained on medical therapy. Seven patients of the ESS group showed a reduction in the need for GCS during the 6 months following surgery, whereas two patients were unchanged and two patients required larger dosages.

Generally, due to a lack of studies investigating the efficacy of GCS in asthmatics with CRS, the same rules apply as for non-asthmatic CRS patients. With regards to the morbidity and potential mortality that is associated with asthma, the use of GCS in asthmatic CRS patients should be directed in the first place by the severity of the lower airway symptoms.

- Evidence level: D.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value in the long-term, except in patients with severe symptomatology.
- Recommendation: Recommendation against. Option in patients with severe symptoms and therapy-resistance.

9. Adverse effects of systemic GCS

Although GCS play a key role in the treatment of various inflammatory disorders, including chronic upper airway disease, a quite extensive range of potential AE's is well-described in literature and the chance to develop these effects seems to increase with higher dose and longer duration of treatment (8,100-102).

However, few studies have actually addressed the risk of common GCS-induced AE in upper airway disease. Also, most of the studies available on GCS focus on high dose or long-term usage for at least 6 months or even 1 year consecutively, which is mostly less relevant in the upper airway disease patient group.

Table 9. Summary of the evidence for 'Efficacy of systemic steroids in sinonasal disease + concomitant asthma.

Study	LOE (1a to 5)	Study Design	Study groups	Clinical Endpoints efficacy	Conclusion
Ikeda et al. 1999	3	Prospective RCT	Adult CRSwNP and CRSsNP patients undergoing ESS	1. Sinonasal and pulmonary symptoms. 2. Systemic GCS need	1. Improvement of FEV_1 2. No significant changes in systemic GCS need.

RCT: randomized controlled trial. CRS: chronic rhinosinusitis. CRSsNP: chronic rhinosinusitis without nasal polyps. CRS: chronic rhinosinusitis. CRSwNP: chronic rhinosinusitis with nasal polyps. GCS: glucocorticosteroids.

In the following section, we aimed at summarizing the data of potential short- as well as long-term AE's of systemic GCS treatments for rhinitis and/or rhinosinusitis in the adult population. Due to the heterogeneity in studies, treatment regimens and patient populations, we classified the side-effects according to the organ-system involved, but no further subdivision was made. When no studies were available for upper airway disease patients, a mention of studies investigating AE's in similar patients (ophthalmologic, asthmatic) was made. Studies investigating side-effects in children will be discussed separately in the next chapter.

Hypothalamic–pituitary–adrenal-axis (HPA) inhibition

Reductions in the level of plasma cortisol are reported after one injection of GCS. They usually decrease in the first 2 weeks after steroid administration, but slowly return to normal after 3 weeks, as has been demonstrated in patients with AR (103). Hedner et al. (104) showed a minor HPA dysfunction in 14 allergic patients treated with a single intra-muscular injection of MP acetate, which returned completely to normal at 4 weeks post-injection. In a double-blind study by Laursen et al. (105) 36 birch pollen allergic patients were treated with either a single injection of betamethasone dipropionate or oral prednisolone 7.5 mg/day for 3 weeks. Only the prednisolone treated patients showed reduction in plasma cortisol levels at 3 weeks. Bonfils et al. (106) prospectively evaluated the HPA- axis in patients with CRSwNP (n = 46), who received at least three short courses of oral GCS in the last year (course 6–8 days, 1 mg/kg/day, mean duration of treatment 4.7 years, mean 6.8 courses/year, mean cumulative prednisone consumption 3,800 mg). The study demonstrated that 48% of patients had an asymptomatic adrenal insufficiency diagnosed with the Synacthen test.

Hyperglycemia and diabetes

A retrospective study based on Danish National Registries, including 47,382 AR patients, demonstrated that treatment with at least one consecutive injection of depot corticosteroid for 3 years on a row was associated with an increased risk of being diagnosed with diabetes later in life (RR 1.4) (107). The degree of new-onset diabetes associated with intermittent short-term oral GCS has not been clearly established.

Osteoporosis

In the same Danish epidemiological study, Aasbjerg et al.(107) showed that, compared to immunotherapy, treating AR with annual depot-steroid injections (i.e. at least one steroid injection in the pollen season for 3 consecutive years) was associated with increased risk of being diagnosed with osteoporosis (RR 1.2). The above-mentioned study from Bonfils, investigating the HPA-axis, prospectively evaluated the occurrence of osteoporosis in patients with CRSwNP (n = 46), receiving at least three short courses of oral GCS in the previous year. Osteopenia of the proximal femur was present in 40.5% and osteoporosis was present in 54% (106). Rajeskaran et al. (108) retrospectively evaluated the risk of osteoporosis in patients with CRS (n = 176), who received oral GCS ≥ 5 mg daily for 3 consecutive months any time in the past. Overall, low bone mineral densities (BMD; osteopenia or osteoporosis) was 38.6%. These studies were recently evaluated in a systematic review which was unfortunately not

able to quantify the overall risk of osteoporosis induced by oral GCS for CRSwNP, due to the low number of studies (109).

The effects of short-course oral GCS on bone mineral density (BMD) have also been investigated in a 4-year longitudinal small study in asthmatic patients. Asthmatic patients receiving frequent short courses of oral GCS (i.e. › 2.5 courses/year; n = 9) compared to those receiving sporadic courses (i.e. ≤ 2.5 courses/year; n = 26) revealed a greater loss of lumbar BMD (T-score 82.0% versus T-score 77.7%) in the frequently treated group (110). Also, a lower Z-score of 93.1% was demonstrated in frequent short courses, versus the sporadic courses that did not show a lower Z-score than the normal population values (Z-score 100.1%).

Avascular necrosis

With regards to avascular necrosis of the femoral head in patients treated with systemic GCS for upper airway disease, we found 1 case report of Nasser et al. (111) describing a single case with severe hay fever that was given at least one depot corticosteroid injection each year for 11 years, leading to avascular necrosis.

More individual case reports highlight the relationship between the use of systemic GCS and avascular necrosis. The risk to develop osteonecrosis seems to be dependent on the prescribed dose, the cumulative dose and route of administration, as well as underlying disease states (SLE patients seem to be particularly at risk) (112-114).

Gastrointestinal disturbances and peptic ulceration

In a randomized double-blind placebo-controlled study by Kirtsreesakul et al. (62) 112 patients with CRSwNP used either 50 mg prednisone or placebo for 14 days and reported significantly more (mild) gastrointestinal disturbances and dyspepsia in the prednisolone treated group. In a double-blind placebo-controlled trial by Venekamp et al. (41) 174 adult patients clinically diagnosed with ARS received either 30 mg/day prednisolone or placebo for 7 days. The incidence of gastrointestinal complaints did not differ between treatment groups.

In a large, nested case–control analysis based on the UK General Practice Research Database, 2105 cases of upper gastro-intestinal complications were compared to 11,500 controls and then evaluated for exposure to certain drugs e.g. corticosteroid use. The adjusted OR for current use of oral GCS was 1.8 (95% CI 1.3–2.4) for upper gastro- intestinal complications overall (115). No statistically significant difference could be objectified for lower versus higher dosage of GCS. To our knowledge no studies in upper airway disease patients report on systemic steroid treatment and peptic ulceration.

Ocular adverse effects

GCS have been described to induce the formation of posterior subcapsular cataract or glaucoma. The risk for patients using repeated (short) courses of systemic GCS for upper airway disease is currently unknown.

There is evidence in rheumatoid arthritis patients that this risk is enhanced after therapy lasting more than 1 year (116). Another study by Huscher et al. (101) analysed dose-related patterns of self-reported symptoms from 1066 patients with RA with ongoing long-term (› 6 months) systemic GCS. These symptom patterns were compared to non-users (no systemic GCS for at least 12 months). The prevalence of self- reported cataract was higher for all dosages of GCS, whereas the prevalence of self-reported glaucoma was only increased in those taking › 7.5 mg/day (6.6% users vs. 2.7% non-users).

Infections

A meta-analysis of randomised controlled clinical trials in which patients were randomised to treatment with or without systemic GCS (n = 4198) showed that the rate of infection was not significantly increased in patients who were given a mean dose of less than 10 mg/day of prednisone or a cumulative dose of less than 700 mg (117). This meta-analysis included a wide variety of diseases warranting systemic GCS. The true risk of developing infection in patients using short courses for upper airway disease remains uncertain.

Local adverse effects of steroid-injections

We found one case report on gluteal subcutaneous atrophy that was seen after a depot steroid injection of triamcinolone for AR (118). A study of Laursen et al. (34) investigated specifically the reporting of all AE's related to GCS injections for AR to the 'Danish Register for the Side-Effects of Drugs' and evaluated the reported events consecutively for a 10-year period. The study demonstrated that one out of 11,785 injections came with any local AE. Most AE's were reversible and primarily skin related, such as skin atrophy.

Cardiovascular adverse effects

Cardiovascular disease is mainly associated with high dose and long-term use, primarily hypertension and acute myocardial infarction are described (110,119).

A population-based cohort study in 68,781 GCS users and 82,202 non-users showed that patients exposed to dosages of GCS › 7.5 mg of prednisolone/ day (or equivalent) during 1 to 5 years of follow-up, had substantially higher rates of myocardial infarction, heart failure, or cerebrovascular disease (adjusted RR of 2.56; 95% CI 2.18–2.99). The risk was not increased in patients using ‹ 7.5 mg prednisolone equivalent daily (120).

Another large, retrospective case–control study with data extracted from the General Practice Research Database (1988–1997) showed in over 100,000 individuals that the use of oral GCS comes with a 25% higher risk of any cardiovascular or cerebrovascular outcome compared to controls. Current use (in the 3 months before the registration of an event) and highest average daily dose give a much stronger association. Current use is also associated with a significantly increased risk of heart failure (adjusted OR of 2.66; 95% CI 2.46–2.87) and ischemic heart disease (OR of 1.20; 95% CI 1.11–1.29), but not ischemic stroke or transient ischemic attack. Cardiovascular risk showed a clear dose–response relationship (121).

To our knowledge, the risk in patients using GCS for intermittent short courses is unknown.

Neuropsychiatric effects
A study from Hissaria et al. (60) investigating 40 CRSwNP patients treated with 50 mg of prednisolone daily for 14 days or placebo, found that sleep disturbances were reported as a significant prevalent AE (40%) compared to placebo (10%). Mood disturbances were more frequently reported, but not significantly different from placebo (25% vs. 10%).

In the above-mentioned controlled trial by Venekamp et al. (41) studying ARS patients treated with 30 mg/ day prednisolone or placebo for 7 days, the incidence of mood or sleep disturbance did not differ between treatment groups.

Two studies in asthmatic and ophthalmologic patients receiving short-courses of GCS, showed a development of (hypo)mania (122,123) as well as depression symptoms (123).

Naber et al. (123) showed in a prospective uncontrolled study in ophthalmologic patients receiving systemic GCS (n = 50) that 26–34% of patients developed (hypo)mania and 10–12% developed depression syndromes when using an initial 119 ± 41 mg/ day MP or fluorcortolone, tapered to 75 ± 22 mg/day at 8 days. The onset of symptoms was within 3 days of use and there was no correlation between daily dose and daily ratings of mood. Brown et al. (122) showed in 32 asthmatic patients using prednisone (mean course 13.9 days, mean dose of 36.9 mg/day) a highly significant increase in self-reported mania, but no increase in depression during the first 3–7 days of therapy. Mood changes returned back to normal after discontinuation of therapy.

Cushingoid features
We found no studies investigating Cushingoid appearance in rhinitis/rhinosinusitis patients treated with GCS and only a few studies addressed the risk of intermittent short courses of GCS and weight gain.

A randomised controlled trial by Campieri et al. (124) in patients with active Crohn's disease demonstrated that 38% of patients on a regimen of prednisolone tapered over 12 weeks (40–45 mg) developed a 'moon face'. Mean body weight increased with 2.1 kg after 8 weeks of

treatment. Bar-Meir et al. (125) showed that patients receiving 8 weeks of prednisone developed a moon face in 33% versus 16% in patients receiving a similar treatment with budesonide.

Benefit and risk of use of GCS in pediatric populations

Inflammatory diseases of the nose and paranasal sinuses in children include upper respiratory tract infections, chronic rhinitis, ARS and CRS. ARS is defined as increase of sinonasal symptoms after 5 days of infection or persistent symptoms after 10 days and characterized by the sudden onset of two or more of the symptoms (discoloured nasal discharge, nasal blockage/obstruction/ congestion, cough at daytime and night-time) for less than 12 weeks (4). Bacterial infection is

expected when at least 3 symptoms are present among which discoloured discharge, purulent secretion in nasal cavity, severe local pain with a unilateral predominance, fever, elevated C-reactive protein or erythrocyte sedimentation rate, and double sickening (i.e. deterioration after an initial milder phase of illness) (4). The definition of pediatric CRS differs from adult CRS by the symptom of cough (4) and is defined by the presence of two or more symptoms, one of which should be either nasal obstruction or nasal discharge (anterior or posterior) with/without facial pain/ pressure with/without cough, lasting for at least 12 weeks (4). The diagnosis is confirmed by either nasal endoscopy showing edema, purulent drainage or nasal polyps in the middle meatus or CT scan showing ostiomeatal complex or sinus opacification. Of note, the presence of nasal polyps is much less common in pediatric patients than in adult patients with CRS (126).

Efficacy of systemic GCS in pediatric CRS and ARS

Three clinical trials can be found in literature that investigated the use of oral GCS in the pediatric rhinosinusitis population, of which only one is controlled (Table 10). This controlled study involved forty-eight children (mean age 8 years) with CRSsNP (66) and investigated the effect of oral GCS as an add-on to antibiotics. 22 participants received either 30-day course of oral amoxicillin–clavulanate and 15-day course of oral MP and 23 participants received only antibiotics and a placebo. The mean change of total symptom score and CT score was significantly higher after treatment with oral GCS and antibiotics compared with placebo and anti- biotics ($P < 0.001$). There was also a significant beneficial effect of oral GCS in cough, nasal obstruction, and post-nasal drainage symptom scores. Complete clinical recovery after 30 days of treatment was obtained in significantly more subjects receiving MP ($P < 0.005$). Recurrence of symptoms 6 months after the end of treatment was not statistically significant between the groups.

Additionally, a retrospective study involving 35 young CRS patients (1–21 years) undergoing serial sinus CT scans due to medical reasons, evaluated Lund Mackay ostiomeatal complex score in relation to three different treatment schemes (127) antibiotics, intranasal topical GCS and oral systemic GCS. The data suggested that the use of systemic GCS was associated with a significant increase in the likelihood of radiologic improvement. The retrospective study design, the small and heterogeneous population, heterogeneous treatment modalities, and the lack of adjustments, limit the possibilities to assess clinical significance of the findings. A second uncontrolled study (5) evaluated cytokine pattern of 30 asthmatic CRS patients (4–12 years) before and after the treatment of amoxicillin–clavulanate, fluticasone propionate aqueous nasal spray and a short course of oral deflazacort. After the treatment, endoscopic resolving of mucopurulent discharge was detected in 25/30 children, the median concentration of IL-4 decreased significantly in all subjects, and the median IFN-γ concentration increased significantly only in the atopic subgroup ($N = 16$). The uncontrolled study design and uncertainty whether the patients used prescribed drugs, limits the possibilities to assess effect of systemic GCS.

Table 10. Summary of the evidence for 'Efficacy of systemic steroids in pediatric sinonasal disease'.

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point efficacy	Conclusion
Ozturk et al.	2011	1b	RCT	1) Children with CRSsNP (6-17 year) receiving antibiotics and methylprednisolone 1 mg/kg and reduced progressively over a 15-day treatment course 2) Children with CRSsNP receiving antibiotics and placebo	1) Change in mean symptom and CT scores pre- and post-treatment 2) Change in individual symptom scores, relapse rate	Beneficial effect of MP in combination with antibiotics on mean symptoms, CT scores, VAS for cough, nasal obstruction and post-nasal drainage. No difference in relapse rate
Scorpinski et al.	2008	3b	Retrospective uncontrolled	1741 children with CRS treated with antibiotics, intranasal topical corticosteroids and oral corticosteroids (>4 days) or combination	CT scores	Improvement of CT scores after oral corticosteroid treatment, in mono- or plurithерapy.
Tosca et al.	2003	4	Uncontrolled prospective cohort study	30 asthmatic CRS children treated with antibiotics, intranasal steroids and a short course of deflazacort (1 mg/kg daily for 2 days, 0.5 mg/kg daily for 4 days and 0.25 mg/kg daily for 4 days)	Nasal endoscopy and cytokine patterns in nasal lavages	Resolving of purulent discharge after combination treatment and decrease of mean IL4-levels in nasal lavage

RCT: randomized controlled trial. CRS: chronic rhinosinusitis. CRSsNP: chronic rhinosinusitis without nasal polyps. CRS: chronic rhinosinusitis. CRSwNP: chronic rhinosinusitis with nasal polyps. MP: methylprednisolone

Harm of GCS in children

There is limited knowledge of risks of using systemic GCS in pediatric CRS or ARS compared to pediatric asthma. As an example, the Childhood Asthma Management Program trial followed the annual bone mineral accretion of 877 children (5–12 years) with mild-to- moderate asthma (128,129). Oral GCS bursts produced a dosage-dependent reduction in bone mineral accretion (0.052, 0.049, and 0.046 g/cm2 per year) and an increase in risk for osteopenia (10%, 14%, and 21%) for 0, 1–4, and ≥ 5 courses, respectively, in boys. The authors conclude that multiple oral GCS bursts over a period of years can produce a dosage-dependent reduction in bone mineral accretion and increased risk for osteopenia in children with asthma. 780 children with asthma were followed fora mean of 4.3 years and it was shown that boys with lower vitamin D levels are significantly more susceptible to the negative effects of GCS on bone mineral accretion over time (129). Regarding studies investigating GCS AE's in upper airway disease, the trial from Ozturk also looked at self-reported AE's during the 15-day course of oral MP (66). In this trial no clinically significant AE's were reported. At the end of the treatment, the mean weight change did not differ statistically significantly between the groups. No data of monitored AE's, nor that of long- term outcomes, nor that of bacterial culture were available in this study.

A systematic review has been performed to determine the most common and serious drug-related AE of long courses of oral GCS in children (130). Literature search of several databases was performed to identify all studies in which systemic GCS had been administered to pediatric patients ranging from 28 days to 18 years of age for at least 15 days of treatment. The group found 91 studies that represented a total of 6653 children and contained reports of 4124 adverse drug reactions, the majority in patients with leukemia, hemangioma and asthma. The three most frequent adverse drug reactions were weight gain (22.4%), Cushingoid features (20.6%) and growth retardation (18.9%). Increased susceptibility to infection was the most serious adverse drug reaction. 24 children died from infections, 10 from varicella zoster. There is insufficient knowledge of the effect and harm of short-term systemic GCS courses in pediatric CRS patients. However, based on studies on pediatric asthma, a single short-term systemic GCS course could be considered in pediatric patients suffering from CRS that is not responding to other therapies such as intranasal GCS, antibiotics, supporting therapy (saline douchings, decongestants) and adenoidectomy. It is mandatory to perform more powered; randomized placebo-controlled clinical trials of pediatric ARS and CRS with long-term follow up and report of AE's.

- Evidence level: B.
- Benefits–harm assessment: AE's of systemic GCS outweigh advantages of therapeutic value in mild and moderate disease.
- Recommendation: Strong recommendation against. Option in patients suffering from very severe and therapy-resistant disease, in combination with antibiotics.

Health economic considerations related to GCS use

Besides clinical consequences, systemic GCS use may also have some health economic implications that should be considered in its benefit-harm trade-off. Generally, the direct costs

for systemic GCS are among the lowest quartile of prices of medications available worldwide. However, the indirect costs due to adverse events of (especially long-term, high-dose) systemic GCS use could be more substantial. Two industry-funded studies have assessed the cumulative economic burden of GCS associated adverse events regardless of dose, duration or indication (131,132). Manson et al. (131) identified 63 studies in which 21 different GCS adverse events were reported with increased fracture risk, gastric and psychiatric conditions being the most frequent ones. Their economic analysis from the UK perspective revealed that taking oral GCS would result in an additional annual cost of at least £165 for treatment of all steroid related adverse events. One study specifically assessed the economic impact of oral GCS on related fractures where hip, vertebral and forearm fractures costed £10,761, £1976 and £863 respectively. Notably, only three studies focused on patients with allergic rhinitis and/or skin diseases and none specifically on rhinosinusitis. A second review (132) included 47 studies reporting on adverse events of systemic GCS. Subsequently, a cost analysis was undertaken from the US perspective. It was unclear whether any patients with allergic rhinitis or rhinosinusitis were included. Most frequently reported adverse events were psychiatric and gastric conditions, infections, and fractures. The authors estimated the potential cost reductions if the daily GCS dose would be reduced. Regarding avoidance of fractures, they estimated that 96 fractures per 10,000 elderly patients could be avoided summing up to $1.76 million ($176 per patient). The findings from both reviews should be interpreted with caution given the heterogeneous and often low-quality and retrospective nature of the studies included and the difficulty in excluding confounding due to underlying disease activity. Besides these two reviews with no particular disease focus, some studies focused on the costs of systemic GCS related adverse events within a specific population such as asthma (133,134) or rheumatologic diseases (135,136) and found increased costs in the GCS exposed populations. None were specifically focusing on rhinitis or rhinosinusitis. We conclude that given the limited amount of current evidence, more studies on the economic burden and cost-effectiveness of systemic GCS use in rhinitis and rhinosinusitis treatment are required.

Alternatives for GCS in upper airway disease

In both rhinitis and rhinosinusitis patients, systemic GCS treatment is in general reserved for those in whom disease control cannot be obtained by baseline medical therapy (intranasal steroids and antihistamine/anti- leukotrienes for AR (30) and intranasal steroids and antibiotics for ARS/CRS (4). However, in AR, allergen immunotherapy (AIT) is an alternative option for patients suffering from uncontrolled symptoms. AIT modifies the natural disease course and recent well-performed trials have demonstrated reductions in both symptoms and use of rescue medication in patients with AR for both the subcutaneous as well as sublingual administration route (137). One study from 1969 compared the efficacy of one depot MP injection with a pre-seasonal administration of an alum precipitated pyridine extracted grass pollen immunotherapy and found similar results between the two groups in terms of symptom improvement (138). However, this paper already stated that the potential AE's of MP do not justify the use of systemic GCS for a condition such as AR. One large Danish registry study including almost 40,000 AR patients actually showed the oral steroid-sparing effect of subcutaneous

AIT (SCIT) for seasonal AR with an annual mean of 1.0 steroid injections in patients receiving SCIT versus a mean of 1.6 injections in the non-SCIT group. Of the SCIT-treated individuals, 84% did not need GCS at all after SCIT treatment (139). Aasbjerg looked at the same registry to compare AE's and found that AR patient treated with systemic GCS showed more diabetes and osteoporosis than those treated with AIT as mentioned above (107).

For CRS patients, current alternatives for oral GCS during exacerbations consist of antibiotics and when patients remain uncontrolled, sinus surgery is the next step in line (4). However, studies investigating biological agents that are available for the treatment of asthma and/or other allergic diseases, have shown very beneficial effects in CRSwNP patients (140) but are currently only available for those with severe concomitant asthma. Gevaert et al. (141) extrapolated results from different studies to compare the efficacy of different treatments in CRSwNP patients. They found a beneficial effect on NP score of doxycycline that was comparable to MP after 8 weeks. Also, omalizumab and mepolizumab treatment had better results on NP score than the oral GCS treatment. Omalizumab and mepolizumab additionally showed better symptom control compared to MP. Currently only data on the oral steroid-sparing effects of mepolizumab and benralizumab in asthma are avail- able (142), but with the increased implementation of these therapies in CRSwNP, studies evaluating the steroid-sparing effect for upper airway exacerbations will be necessary.

CONCLUSION

When disease control in upper airway disease cannot be obtained with intranasal steroids or other medical treatment prescribed by the respective guidelines, severe cases of AR, ARS, AFRS and CRSwNP can be treated with a short-term course of systemic GCS to improve symptoms. This manuscript provided an overview of the current evidence for the beneficial effects of systemic GCS in the different subtypes of upper air- way diseases, as well as in the pediatric age group and aimed at providing recommendations for the specific disease entities. However, multiple AEs have been widely described and therefore physicians should be aware of the risks associated with oral GCS and make a good risk–benefit assessment prior to prescribing them. In this paper, we summarize these potential AEs; given the current evidence in literature, a clear assessment of the risks associated with oral steroid use in upper airway disease cannot be made. Currently available data show a wide variability in diseases, patients, duration of

treatment and follow-up and therefore this topic needs to be addressed in a systematic way in order to provide a substantiated recommendation for the use and dosing of oral GCS in the upper airway disease population.

We can conclude that, although some beneficial effects of systemic GCS have been demonstrated in chronic upper airway diseases such as AR and CRSwNP, systemic GCS should not be considered as a first line of treatment for these disease types.

Acknowledgements
Not applicable.

Authors' contributions
All authors contributed to the design, drafting, writing, and revising of the document. All authors read and approved the final manuscript.

Funding
This work was funded by an EAACI Task Force budget.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
GS: Honoraria for articles, speaker and advisory boards: ALK, Astra Zeneca, Brittania Pharmaceuticals, Capnia, Church & Dwight, Circassia, Groupo Uriach, GSK, Meda/Mylan, Merck, MSD, Ono Pharmaceuticals, Oxford Therapeutics, Sanofi-Aventis, UCB. Travel funding: ALK, Bayer, GSK, Meda. Chair of BSACI Rhinitis guidelines, EAACI Ethics Committee, Rhinology & Laryngology Research Fund. Chair of Data Monitoring Board for Acarizax paediatric AR trial.

CH: Reimbursed for Advisory Board work for sanofi, Smith and Nephew and speakers bureau for Medtronic.

CB: Advisory board of Sanofi, GSK, Novartis, Astra-Zeneca, Mylan and reimbursed for presentations and travel.

TVZ: Consult- ant for Medtronic and 3NT.STS: has acted as paid consultant for ERT and Roche Products. All these are outside the submitted work.

All other authors declare that they have no competing interests.

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SUPPLEMENTARY DATA

Additional file 1.

Search terms

Search terms on diseases included rhinitis or rhinoconjunctivitis or rhinosinusitis or sinusitis or "nasal polyps" or polyposis. Search terms on treatment included corticosteroid or corticoid or glucosteroid or glucocorticoid or corticotherapy or methylprednisolone or medrol or prednisone or prednisolone methasone or celestone or dexamethasone, coupled with oral or intramuscular or systemic or injection or depot or intravenous.

Search strategy for the pediatric population included all of the above and was coupled with pediatric or paediatric or children or young or adolescents.

Search terms on adverse events were the following:

- long term adverse effects or "drug-related side effects and adverse reactions" or "metabolic side effects of drugs and substances" or adverse drug reaction reporting systems or pharmacovigilance or safety or patient harm or patient safety

- iatrogenic disease

- pharmacovigilance or vigilance or FDA or harm alert

- (adverse or side effect or ((longterm or long-term) complicat) or sequel or harm or safe or safety or toxic or iatrogen

- (corticosteroid or corticoid or steroid or glucosteroid or glucocortico or methylpred or medrol or metipred or urbason or prednis or prednime or encortn or desoxycorticosteron or betamethason or celeston or budesonid or Pulmicort or Rhinocort or dexamethason) adj (induced or associated or related or harm)

- ((complicat or adverse of side effect or harm or toxic) adj (corticosteroid or corticoid or steroid or glucosteroid or glucocortico or methylpred or medrol or metipred or urbason or prednis or prednime or encortn or desoxycorticosteron or betamethason or celeston or budesonid or Pulmicort or Rhinocort or dexamethason)) and (long-term or longterm or chronic or prolonged or continous or oral or inhal or depot or intramuscul)

- ((risk or harm) adj3 benefit) and (long-term or longterm or prolonged or (long adj period) or ((long or continuous or chronic or frequent or months or weeks or regimen) adj3 ("use" or usage)) or oral or systemic or inhal or intravenous or intramuscul or depot or iv or ICS)

Coupled with

- (adrenal cortex hormones or exp glucocorticoids) and (adrenal cortex hormones to or exp glucocorticoids)

- (methylpred or medrol or metipred or urbason or prednis or prednime or encortn or desoxycorticosteron or betamethason* or celeston* or budesonid* or Pulmicort or Rhinocort or dexamethason* or (systemic adj3 triamcinolon*) or Kenacort

(
((corticosteroid* or corticoid* or steroid or steroids or glucosteroid* or glucocortico* or corticotherap* or cortico-therap*) not (non-steroid* or (((corticost* or steroid*) adj inject*) or ((sex or gonadal or hormon*) adj2 steroid*) or ((steroid or corticoster* or glucocorticoid*) adj (responsive* or sparing or dependent or receptor* or sensitivity or contracept*)) or anti-glucocortic* or anabol*))

CHAPTER 5

ENDOSCOPIC SINUS SURGERY IN ADULT PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (POLYPESS): STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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Trials. 2017 Jan 23;18(1):39

ABSTRACT

Background

Chronic rhinosinusitis with nasal polyps is a chronic disease frequently seen in otorhinolaryngological practice. Along with its chronic disease burden it creates high societal costs. Therapy consists of long-term use of medication and, if insufficient, endoscopic sinus surgery. No consensus exists on the right timing and extent of disease that warrants surgery. Furthermore, there is lack of clinical knowledge about the benefit of surgery over medication only. The current trial evaluates the clinical effectiveness and cost-effectiveness of endoscopic sinus surgery in addition to drug treatment versus medication exclusively in the adult patient group with nasal polyps.

Methods

A prospective, multicentre, superiority, randomised controlled (PolypESS) trial in 238 patients aged 18 years or older selected for primary or revision endoscopic sinus surgery by the otorhinolaryngologist was designed. Patients will be randomised to either endoscopic sinus surgery in addition to medication or medical therapy only. Relevant data will be collected prior to randomisation, at baseline and 3, 6, 12, 18 and 24 months after start of treatment. Complete follow-up will be 24 months. Primary outcome is disease-specific Health-related Quality of Life quantified by the SNOT-22 after 12-month follow-up. Secondary outcomes are generic Health-related Quality of Life, cost-effectiveness, objective signs of disease and adverse effects of treatment. Subgroup analyses will be performed to verify whether treatment effects differ among patient phenotypes.

Discussion

The PolypESS trial will investigate tailored care in adult patients with chronic rhinosinusitis with nasal polyps and will result in improved clinical pathways to help to determine in which circumstances to perform surgery.

Trial registration

Dutch Trial Register, NTR4978. Registered on 27 November 2014.

BACKGROUND

Chronic rhinosinusitis (CRS) can manifest as a disease with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP). The prevalence of both forms of CRS in Europe is around 11% (1). CRSwNP is the more serious form of CRS and is associated with a prevalence of 1–4% (2). Patients with CRS experience a significant impact on most aspects of Health-related Quality of Life (HRQOL) and investigation has shown this to exceed the impact on HRQOL of patients with chronic heart failure, diabetes and chronic back pain (3,4). The high prevalence and significant negative impact on most aspects of HRQOL burdens the diagnostic process and treatment with high medical resource usage and high societal costs (1).

(Inter-)national clinical CRS guidelines advise starting drug treatment for at least 1 month before considering surgery; however, there is no guideline that advises or specifies conditions that warrant surgery (3,5,6). Currently, patients failing drug treatment are offered a more intensive drug regimen or endoscopic sinus surgery (ESS) in addition to drug treatment. In The Netherlands most otorhinolaryngologists prefer surgery, though practice variance is high with regard to the timing and rationale of ESS. These differences lead to inefficient health care practice. Also, if ESS is not proven to be (cost-)effective, risks are generated in exposing patients to ineffective treatment.

A national audit in the UK demonstrated that 69% of ESS is performed for CRSwNP (7). Corresponding data in The Netherlands are lacking, but may be expected to be similar. A recent Chronic Rhinosinusitis Epidemiology Study (CRES) performed in the UK demonstrated that from all respondents with CRSwNP (N = 651) 57% underwent previous sinonasal surgery and 20% underwent multiple surgeries (8). This high burden of primary and revision surgery remains unclear in aetiology, but highlights the need for more research concerning endotyping and phenotyping patients with CRSwNP as well as more research concerning aspects of surgery itself.

A recent analysis of the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis depicted that almost 40% of patients undergoing ESS suffered more than 5 years from their symptoms related to CRS (9). Hopkins et al. specifically looked at the timing of ESS and its influence on symptoms. In the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis (7) the effect of patient time to surgery on symptomatic outcomes was evaluated and it was found that patients treated at an early stage in the course of disease (i.e. within 12 months after first diagnosis of CRS) experience more improvement in symptoms after surgical intervention compared to patients treated after a longer burden of CRS (i.e. after 5 years from first diagnosis of CRS) (9). On top of this finding, the cohort of patients treated after a longer period of CRS had greater CRS-related health care needs postoperatively, consisting of medical visits and prescriptions per patient per year (10). This available data raises more questions about the right timing of ESS.

The systematic review of the Cochrane Review Group on ESS for CRS (2006) concluded, with the limited evidence available, that ESS has not demonstrated an additional benefit in comparison to drug treatment. The need for more randomised trials was highlighted in the review (11).

A recent non-randomised, multicentre cohort study by Smith et al. looked at the differences in HRQOL in a CRS patient group that self-selected ESS versus a patient group that self-selected drug treatment. They demonstrated a significantly better improvement in HRQOL in addition to less use of systemic medication usage after ESS in comparison to ongoing medication until 6-month follow-up (12). They also found a better HRQOL in patients that self-selected ESS at 1-year follow-up (13).

Scientific evidence for the effectiveness and the severity of disease that warrants ESS, ideally retrieved from a well-designed randomised controlled trial, is missing.

The aim of the present trial is to investigate in a randomised fashion whether two regularly applied treatment strategies used in adult patients with CRSwNP, ESS in addition to drug treatment or drug treatment only, differ in generic and disease-specific HRQOL and to establish the presumed superiority of ESS. A comparison with respect to cost-effectiveness will also be made.

METHODS

Study objectives

The primary aim of the PolypESS trial is to assess the effectiveness of ESS in addition to drug treatment as compared to drug treatment alone in adults with CRSwNP in terms of improving patients' HRQOL, measured by the Sinonasal Outcome Test 22 (SNOT-22) at 12-month follow-up. Key secondary aims of the trial are evaluation of the effectiveness of ESS in addition to drug treatment as compared to drug treatment alone in the short (3–6 months) and long (12–24 months) term, in terms of generic HRQOL, objective signs of disease and adverse effects of treatment. This trial will also evaluate which patient phenotypes within CRSwNP benefit from ESS in addition to drug treatment as compared to drug treatment alone. Furthermore, the relation between health care resource use and patient costs and effects of ESS will be determined from a societal point of view. It is hypothesised that a more tailored approach for patients with CRSwNP will be associated with lower medical and indirect costs (health care utilisation and productivity loss).

Study design

The PolypESS is an investigator-initiated, prospective, open, national, multicentre randomised controlled trial investigating the (cost-)effectiveness of ESS in patients suffering from CRSwNP. Suitable patients will be randomised into two treatment groups. In the first group patients will undergo ESS in addition to medication, in the second group patients will receive an intensified drug treatment only. Total follow-up is 24 months for all included consecutive patients.

Otorhinolaryngologists in the participating centres are asked to recruit patients. Any patient who meets the inclusion criteria (described in detail below in 'Study population' section) will be informed about the trial and asked to participate. The coordinating trial centre (Academic Medical Centre, Amsterdam, The Netherlands) will contact patients who have expressed interest in the trial. The study team member will provide detailed written and oral information about the trial and answer any questions. If patients agree to participate, inclusion and exclusion criteria will be checked and a baseline visit will be scheduled. Potential participants have sufficient time before they give their final consent to participate in the trial. If patients decline participation, known clinical data on disease-specific HRQOL and objective signs of disease are used to evaluate whether the findings of the consecutive sampling are generalisable to the target population. The trial reporting is according to the CONsolidated Standards of Reporting Trials (CONSORT) guidelines and the CONSORT extension for nonpharmacological interventions (Fig. 1) (14,15). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: 'Recommended items to address in a clinical trial protocol and related documents', can be found in Additional file 1. The SPIRIT participant schedule is shown in Table 1.

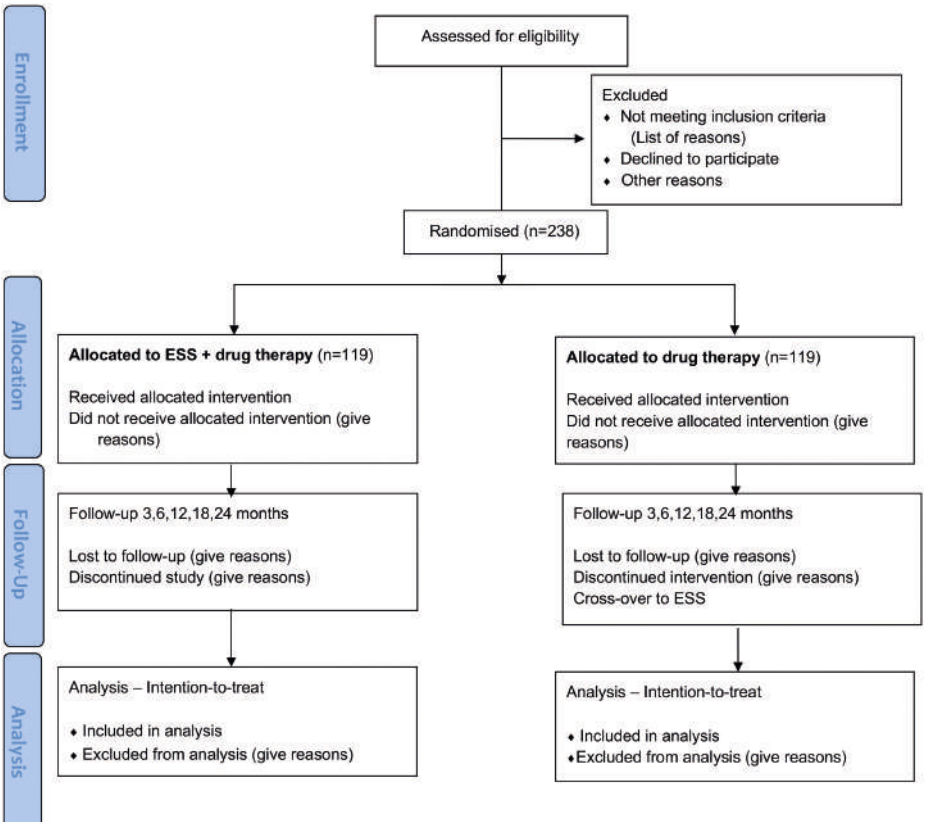

Figure 1. CONsolidated Standards of Reporting Trials (CONSORT) flow diagram of PolypESS study (ESS, endoscopic sinus surgery)

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule patient enrolment, interventions and assessments

Timepoints	**Visit -2** <10 wks	**Visit -1** <6 wks	**Visit 0**	**Visit 1** 3 months	**Visit 2** 6 months	**Visit 3** 12 months	**Telephone consult** 18 months	**Visit 4** 24 months
ENT-surgeons asks patient to participate	x							
Informed Consent		x						
Demographic Data		x						
Medical History including earlier sinus surgery		x						
Inclusion Criteria		x						
Exclusion criteria		x						
Randomisation		x						
ESS or intensify medical treatment based on randomisation			x					
Vital Signs and bodyweight		x						
Symptoms		x		x	x	x	x	x
Disease specific HRQOL and symptoms (SNOT-22)		x		x	x	x	x	x
Generic HRQOL (EQ-5D-5L)		x		x	x	x	x	x
Endoscopic assessment of the nose		x		x	x	x		x
Olfactory function (Sniffin' Sticks)		x		x	x	x		x
Nasal obstruction (PNIF)		x		x	x	x		x
Daily records cards (DRC)		x		x	x	x	x	x
CRS disease control		x		x	x	x		x
Asthma control		x		x	x	x	x	x
Healthcare resource use				x	x	x	x	x
Adverse effects				x	x	x	x	x
CT scan (Lund-Mackay score)		x						
Surgical report			x					
Laboratory tests, pregnancy test		x						
Skin Prick test (if done in the last year, results are recorded)		x						

Wks weeks, *HRQOL* health-related quality of life, *SNOT-22* sinonasal outcome test 22, *EQ-5D-5L* EuroQol-5D-5L questionnaire, *PNIF* peak nasal inspiratory flow

Setting

The trial is performed in 15 hospitals, three university- affiliated hospitals (The Academic Medical Centre, Amsterdam; Erasmus Medical Centre, Rotterdam; VU Medical Centre, Amsterdam) and teaching hospitals (Amstelland Hospital, Amstelveen; Alrijne Hospital, Leiderdorp and Alphen aan den Rijn; BovenIJ Hospital, Amsterdam; Deventer Hospital, Deventer; Flevo Hospital, Almere; Haga Hospital, Den Haag; Onze Lieve Vrouwe Gasthuis location East, Amsterdam; Onze Lieve Vrouwe Gasthuis location West, Amsterdam; Spaarne Hospital, Hoofddorp; Spaarne Hospital, Haarlem; Tergooi Hospital, Hilversum and Blaricum; and Westfries Gasthuis, Hoorn) in The Netherlands. The same medical researcher and research nurses perform all trial assessments in the participating centres, apart from nasal endoscopy. Nasal endoscopy is performed by the local ENT surgeon as part of standard care.

Study population

Adult patients (aged 18 years of age or older) with bilateral CRSwNP who have been selected by their ENT surgeon as candidates for primary or revision ESS are eligible for participation. If patients are excluded from participation, reason(s) for exclusion are registered. Exclusion criteria include the presence of systemic diseases affecting the nose (e.g. Wegener's granulomatosis,

sarcoidosis, primary ciliary dyskinesia, cystic fibrosis), antrochoanal polyps, malignant polyps, inverted papilloma, sinonasal tumours, absolute need for surgical therapy, contraindications for surgical therapy, need for radical surgery (Draf III, Denker surgery, medial maxillectomy), polypectomy without ethmoidectomy, continuous use of systemic corticosteroids for diseases other than CRSwNP, continuous medication for other diseases influencing CRSwNP (e.g. other immunosuppressive drugs), pregnancy at enrolment, mental or systemic illnesses preventing adequate participation in the trial and any other scheduled surgical intervention preventing adequate participation in the trial. Furthermore, potential participants are not allowed to have used any systemic corticosteroids in the previous 4 weeks before enrolment and they should not have suffered from an acute upper or lower respiratory tract infection at the time of enrolment or during the previous 2 weeks.

Patient enrolment

Selection of patients follows a two-stage procedure. Consecutive patients are screened for eligibility by a recruiting local otorhinolaryngologist in the outpatient department. Additionally a telephone interview is scheduled by the medical researcher in the Academic Medical Centre during which eligibility will be reassessed. Patients will be enrolled by the medical researcher during a clinic visit in the concerning hospital. Patients meeting all inclusion criteria and no exclusion criteria can be included and will be randomly assigned, after informed consent is given.

Baseline measurements

On the day of enrolment, patients will undergo the same HRQOL and objective evaluation, including the SNOT-22, the EuroQol-5D-5L questionnaire (EQ-5D-5L, the EuroQol Group) and nasal endoscopy, that will be used after treatment (see "Outcomes" section). Clinical data is

collected by the enrolling medical researcher and focuses on the (severity of) patient-reported symptoms, previous clinical examinations, previous sinonasal surgery, previous conservative treatment and complete medical history. Demographic variables include age, gender, ethnicity, marital status, family situation and highest level of education. Additional study information includes the presence or absence of asthma, acetylsalicylic acid (ASA) intolerance, allergy, occupational exposure, smoking habits and alcohol consumption. Objective measurements recorded are baseline height, weight, blood pressure, resting heart rate, total IgE, serum eosinophil level and computed tomography (CT) scores using the Lund-Mackay scoring system. This system uses a 0–1–2 score dependent upon absent, partial or complete opacification, respectively, of each individual sinus and the ostiomeatal complex, contributing to a maximum score of 12 per side. The total score of the two sides can reach a maximal 24 points (16). A urine pregnancy test will be performed in female patients with childbearing potential if in doubt of pregnancy.

Skin Prick Test

To assess allergic sensitisation, the Global Allergy and Asthma European Network's (GA^2LEN) standardised method of the Skin Prick Test (SPT) is used (17). Patients are instructed to stop taking antihistamine medication 5 days before the SPT. A positive reaction to the SPT is defined as a skin reaction larger than 3 mm for one or more of the tested allergens (at least tree, grass, Dermatophagoides pteronyssinus, cat, dog, moulds) and no reaction to the negative control.

Interventions

Patients will be assigned to a surgical strategy (ESS in addition to drug treatment) or a drug treatment strategy exclusively. Clinicians and patients will not be blinded to the treatment arm of the study. Those assigned to surgery will be offered ESS within 6 weeks of randomisation. Those assigned to drug treatment will be seen by the otorhinolaryngologist within 6 weeks of randomisation to define the need for additional medication. As this is a pragmatic trial, ESS refers to the surgery performed regularly by otorhinolaryngologists in The Netherlands. The extent of surgery is tailored to the extent of the disease. Drug treatment comprises any usual care medication.

OUTCOMES

Primary study outcome

The effectiveness of both interventions is evaluated by the SNOT-22 after 12 months of follow-up. The SNOT-22 is a patient-reported measure of outcome (PROM) consisting of 22 individual custom-designed questions for use in CRS with or without nasal polyposis. The SNOT-22 covers a broad range of disease-specific HRQOL topics including physical complaints, functional limitations and emotional consequences. This questionnaire has shown to be reliable and valid in clinical practice to assess the impact of CRS on a patient's disease-specific HRQOL and to measure treatment-related changes (18).

Secondary study outcomes

Clinical outcome data will be collected at 3, 6, 12, 18 and 24 months after start of treatment. All measurements are performed by an adequately trained medical researcher and research nurses. All measurements are carried out according to protocol procedures and defined standard operating procedures.

HRQOL measurements

To assess generic HRQOL the EQ-5D-5L is administered (19). The questionnaire comprises five domains/questions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. An EQ-5D-5L index can be calculated and quantifies a participant's health status on a scale ranging from 0 (very bad health) to 1 (perfect health). Patients are also instructed to rate their overall generic HRQOL using a Visual Analogue Scale (EuroQol-5D VAS) ranging from 0 (very bad health) to 100 (perfect health). In this study the validated Dutch translation is used.

Symptoms

Total clinical symptoms, symptoms of rhinorrhoea, facial pain/headache, loss of smell and nasal blockage are measured with a Visual Analogue Scale (VAS) ranging from 0 (no problem) to 10 (worst imaginable problem).

Olfactory function

The 'Sniffin' Sticks Identification Test is used to assess olfactory performance. These twelve sticks are odour- dispensing devices that resemble felt-tipped pens and are held under the participant's nose for 3–4 s. The participant must make a forced choice from a list of four options as to the nature of the odour. The score corresponds to the amount of correct answers.

Nasal obstruction

The peak nasal inspiratory flow (PNIF) method is used to quantify nasal obstruction. A portable Youlten Peak Flow Meter (Clement Clarke International) is used. After applying a ventilation mask to firmly cover the nose and the mouth, participants are instructed to inhale as strongly as possible through the nose with the mouth closed. Three maximal inspirations are performed and the highest value (L/min) is used for analysis.

Endoscopic nasal assessment

Three different nasendoscopic measurements are used:

1. The **Meltzer Clinical Scoring System** is a 0–4 polyp grading system (0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps extending beyond middle meatus, 4 = polyps completely obstructing the nasal cavity)
2. The **Modified Lund-Kennedy Endoscopy Score** is a 0–2 scoring system in which the endoscopic appearances of both nasal fossae are rated for polyps, oedema and discharge (*polyps*: 0 = no polyps, 1 = polyps con- fined to the middle meatus, 2 = polyps beyond the middle meatus; *oedema*: 0 = no oedema, 1 = mild oedema, 2 = severe oedema; *discharge*: 0 = none, 1 = clear and thin, 2 = thick and eosinophilic) (20)

3. The **Modified Lund-Mackay Postoperative Endoscopy Score (MLMES)** applies to all participants who previously underwent sinus surgery. The endoscopic appearances of all ten cavities (left and right maxillary, ethmoid, sphenoid and frontal sinuses and olfactory fossa) are quantified for *mucosal inflammation* (0–6: 0 = normal mucosa, 1 = mild oedematous mucosa with patent cavity, 2 = severely oedematous mucosa with compromised cavity, 3 = mild polypoid mucosa with patent cavity, 4 = severe polypoid mucosa with compromised cavity, 5 = polyp confined within cavity, 6 = polyp extending beyond cavity), *mucus* (0–2: 0 = none, 1 = clear and thin, 2 = thick and eosinophilic) and *purulent discharge* (0–2: 0 = absent, 2 = present). This system produces a score of 0–100. Draf III cavities are scored as two frontal sinuses separately. Non pneumatised sinuses and non diseased sinuses that have not undergone surgery are scored as 0. The olfactory fossa is evaluated by assessing the cleft between the nasal septum and the middle turbinate anteriorly and the superior turbinate posteriorly (21).

CRS disease control

Disease control will be evaluated as suggested by the European Position Paper on Chronic Rhinosinusitis (EPOS 2012) (see Additional file 2). Nasal blockage, rhinorrhoea/postnasal drip, facial pain/headache, olfactory function, sleep disturbance or fatigue, nasendoscopy and systemic medication needed to control disease are evaluated. Each characteristic is rated as currently controlled or partly controlled, contributing to a general conclusion of CRS being controlled, partly controlled or uncontrolled at the time of assessment (3).

Asthma control

As asthma is a common comorbid condition in patients with CRSwNP, the Asthma Control Test (2002 TM QualityMetric Incorporated) is used in the subpopulation of patients with asthma. This validated appraisement contains five individual questions to assess asthma disease control.

Diaries

Participants are instructed to complete a diary 2 weeks before a follow-up visit until 2 weeks after a follow-up visit. Daily nasal symptoms and medication compliance will be recorded. The diary is also suitable to record symptomatic exacerbations, other medical problems and adverse effects or events. The nasal symptom scores, used to evaluate efficacy as a measure of compliance, will be calculated from the daily subject-rated scores of four nasal symptoms: headache/facial pain, rhinorrhoea, nasal congestion and loss of smell. Severity of symptoms is scored on a 0 to 3 scale; 0 = none (symptom is not present), 1 = mild (sign/symptom is clearly present but minimal awareness; easily tolerated), 2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable), 3 = severe (sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping). Subjects will be instructed to score and document their symptoms every 24 h in a reflective manner using the (electronic) diary.

Exacerbations and adverse effects
Medical files and patient diaries are used to record any unwanted side effects and readmissions during the study period. Participants are actively queried every follow-up visit as to whether they experienced any complications or adverse effects.

Health care resource use and costs
Resource use and costs of health care utilisation, out-of- pocket expenses and lost productivity are retrieved from hospital databases, financial reports, medical files, patient diaries and a modified version of the Erasmus iMTA 'Productivity Cost Questionnaire' and modified iMTA 'Medical Consumption Questionnaire' (22,23).

Data collection, management and storage

Source documents are a custom-designed paper Case Report Form and patient medical files. In addition, electronic questionnaires are used whenever possible (Limesurvey®). All VAS questionnaires are carried out on paper. The electronic diary is compatible across all browsers (https://kno-polypess.minddistrict.nl), smartphones and tablet devices (Minddistrict® application). Participants receive a personal username and create a password. If electronic device utilisation is not feasible, paper diaries are administered.

Clinical data will be stored in a custom-designed, password-protected study database (OpenClinica® soft- ware). Paper Case Report Forms, paper questionnaires and signed informed consents are stored in locked cabinets. A Data Monitoring Committee is allowed to access the collected clinical data mother file, wherein no identifiable patient data is stored; unique patient identification codes are used instead.

Sample size

PolypESS is a superiority trial in which disease-specific HRQOL, measured with the SNOT-22 at 12-month follow-up, is the primary outcome of interest. The sample size calculation is build on the literature-based assumption that the minimal clinically important difference (MCID) for SNOT-22 is 8.9 points (SD 20.0) (18). Using a 5% significance level and a power of 90% yields a sample size of 238 patients, which includes a 10% anticipated loss to follow-up.

Randomisation

A randomisation sequence is generated using block sizes of 6 stratified by study centre. A central, password- protected, consistently available automated randomisation system (ALEA® software, Trans European Network for clinical trial services (TenALEA) consortium, Amsterdam, The Netherlands) has been developed by the independent Clinical Research Unit in the Academic Medical Centre, Amsterdam, The Netherlands. Due to the nature of both interventions, blinding is not possible.

Statistical methods

Primary data analysis

Results will be based on the intention-to-treat method. In addition, per-protocol analysis, including only patients who adhered completely to the clinical trial instructions and treatment specified in the protocol, will also be performed to check the robustness of results. Continuous normally distributed variables will be expressed by their mean and standard deviation or, when not normally distributed, as medians and their interquartile ranges. Categorical variables will be expressed as counts (n) and percentages (%). Effects on HRQOL, nasal endoscopy and symptom score will be calculated as mean differences with 95% confidence intervals. HRQOL, short- and long-term effects will be additionally evaluated at 3, 6, 12, 18 and 24 months' follow-up, respectively. It is expected that randomisation will balance patients' baseline characteristics. However, if imbalances occur between groups that are related to possible effect modification, subgroup analyses will be performed according to the indication for surgery.

A further detailed statistical analysis plan will be developed and reported by the chief investigators prior to the database being locked at the end of follow-up for final analysis.

Cost-effectiveness analysis (CEA)

General considerations Alongside the randomised clinical trial an economic study will be performed. The economic evaluation will be set up as a cost-effectiveness analysis (CEA). The CEA focuses on the possible gained benefits of ESS in addition to drug treatment versus drug treatment alone and the related health care costs. The economic evaluation will be performed from a societal point of view.

Patient outcomes

The SNOT-22 will be measured to evaluate impact of both treatments. This will be used as endpoint in the economic evaluation. The cost- effectiveness of the interventions will be compared by assessing cost per Quality-adjusted Life Year (QALY), calculated from the health utility scores obtained with the EQ-5D-5L.

Cost analysis

Costs will be primarily assessed by the intervention study (and not the additional costs of underlying comorbid diseases). The time horizon of this cost analysis will be limited to 12-month follow-up. With this time horizon no discounting of costs and effects will be performed. The societal perspective captures the value of all resources used. Costs associated with treatment from a long-term perspective will be estimated and incorporated in a scenario analysis. Subgroup analyses will be done. Overall costs will be compared across the treatment groups and, where relevant, differences will be calculated, inclusive of 95% confidence intervals. Incremental cost-effectiveness ratios (iCERs) will be calculated.

Measurements

The prospective cost evaluation will primarily focus on health care utilisation (direct medical costs), travel expenses (direct nonmedical costs) and lost productivity (indirect costs) due to absence from work or decreased performance at work (productivity loss). The direct medical costs include the costs of all procedures associated with both treatment strategies (e.g. doctor's visits, medication, hospital admissions and surgical interventions, sinus CT, endoscopy and exacerbations). Out-of-pocket expenses include additional over-the- counter drugs and travel costs. Additional costs as a result of comorbid conditions (e.g. asthma) will be excluded. In the base case analysis, indirect costs (based on lost productivity) will be calculated using the friction cost method. Productivity losses will be estimated based on data concerning absence from work. Health service resource use and costs of both treatment strategies will be measured from a health service and societal perspective. Protocol-driven costs will be excluded.

Unit costs

Costs are defined as the volumes of used resources multiplied by calculated unit prices. For the valuation of health care utilisation, standard prices published in the Dutch costing guidelines and market prices will be used (24). Standard guideline prices will be used for all diagnostic interventions, hospital admissions, post-operative care, outpatient visits and travelling.

Statistical analysis

As most volumes of resource utilisation follow a skewed distribution, differences between the two groups will be statistically evaluated with bias- corrected bootstrap analysis. An iCER will be calculated, with the observed HRQOL as effect parameter.

The economic analysis will be expanded with a scenario-analysis to extrapolate the consequences of implementation and actual performance of the screening strategy in the targeted population. In sensitivity analysis the validity of the developed scenarios is evaluated. Uncertainty will be addressed by means of bootstrapping.

Budget impact analysis (BIA)

General considerations

In addition to the assessment of cost-effectiveness, a budget impact analysis (BIA) will be performed to determine the potential financial impact of more tailored treatment for patients with CRSwNP on national total health care costs in the future. The analysis will be performed according to the ISPOR Task Force guidelines (25). The BIA will be conducted from the viewpoint of the publicly funded health and social care system. No discounting will be applied, tariffs and prices will be held constant over the years.

Cost analysis
The BIA will be based on clinical data that reflect the size and characteristics of the population, the current treatment mix, the effectiveness of ESS, and the resource use and costs for ESS (surgery, post-operative care, exacerbations and reinterventions).

Monitoring, safety and reporting of adverse events

An independent Good Clinical Practice (GCP)-certified Monitoring Committee has been established. Members of the independent Clinical Research Unit of the Academic Medical Centre will perform monitoring and it will be conducted according to International Conference on Harmonisation (ICH)-GCP guidelines. A detailed study-specific monitor plan (version 3, 1 August 2016) has been formulated. The monitor plan is designed to verify that the rights and wellbeing of the participants is protected, that the reported trial data are accurate, complete and verifiable from the source documents and that the conduct of the trial is in compliance with the currently approved

protocol, GCP and applicable regulatory requirements. Every participating site will be physically visited at least once during the study period. All other monitoring activities will be centralised to detect sources of data irregularities, by exploring the clinical trial database. The monitoring plan will be updated and revised as needed. The risk of the current trial is estimated to be low. Patients will only be asked to participate if there is an indication for surgery as decided by their otorhinolaryngologist. The surgery performed and the medication prescribed is according to standard of care in patients with CRSwNP. Written informed consent is obtained from every participant. The patient is free to withdraw from the study at any time. Collected clinical data will be anonymised with unique patient identification codes.

Adverse events (AEs) to be reported are complications after SPT, ESS and adverse effects from any drug treatment started for CRSwNP. All study-specific AEs reported spontaneously by the participant or observed by the investigators will be recorded each visit. At every follow-up visit or interim telephone contact the investigators should inquire about AEs by asking the patients and by actively screening the patient's medical file. Serious adverse events (SAEs) possibly related to the study procedure will be reported to the principal investigator within 24 h. The local investigator informs the study coordinator in the Academic Medical Centre and is responsible for reporting SAEs annually to the accredited Medical Ethics Committee that approved the protocol in a line-listing format combined with the annual progress report. In case of life-threatening SAEs or death, reporting to the accredited Medical Ethics Committee will occur not later than 7 days after the study coordinator's knowledge of the event.

Dissemination

Presentations at (inter)national scientific conferences will be part of dissemination. Results will also be published in scientific journals. The raw trial data will be made available to the members of the Dutch Society of Otorhinolaryngology and Head and Neck Surgery.

DISCUSSION

The timing and indications for ESS in the management of CRSwNP/CRSsNP are mainly based on practitioners' knowledge. National and international clinical guidelines advise to start with drug treatment for at least 1 month before considering surgical treatment. Based on clinical findings patients start a drug treatment consisting of nasal corticosteroids, eventually supplemented with a short course of systemic corticosteroids or a longer course of antibiotics (3,5,6,26-28). Patients failing drug treatment are offered a choice between more intensive drug treatment and surgery in addition to drug treatment. Shared decision-making between the otorhinolaryngologist and the patient decides the moment that surgery is needed for relief of symptoms. Because of the chronic nature of the (mucosal) disease, the optimal treatment would be local treatment with medication combined with surgery.

Rudmik et al. have already shown in a Markov decision-tree economic evaluation that ESS would be the most cost-effective intervention compared to continued medical therapy from a long-term perspective, at least with 74% certainty (29). Limitation of this study, however, is that this economic evaluation was not performed alongside a RCT. The current study will be the first high-quality multicentre RCT (N = 238) to evaluate the role of ESS and to assess the cost-effectiveness of ESS in addition to drug treatment compared to drug treatment alone in adults with CRSwNP.

Currently, this trial is being conducted in 15 hospitals in The Netherlands. To the best knowledge of the investigators no other randomised studies to evaluate the same question are currently being per- formed. The objective is to demonstrate a higher HRQOL after ESS compared to drug treatment only in the treatment of CRSwNP. The outcome measurements are chosen according to experience in the field. Patient symptoms are thought to be an important parameter because patients seek medical advice in case of symptoms, regardless of the extent of disease visible on nasal imaging or with nasendoscopy. The usage of PROMs in clinical trials is growing and HRQOL is a frequently used clinical endpoint in clinical trials for CRS.

After the two-arm randomisation process, the medical intervention consists of any drug treatment that can be given to patients with CRSwNP in routine medical practice. The drug treatment purposefully is not standardised so as to stay closest to standard care. Also, patients' need for drug treatment varies with time and extent of disease. Naturally, this design enhances diversity; however, it also enhances generalisation of the results in the real-world situation. Surgical intervention consists of ESS, which is described as any surgery performed regularly by the otorhinolaryngologists in The Netherlands. The extent of the surgery is tailored to the extent of disease. This introduces a performance bias; however, this will also be closest to normal care.

The results of this RCT are intended to create a tailored strategy and selective use of ESS in CRSwNP patients. The results will be generalised to the Dutch situation and implemented in clinical guidelines.

Trial status

The study is currently in the first phase of patient recruitment and inclusion in 15 Dutch hospitals. Enrolment started on 13 February 2015. The anticipated recruitment completion is Summer 2017.

Acknowledgements

Not Applicable.

Funding

This study is funded by The Dutch Organisation for Health Research and Development (ZonMw), the European Rhinologic Society and the Academic Medical Centre.

Availability of data and materials

Not Applicable.

Author's contributions

WJF is the principal investigator in the Academic Medical Centre and coordinating investigator with regard to all participating sites. MV is the principal investigator in the Flevo Hospital. CAJMB, WJF and MV are responsible for trial design. ESL is the trial coordinator and has prepared the manuscript together with WJF and CAJMB. All authors read and approved the final manuscript.

Competing interests

WJF receives public sector research support from ZonMw (The Netherlands). There are no other potential conflicts of interest.

Ethics approval and consent to participate

The trial is conducted according to the principles of the Declaration of Helsinki [30], the Dutch law of Medical Research Involving Human Subjects (WMO) and GCP Guidelines (GCP). Approval of the Medical Ethics Committee (MEC) located in the Academic Medical Centre (Amsterdam, The Netherlands) has been obtained for each participating centre. Written informed consent is obtained from all participants before any trial-related procedure is performed. The trial protocol is reviewed and approved by the MEC of the Academic Medical Centre (protocol 2014_110). The trial was registered in the Dutch Trial Register (http://www.trialregister.nl/trialreg/ admin/rctview.asp?TC=4978): NTR4978 on 27 November 2014.

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SUPPLEMENTARY DATA

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Not named in protocol
	2b	All items from the World Health Organization Trial Registration Data Set	Not named in protocol
Protocol version	3	Date and version identifier	_____2_____
Funding	4	Sources and types of financial, material, and other support	Not named in protocol, but stated in other document.
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____2-6_____
	5b	Name and contact information for the trial sponsor	_____4_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16,22_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not specifically stated in protocol, however named in data management plan.

[continued on next page]

Additional file 1. *[continued]*

Section/item	Item No	Description	Addressed on page number
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___13-14_____
	6b	Explanation for choice of comparators	__13-14 _____
Objectives	7	Specific objectives or hypotheses	____15_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___16-18_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____2-3_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____18_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____20_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____26_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not described in protocol, used in Standard Operating Procedures. Monitoring described in monitor plan.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Exclusion criteria only.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___21-25_____

[continued on next page]

Additional file 1. *[continued]*

Section/item	Item No	Description	Addressed on page number
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____17_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____19_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Not described in protocol.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____22_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____22_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___22-25_____

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Additional file 1. *[continued]*

Section/item	Item No	Description	Addressed on page number
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not described in protocol, statistical analysis plan.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Not described in protocol, instead in separate data management plan.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____31_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____31_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Not described in protocol, statistical analysis plan.
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____27_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__28-29_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/ institutional review board (REC/IRB) approval	_____32_____

[continued on next page]

Additional file 1. *[continued]*

Section/item	Item No	Description	Addressed on page number
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____33_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____32_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____33_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Not described in study protocol
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data management plan
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____32_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Not described in study protocol
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____34_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not described in protocol.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Informed consent form, separate document.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Additional file 2. Assessment of current clinical control of CRS (in the last month), EPOS 2012.

Assessment of current clinical control of CRS (in the last month)			
Characteristic	**Controlled (all of the following)**	**Partly Controlled (at least one present)**	**Uncontrolled**
Nasal blockage	Not present or not bothersome	Present on most days of the week	Three or more features of partly controlled CRS
Rhinorrhea/ Postnasal drip	Little and mucous	Mucopurulent on most days of the week	
Facial pain/headachec	Not present or not bothersome	Present	
Smell	Normal or only slightly impaired	Impaired	
Sleep disturbance or fatigue	Not impaired	Impaired	
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa (nasal polyps, mucopurulent secretions, inflamed mucosa)	
Systemic medication needed to control disease	Not needed	Need of a course of antibiotics or systemic corticosteroids **in the last three months**	Need of long term antibiotics or systemic corticosteroids **in the last month**

CHAPTER 6

ENDOSCOPIC SINUS SURGERY IN ADULT PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (POLYPESS)– STATISTICAL ANALYSIS PLAN FOR A MULTICENTRE RANDOMISED CONTROLLED TRIAL

E.S. Lourijsen, M. Vleming, S. Reitsma, W.J. Fokkens

Rhinology online, 2021; 4: 58-65

ABSTRACT

Background

Chronic rhinosinusitis with nasal polyps (CRSwNP) afflicts 2-4% of the population and comes with a long time burden of disease and high societal costs. The current treatment consists of medical treatment alone or in combination with endoscopic sinus surgery. No consensus exists on the right timing and extent of disease that warrants surgery. Furthermore, there is lack of clinical knowledge about the benefit of surgery over medication only. The current study evaluates the clinical effectiveness and cost-effectiveness of endoscopic sinus surgery in addition to medical treatment versus medication alone in the adult patient group with nasal polyps (CRSwNP).

Methods

The PolypESS trial is designed as a prospective, randomised, multicentre trial in adult patients with CRSwNP selected for primary or revision endoscopic sinus surgery by their otorhinolaryngologist. Patients are randomly assigned to endoscopic sinus surgery in addition to medication or medical therapy only. This paper details the statistical analysis plan (SAP) of this trial and was submitted before outcome data were available.

Results

The primary outcome of the trial is disease-specific Health-Related Quality of Life quantified by the SNOT-22 at 12-months follow-up. Secondary outcomes consist of generic and disease-specific Health-Related Quality of Life, objective signs of disease and adverse events of treatment. Subgroup analyses will be performed to verify if treatment effects differ among patient phenotypes. Analyses will be completed according to this pre-specified SAP. The main analysis will be performed as a standard ITT analysis.

Discussion

The PolypESS trial will show whether addition of endoscopic sinus surgery to medical treatment improves the disease-specific Health-Related Quality of Life quantified by the SNOT-22 at 12-months follow-up. Unforeseen deviations from the SAP at the time of analysis will be motivated and discussed in the final publication of the primary outcome of this study.

INTRODUCTION

Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) experience a significant impact on most aspects of their Health- related Quality of Life (HrQOL) (1-3). Together with the high prevalence of disease (1-4%), the diagnosis and treatment give high healthcare costs (4-6). The current treatment exists of medical treatment alone or in combination with endoscopic sinus surgery (ESS) (5, 7-11). It is unclear what the benefit is of the addition of surgical treatment on top of on-going medical treatment and at what time point in the disease course a patient should be offered surgery. The PolypESS study is the first multicentre, randomised controlled trial investigating the impact of ESS on disease-specific HrQOL in adult patients suffering from CRSwNP in comparison to on-going medical treatment. Currently a large RCT comparing ESS with a prolonged course of Claritromycine in patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and CRSwNP is conducted in the UK (12). Further details on the background of our current study are described in the previously published trial protocol (13).

STUDY OBJECTIVES

The primary objective is to assess the effect of performing ESS in addition to medical treatment instead of medical treatment alone on patient health-related quality of life (HrQOL) and cost-effectiveness in adults with CRSwNP. Primary hypothesis is that the addition of ESS is better than medical treatment alone considering the mean difference (95% CI) in total SNOT-22 score at 12 months follow-up. We will test for superiority. The secondary hypotheses will be evaluated for risk difference (%) or mean difference (95% CI) between intervention groups. The following EQ-5D-5L), ESS is better in improving objective signs of disease (as measured with the nasal polyp score, Modified Lund-Kennedy score, Modified Lund- Mackay Postoperative Endoscopy score), ESS comes with better olfactory function (as measured with the Sniffin Sticks Test) and ESS gives higher improvement in nasal obstruction (as measured with the Peak Nasal Inspiratory Flow). Furthermore ESS comes with better disease control (as measured with the EPOS Control Test (14)), better asthma control (as measured with the Asthma Control Test (15)) and less symptomatic exacerbations requiring further treatment including ESS at 12 months follow-up. We will descriptively report (serious) adverse events in both treatment groups. We hypothesize more adverse events in the medical treatment group at 12 months follow-up. For more details on the process of data collection and a description of all secondary outcome measurements we refer to the published study protocol article (13).

PROTOCOL DEVELOPMENTS

PolypESS is an investigator-initiated, prospective, open, multicentre randomised clinical superiority trial with parallel treatment groups. Participants are randomised to either ESS in addition to medical treatment or medical treatment alone. Medical treatment can be any treatment available for CRSwNP. The trial protocol is reviewed and approved by the Medical Ethics Committee (MEC) of the Amsterdam University Medical Centres, location AMC (Amsterdam,

The Netherlands) and has been obtained for each participating centre. Written informed consent is obtained from all participants before any trial-related procedure is performed. The trial was registered in The Netherlands National Trial Register (http://www.trialregister.nl/trialreg/ admin/rctview.asp?TC=4978): NTR4978 on 27 November 2014. There were no amendments apart from some small changes of wording in the patient letter and amendments concerning change of local investigators. In total 15 study centres (3 university centres and 12 otolaryngological hospital clinics) included patients in the trial. No changes were made regarding the sample size. The date of the inclusion of the first patient was 15- 02-2015. The expected date of the completion of follow-up (24 months) for the last patient is 01-09-2021. The trial is conducted according to the principles of the Declaration of Helsinki (16) the Dutch law of Medical Research Involving Human Subjects (WMO) and GCP Guidelines (GCP).

STATISTICAL ANALYSIS PLAN

General principles

The analyses will be done by the investigators of the study group supervised by an independent statistician. The analyses will be performed after data verification and validation have been carried out and after this SAP has been accepted for publication. The statistical programming and analysis to produce all tables and figures will use the SPSS v. 26 (IBM Corporation, Armonk, NY, USA) and the software environment R (latest version 4.0.3)(17). Descriptive statistics, means with SD for continuous normally distributed variables, medians and interquartile ranges for continuous skewed variables, and frequency counts with percentages for nominal variables will be used to summarize variables. Normality will be checked for with a Normal Q-Q plot and histogram. No statistical normality tests will be performed.

Patient flow diagram

A flow diagram of study participants will be displayed in line with the Consolidation Standard of Reporting Trials (CONSORT) recommendations and finalized upon external peer review (Figure 1)(18).

Treatment according to protocol and withdrawal

Treatment was regarded to have proceeded according to the study protocol if a patient had surgery or a discussion about additional medical treatment within 6 weeks after inclusion. All patients that attended the baseline visit will be included in the ITT population. Primary outcome is measured after 12 months, planned 12 months after the start of the allocated intervention. For all time points within or at 12 months of follow-up a window of 30 days before or after the scheduled time point is accepted. The numbers of losses to follow-up (withdrawal from follow-up) and dropouts (withdrawal from intervention) will be summarized by study arm. A line-by-line listing of reasons for withdrawal or loss to follow-up will be presented in an Appendix. A patient is considered lost to follow-up if both a scheduled study visit or replacement telephone visit could not be performed at 6 months follow-up and at 12 months follow-up (after at least three phone calls, two e-mails, sending postal questionnaires and a

letter). If patients miss the 12 months visit, multiple imputations will be conducted if needed. A study visit is set to be missing if no SNOT-22 is obtained and the patient could not be contacted for study-related questions.

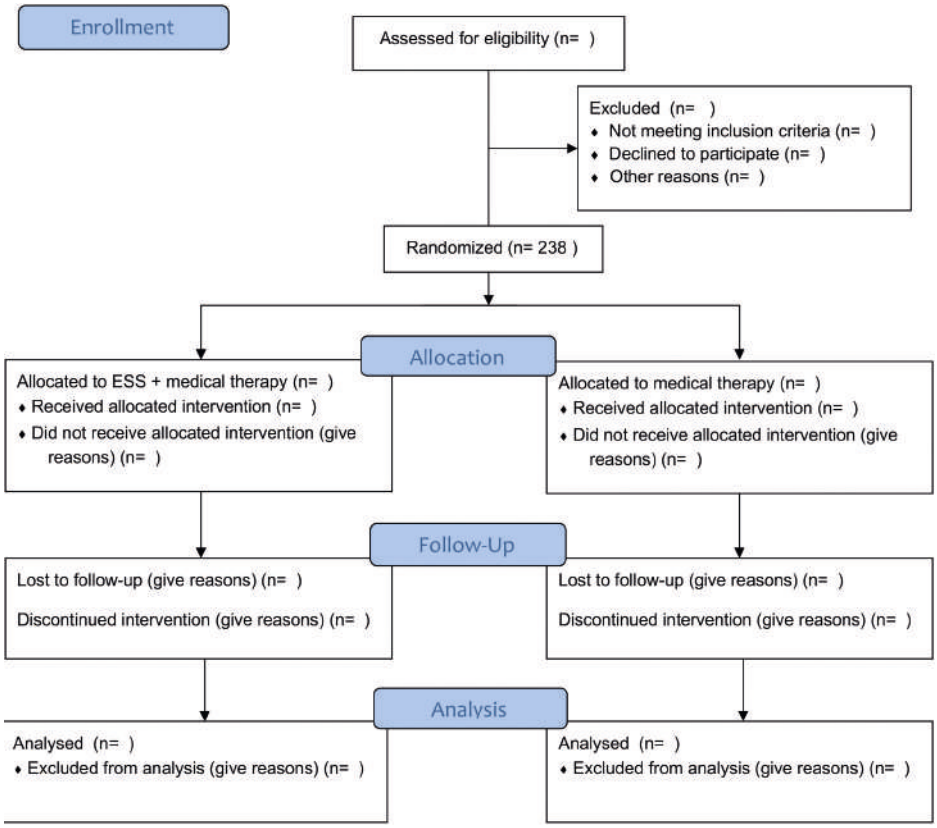

Figure 1. PolypESS CONSORT 2010 flow diagram

Definition of intention-to-treat, per-protocol and as-treated sets. The main analysis will follow the intention-to-treat (ITT) principle with all patients analysed in their randomisation group, irrespective of protocol adherence. This includes patients that crossed over to the other study treatment group during the course of the study (only possible from medication to ESS). Only patients with a protocol violation concerning eligibility are excluded from the ITT analysis. Protocol violation in eligibility refers to randomised patients who did not fulfil inclusion criteria or randomised patients who did meet an exclusion criterion. Baseline characteristics will be evaluated for these patients and compared to the ITT population. In addition, a per-protocol and as-treated analysis will be performed. Baseline characteristics will be compared between ITT,PP and as-treated with adjustment for confounding in the ITT and as treated analysis. The per-protocol analysis will include patients that were included and treated according to the study protocol. This means that patients who crossed over to the ESS treatment group

will be excluded. The as-treated analysis includes patients that switched treatment (from medical to surgical). A summary of the inclusion and exclusion of patients in the analysis sets is displayed in Figure 2.

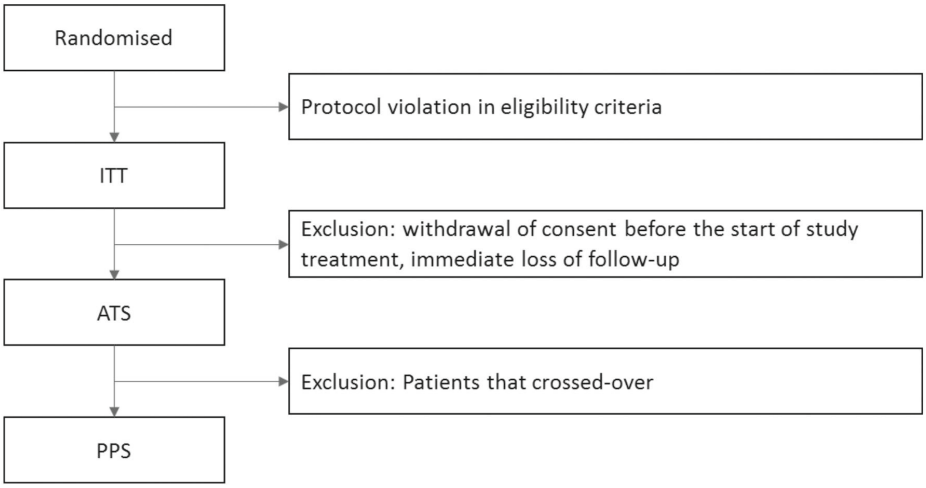

Figure 2. Summary of participant inclusion for the intention-to treat (IIT), as treated (ATS) and per-protocol set (PPS).

Representativeness of study sample

The total number of participants that were eligible will be reported including distribution of gender, age and when available disease-specific health-related quality of life (SNOT-22). To evaluate whether the randomised group is representative for all eligible patients, a comparison will be made between patients who declined to participate but were willing to fill in a SNOT-22 questionnaire and the randomised population. Mean age, percentage of males and mean or median disease-specific health- related quality of life, measured at baseline, will be compared.

Sample size

The power analysis is based on the literature-based assumption that the minimal clinically important difference (MCID) for the SNOT-22 is 8.9 points (SD 20.0) (19). A two-group t-test with a two- sided p-value of 0.05, a power of 90% to detect a difference and an anticipated 10% loss of follow-up led to 238 patients needed for the main analysis.

Patient replacement and handling of missing data

Patients not fulfilling eligibility criteria resulting in the exclusion of the ITT analysis will not be replaced. An analysis of missing data will be performed to check for the assumptions regarding the missing data. In participants with missing data for the primary outcome (SNOT-22 at 12 months follow-up), multiple imputation will be used to predict the outcome if more than 60% of data is present (≤40% missing data). Considering the type of variables for which data could be missing and the nature of the trial, missing data will probably be missing at random and

will be multiple imputed using chained equations (MICE). Results for the primary outcome at 12 months will be compared to complete cases.

Table 1. Baseline characteristics (data will be reported for both groups, total N=238).

Item	Description	Scale of measurement	Statistical analysis
Patient characteristics			
Gender	Males	Nominal	Percentage (and frequency count)
Age	Age in years	Discrete	Range, mean, SD or median and inter-quartile range in case of skewed data
Sensitisation for common aeroallergens	Proportion presence aero-allergy	Nominal	Percentage (and frequency count)
Total IgE	Total IgE expressed in kU/L	Continuous	Range, mean, SD or median and inter-quartile range in case of skewed data
Eosinophil count	Absolute count expressed in units 109/L	Continuous	Range, mean, SD or median and inter-quartile range in case of skewed data
Nasal polyp size (left and right)	0-8 points	Nominal	Percentage (and frequency count)
Lund-Mackay score	0-4 points 5-9 points 10-14 points 15-24 points	Nominal	Percentage (and frequency count)
Patient reported data			
Asthma	Presence	Nominal	Percentage (and frequency count)
NSAID-exacerbated respiratory disease	Presence	Nominal	Percentage (and frequency count)
Previous sinus surgery	Presence of previous sinonasal surgery	Nominal	Percentage (and frequency count)
Last sinus surgery	Proportion of years since last surgery 0-4 years 5-10 years › 10 years	Nominal	Percentage (and frequency count)
Smoking	Active smoker, former smoker	Nominal	Percentage (and frequency count)
Topical nasal corticosteroids	Proportion of current users	Nominal	Percentage (and frequency count)

Table 2. The analysis of primary and secondary outcomes.

	Methods	Unit of measurement
Primary outcome		
Disease-specific HRQOL as measured with the Sinonasal Outcome Test 22 (SNOT-22)	The definition of the SNOT-22 is presented in the published study protocol	The difference / contrast in absolute SNOT-22 score between treatment groups and ac- companying 95% CI. In addition, mean delta SNOT-22 will be reported (change from baseline)
Secondary outcomes		
Generic HRQOL as measured with the EQ- 5D-5L	A questionnaire comprising five domains/ questions: mobility, self-care, usual acti- vities, pain or discomfort and anxiety or depression. The EQ-5D-5L can describe 3125 (55) unique health states. In addition, a VAS for health status is applied (0-100)	1. Difference between treat- ment groups in utility scores 2. Difference between treat- ment groups in VAS calculated from EQ-5D-5L
CRS Symptoms	Total clinical symptoms, nasal blockage, symptoms of rhinorrhoea, symptoms of postnasal drip, facial pain / headache and loss of smell are measured with a Visual Analogue Scale (VAS) ranging from 0-10.	Difference between treatment groups in mean VAS scores
Asthma Control	Asthma Control Test (2002 TM QualityMetric Incorporated) is used in the subpopulation of patients with asthma. It contains five individual questions (total score 5-25 points)	Difference between treatment groups in level of control.
Nasal polyp score	Left and right side of the nose is scored for size of nasal polyps (0-4 on both sides). For a description of the scoring system, see the published protocol.	Difference between treatment groups in percentage and count of each category.
Modified Lund-Kennedy endoscopy score (MLK)	Left and right side of the nose is scored for presence or absence of polyp, oedema and discharge (total score 0-12). For a description of the scoring system see, the published protocol.	Difference between treatment groups in mean total MLK score
Modified Lund Mackay Postoperative Endoscopy Score (MLMES)	Left and right maxillary, ethmoid, sphenoid, frontal sinuses and olfactory fossa are scored for mucosal inflammation, mucus and purulent discharge (total score 0-100). For a description of the scoring system see, the published protocol.	Difference between treatment groups in mean total MLMES scores. Only for patients that underwent ESS in the past or as part of the study treatment.
Nasal obstruction	Peak nasal inspiratory flow method (PNIF) is used to quantify nasal obstruction. For a description of measurement, see the published protocol.	Difference between treatment groups in PNIF score

	Calculations or transformations	Timing of measurement	Primary analysis
	Items on the SNOT-22 will be summed to calculate a total score (0-110). The delta will be calculated for each patient or for the treatment group depending on the amount of missing values.	Baseline and 12 months follow-up	Analysis in ITT and PP analysis. First a descriptive analysis will be performed. Mean difference with 95% CI will be reported.
	A health state index score will be calculated from individual health profiles using the Dutch time trade-off-based health utility algorithm for the EQ-5D-5L.	12 months follow-up	Analysis in ITT. Mean, standard deviation (SD) or median and interquartile range in case of skewed data will be provided for the study population by visit and by treatment.
	No calculations needed	12 months follow-up	Analysis in ITT. Mean, standard deviation (SD), or median and interquartile range in case of skewed data will be provided per item by treatment group if there is a relevant difference between treatment groups.
	Items on the five questions will be summed to calculate a total score which represents a category of control Level of control: <20 = uncontrolled asthma, 20-24= controlled asthma, 25 = well controlled asthma	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported.
	Score of left and right side will be summed to get a total score.	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported.
	Scores for three items on each side of the nose will be summed to calculate a total score.	12 months follow-up	Analysis in ITT. Range, mean, SD or median and interquartile range in case of skewed data will be reported.
	Scores for five items on each side of the nose will be summed to calculate a total score.	12 months follow-up	Analysis in ITT. Range, mean, SD or median and interquartile range in case of skewed data will be reported.
	No calculations needed. Only the highest value will be used for an individual patient.	12 months follow-up	Analysis in ITT. Mean, SD or median and interquartile range in case of skewed data will be reported.

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Table 2. *[continued]*

	Methods	Unit of measurement
Olfactory function	The 'Sniffin' Sticks Identification test is used to assess olfactory performance by a 12-odor identification test. For a description of measurement, see the published protocol.	Difference between treatment groups in percentage of normosmic, hyposmic and anosmic patients.
Disease control of CRS	Control is evaluated as suggested by the European Position Paper on Chronic Rhinosinusitis (EPOS 2012). Symptoms of nasal blockage, rhinorrhoea/postnasal drip, facial pain/headache, olfactory function, sleep disturbance or fatigue will be evaluated together with nasendoscopic findings and any systemic medication needed to control disease.	Difference between treatment groups in percentage of controlled, partially controlled or uncontrolled patients.
Exacerbations of CRS	Symptoms of CRSwNP requiring further treatment (surgical or medical) collected in clinical practice.	Difference between treatment groups in count and percentage of exacerbations.
Adverse events	Serious and non-serious adverse events related to treatment for CRSwNP (as defined by researcher) as measured by anamnesis and patient diaries.	Difference in (serious) adverse event rate (number and percentage) between treatment groups.
Daily nasal symptoms	Nasal symptoms will be recorded by patients each day 2 weeks before a visit until 2 weeks after a visit (score 0-3 for headache/ facial pain, rhinorrhea, nasal congestion, loss of smell). For a description of scoring, see the published protocol.	Difference in weekly daily symptom scores between treatment groups
Medication compliance	Compliance to drug treatment for CRSwNP is measured with daily patient diaries filled in each day 2 weeks before a visit until 2 weeks after a visit	Difference between treatment groups in ratio between as administered daily dose/prescribed daily dose using the patient medical record.

Calculations or transformations	Timing of measurement	Primary analysis
Correctly identified odours will be summed and classified as normosmic (11-12 correct), hyposmic (7-10 correct) or anosmic (0-6 correct)	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported for the study population by visit and treatment.
Classification based on the answers for individual symptoms, findings during nasendoscopy or need for additional systemic medication. Scoring: • No symptoms and normal mucosa without need for systemic medication= controlled disease • ≥1 symptom or presence of diseased mucosa or need for systemic medication in the past 3 months = partially controlled disease. • ≥3 features of disease = uncontrolled disease. • Need for systemic medication in the past month= uncontrolled disease.	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported.
Number of episodes requiring intervention will be calculated for each patient between time points.	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported
Adverse events will be sum- med between baseline and 12 months follow-up	12 months follow-up	Analysis in ITT. Percentage and frequency count of adverse events will be reported for the study population by treatment. Number of people with an event will be reported in both tre- atment arms. In the Ap- pendix a line listing will be added of all adverse events per treatment group.
The main daily symptom sum-score is calculated for each patient as the sum of all individual symptom scores, representing the sum of the severity of the most common nasal symptoms (0-12)	12 months follow-up	Analysis in ITT. Only patients with ≥ 4 ob- servations per week will be included. Mean, SD or median and interquartile range in case of skewed data will be reported.
Weekly ratio is calculated for each patient as the sum of daily ratios per medicine for CRSwNP	12 months follow-up	Analysis in ITT. Mean, SD or median and inter- quartile range in case of skewed data will be reported.

Baseline characteristics

The mock-up of the baseline characteristics table can be found in Table 1. The baseline characteristics of all study participants will be presented in a table. Nominal variables will be presented as percentages and frequency counts for each category per treatment group. Categories will be displayed in the table if relevant. Continuous variables with a normal distribution will be summarized using means and standard deviations, whereas medians and interquartile ranges will be used in case of non-normal distributions. Mean SNOT-22 scores will be dealt with as described above. Other missing data will not be imputed. The number of patients in the variable row will be reported when more than five patients have missing data for the variable of interest. We will not test for differences between study groups.

Assessment and analysis of primary outcome

The mock-up of the analysis of primary and secondary outcomes is shown in Table 2. For the primary outcome, SNOT-22 at 12 months, first a descriptive analysis will be performed. The mean difference with 95% CI will be reported for each treatment group. Analyses will be stratified by baseline nasal polyp size, CT-sinus Lund-Mackay score, presence or absence of NSAID-Exacerbated Respiratory Disease (N-ERD) and tertiary care centres versus secondary care centres. If potential modification of the effect of ESS is suspected, subgroup analysis will be done further by multiple regression.

Assessment and analysis of secondary outcomes

Following the strategy for the primary outcome as described above, secondary outcome measures will be analysed to further evaluate the added value of ESS over medication alone. These outcome measures are described in Table 2.

Analysis of safety outcomes

Safety outcomes are serious adverse events (SAE) and non- serious adverse events (AE). Both will be explored and reported for each treatment group, listed in a table, if they are related to study treatment or study activities.

DISCUSSION

The aim of the PolypESS trial is to provide evidence regarding the effect of ESS in adult patients with CRSwNP. In this statistical analysis plan, we present the methods we will use to evaluate whether or not ESS is of additional value in the care of patients with CRSwNP. We have chosen the widely accepted SNOT-22 as primary outcome measure as it reflects our main interest: whether a patient reports a better HrQOL after surgery. In order to approach the real-life situation, patients from secondary and tertiary care hospitals are included whenever the treating otorhinolaryngologists would consider surgery to be indicated. Following the real-life dogma in which patients may need additional treatment over time, the study protocol enables crossover from medical treatment alone to the addition of surgery. Still, we will analyse the data primarily in an intention-to-treat fashion as described here. Unforeseen deviations from

the SAP at the time of analysis will be motivated and discussed in the paper describing the primary and secondary outcomes.

Authorship contribution

WJF is the principal investigator in the Academic Medical Centre and coordinating investigator with regard to all participating sites. ESL, SR and WJF prepared the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The authors thank Prof. Dr. M. Rovers, affiliated to the Radboud Institute for Health Sciences, for her expertise and assistance in preparing this Statistical Analysis Plan.

Funding

This trial is funded by The Dutch Organisation for Health Re- search and Development (ZonMw), the European Rhinologic Society and Amsterdam UMC, location Academic Medical Centre.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interest

There are no conflicts of interest to report for this manuscript.

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CHAPTER 7

ENDOSCOPIC SINUS SURGERY WITH MEDICAL THERAPY VERSUS MEDICAL THERAPY FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPS: A MULTICENTRE, RANDOMISED, CONTROLLED TRIAL

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Lancet Respir Med. 2022 Apr;10(4):337-346

SUMMARY

Background

Endoscopic sinus surgery (ESS) is a common operation for patients with chronic rhinosinusitis with nasal polyps (CRSwNP) when medical therapy alone is insufficient. No randomised controlled trials on the efficacy of ESS have been published. We aimed to assess the efficacy of ESS plus medical therapy versus medical therapy alone in patients with CRSwNP.

Methods

We performed an open-label, multicentre, pragmatic, randomised, controlled trial in three tertiary care centres and 12 secondary care centres in 11 cities in the Netherlands (Almere, Amstelveen, Amsterdam, Blaricum, Den Haag, Deventer, Haarlem, Hoofddorp, Hoorn, Leiderdorp, and Rotterdam). Adults (aged ≥18 years) with CRSwNP and an indication for ESS were randomly assigned (1:1) using block randomisation (block sizes of six), stratified by study centre, to receive either ESS plus medical therapy or medical therapy. ESS was performed according to local practice, although anterior ethmoidectomy was mandatory. Medical therapy was prescribed at the patient's otorhinolaryngologist's discretion, and could be, but was not limited to, nasal corticosteroids, nasal rinsing, systemic corticosteroids, or systemic antibiotics. The primary outcome was disease-specific health-related quality of life (HRQoL) at 12 months of follow up, measured with the validated Sinonasal Outcome Test 22 (SNOT-22; where each item is scored from 0 to 5, where 0 indicated no problems and 5 indicates problems as bad as can be, with a total score of 0–110 points), and the minimal clinically important difference of the SNOT-22 is 9·0 points. Primary and safety analyses were performed on an intention-to-treat (ITT) basis. The ITT population comprised all patients who were randomly assigned to treatment according to their randomisation group and without any protocol violation. This study is registered with the Netherlands Trial Register, NTR4978, and is ongoing.

Findings

Between Feb 15, 2015, and Aug 27, 2019, 371 patients were screened for eligibility, of whom 238 were eligible, willing to participate, and randomly assigned to ESS plus medical therapy (n=121) or medical therapy (n=117) and 234 were included in the baseline ITT population (n=118 ESS plus medical therapy; n=116 medical therapy). 142 (61%) of 234 patients at baseline were men and 92 (39%) were women, and the mean age was 50·4 years (SD 12·7). 206 participants were analysed at 12 months for the primary outcome (n=103 in the ESS plus medical therapy group; n=103 in the medical therapy group). At 12 months follow-up, the mean SNOT-22 score in the ESS plus medical therapy group was 27·9 (SD 20·2; n=103) and in the medical therapy group was 31·1 (20·4; n=103), with an adjusted mean difference of −4·9 (95% CI −9·4 to −0·4), favouring ESS plus medical therapy. Adverse events were similar between the groups. The most common adverse events were minor epistaxis or gastrointestinal problems. No treatment-related deaths occurred, but one patient died due to congestive heart failure.

Interpretation
ESS plus medical therapy is more efficacious than medical therapy alone in patients with CRSwNP, although the minimal clinically important difference was not met. Long-term follow-up data are needed to determine whether the effect persists. The current results are a basis for further development of evidence-based guidelines.

Funding
The Netherlands Organisation for Health Research and Development (ZonMw).

INTRODUCTION

Nasal polyposis is a form of chronic rhinosinusitis (chronic rhinosinusitis with nasal polyps; CRSwNP) that has a substantial effect on quality of life and health-care costs (1,2). The prevalence of this condition in Europe and the USA is around 2–4% (1,3). It has a strong association with lower airway diseases such as asthma (4).Primary treatment consists of medical therapy, such as nasal corticosteroids, saline rinsing, and short courses of systemic corticosteroids, with endoscopic sinus surgery (ESS) plus medical therapy being reserved for cases that are unresponsive to appropriate medical therapy (1,5). The aim of sinus surgery is to create more space in the nasal cavity and sinuses and better conditions for local medications to work on mucosal disease. The goal of treatment for CRSwNP is improvement in control of disease.

Non-randomised and uncontrolled studies show that addition of ESS to medical therapy significantly improves symptoms and health-related quality of life (HRQoL) (1,5-7). However, rates of revision of ESS are substantial at 5–10 years after surgery (20–30%) (8-10).

National and international guidelines, such as the Commissioning Guide on Rhinosinusitis for the UK, the European Position Paper on rhinosinusitis and nasal polyps (EPOS), the Clinical Practice Guideline of the American Academy of Otolaryngology and Head and Neck Surgery for the USA, and the International Consensus statement on Allergy and Rhinology provide recommendations for the adequate medical management of CRSwNP (1,5,11,12). However, no randomised controlled trials of ESS have been done to date (13). Large variations in the management of CRSwNP exist both between and within countries and among individual specialists, which can lead to inefficient and inappropriate care (14-16).

METHODS

Study design and participants
We performed an open-label, multicentre, pragmatic, randomised, controlled trial in 15 hospitals (12 secondary and three tertiary) in 11 cities in the Netherlands (Almere, Amstelveen, Amsterdam, Blaricum, Den Haag, Deventer, Haarlem, Hoofddorp, Hoorn, Leiderdorp, and Rotterdam).

Briefly, adult patients (aged ≥18 years) visiting the outpatient clinic for CRSwNP were approached by their otorhinolaryngologist for trial participation if they had an indication for ESS (i.e., failure of appropriate medical treatment; both primary and revision ESS were acceptable) (19). Exclusion criteria were the presence of systemic diseases affecting the nose (e.g., granulomatosis with polyangiitis, sarcoidosis, primary ciliary dyskinesia, cystic fibrosis), antrochoanal polyps, malignant polyps, inverted papilloma, sinonasal tumours, absolute need for surgical therapy as indicated by complications of disease (e.g., mucoceles), contraindications for surgical therapy, need for more extensive surgery (Draf III, Denker surgery, medial maxillectomy), proposed polypectomy without ethmoidectomy, continuous use of systemic corticosteroids for diseases other than CRSwNP, continuous medication (for other diseases) that might affect CRSwNP (e.g., other immunosuppressive drugs), pregnancy at enrolment, mental or systemic illnesses preventing adequate participation in the trial, and any other scheduled surgical intervention preventing adequate participation in the trial. Additionally, participants were excluded if they had used any systemic corticosteroids in the 4 weeks before enrolment or had an acute upper or lower respiratory tract infection at the time of enrolment or during the past 2 weeks.

Eligible patients who were willing to participate were invited for a baseline visit, during which written informed consent for trial participation was obtained. At baseline, demographic and disease-specific data were collected, including the SinoNasal Outcome Test 22 (SNOT-22) a standardised patient-reported outcome measurement consisting of 22 questions concerning disease-specific HRQoL. Next, participants were randomly assigned to treatment. Those who refused to participate were asked to fill in the SNOT-22, and sex and age were noted for comparison with the study participant population.

The trial protocol (20) was approved by the accredited medical ethics committee of the Amsterdam University Medical Centres, location AMC (NL48200.18). This trial is a stage 3 trial according to IDEAL, because it is the first trial in this field (21). Data are reported according to the CONSORT statement.

Randomisation and masking

Participants were randomly assigned (1:1) to either ESS plus medical therapy or medical therapy. Randomisation was done using computer-generated codes (ALEA software version 2.2 and 16), in block sizes of six, stratified by study centre. Because of the nature of the study intervention, no masking could be applied for the study team, otorhinolaryngologists, or patients.

Procedures

The involved otorhinolaryngologists in the tertiary referral centres were rhinologists. The other participating otorhinolaryngologists in the secondary care centres were general otorhinolaryngologists with rhinology as an area of interest (listed in the appendix).

Participants assigned to the ESS plus medical therapy group had surgery within 6 weeks after the baseline visit. Otorhinolaryngologists were allowed to operate according to their regular

practice; anterior ethmoidectomy was mandatory, but no instructions regarding the further extent of ESS were given (19). A detailed and standardised operation report was used (available in Dutch in the appendix). Patients could be prescribed any kind of medication suitable for CRSwNP post-operatively including nasal rinsing.

Participants assigned to the medical therapy group could be prescribed any suitable medical therapy, except for biologicals, by their otorhinolaryngologist. The medical therapy could be, but was not limited to, nasal corticosteroids (spray or drops, or both), nasal rinsing with saline solution, systemic corticosteroids (either short courses or long-term tapered treatment), or systemic antibiotics. In a shared decision-making process between patient and their otorhinolaryngologist, patients could have ESS performed during the course of the study if bothersome symptoms persisted despite medical therapy; this was considered a crossover to the ESS plus medical therapy group.

At baseline, inflammatory markers like blood eosinophils, total IgE, and CT-sinus Lund-Mackay score were collected and reported. The Lund-Mackay score is a score dependent on absent (0), partial (1), or complete (2) opacification of each individual sinus and the ostiomeatal complex, contributing to a maximum score of 12 per side. The total score of the two sides can reach a maximal 24 points. Follow-up visits were scheduled for 3, 6, 12, 18, and 24 months after the start of allocated treatment. Here we report 3, 6, and 12 month data. 18–24 month follow-up data will be reported elsewhere. The use and importance of local therapy (nasal corticosteroids or rinses, or both) was discussed with patients during study visits if they had been prescribed such therapies. Patient compliance was not measured.

Medical files and patient diaries were used to record any adverse effects. Participants were asked at every follow-up visit about whether they experienced any complications or adverse effects.

Each of the participating centres was visited regularly by the study physician (ESL) or research nurses to assure the collection of data.

Outcomes

The primary outcome was disease-specific HRQoL, measured using the SNOT-22 at 12 months. Each item is scored from 0 to 5, with 0 indicating no problems and 5 indicating the problem is as bad as can be, resulting in a total score range of 0–110 points. SNOT-22 scores are presented as total scores and as categorised total scores (‹20, 20 to ‹40, 40 to ‹60, 60 to ‹80, and ≥80 points) to indicate the distribution of symptom severity in both treatment groups.

Secondary outcomes were general HRQoL (measured with the EQ-5D-5L), nasal polyp scores (nasal polyp size is scored on a range of 0–8; each nasal cavity can be given a score of 0–4, where 0 is no polyps, 1 is polyps confined to the middle meatus, 2 is multiple polyps occupying the middle meatus, 3 is polyps extending beyond middle meatus, and 4 is polyps completely

obstructing the nasal cavity), Modified Lund-Kennedy endoscopy score (a 0–2 scoring system in which the endoscopic appearances of both nasal fossae are rated for polyps, oedema, and discharge [polyps: 0 indicates no polyps, 1 indicates polyps confined to the middle meatus, and 2 indicates polyps beyond the middle meatus; oedema: 0 indicates no oedema, 1 indicates mild oedema, and 2 indicates severe oedema; and for discharge: 0 indicates no discharge, 1 indicates clear and thin discharge, and 2 indicates thick and eosinophilic discharge]), nasal symptoms of chronic rhinosinusitis (measured using a visual analogue scale [VAS] of 0–100, where 0 is no complaints and 100 is maximum number of complaints), chronic rhinosinusitis control (measured with the EPOS control test) and asthma control (measured with the Asthma Control Test), olfactory performance (using the Sniffin' Sticks identification test), nasal airway patency (measured using peak nasal inspiratory flow [PNIF]), exacerbations of chronic rhinosinusitis or asthma (defined as episodes of increased symptoms warranting additional treatment with antibiotics or systemic steroids), and adverse events. Secondary outcomes are reported here at 3, 6, and 12 months. The secondary outcomes of diaries to record daily nasal symptoms and compliance, and health-care resource use and costs will be reported elsewhere (20).

Statistical analysis

We did analyses as described in our statistical analysis plan (22). The primary outcome measure (SNOT-22) was used for the power and sample size calculation. The minimal clinically important difference of the SNOT-22 is 9·0 points (23,24). With an α value of 0·05, a power of 90% and an expected loss to follow-up of 10%, we calculated that 238 patients (119 per group) were needed for the study.

We describe patient and treatment-related characteristics as count with percentages, mean (SD), or median (IQR), as appropriate. We calculated effects of either treatment on disease-specific HRQoL or other continuous outcomes as mean differences with 95% CIs. We did non-adjusted and adjusted analyses for each outcome, adjusting for their accompanying baseline score and type of hospital (tertiary care or secondary care). Adjustment for each individual hospital was not possible because of the varying (sometimes small) numbers of patients included (per intervention group) at some hospitals. We used the x^2 test in non-adjusted analyses for calculation of between-group differences in all categorical outcomes and we reported unadjusted risk differences. We did multinomial regression for the adjusted analysis of categorical outcomes, but we do not report these data here because this analysis provided unrealistic estimates due to the large spread in filled categories. We did all analyses using the intention-to-treat (ITT) principle. The ITT population included all eligible patients who were randomly assigned to treatment according to their randomisation group, irrespective of protocol adherence. Only patients with a protocol violation (i.e., who did not meet eligibility criteria) were excluded from the ITT analysis. We also did analyses in the per-protocol population (i.e., all randomly assigned patients who received their assigned treatment [i.e., excluding those who crossed over]) and as-treated population (i.e., all randomly assigned patients, according to the treatment they received) for the primary and secondary outcomes. Safety was assessed

in all patients who received study treatment and who were not lost to follow-up before the first follow-up visit (at 3 months).

We did stratified analysis of the primary outcome for nasal polyp size, non-steroidal anti-inflammatory drug- exacerbated respiratory disease (N-ERD), CT-sinus Lund- Mackay score, and tertiary versus secondary hospitals as potential effect modifiers. We adjusted all stratified analyses for baseline SNOT-22 score. If the stratified analysis had indicated potential effect modification, we were going to analyse subgroups of the effect modifier within treatment groups using multiple regression analysis; however, this was not something we needed to do.

We did three post-hoc analyses. First, we analysed medication use between intervention groups (nasal corticosteroids, antibiotics, systemic corticosteroids and aspirin desensitisation). We report mean (SD) or count with percentage, and for cumulative corticosteroid use we report mean difference (95% CI). We recalculated the systemic corticosteroid dose to prednisolone-equivalent dose in mg to be able to provide a cumulative dose. Second, we analysed the extent of surgery in patients randomly assigned to ESS plus medical therapy, reported as count with percentages. Finally, we compared baseline characteristics and SNOT-22 of patients with CRSwNP who refused to participate with the data of the trial participants, reported as mean (SD) or count with percentage.

We also had a prespecified cost-effectiveness analysis; however, this will be reported separately.

Missing data were assumed to be missing at random. We did multiple imputations for the primary outcome. Additional information about the imputation model is in the appendix.

We did all analyses using SPSS (version 26) and R (version 4.1.0). This study is registered in the Netherlands Trial Register, NTR4978.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Between Feb 15, 2015, and Aug 27, 2019, 371 patients who had an indication for ESS plus medical therapy were screened, of whom 238 patients were enrolled, gave informed consent, and were randomly assigned to the ESS plus medical therapy group (n=121) or medical therapy group (n=117; Figure 1).

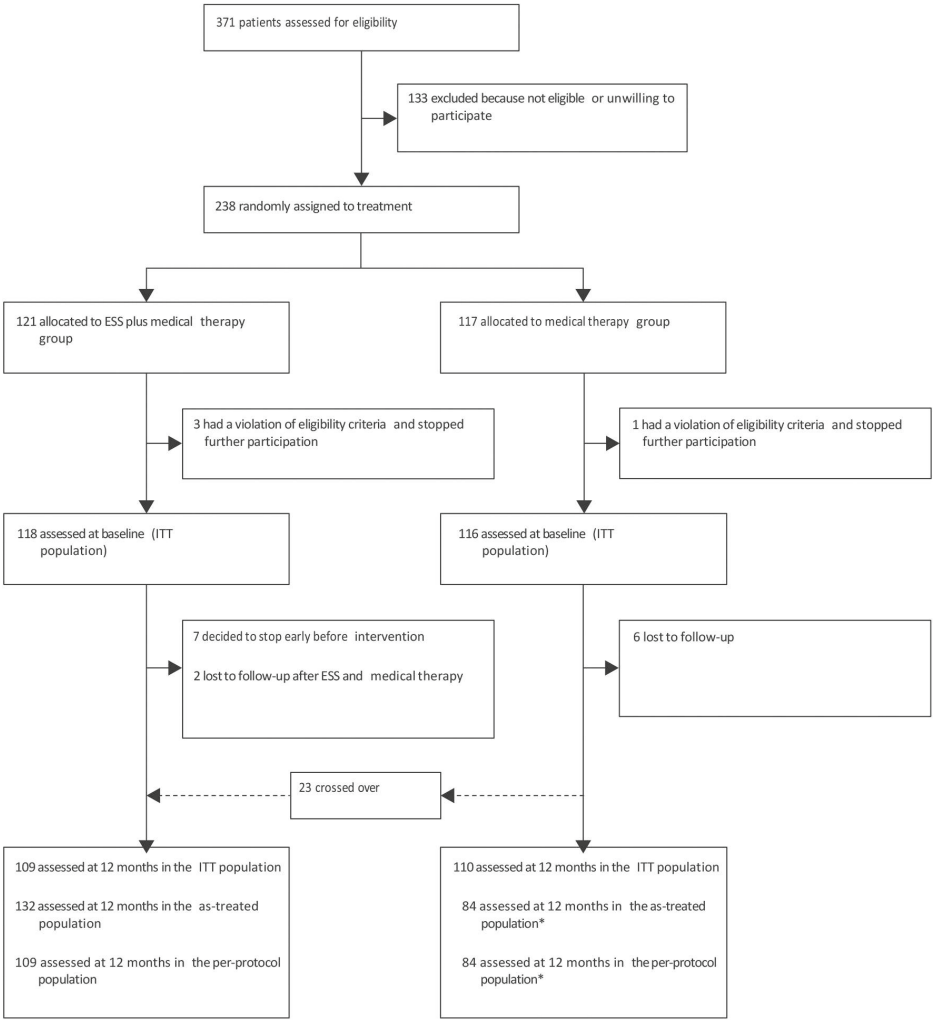

Figure 1. Trial profile. *ESS=endoscopic sinus surgery. ITT=intention-to-treat. *Three patients were lost to follow-up after 6 months of follow-up, and so were excluded from the per-protocol and as-treated analyses*

After inclusion in the study after ESS and medical therapy. In the medical therapy group, 23 patients crossed-over to the ESS plus medical therapy group; three (3%) patients were lost to follow-up after 6 months, and so we do not know if they had surgery after this point (considered to be missing in the per-protocol and as-treated analyses); and six other patients were lost to follow-up before the 6 month follow-up visit. Therefore, 84 (72%) of 117 patients adhered to study protocol and did not undergo surgery (included in per-protocol and as-treated analyses).

Overall baseline characteristics were similar between intervention groups (Table 1). 142 (61%) of 234 patients assessed at baseline were men and 92 (39%) were women, and the mean age was 50·4 years (SD 12·7). The baseline mean SNOT-22 score was 51·2 (SD 20·0). Most

patients rated their nasal complaints as severe, with a mean VAS scores of more than 70 mm for nasal complaints in general. Loss of smell was the most severe symptom, with mean VAS scores of 86·0 mm in both groups, which is also reflected in the results of the Sniffin' Sticks smell test with approximately 70% of patients classified as anosmic. Nearly all patients were actively using nasal corticosteroids at time of study enrolment (Table 1). In most patients, nasal polyps were of moderate size (i.e., a score of 5–6; 154 [66%]). 149 (64%) of 234 patients had previously had ESS for CRSwNP. Lund-Mackay scores of the CT scan showed values of 10 or higher in 217 (93%) of 234 patients. 131 (56%) patients at baseline had concomitant asthma and 46 (20%) had N-ERD.

Table 1. Baseline characteristics of the intention-to-treat population

	ESS+MT (n=118)	**MT (n=116)**
Age years	51·1 (12·1)	49·8 (13·2)
Gender		
Female	47 (40%)	45 (39%)
Male	71 (60·2%)	71 (61·2%)
Asthma	66 (55·9%)	65 (56·0%)
NERD	22 (18·6%)	24 (20·7%)
Current smoker	17 (14·4%)	18 (15·5%)
No history of smoking	53 (45%)	52 (45%)
Former smoker	48 (40·7%)	46 (39·7%)
Former sinonasal surgery		
- None	34 (28·8%)	40 (34·5%)
- Polypectomy only	8 (6·7%)	3 (2·6%)
- ESS	76 (64·4%)	73 (62·9%)
Number of previous ESS		
-1	29 (38·2%)	33 (45·2%)
-2-3	33 (43·4%)	32 (43·8%)
-4-5	7 (9·2%)	8 (11·0%)
- ≥ 6	7 (9·2%)	0 (0·0%)
Time since last sinus surgery, including polypectomy, years		
0-5 years ago	46/84 (54·8%)	48/76 (63·2%)
≥5 -10 years ago	21/84 (25·0%)	16/76 (21·1%)
≥10 years ago	17/84 (20·2%)	12/76 (15·8%)
Current use of local corticosteroids	117 (99·2%)	113 (97·4%)

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Table 1. *[continued]*

	ESS+MT (n=118)	MT (n=116)
Lund Mackay score (mean)	18·4 (4·3)	18·5 (4·9)
Lund-Mackay score		
- 0-4	1/112 (0·9%)	0/111 (0%)
- 5-9	1/112 (0·9%)	4/111 (3·6%)
- 10-14	20/112 (17·9%)	27/111 (24·3%)
- 15-24	90/112 (80·4%)	80/111 (72·1%)
Aeroallergen sensitisation	64 (54·2%)	62 (53·4%)
Primary outcome		
SNOT-22 score (mean)	51·9 (20·4)	50·5 (19·7)
Secondary outcomes		
SNOT-22 score		
0-20	10 (8·5%)	4 (3·4%)
≥20 - 40	24 (20·3%)	33 (28·4%)
≥40 - 60	39 (33·1%)	42 (36·2%)
≥60 - 80	34 (28·8%)	28 (24·1%)
≥ 80	11 (9·3%)	9 (7·8%)
EQ-5D-5L utility score	0·8 (0·2)	0·8 (0·2)
EQ-5D-5L VAS (mm)	70·9 (17·2)	70·0 (17·2)
Nasal polyp size (mean)	5·9 (1·0)	5·7 (1·4)
Nasal polyp size score		
0-4	13 (11·0%)	22 (19·1%)
5-6	85 (72·0%)	69 (59·0%)
7-8	20 (16·9%)	24 (20·9%)
Modified Lund-Kennedy score (mean)	7·4 (2·5)	7·7 (2·6)
Modified Lund-Kennedy score		
0-4	20/115 (17·4)	18/114 (15·8)
5-8	62/115 (53·9)	55/114 (48·2)
9-12	33/115 (28·7)	41/114 (36·0)
CRS Symptoms (VAS; mm)		
Nasal symptoms in general	79·0 (14·0)	74·0 (20·0)
Nasal obstruction	74·0 (21·0)	71·0 (25·0)

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Table 1. *[continued]*

	ESS+MT (n=118)	MT (n=116)
Rhinorrhoea	67·0 (25·0)	60·0 (28·0)
Postnasal drip	56·0 (30·0)	51·0 (31·0)
Loss of smell	86·0 (25·0)	86·0 (21·0)
Facial pressure	51·0 (32·0)	44·0 (34·0)
Headache	41·0 (33·0)	35·0 (32·0)
EPOS CRS Control Test		
Controlled CRS	0 (0%)	0 (0%)
Partially controlled CRS	5 (4·2%)	4 (3·4%)
Uncontrolled CRS	113 (95·8%)	112 (96·6%)
Asthma Control Test		
Well controlled asthma	9/66 (13·6%)	6/63 (9·5%)
Controlled asthma	25/66 (37·9%)	19/63 (30·2%)
Uncontrolled asthma	32/66 (48·5%)	38/63 (60·3%)
Sniffin' Sticks Smell test (mean)	5·1/66 (3·1)	5·3/63 (3·1)
Sniffin' Sticks Smell test		
Normosmic	10 (8·5%)	12 (10·3%)
Hyposmic	21 (17·8%)	25 (21·6%)
Anosmic	87 (73·7%)	79 (68·1%)
Peak Nasal Inspiratory Flow (L/min)	89·9 (43·3)	96·2 (52·2)
Total IgE (kU/L)	206·7 (279·2)	310·7 (971·3)
Absolute eosinophils (x10^9/L)	0·5 (0·5)	0·6 (0·4)

Data are presented as mean (SD) or n (%). EPOS= European Position Paper on rhinosinusitis and nasal polyps. ESS=endoscopic sinus surgery. NERD= non-steroidal anti-inflammatory drug-exacerbated respiratory disease. SNOT-22=Sinonasal Outcome Test 22. VAS=visual analogue scale.
* VAS is measured on a 0–100 mm scale.

At 12 months of follow-up, 103 patients in each of the ESS plus medical therapy group and in the medical therapy group were assessable for SNOT-22 and the mean SNOT-22 score of patients randomly assigned to ESS plus medical therapy was 27·9 (SD 20·2) and for medical therapy 31·1 (SD 20·4)—i.e., adjusted mean difference of –4·9 (95% CI –9·4 to –0·4). After correction for baseline SNOT-22, stratified analyses for SNOT-22 outcomes at 12 months by CT-sinus, Lund Mackay score, nasal polyp size, N-ERD, and tertiary versus secondary centre did not show potential effect modification (appendix). At 3 months of follow-up the adjusted mean difference was –15·2 (95% CI –19·8 to –10·7) and at 6 months was –8·3 (–13·0 to –3·6; figure 2). Table 2 provides an overview of all adjusted outcomes at 12 months of follow-up. Unadjusted data are in the appendix.

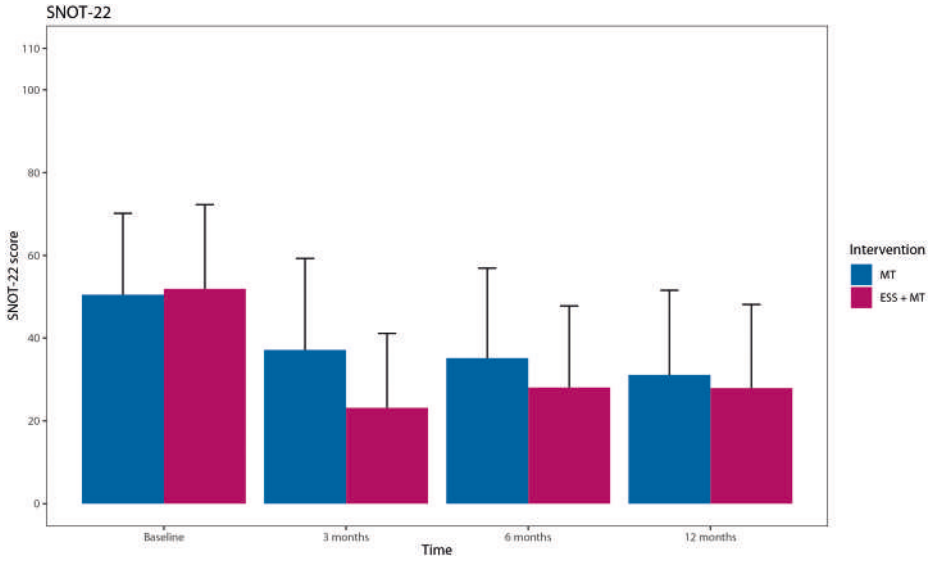

Figure 2. SNOT-22 scores at each time point. Bar charts show mean scores, with error bars indicating SDs. In the medical therapy group, 116 patients were assessable at baseline, 113 at 3 months, 107 at 6 months, and 103 at 12 months. In the ESS plus medical therapy group, 118 patients were assessable at baseline, 106 at 3 months, 107 at 6 months, and 103 at 12 months.
ESS=endoscopic sinus surgery. SNOT-22= Sinonasal Outcome Test-22
MT= medical therapy

Table 2. Primary and secondary outcomes at 12 months

	ESS+MT n=109	**MT n=110**	**Adjusted outcomes ESS+MT vs. MT n=219**
Primary outcome	n=103	n=103	
SNOT-22	27·9 (20·2)	31·1 (20·4)	-4·9 (-9·4 to - 0·4)
SNOT-22 categories			NE
0-20	46/103 (44·7%)	36/103 (35·0%)	
≥20 - 40	32/103 (31·1%)	36/103 (35·0%)	
≥40 - 60	19/103 (18·4%)	18/103 (17·5%)	
≥60 - 80	3/103 (2·9%)	13/103 (12·6%)	
≥ 80	3/103 (2·9%)	0/103 (0·0%)	
Secondary outcomes			
EQ-5D-5L utility score	0·9 (0·15)	0·9 (0·14)	0·01 (-0·03 to 0·04)
EQ-5D-5L VAS (mm)*	76·4 (16·4)	76·3 (14·2)	-0·03 (-4·2 to 4·1)
Nasal polyp size	2·20 (2·04)	3·83 (2·52)	-1·7 (-2·4 to -1·1)
Nasal polyp size categories			NE
0-4	83/99 (83·8%)	49/95 (51·6%)	

[continued on next page]

Table 2. *[continued]*

	ESS+MT n=109	MT n=110	Adjusted outcomes ESS+MT vs. MT n=219
5-6	16/99 (16,2%)	36/95 (37·9%	
7-8	0/99 (0·0%)	10/95 (10·5%)	
Modified Lund-Kennedy Score	4·4 (3·3)	5·9 (3·4)	-1·5 (-2·5 to -0·6)
Modified Lund-Kennedy Score categories			NE
0-4	53/99 (53·5%)	37/95 (38·9%)	
5-8	36/99 (36·5%)	36/95 (37·9%)	
9-12	10/99 (10·1%)	22/95 (23·2%)	
CRS Symptoms (VAS; mm)*			
Nasal symptoms in general	31·5 (29·7)	45·5 (30·3)	-15·9 (-24·0 to -7·8)
Nasal obstruction	34·0 (29·6)	43·2 (30·9)	-11·1 (-19·2 to -3·1)
Rhinorrhoea	34·0 (29·3)	36·0 (30·2)	-6·5 (-13·9 to 0·8)
Postnasal drip	35·5 (31·0)	36·6 (29·3)	-4·7 (-12·3 to 2·9)
Loss of smell	56·9 (38·2)	63·8 (36·6)	-7·7 (-16·9 to 1·6)
Facial pressure	21·4 (28·4)	19·0 (23·8)	-0·6 (-7·0 to 5·9)
Headache	20·1 (27·8)	19·3 (24·5)	-1·7 (-8·5 to 5·1)
EPOS CRS Control Test			NE
Controlled	11/100 (11%)	4/99 (4·4%)	
Partially controlled	43/100 (43·0%)	32/99 (32·3%)	
Uncontrolled	46/100 (46·0%)	63/99 (63·3%)	
Asthma Control Test			NE
Well controlled asthma	7/54 (13·0%)	6/54 (11·1%)	
Controlled asthma	13/54 (24·1%)	15/54 (27·8%)	
Uncontrolled asthma	34/54 (63·0%)	33/54 (61·1%)	
Sniffin' Sticks Smell Test	6·32 (3·28)	6·31 (3·15)	0·1 (-0·6 to 0·9)
Sniffin' Sticks Smell Test categories			NE
Normosmic	14/100 (14·0%)	9/95 (9·5%)	
Hyposmic	32/100 (32·0%)	37/95 (38·9%)	
Anosmic	54/100 (54·0%)	49/95 (51·6%)	
Peak Nasal Inspiratory Flow (L/min)	125·4 (44·0)	117·2 (50·2)	10·0 (-2·1 to 22·2)

Data are presented as mean (SD) or n (%). Adjusted mean differences between intervention groups are presented as mean differences (95% CI). Adjusted analyses for risk differences between categorical outcomes were NE. Adjusted values are adjusted for accompanying baseline value and tertiary versus secondary hospital. EPOS=European Position Paper on rhinosinusitis and nasal polyps. ESS=endoscopic sinus surgery. NE=not estimable. SNOT-22=Sinonasal Outcome Test 22. VAS=visual analogue scale.
* VAS is measured on 0–100 mm scale.

All secondary outcomes are shown in table 2.

At 12 months of follow-up, nasal polyp size score of 0–4 was seen in 83 (84%) of 99 patients in the ESS plus medical therapy group versus 49 (52%) of 95 in the medical therapy group (non-adjusted risk difference 32·3% [95% CI 19·9 to 44·7]). 53 (54%) of 99 patients in the ESS plus medical therapy group and 37 (39%) of 95 patients in the medical therapy group had a Modified Lund-Kennedy score of 0–4 (non-adjusted risk difference 14·6% [95% CI 0·7 to 28·5]). Patients in the ESS plus medical therapy group reported lower VAS scores for their nasal symptoms in general (adjusted mean difference –15·9 [95% CI –24·0 to –7·8]) and for nasal obstruction (–11·1 [–19·2 to –3·1]). Uncontrolled chronic rhinosinusitis was present in 46 (46%) of 100 patients in the ESS plus medical therapy group versus 63 (63%) of 99 in the medical therapy group (non-adjusted risk difference –17·6% [95% CI –31·2 to –4·0]). In most patients with asthma in both treatment groups, asthma was uncontrolled.

A lower proportion of patients in the ESS plus medical therapy group had exacerbations of chronic rhinosinusitis than did in the medical therapy group (Table 3). In post-hoc analyses, patients in the ESS plus medical therapy group used a cumulative mean dose of 266 mg (SD 505) prednisolone-equivalent versus 587 mg (740) in the medical therapy group: a difference of 316 mg (95% CI –468 to –166). There was no difference in antibiotic use between study groups (appendix).

Table 3. Revision surgery and exacerbations of CRS and asthma

	ESS+MT	MT
ESS during follow-up		
0-3 months FU	0/109 (0%)	1/114 (1%)
3-6 months FU	0/109 (0%)	5/108 (5%)
6-12 months FU	1/103 (1%)	17/105 (16%)
Exacerbations of CRS		
0-3 months FU	9/107 (8%)	11/114 (10%)
3-6 months FU	11/108 (10%)	20/108 (19%)
6-12 months FU	14/104 (13%)	32/105 (30%)
Exacerbations of asthma		
Diagnosed new onset asthma 0-12 months FU	4/109 (4%)	0/110 (0%)
Asthma exacerbations 0-12 months FU	6/109 (6%)	3/110 (3%)

Study visits occurred at baseline (month 0), month 3, month 6, and month 12, such that (for instance) data for the 3–6-month period covers the period after the 3 month visit, and up to and including the 6 month visit. Data are presented as n/N (%). ESS=endoscopic sinus surgery.

Table 4. Adverse events in the safety population

	ESS+MT (n=109)	MT (n=110)
Serious adverse events		
In-house cardiac arrest	1 (0·9%)	0 (0·0%)
Cerebrovascular accident	1 (0·9%)	0 (0·0%)
Myocardial infarction	0(0.0%)	1 (0·9%)
Death caused by congestive heart failure	1 (0.0%)	0(0·9%)
Adverse events		
Perioperative lamina papyracea damage	2 (1·8%)	0 (0·0%)
Septal synechiae formation	1 (0·9%)	1 (4·1%)
Deep venous leg thrombosis	1(0·9%)	0 (0·0%)
Minor epistaxis	5 (4·6%)	5 (4·5%)
Irritated nose	0 (0·0%)	2 (1·8%)
Headache	0 (0·0%)	1 (0·9%)
Raised appetite	0 (0·0%)	(1·8%)
Weight gain (patient-reported)	1 (0·9%)	3 (2·7%)
Petechial laesions extremities	0 (0·0%)	1 (0·9%)
Sleep disorders	2(1·8%)	2(1·8%)
Euphoria, agitation, or hyperactivity	1 (0·9%)	5(4·5%)
Depressive feelings	0 (0·0%)	2(1·8%)
Gastro-intestinal problems	4 (3·7%)	3(2·7%)
Skin rash	2(1·8%)	2(1·8%)
Oral candidiasis	0 (0·0%)	3 (2·7%)
Urticaria	1(0·9%)	1(0·9%)

Data are presented as n (%) or n/N (%) when denominator differs from that at the top of the column. ESS= endoscopic sinus surgery.
* 23 patients crossed-over to ESS plus medical therapy.

In the medical therapy group, 23 (20%) of 116 patients crossed over to ESS plus medical therapy. In the ESS plus medical therapy group, one revision ESS and two additional outpatient polypectomies were performed (Table 3).

109 patients in the ESS plus medical therapy group and 110 patients in the medical therapy group were included in the safety analyses. Three serious adverse events occurred in patients assigned to the ESS plus medical therapy group; one (1%) of 109 patients had a stroke within 48 h of surgery, one (1%) patient had an in-house cardiac arrest directly after surgery (both

survived), and one (1%) patient died before the 12-month follow-up visit because of severe congestive heart failure. Two (2%) patients had a lamina papyracea defect during surgery. One serious adverse event occurred among the patients who had medical therapy, one (1%) of 110 patients had a myocardial infarction and survived (Table 4). Most other adverse events were mild or moderate in nature and required no additional treatment (Table 4).

Additional analyses of the primary and secondary outcomes in the per-protocol and as-treated populations did not alter our findings (appendix).

Results of post-hoc analysis of the extent of surgery performed in all patients are in the appendix. We found no differences in baseline characteristics or SNOT-22 of patients with CRSwNP who refused to participate versus the trial participants.

DISCUSSION

In this pragmatic randomised controlled trial, we found that ESS plus medical therapy is more efficacious than medical therapy alone in adults with CRSwNP. After 12 months of follow-up, patients assigned to ESS plus medical therapy scored better than patients assigned to medical therapy on disease-specific HRQoL using the SNOT-22—although the minimal clinically important difference was not met—and scored better for general nasal symptoms (especially nasal obstruction [VAS], control of chronic rhinosinusitis, and nasal polyp size), and had lower use of systemic corticosteroids. To date, evidence for the efficacy of ESS plus medical therapy was based on non-randomised and observational studies, comparing preoperative and postoperative measurements of quality of life and medication use (6,7). These studies have a high risk of bias because the reported effects could also be explained by other factors (e.g., patients with more severe disease choosing surgery or due to the natural course of the disease).

Thus, the main strength of our trial is that this is the first randomised controlled trial to gather evidence on the efficacy of ESS plus medical therapy versus medical therapy alone in a relatively large group of patients from multiple hospitals. A second strength of the trial is that it measures disease-specific HRQoL with SNOT-22, which has been identified as one of the core tools to measure symptoms and disease-specific HRQoL in trials in patients with chronic rhinosinusitis, according to the Core Outcome Set Chronic Rhinosinusitis Outcome Measures (CHROME) (25).

Most of our data, including disease-specific HRQoL (SNOT-22), general nasal symptoms, and control of chronic rhinosinusitis, seem to consistently point in the direction of surgical benefit at 3 months, 6 months, and 12 months. These findings are supported by our additional as-treated and per-protocol analyses. However, at 12 months, the differences in SNOT-22 scores between the groups were smaller than the minimal clinically important difference of 9 points. To interpret this finding, one should consider the larger context of the particular patients and the disease. Factors other than SNOT-22 score alone could affect the shared decision-making process for medical therapy or ESS plus medical therapy (such as the amount of oral

corticosteroid use). Both strategies have their own advantages, disadvantages, and risks; these should be weighed both by the patient and by the surgeon.

Our study also has some limitations. First, masking of participants was not possible because medical ethics committees in the Netherlands consider sham surgery to be unethical. Second, about 20% of patients (n=23) assigned to the medical therapy group crossed over to ESS plus medical therapy. The possibility of a cross-over is part of the pragmatic nature of the trial, directed at assessing the effect of ESS plus medical therapy in daily practice. Even with a cross-over rate of 20%, analyses on an ITT basis, and per-protocol and as-treated analysis, showed that

ESS plus medical therapy resulted in better HRQoL than medical therapy. This level of crossover is in line with other non-randomised trials of surgical versus medical management for chronic rhinosinusitis (7,26). No significant differences in SNOT-22 were found at baseline or at 12 months of follow-up when comparing patients in the medical therapy group that were treated per-protocol versus the crossovers (data not shown). Third, generic HRQoL measured with EQ-5D-5L did not show a significant difference between the treatment groups. This is likely due to the clinimetrics of the instruments rather than the intervention, given the overall consistency of our findings. The EQ-5D-5L is valuable to assess utility of an intervention, but has low sensitivity and ceiling effects (27).

Despite medical treatment or surgery, many patients remained anosmic. Loss of smell is a debilitating symptom and this trial clearly shows the limitations of the current treatment options. New options with (still very expensive) biologicals, which appear to have a positive effect on sense of smell, have recently become available (28). We could find only one modelling study comparing cost-effectiveness of ESS versus treatment with a biological, and it showed ESS to be more cost-effective than a biological for the treatment of CRSwNP. We are planning a future cost-effectiveness analysis. At the moment, gaining approval for the use of these drugs is problematic in many countries due to expense and absence of cost-effectiveness data (29).

Fourth, recruiting a patient population that is representative of the whole target population might be a challenge in randomised controlled trials. However, we believe that the results of this multicentre, pragmatic trial are applicable to all patients with CRSwNP, as seen in daily practice. Fifth, another limitation is the sample size, which would have led to any in-depth subanalyses being underpowered. One might wonder whether the extent of surgery would affect outcomes in the ESS plus medical therapy group; however, in our study, such an assessment would have too few patients within the subgroups to allow reliable results. Generally, the reported extent of surgery reflects what could be expected in the treatment of patients with CRSwNP and seems representative of the current medical practice in the Netherlands. Finally, our follow-up period was relatively short. The trial protocol stipulates another year of follow up (trial visits at 18 and 24 months after start of treatment) and we will report on the outcomes at 2 years in a future publication. Whether the additional effect of surgery on outcomes and

on corticosteroid use is still present after 24 months remains to be seen. Literature suggests that at least the effect of surgery can be retained for up to 5 years (8).

The clinical implications of this randomised controlled trial are far reaching. Despite the globally acknowledged evidence gap, ESS plus medical therapy has remained one of the most common procedures within the field of otorhinolaryngology. Our trial shows that many patients continue to have symptoms of CRSwNP one year after either treatment approach. Moreover, in post-hoc analyses we found that patients in the medical therapy group received significantly more systemic corticosteroids. The adverse events of systemic corticosteroid use generally outweigh advantages of therapeutic value in the long term, except in patients with severe symptomatology (30) . The data from this trial provide a basis for further development of evidence-based guidelines on the treatment of CRSwNP.

Contributors

WJF and MV conceived the trial and initiated the design. ESL, WJF, and SR ran the trial. ESL, MMR, GH, SR, and WJF analysed the data.

All authors had full access to all the data in the trial. All authors drafted this manuscript and approved the final version. WJF and MMR had final responsibility for the decision to submit the report for publication. GH and ESL had access to and verified the underlying study data.

Declaration of interests

ESL, SR, MV, and WJF report a grant from the Netherlands Organisation for Health Research and Development (ZonMw) to do the study. WJF further reports receiving grants from Sanofi and Novartis; receiving consulting fees and speaker honoraria from Sanofi and GSK; participating on a data safety monitoring board for Lyra; is Secretary General of the European Rhinologic Society, chairperson of EPOS, founding member of EUFOREA, and a member of the Medical Advisory Board of the Dutch Patient Society for CRSwNP (all unpaid). SR reports grants, consulting fees, and honoraria from Sanofi and Novartis, and roles as a steering committee member (unpaid) for EPOS and for the European Chronic Rhinosinusitis Outcome Registry, and as being member (unpaid) of the Medical Advisory Board of the Dutch Patient Society for CRSwNP. All other authors report no competing interests.

Data sharing

De-identified participant data will be made available after completion of the trial to researchers whose proposed use of the data has been approved by the principal investigators (MMR and WJF), with a signed data access agreement and only for purposes specified in the approved research proposal. Requests for data must be sent to w.j.fokkens@ amsterdamumc.nl. The trial protocol and SAP are available online (20,22).

Acknowledgments

We thank the patients who participated in the trial; the otorhinolaryngologists who contributed to the enrolment of trial participants. We thank research nurses Inge Bruins, Iris Oving, and Yasmin te Winkel for support in collecting data and administrative support. We thank the Dutch ENT society for supporting the trial's initiation and conduct. The trial was funded by the Netherlands Organisation for Health Research and Development (ZonMw), project number 837002522.

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SUPPLEMENTARY DATA

Content

1. Overview of primary and secondary outcomes for all time points (Intention-to-treat)

Table S1. Overview of crude outcomes at 3, 6, and 12 months follow-up.

	ESS+MT			MT			ESS+MT versus MT		
	T3 n=109	T6 n=109	T12 n=109	T3 n=114	T6 n=110	T12 n=110	T3 n=223	T6 n=219	T12 n=219
Primary outcome	n= 106	n=107	n=103	n=113	n=107	n=103			
SNOT-22	23·2 (17·9)	28·1 (19·7)	27·9 (20·2)	37·1 (22·2)	35·2 (21·8)	31·1 (20·4)	-14·0 (-19·4 to -8·6)	-7·1 (-12·7 to -1·5)	-3·2 (-8·7 to 2·4)
Secondary outcomes									
SNOT-22 categories							x2 (4, n=212) 23·7, p<0·0001	x2 (4, n=214) 7·0, p=0·14	x2 (4, n=206) 10·7, p=0·03
0-20	53 (50·0%)	45 (42·1%)	46 (44·7%)	29 (25·7%)	28 (26·2%)	36 (35·0%)			
≥20 - 40	37 (34·9%)	33 (30·8%)	32 (31·1%)	35 (31·0%)	38 (35·5%)	36 (35·0%)			
≥40 - 60	10 (9·4%)	19 (17·8%)	19 (18·4%)	29 (25·7%)	23 (21·5%)	18 (17·5%)			
≥60 - 80	5 (4·7%)	9 (8·4%)	3 (2·9%)	16 (14·2%)	16 (15·0%)	13 (12·6%)			
≥ 80	1 (0·9%)	1 (0·9%)	3 (2·9%)	4 (3·5%)	2 (1·9%)	0 (0·0%)			
EQ-5D-5L utility score	0·87 (0·2)	0·85 (0·2)	0·88 (0·2)	0·84 (0·2)	0·87 (0·1)	0·87 (0·2)	0·03 (-0·01 to 0·07)	0·01 (-0·02 to 0·05)	0·004 (-0·04 to 0·05)
EQ-5D-5L VAS (mm)	78·6 (14·2)	76·6 (15·3)	76·4 (16·4)	72·3 (15·7)	73·0 (15·7)	76·3 (14·2)	6·3 (2·3 to 10·3)	3·7 (-0·5 to 7·8)	0·1 (-4·0 to 4·4)
Nasal polyp size	1·1 (1·2)	1·8 (1·8)	2·2 (2·0)	4·8 (2·2)	4·7 (2·2)	3·8 (2·5)	-3·7 (-4·2 to -3·2)	-2·9 (-3·5 to -2·4)	-1·6 (-2·3 to -1·0)
Nasal polyp size categories							x2 (2, n=213) 98·8, p<0·0001	x2 (2, n=211) 64·3, p<0·0001	x2(2, n=194) 26·4, p<0·0001
0-4	102 (99·0%)	98 (92·5%)	83 (83·8%)	39 (34·5%)	43 (41·0%)	49 (51·6%)			
5-6	1 (1·0%)	8 (7·5%)	16 (16·2%)	56 (49·6%)	45 (42·9%)	36 (37·9%			
7-8	0 (0·0%)	0 (0·0%)	0 (0·0%)	18 (15·9%)	17 (16·2%)	10 (10·5%)			

[continued on next page]

Table S1. *[continued]*

	ESS+MT			MT			ESS+MT versus MT		
	T3 n=109	T6 n=109	T12 n=109	T3 n=114	T6 n=110	T12 n=110	T3 n=223	T6 n=219	T12 n=219
Modified Lund-Kennedy Score	3·7 (3.0)	4·2 (3·3)	4·4 (3·3)	6·2 (3·0)	6·7 (2·8)	5·9 (3·4)	-2·6 (-3·4 to -1·8)	-2·4 (-3·3 to -1·6)	-1·4 (-2·4 to -0·5)
Modified Lund-Kennedy Score categories							x2 (2, n=214) 19·3, p<0·0001	x2 (2, n=209) 27·7, p<0·0001	x2 (2, n=194) 7·3, p=0·03
0-4	63 (61·2%)	65 (61·3%)	53 (53·5%)	39 (35·1%)	26 (25·2%)	37 (38·9%)			
5-8	35 (34·0%)	26 (24·5%)	36 (36·5%)	49 (44·1%)	49 (47·6%)	36 (37·9%)			
9-12	5 (4·9%)	15 (14·2%)	10 (10·1%)	23 (20·7%)	28 (27·2%)	22 (23·2%)			
CRS Symptoms (VAS; mm)									
Nasal symptoms in general	22·5 (26·0)	26·1 (29·8)	31·5 (29·7)	58·2 (29·3)	53·0 (31·4)	45·5 (30·3)	-35·8 (-43·2 to -28·4)	-26·9 (-35·1 to -18·6)	-13·9 (-22·2 to -5·7)
Nasal obstruction	25·0 (27·3)	26·9 (30·6)	34·0 (29·6)	52·0 (31·4)	50·3 (31·5)	43·2 (30·9)	-27·0 (-34·9 to -19·2)	-23·3 (-31·7 to-15·0)	-9·3 (-17·6 to -0·9)
Rhinorrhoea	24·5 (26·2)	28·6 (29·5)	34·0 (29·3)	41·8 (31·9)	43·7 (31·5)	36·0 (30·2)	-17·3 (-25·1 to -9·4)	-15·1 (-23·3 to -6·9)	-2·0 (-10·2 to 6·2)
Postnasal drip	28·6 (28·4)	33·3 (28·1)	35·5 (31·0)	36·7 (29·8)	40·1 (29·4)	36·6 (29·3)	-8·1 (-15·8 to -0·3)	-6·9 (-14·6 to 0·9)	-1·1 (-9·4 to 7·2)
Loss of smell	52·1 (38·5)	53·3 (39·4)	56·9 (38·2)	69·1 (34·5)	67·6 (35·4)	63·8 (36·6)	-16·9 (-26·7 to -7·2)	-14·3 (-24·4 to -4·2)	-6·9 (-17·2 to 3·3)
Facial pressure	19·3 (28·2)	22·3 (29·8)	21·4 (28·4)	31·4 (32·7)	29·3 (31·5)	19·0 (23·8)	-12·1 (-20·3 to -3·9)	-6·9 (-15·2 to 1·3)	2·3 (-4·9 to 9·5)
Headache	19·5 (28·4)	22·2 (29·3)	20·1 (27·8)	26·4 (29·0)	25·4 (29·9)	19·3 (24·5)	-6·9 (-14·6 to 0·7)	-3·3 (-11·2 to 4·7)	0·8 (-6·4 to 8·1)

[continued on next page]

Table S1. *[continued]*

	ESS+MT			MT			ESS+MT versus MT		
	T3 n=109	T6 n=109	T12 n=109	T3 n=114	T6 n=110	T12 n=110	T3 n=223	T6 n=219	T12 n=219
EPOS Control Test							x2 (2, n=220) 41·7, p<0·0001	x2 (2, n=209) 28·8, p<0·0001	x2 (2, n=199) 7·5, p=0·02
Controlled	18 (17·0%)	18 (17·0%)	11 (11%)	1 (0·9%)	2 (1·9%)	4 (4·4%)			
Partial controlled	49 (46·2%)	45 (42·5%)	43 (43·0%)	25 (21·9%)	24 (23·3%)	32 (32·3%)			
Uncontrolled	39 (36·8%)	43 (40·6%)	46 (46·0%)	88 (77·2%)	77 (74·8%)	63 (63·3%)			
Asthma Control Test	N=53	N=54	N=54	N=54	N=54	N=54	x2 (2,n=107) 0·81, p=0·67	x2 (2, n=108) 1·22, p=0·54	x2 (2, n=108) 0·24, p=0·89
Well controlled asthma	7 (13·2%)	9 (16·7%)	7 (13·0%)	6 (11·1%)	6 (11·1%)	6 (11·1%)			
Controlled asthma	26 (49·1%)	24 (44·4%)	13 (24·1%)	23 (42·6%)	22 (40·7%)	15 (27·8%)			
Uncontrolled asthma	20 (37·7%)	21 (38·9%)	34 (63·0%)	25 (46·3%)	26 (48·1%)	33 (61·1%)			
Sniffin' Sticks Smell Test	7·1 (3·2)	6·3 (3·3)	6·3 (3·2)	6·1 (3·4)	6·5 (3·2)	6·3 (3·3)	0·9 (0·05 to 1·8)	0·2 (-0·6 to 1·1)	0·01 (-0·9 to 0·9)
Sniffin' Sticks Smell Test categories							x2 (2, n=216) 7·2, p=0·03	x2 (2, n=212) 0·02, p=0·99	x2(2, n=196) 1·5, p=0·47
Normosmic	22 (21·6%)	14 (13·2%)	14 (14·0%)	13 (11·4%)	14 (13·2%)	9 (9·5%)			
Hyposmic	39 (38·2%)	35 (33·0%)	32 (32·0%)	36 (31·6%)	36 (34·0%)	37 (38·9%)			
Anosmic	41 (40·2%)	57 (53·8%)	54 (54·0%)	65 (57·0%)	56 (52·8%)	49 (51·6%)			
Peak Nasal Inspiratory Flow (L/min)	122·7 (41·3)	123·7 (43·0)	125·4 (44·0)	110·5 (55·2)	114·1 (56·2)	117·2 (50·2)	12·2 (-1·0 to 25·4)	9·7 (-3·9 to 23·2)	8·2 (-5·2 to 21·5)

Data are presented as mean (SD) or n (%). Crude mean differences between intervention groups are presented as mean differences (95% CI). For categorical outcomes, between-group differences are presented as Chi-squared test results with accompanying p-value (additional risk differences (95% CI) for 12 months follow-up).
ESS= endoscopic sinus surgery; MT= medical therapy; NE= Not estimable; SNOT-22= Sinonasal Outcome Test 22; VAS= Visual Analogue Scale measured on 0-100 mm scale; EQ-5D-5L= five-level EuroQol, five dimensions.

2. Missing data and imputations

Multiple imputation was used to predict the outcome in participants with missing outcome data. In our study 0·4-12% of the eligible participants had at least one missing value for the set of variables considered relevant for the subsequent regression analyses at the primary time point of 12 months. At 12 months, the fraction of missing for SNOT-22 was 12%. The distribution of missing data was balanced in both arms.

We used multivariate imputation by chained equations using the 'mice' package (version 3.13.0) in R software, version 4.1.0 (R Project for Statistical Computing). This method assumes that data are missing at random (MAR), meaning that any systematic differences between the observed and missing values can be explained by differences in the observed data. To satisfy the assumption of data MAR, it is recommended to perform an inclusive analysis strategy, incorporating a number of auxiliary variables into the analysis model or into the imputation process. We performed an inclusive analysis strategy and additionally used conditional histograms to inspect if the missingness of the outcome variables depended on the other variables (e.g., right-tailed or left-tailed MAR missingness). We used information about the treatment allocation and all available values of baseline variables and outcomes to predict missing values in 15 imputed datasets using predictive mean matching. In addition, to consider potential clustering (i.e., tertiary and secondary referral hospitals), multilevel imputation was performed. Convergence of the chained equation procedure was visually evaluated from trace plots of the mean and standard deviation of the imputed data against iteration number. In order to assess the plausibility of imputations, potential discrepancies between the distribution of observed and imputed data were visually inspected. Parameter estimates from analysing the imputed datasets were pooled according to Rubin's rule.

Table S2. Analyses of complete cases versus analyses of imputed data for the primary outcome SNOT-22 at the primary time point of 12 months.

	Mean difference	95 % CI
Complete case analysis	-4·9	- 9·4 to -0·4
PMM	-6·07	-10·6 to -1·5
Multilevel imputation	-5·9	-10·6 to -1·1

Data are presented as mean difference (95% CI). PMM= predictive mean matching.

3. Stratified analyses

Analyses were stratified by CT-sinus Lund Mackay score, nasal polyp score, NSAID-exacerbated respiratory disease and tertiary versus secondary centres to test for interaction. Interaction tests were adjusted for baseline SNOT-22. As stratified analyses did not point towards potential effect modification of the effect of study treatment on SNOT-22 outcomes at 12 months, subgroups were not further analysed. In Table S3 an overview is presented of interaction estimates and 95% CI.

Table S3. Stratified analyses of the primary outcome SNOT-22 at 12 months.

	Interaction estimate	95% CI
CT-sinus Lund Mackay Score	0·8	-0·2 to 1·8
Nasal polyp score	-0·2	-4·1 to 3·6
NERD	-3·9	-15·0 to 7·2
Type of centre (tertiary vs. secondary)	1·37	-7·9 to 10·7

Data are presented as mean interaction estimate (95% CI). NERD= NSAID-exacerbated respiratory disease.

4. Additional analyses

Additional per-protocol analysis and as-treated analysis were performed. Per-protocol analysis (Table S4): ESS+MT n=109, MT n=84. Primary endpoint was available for n=103 patients in the ESS+MT group and n=81 patients in the MT group. As-treated analysis (Table S5): ESS + MT n=132, MT n=84. Primary endpoint was available for n=125 patients in the ESS+MT group and n=81 patients in the MT group. Analyses of both per-protocol and as-treated did not alter the direction of our findings for the primary outcome.

Table S4. Per-protocol analysis

	ESS+MT (n=109)	**MT** (n=84)	**ESS+MT versus MT** (n=193)
Primary outcome	n=103	n=81	
SNOT-22	27·9 (20·2)	31·2 (20·8)	-6·0 (-10·8 to -1·1)
Secondary outcomes			
SNOT-22 categories			NE
0-20	46 (44·7%)	28 (34·6%)	
≥20 - 40	32 (31·1%)	29 (35·8%)	
≥40 - 60	19 (18·4%)	13 (16·0%)	
≥60 - 80	3 (2·9%)	11 (13·6%)	
≥ 80	3 (2·9%)	0 (0·0%)	
EQ-5D-5L utility score	0·88 (0·15)	0·87 (0·14)	0·01 (-0·03 to 0·05)
EQ-5D-5L VAS (mm)	76·4 (16·4)	76·6 (14·6)	0·1 (-4·4 to 4·6)
Nasal polyp size	2·2 (2·0)	4·3 (2·4)	-2·4 (-3·0 to -1·7)
Nasal polyp size categories			NE
0-4	83 (83·8%)	30 (41·7%)	
5-6	16 (16·2%)	33 (45·8%)	
7-8	0 (0·0%)	9 (12·5%)	

	ESS+MT (n=109)	**MT** (n=84)	**ESS+MT versus MT** (n=193)
Modified Lund-Kennedy Score	4·4 (3·3)	6·1 (3·4)	-1·8 (-2·8 to -0·8)
Modified Lund-Kennedy Score categories			NE
0-4	53 (53·5%)	25 (34·7%)	
5-8	36 (36·4%)	30 (41·7%)	
9-12	10 (10·1%)	17 (23·6%)	
CRS Symptoms (VAS; mm)			
Nasal symptoms in general	31·5 (29·7)	49·3 (29·7)	-20·7 (-29·4 to -12·1)
Nasal obstruction	34·0 (29·6)	44·6 (31·3)	-14·1 (-22·7 to -5·4)
Rhinorrhoea	34·0 (29·3)	37·5 (30·9)	-8·9 (-16·8 to -0·9)
Postnasal drip	35·5 (31·0)	37·9 (29·3)	-6·2 (-14·3 to -2·0)
Loss of smell	56·9 (38·2)	64·4 (36·6)	-8·6 (-18·5 to 1·3)
Facial pressure	21·4 (28·4)	19·9 (24·5)	-1·7 (-8·8 to 5·3)
Headache	20·1 (27·8)	20·0 (25·1)	-2·8 (-10·0 to 4·5)
EPOS Control Test			NE
Controlled	11 (11·0%)	2 (2·6%)	
Partial controlled	43 (43·0%)	21 (27·6%)	
Uncontrolled	46 (46·0%)	53 (69·7%)	
Asthma Control Test	n=54	n=43	NE
Well controlled asthma	7 (13·0%)	4 (9·3%)	
Controlled asthma	13 (24·1%)	12 (27·9%)	
Uncontrolled asthma	34 (63·0%)	27 (62·8%)	
Sniffin' Sticks Smell Test	6·3 (3·3)	6·4 (3·2)	0·1 (-0·7 to 1·0)
Sniffin' Sticks Smell Test categories			NE
Normosmic	14 (14·0%)	7 (9·5%)	
Hyposmic	32 (32·0%)	31 (41·9%)	
Anosmic	54 (54·0%)	36 (48·6%)	
Peak Nasal Inspiratory Flow (L/min)	125·4 (43·9)	115·4 (49·5)	15·7 (3·0 to 28·3)

Data are presented as mean (SD) or n (%). Adjusted mean differences between intervention groups are presented as mean differences [95% CI]. Adjusted analyses for risk differences between categorical outcomes were not estimable (NE). Adjusted values are corrected for accompanying baseline value and tertiary versus secondary hospital.

ESS= endoscopic sinus surgery; MT= medical therapy; SNOT-22= Sinonasal Outcome Test 22; VAS= Visual Analogue Scale measured on 0-100 mm scale; EQ-5D-5L= five-level EuroQol five dimensions.

Table S5. As-treated analysis

	ESS+MT (n=132)	**MT** (n=84)	**ESS+MT versus MT** (n=216)
Primary outcome	n=125	n=81	
SNOT-22	28·4 (19·9)	31·3 (20·8)	-5·8 (-10·4 to -1·2)
Secondary outcomes			
SNOT-22 categories			NE
0-20	54 (43·2%)	28 (34·6%)	
≥20 - 40	39 (31·2%)	29 (35·8%)	
≥40 - 60	24 (19·2%)	13 (16·0%)	
≥60 - 80	5 (4·0%)	11 (13·6%)	
≥ 80	3 (2·4%)	0 (0·0%)	
EQ-5D-5L utility score	0·87 (0·14)	0·88 (0·15)	0·01 (-0·02 to 0·05)
EQ-5D-5L VAS (mm)	76·2 (15·8)	76·6 (14·6)	0·2 (-4·0 to 4·5)
Nasal polyp size	2·2 (2·1)	4·3 (2·4)	-2·4 (-3·0 to -1·8)
Nasal polyp size categories			NE
0-4	102 (83·6%)	30 (41·7%)	
5-6	19 (15·6%)	33 (45·8%)	
7-8	1 (0·8%)	9 (12·5%)	
Modified Lund-Kennedy Score	4·6 (3·3)	6·1 (3·4)	-1·6 (-2·6 to -0·7)
Modified Lund-Kennedy Score categories			NE
0-4	65 (53·3%)	25 (34·7%)	
5-8	42 (34·4%)	30 (41·7%)	
9-12	15 (12·3%)	17 (23·6%)	
CRS Symptoms (VAS; mm)			
Nasal symptoms in general	31·6 (29·4)	49·3 (29·7)	-20·6 (-28·8 to -12·4)
Nasal obstruction	34·7 (29·6)	44·6 (31·3)	-13·9 (-22·2 to -5·5)
Rhinorrhoea	33·4 (28·9)	37·5 (30·9)	-9·1 (-16·7 to -1·6)
Postnasal drip	34·9 (30·6)	37·9 (29·3)	-6·4 (-14·1 to -1·4)
Loss of smell	57·7 (37·9)	64·4 (36·6)	-7·9 (-17·4 to 1·6)
Facial pressure	20·5 (27·3)	19·9 (24·5)	-2·2 (-8·8 to 4·4)
Headache	19·5 (27·0)	20·0 (25·1)	-2·8 (-9·7 to 4·1)
EPOS Control Test			NE
Controlled	13 (10·6%)	2 (2·6%)	

	ESS+MT (n=132)	MT (n=84)	ESS+MT versus MT (n=216)
Partial controlled	54 (43·9%)	21 (27·6%)	
Uncontrolled	56 (45·5%)	53 (69·7%)	
Asthma Control Test	n=65	n=43	NE
Well controlled asthma	9 (13·8%)	4 (9·3%)	
Controlled asthma	16 (24·6%)	12 (27·9%)	
Uncontrolled asthma	40 (61·5%)	27 (62·8%)	
Sniffin' Sticks Smell Test	6·3 (3·3)	6·4 (3·2)	0·1 (-0·7 to 0·9)
Sniffin' Sticks Smell Test categories			NE
Normosmic	16 (13·2%)	7 (9·5%)	
Hyposmic	38 (31·4%)	31 (41·9%)	
Anosmic	67 (55·4%)	36 (48·65)	
Peak Nasal Inspiratory Flow (L/min)	125·1 (45·5)	115·4 (49·5)	17·6 (5·1 to 30·2)

Data are presented as mean (SD) or n (%). Adjusted mean differences between intervention groups are presented as mean differences [95% CI]. Adjusted analyses for risk differences between categorical outcomes were not estimable (NE). Adjusted values are corrected for accompanying baseline value and tertiary versus secondary hospital. ESS= endoscopic sinus surgery; MT= medical therapy; SNOT-22= Sinonasal Outcome Test 22; VAS= Visual Analogue Scale measured on 0-100 mm scale; EQ-5D-5L= five-level EuroQol, five dimensions.

5. Extent of surgery

Most patients that were allocated to ESS+MT had infundibulotomy with anterior and posterior ethmoidectomy, with or without sphenodotomy (n=47 [42·3%]). In more than half of the patients (n=57 [51·4%]) a Draf IIa was performed. Four patients (3.6%) had nasal surgery performed combined with ESS+MT ((i.e., septoplasty or turbinate reduction). No differences were found in outcomes when excluding these four patients, suggesting the additional nasal surgery did not influence outcomes in this trial.

Table S6. Extent of endoscopic sinus surgery in ESS+MT group

	Left side	Right side
Infundibulotomy with anterior ethmoidectomy	10 (9·0%)	8 (7·2%)
Infundibulotomy with anterior and posterior ethmoidectomy (with or without sphenodotomy)	44 (39·6%)	47 (42·3%)
Infundibulotomy with anterior and posterior ethmoidectomy and Draf IIa	25 (22·5%)	25 (22·5%)
Infundibulotomy with anterior and posterior ethmoidectomy, sphenodotomy and Draf IIa	32 (28·8%)	31 (27·9%)
Additional nasal surgery (i.e. septoplasty or turbinate reduction)	4 (3.6%)	3 (2.7%)

Data are presented as n (%) per side of the nose. ESS= endoscopic sinus surgery; MT= medical therapy.

Table S6 portrays the extent of surgery for left and right side of the nose separately.

6. Generalisability of results

After screening for study inclusion, 133 patients were unwilling to participate after meeting the inclusion criteria. Most of these patients chose not to participate due to specific preferences in type of treatment or the inability to invest time and effort in study-related procedures, including surgery. When patients agreed to share personal information after deciding not to participate, the study team or the referring ENT-specialist were asked to record gender, age and ask each patient to fill in a SNOT-22 questionnaire.

Personal data was recorded for all 133 patients and SNOT-22 specific data could be retrieved in 43 patients. No differences were seen between the trial participants and the patients who had an indication for ESS, which did not participate: 59·4% of patients were male with a mean age in years of 49·5 (SD 13·7). The mean SNOT-22 score was 49·5 (SD 22·4). This is fully comparable to the baseline data of our trial participants.

7. Prescribed medication

All patients were prescribed intranasal corticosteroids from start of treatment (sprays or drops). Table S7 provides an overview of medication prescribed during the study in both study groups: intranasal corticosteroids, antibiotics, systemic corticosteroids and aspirin desensitisation are reported. There were no differences of clinical relevance between groups for intranasal corticosteroids or antibiotics. Significantly, more systemic corticosteroids were used in the MT group: an adjusted difference of -316 mg [95% CI -468 to -166] (adjusted for type of hospital).

Table S7. Prescribed medication for CRSwNP during 12 months follow-up

	ESS+MT (n=109)	**MT** (n=110)
Intranasal corticosteroids prescribed* (n, %)	109 (100)	110 (100)
Quantity of antibiotic courses prescribed (n, %)		
1	18 (16.5)	19 (17.3)
2	5 (4.6)	5 (4.5)
3	1 (0.9)	0 (0.0)
4	0 (0.0)	1 (0.9)
Cumulative dose systemic corticosteroids used (mg)	265.5 (505.0)	586.7 (739.8)
Aspirin desensitisation (n, %)	0 (0.0)	0 (0.0)

Data are presented as mean (SD) or n (%). * Intranasal corticosteroids were either intranasal sprays or drops
ESS= endoscopic sinus surgery; MT= medical therapy; CRSwNP = chronic rhinosinusitis with nasal polyps.

8. Standardised surgical report

Sinus	Opened during ESS	Normal mucosa	Mucosal edema	Polypoid mucosa	Polyps	No mucus	Thin mucus	Glue	Purulence	Air-filled sinus
Maxillary left	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Maxillary right	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Anterior ethmoid left	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Anterior ethmoid right	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Posterior ethmoid left	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Posterior ethmoid right	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sphenoid left	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sphenoid right	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Frontal left	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Frontal right	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Peroperative complications

Did any perioperative complications occur? O Yes O No
If " Yes", specify: ☐ Bleeding ☐ Lamina papyracea injury ☐ Orbital hematoma
☐ Nasal liquorrhea ☐ Other, namely……

9. Overview of trial centres and specialists

Table S9. Participating ENT-specialists

Site	Participating ENT-specialists/doctors
Academic Medical Centre	Prof. dr. W.J. Fokkens G.F.J.P.M. Adriaensen M.E. Cornet M.G.E. van de Goor D.R. Hoven C.A. Hellingman J.L.A. Embrechts S. Reitsma
Erasmus Medical Centre	A.P. Nagtegaal
Vu Medical Centre	J.H. Bretschneider
Amstelland Hospital	J.H. Schmidt L.D.G. Stanojcic A.M. Kreeft
Alrijne Hospital	M. Sassen
BovenIJ Hospital	J. van der Borden
Deventer Hospital	J. Buwalda W.J.M. Videler
Dijklander Hospital	R.M. van Haastert C.L. Segboer M.E.C. Raming
Flevohospital	M. Vleming
Haga Hospital	C.C. Bommeljé J. Brouwer
OLVG location Oost	G.W. van Deelen W. Derks J.P. van Maanen
Tergooi Hospital	M.L. Tan S.M. Reinartz
Spaarne Hospital location Haarlem	J.A. Veldhuizen
Spaarne Hospital location Hoofddorp	E.B.J. van Nieuwkerk

10. CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4, Supp Appendix section 9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5-6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	5-6
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5

[continued on next page]

10. CONSORT 2010 *[continued]*

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
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[continued on next page]

10. CONSORT 2010 *[continued]*

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CHAPTER 8

TRANEXAMIC ACID FOR THE REDUCTION OF BLEEDING DURING FUNCTIONAL ENDOSCOPIC SINUS SURGERY

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Cochrane Database Syst Rev. 2023 Feb 21;2(2)

ABSTRACT

Background

Chronic rhinosinusitis, with or without nasal polyps, can have a major impact on a person's quality of life. Treatment is usually conservative and may include nasal saline, intranasal corticosteroids, antibiotics or systemic corticosteroids. If these treatments fail endoscopic sinus surgery can be considered. During surgery, visibility of the surgical field is important for the identification of important anatomic landmarks and structures that contribute to safety. Impaired visualisation can lead to complications during surgery, inability to complete the operation or a longer duration of surgery. Different methods are used to decrease intraoperative bleeding, including induced hypotension, topical or systemic vasoconstrictors or total intravenous anaesthesia. Another option is tranexamic acid, an antifibrinolytic agent, which can be administered topically or intravenously.

Objectives

To assess the effects of peri-operative tranexamic acid versus no therapy or placebo on operative parameters in patients with chronic rhinosinusitis (with or without nasal polyps) who are undergoing functional endoscopic sinus surgery (FESS).

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Trials Register; Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 10 February 2022.

Selection criteria

Randomised controlled trials (RCTs) comparing intravenous, oral or topical tranexamic acid with no therapy or placebo in the treatment of patients (adults and children) with chronic rhinosinusitis, with or without nasal polyps, undergoing FESS.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. Primary outcome measures were surgical field bleeding score (e.g. Wormald or Boezaart grading system), intraoperative blood loss and significant adverse effects (seizures or thromboembolism within 12 weeks of surgery). Secondary outcomes were duration of surgery, incomplete surgery, surgical complications and postoperative bleeding (placing of packing or revision surgery) in the first two weeks after surgery. We performed subgroup analyses for methods of administration, different dosages, different forms of anaesthesia, use of thromboembolic prophylaxis and children versus adults. We evaluated each included study for risk of bias and used GRADE to assess the certainty of the evidence.

MAIN RESULTS

We included 14 studies in the review, with a total of 942 participants. Sample sizes in the included studies ranged from 10 to 170. All but two studies included adult patients (≥ 18 years). Two studies included children. Most studies had more male patients (range 46.6% to 80%). All studies were placebo-controlled and four studies had three treatment arms. Three studies investigated topical tranexamic acid; the other studies reported the use of intravenous tranexamic acid.

For our primary outcome, surgical field bleeding score measured with the Boezaart or Wormald grading score, we pooled data from 13 studies. The pooled result demonstrated that tranexamic acid probably reduces the surgical field bleeding score, with a standardised mean difference (SMD) of -0.87 (95% confidence interval (CI) -1.23 to -0.51; 13 studies, 772 participants; moderate-certainty evidence). A SMD below -0.70 represents a large effect (in either direction).

Tranexamic acid may result in a slight reduction in blood loss during surgery compared to placebo with a mean difference (MD) of -70.32 mL (95% CI -92.28 to -48.35 mL; 12 studies, 802 participants; low-certainty evidence).

Tranexamic acid probably has little to no effect on the development of significant adverse events (seizures or thromboembolism) within 24 hours of surgery, with no events in either group and a risk difference (RD) of 0.00 (95% CI -0.02 to 0.02; 8 studies, 664 participants; moderate- certainty evidence). However, there were no studies reporting significant adverse event data with a longer duration of follow-up.

Tranexamic acid probably results in little difference in the duration of surgery with a MD of -13.04 minutes (95% CI -19.27 to -6.81; 10 studies, 666 participants; moderate-certainty evidence). Tranexamic acid probably results in little to no difference in the incidence of incomplete surgery, with no events in either group and a RD of 0.00 (95% CI -0.09 to 0.09; 2 studies, 58 participants; moderate-certainty evidence) and likely results in little to no difference in surgical complications, again with no events in either group and a RD of 0.00 (95% CI -0.09 to 0.09; 2 studies, 58 participants; moderate-certainty evidence), although these numbers are too small to draw robust conclusions. Tranexamic acid may result in little to no difference in the likelihood of postoperative bleeding (placement of packing or revision surgery within three days of surgery) (RD -0.01, 95% CI -0.04 to 0.02; 6 studies, 404 participants; low-certainty evidence). There were no studies with longer follow-up.

Authors' conclusions

There is moderate-certainty evidence to support the beneficial value of topical or intravenous tranexamic acid during endoscopic sinus surgery with respect to surgical field bleeding score. Low- to moderate-certainty evidence suggests a slight decrease in total blood loss during surgery and duration of surgery. Whilst there is moderate-certainty evidence that tranexamic

acid does not lead to more immediate significant adverse events compared to placebo, there is no evidence regarding the risk of serious adverse events more than 24 hours after surgery. There is low-certainty evidence that tranexamic acid may not change postoperative bleeding. There is not enough evidence available to draw robust conclusions about incomplete surgery or surgical complications.

PLAIN LANGUAGE SUMMARY

Does tranexamic acid (a medicine used to improve blood clotting) reduce bleeding during endoscopic surgery for chronic rhinosinusitis?

What is chronic rhinosinusitis?

Chronic rhinosinusitis is an inflammation of the sinuses that has lasted for at least 12 weeks. People with chronic rhinosinusitis can experience symptoms such as a blocked or runny nose, a feeling of facial pain or pressure, or a reduction or loss of the sense of smell. Some people may also have polyps in their nose, which can worsen the symptoms.

How is chronic rhinosinusitis treated?

Chronic rhinosinusitis is usually treated with medicines such as saline sprays or rinses, anti-inflammatory sprays/drops (steroids), antibiotics or anti-inflammatory steroid tablets. If the symptoms continue despite this treatment, surgery can be performed.

What did we want to find out?

We wanted to see if tranexamic acid, a medicine used to improve blood clotting, could be elective during endoscopic sinus surgery by reducing bleeding, which then potentially reduces the risk of complications. Less bleeding means that surgeons have a better view of the sinuses when they are operating.

What did we do?

We searched for studies that investigated tranexamic acid (either given in the vein or directly applied in the nose by sprays or drops) compared with a placebo (dummy treatment) or no tranexamic acid. We were interested in both children and adults. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 14 studies, with a total of 942 participants, which compared tranexamic acid to normal saline (placebo - dummy treatment) in patients having endoscopic sinus surgery. In 10 studies the treatment was given in a vein and in three it was applied in the nose. All studies used different amounts of the drug.

We found that tranexamic acid probably greatly improves the view of the surgeon (based on 13 studies), may slightly reduce total blood loss during surgery (12 studies) and likely does not cause any serious side effects within 24 hours of surgery (i.e. blood clot formation in the brain or seizures - there were no such events in either the treatment or placebo groups) (eight studies). Unfortunately, there is no evidence with respect to serious side effects at a longer duration of follow-up.

The duration of the surgery was investigated in 10 studies. The duration of surgery is probably slightly lower with tranexamic acid.

Only two studies investigated complications related to surgery and difficulty completing the surgery as planned. In these studies no difference was seen between the tranexamic acid and placebo groups. However, because these complications are rare no conclusions can be drawn based on these studies.

Nosebleeds after surgery that required intervention (placing of nasal tampons or further surgery) were investigated in six studies. Only two studies reported a patient treated with saline solution (placebo) who experienced a nosebleed after surgery. Tranexamic acid may not make a difference to the likelihood of postoperative bleeding.

Based on the evidence in the studies we cannot conclude whether tranexamic acid given either in a vein or applied in the nose is better. We also cannot conclude whether a particular dose of tranexamic acid is better.

What are the limitations of the evidence?
We are moderately confident about the evidence for the improvement of the view of the surgeon during surgery, but further research may have an impact on the estimate of the effect. We have less confidence in the evidence for lower blood loss during surgery, meaning that the true effect could be very different after more research. For the occurrence of serious side effects within 24 hours after surgery (blood clot formation in the brain or seizures) we are confident that more research would probably not change our findings.

How up-to-date is the evidence?
The evidence is up-to-date to February 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Tranexamic acid versus placebo (saline solution or sterile water) for the reduction of bleeding during functional endoscopic sinus surgery

Tranexamic acid versus placebo (saline solution or sterile water) for the reduction of bleeding during functional endoscopic sinus surgery			
Patient population: adults and children with chronic rhinosinusitis with or without nasal polyps			
Setting: secondary or tertiary care hospitals (non-European and non-USA hospitals)			
Intervention: tranexamic acid			
Comparison: placebo (saline solution or sterile water)			
	Absolute effects* (95% CI)		
Outcomes	**Risk with placebo (saline solution or sterile water)**	**Risk with tranexamic acid**	**Relative effect (95% CI)**
Surgical field bleeding score (during surgery or ‹ 30 minutes after surgery) Assessed with: Boezaart bleeding score (range 0 to 5) or Wormald grading scale (range 0 to 10)	—	The standardised mean difference was 0.87 points lower in the intervention group (1.23 lower to 0.51 lower)	—
Intraoperative blood loss Assessed as: total amount of blood loss during surgery in mL	Mean blood loss ranged from 68 mL to 439 mL in the control group	Mean blood loss ranged from 36 mL to 405 mL Mean blood loss was 70.32 mL lower in the intervention group (92.28 lower to 48.35 lower)	—
Significant adverse events (seizures, thrombo-embolism) within 24 hours of surgery)	Study population		RD 0.00 (-0.02 to 0.02)
	0 per 1000	0 per 1000	
Duration of surgery (minutes) Assessed as: total surgical time	Mean duration of surgery ranged from 66 to 158 minutes in the control group	Mean duration of surgery ranged from 45 to 126 minutes. Mean duration was 13.04 minutes lower in the intervention group (19.27 lower to 6.81 lower)	—
Incomplete surgery	Study population		RD 0.0 (-0.09 to 0.09)
	0 per 1000	0 per 1000	
Surgical complications	Study population		RD 0.0 (-0.09 to 0.09)
	0 per 1000	0 per 1000	
Postoperative bleeding (place of packing or revision surgery within 14 days of surgery)	Study population		RD -0.01 (-0.04 to 0.02)
	10 per 1000	3 per 1000	

CI: confidence interval; **RCT:** randomised controlled trial; **RD:** risk difference; **RR:** risk ratio

[continued on next page]

Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
772 (13 RCTs)	⨁⨁⨁◯ **moderate**[1,2]	Tranexamic acid probably results in a large reduction in the surgical field bleeding score.
802 (12 RCTs)	⨁⨁◯◯ **low**[3,4]	Tranexamic acid may result in a slight reduction in intraoperative blood loss.
664 (8 RCTs)	⨁⨁⨁◯ **moderate**[5]	Tranexamic acid probably has little to no effect on the development of significant adverse events within 24 hours of surgery. (No studies reported up to 12 weeks).
666 (10 RCTs)	⨁⨁⨁◯ **moderate**[6]	Tranexamic acid probably results in little difference in the duration of surgery (minutes).
58 (2 RCTs)	⨁⨁⨁◯ **moderate**[7]	Tranexamic acid probably results in little to no difference in the incidence of incomplete surgery.
58 (2 RCTs)	⨁⨁⨁◯ **moderate**[7]	Tranexamic acid likely results in little to no difference in surgical complications.
404 (6 RCTs)	⨁⨁◯◯ **low**[8,9]	Tranexamic acid may result in little to no difference in the likelihood of postoperative bleeding (follow-up 1 to 3 days after surgery).

Summary of findings *[continued]*

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Considerable heterogeneity (I2 = 80%). We downgraded by one level due to inconsistency.
[2] Decision based on confidence interval: upper limit excludes threshold of -0.2 (SMD).
[3] Probably does not cross the meaningful clinical threshold (the authors feel that › 100 mL would be relevant). Large confidence interval. We downgraded one level due to imprecision.
[4] Considerable heterogeneity (I2 = 95%). We downgraded by one level due to inconsistency.
[5] Results available for 24 hours after surgery, not 12 weeks follow-up. Downgraded by one level for indirectness related to the measurement of the outcome.
[6] Considerable heterogeneity (I2 = 81%). We downgraded by one level due to inconsistency.
[7] Only two studies with a very limited number of participants. Downgraded by one level due to imprecision.
[8] The CI for the RR did not exclude no effect (1.0). We downgraded by one level.
[9] Does not answer the review question properly (only one to three days of follow-up instead of two weeks). We feel that this is a too short a follow-up for this outcome. We downgraded by one level.

BACKGROUND

Description of the condition

Chronic rhinosinusitis is a disease characterised by symptomatic inflammation of the mucosa of the nose and paranasal sinuses, which lasts longer than 12 weeks. It is a common condition and can have a major impact on patients' quality of life (Slovick 2016).

In adults chronic rhinosinusitis is defined as an inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and/or facial pain/pressure and/or reduction or loss of smell and either endoscopic signs of nasal polyps and/or mucopurulent discharge primarily from the middle meatus and/or relevant computerised tomography (CT) changes (Fokkens 2012; Fokkens 2020). Chronic rhinosinusitis with nasal polyps (CRSwNP) is defined by bilateral polyps in the middle meatus, which can be visualised endoscopically. In chronic rhinosinusitis without nasal polyps (CRSsNP) there are no visible polyps in the middle meatus. These definitions accept that there is a spectrum of disease that includes polypoid change in the sinuses and/or middle meatus but excludes patients with polypoid disease presenting in the nasal cavity in order to avoid overlap (Fokkens 2012; Fokkens 2020).

Chronic rhinosinusitis is commonly managed with either topical or systemic medications, which include steroids, antibiotics and saline. If these conservative measures fail functional endoscopic sinus surgery (FESS) can be considered. Among patients with chronic rhinosinusitis with nasal polyps, 57% will undergo sinus surgery and 20% of these will undergo multiple procedures (Rudmik 2015). In Canada, 10,000 to 15,000 FESS procedures are undertaken per year (Rudmik 2015). The goal of FESS is to re-establish normal ventilation and mucus drainage from the sinuses, to resect irreversibly changed mucosa and to allow direct access for topical medications (Cornet 2012).

Visibility of the surgical field is key to the safety of the FESS procedure, which can be compromised by bleeding. Bleeding can lead to difficulty in recognising important anatomic landmarks and structures. It can increase the risk of intraoperative complications, prolong the operating time and result in incomplete surgery (Timperley 2010). The degree of surgical bleeding during FESS can be measured with Boezaart's scale and/or the Wormald scale (Athanasiadis 2008; Boezaart 1995).

Multiple methods exist to improve surgical field visibility, including induced hypotension, use of various anaesthetic and vasoconstrictive agents, and the administration of total intravenous anaesthesia (TIVA) (Hathorn 2013; Ko 2008; Wormald 2005). As the presence of polyps, active infection and fungal rhinosinusitis are known to lead to significantly higher blood loss during FESS (Ko 2008; Wormald 2005), preoperative steroids have been used to reduce the degree of bleeding (Sieskiewicz 2006). Use of a microdebrider in comparison to traditional instruments for endoscopic sinus surgery has also been studied, however despite a shorter operating time no difference in blood loss has been shown (Cornet 2012; Ko 2008).

The antifibrinolytic agent tranexamic acid is a last, often overlooked, intervention used to reduce intraoperative bleeding during FESS.

Description of the intervention

There is strong evidence that tranexamic acid reduces blood loss in surgery (Ker 2012). It can be applied both locally and intravenously and it has been used in patients with hereditary bleeding disorders and haemorrhage, to increase survival in patients with acute traumatic injury (Roberts 2013b) and to lessen menorrhagia (Naoulou 2012). In surgery, tranexamic acid is widely used systemically in cardiothoracic (Hasegawa 2014; Taghaddomi 2009), orthopaedic (Huang 2014; Wang 2015), gynaecological (Wang 2015a; Wang 2017) and urological procedures (Rannikko 2004) to reduce perioperative blood loss. Topical administration is used in orthopaedic surgery (e.g. total knee replacement) (Alshryda 2014) and spinal surgery (Panteli 2013). Tranexamic acid can also be used topically as a mouth wash following dental or oral surgery (Robb 2014).

In otorhinolaryngological practice, tranexamic acid is widely used in the treatment of epistaxis (Kamhieh 2016; Mehta 2019) and in head and neck surgery (Das 2015), including parotid surgery and tonsillectomy (Robb 2014). Published literature supports the use of tranexamic acid as a means of reducing intraoperative blood loss during tonsillectomy, however it has not been shown to reduce postoperative haemorrhage (Chan 2013).

When given intravenously tranexamic acid is used at a dosage of 10 mg/kg (Novikova 2015). Slow administration is advised (1 mL/min) over the required time to avoid significant hypotension. Given orally, the recommended standard dose is 15 to 25 mg/kg two to three times daily. Tablets are produced at 500 mg strength and tranexamic acid solution at 100 mg/mL. There are no clear recommendations concerning the dosage or method of topical application.

How the intervention might work

Tranexamic acid (trans-4 amino methyl-cyclohexane carboxylic acid) is a synthetic lysine analogue that binds to the lysine binding site of plasminogen, consequently preventing fibrinolysis by inhibiting the interaction between plasminogen and fibrin (Robb 2014). Its antifibrinolytic effect is quickly reached, acting within two to three hours after oral administration and immediately after intravenous administration (Novikova 2015). It has a short half-life of approximately two hours. The most common adverse events are gastrointestinal side effects, including nausea, diarrhoea and abdominal cramping, which are dose-dependent and uncommon (Robb 2014). The risk of thromboembolic events was found to be uncertain in a large meta-analysis of 129 trials totalling 10,488 patients (myocardial infarction: risk ratio (RR) 0.68, 95% confidence interval (CI) 0.43 to 1.09, P = 0.11; stroke: RR 1.14, 95% CI 0.65 to 2.00, P = 0.65, deep vein thrombosis: RR 0.86, 95% CI 0.53 to 1.39, P = 0.54; pulmonary embolism: RR 0.61, 95% CI 0.25 to 1.47, P = 0.27) (Ker 2012). Data were sparse in another large meta-analysis (Henry 2011), and findings from more recent meta-analyses have not resolved this uncertainty (Abu-Zaid 2022; Leverett 2022).

Why it is important to do this review

Among ear, nose and throat (ENT) professionals tranexamic acid is mainly known for its role in treating patients with epistaxis and those undergoing tonsillectomy (Chan 2013; Robb 2014).

Any intervention that is shown to reduce blood loss during endoscopic sinus surgery with consequent improvement of surgical field quality and safety will be of clinical benefit for adults, as well as children, and may reduce the duration of surgery. A meta-analysis evaluating the evidence for the role of tranexamic acid in patients undergoing endoscopic sinus surgery has previously been performed (Pundir 2013). The authors concluded that intraoperative use of topical and intravenous tranexamic acid significantly reduces estimated blood loss and improves surgical field quality. However, the authors pooled the data irrespective of the method of application. Although it can be hypothesised that intravenous tranexamic acid is more effective than topical application, the latter may have the benefit of reducing bleeding from surgical wounds without inducing systemic toxicity and thromboembolism. In addition, since the publication of this meta-analysis, various further studies have been published (Jahanshahi 2014; Nuhi 2015; Sahar 2015; Shehata 2014).

In view of this, an up-to-date Cochrane Review addressing the question of whether tranexamic acid reduces estimated blood loss and improves surgical field quality, with subgroup analyses to compare methods of administration, is of added value in evidence-based rhinological practice.

OBJECTIVES

To assess the effects of peri-operative tranexamic acid versus no therapy or placebo on operative parameters in patients with chronic rhinosinusitis (with or without nasal polyps) who are undergoing functional endoscopic sinus surgery (FESS).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cluster-randomised trials. We excluded cross-over trials as they are not relevant for this intervention (since the main outcomes are evaluated at the time of surgery it would be incoherent to switch from placebo to active treatment or vice versa during surgery). We included studies irrespective of publication status, date of publication or language.

Types of participants

Patients (adults and children) with chronic rhinosinusitis (with or without nasal polyps) undergoing endoscopic sinus surgery.

Exclusion criteria

- Wegener's disease
- Sarcoidosis
- Sinonasal malignancy
- Bleeding disorders

Types of interventions

Tranexamic acid irrespective of the dose, duration or method of administration.

The comparison was:

- topical or systemic tranexamic acid compared with placebo or no tranexamic acid.

Types of outcome measures

We analysed the following outcomes in the review, but did not use them as a basis for including or excluding studies.

Primary outcomes

- Surgical field bleeding score (e.g. Wormald or Boezaart grading system for bleeding during endoscopic sinus surgery. Where both were reported we chose the Boezaart grading system).
- Intraoperative blood loss measured at the end of surgery (mL).
- Significant adverse effects: of relevance are seizures and thromboembolism within 12 weeks of surgery.

Secondary outcomes

- Duration of surgery (minutes).
- Incomplete surgery.
- Surgical complications (during surgery or directly after surgery).
- Postoperative bleeding (placing of packing or revision surgery) in the first two weeks after surgery.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 10 February 2022.

Electronic searches

The Information Specialist searched:

- Cochrane ENT Trials Register (via Cochrane Register of Studies Web, searched 10 February 2022);
- Central Register of Controlled Trials (CENTRAL via CRS Web, searched 10 February 2022);

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 10 February 2022);
- Ovid EMBASE (1974 to 10 February 2022);
- Web of Knowledge, Web of Science (1945 to 10 February 2022);
- LILACS (BIREME) (searched 10 February 2022);
- ClinicalTrials.gov (search via the Cochrane ENT Register and www.clinicaltrials.gov searched 10 February 2022);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched 10 February 2022);
- CNKI (searched via Google Scholar 10 February 2022).

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two authors (KA and EL, a rhinology fellow and a junior otorhinolaryngology trainee, respectively) independently examined the titles and abstracts of the studies to remove obviously irrelevant reports. We then retrieved the full texts of potentially relevant articles. The same two authors independently examined the full-text reports for compliance with the eligibility criteria. We contacted the study authors, where appropriate, to clarify study eligibility. The two authors independently decided on study inclusion. Any difference in opinion regarding the inclusion of studies was resolved by discussion until a consensus was reached, or by referral to a third review author (VP).

We have included a graphical representation of the flow of citations reviewed in the course of this review in the review, as described in the PRISMA statement (Moher 2009).

Data extraction and management

Two authors (KA and EL) independently extracted data from the study reports using the generic Cochrane ENT data collection form (Appendix 2). If additional information was needed concerning details of the study or numerical results, we contacted the authors of the study reports and original investigators. We extracted data into Review Manager (RevMan) 5 (RevMan 2020). If multiple reports of the same study existed, each author collected data separately from each report and then collated this into a single study report. We resolved disagreements by discussion. If necessary, disagreements were resolved by arbitration by a third author (VP). We collected data from each study for analyses of dichotomous outcomes, continuous outcomes and other types of outcome data as described in chapter 7.7 'Extracting study results' in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

Two review authors (EL and KA) undertook assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane risk of bias tool in RevMan 2020, which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Lack of blinding in itself was sufficient to label a study as at high risk of bias if all outcomes were subjective, e.g. surgeon reporting of clarity of field.

Measures of treatment effect

For continuous outcomes we reported the mean difference (MD) with standard deviation (SD) or, when necessary, the standardised mean difference (SMD). We anticipated that different intraoperative bleeding scales would have been used in different studies: namely the Boezaart and Wormald scales. We used the SMD as the summary statistic to standardise the results of studies to a uniform scale. If studies reported both bleeding scales we chose to report the Boezaart scale. In case of different time point measurements for the intraoperative bleeding scales, we chose to use the time point closest to 30 minutes after the dose of tranexamic acid or the start of surgery. The inhibitory activity of tranexamic acid on fibrinolysis is maximal at this time point.

In the case of dichotomous outcomes, we calculated the risk ratio (RR) with a 95% confidence interval (CI). Where there were no events in either treatment group, we calculated a risk difference (RD) with a 95% CI.

Unit of analysis issues

We determined appropriate units of analysis from the included studies. We only considered split-body trials when the administration route of treatment was intranasal, with two experimental units of analysis (both sides of the nose, which are correlated in chronic rhinosinusitis with or without nasal polyps). There would be a very low risk of a 'carry-over effect', since the patient lies on their back during surgery and leakage would be implausible. However, there could be a risk of underestimation of the treatment effect, since the comparison is placebo. If the trial correctly analysed and reported the data (analysis for paired outcomes), we used the mean postoperative values as a summary measure and used a two-group comparison in the review.

Cluster-randomised trials

We analysed cluster-randomised trials based on the level of allocation, i.e. clusters of participants.

Multi-armed trials

When analysing multi-armed trials, we combined all relevant experimental intervention groups in the study into a single group and all relevant control intervention groups into a single control group. If we considered one of the arms to be irrelevant, we excluded it from analysis.

For dichotomous outcomes, we summed both the sample sizes and the numbers of people with events across groups. For continuous outcomes, we combined means and standard deviations using the methods described in Chapter 7 (section 7.7.3.8) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We contacted study authors via email whenever the outcome of interest was not reported if the methods of the study suggested that the outcome was measured. We did the same if not all data required for meta-analysis were reported, unless the missing data were standard deviations. If standard deviation data were not available we approximated these using standard estimation methods: from P values, standard errors or 95% CIs if these were reported, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Where it was impossible to estimate these, we contacted the study authors.

Apart from imputations for missing standard deviations, we did not conduct any other imputations. We extracted and analysed data for all outcomes using the available case analysis method.

Assessment of heterogeneity

We assessed clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included studies for potential differences between them in

the types of participants recruited (including age of participants), interventions or controls used and the outcomes measured.

We assessed statistical heterogeneity by visually inspecting the forest plots and by considering the Chi^2 test (with a significance level set at $P < 0.10$) and the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with I^2 values over 50% suggesting substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

We created a funnel plot to detect reporting biases if at least 10 studies were included in the meta-analysis. We assessed reporting bias as between-study publication bias and within-study outcome reporting bias. If we identified small studies with larger treatment effects, we planned to perform a sensitivity analysis excluding these studies.

Data synthesis

We used the Cochrane software package RevMan 5 for quantitative meta-analysis of the extracted data (RevMan 2020). We expressed continuous data as the MD or SMD with 95% CI. We expressed dichotomous data as the RR with 95% CI. We pooled the results using a random-effects model because we expected there to be substantial clinical heterogeneity.

Subgroup analysis and investigation of heterogeneity

Where data were available, we planned to conduct some subgroup analyses regardless of whether statistical heterogeneity was observed, as these are widely suspected to be potential effect modifiers. For this review, this included the following:

Primary subgroup:

- Different methods of administration of tranexamic acid (topical versus intravenous).

Secondary subgroups:

- Different dosages.
- Patients with chronic rhinosinusitis with and without nasal polyps.
- Patients that use local corticosteroids in the month before surgery versus no corticosteroids.
- Patients that use systemic corticosteroids in the month before surgery including the day of surgery versus local corticosteroids or no corticosteroids.
- Different forms of anaesthesia and other intraoperative interventions.
- Patients with thromboembolic prophylaxis versus patients without thromboembolic prophylaxis.
- Children (< 18) versus adults (≥ 18).

Sensitivity analysis

We intended to carry out sensitivity analyses on the basis of the methodological diversity of the included studies. We considered the following when repeating the analysis:

- excluding studies with high risk of bias (defined as four out of seven domains deemed to have high risk);
- excluding small studies with larger treatment effects;
- excluding industry-sponsored studies;
- excluding studies with significant author financial and other conflicts of interest;
- statistical model of analysis (fixed-effect versus random-effects model);
- assumptions about missing data (considering the scenarios outlined above in Dealing with missing data).

Summary of findings and assessment of the certainty of the evidence

Two authors (KA and EL) independently applied the GRADE approach to rate the overall certainty of evidence. The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We created a summary of findings table in GRADEpro GDT, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We included the following outcomes in the summary of findings table:

- surgical field bleeding score;
- intraoperative blood loss (mL);
- significant adverse effects: seizures, thromboembolism;
- duration of surgery (minutes);
- incomplete surgery;
- surgical complications;
- postoperative bleeding (place of packing or revision surgery within three days).

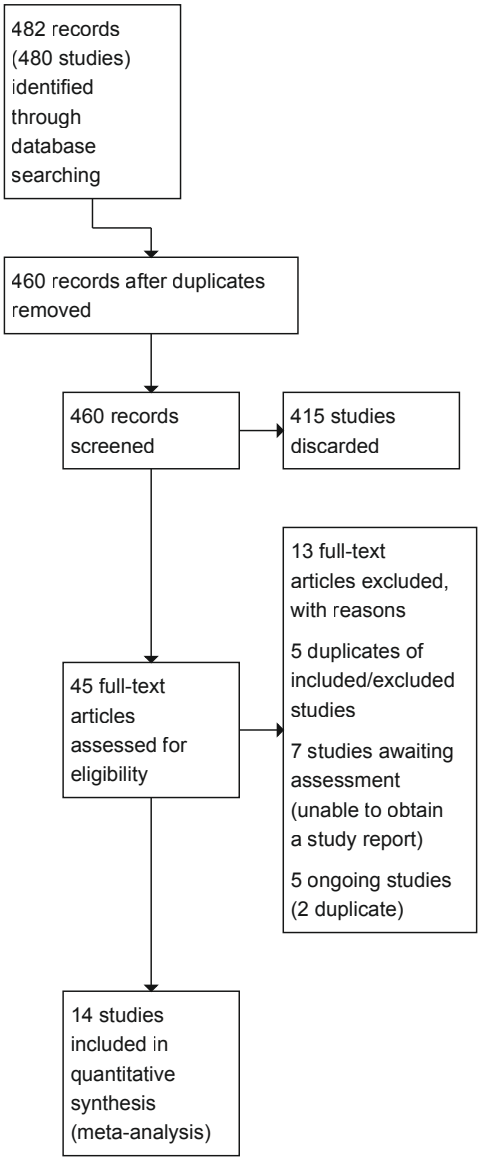

Figure 1. Process for sifting search results and selecting studies for inclusion

RESULTS

Description of studies

Results of the search

The search retrieved a total of 482 records (480 studies). After removing duplicates we screened 460 titles and abstracts and subsequently removed 415 studies. We assessed 45 full texts for

eligibility and excluded 13 individual studies from the review. We found an additional study in the reference list of a systematic review. Five identified studies are ongoing. Seven studies are awaiting assessment, either because no full-text report was found or we were unable to obtain the paper. We included 14 studies in the review.

A flow chart of study retrieval and selection is provided in Figure 1.

Included studies

We included 14 studies (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Dongare 2018; Eldaba 2013; El Shal 2015; El-Ozairy 2021; Jabalameli 2006; Langille 2013; Nuhi 2015; Padhy 2019; Pannerselvam 2019; Quiroga 2018; Yang 2021). See Characteristics of included studies.

Design

All studies were randomised, controlled and blinded.

Sample size and participants

The included studies ranged from a sample size of 10 (Quiroga 2018) up to 170 (Nuhi 2015). All participants underwent endoscopic sinus surgery for chronic rhinosinusitis.

Ten studies included adult patients of at least 18 years (the age range of included patients was 18 to 80 years). One study included children between 5 and 10 years old and one study included patients between 12 and 60 years of age. More male patients were included in almost all studies (range 46.6% to 80%). Only one study included male and female patients in a 50:50 ratio (Nuhi 2015). In the studies Baradaranfar 2017, Dongare 2018 and Padhy 2019 all patients had chronic rhinosinusitis with nasal polyps. In Yang 2021, more than 70% of patients had nasal polyps. Langille 2013 included five participants with chronic rhinosinusitis without nasal polyps and 23 patients with chronic rhinosinusitis with nasal polyps. No specification of presence or absence of nasal polyps was given in the other studies.

Setting

All studies were performed in single centres in secondary or tertiary care clinics of departments of Anesthesiology or Otorhinolaryngology. The Middle East was strongly represented with four studies conducted in Iran and three studies performed in Egypt. The other studies were performed in the Philippines, India, Australia, Canada and China. There were no studies from Europe or the USA.

Interventions

All studies were placebo-controlled, although two studies had three arms, also including epsilon-aminocaproic acid, a synthetic inhibitor of the plasmin-plasminogen system, in the comparison (Athanasiadis 2007; El Shal 2015). We excluded this arm from the analyses. Three studies used topical application of tranexamic acid as a spray (Athanasiadis 2007), or local irrigation (Baradaranfar 2017; Jabalameli 2006), while the other 10 studies used intravenous

tranexamic acid (Alimian 2011; Dongare 2018; Eldaba 2013; El Shal 2015; Langille 2013; Nuhi 2015; Padhy 2019; Pannerselvam 2019; Quiroga 2018; Yang 2021). El-Ozairy 2021 compared topical application, intravenous application or both with placebo. Two studies compared two different dosages of tranexamic acid: topical 100 mg versus 1000 mg (Athanasiadis 2007) and intravenous 15 mg/kg and 5 mg/kg (Pannerselvam 2019).

In the studies that applied intravenous tranexamic acid, a single bolus was given in three studies (Alimian 2011; Dongare 2018; Nuhi 2015), infusion over 30 minutes in Yang 2021, and a single bolus plus infusion (over an unclear period of time) in Langille 2013. It was unclear in the other studies whether a bolus or infusion was applied (Eldaba 2013; El Shal 2015; Padhy 2019; Pannerselvam 2019; Quiroga 2018).

The details of the interventions are described in Table 1 ‹Summary of studies comparing topical tranexamic acid with placebo›, Table 2 ‹Summary of studies comparing intravenous application of tranexamic acid with placebo› and Table 3 ‹Summary of studies comparing low- versus high-dose tranexamic acid with placebo›.

Most studies mentioned in their exclusion criteria that participants were not allowed to use any anticoagulant medications before inclusion in the study. Jabalameli 2006 only reported that no patients on anticoagulant medication were included. Langille 2013 and Baradaranfar 2017 did not mention any prohibited medications. Langille 2013 reported that no participants used acetylsalicylic acid preoperatively and there were no baseline differences in the use of systemic corticosteroids between the tranexamic acid and placebo group. Pannerselvam 2019 mentioned the exclusion of patients with thrombotic diathesis, however it did not specifically mention anticoagulant therapy. In this study all participants received prednisolone 1 mg/kg daily pre-operatively for five days plus intravenous amoxycillin-clavulanic acid 1200 mg twice daily the first 48 hours. Eldaba 2013 mentioned in addition that no non-steroidal anti-inflammatory drugs were allowed in the seven days before surgery.

Outcomes

Surgical field bleeding score

Studies reported a surgical field bleeding score according to Wormald (Athanasiadis 2007, Langille 2013, Pannerselvam 2019) or Boezaart (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Dongare 2018; El Shal 2015; Eldaba 2013; El-Ozairy 2021; Jabalameli 2006; Padhy 2019; Quiroga 2018; Yang 2021). Nuhi 2015 mentioned this outcome in their methods section, however they did not report it. Eleven studies were used in our meta-analyses.

Some studies reported the number of participants who were assigned each score (for example 0, 1, 2, 3, 4, 5). We calculated the mean score and standard deviation for each group based on these data (Alimian 2011; Dongare 2018; El Shal 2015; Eldaba 2013; Jabalameli 2006; Padhy 2019; Quiroga 2018). Langille 2013 reported median and range, which we transformed into

mean and standard deviation. The study El-Ozairy 2021 only reported median and interquartile range, therefore we transformed the data into mean and standard deviation.

El Shal 2015 assessed Boezaart's grading scale at multiple time points. We decided to use 30 minutes after starting surgery. The other time points (60, 90, 120, 150 minutes) were not used in the meta-analysis, because they would differ too much from the reported time points in other studies. Dongare 2018 reported Boezaart bleeding scores after 15, 30 and 45 minutes. Again we decided to use 30 minutes after starting surgery.

Athanasiadis 2007 presented mean scores for 2, 4, 6, 8 and 10 minutes after application of tranexamic acid or placebo for both low-dose and high-dose tranexamic acid. They reported both the Wormald and Boezaart scale. We chose to use the Boezaart scale and the 10-minute time point after surgery. In Eldaba 2013, the field was scored 15 and 30 minutes after starting surgery. We decided to use the values for 30 minutes after starting surgery. Jabalameli 2006, Quiroga 2018, Langille 2013 and Yang 2021 all reported intraoperative bleeding at one time point (unclear at what time during surgery). Pannerselvam 2019 reported the Wormald scale for the low and higher dose of tranexamic acid.

Intraoperative blood loss (mL)
Only Athanasiadis 2007 and El-Ozairy 2021 did not report this outcome. Twelve studies could be meta-analysed.

Significant adverse effects: seizures, thromboembolism within 12 weeks of surgery
All but five studies (Baradaranfar 2017; Jabalameli 2006; Langille 2013; Padhy 2019; Pannerselvam 2019) reported the occurrence of any significant adverse events, however none of the studies had a long follow-up. Therefore none of the studies could report events after a full 12-week follow-up period. All but one of the studies reported events only on the day of surgery, therefore our analysis is limited to 24-hour follow-up. Dongare 2018 mentioned follow-up for thrombotic complications until discharge home, however it remains unclear how long patients needed to be hospitalised after surgery.

Meta-analysis could only be performed for eight studies, because Athanasiadis 2007 used the left and right nostril from each patient as the intervention and control group. This complicates the interpretation of the relation of the effect to the type of treatment.

Duration of surgery (minutes)
All but four studies reported the duration of surgery (Athanasiadis 2007; Jabalameli 2006; Nuhi 2015; Padhy 2019). Ten studies could be meta-analysed.

Incomplete surgery and surgical complications
Langille 2013 and Padhy 2019 mentioned surgical complications and incomplete surgery. Both studies had a small sample size (N = 28 and N = 30 respectively).

Postoperative bleeding (placing of packing or revision surgery) in the first two weeks after surgery
Six studies reported on the occurrence of epistaxis, however follow-up was very short. All studies that reported this outcome reported epistaxis at least on the day of surgery (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Eldaba 2013; El Shal 2015; Yang 2021). Alimian 2011 had three days follow-up. Athanasiadis 2007 and Eldaba 2013 had unclear follow-up. Baradaranfar 2017 had follow-up for the length of hospitalisation, which was not reported. El Shal 2015 and Yang 2021 had follow-up for 24 hours. Due to this variability in outcome reporting we were only able to undertake a meta-analysis with results that are most likely limited to 24 to 72 hours of follow-up.

Funding sources

Three studies reported information about funding. Alimian 2011 was funded by department sources only. Baradaranfar 2017 was funded by a grant from Shahid Sadoughi University of Medical Sciences in Iran. Yang 2021 was supported by Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support.

Missing data

We contacted the authors of Nuhi 2015 and El-Ozairy 2021 with a request to provide means and standard deviations (SDs) for the intervention groups for missing clinically relevant outcomes. The authors contacted did not provide us with these data.

Excluded studies

We excluded 13 studies after reading the full text. Reasons for exclusion can be found in the Characteristics of excluded studies table.

We excluded five studies because they had the wrong study design (Athanasiadis 2009; Beule 2010; Kurozumi 1977; Shehata 2014; Yaniv 2006). Beule 2010 used a human fibroblast model to investigate wound healing. Nasal fibroblasts were used from three patients with chronic rhinosinusitis with nasal polyps and three controls and were grown in culture. Kurozumi 1977 was a non-randomised study in patients undergoing sinectomy using the Caldwell-Luc technique. Shehata 2014 was a non-randomised study in patients with chronic rhinosinusitis and compared topical tranexamic acid with hot water irrigation or normal saline. Yaniv 2006 was a non-randomised study in patients that underwent combined functional endoscopic sinus surgery with conchotomy and septoplasty with or without the use of oral tranexamic acid.

NCT00671281 was a study registration for a study that was cancelled.

IRCT2015092824241N1 used patients scheduled for elective open rhinoplasty and was therefore excluded. IRCT201203242963N7 2012 compared two different dosages of tranexamic acid without a placebo group. Chhappola 2011 was a study with patients undergoing endoscopic nasal surgery for a variety of indications, including nasal mass, sinusitis and septoplasty. Also patients were operated on under different circumstances, with about 70% of patients operated under local

anaesthesia and the others with more severe disease under general anaesthesia. Due to this heterogeneity in the type of patients and surgical procedures we excluded the study from this review. Kulkarni 2018 compared tranexamic acid with ethamsylate as single bolus. Jahanshahi 2014 compared topical tranexamic acid with topical phenylephrine and was therefore excluded (as was its trial registration IRCT201212139014N15). IRCT2015062021436N2 and Abbasi 2012 (with trial registration IRCT201203242963N7) investigated two different dosages of tranexamic acid, but no comparator group was present. We therefore excluded these studies.

Studies awaiting classification

We were unable to retrieve the full-text articles for Kurozumi 1976, 32971 2018, IRCT2012-111411455N1 2013 CRSSTD-7068603, IRCT2013012911822N3 2013 CRSSTD-7068595, IRCT2014031016924N1 2016 CRSSTD-7068683 and Moise 2010. Amal Das 2012 CRSSTD-7068696 was most likely a thesis or book chapter, although it could not be found by the Cochrane Information Specialist using a worldwide search. Athanasiadis 2009 was a full thesis exploring the progressive understanding of the interaction between haemostasis and wound healing with possible development of a novel agent. This thesis also could not be retrieved.

Ongoing studies

We found a trial registration for a double-blind, randomised, placebo-controlled trial in 112 adult patients with chronic rhinosinusitis requiring sinus endoscopic surgery in which intranasal pre-operative phenylephrine 0.05% and tranexamic acid at a dose of 15 mg/kg or placebo are compared with respect to bleeding during surgery (IRCT20180730040640N1). This study is currently recruiting.

We found another ongoing randomised controlled trial in adult patients with chronic rhinosinusitis requiring endoscopic sinus surgery (NCT03965767). In this study four treatment groups were used: an intravenous dose of 15 mg/kg of tranexamic acid with irrigation fluid 400 mL of normal saline; intravenous dose of 10 mL normal saline with irrigation fluid 400 mL of normal saline with 2 g of tranexamic acid added to it; intravenous dose of 15 mg/kg of tranexamic acid in a 10 mL with irrigation fluid 400 mL of normal saline with 2 g of tranexamic acid added to it; intravenous dose of 10 mL normal saline with irrigation fluid 400 mL of normal saline. The primary outcome is bleeding during surgery. This study should have completed recruitment.

We found another trial registration for a randomised controlled trial in 40 adults scheduled to undergo elective sinus or nasal surgery. Patients will be randomised to either intravenous tranexamic acid 1000 mg or normal saline solution. The study is recruiting (NCT04754230).

Another randomised controlled trial that is currently recruiting will investigate two different nebulised tranexamic acid dosages (500 mg or 1000 mg) compared to nebulised saline solution in 90 adults patients selected for elective functional endoscopic sinus surgery (NCT04905901).

The last ongoing randomised controlled trial is being performed in 47 adult patients who are candidates for FESS. It compares an injection of 250 mg/5 mL tranexamic acid with an injection of saline solution (TCTR20210531005).

See Characteristics of ongoing studies for a more detailed description of these studies.

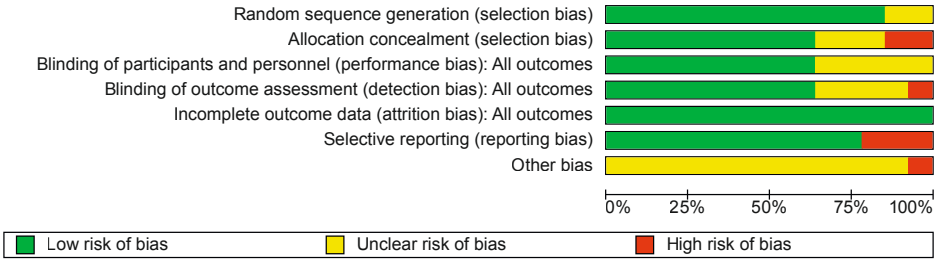

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

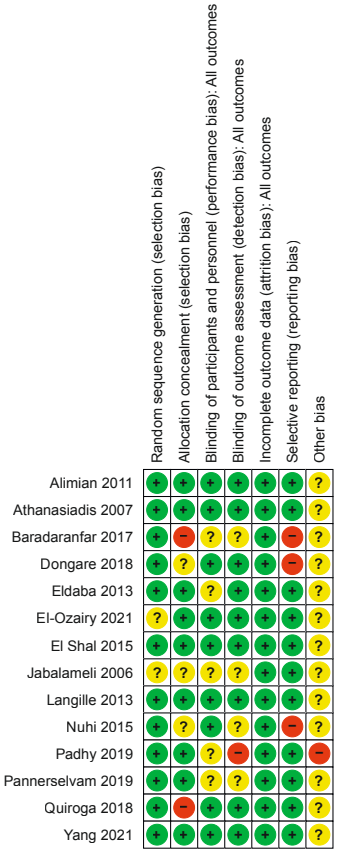

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Risk of bias in included studies

Full details of the risk of bias in the included studies can be found in the risk of bias tables (Characteristics of included studies). A risk of bias graph shows our judgements about each risk of bias item presented as percentages across all included studies (Figure 2). Details of the risk of bias for each study can be found in Figure 3.

Allocation

Sequence generation and allocation concealment

All included studies were randomised and controlled. We assessed Jabalameli 2006 and El-Ozairy 2021 as having unclear risk of bias for sequence generation, since the method of randomisation was not precisely described. We considered all other studies at low risk of bias for sequence generation. Alimian 2011, Baradaranfar 2017 and Dongare 2018 used a table of random numbers to divide participants. El Shal 2015 performed randomisation by means of computer-generated codes. Eldaba 2013 and Padhy 2019 performed randomisation using a computer-based random number generator. Langille 2013 and Pannerselvam 2019 used a block randomisation scheme. Nuhi 2015 performed randomisation using sequential numbers. Quiroga 2018 used simple random sampling for randomisation. Athanasiadis 2007 used computer randomisation. Yang 2021 used a computer-generated random number list and the allocation was sealed in an envelope.

We considered allocation concealment a low risk of bias in most studies. However, Baradaranfar 2017 used a random number table, without sealed envelopes. Quiroga 2018 used folded papers with numbers on: the odd number was assigned to the treatment group. Therefore we defined these two studies as being at high risk of bias. We classified Dongare 2018 and Jabalameli 2006 as at unclear risk for allocation concealment, since no information was presented about how and by whom the randomisation was performed, or how it remained concealed.

Blinding

Performance bias

We scored all but five studies as having a low risk of performance bias. Baradaranfar 2017 and Jabalameli 2006 did not provide information on who was blinded with respect to the study personnel or patients. Eldaba 2013, Padhy 2019 and Pannerselvam 2019 reported nothing about blinding of patients, therefore we feel that these studies have an unclear risk of bias.

Alimian 2011 mentioned that only the pharmacy involved was aware of the allocation of treatment. Athanasiadis 2007 was reported as a double-blinded study and mentioned that the surgical team was not aware of treatment allocation. Dongare 2018 reported that a blinded observer applied the contents of the syringes to the patients. It is unclear if the syringes were identical in colour/appearance. It was not specifically reported that patients were blinded to the treatment, but this is plausible. El Shal 2015 mentioned that anaesthesiologists,

surgeons and patients were blinded to study treatment. An anaesthesiologist not involved in the study prepared the syringes. El-Ozairy 2021 was double-blinded. A pharmacist prepared the drugs. Anaesthesiologist and surgeon were blinded to the category of study group. Langille 2013 mentioned that one investigator knew the randomisation and this person was responsible for preparing the study drugs. Other personnel and patients were blinded. In Nuhi 2015, participants and study staff were blinded to treatment allocation. Quiroga 2018 was a double-blind study and the surgeons and anaesthesiologists were blinded to treatment allocation. Yang 2021 mentioned that one researcher knew the randomisation code and prepared the sealed envelopes, which were blinded to the surgeons, patients and anaesthesiologists.

Detection bias

Most studies had low risk of detection bias. Baradaranfar 2017 and Jabalameli 2006 did not provide information on who was blinded as outcome assessor, so this is an unclear risk of bias. Padhy 2019 mentioned that the surgical team was blinded to treatment group to ensure blinding for the surgical field outcome score, however the anaesthesiologist was not blinded to the treatment group, being responsible for the calculation of total blood loss. Therefore we rated this as a high risk of bias.

Nuhi 2015 used the attending anaesthesiologist and the surgeon as outcome assessors, however it is unclear if they were part of the blinded study site staff. In Pannerselvam 2019, study staff were reported to be adequately blinded, but who assessed the primary and secondary outcome parameters remains unclear, although we can assume this was the surgical team. We rated both studies as having unclear risk of bias.

The other studies were adequately blinded. Alimian 2011 used the surgeons as outcome assessors and they were adequately blinded. Athanasiadis 2007 reported an independent observer who was adequately blinded. Dongare 2018 reported that the surgeons were blinded to treatment and performed the measurement of the bleeding score. El Shal 2015, Eldaba 2013 and El-Ozairy 2021 seemed to have adequate blinding of outcome assessors. Langille 2013 had two investigators blinded; only one investigator not involved in data extraction knew the allocation. In Quiroga 2018, only one surgeon performed all procedures and they were blinded to treatment allocation. Yang 2021 mentioned that the primary outcome was assessed by a surgically trained researcher who was blinded to the group allocation.

Incomplete outcome data

We assessed all studies as being at low risk of bias for incomplete outcome data. All patients randomised were reported and analysed. Since almost all outcomes were assessed during surgery or shortly afterwards this finding is not unexpected.

Selective reporting

We did not find published protocols for any of the studies except for Alimian 2011, El-Ozairy 2021, Langille 2013 and Yang 2021. In these studies all pre-specified outcomes were reported.

We assessed Baradaranfar 2017 as having a high risk of bias, because it is unclear how much of the total amount of irrigation fluid with tranexamic acid was used in each participant during surgery. Therefore we cannot be certain how much of the tranexamic acid was actually given to each patient. We considered Dongare 2018 to have a high risk of bias since the bleeding score was not reported at 60 minutes although measured, with no reason provided. Although we did not use this time point, we feel that it adds to a higher risk of bias in this study. We assessed Nuhi 2015 as having a high risk of bias because the surgical field bleeding score was not fully reported, which made it impossible to use for meta-analysis.

We assessed El Shal 2015, Eldaba 2013, El-Ozairy 2021, Jabalameli 2006, Padhy 2019, Pannerselvam 2019, Quiroga 2018 and Yang 2021 as having a low risk of bias, since all outcome parameters in the methods sections were adequately reported.

Other potential sources of bias

Baseline characteristics
All 14 included studies were randomised and controlled. Thirteen studies reported on baseline differences between intervention groups, with the exception of Padhy 2019. It is unclear whether there were baseline differences between groups and what these potentially were. We do not know how many males and females were included or what the participants' ages were. We interpreted this lack of reporting as a high risk of bias.

Other
In Dongare 2018, patients were followed up for thrombotic events until discharge. This period of time was probably variable for patients and the study does not specifically report on the duration of hospitalisation.

Effects of interventions

Tranexamic acid versus no treatment or placebo
See Summary of findings table 1.

We analysed the prespecified primary and secondary outcomes. Fourteen studies compared tranexamic acid with placebo, with a total of 942 participants (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Dongare 2018; Eldaba 2013; El Shal 2015; El-Ozairy 2021; Jabalameli 2006; Langille 2013; Nuhi 2015; Padhy 2019; Pannerselvam 2019; Quiroga 2018; Yang 2021). In three studies only topical tranexamic acid was applied (see Table 1). In 10 studies intravenous tranexamic acid was used (see Table 2). In one study either topical, intravenous or a combination was applied (El-Ozairy 2021). There was a lot of variation in the dosage of tranexamic acid used. Two studies compared two different dosages of topical tranexamic acid with placebo (see Table 3).

Subgroup analysis for chronic rhinosinusitis with or without nasal polyps, use of local or systemic corticosteroids in the month before surgery and use of thrombo-embolic prophylaxis could not be conducted due to incomplete reporting of these parameters by most studies.

Primary outcomes

Surgical field bleeding score

Thirteen studies assessed and adequately reported this outcome and were used for meta-analysis (n = 428 tranexamic acid and n = 344 placebo) (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Dongare 2018; Eldaba 2013; El-Ozairy 2021; El Shal 2015; Jabalameli 2006; Langille 2013; Padhy 2019; Pannerselvam 2019; Quiroga 2018; Yang 2021). Langille 2013 and Pannerselvam 2019 used the Wormald scale. The Boezaart scale was used by the other included studies.

When we combined the studies we found evidence that tranexamic acid likely results in a large reduction in the surgical field bleeding score compared with placebo, with a standardised mean difference (SMD) of -0.87 (95% confidence interval (CI) -1.23 to -0.51, random-effects model; P < 0.0001; 13 studies, 772 participants; moderate-certainty evidence) (Analysis 1.1). This can be interpreted as a large effect (< -0.70) (Cohen 1988; Handbook 2011). There was considerable heterogeneity in this analysis ($Chi^2 = 61.11$; $I^2 = 80\%$).

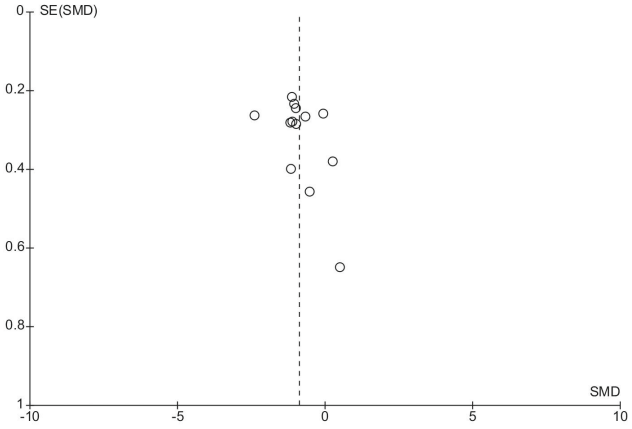

Figure 4. Funnel plot (1.1 Surgical field bleeding score (during surgery))

The funnel plot showed slight asymmetry (Figure 4). After a sensitivity analysis excluding studies with a total population of fewer than 30 participants, the asymmetry did not entirely disappear from the funnel plot and the direction of treatment effect did not change compared to the main analysis (Analysis 1.7; Figure 5). A fixed-effect model analysis did not change the overall treatment effect (Analysis 1.8).

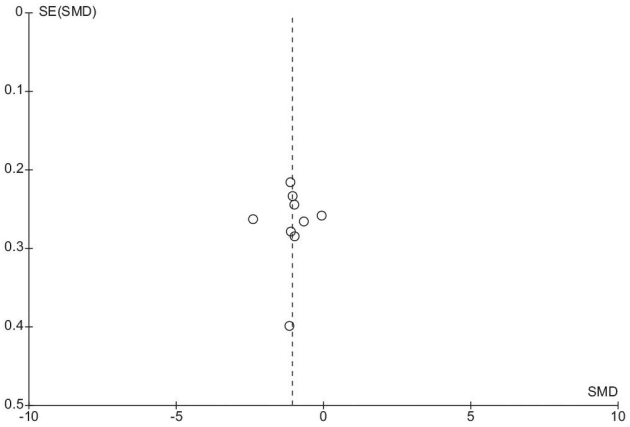

Figure 5. Funnel plot (1.7 Surgical field bleeding score (during surgery) excluding small sized studies)

Subgroup analyses

The route of administration of tranexamic acid was mainly intravenous. Only four studies applied topical tranexamic acid (Athanasiadis 2007; Baradaranfar 2017; El-Ozairy 2021; Jabalameli 2006). In the study El-Ozairy 2021 patients received either intravenous, topical or combined intravenous/topical tranexamic acid. One can assume that the mechanism of action by which the agent diminishes bleeding is different. We therefore performed subgroup analyses, primarily for the method of administration.

When comparing routes of administration we found evidence of subgroup differences (test for subgroup differences: $Chi^2 = 25.41$, df = 2 ($P < 0.00001$), $I^2 = 92.1\%$; Analysis 1.3). We could not use the intravenous tranexamic subgroup from El-Ozairy 2021 for subgroup analysis because the calculated standard deviation was 0.

Only one study was performed solely in children (Eldaba 2013). There was no evidence of a difference between the younger and adult subgroup (test for subgroup differences: $Chi^2 = 0.02$, df = 1 ($P = 0.88$), $I^2 = 0\%$; Analysis 1.2). We could not use Padhy 2019 in this subgroup analysis because they did not report baseline characteristics in both groups.

A subgroup analysis of dosages (nine different dosages used in 13 studies) showed evidence of a subgroup difference (test for subgroup differences: $Chi^2 = 41.92$, df = 9 ($P < 0.00001$), $I^2 = 78.5\%$; Analysis 1.4). There was evidence of a difference in favour of tranexamic acid in the subgroups intravenous 10 mg/kg, intravenous 5 mg/kg or 15 mg/kg, intravenous 15 mg/kg, intravenous 25 mg/kg, topical 1000 mg and intravenous 15 mg/kg with topical 2000 mg. However, we noted no evidence of a difference between tranexamic acid and control for the other dose subgroups (intravenous 500 mg, topical 100 mg or 1000 mg, topical 2000 mg, intravenous 15 mg/kg + infusion 1 mg/kg).

There was no evidence of a subgroup difference between types of anaesthesia (test for subgroup differences: $Chi^2 = 0.21$, df = 2 (P = 0.90), $I^2 = 0\%$; Analysis 1.5). Athanasiadis 2007 and Padhy 2019 could not be used for meta-analysis because they did not report the type of anaesthesia used.

Finally there was no evidence of a subgroup difference between use of pre- or intraoperative vasoconstrictive agents (test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.86), $I^2 = 0\%$; Analysis 1.6). Three studies could not be used for subgroup analysis because they did not report the use of any vasoconstrictive agents (Athanasiadis 2007; Baradaranfar 2017; El Shal 2015).

Intraoperative blood loss

Twelve studies reported useful data on this outcome (n = 428 tranexamic acid and n = 374 placebo) (Alimian 2011; Baradaranfar 2017; Dongare 2018; Eldaba 2013; El Shal 2015; Jabalameli 2006; Langille 2013; Nuhi 2015; Padhy 2019; Pannerselvam 2019; Quiroga 2018; Yang 2021). Combining the results of 12 studies we found that tranexamic acid may result in a slight reduction in blood loss during surgery compared to placebo with a mean difference (MD) of -70.32 mL (95% CI -92.28 to -48.35 mL, P < 0.00001, random-effects model; 12 studies, 802 participants; $Chi^2 = 204.40$; $I^2 = 95\%$, low-certainty evidence) (Analysis 1.9). We feel that the mean difference of -70.32 mL is not clinically relevant.

The funnel plot showed slight asymmetry, probably indicating larger treatment effects for smaller studies (Figure 6). After a sensitivity analysis excluding studies with a total population of fewer than 30 participants, the asymmetry did not fully disappear and the direction of treatment effect did not change compared to the main analysis (Analysis 1.15; Figure 7). A fixed-effect model analysis showed a smaller main treatment effect than the random-effects model, suggesting that tranexamic acid is more effective in the smaller studies (Analysis 1.16).

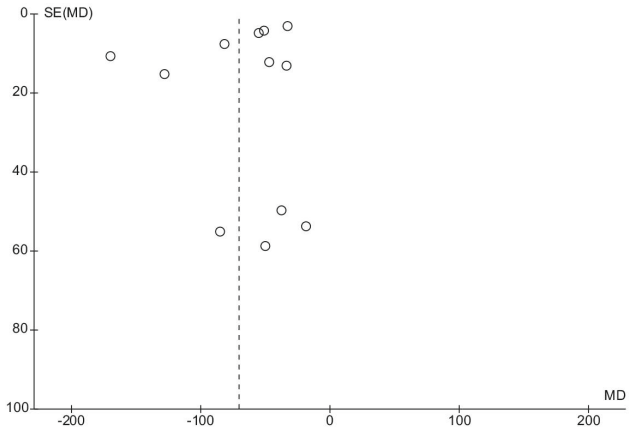

Figure 6. Funnel plot (1.9 Intraoperative blood loss (mL))

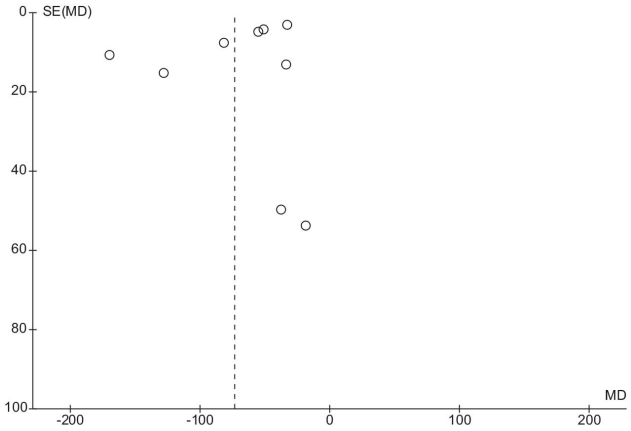

Figure 7. Funnel plot (1.15 Intraoperative blood loss (mL) excluding small sized studies)

Subgroup analyses

Subgroup analyses for age (adults versus children) (P = 0.10; Analysis 1.10), route of administration (P = 0.24; Analysis 1.11), type of anaesthesia (P = 0.13; Analysis 1.13) and use of vasoconstrictive agents (P = 0.56; Analysis 1.14) showed no evidence of a difference between subgroups.

A subgroup analysis of dosages (eight different dosages used in 12 studies) showed evidence of a subgroup difference (test for subgroup differences: $Chi^2 = 64.31$, df = 7 (P < 0.00001), $I^2 = 89.1\%$). We noted evidence of a difference in favour of tranexamic acid in the subgroups intravenous 5 mg/kg, intravenous 10 mg/kg, intravenous 15 mg/kg, intravenous 25 mg/kg and topical 1000 mg (Analysis 1.12).

We could not use Padhy 2019 in the age subgroup meta-analysis, because they did not report baseline characteristics in both groups. Nuhi 2015 and Padhy 2019 could not be included in Analysis 1.13, because the type of anaesthesia was not reported. El Shal 2015 and Nuhi 2015 were not included in Analysis 1.14, because the use of vasoconstrictors was not reported.

Possible reasons for heterogeneity should be viewed in the light of clinical diversity and could be the following:

- Participants across studies most likely had different degrees of disease.
- Some studies included participants with chronic rhinosinusitis with nasal polyps and other studies only participants with chronic rhinosinusitis without nasal polyps or mixed disease.
- Different methods of calculation of total blood loss were used (e.g. weight of gauze pads or sponges, blood in suction bottles).
- Different surgical instruments were used (grabbing, cutting and debrider devices).

One study used topical tranexamic acid (Jabalameli 2006); the other 11 studies used intravenous tranexamic acid. We estimated the quality of Jabalameli 2006 to be low and therefore we cannot be certain whether there is an actual difference between treatment modalities in reducing intraoperative blood loss.

Significant adverse effects (seizures, thromboembolism within 12 weeks of surgery)
There were eight studies (N = 664) that could be meta-analysed (Alimian 2011; Dongare 2018; Eldaba 2013; El Shal 2015; El-Ozairy 2021; Nuhi 2015; Quiroga 2018; Yang 2021). When we combined studies we found that tranexamic acid probably has little to no effect on the development of significant adverse events (seizures or thromboembolism) within 24 hours of surgery, with no events in either group (risk difference (RD) 0.00, 95% CI -0.02 to 0.02; 8 studies, 664 participants; moderate-certainty evidence) (Analysis 1.17). In Athanasiadis 2007, which was not included in this meta-analysis due to a split-body design, no adverse effects occurred in either group.

Follow-up was not as long as 12 weeks after surgery in any of the studies that reported on adverse effects. All studies reported events on the day of surgery, except for Dongare 2018, in which thrombo-embolic events were evaluated up until discharge (but it is unknown when patients were discharged after surgery). Therefore our results are limited.

Secondary outcomes

Duration of surgery
Ten studies were suitable for meta-analysis, comprising participants that received intravenous tranexamic acid (Alimian 2011; Dongare 2018; Eldaba 2013; El Shal 2015; Langille 2013; Pannerselvam 2019; Quiroga 2018; Yang 2021), topical tranexamic acid (Baradaranfar 2017), or either intravenous, topical or combined tranexamic acid (El-Ozairy 2021). We found that tranexamic acid probably results in a small difference in the duration of surgery with a mean difference (MD) of -13.04 minutes (95% CI -19.27 to -6.81, P < 0.00001, random-effects model; 10 studies, 666 participants; moderate-certainty evidence) (Analysis 1.18).

The funnel plot showed asymmetry (Figure 8). This probably does not indicate reporting bias, but might rather be the effect of heterogeneity in study design or a larger effect from the small studies. After a sensitivity analysis excluding studies with a total population of fewer than 30 participants, the asymmetry did disappear from the funnel plot (Analysis 1.24; Figure 9). Baradaranfar 2017 and Quiroga 2018 found no differences in surgical time between the two intervention groups. Quiroga 2018 was a small study with only 10 participants. Baradaranfar 2017 did not report the actual dose given to the patient. A fixed-effect model analysis did not change the overall treatment effect (Analysis 1.25).

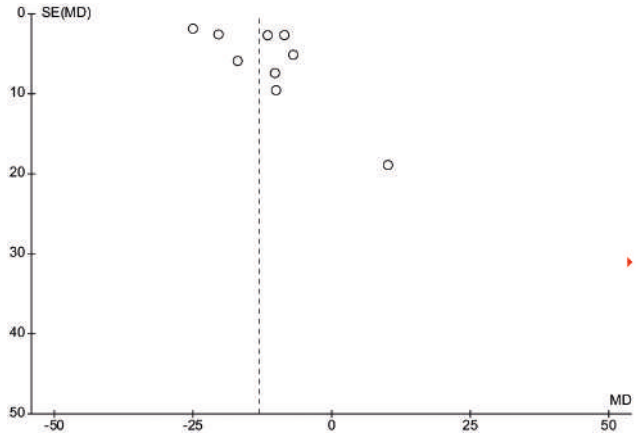

Figure 8. Funnel plot (1.18 Duration of surgery (minutes))

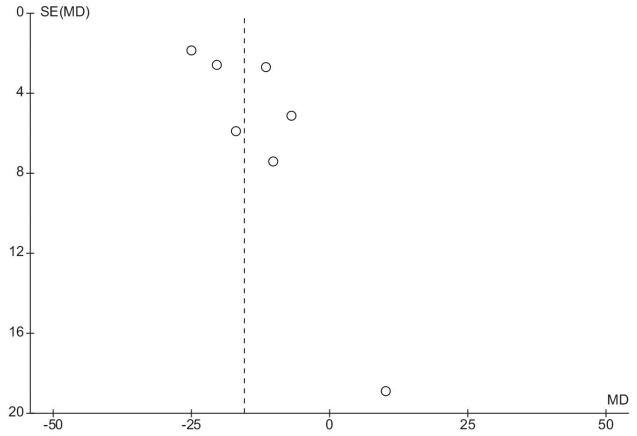

Figure 9. Funnel plot (1.24 Duration of surgery (minutes) excluding small sized studies)

Subgroup analyses

There was substantial heterogeneity in the main analysis ($Chi^2 = 48.41$; $I^2 = 81\%$). This heterogeneity might be due to diversity in the extensiveness of surgery and the presence or absence of nasal polyps. Subgroup analysis for route of administration (P = 0.33; Analysis 1.19), type of anaesthesia (P = 0.28; Analysis 1.21), use of peri- or preoperative vasoconstrictors (P = 0.81; Analysis 1.22) and population age (P = 0.05; Analysis 1.23) showed no evidence of a difference between subgroups.

El Shal 2015 could not be included in Analysis 1.22, because this information was not reported by the study. There was evidence of subgroup differences in the duration of surgery for dosage, probably due to the large heterogeneity (eight different dosages used and compared, within 10 studies (test for subgroup differences: $Chi^2 = 91.65$, df = 7 ($P < 0.00001$), $I^2 = 92.4\%$; Analysis 1.20). We noted evidence of a difference in favour of tranexamic acid in the subgroups: intravenous 5 mg/kg, intravenous 15 mg/kg, intravenous 25 mg/kg, intravenous 15 mg/kg plus 400 mL

saline solution with 2 g tranexamic acid. However, we noted no evidence of a difference between tranexamic acid and control for the other dose subgroups (intravenous 500 mg, intravenous 10 mg/kg, intravenous 15 mg/kg + 1 mg/kg/hour, topical 2000 mg).

Incomplete surgery
The only two studies reporting this outcome were Langille 2013 and Padhy 2019. There were no incidents of incomplete surgery in either treatment group (RD 0.00, 95% CI -0.09 to 0.09; 2 studies, 58 participants; moderate-certainty evidence) (Analysis 1.26). Tranexamic acid probably neither increases nor decreases the incidence of incomplete surgery.

Surgical complications
The only two studies reporting this outcome were Langille 2013 and Padhy 2019. In the total of 58 participants no surgical complications were seen (RD 0.00, 95% CI -0.09 to 0.09; 2 studies, 58 participants; moderate-certainty evidence) (Analysis 1.27). Tranexamic acid likely results in little to no difference in surgical complications.

Postoperative bleeding (placement of packing or revision surgery) in the first two weeks after surgery
Six studies investigated postoperative bleeding, comprising 404 patients (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Eldaba 2013; El Shal 2015; Yang 2021). In all studies follow-up was limited to one to three days after surgery for this outcome. There were no postoperative bleeding events in the tranexamic acid group. Alimian 2011 reported that one participant in the placebo group experienced postoperative bleeding within three days after surgery. El Shal 2015 reported that one participant in the placebo group experienced postoperative bleeding within 24 hours of surgery. Tranexamic acid may not change the likelihood of postoperative bleeding in the first three days after surgery (placement of packing or revision surgery) (RD -0.01, 95% CI -0.03 to 0.02; 6 studies, 404 participants; low-certainty evidence) (Analysis 1.28). A fixed-effect analysis did not change the result (Analysis 1.29).

DISCUSSION

Summary of main results

See Summary of findings table 1.

The primary outcome measures in this review were surgical field bleeding score, intraoperative blood loss and significant adverse effects (seizures and thromboembolism within 12 weeks after surgery). In total, we included 14 studies. The primary subgroup analysis of interest was the method of administration of tranexamic acid (either topical or intravenous).

In the 13 included studies that evaluated surgical field bleeding score as an outcome we found moderate-certainty evidence that tranexamic acid likely results in a large decrease in surgical field bleeding score compared to placebo. Tranexamic acid was used in a topical

fashion in four studies, topical and/or intravenous in one study, and intravenous in the other eight studies. Subgroup analyses by age, type of anaesthesia and use of pre- or intraoperative vasoconstrictors did not indicate subgroup differences. We noted evidence of a difference in favour of tranexamic acid with the combined administration and intravenous administration. We noted evidence of a difference in favour of tranexamic acid for a dose of intravenous 5 mg/kg, intravenous 10 mg/kg, intravenous 15 mg/kg, intravenous 25 mg/kg, topical 1000 mg and intravenous 15 mg/kg with topical 2000 mg. However, no evidence of a difference was noted between tranexamic acid and control for the other dose subgroups. These other dose subgroups were used in the smallest studies, which might be an explanation. Furthermore, in the study using topical 2000 mg in 400 mL saline whenever the field became obscured, we do not know how much tranexamic acid each patient received (Baradaranfar 2017).

We combined 12 studies, which suggested that tranexamic acid may slightly reduce blood loss during surgery (mL) compared to placebo (low-certainty evidence). Subgroup analysis for age, administration route, method of administration, population, type of anaesthesia and use of pre- or intraoperative vasoconstrictors did not change the direction of the overall treatment effect. Evidence of a difference in favour of tranexamic was noted in the subgroups intravenous 5 mg/kg, intravenous 10 mg/kg, intravenous 15 mg/kg, intravenous 25 mg/kg and topical 1000 mg. However, no evidence of a difference was noted between tranexamic acid and control for the other dose subgroups. Again, these other dose subgroups were used in the smallest studies and again we do not know how much tranexamic acid each patient received in Baradaranfar 2017.

Topical application was used in only one study in this analysis (Jabalameli 2006). We considered this study to have unclear risk of bias for allocation concealment and blinding. We therefore cannot establish whether topical application of tranexamic acid leads to a reduction in blood loss.

No study reported on significant adverse effects with a follow-up of 12 weeks. Our evidence is therefore limited to 24 hours of follow-up after surgery. Evidence from eight included studies showed that, compared to placebo, tranexamic acid probably has little to no effect on the development of immediate significant adverse events (seizures or thromboembolism) within 24 hours of surgery, with no events in either group (moderate-certainty evidence), but there is no evidence regarding the risk of serious adverse effects more than 24 hours after surgery. Considering the biochemical properties of tranexamic acid one would expect adverse events to occur fast in the case of a single dose of the medicine (day of surgery). Tranexamic acid prevents haemorrhage by inhibiting plasminogen (and so stabilising clot formation). The route of administration and metabolism play a significant role. About 90% of an intravenous dosage of this drug is excreted in the urine within 24 hours. The half-life of the drug is two hours. If the drug is repeatedly administered then the drug will still be present in the body and active in the tissue for almost 24 hours. We feel that in this case, where all patients received tranexamic acid only on the day of surgery, a 12-week follow-up would probably not lead to more seizures or thromboembolism.

In the eight studies that we meta-analysed for duration of surgery the results suggest that tranexamic acid probably results in a small difference in the duration of surgery compared to placebo (moderate-certainty evidence). Subgroup analysis by age, route of administration, type of anaesthesia and use of pre- or intraoperative vasoconstrictors did not show a different direction of the overall treatment effect. Evidence of a difference in favour of tranexamic acid was noted in the subgroups: intravenous 5 mg/kg, intravenous 15 mg/kg, intravenous 25 mg/kg, intravenous 15 mg/kg plus 400 mL saline solution with 2 g tranexamic acid. Topical application was used in only two studies in this analysis (Baradaranfar 2017; El-Ozairy 2021). We therefore cannot establish whether topical application of tranexamic acid influences the duration of surgery.

Completeness of surgery and surgical complications were only recorded in two small studies using intravenous tranexamic acid. Tranexamic acid probably neither increases nor decreases the incidence of incomplete surgery, with no events in either group (moderate-certainty evidence) and likely results in little to no difference in surgical complications, again with no events in either group (moderate-certainty evidence), although the numbers are too small to draw firm conclusions.

When we pooled six studies (two topical application and four intravenous application) we found that tranexamic acid may not change the likelihood of postoperative bleeding (placement of packing or revision surgery within two weeks of surgery) (low-certainty evidence). The follow-up in the included studies was limited to one to three days after surgery, instead of the aimed for two weeks follow-up. Two events were recorded in the placebo group, compared to zero events in the tranexamic acid group.

Overall completeness and applicability of evidence

The 14 included studies in this review only addressed some of the review questions and the evidence is not complete.

The participants included in this review were both children and adults and form a representative sample, although few studies reported the extent of nasal disease, which could well influence outcomes such as duration of surgery and blood loss.

The included studies highlight the different delivery modalities used and dosing differences. With the currently available evidence we are not able to answer the question of whether there is any clear beneficial effect of intravenous administration over topical administration or vice versa; nor are we able to conclude whether there is a preferential dose of tranexamic acid. Based on subgroup analysis, the evidence with respect to surgical field bleeding score and duration of surgery suggests a benefit of intravenous application over topical application and that an intravenous dose › 500 mg for adults may be optimal (at least 5 mg/kg). However, due to the large heterogeneity in dosing (which leads to fewer options for pooling dosages), in combination with the small sample sizes, no clear conclusions can be drawn. We did not find

a clear dose-response relationship for either beneficial or harmful effects and other available literature did not provide more clarity (Abu-Zaid 2022; Leverett 2022). In a large systematic review and meta-analysis of 216 studies comprising 125,550 patients undergoing surgical procedures, no dose-dependent association with thrombo-embolic events was detected (Taeuber 2021).

For the primary outcome, bleeding score, it was unclear in four studies used in the meta-analysis at what time point the bleeding score was calculated. For the other included studies the scores represent 10 to 30 minutes after the start of surgery or after the administration of tranexamic acid. Therefore we could not establish at which time point the most effect of tranexamic acid would be expected.

There was a lack of studies investigating completeness of surgery and surgical complications as outcome parameters. The evidence regarding adverse events is limited to 24 hours follow-up postoperatively, which might be sufficient considering the specific adverse events of interest (seizures and thromboembolic events), however it would have been preferential to have a longer follow-up after surgery. The same follow-up duration was used for postoperative bleeding, which was not recorded for a follow-up duration of two weeks in any of the studies. We feel that this is insufficient for this outcome.

Quality of the evidence

The evidence in this review (14 studies with a total of 942 participants) is not fully sufficient to allow robust conclusions to be drawn. The certainty of evidence for the outcomes assessed ranged from low to moderate. We downgraded the evidence for all outcomes mainly because of imprecision, indirectness or heterogeneity. See Summary of findings table 1.

Potential biases in the review process

This review is based on a published protocol (Ravesloot 2017). There have been some changes to the search methods (see Differences between protocol and review). The search terms used should have identified all randomised controlled trials comparing the use of tranexamic acid during endoscopic sinus surgery to placebo (saline solution) or no tranexamic acid. The methodology of the review is unlikely to have introduced any bias into the review process.

We did decide to proceed with meta-analysis even in the presence of statistical heterogeneity. We feel that there will always be clinical and methodological diversity in this area. We have quantified the level of heterogeneity in order to be able to interpret the impact on the meta-analysis. We chose the random-effects model for data synthesis in all analyses and additional fixed-effect analysis if relevant.

For the surgical field bleeding score outcome we had to make some modifications to be able to perform meta-analysis. We transformed N (%) or median and ranges into means (SD). We chose to use one measurement per study (highest time point after start of surgery), with a

maximum of 30 minutes after surgery, to assess bleeding score because most studies reported within 30 minutes of surgery.

Agreements and disagreements with other studies or reviews

We are aware of two systematic reviews that have looked into the role of tranexamic acid in nasal surgery (Kim 2019; Pundir 2013). Pundir 2013 also included rhinoplasty and septoplasty and identified six of the studies included in our review (Alimian 2011; Athanasiadis 2007; Baradaranfar 2017; Jabalameli 2006; Langille 2013; Nuhi 2015). They concluded that intraoperative use of topical and intravenous tranexamic acid could significantly reduce estimated blood loss and improve surgical field quality, but highlighted that it would probably not reduce operation time. Kim 2019 included seven studies (Alimian 2011; Dongare 2018; El Shal 2015; Langille 2013; Nuhi 2015; Chhappola 2011; Moise 2010), five of which were also included in our review (Alimian 2011; Dongare 2018; El Shal 2015; Langille 2013; Nuhi 2015), and two of which we excluded (Chhappola 2011; Moise 2010). They concluded that the systemic administration of tranexamic acid could decrease operative time and intraoperative blood loss, and increase the satisfaction of surgeons. Both reviews drew conclusions within the limitations of the small number of studies available, the heterogeneity in the surgeries performed and the different dosing schemes used. The mainly low- and moderate-certainty evidence in our review points in the same direction as these two reviews.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-certainty evidence that topical or intravenous tranexamic acid probably reduces the surgical field bleeding score substantially within 30 minutes of the start of surgery or application of tranexamic acid. There is low-certainty evidence that tranexamic acid may slightly reduce intraoperative blood loss. Whilst there is moderate-certainty evidence that tranexamic acid probably does not lead to more immediate significant adverse events compared to placebo, there is no evidence regarding the risk of serious adverse events more than 24 hours after surgery.

There is moderate-certainty evidence that tranexamic acid probably results in a small difference in the total duration of surgery. There is not enough evidence available to draw robust conclusions about incomplete surgery or surgical complications. There is low-certainty evidence that tranexamic acid may not change postoperative bleeding within three days of surgery. Unfortunately, there is no evidence with respect to adverse events at a longer duration of follow-up.

Implications for research

Most included randomised controlled trials were performed after 2013, although two studies were performed in 2006 and 2007. This review has found evidence that there is a general benefit of tranexamic acid during endoscopic sinus surgery with respect to surgical field

bleeding score, intraoperative blood loss and duration of surgery. Since there was a great deal of heterogeneity in the included studies the effect size cannot be estimated with high certainty. The only study that fully reported on important potential effect modifiers was Langille 2013. It is highly desirable for upcoming trials to report relevant baseline characteristics such as the severity of disease for which endoscopic sinus surgery is required, the extent of surgery, the surgical position of the patient and the surgical instruments used. More randomised controlled trials would be informative and should help to identify a preferable dose or route of administration of tranexamic acid. The main focus should be on surgical complications and adverse events, with a longer duration of follow-up after surgery than in the current studies.

Acknowledgements

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Evidence Synthesis Programme, NIHR, NHS or the Department of Health.

Editorial and peer reviewer contributions

Cochrane ENT supported the authors in the development of this review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Professor Martin Burton, Co-ordinating Editor, Cochrane ENT.
- Managing Editor (selected peer reviewers, collated peer reviewer comments, provided editorial guidance to authors, edited the article): Jenny Bellorini, Cochrane ENT.
- Copy Editor (copy editing and production): Jenny Bellorini, Cochrane ENT.
- Peer reviewers (provided comments and recommended an editorial decision): Professor Carl Philpott, Department of Medicine, Norwich Medical School, University of East Anglia (clinical/content review), Samuel MacKeith, Assistant Co-ordinating Editor Cochrane ENT (clinical/content review), Adrian James, Editor Cochrane ENT (clinical/content review), Richard Harvey, Editor Cochrane ENT (clinical/content review), Richard Rosenfeld, Editor Cochrane ENT (clinical/content review), Jacqueline Coupe (consumer review), Brian Duncan (consumer review), Nuala Livingstone (methods review).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [*ordered by study ID*]

Alimian 2011

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment only once during surgery and a 3-day follow-up
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Department of Anesthesiology, Rasul Akram Hospital, Teheran University of Medical Science, Teheran, Iran **Study dates:** June 2008 to February 2009 **Sample size:** 84 **Number randomised:** 84 **Participant (baseline) characteristics:** Median age: 35 (average for treatment groups altogether) Gender (male/female): 25/17 (TXA), 24/18 (placebo) Application of Trendelenburg position during surgery: not mentioned Use of vasoconstrictive agents pre- or intraoperative: none used Use of anaesthesia: total intravenous anaesthesia (TIVA) Mean arterial pressure: equal in both groups Surgical instruments applied: cutting forceps, grabbing instruments Presence of polyps, active infection or fungal rhinosinusitis: unclear **Inclusion criteria:** patients aged 19 to 64 years scheduled for endoscopic sinus surgery for CRS **Exclusion criteria:** patients receiving anticoagulants or having a bleeding diathesis
Interventions	**Tranexamic acid (N = 42):** intravenous bolus of 10 mg/kg TXA after induction of TIVA **Placebo (N = 42):** intravenous bolus of 0.1 mL/kg sterile water after induction of TIVA **Additional interventions:** TIVA and all patients underwent ESS
Outcomes	**Primary outcome:** Surgical field bleeding score (Boezaart grading system for bleeding during endoscopic sinus surgery) Intraoperative blood loss (mL) Significant adverse effects: seizures, thromboembolism within 3 days of surgery **Secondary outcomes:** Duration of surgery (minutes) Postoperative bleeding (placing of packing or revision surgery) in the first 3 days after surgery **Other outcomes reported by the study:** Surgeon satisfaction score of surgical field Comparison of pre- and postoperative coagulation parameters
Funding sources	Departmental sources only
Declarations of interest	None declared
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: hospital pharmacy randomised by using a table of random numbers. Probably done and not visible for study personnel.
Allocation concealment (selection bias)	Low risk	Comment: patients and medical personnel were unaware of the table with random numbers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: only the pharmacy was aware of the allocation. After the allocation and during the surgery no medical personnel involved in the care of the patient were aware of the study assignment. It is not reported how long the blinding was after surgery.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: surgeons were outcome assessors and they were adequately blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no patients dropped out of the study.
Selective reporting (reporting bias)	Low risk	Comment: there is a trial registration available and all outcomes are reported.
Other bias	Unclear risk	No obvious further issues.

Athanasiadis 2007

Study characteristics	
Methods	Parallel-group randomised controlled trial, with unclear follow-up
Participants	**Location:** Australia, 1 site **Setting of recruitment:** Department of Otorhinolaryngology, Head and Neck Surgery, The Queen Elizabeth Hospital, University of Adelaide, Australia **Study dates:** January to December 2005 **Sample size:** 20 **Number randomised:** 20 **Participant (baseline) characteristics:** Median age: 51 (range 19 to 79) Gender (male/female): 19/11 Application of Trendelenburg position during surgery: not mentioned Use of vasoconstrictive agents pre- or intraoperative: not mentioned Use of anaesthesia: not mentioned Mean arterial pressure: equal in both groups Surgical instruments applied: unclear Presence of polyps, active infection or fungal rhinosinusitis: unclear **Inclusion criteria:** patients aged › 18 years scheduled for ESS involving complete sphenoidectomy and frontal recess clearance for CRS **Exclusion criteria:** patients with asymmetric disease, known allergy to antifibrinolytics, pregnancy or breastfeeding, bleeding diathesis, anticoagulant medication
Interventions	**Tranexamic acid 100 mg one nostril (N = 10):** 100 mg TXA applied during surgery **Tranexamic acid 1000 mg one nostril (N = 10):** 1000 mg TXA applied during surgery **Placebo contralateral nostril (N = 20):** not mentioned what agent was applied **Additional interventions:** unclear
Outcomes	**Outcomes (primary and secondary not specifically reported)** Surgical field grade using Wormald and Boezaart grading scale INR and aPTT pre- and post application of topical agents Adverse events: thrombus development and postoperative epistaxis
Funding sources	Not reported
Declarations of interest	Not reported
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "by computer randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "to a code in a sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The surgical team and the independent observer thus were blinded as to which agent the patient was receiving". The study is reported to be double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The surgical team and the independent observer thus were blinded as to which agent the patient was receiving"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no exclusions reported. All included patients were analysed. Both grading scales are reported as mentioned in the 'Aims' section.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes are reported.
Other bias	Unclear risk	Comment: no other obvious issues.

Baradaranfar 2017

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment during surgery and follow-up for the length of hospitalisation
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Otorhinolaryngology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran **Study dates:** unclear **Sample size:** 60 **Number randomised:** 60 **Participant (baseline) characteristics:** Mean age: 38.6 (TXA), 40.7 (placebo) Gender (male/female): 22/8 (TXA), 21/9 (placebo) Lund-Mackay score (mean): 15.7 (TXA), 16.8 (placebo) Application of Trendelenburg position: not reported Use of vasoconstrictive agents pre- or intraoperative: epinephrine 1/2000-soaked pledges were used when there was excessive bleeding based on surgeon preference Use of anaesthesia: combined total anaesthesia TIVA/inhalational N20 Mean arterial pressure: not reported Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: all patients had nasal polyps **Inclusion criteria:** CRSwNP patients who did not respond to medical treatment and were candidates for ESS **Exclusion criteria:** previous sinus or nasal surgery, underlying disease with increased risk of thrombosis (hypercoagulable states) such as Factor V Leiden, antiphospholipid syndrome, heparin-induced thrombocytopenia, cancer, pregnancy, high blood pressure (systolic › 140 mmHg and/or diastolic › 90 mmHg), contraindications for the use of tranexamic acid (active clot inside arteries), and patient unwillingness or participation in other similar clinical trials
Interventions	**Tranexamic acid (n = 30):** 2 g in 400 mL saline solution rinsed during surgery whenever the field became obscured **Placebo (n = 30):** normal saline solution 400 mL rinsed during surgery whenever the field became obscured **Additional interventions:** TIVA/inhalational N20, all patients underwent ESS and received systemic prednisone 1 mg/kg for 5 days before surgery. Epinephrine 1/2000-soaked pledges were used when there was excessive bleeding during surgery as preferred by surgeon.
Outcomes	**Primary outcome:** Intraoperative blood loss (mL) **Secondary outcomes:** Duration of surgery (minutes) Surgical field bleeding score (Boezaart grading system for bleeding during endoscopic sinus surgery) **Other outcomes reported by the study:** Surgeon satisfaction score (Likert scale) Complications during surgery and hospitalisation

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Baradaranfar 2017 *[continued]*

Study characteristics	
Funding sources	Study supported by a grant from Shahid Sadoughi University of Medical Sciences,Yazd, Iran
Declarations of interest	None declared
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly divided"
Allocation concealment (selection bias)	High risk	Quote: "using a random number table"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the surgical team were unaware which solution was used for each patient. However, it is unclear who prepared the solutions and how they were presented. Unclear if anaesthesia team was blinded (and if mean blood loss was estimated by them).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: unclear who assessed mean total blood loss during surgery.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no patients dropped out of the study.
Selective reporting (reporting bias)	High risk	Comment: the total amount of irrigation fluid used in each patient during surgery is also unclear.
Other bias	Unclear risk	No further obvious issues.

Dongare 2018

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment once during surgery
Participants	**Location:** India, probably 1 site **Setting of recruitment:** Department of Anaesthesia and Critical Care, probably in the General Hospital, Pune, Maharashtra, India **Study dates:** unclear **Sample size:** 60 **Number randomised:** 60 **Participant (baseline) characteristics:** Age (mean, SD): 39.0 (± 8.5) (TXA), 40.2 (± 9.7) (control) Weight (kg, mean, SD) 62.1 (± 6.9) 63.2 (± 8.5) (control) Gender (male/female): 13/17 (TXA), 15/15 (control) Application of Trendelenburg position: yes in both groups Use of vasoconstrictive agents pre- or intraoperative: infiltration with 5 mL to 6 mL of 2% lignocaine with adrenaline (1:200000) Use of anaesthesia: induction with propofol, maintenance with isoflurane Mean arterial pressure: equal in both groups Surgical instruments applied: the instruments and microdebrider were the same in both groups (unclear specifics of instruments used) Presence of polyps, active infection or fungal rhinosinusitis: all patients had chronic rhinosinusitis with nasal polyps **Inclusion criteria:** ASA grade I and II patients Age 18 to 60 years Posted for functional endoscopic sinus surgery for nasal polyposis **Exclusion criteria:** Cardiorespiratory illness Hypertension Asthma Obesity (BMI › 30) Known coagulopathies Anticoagulants, antiplatelets or NSAIDs History of deep vein thrombosis, stroke, ischaemic heart disease, peripheral vascular disease Active haematuria Convulsive disorders Oral contraceptives Psychiatric illness
Interventions	**Tranexamic acid (N = 30):** pre-medication with tranexamic acid 15 mg/kg as a slow intravenous bolus **Placebo (N = 30):** 10 mL normal saline as intravenous bolus

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Dongare 2018 *[continued]*

Study characteristics	
Outcomes	**Outcomes (primary and secondary not specifically reported)** Bleeding score by a scale adapted from Boezaart, measured at 15, 30, 45 and 60 minutes after start f surgery Intraoperative blood loss Duration of surgery Adverse events: nausea, vomiting, hypotension, convulsions, haemorrhagic or thrombotic complications for 24 hours. Thrombotic complications until discharge.
Funding sources	Not reported
Declarations of interest	Not reported
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: randomisation was done with a random number table.
Allocation concealment (selection bias)	Unclear risk	Comment: unclear how the allocated treatment remained concealed. The authors did not provide this information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: a blinded observer applied the contents of the syringes to the patients. It is unclear if the syringes were identical in colour/appearance. It is not specifically reported that patients were blinded to the treatment, but this is plausible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the surgeons were blinded to treatment and performed the measurement of the bleeding score.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing patients or exclusions, and all patients were analysed in the allocated group.
Selective reporting (reporting bias)	High risk	Comment: no study protocol or statistical analysis plan available. Bleeding score was not reported at 60 minutes, although measured, with no reason provided. Only 15, 30, 45 minutes were reported (significant results).
Other bias	Unclear risk	Comment: patients were followed up for thrombotic events until discharge. This period of time probably was variable for patients; the study does not specifically mention this.

Eldaba 2013

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment once during surgery
Participants	**Location:** Egypt, 1 site **Setting of recruitment:** Department of Anesthesia and Surgical Intensive Care, Tanta University, Tanta, Egypt **Study dates:** unclear **Sample size:** 100 **Number randomised:** 100 **Participant (baseline) characteristics:** Age (mean, SD): 7.5 (3.5) (TXA), 7.2 (3.2) (placebo) Gender (male/female): 29/21 (TXA), 33/17 (placebo) Application of Trendelenburg position: not reported Use of vasoconstrictive agents pre- or intraoperative: before surgery topical decongestant and after surgery infiltration with epinephrine 1:200.000 Use of anaesthesia: maintenance with sevoflurane (inhalational anaesthesia) Mean arterial pressure: equal in both groups Surgical instruments applied: cutting forceps and grabbing instruments, no microdebrider was used Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** Children between 5 and 10 years old CRS First-time FESS **Exclusion criteria:** Refusal of parents Systemic diseases affecting the nose Medical treatment affecting the study Congenital anomalies Pre-existing hepatic disorders Bleeding diathesis Abnormal prothrombin time, partial thromboplastin time (PTT) or platelet counts Usage of non-steroidal anti-inflammatory drugs within 7 days of surgery
Interventions	**Tranexamic acid (N = 50):** IV 25 mg/kg diluted in 10 mL saline solution after induction of anaesthesia **Placebo (N = 50):** IV 10 mL of normal saline solution after induction of anaesthesia

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Eldaba 2013 *[continued]*

Study characteristics	
Outcomes	**Outcomes (primary and secondary not specifically reported)** Non-invasive blood pressure and heart rate Quality of the surgical field every 15 minutes during the surgical procedure with a predefined scale adapted from that of Boezaart et al. 0 = no bleeding, 1 = minimal bleeding: not a surgical nuisance and no suction required, 2 = mild bleeding: occasional suction required, but does not affect dissection, 3 = moderate bleeding: slightly compromises surgical field, frequent suction required, 4 = severe bleeding: significantly compromises surgical field, frequent suction required, bleeding threat field just after removal of suction, 5 = massive bleeding: prevents dissection Blood loss Time of operation (from induction to extubation) Side-effects of TXA such as nausea, vomiting, pruritus, haematoma or haemorrhage, thrombotic complications, local infection, fever or convulsive seizures
Funding sources	Not reported
Declarations of interest	None declared
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: randomisation by computer-based random number generator
Allocation concealment (selection bias)	Low risk	Comment: assignment entered in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "anesthesiologists, operating personnel, and study staff were blind as to treatment groups". "A blinded chief nurse who did not participate in the study protocol or data collection prepared the syringes". No statement is made about patient blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study staff were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing patients, all were analysed.
Selective reporting (reporting bias)	Low risk	Comment: no study protocol available, however all measurements reported in the methods section were reported.
Other bias	Unclear risk	No further obvious issues.

El-Ozairy 2021

Study characteristics	
Methods	Randomised, controlled, double-blind trial with treatment during surgery
Participants	**Location:** Egypt, 1 site **Setting of recruitment:** Department of Otorhinolaryngology at Ain Shams University Hospital, Cairo, Egypt **Study dates:** June 2019 to January 2020 **Sample size:** 120 **Number randomised:** 120 **Participant (baseline) characteristics:** Age (mean, SD): 28.8 (6.7) (IV TXA), 30.1 (8.2) (topical TXA), 33.8 (7.2) (combined IV + topical TXA), 31.5 (7.9) (placebo) Gender (male/female): 49/41 (TXA), 14/16 (placebo) Application of Trendelenburg position: yes (30 degree heads up) Use of vasoconstrictive agents pre- or intraoperative: before surgery topical nasal pack with epinephrine 1:2000, also infiltration with 2 mL epinephrine 1:100,000 Use of anaesthesia: maintenance with isoflurane (inhalational anaesthesia) Mean arterial pressure: equal in groups at baseline Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** Adult ASA I-II patients (18 to 50 years) that underwent endoscopic sinus surgery **Exclusion criteria:** Patients with uncontrolled hypertension or coronary artery disease Anaemia End-stage renal failure Liver cirrhosis Patients with coagulopathy or receiving drugs influencing blood coagulation Cerebrovascular thrombosis or history of thrombotic events Pregnancy Known sensitivity to any of the study drugs Patients' refusal to participate in the study
Interventions	**Tranexamic acid (N = 90):** either TXA IV 15 mg/kg diluted in 20 mL saline over 30 minutes or irrigation fluid 400 mL saline solution with 2 g TXA, or both **Placebo (N = 30):** IV 20 mL of saline solution over 30 minutes and irrigation fluid 400 mL of saline solution **Other interventions:** All patients were instructed to take oral prednisone 1 mg/kg 5 days before surgery to reduce inflammation. Upon admission, all patients were pre-medicated with IV midazolam 0.05 mg/kg, ranitidine 50 mg and dexamethasone 10 mg, 15 minutes prior to surgery.
Outcomes	**Primary outcome** Effectiveness of local, IV and combined use of TXA in improving the surgical field quality during FESS **Secondary outcomes** Total fentanyl and esmolol consumption, operative time, recovery time and postoperative complications

[continued on next page]

El-Ozairy 2021 *[continued]*

Study characteristics	
Funding sources	Not reported
Declarations of interest	None of the authors have any conflicts of interest to declare
Notes	We contacted the corresponding author with a request to provide means and standard deviations (SDs) for the intervention groups for missing clinically relevant outcomes. The authors contacted did not provide us with these data.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: randomisation is mentioned - use of a computer-generated list. No further details are provided.
Allocation concealment (selection bias)	Low risk	Comment: it is unclear how the interventions were allocated exactly and who created the computer-generated list, however the drugs were prepared by a pharmacist and only had the patient number on them (not the name of the drugs).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study was double-blinded. A pharmacist prepared the drugs. Anaesthesiologist and surgeon were blinded to the study group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: surgeon was blinded to study group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes reported for all randomised patients. No patients lost to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes (pre-specified in the clinical trials register) were reported.
Other bias	Unclear risk	No other issues identified.

El Shal 2015

Study characteristics	
Methods	Three-arm, parallel-group randomised controlled trial with treatment once during surgery and 24 hours follow-up
Participants	**Location:** Egypt, 1 site **Setting of recruitment:** Department of Anesthesia, Faculty of Medicine, Cairo University, Egypt **Study dates:** unclear **Sample size:** 90 **Number randomised**: 90 **Participant (baseline) characteristics:** Age (mean, SD): 36.5 ± 6.9 9 (TXA), 36.3 ± 5.5 (placebo) Gender (male/female): 22/8 (TXA), 23/7 (placebo) Application of Trendelenburg position: head-up 30 degree position Use of vasoconstrictive agents pre- or intraoperative: not reported Use of anaesthesia: total inhalational anaesthesia Mean arterial pressure: equal in both groups Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** patients aged from 18 to 50 years and undergoing FESS for chronic sinusitis; ASA I and II **Exclusion criteria:** Patients with uncontrolled hypertension Renal or hepatic dysfunction Coronary or cerebral artery disease Autonomic disturbance Deep vein thrombosis or peripheral vascular disease Bleeding diathesis Patients receiving anticoagulants
Interventions	**Tranexamic acid (N = 30):** IV 10 mg/kg diluted in 100 mL saline solution after induction of anaesthesia **EACA (N = 30):** IV epsilon aminocaproic acid (EACA) 100 mg/kg diluted in 100 mL normal saline solution after induction of anaesthesia **Placebo (N = 30):** IV 100 mL normal saline solution after induction of anaesthesia **Additional interventions:** total inhalational anaesthesia and all patients underwent ESS
Outcomes	**Outcomes (primary and secondary not specifically reported)** Intraoperative blood loss (mL) Duration of operation (from induction to extubation) Assessment of nitroglycerine requirement Pre- and postoperative haemoglobin concentration Haemodynamic parameters: mean arterial blood pressure (MAP) and heart rate (HR) were recorded before induction of anaesthesia as a baseline, after induction of anaesthesia, and recorded every 15 minutes until the end of surgery Assessment of the quality of the surgical field by the surgeon with a predefined scale (Boezaart scale) at half an hour interval

[continued on next page]

El Shal 2015 *[continued]*

Study characteristics	
	Surgical field quality was graded by 5 items Likert scale as 1: not satisfied at all, 2: slightly satisfied, 3: moderately satisfied, 4: very satisfied, 5: extremely satisfied The incidence of any side effects e.g. nausea, vomiting, pruritus, fever, postoperative epistaxis and clinical evidence of thrombus development for at least 24 hours
Funding sources	Not reported
Declarations of interest	Not reported
Notes	The trial is a 3-arm treatment arm comparing 2 antifibrinolytic agents and placebo. For the purposes of this review the EACA group was not included.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: parallel-group randomised controlled trial.
Allocation concealment (selection bias)	Low risk	Comment: randomisation was done by means of computer-generated codes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the anaesthesiologists, surgeons and patients were blinded to study drugs and an anaesthesiologist not involved in the study prepared the infusion drugs before induction of anaesthesia.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: unlikely that the blinding could have been broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing outcome data.
Selective reporting (reporting bias)	Low risk	Comment: no trial protocol available, however in the methods section pre-specified outcome parameters.
Other bias	Unclear risk	No obvious further issues.

Jabalameli 2006

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment once during surgery
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Department of Anesthesiology and Intensive Care, Alzahra General Hospital, Isfahan University of Medical Sciences, Isfahan, Iran **Study dates:** unclear **Sample size:** 56 **Number randomised**: 56 **Participant (baseline) characteristics:** Gender (male/female): 38/18 Age (average range): 18 to 55 years Application of Trendelenburg position: not reported Use of vasoconstrictive agents pre- or intraoperative: drop of nasal phenylephrine (0.5%) at 15 minutes before induction of anaesthesia Use of anaesthesia: total intravenous anaesthesia Mean arterial pressure: 30% lower intraoperatively compared to pre-operatively Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** Patients with class I and II ASA Patients scheduled for elective endoscopic sinus surgery under general anaesthesia **Exclusion criteria:** Medications affecting coagulation system, history of thromboembolic events, disseminated intravascular coagulopathy, haemophilia, hypersensitivity to drugs and normal renal function
Interventions	**Tranexamic acid (N = 26):** topical 1000 mg diluted in 20 mL saline once during surgery **Placebo (N = 30):** topical 20 mL normal saline solution once during surgery **Additional interventions:** total intravenous anaesthesia and all patients underwent ESS
Outcomes	**Outcomes (primary and secondary not specifically reported)** Intraoperative bleeding score Intraoperative blood loss (mL)
Funding sources	Not reported
Declarations of interest	Not reported
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "... and then they were randomly assigned to TA (n=26) and placebo groups (n=30)"
Allocation concealment (selection bias)	Unclear risk	Comment: no information about how randomisation was performed or by whom.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information about who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: unclear if surgeon could have known randomisation - there is no information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	Comment: no trial protocol, however outcome of interest is fully reported.
Other bias	Unclear risk	Comment: no further obvious issues.

Langille 2013

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment during surgery
Participants	**Location:** Canada, 1 site **Setting of recruitment:** Division of Otolaryngology – Head and Neck Surgery, University of Alberta, Edmonton, AB, Canada **Study dates:** March 2010 to November 2011 **Sample size:** 28 **Number randomised**: 28 **Participant (baseline) characteristics:** Gender (male/female): 17/11 Age (median, range): 45, 23 to 80 Lund Mackay Score (median, SD): TXA 11 (1.9), placebo 10 (2.7) Application of Trendelenburg position: the head of bed was elevated 15 degrees Use of vasoconstrictive agents pre- or intraoperative: all patients underwent decongestion of the nasal mucosa with oxymetazoline and nasal pledgets soaked in 1:1000 epinephrine. A bilateral intranasal injection was performed in the region of the sphenopalatine artery with 1% lidocaine with 1:100,000 epinephrine Use of anaesthesia: all patients received inhalational anaesthesia Mean arterial pressure: TXA 66.7 (5.4), placebo 66.3 (6.2) Surgical instruments applied: combination of through-cutting instrumentation and microdebrider (Medtronic, Minneapolis, MN) Presence of polyps, active infection or fungal rhinosinusitis: CRSsNP (n = 5), CRSwNP (n = 23)
	Inclusion criteria: Failed medical management for the diagnosis of CRS or CRSwNP and were thus undergoing ESS (bilateral complete sphenoethmoidectomies) **Exclusion criteria:** History of hypertension, renal failure or vascular disease American Society of Anesthesiologists (ASA) class III or greater
Interventions	**Tranexamic acid (N = 14):** IV bolus 15 mg/kg + infusion 1 mg/kg/hour in 100 mL saline **Placebo (N = 14):** IV equivalent amount of normal saline solution **Additional interventions:** inhalational anaesthesia and all patients underwent ESS
Outcomes	**Primary outcome** Wormald grading scale **Secondary outcomes** Total estimated blood loss Lund Kennedy endoscopic score Peri-operative sinus endoscopy score (POSE) **Other outcomes reported:** data on acetylsalicylic acid and oral steroid use
Funding sources	Not reported
Declarations of interest	None to declare
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: parallel-group randomised controlled trial with block randomisation.
Allocation concealment (selection bias)	Low risk	Quote: "the randomisation scheme was not revealed until data had been collected from all patients"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the study was double-blinded. Only 1 study investigator knew the randomisation and was responsible for preparing tranexamic acid solution and normal saline solution.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: two blinded investigators were involved in outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes are reported.
Other bias	Unclear risk	No further obvious issues.

Nuhi 2015

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment once on the day of surgery
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Department of Otorhinolaryngology, Shahid Beheshti University of Medical Sciences, Taleghani Hospital, Tehran, Iran **Study dates:** 2009 to 2011 **Sample size:** 170 **Number randomised**: 170 **Participant (baseline) characteristics:** Gender (male/female): TXA 45/55, placebo 40/30 Age (mean, SD): TXA 32.4 (3.24), placebo 29.7 (4.32) Application of Trendelenburg position: not reported Use of vasoconstrictive agents pre- or intraoperative: not reported Use of anaesthesia: unclear which type Mean arterial pressure: not reported Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** Patients scheduled for elective ESS because of chronic sinusitis **Exclusion criteria:** Anaemia, end-stage renal failure, myocardial ischaemia, cerebrovascular thrombosis, ongoing anticoagulant therapy or presence of a bleeding diathesis or history of thrombotic events
Interventions	**Tranexamic acid (N = 100):** IV 15 mg/kg once on the day of surgery **Placebo (N = 70):** IV normal saline, unclear dose **Additional interventions:** all patients underwent ESS
Outcomes	**Outcomes (primary and secondary not specifically reported)** Intraoperative haemorrhage Surgical field bleeding score Side effects of treatment Visual analogue pain scale Haemodynamic parameters
Funding sources	Not reported
Declarations of interest	Not reported
Notes	We contacted the corresponding author with a request to provide means and standard deviations (SDs) for the intervention groups for missing clinically relevant outcomes. The authors contacted did not provide us with these data.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: parallel-group randomised controlled trial.
Allocation concealment (selection bias)	Unclear risk	Quote: "sequential numbers".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both participants and study staff (site investigators and trial coordinating center staff) were blinded to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: attending anaesthesiologist and the surgeon estimated blood loss and surgical field grading. It is unknown if these are considered part of the study staff, but most likely they were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing outcome data.
Selective reporting (reporting bias)	High risk	Comment: surgical field bleeding score is reported inadequately so that it could not be used for (meta)-analysis.
Other bias	Unclear risk	Comment: no further obvious issues.

Padhy 2019

Study characteristics	
Methods	Randomised controlled trial with treatment once during surgery
Participants	**Location:** Department of Otolaryngology - Head and Neck Surgery, Command Hospital (Eastern Command), Kolkata, tertiary care centre, 1 site **Setting of recruitment:** Department of Otolaryngology - Head and Neck Surgery, Command Hospital (Eastern Command), Kolkata **Study dates:** January 2017 to June 2018 **Sample size:** 30 **Number randomised**: 30 **Participant (baseline) characteristics:** Gender (male/female): not published Age (range): 12 to 60 years Application of Trendelenburg position: not reported Use of vasoconstrictive agents pre- or intraoperative: all patients received topical vasoconstrictors Use of anaesthesia: unclear which type Mean arterial pressure: not reported Surgical instruments applied: microdebrider in all patients Presence of polyps, active infection or fungal rhinosinusitis: all patients had polyps **Inclusion criteria:** CRS with polyposis with comparable clinical profile in terms of no. of polyps and sinuses involved ASA grade I/II **Exclusion criteria:** Hypertension, chronic kidney disease, chronic lung disease, malignancies, bleeding diatheses, patients having history of thromboembolic phenomena or anticoagulant therapy
Interventions	**Tranexamic acid (N = 15):** IV 10 mg/kg after induction of anaesthesia **Placebo (N = 15):** IV normal saline **Additional interventions:** all patients underwent ESS. All patients received prednisolone 1 mg/kg daily pre-operatively for 5 days plus IV amoxycillin-clavulanic acid 1200 mg twice daily was given the first 48 hours in all patients.
Outcomes	**Outcomes (primary and secondary not reported separately)** Intraoperative surgical field quality as measured with the Boezaart and van de Merwe grading scale Total blood loss
Funding sources	Not reported
Declarations of interest	Not reported
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: randomised controlled trial.
Allocation concealment (selection bias)	Low risk	Comment: the authors used a computer-based random number table.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the surgeon was not aware of which patient received the intervention. The anaesthesiologist was not blinded. There is no statement about patient blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: the surgeon was blinded and performed the surgical field scoring. The anaesthesiologist was not blinded and performed the total blood loss calculation after the surgery.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised patients were analysed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes are reported.
Other bias	High risk	Comment: adequate baseline characteristics are missing.

Pannerselvam 2019

Study characteristics	
Methods	Randomised, double-blind clinical trial with treatment once short before surgery
Participants	**Location:** Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India, probably 1 site **Setting of recruitment:** unclear **Study dates:** January 2013 to December 2013 **Sample size:** 84 **Number randomised**: 84 **Participant (baseline) characteristics:** Gender (male/female): TXA 15 mg/kg 22/6, TXA 5 mg/kg 18/10, placebo 15/13 Age (mean, SD): TXA 15 mg/kg 32.79 (10.48), TXA 5 mg/kg 31.68 (9.59), placebo 33.00 (11.25) Systolic blood pressure at 30 minutes (mean, SD): TXA 15 mg/kg 115.43 (6.44), TXA 5 mg/kg 115.26 (6.89), placebo 113.50 (6.50) Diastolic blood pressure at 30 minutes (mean, SD): TXA 15 mg/kg 71.43 (5.25), TXA 5 mg/kg 66.57 (8.37), placebo 71.43 (6.31) Application of Trendelenburg position: positioned 15° head-up Use of vasoconstrictive agents pre- or intraoperative: not prescribed with pre-anaesthetic medications Use of anaesthesia: combined intravenous and inhalational Mean arterial pressure: systolic and diastolic blood pressure measured during surgery. No significant changes between groups except for diastolic blood pressure, group B lower than group A and C. Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** Patients undergoing functional endoscopic sinus surgery Age 18 to 60 years ASA grade I/II **Exclusion criteria:** ASA class III and IV Contraindication to the study drug (tranexamic acid) Thrombotic diathesis Vascular disease Renal failure
Interventions	**Group A tranexamic acid** (N = 28): IV 15 mg/kg 20 minutes prior to surgery **Group B tranexamic acid** (N = 28)**:** IV 5 mg/kg 20 minutes prior to surgery **Group C placebo** (N = 28): IV normal saline **Additional interventions:** all patients underwent ESS
Outcomes	**Outcomes** **Primary** Surgical field quality assessed by Wormald grading scale **Secondary** Total blood loss Surgical time Surgeons satisfaction score which was assessed by Likert scale

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Pannerselvam 2019 *[continued]*

Study characteristics	
Funding sources	Not reported
Declarations of interest	Not reported
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: patients were randomised by computer-generated block randomisation.
Allocation concealment (selection bias)	Low risk	Comment: central allocation by computer.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: anaesthesiologists, surgeons, nurses and other staff were blinded to study protocol. Independent anaesthesiologist prepared study treatment. No statement is made about patient blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: study staff was reported to be adequately blinded, but who assessed the primary and secondary outcome parameters remains unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised patients were analysed.
Selective reporting (reporting bias)	Low risk	Comment: predefined primary and secondary outcome parameters were reported.
Other bias	Unclear risk	No other obvious issues.

Quiroga 2018

Study characteristics	
Methods	Parallel-group randomised controlled trial with treatment once during surgery
Participants	**Location:** Philippines, 1 site **Setting of recruitment:** Department of Otorhinolaryngology Head and Neck Surgery, Quirino Memorial Medical Center Quezon City, Philippines **Study dates:** September 2016 to August 2017 **Sample size:** 10 **Number randomised**: 10 **Participant (baseline) characteristics:** Gender (male/female): TXA 4/1, placebo 4/1 Age (mean, SD): TXA 53.8 (8.01), placebo 49.4 (13.37) Application of Trendelenburg position: not reported Use of vasoconstrictive agents pre-or intraoperative: nasal mucosa was decongested with nasal strips soaked in 1:100.000 epinephrine after induction of anaesthesia, prior to surgery Use of anaesthesia: endotracheal anaesthesia Mean arterial pressure: not reported Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: not reported **Inclusion criteria:** 18 to 75 years old CRS unresponsive to treatment **Exclusion criteria:** Cardiovascular disease Renal disease Bleeding diathesis Anaemia History of previous endoscopic sinus surgery Anticoagulants
Interventions	**Tranexamic acid (N = 5):** IV 500 mg of tranexamic acid per 5 mL 1 hour prior to surgery **Placebo (N = 5):** IV normal saline solution 1 hour prior to surgery **Additional interventions:** general anaesthesia and all patients underwent FESS
Outcomes	**Outcomes (primary and secondary not specifically reported)** Duration of surgery Blood loss Boezaart's grading scale **Other outcomes reported:** Adverse effects until after surgery
Funding sources	Not reported
Declarations of interest	None declared
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "double-blind, randomized, placebo-controlled trial"
Allocation concealment (selection bias)	High risk	Quote: "... randomized using simple random sampling. They were asked to pick a folded paper with written number from a bowl. Those who picked the paper with "odd" numbers were assigned to the treatment group".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The surgeons and anesthesiologists were blinded to treatment allocation". The study was reported to be double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The surgeons and anesthesiologists were blinded to treatment allocation". One person who was not included in surgery prepared the medications.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes are reported.
Other bias	Unclear risk	No further obvious issues.

Yang 2021

Study characteristics	
Methods	Randomised, controlled, double-blind trial with treatment during surgery
Participants	**Location:** China, 1 site **Setting of recruitment:** Department of Otorhinolaryngology at Beijing Tongren Hospital, Beijing, China **Study dates:** unclear **Sample size:** 60 **Number randomised:** 60 **Participant (baseline) characteristics** Age (mean, SD): 44.2 (12.6) (placebo), 44.1 (10.3) (TXA) Gender (male/female): 12/18 (placebo), 16/14 (TXA) Lund-Mackay scale score: 20.0 (IQR 14.8 to 22.0) (placebo), 18.5 (IQR 15.8 to 22.0) (TXA) Application of Trendelenburg position: 10-degree reverse Trendelenburg position Use of vasoconstrictive agents pre- or intraoperative: 10 cotton patties soaked in 10 mL mixture of 1:10,000 epinephrine and 1% tetracaine; 20 other epinephrine-soaked patties were prepared for intraoperative haemostasis as required Use of anaesthesia: intravenous anaesthesia Mean arterial pressure: equal in groups at baseline, MAP, mmHg 74.1 (6.0) (placebo), 72.6 (6.5) (TXA) Surgical instruments applied: not reported Presence of polyps, active infection or fungal rhinosinusitis: nasal polyps, n = 25 (83.3%) (placebo), n = 22 (73.3%) (TXA) **Inclusion criteria:** Adult patients (18 to 65 years) that underwent endoscopic sinus surgery for high-grade chronic rhinosinusitis (Lund-Mackay score 12 or greater out of a maximum of 24 points) **Exclusion criteria:** Patient refusal to participate in the study American Society of Anesthesiology (ASA) grade greater than or equal to grade 3 Body mass index (BMI) › 30 Previous history of thromboembolic disease Allergy to TXA Long-term preoperative use of anticoagulants or antiplatelet drugs Diagnosis of coagulation dysfunction
Interventions	**TXA (N = 30):** intravenous drip of TXA 15 mg/kg in 100 mL normal saline over 30 minutes **Placebo (N = 30):** 100 mL of normal saline only over 30 minutes
Outcomes	**Primary outcome:** Boezaart grading scale **Secondary outcomes:** Total blood loss, operation time, bleeding rate, postoperative complications (including nausea, vomiting, anaphylaxis, visual impairment, seizure, venous thromboembolism (VTE) and postoperative intervention for excessive fresh bleeding in the first 24 hours after the operation)

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Yang 2021 *[continued]*

Study characteristics	
Funding sources	This study was supported by Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support
Declarations of interest	No conflicts of interest
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: randomisation by a computer-generated random number list
Allocation concealment (selection bias)	Low risk	Comment: the computer-generated random number list was performed by IBM SPSS Statistics 26.0 and allocation was sealed in an envelope by one researcher not involved in the treatment/surgery.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: allocation for each participant was sealed in an envelope by one researcher who was blinded to the surgeons, patients, anaesthesiologists and recorders.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessors were blinded. Primary outcome was assessed by a surgically trained researcher (who was blinded to the group allocation). All surgeries were performed by 2 experienced surgeons.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no patients were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported.
Other bias	Unclear risk	The study appears to be free of other sources of bias.

aPTT: activated partial thromboplastin time
ASA: American Society of Anesthesiologists
BMI: body mass index
CRS: chronic rhinosinusitis
CRSsNP: chronic rhinosinusitis without nasal polyps
CRSwNP: chronic rhinosinusitis with nasal polyps
EACA: epsilon aminocaproic acid
ESS: endoscopic sinus surgery
FESS: functional endoscopic sinus surgery
INR: international normalised ratio
IQR: interquartile range
IV: intravenous
NSAIDs: non-steroidal anti-inflammatory drugs
SD: standard deviation
TIVA: total intravenous anaesthesia
TXA: tranexamic acid

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abbasi 2012	ALLOCATION: randomised PARTICIPANTS: patients with chronic rhinosinusitis undergoing endoscopic sinus surgery INTERVENTIONS: patients received tranexamic acid in both treatment groups
Athanasiadis 2009	ALLOCATION: not randomised
Beule 2010	ALLOCATION: not randomised
Chhappola 2011	ALLOCATION: randomised PARTICIPANTS: patients undergoing different endoscopic nasal surgeries (ESS, septoplasty, excision of nasal mass)
IRCT201203242963N7 2012	ALLOCATION: randomised PARTICIPANTS: candidates for endoscopic sinus surgery INTERVENTIONS: 2 different dosages of tranexamic acid, no control group
IRCT2015062021436N2	ALLOCATION: randomised PARTICIPANTS: patients with chronic rhinosinusitis undergoing endoscopic sinus surgery INTERVENTIONS: patients received tranexamic acid in both treatment groups
IRCT2015092824241N1	ALLOCATION: randomised PARTICIPANTS: patients undergoing open rhinoplasty
Jahanshahi 2014	ALLOCATION: randomised PARTICIPANTS: patients with chronic rhinosinusitis undergoing endoscopic sinus surgery INTERVENTIONS: patients received tranexamic acid or phenylephrine soaked pledgets
Kulkarni 2018	ALLOCATION: randomised PARTICIPANTS: patients with chronic rhinosinusitis undergoing endoscopic sinus surgery INTERVENTIONS: patients received tranexamic acid or ethamsylate
Kurozumi 1977	ALLOCATION: not randomised; cross-over trial
NCT00671281	Study got cancelled
Shehata 2014	ALLOCATION: not randomised
Yaniv 2006	ALLOCATION: not randomised

ESS: endoscopic sinus surgery

Characteristics of studies awaiting classification [ordered by study ID]

32971 2018

Methods	Double-blind clinical trial on 56 patients with chronic rhinosinusitis requiring endoscopic sinus surgery
Participants	Patients with chronic rhinosinusitis that did not respond to drug therapy
Interventions	Intervention: a mesh soaked in a mixture of phenylephrine 0.05% volume and tranexamic acid at a dose of 15 mg/kg for 10 minutes placed in the nose Control group: a mesh soaked in phenylephrine
Outcomes	Bleeding during surgery; quality of surgical field
Notes	Unable to retrieve paper

Amal Das 2012 CRSSTD-7068696

Methods	30 patients subjected to endoscopic sinus surgery and randomised within-patient to topical intervention one side and control other side
Participants	Bilateral sphenoethmoidal disease
Interventions	Intervention: 5 mL (100 mg/mL) of tranexamic acid spray Comparison: normal saline spray
Outcomes	Bleeding was documented using Boezaart's and Wormald's surgical field grading scales
Notes	Unable to retrieve paper

IRCT2012111411455N1 2013 CRSSTD-7068603

Methods	Double-blind randomised controlled trial in 66 patients
Participants	16- to 40-year olds ASA class 1 with chronic sinusitis and candidates for surgery
Interventions	Intervention group: 10 mg/kg tranexamic acid Control group: 50 cc normal saline infusion
Outcomes	Intraoperative bleeding, intraoperative pressure
Notes	No full-text paper found

IRCT2013012911822N3 2013 CRSSTD-7068595

Methods	Double-blinded randomised controlled trial in 70 patients that underwent nasal surgery
Participants	18- to 65-year olds undergoing nasal surgery
Interventions	Intervention: 500 mg intravenous tranexamic acid mixed up in 500 mL lactated Ringer's solution with concentration 1 mg/mL and maximum infusion rate 100 mg/min and maximum dosage 15 mg/kg Control group: lactated Ringer's solution as maintenance therapy
Outcomes	Primary outcomes: (a) quality of surgical field every 20 minutes during surgery using Boezaart scale; (b) determine blood volume accumulated in the suction chamber after operation; (c) changes haemoglobin and haematocrit 6 hours after surgery; (d) satisfaction of surgeon at end of operation Secondary outcomes: measurement of (a) seizures; (b) nausea; (c) vomiting; (d) and impaired colour vision 24 hours after surgery
Notes	No full-text paper found

IRCT2014031016924N1 2016 CRSSTD-7068683

Methods	Randomised (unblinded) clinical trial in 90 patients
Participants	90 patients ages 15 to 75 years; ASA class 1 and 2
Interventions	3 groups of N = 30 Group 1: 1 g oral tranexamic acid 2 hours before surgery Group 2: 1 mg/kg/day oral prednisolone for 5 days Group 3: no drug
Outcomes	Quality of the surgery zone and volume of bleeding at the end of surgery
Notes	No full-text paper found

Kurozumi 1976

Methods	Double-blind comparative study using a cross-over design
Participants	63 patients with sinusitis in which lesions were almost the same on both sides
Interventions	Intervention: tranexamic acid on one side of the nose Control: placebo on one side of the nose
Outcomes	Total and per minute bleeding amount
Notes	Unable to retrieve paper

Moise 2010

Methods	Prospective, double-blinded, randomised clinical trial
Participants	60 patients admitted to the ENT Department for FESS treatment for chronic rhinosinusitis
Interventions	Intervention: 10 mg/kg tranexamic acid in 10 mL saline solution with 2 administrations: before induction and before nasal pack removal Control: 10 mL saline solution with 2 administrations: before induction and before nasal pack removal
Outcomes	Intraoperative bleeding, nasal pack bleeding, blood coughed up, vomiting, preoperative, postoperative and after nasal pack removal haemoglobin
Notes	Unable to retrieve paper

ASA: American Society of Anesthesiologists
FESS: functional endoscopic sinus surgery

Characteristics of ongoing studies [ordered by study ID]

IRCT20180730040640N1

Study name	'The effect of topical tranexamic acid on bleeding reduction during functional endoscopic sinus surgery in choronic rhinosinousitis patient'
Methods	Double-blind randomised controlled trial
Participants	TXA: 56 patients requiring chronic rhinosinusitis Placebo: 56 patients **Inclusion criteria:** Patients with chronic rhinosinusitis who do not respond to drug therapy and require sinus surgery The age of the participant(s) must be between 18 and 60 years old The amount of haemoglobin of the participant should be above 10 g/dL The amount of bleeding time (BT), prothrombin time (PT), partial thromboplastin time (PTT), international normalised ratio (INR) should be normal in participants **Exclusion criteria:** Participants with cardiovascular disorders Participants who have coagulation disorders or who are taking anticoagulant medicines (drugs) Participants with inherited coagulation disorders such as thrombophilia Participants with coagulation disorder history in the past Participants who have a history (record) of allergy to any drug(s) in the past Participants who have been suffering from renal deficiency in the past Participants with cirrhosis Participants with chronic diseases, such as diabetes and hypertension Participants who are pregnant Participants with malignant nasal tumours Colour blindness
Interventions	Intervention 1: a mesh soaked in a mixture of phenylephrine 0.05% vol and tranexamic acid at a dose of 15 mg/kg for 10 minutes will be placed in the nose (nasal cavity) of the patient by an operating room technician, then it will get extracted and operation (procedure) will begin Intervention 2: a mesh soaked in a solution of 0.05% vol of phenylephrine for 10 minutes will be placed in the nose (nasal cavity) of the patient by an operating room technician, then the mesh will get extracted and operation (procedure) will begin
Outcomes	**Primary outcome** Bleeding during surgery (time point: at the 15th, 30th and 45th minute after intervention) Method of measurement: Boezaart scale **Secondary outcome** Bleeding volume (time point: every 15 minutes after start of surgery) Method of measurement: suction device
Starting date	23 September 2018
Contact information	Allahkaram Akhlaghi Units 16, Block 1, Fatemeh Zahra pension, Moallem square, Siraf Ave 7517933755 Boushehr Iran (Islamic Republic of) Akhlaghidr@gmail.com
Notes	—

NCT03965767

Study name	'Does the combined use of local and intravenous tranexamic acid offer better surgical field quality during functional endoscopic sinus surgery? A placebo-controlled clinical trial'
Methods	Parallel-group randomised controlled trial
Participants	Each treatment group: 30 patients **Inclusion criteria** Patients undergoing endoscopic sinus surgery Age 18 to 50 years **Exclusion criteria** Patients with uncontrolled hypertension or coronary artery disease, anaemia, end-stage renal failure, liver cirrhosis, patients with coagulopathy or receiving drugs influencing blood coagulation, cerebrovascular thrombosis or history of thrombotic events, pregnancy, known sensitivity to any of the study drug and patients' refusal to participate in the study
Interventions	**Group I:** patients will receive an intravenous dose of 15 mg/kg-1 of tranexamic acid in a 10 mL syringe. The irrigation fluid will be 400 mL of normal saline **Group II:** patients will receive an intravenous dose of 10 mL normal saline in a 10 mL syringe. Irrigation fluid will be 400 mL of normal saline with 2 g of tranexamic acid added to it. If more irrigation is needed, normal saline will be used. **Group III:** patients will receive an intravenous dose of 15 mg/kg-1 of tranexamic acid in a 10 mL syringe. Irrigation fluid will be 400 mL of normal saline with 2 g of tranexamic acid added to it. If more irrigation is needed, normal saline will be used. **Group IV (control):** patients will receive intravenous dose of 10 mL normal saline in 10 mL syringe. The irrigation fluid will be 400 mL of normal saline.
Outcomes	**Primary outcome** Bleeding during surgery (time frame: time of surgery) Surgeon satisfaction
Starting date	25 April 2019
Contact information	Ossama Mady, Faculty of Medicine Ain Shams University, MD 01117341201 ext 202; omady84@gmail.com; Cairo, Egypt
Notes	—

NCT04754230

Study name	'Effect of tranexamic acid on postoperative bleeding following sinus and nasal surgery'
Methods	Parallel randomised clinical trial
Participants	**Sample size:** n = 250 **Inclusion criteria:** Scheduled to undergo elective sinus or nasal surgery (e.g. septoplasty, inferior turbinate reduction, endoscopic sinus surgery) Age 18 or greater English-speaking Able to provide consent **Exclusion criteria:** Minors (age ‹ 18) Pregnant or may become pregnant by time of surgery Prisoners Non-English speaking Foreign citizens Unable to provide consent Known pro-thrombotic coagulation disorders Active intranasal drug use (e.g. cocaine) Surgery is for a sinonasal tumour or other sinus pathology not described in inclusion criteria Enrollment is in conflict with existing study participation
Interventions	Intervention: 1000 mg IV tranexamic acid Comparator: normal saline solution
Outcomes	**Primary outcome:** Bleeding score (visual analogue scale) daily for 7 days **Secondary outcomes:** Proportion of patients in each arm requiring evaluation for bleeding concerns expressed by the recovery nurse
Starting date	17 June 2021
Contact information	Principal Investigator: Zara M. Patel, MD, Stanford University, California, United States, 94305
Notes	—

NCT04905901

Study name	'Nebulized tranexamic acid in sinus surgery'
Methods	Parallel-group randomised controlled trial
Participants	**Site:** Egypt, 1 site **Sample size:** N = 90 (30 patients in each group) **Inclusion criteria:** Either sexes (age 18 to 65 years) of ASA I-II who are listed for elective functional endoscopic sinus surgery under general anaesthesia Normal accepted coagulation profile and haematocrit value ≥ 30 **Exclusion criteria:** Chronic renal failure Liver cirrhosis Bleeding disorders Current anticoagulant therapy Pregnancy or breastfeeding Impaired colour vision Severe vascular ischemia History of venous thrombosis, pulmonary embolism Long-term treatment with acetylsalicylic acid or non-steroidal anti-inflammatory drugs not discontinued before surgery Haemoglobin (HB) concentration ‹ 10 mg/dl Allergy to TXA
Interventions	**TXA group 1:** nebulised tranexamic acid 500 mg 15 minutes before operation **TXA group 2:** nebulised tranexamic acid 1 g 15 minutes before operation **Comparator group 3:** normal saline nebulisation 15 minutes before operation
Outcomes	**Primary outcome:** Modena Bleeding Score (MBS) assessing surgical field **Secondary outcomes:** Heart rate Mean blood pressure mmHg Anaesthetic consumption Postoperative complications
Starting date	6 May 2021
Contact information	Contact: Omar Soliman Email: omarmakram347@yahoo.com
Notes	—

TCTR20210531005

Study name	'Effect of local injection of tranexamic acid on surgical field during functional endoscopic sinus surgery in patients with chronic rhinosinusitis: a prospective randomized controlled trial'
Methods	Parallel-group randomised controlled trial
Participants	Sample size: N = 47 **Inclusion criteria:** Being candidate for FESS based on EPOS 2020 criteria Age 18 to 60 years Haemoglobin › 10 mg/dL Normal INR, PT, PTT **Exclusion criteria:** Having diathesis haemorrhage such as haemophilia Having history of thrombosis Acute or chronic renal failure Using heparin during 48 hours before surgery Using aspirin during 7 days before surgery Allergy to TXA Cirrhosis Pregnancy Having a cardiac stent Having a nasal tumour Patients who are unable to undergo surgery in the opinion of an internist Refuse to participate
Interventions	**TXA:** injection of 250 mg/5 mL **Comparator:** normal saline solution injection
Outcomes	**Primary outcome:** The quality of surgical field at 15, 30 and 45 minutes after the start of surgery (Boezaart surgical field grading system or Wormald surgical field grading system) **Secondary outcomes:** Operative blood loss at 15, 30 and 45 minutes after the start of surgery Duration of surgery Side effects 24 hours after operation questionnaire
Starting date	1 July 2021
Contact information	Kshidej Bongsabhikul Department of Otolaryngology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270, Rama VI Road, Toong Phaya Thai, Ratchathewi 10400 Bangkok Thailand Telephone: 0993546456 Email: kshidej@gmail.com Affiliation: Faculty of Medicine, Mahidol University
Notes	—

ASA: American Society of Anesthesiologists
FESS: functional endoscopic sinus surgery
INR: international normalised ratio
IV: intravenous
PTT: partial thromboplastin time
TXA: tranexamic acid

DATA AND ANALYSES

Comparison 1 Tranexamic acid versus placebo (saline solution or sterile water)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Surgical field bleeding score (during surgery)	13	772	Std. Mean Difference (IV, Random, 95% CI)	-0.87 [-1.23, -0.51]
1.2 Surgical field bleeding score by age (during surgery or within 30 minutes after surgery)	12	739	Std. Mean Difference (IV, Random, 95% CI)	-1.07 [-1.68, -0.46]
1.2.1 Adults (≥ 18 years of age)	11	639	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.76, -0.37]
1.2.2 Children	1	100	Std. Mean Difference (IV, Random, 95% CI)	-1.12 [-1.55, -0.70]
1.3 Surgical field bleeding score by administration route (during surgery or within 30 minutes after surgery)	13	772	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.30, -0.63]
1.3.1 Topical application	4	196	Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.52, -0.08]
1.3.2 Intravenous administration	9	516	Std. Mean Difference (IV, Random, 95% CI)	-0.90 [-1.16, -0.63]
1.3.3 Combined administration	1	60	Std. Mean Difference (IV, Random, 95% CI)	-2.87 [-3.61, -2.14]
1.4 Surgical field bleeding score by dosage (during surgery or within 30 minutes after surgery)	13	772	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.33, -0.63]
1.4.1 IV 10 mg/kg	3	174	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.42, -0.78]
1.4.2 IV 25 mg/kg	1	100	Std. Mean Difference (IV, Random, 95% CI)	-1.12 [-1.55, -0.70]
1.4.3 IV 500 mg	1	10	Std. Mean Difference (IV, Random, 95% CI)	0.50 [-0.77, 1.77]
1.4.4 IV 15 mg/kg + infusion 1 mg/kg/hour	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.74, 0.74]
1.4.5 IV 15 mg/kg	2	120	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.41, -0.41]
1.4.6 Topical 1000 mg	1	56	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.54, -0.42]
1.4.7 Topical 100 mg or 1000 mg	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.42, 0.37]

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Comparison 1 *[continued]*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.8 Topical 2000 mg in 400 mL saline	2	120	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-2.58, 0.77]
1.4.9 IV 5 mg/kg or 15 mg/kg	1	84	Std. Mean Difference (IV, Random, 95% CI)	-0.99 [-1.47, -0.51]
1.4.10 IV 15 mg/kg and topical 2000 mg in 400 mL saline	1	60	Std. Mean Difference (IV, Random, 95% CI)	-3.04 [-3.79, -2.28]
1.5 Surgical field bleeding score by type of anaesthesia (during surgery or within 30 minutes after surgery)	11	722	Std. Mean Difference (IV, Random, 95% CI)	-0.89 [-1.28, -0.50]
1.5.1 Total intravenous anaesthesia (TIVA)	3	200	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.20, -0.62]
1.5.2 Inhalational anaesthesia	5	318	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.76, -0.08]
1.5.3 Combined anaesthesia	3	204	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.41, -0.07]
1.6 Surgical field bleeding score and use of vasoconstrictive agents (during surgery or within 30 minutes after surgery)	10	635	Std. Mean Difference (IV, Random, 95% CI)	-1.00 [-1.39, -0.61]
1.6.1 Use of pre-operative or perioperative vasoconstrictors	8	464	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.49, -0.44]
1.6.2 No use of pre-operative or perioperative vasoconstrictors	2	171	Std. Mean Difference (IV, Random, 95% CI)	-1.02 [-1.35, -0.70]
1.7 Surgical field bleeding score (during surgery) excluding small sized studies	9	654	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.46, -0.66]
1.8 Surgical field bleeding score (during surgery) using fixed-effect model	13	772	Std. Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.12, -0.81]
1.9 Intraoperative blood loss (mL)	12	802	Mean Difference (IV, Random, 95% CI)	-70.32 [-92.28, -48.35]
1.10 Intraoperative blood loss (mL) by age	11	772	Mean Difference (IV, Random, 95% CI)	-74.45 [-97.99, -50.91]
1.10.1 Adult patients ≥ 18 years of age	10	672	Mean Difference (IV, Random, 95% CI)	-76.95 [-106.97, -46.92]
1.10.2 Children	1	100	Mean Difference (IV, Random, 95% CI)	-51.00 [-59.27, -42.73]
1.11 Intraoperative blood loss by administration route	12	802	Mean Difference (IV, Random, 95% CI)	-70.33 [-92.29, -48.37]

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Comparison 1 *[continued]*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.1 Topical application	1	56	Mean Difference (IV, Random, 95% CI)	-55.10 [-64.54, -45.66]
1.11.2 Intravenous administration	11	746	Mean Difference (IV, Random, 95% CI)	-71.84 [-98.36, -45.33]
1.12 Intraoperative blood loss by dosage	12	827	Mean Difference (IV, Random, 95% CI)	-66.40 [-85.28, -47.51]
1.12.1 IV 10 mg/kg	3	174	Mean Difference (IV, Random, 95% CI)	-110.64 [-194.01, -27.26]
1.12.2 IV 25 mg/kg	1	100	Mean Difference (IV, Random, 95% CI)	-51.00 [-59.27, -42.73]
1.12.3 IV 500 mg	1	10	Mean Difference (IV, Random, 95% CI)	-50.00 [-165.12, 65.12]
1.12.4 IV 15 mg/kg	4	343	Mean Difference (IV, Random, 95% CI)	-56.53 [-81.08, -31.97]
1.12.5 IV 15 mg/kg + 1 mg/kg/hour	1	28	Mean Difference (IV, Random, 95% CI)	-85.00 [-192.95, 22.95]
1.12.6 Topical 1000 mg	1	56	Mean Difference (IV, Random, 95% CI)	-55.10 [-64.54, -45.66]
1.12.7 Topical 2000 mg in 400 mL saline solution	1	60	Mean Difference (IV, Random, 95% CI)	-18.50 [-123.83, 86.83]
1.12.8 IV 5 mg/kg	1	56	Mean Difference (IV, Random, 95% CI)	-21.54 [-26.77, -16.31]
1.13 Intraoperative blood loss by type of anaesthesia	10	602	Mean Difference (IV, Random, 95% CI)	-73.38 [-98.98, -47.78]
1.13.1 Total intravenous anaesthesia	3	200	Mean Difference (IV, Random, 95% CI)	-79.46 [-139.51, -19.41]
1.13.2 Inhalational anaesthesia	4	198	Mean Difference (IV, Random, 95% CI)	-93.06 [-179.34, -6.77]
1.13.3 Combined anaesthesia	3	204	Mean Difference (IV, Random, 95% CI)	-33.62 [-39.44, -27.81]
1.14 Intraoperative blood loss and use of vasoconstrictive agents	10	544	Mean Difference (IV, Random, 95% CI)	-53.81 [-68.73, -38.90]
1.14.1 Use of perioperative or pre-operative vasoconstrictive agents	8	404	Mean Difference (IV, Random, 95% CI)	-51.38 [-57.20, -45.55]
1.14.2 No use of perioperative or pre-operative vasoconstrictive agents	2	140	Mean Difference (IV, Random, 95% CI)	-79.26 [-172.50, 13.98]

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Comparison 1 *[continued]*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.15 Intraoperative blood loss (mL) excluding small sized studies	9	704	Mean Difference (IV, Random, 95% CI)	-73.28 [-97.98, -48.59]
1.16 Intraoperative blood loss (mL) using fixed-effect model	12	802	Mean Difference (IV, Fixed, 95% CI)	-51.03 [-54.95, -47.12]
1.17 Significant adverse events (seizures, thromboembolism within 12 weeks of surgery)	8	664	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.02, 0.02]
1.18 Duration of surgery (minutes)	10	666	Mean Difference (IV, Random, 95% CI)	-13.04 [-19.27, -6.81]
1.19 Duration of surgery (minutes) by route of administration	10	726	Mean Difference (IV, Random, 95% CI)	-13.59 [-19.28, -7.90]
1.19.1 Intravenous administration	9	546	Mean Difference (IV, Random, 95% CI)	-13.69 [-20.05, -7.33]
1.19.2 Topical application	2	120	Mean Difference (IV, Random, 95% CI)	-7.14 [-20.67, 6.39]
1.19.3 Combined administration	1	60	Mean Difference (IV, Random, 95% CI)	-22.50 [-37.67, -7.33]
1.20 Duration of surgery by dosage (minutes)	10	754	Mean Difference (IV, Random, 95% CI)	-15.82 [-24.19, -7.45]
1.20.1 IV 10 mg/kg	2	144	Mean Difference (IV, Random, 95% CI)	-16.58 [-34.27, 1.11]
1.20.2 IV 25 mg/kg	1	100	Mean Difference (IV, Random, 95% CI)	-51.00 [-59.27, -42.73]
1.20.3 IV 500 mg	1	10	Mean Difference (IV, Random, 95% CI)	62.40 [1.57, 123.23]
1.20.4 IV 15 mg/kg + 1 mg/kg/hour	1	28	Mean Difference (IV, Random, 95% CI)	-85.00 [-192.95, 22.95]
1.20.5 IV 15 mg/kg	4	236	Mean Difference (IV, Random, 95% CI)	-11.59 [-15.71, -7.47]
1.20.6 Topical 2000 mg in 400 mL saline solution	2	120	Mean Difference (IV, Random, 95% CI)	-7.14 [-20.67, 6.40]
1.20.7 IV 15 mg/kg diluted in 20 mL saline and irrigation fluid 400 mL saline solution with 2 g TXA	1	60	Mean Difference (IV, Random, 95% CI)	-22.50 [-37.67, -7.33]
1.20.8 IV 5 mg/kg	1	56	Mean Difference (IV, Random, 95% CI)	-8.03 [-13.49, -2.57]
1.21 Duration of surgery by type of anaesthesia (minutes)	10	666	Mean Difference (IV, Random, 95% CI)	-27.98 [-48.38, -7.58]

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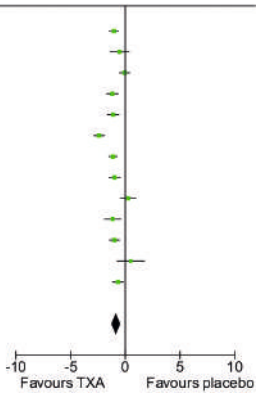
Comparison 1 *[continued]*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21.1 Total intravenous anaesthesia	2	144	Mean Difference (IV, Random, 95% CI)	-7.88 [-16.30, 0.55]
1.21.2 Inhalational anaesthesia	5	318	Mean Difference (IV, Random, 95% CI)	-52.19 [-106.14, 1.76]
1.21.3 Combined anaesthesia	3	204	Mean Difference (IV, Random, 95% CI)	-9.79 [-13.49, -6.10]
1.22 Duration of surgery and use of vasoconstrictive agents (minutes)	9	606	Mean Difference (IV, Random, 95% CI)	-11.51 [-16.90, -6.12]
1.22.1 Use of perioperative or pre-operative vasoconstrictive agents	7	438	Mean Difference (IV, Random, 95% CI)	-11.62 [-19.55, -3.70]
1.22.2 No use of perioperative or pre-operative vasoconstrictive agents	2	168	Mean Difference (IV, Random, 95% CI)	-10.52 [-15.19, -5.84]
1.23 Duration of surgery by age (minutes)	10	666	Mean Difference (IV, Random, 95% CI)	-13.05 [-19.30, -6.80]
1.23.1 Adults › 18 years of age	9	566	Mean Difference (IV, Random, 95% CI)	-11.40 [-18.86, -3.93]
1.23.2 Children	1	100	Mean Difference (IV, Random, 95% CI)	-20.40 [-25.46, -15.34]
1.24 Duration of surgery (minutes) excluding small sized studies	7	568	Mean Difference (IV, Random, 95% CI)	-15.42 [-21.74, -9.10]
1.25 Duration of surgery (minutes) using fixed-effect model	10	666	Mean Difference (IV, Fixed, 95% CI)	-17.15 [-19.32, -14.99]
1.26 Incomplete surgery	2	58	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.09, 0.09]
1.27 Surgical complications	2	58	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.09, 0.09]
1.28 Postoperative bleeding (place of packing or revision surgery within 14 days of surgery)	6	404	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.02]
1.29 Postoperative bleeding (place of packing or revision surgery within 14 days of surgery) using fixed-effect model	6	404	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.04, 0.02]

Analysis 1.1. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 1: Surgical field bleeding score (during surgery)

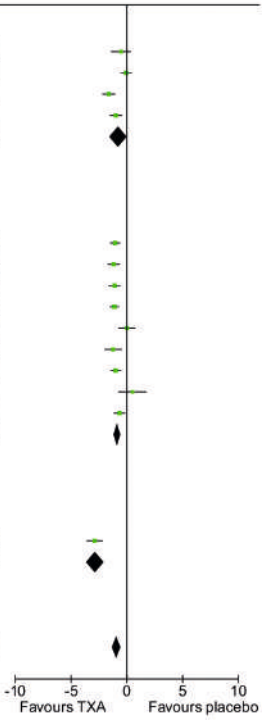
Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alimian 2011	1.93	0.59	42	2.57	0.62	42	8.6%	-1.05 [-1.51 , -0.59]
Athanasiadis 2007	0.46	0.7	10	0.9	0.9	10	6.2%	-0.52 [-1.42 , 0.37]
Baradaranfar 2017	2.73	4.272236	30	3	4.272236	30	8.4%	-0.06 [-0.57 , 0.44]
Dongare 2018	2.13	0.86	30	3.06	0.69	30	8.1%	-1.18 [-1.73 , -0.63]
El Shal 2015	1.8	0.98	30	2.7	0.57	30	8.2%	-1.11 [-1.65 , -0.56]
El-Ozairy 2021	1.8767	0.7502	90	3.7	0.78	30	8.3%	-2.39 [-2.91 , -1.88]
Eldaba 2013	1.8	0.53	50	2.4	0.53	50	8.8%	-1.12 [-1.55 , -0.70]
Jabalameli 2006	2.1	0.67	26	2.7	0.54	30	8.1%	-0.98 [-1.54 , -0.42]
Langille 2013	5.65	1.74	14	5.15	2	14	7.0%	0.26 [-0.49 , 1.00]
Padhy 2019	2.2	0.4	15	2.7	0.44	15	6.8%	-1.16 [-1.94 , -0.38]
Pannerselvam 2019	2.4	3.97	56	5.98	2.62	28	8.5%	-0.99 [-1.47 , -0.51]
Quiroga 2018	3	0.89	5	2.6	0.49	5	4.5%	0.50 [-0.77 , 1.77]
Yang 2021	1.99	0.36	30	2.24	0.38	30	8.3%	-0.67 [-1.19 , -0.15]
Total (95% CI)			**428**			**344**	**100.0%**	**-0.87 [-1.23 , -0.51]**

Heterogeneity: Tau² = 0.34; Chi² = 61.11, df = 12 (P < 0.00001); I² = 80%
Test for overall effect: Z = 4.71 (P < 0.00001)
Test for subgroup differences: Not applicable



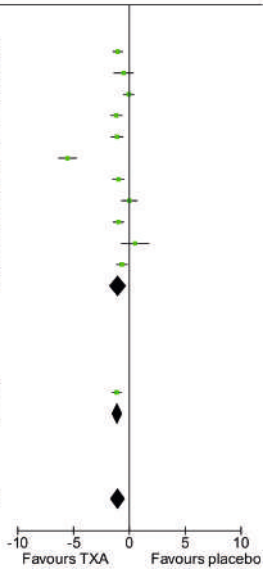
Analysis 1.2. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 2: Surgical field bleeding score by age (during surgery or within 30 minutes after surgery)

Study or Subgroup	Tranexamic acid Mean	Tranexamic acid SD	Tranexamic acid Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Topical application								
Athanasiadis 2007	0.46	0.7	10	0.9	0.9	10	5.7%	-0.52 [-1.42 , 0.37]
Baradaranfar 2017	2.73	4.27	30	3	4.27	30	7.9%	-0.06 [-0.57 , 0.44]
El-Ozairy 2021	2.3	0.8	30	3.6	0.78	30	7.4%	-1.62 [-2.21 , -1.04]
Jabalameli 2006	2.1	0.67	26	2.7	0.54	30	7.6%	-0.98 [-1.54 , -0.42]
Subtotal (95% CI)			**96**			**100**	**28.7%**	**-0.80 [-1.52 , -0.08]**
Heterogeneity: Tau² = 0.43; Chi² = 16.43, df = 3 (P = 0.0009); I² = 82%								
Test for overall effect: Z = 2.19 (P = 0.03)								
1.3.2 Intravenous administration								
Alimian 2011	1.93	0.59	42	2.57	0.62	42	8.2%	-1.05 [-1.51 , -0.59]
Dongare 2018	2.13	0.86	30	3.06	0.69	30	7.7%	-1.18 [-1.73 , -0.63]
El Shal 2015	1.8	0.98	30	2.7	0.57	30	7.7%	-1.11 [-1.65 , -0.56]
Eldaba 2013	1.8	0.53	50	2.4	0.53	50	8.4%	-1.12 [-1.55 , -0.70]
Langille 2013	5.8	1.9	14	5.8	2	14	6.6%	0.00 [-0.74 , 0.74]
Padhy 2019	2.2	0.4	15	2.73	0.44	15	6.3%	-1.23 [-2.02 , -0.44]
Pannerselvam 2019	2.4	3.97	56	5.98	2.62	28	8.1%	-0.99 [-1.47 , -0.51]
Quiroga 2018	3	0.89	5	2.6	0.49	5	4.1%	0.50 [-0.77 , 1.77]
Yang 2021	1.99	0.36	30	2.24	0.38	30	7.8%	-0.67 [-1.19 , -0.15]
Subtotal (95% CI)			**272**			**244**	**64.7%**	**-0.90 [-1.16 , -0.63]**
Heterogeneity: Tau² = 0.07; Chi² = 14.75, df = 8 (P = 0.06); I² = 46%								
Test for overall effect: Z = 6.70 (P < 0.00001)								
1.3.3 Combined administration								
El-Ozairy 2021	1.3	0.8	30	3.6	0.78	30	6.6%	-2.87 [-3.61 , -2.14]
Subtotal (95% CI)			**30**			**30**	**6.6%**	**-2.87 [-3.61 , -2.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.67 (P < 0.00001)								
Total (95% CI)			**398**			**374**	**100.0%**	**-0.96 [-1.30 , -0.63]**
Heterogeneity: Tau² = 0.31; Chi² = 58.72, df = 13 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 5.60 (P < 0.00001)								
Test for subgroup differences: Chi² = 25.41, df = 2 (P < 0.00001), I² = 92.1%								

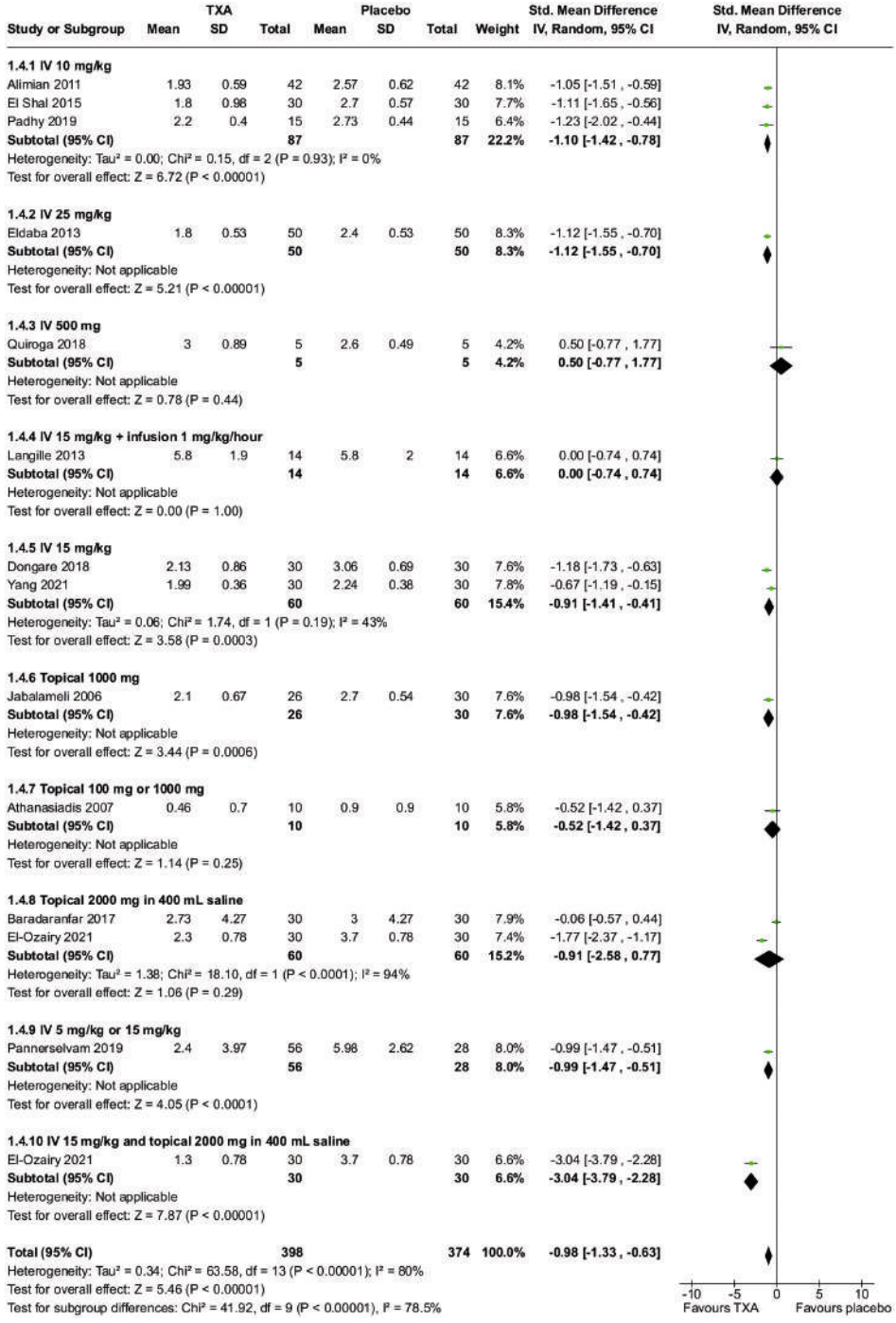


Analysis 1.3. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 3: Surgical field bleeding score by administration route (during surgery or within 30 minutes after surgery)

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Adults (≥ 18 years of age)								
Alimian 2011	1.93	0.59	42	2.57	0.62	42	8.8%	-1.05 [-1.51 , -0.59]
Athanasiadis 2007	0.46	0.7	10	0.9	0.9	10	7.7%	-0.52 [-1.42 , 0.37]
Baradaranfar 2017	2.73	4.27	30	3	4.27	30	8.7%	-0.06 [-0.57 , 0.44]
Dongare 2018	2.13	0.86	30	3.06	0.69	30	8.6%	-1.18 [-1.73 , -0.63]
El Shal 2015	1.8	0.98	30	2.7	0.57	30	8.6%	-1.11 [-1.65 , -0.56]
El-Ozairy 2021	1.5	0.09	90	3.7	0.78	30	7.9%	-5.54 [-6.37 , -4.72]
Jabalameli 2006	2.1	0.67	26	2.7	0.54	30	8.6%	-0.98 [-1.54 , -0.42]
Langille 2013	5.8	1.9	14	5.8	2	14	8.1%	0.00 [-0.74 , 0.74]
Pannerselvam 2019	2.4	3.97	56	5.98	2.62	25	8.7%	-0.98 [-1.48 , -0.49]
Quiroga 2018	3	0.89	5	2.6	0.49	5	6.6%	0.50 [-0.77 , 1.77]
Yang 2021	1.99	0.36	30	2.24	0.38	30	8.7%	-0.67 [-1.19 , -0.15]
Subtotal (95% CI)			**363**			**276**	**91.1%**	**-1.06 [-1.76 , -0.37]**
Heterogeneity: $Tau^2 = 1.26$; $Chi^2 = 145.47$, df = 10 (P < 0.00001); $I^2 = 93\%$								
Test for overall effect: Z = 2.99 (P = 0.003)								
1.2.2 Children								
Eldaba 2013	1.8	0.53	50	2.4	0.53	50	8.9%	-1.12 [-1.55 , -0.70]
Subtotal (95% CI)			**50**			**50**	**8.9%**	**-1.12 [-1.55 , -0.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.21 (P < 0.00001)								
Total (95% CI)			**413**			**326**	**100.0%**	**-1.07 [-1.68 , -0.46]**
Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 145.83$, df = 11 (P < 0.00001); $I^2 = 92\%$								
Test for overall effect: Z = 3.42 (P = 0.0006)								
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$								

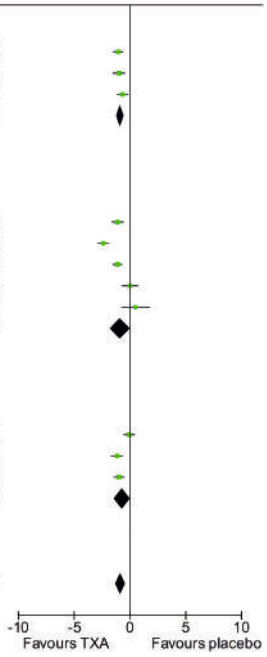


Analysis 1.4. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 4: Surgical field bleeding score by dosage (during surgery or within 30 minutes after surgery)

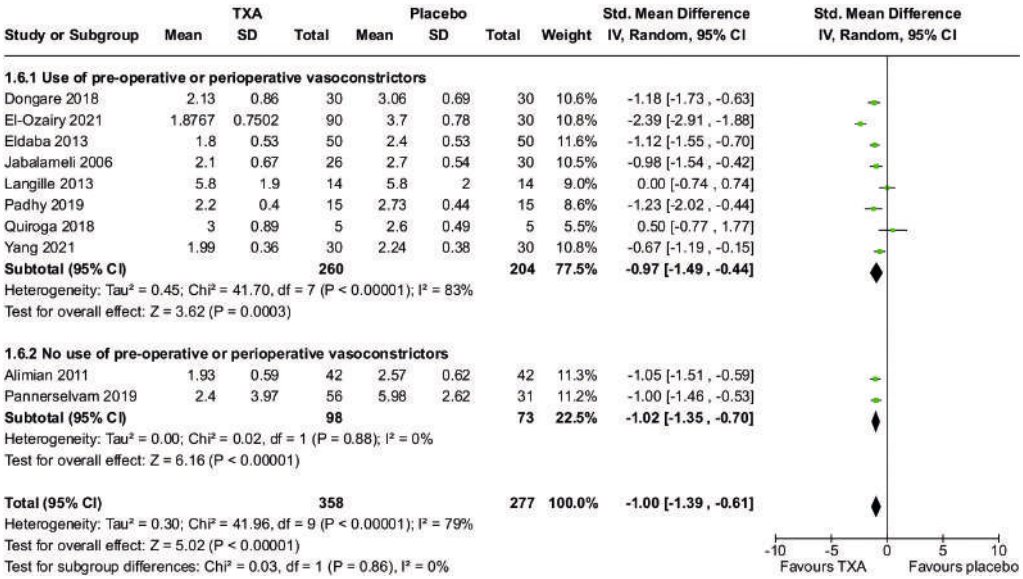


Analysis 1.5. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 5: Surgical field bleeding score by type of anaesthesia (during surgery or within 30 minutes after surgery)

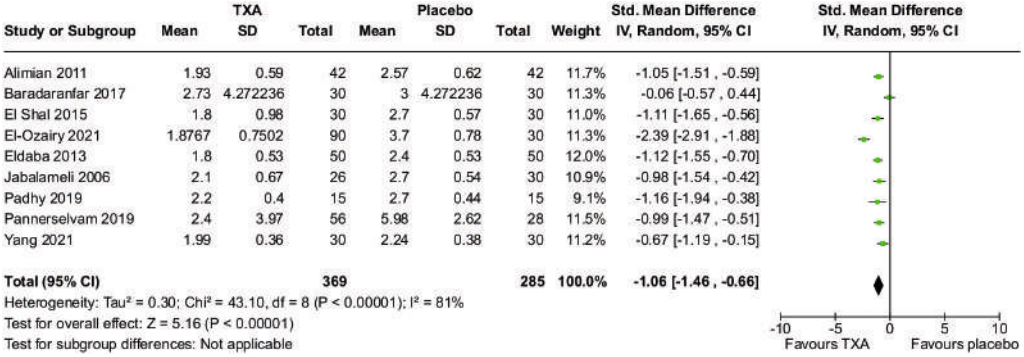
Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Total intravenous anaesthesia (TIVA)								
Alimian 2011	1.93	0.59	42	2.57	0.62	42	9.9%	-1.05 [-1.51 , -0.59]
Jabalameli 2006	2.1	0.67	26	2.7	0.54	30	9.3%	-0.98 [-1.54 , -0.42]
Yang 2021	1.99	0.36	30	2.24	0.38	30	9.5%	-0.67 [-1.19 , -0.15]
Subtotal (95% CI)			**98**			**102**	**28.8%**	**-0.91 [-1.20 , -0.62]**
Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 2 (P = 0.54); I² = 0%								
Test for overall effect: Z = 6.09 (P < 0.00001)								
1.5.2 Inhalational anaesthesia								
El Shal 2015	1.8	0.98	30	2.7	0.57	30	9.4%	-1.11 [-1.65 , -0.56]
El-Ozairy 2021	1.8767	0.7502	90	3.7	0.78	30	9.6%	-2.39 [-2.91 , -1.88]
Eldaba 2013	1.8	0.53	50	2.4	0.53	50	10.1%	-1.12 [-1.55 , -0.70]
Langille 2013	5.8	1.9	14	5.8	2	14	8.1%	0.00 [-0.74 , 0.74]
Quiroga 2018	3	0.89	5	2.6	0.49	5	5.2%	0.50 [-0.77 , 1.77]
Subtotal (95% CI)			**189**			**129**	**42.4%**	**-0.92 [-1.76 , -0.08]**
Heterogeneity: Tau² = 0.79; Chi² = 37.68, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.15 (P = 0.03)								
1.5.3 Combined anaesthesia								
Baradaranfar 2017	2.73	4.27	30	3	4.27	30	9.6%	-0.06 [-0.57 , 0.44]
Dongare 2018	2.13	0.86	30	3.06	0.69	30	9.4%	-1.18 [-1.73 , -0.63]
Pannerselvam 2019	2.4	3.97	56	5.98	2.62	28	9.8%	-0.99 [-1.47 , -0.51]
Subtotal (95% CI)			**116**			**88**	**28.8%**	**-0.74 [-1.41 , -0.07]**
Heterogeneity: Tau² = 0.28; Chi² = 10.35, df = 2 (P = 0.006); I² = 81%								
Test for overall effect: Z = 2.16 (P = 0.03)								
Total (95% CI)			**403**			**319**	**100.0%**	**-0.89 [-1.28 , -0.50]**
Heterogeneity: Tau² = 0.35; Chi² = 56.02, df = 10 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%								



Analysis 1.6. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 6: Surgical field bleeding score and use of vasoconstrictive agents (during surgery or within 30 minutes after surgery)



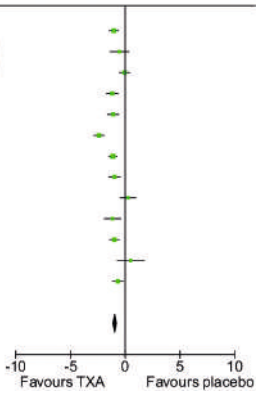
Analysis 1.7. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 7: Surgical field bleeding score (during surgery) excluding small sized studies



Analysis 1.8. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 8: Surgical field bleeding score (during surgery) using fixed-effect model

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Alimian 2011	1.93	0.59	42	2.57	0.62	42	11.6%	-1.05 [-1.51 , -0.59]
Athanasiadis 2007	0.46	0.7	10	0.9	0.9	10	3.0%	-0.52 [-1.42 , 0.37]
Baradaranfar 2017	2.73	4.272236	30	3	4.272236	30	9.5%	-0.06 [-0.57 , 0.44]
Dongare 2018	2.13	0.86	30	3.06	0.69	30	8.0%	-1.18 [-1.73 , -0.63]
El Shal 2015	1.8	0.98	30	2.7	0.57	30	8.1%	-1.11 [-1.65 , -0.56]
El-Ozairy 2021	1.8767	0.7502	90	3.7	0.78	30	9.1%	-2.39 [-2.91 , -1.88]
Eldaba 2013	1.8	0.53	50	2.4	0.53	50	13.5%	-1.12 [-1.55 , -0.70]
Jabalameli 2006	2.1	0.67	26	2.7	0.54	30	7.8%	-0.98 [-1.54 , -0.42]
Langille 2013	5.65	1.74	14	5.15	2	14	4.4%	0.26 [-0.49 , 1.00]
Padhy 2019	2.2	0.4	15	2.7	0.44	15	4.0%	-1.16 [-1.94 , -0.38]
Pannerselvam 2019	2.4	3.97	56	5.98	2.62	28	10.6%	-0.99 [-1.47 , -0.51]
Quiroga 2018	3	0.89	5	2.6	0.49	5	1.5%	0.50 [-0.77 , 1.77]
Yang 2021	1.99	0.36	30	2.24	0.38	30	8.9%	-0.67 [-1.19 , -0.15]
Total (95% CI)			**428**			**344**	**100.0%**	**-0.97 [-1.12 , -0.81]**

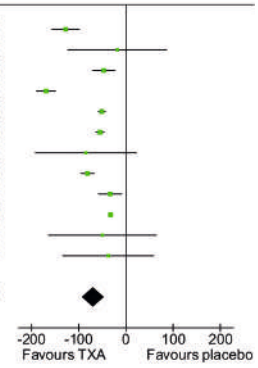
Heterogeneity: Chi² = 61.11, df = 12 (P < 0.00001); I² = 80%
Test for overall effect: Z = 12.15 (P < 0.00001)
Test for subgroup differences: Not applicable



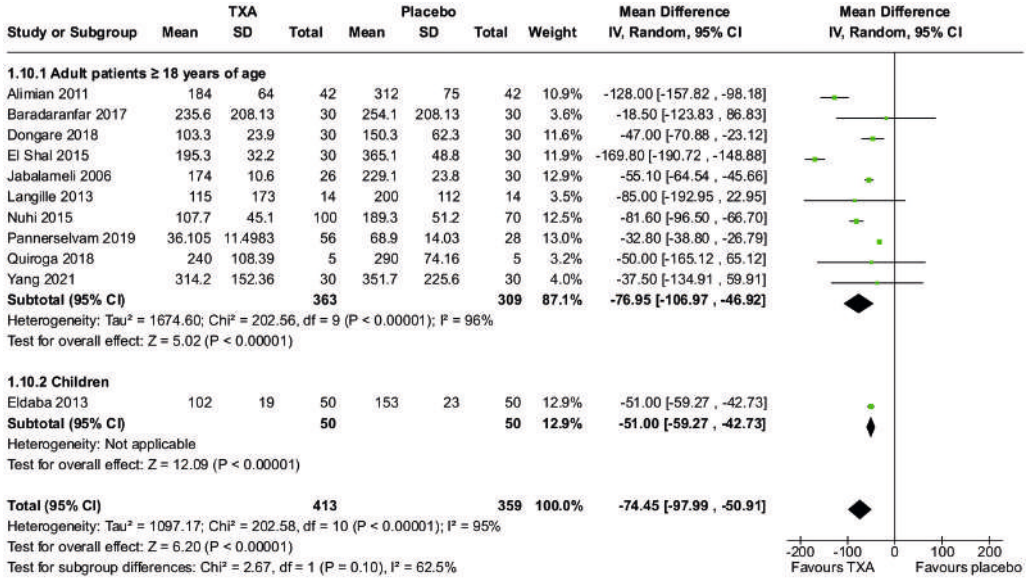
Analysis 1.9. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 9: Intraoperative blood loss (mL)

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alimian 2011	184	64	42	312	75	42	9.7%	-128.00 [-157.82 , -98.18]
Baradaranfar 2017	235.6	208.13	30	254.1	208.13	30	3.2%	-18.50 [-123.83 , 86.83]
Dongare 2018	103.3	23.9	30	150.3	62.3	30	10.4%	-47.00 [-70.88 , -23.12]
El Shal 2015	195.3	32.2	30	365.1	48.8	30	10.7%	-169.80 [-190.72 , -148.88]
Eldaba 2013	102	19	50	153	23	50	11.7%	-51.00 [-59.27 , -42.73]
Jabalameli 2006	174	10.6	26	229.1	23.8	30	11.6%	-55.10 [-64.54 , -45.66]
Langille 2013	115	173	14	200	112	14	3.1%	-85.00 [-192.95 , 22.95]
Nuhi 2015	107.7	45.1	100	189.3	51.2	70	11.3%	-81.60 [-96.50 , -66.70]
Padhy 2019	404.7	30.67	15	438.3	40.34	15	10.2%	-33.60 [-59.24 , -7.96]
Pannerselvam 2019	36.105	11.4983	56	68.9	14.03	28	11.8%	-32.80 [-38.80 , -26.79]
Quiroga 2018	240	108.39	5	290	74.16	5	2.8%	-50.00 [-165.12 , 65.12]
Yang 2021	314.2	152.36	30	351.7	225.6	30	3.6%	-37.50 [-134.91 , 59.91]
Total (95% CI)			**428**			**374**	**100.0%**	**-70.32 [-92.28 , -48.35]**

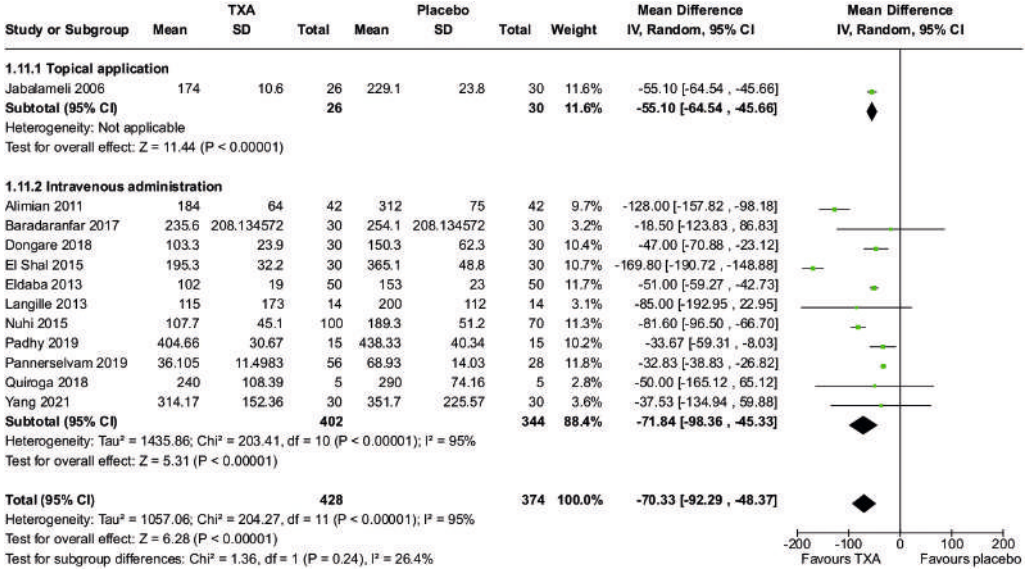
Heterogeneity: Tau² = 1057.78; Chi² = 204.40, df = 11 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.27 (P < 0.00001)
Test for subgroup differences: Not applicable



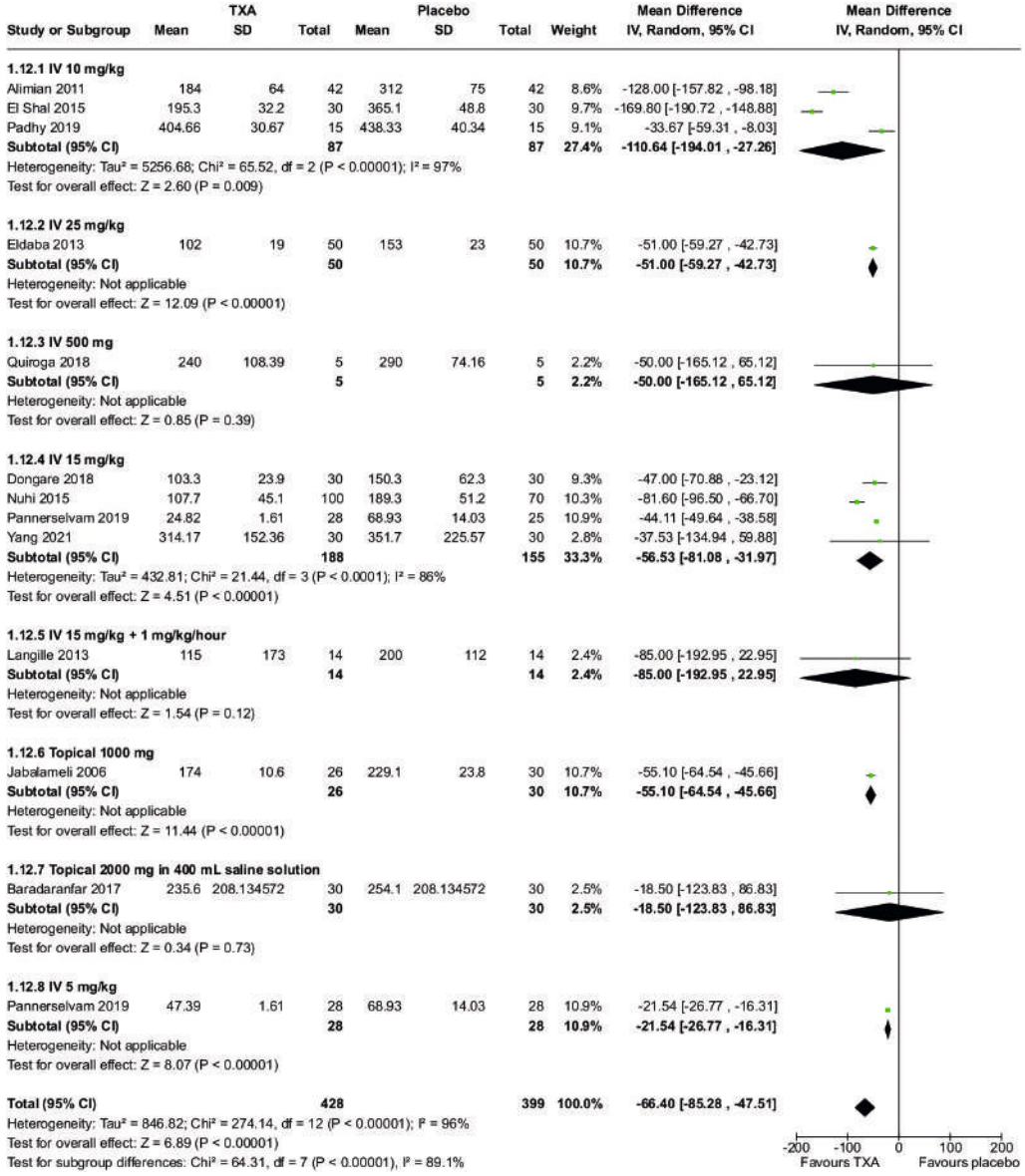
Analysis 1.10. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 10: Intraoperative blood loss (mL) by age



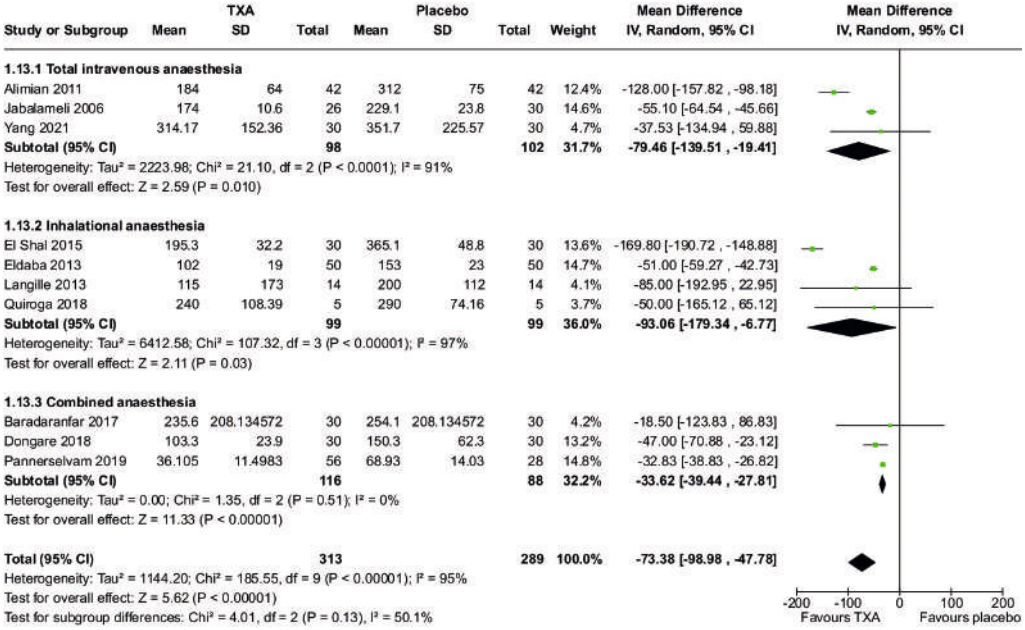
Analysis 1.11. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 11: Intraoperative blood loss by administration route



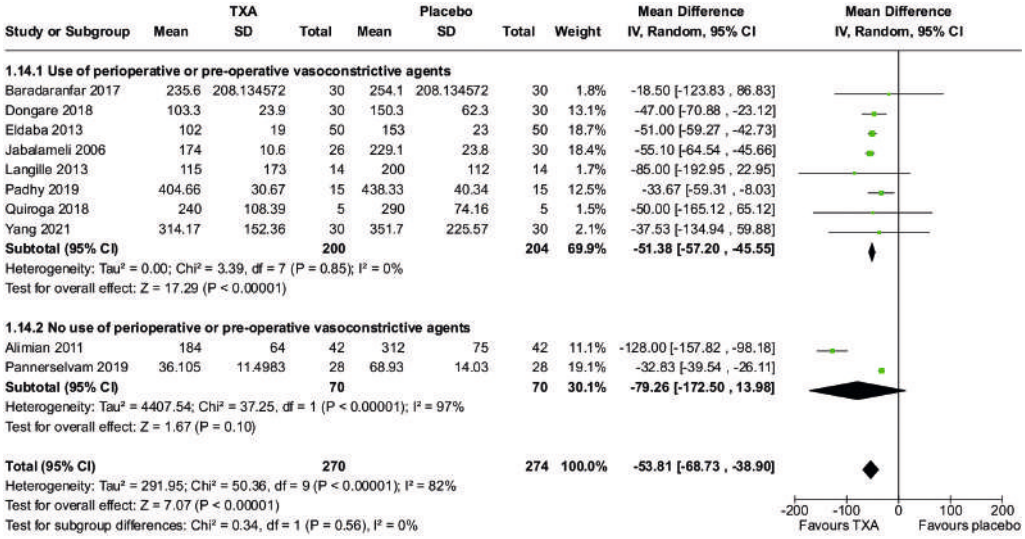
Analysis 1.12. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 12: Intraoperative blood loss by dosage



Analysis 1.13. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 13: Intraoperative blood loss by type of anaesthesia



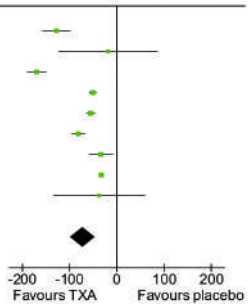
Analysis 1.14. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 14: Intraoperative blood loss and use of vasoconstrictive agents



Analysis 1.15. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 15: Intraoperative blood loss (mL) excluding small sized studies

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alimian 2011	184	64	42	312	75	42	11.7%	-128.00 [-157.82 , -98.18]
Baradaranfar 2017	235.6	208.13	30	254.1	208.13	30	4.0%	-18.50 [-123.83 , 86.83]
El Shal 2015	195.3	32.2	30	365.1	48.8	30	12.8%	-169.80 [-190.72 , -148.88]
Eldaba 2013	102	19	50	153	23	50	13.8%	-51.00 [-59.27 , -42.73]
Jabalameli 2006	174	10.6	26	229.1	23.8	30	13.8%	-55.10 [-64.54 , -45.66]
Nuhi 2015	107.7	45.1	100	189.3	51.2	70	13.4%	-81.60 [-96.50 , -66.70]
Padhy 2019	404.7	30.67	15	438.3	40.34	15	12.2%	-33.60 [-59.24 , -7.96]
Pannerselvam 2019	36.105	11.4983	56	68.9	14.03	28	14.0%	-32.80 [-38.80 , -26.79]
Yang 2021	314.2	152.36	30	351.7	225.6	30	4.4%	-37.50 [-134.91 , 59.91]
Total (95% CI)			**379**			**325**	**100.0%**	**-73.28 [-97.98 , -48.59]**

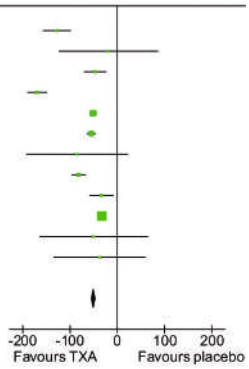
Heterogeneity: Tau² = 1128.33; Chi² = 203.91, df = 8 (P < 0.00001); I² = 96%
Test for overall effect: Z = 5.82 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 16: Intraoperative blood loss (mL) using fixed-effect model

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Alimian 2011	184	64	42	312	75	42	1.7%	-128.00 [-157.82 , -98.18]
Baradaranfar 2017	235.6	208.13	30	254.1	208.13	30	0.1%	-18.50 [-123.83 , 86.83]
Dongare 2018	103.3	23.9	30	150.3	62.3	30	2.7%	-47.00 [-70.88 , -23.12]
El Shal 2015	195.3	32.2	30	365.1	48.8	30	3.5%	-169.80 [-190.72 , -148.88]
Eldaba 2013	102	19	50	153	23	50	22.5%	-51.00 [-59.27 , -42.73]
Jabalameli 2006	174	10.6	26	229.1	23.8	30	17.2%	-55.10 [-64.54 , -45.66]
Langille 2013	115	173	14	200	112	14	0.1%	-85.00 [-192.95 , 22.95]
Nuhi 2015	107.7	45.1	100	189.3	51.2	70	6.9%	-81.60 [-96.50 , -66.70]
Padhy 2019	404.7	30.67	15	438.3	40.34	15	2.3%	-33.60 [-59.24 , -7.96]
Pannerselvam 2019	36.105	11.4983	56	68.9	14.03	28	42.6%	-32.80 [-38.80 , -26.79]
Quiroga 2018	240	108.39	5	290	74.16	5	0.1%	-50.00 [-165.12 , 65.12]
Yang 2021	314.2	152.36	30	351.7	225.6	30	0.2%	-37.50 [-134.91 , 59.91]
Total (95% CI)			**428**			**374**	**100.0%**	**-51.03 [-54.95 , -47.12]**

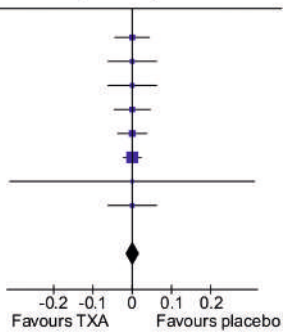
Heterogeneity: Chi² = 204.40, df = 11 (P < 0.00001); I² = 95%
Test for overall effect: Z = 25.52 (P < 0.00001)
Test for subgroup differences: Not applicable



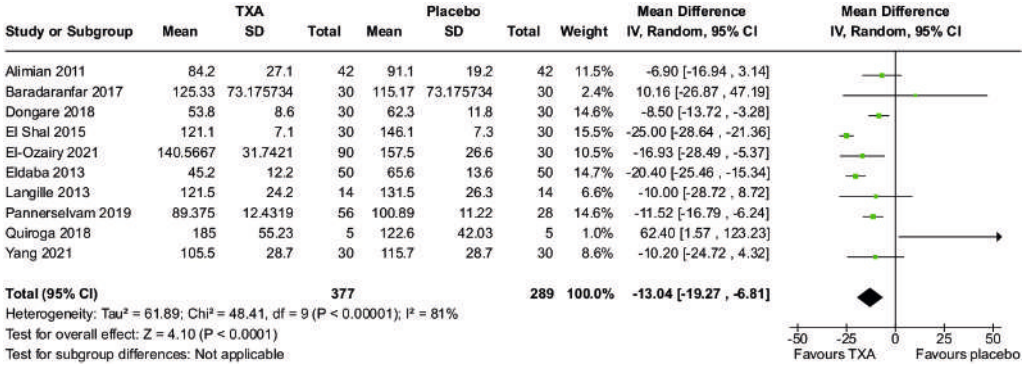
Analysis 1.17. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 17: Significant adverse events (seizures, thromboembolism within 12 weeks of surgery)

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Alimian 2011	0	42	0	42	11.7%	0.00 [-0.05 , 0.05]
Dongare 2018	0	30	0	30	6.1%	0.00 [-0.06 , 0.06]
El Shal 2015	0	30	0	30	6.1%	0.00 [-0.06 , 0.06]
El-Ozairy 2021	0	90	0	30	10.9%	0.00 [-0.05 , 0.05]
Eldaba 2013	0	50	0	50	16.4%	0.00 [-0.04 , 0.04]
Nuhi 2015	0	100	0	70	42.4%	0.00 [-0.02 , 0.02]
Quiroga 2018	0	5	0	5	0.2%	0.00 [-0.31 , 0.31]
Yang 2021	0	30	0	30	6.1%	0.00 [-0.06 , 0.06]
Total (95% CI)		**377**		**287**	**100.0%**	**0.00 [-0.02 , 0.02]**
Total events:	0		0			

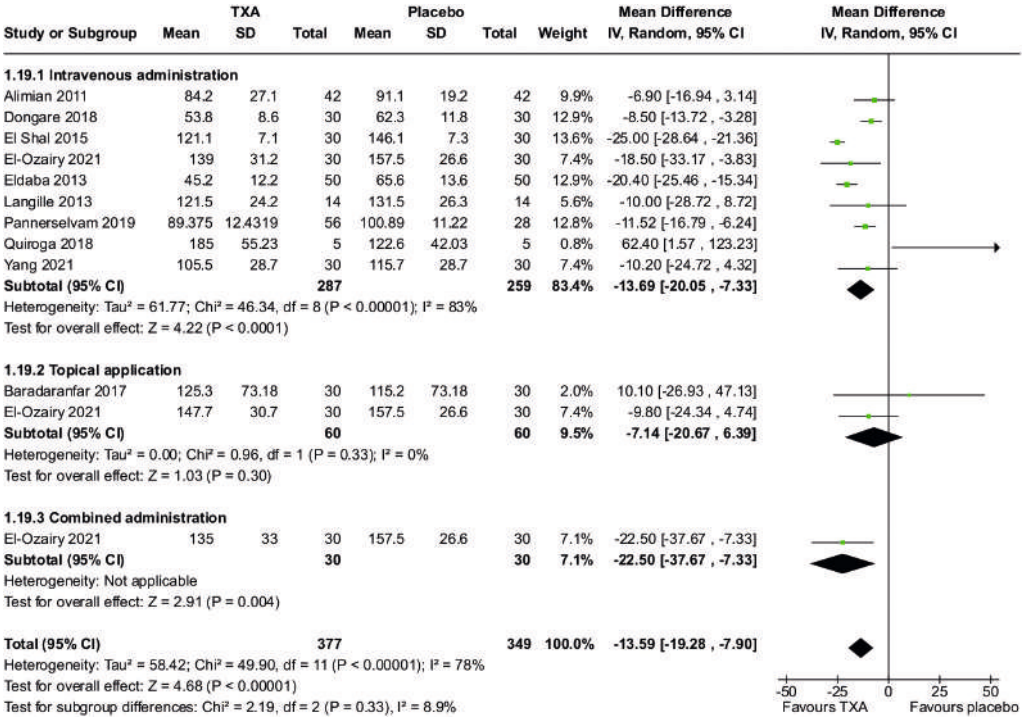
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 7 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



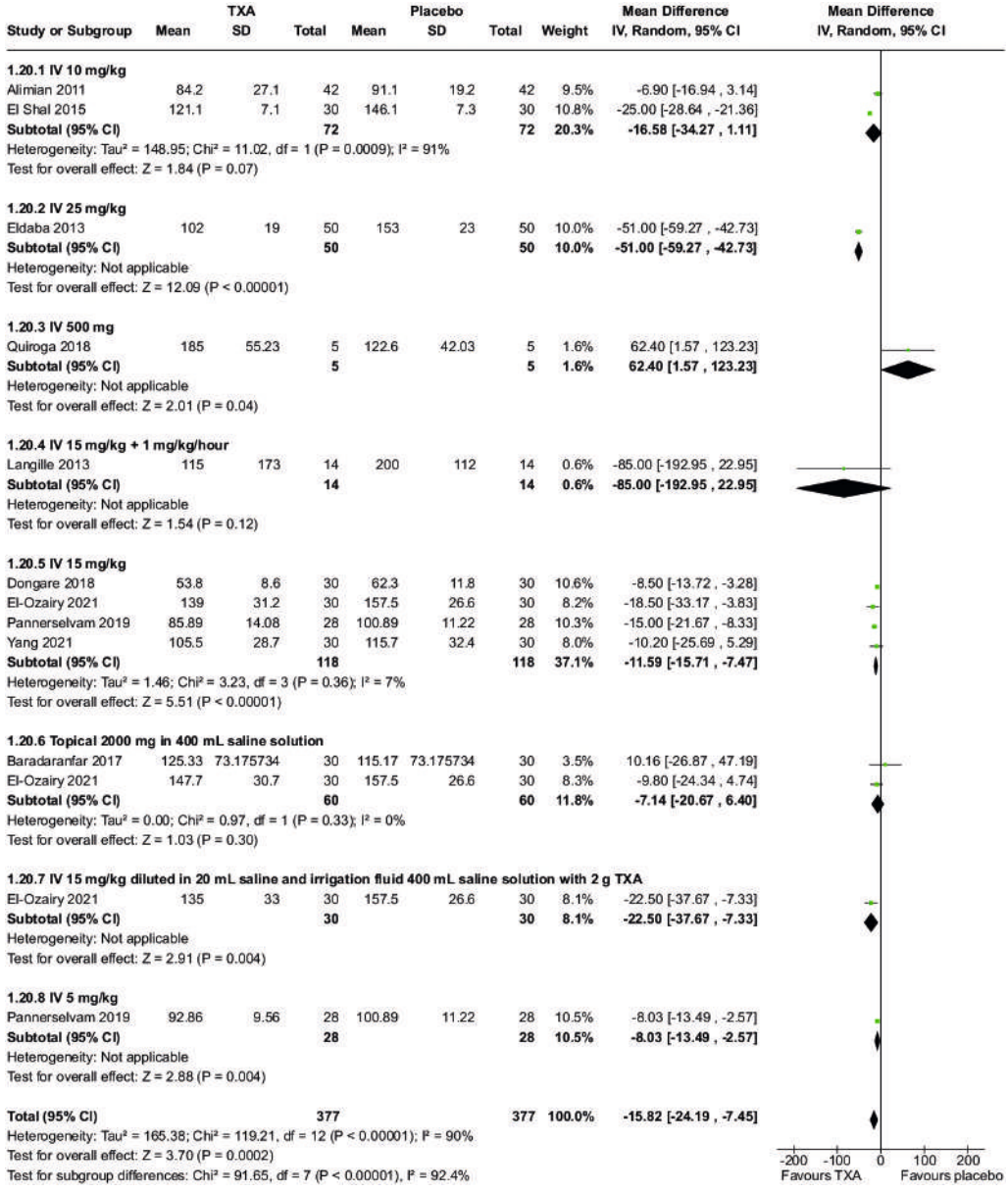
Analysis 1.18. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 18: Duration of surgery (minutes)



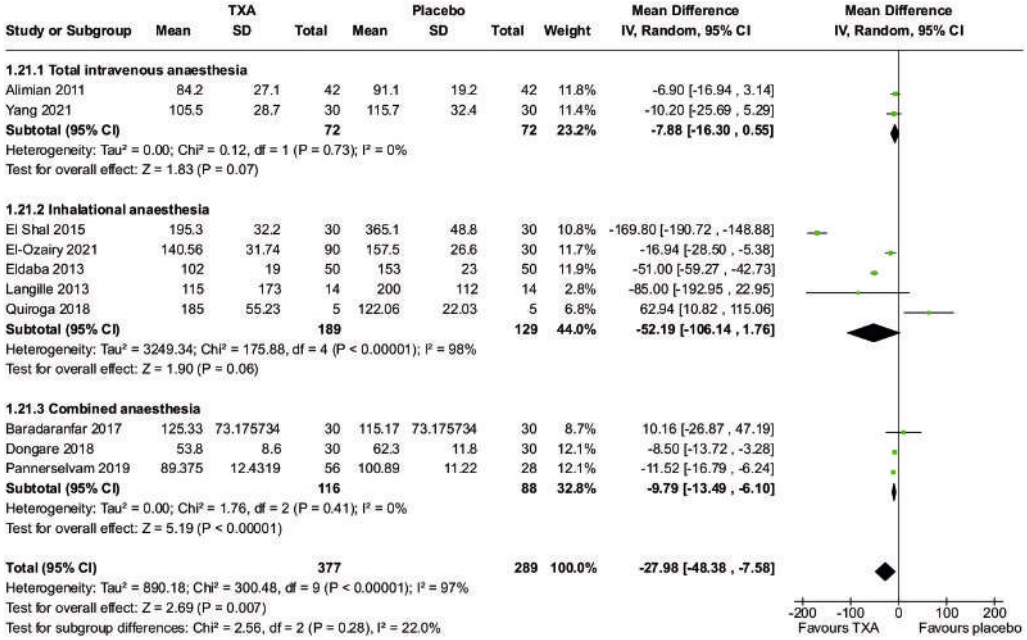
Analysis 1.19. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 19: Duration of surgery (minutes) by route of administration



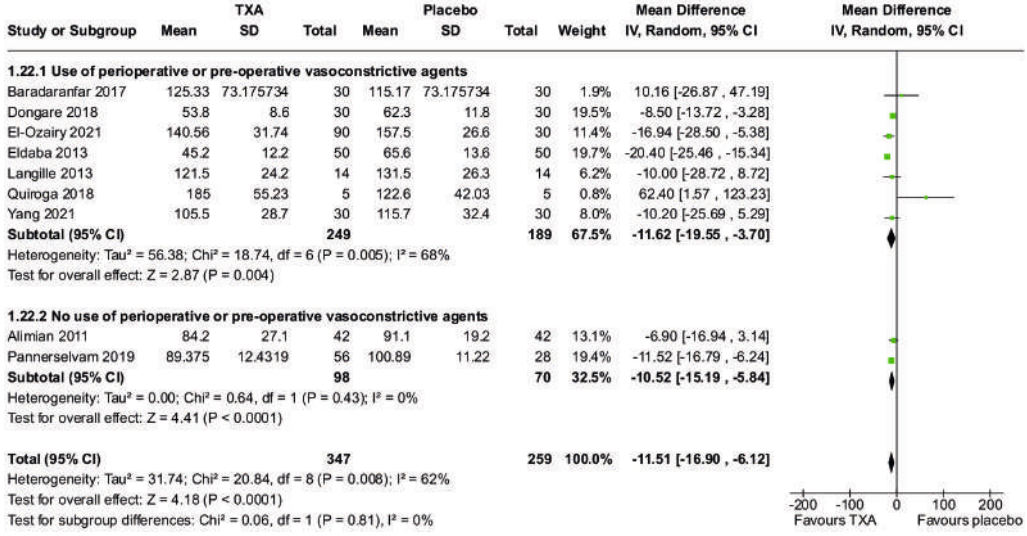
Analysis 1.20. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 20: Duration of surgery by dosage (minutes)



Analysis 1.21. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 21: Duration of surgery by type of anaesthesia (minutes)

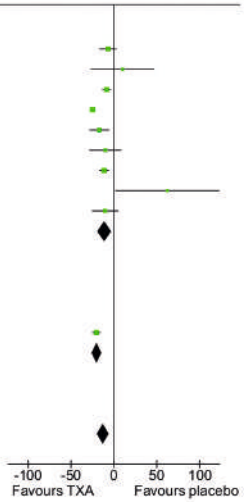


Analysis 1.22. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 22: Duration of surgery and use of vasoconstrictive agents (minutes)



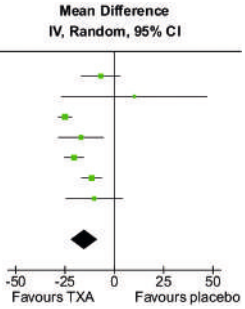
Analysis 1.23. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 23: Duration of surgery by age (minutes)

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.23.1 Adults > 18 years of age								
Alimian 2011	84.2	27.1	42	91.1	19.2	42	11.5%	-6.90 [-16.94 , 3.14]
Baradaranfar 2017	125.33	73.175734	30	115.17	73.175734	30	2.4%	10.16 [-26.87 , 47.19]
Dongare 2018	53.8	8.6	30	62.3	11.8	30	14.7%	-8.50 [-13.72 , -3.28]
El Shal 2015	121.1	7.1	30	146.1	7.3	30	15.5%	-25.00 [-28.64 , -21.36]
El-Ozairy 2021	140.56	31.74	90	157.5	26.6	30	10.5%	-16.94 [-28.50 , -5.38]
Langille 2013	121.5	24.2	14	131.5	26.3	14	6.6%	-10.00 [-28.72 , 8.72]
Pannerselvam 2019	89.375	12.4319	56	100.89	11.22	28	14.7%	-11.52 [-16.79 , -6.24]
Quiroga 2018	185	55.23	5	122.6	42.03	5	1.0%	62.40 [1.57 , 123.23]
Yang 2021	105.5	28.7	30	115.7	32.4	30	8.2%	-10.20 [-25.69 , 5.29]
Subtotal (95% CI)			**327**			**239**	**85.2%**	**-11.40 [-18.86 , -3.93]**
Heterogeneity: Tau² = 80.43; Chi² = 46.40, df = 8 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 2.99 (P = 0.003)								
1.23.2 Children								
Eldaba 2013	45.2	12.2	50	65.6	13.6	50	14.8%	-20.40 [-25.46 , -15.34]
Subtotal (95% CI)			**50**			**50**	**14.8%**	**-20.40 [-25.46 , -15.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.90 (P < 0.00001)								
Total (95% CI)			**377**			**289**	**100.0%**	**-13.05 [-19.30 , -6.80]**
Heterogeneity: Tau² = 61.98; Chi² = 48.31, df = 9 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Test for subgroup differences: Chi² = 3.83, df = 1 (P = 0.05), I² = 73.9%								



Analysis 1.24. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 24: Duration of surgery (minutes) excluding small sized studies

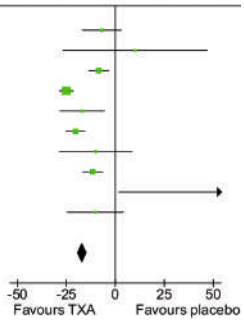
Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alimian 2011	84.2	27.1	42	91.1	19.2	42	14.3%	-6.90 [-16.94 , 3.14]
Baradaranfar 2017	125.33	73.175734	30	115.17	73.175734	30	2.6%	10.16 [-26.87 , 47.19]
El Shal 2015	121.1	7.1	30	146.1	7.3	30	20.9%	-25.00 [-28.64 , -21.36]
El-Ozairy 2021	140.56	31.74	90	157.5	26.6	30	12.8%	-16.94 [-28.50 , -5.38]
Eldaba 2013	45.2	12.2	50	65.6	13.6	50	19.6%	-20.40 [-25.46 , -15.34]
Pannerselvam 2019	89.375	12.4319	56	100.89	11.22	28	19.4%	-11.52 [-16.79 , -6.24]
Yang 2021	105.5	28.7	30	115.7	28.7	30	10.3%	-10.20 [-24.72 , 4.32]
Total (95% CI)			**328**			**240**	**100.0%**	**-15.42 [-21.74 , -9.10]**
Heterogeneity: Tau² = 46.31; Chi² = 27.88, df = 6 (P < 0.0001); I² = 78%								
Test for overall effect: Z = 4.78 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Analysis 1.25. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 25: Duration of surgery (minutes) using fixed-effect model

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Alimian 2011	84.2	27.1	42	91.1	19.2	42	4.7%	-6.90 [-16.94 , 3.14]
Baradaranfar 2017	125.33	73.175734	30	115.17	73.175734	30	0.3%	10.16 [-26.87 , 47.19]
Dongare 2018	53.8	8.6	30	62.3	11.8	30	17.2%	-8.50 [-13.72 , -3.28]
El Shal 2015	121.1	7.1	30	146.1	7.3	30	35.4%	-25.00 [-28.64 , -21.36]
El-Ozairy 2021	140.56	31.74	90	157.5	26.6	30	3.5%	-16.94 [-28.50 , -5.38]
Eldaba 2013	45.2	12.2	50	65.6	13.6	50	18.3%	-20.40 [-25.46 , -15.34]
Langille 2013	121.5	24.2	14	131.5	26.3	14	1.3%	-10.00 [-28.72 , 8.72]
Pannerselvam 2019	89.375	12.4319	56	100.89	11.22	28	16.9%	-11.52 [-16.79 , -6.24]
Quiroga 2018	185	55.23	5	122.6	42.03	5	0.1%	62.40 [1.57 , 123.23]
Yang 2021	105.5	28.7	30	115.7	28.7	30	2.2%	-10.20 [-24.72 , 4.32]
Total (95% CI)			**377**			**289**	**100.0%**	**-17.15 [-19.32 , -14.99]**

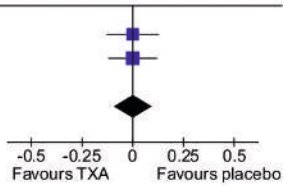
Heterogeneity: Chi² = 48.41, df = 9 (P < 0.00001); I² = 81%
Test for overall effect: Z = 15.51 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 26: Incomplete surgery

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Langille 2013	0	14	0	14	46.8%	0.00 [-0.13 , 0.13]
Padhy 2019	0	15	0	15	53.2%	0.00 [-0.12 , 0.12]
Total (95% CI)		**29**		**29**	**100.0%**	**0.00 [-0.09 , 0.09]**
Total events:	0		0			

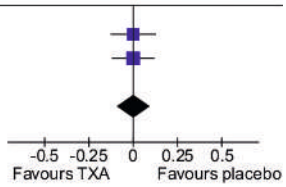
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 27: Surgical complications

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Langille 2013	0	14	0	14	46.8%	0.00 [-0.13 , 0.13]
Padhy 2019	0	15	0	15	53.2%	0.00 [-0.12 , 0.12]
Total (95% CI)		**29**		**29**	**100.0%**	**0.00 [-0.09 , 0.09]**
Total events:	0		0			

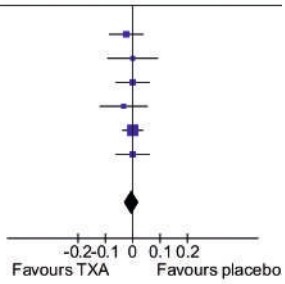
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 28: Postoperative bleeding (place of packing or revision surgery within 14 days of surgery)

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Alimian 2011	0	42	1	42	14.7%	-0.02 [-0.09 , 0.04]
Athanasiadis 2007	0	20	0	20	7.0%	0.00 [-0.09 , 0.09]
Baradaranfar 2017	0	30	0	30	15.1%	0.00 [-0.06 , 0.06]
El Shal 2015	0	30	1	30	7.7%	-0.03 [-0.12 , 0.05]
Eldaba 2013	0	50	0	50	40.5%	0.00 [-0.04 , 0.04]
Yang 2021	0	30	0	30	15.1%	0.00 [-0.06 , 0.06]
Total (95% CI)		**202**		**202**	**100.0%**	**-0.01 [-0.03 , 0.02]**
Total events:	0		2			

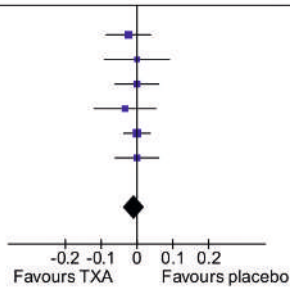
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 5 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1: Tranexamic acid versus placebo (saline solution or sterile water), Outcome 29: Postoperative bleeding (place of packing or revision surgery within 14 days of surgery) using fixed-effect model

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Alimian 2011	0	42	1	42	20.8%	-0.02 [-0.09 , 0.04]
Athanasiadis 2007	0	20	0	20	9.9%	0.00 [-0.09 , 0.09]
Baradaranfar 2017	0	30	0	30	14.9%	0.00 [-0.06 , 0.06]
El Shal 2015	0	30	1	30	14.9%	-0.03 [-0.12 , 0.05]
Eldaba 2013	0	50	0	50	24.8%	0.00 [-0.04 , 0.04]
Yang 2021	0	30	0	30	14.9%	0.00 [-0.06 , 0.06]
Total (95% CI)		**202**		**202**	**100.0%**	**-0.01 [-0.04 , 0.02]**
Total events:	0		2			

Heterogeneity: Chi² = 0.95, df = 5 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Summary of studies comparing topical tranexamic acid with placebo

Study ID	Intervention	Comparison	Drug delivery	Dose
Athanasiadis 2007	Tranexamic acid	Placebo	Spray	100 mg or 1000 mg once during the conclusion of surgery in one nostril; the contralateral nostril received placebo
Baradaranfar 2017	Tranexamic acid	Placebo	Rinsing	2 g in 400 mL saline in case the field became obscured
El-Ozairy 2021	Tranexamic acid	Placebo	Rinsing	2 g in 400 mL saline solution (study also compares intravenous application with placebo, or combined)
Jabalameli 2006	Tranexamic acid	Placebo	Rinsing	1 g in 20 mL saline once during surgery

Table 2. Summary of studies comparing intravenous application of tranexamic acid with placebo

Study ID	Intervention	Comparison	Drug delivery	Dose
Alimian 2011	Tranexamic acid	Placebo	Intravenous administration	Bolus of 10 mg/kg after induction of TIVA
Dongare 2018	Tranexamic acid	Placebo	Intravenous administration	Bolus of 15 mg/kg pre-operative
El Shal 2015	Tranexamic acid	Placebo	Intravenous administration	10 mg/kg diluted in 100 mL saline solution after induction of anaesthesia
Eldaba 2013	Tranexamic acid	Placebo	Intravenous administration	25 mg/kg diluted in 10 mL saline solution after induction of anaesthesia
El-Ozairy 2021	Tranexamic acid	Placebo	Intravenous administration	15 mg/kg diluted in 20 mL saline over 30 minutes (study also compares topical treatment with placebo, or combined)
Langille 2013	Tranexamic acid	Placebo	Intravenous administration	Bolus 15 mg/kg + infusion 1 mg/kg/hour in 100 mL saline
Nuhi 2015	Tranexamic acid	Placebo	Intravenous administration	15 mg/kg once on the day of surgery
Padhy 2019	Tranexamic acid	Placebo	Intravenous administration	10 mg/kg after induction phase
Pannerselvam 2019	Tranexamic acid	Placebo	Intravenous administration	5 mg/kg or 15 mg/kg 20 minutes prior to surgery
Quiroga 2018	Tranexamic acid	Placebo	Intravenous administration	500 mg per 5 mL 1 hour prior to surgery
Yang 2021	Tranexamic acid	Placebo	Intravenous administration	15 mg/kg in 100 mL normal saline over 30 minutes

TIVA: total intravenous anaesthesia

Table 3. Summary of studies comparing low- versus high-dose tranexamic acid with placebo

Study ID	Intervention	Comparison	Drug delivery	Dose
Athanasiadis 2007	Tranexamic acid 100 mg	Tranexamic acid 1000 mg	Topical spray	Once during the conclusion of surgery in one nostril; the contralateral nostril received placebo
Pannerselvam 2019	Tranexamic acid 5 mg/kg	Tranexamic acid 15 mg/kg	Intravenous	Once 20 minutes before surgery diluted in 100 mL of saline solution

APPENDICES

Appendix 1. Search strategies

CENTRAL (via CRS Web)	Cochrane ENT Register (via CRS Web)
1 MESH DESCRIPTOR Sinusitis EXPLODE ALL AND CENTRAL:TARGET 2 MESH DESCRIPTOR Rhinitis AND CENTRAL:TARGET 3 MESH DESCRIPTOR Rhinitis, Atrophic EXPLODE ALL AND CENTRAL:TARGET 4 MESH DESCRIPTOR Rhinitis, Vasomotor EXPLODE ALL AND CENTRAL:TARGET 5 MESH DESCRIPTOR Paranasal Sinus Diseases AND CENTRAL:TARGET 6 MESH DESCRIPTOR Paranasal Sinuses EXPLODE ALL AND CENTRAL:TARGET 7 (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 8 (kartagener* near syndrome*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 9 (inflamm* near sinus*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 10 ((maxilla* or frontal*) near sinus*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 12 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET 13 MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET 14 (chronic or persis* or recurrent*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 15 #12 OR #13 OR #14 16 #11 AND #15 17 ((sinusitis or rhinitis) near (chronic or persis* or recurrent*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 18 (CRSwNP or CRSsNP or ARS or RARS or ARR):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 19 #16 OR #17 OR #18 20 MESH DESCRIPTOR Nasal Polyps EXPLODE ALL AND CENTRAL:TARGET 21 MESH DESCRIPTOR Nose EXPLODE ALL AND CENTRAL:TARGET 22 MESH DESCRIPTOR Nose Diseases EXPLODE ALL AND CENTRAL:TARGET 23 #21 OR #22 24 MESH DESCRIPTOR Polyps EXPLODE ALL AND CENTRAL:TARGET 25 #23 AND #24 26 ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) near (papilloma* or polyp*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 27 (rhinopolyp*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 28 #19 OR #20 OR #25 OR #26 OR #27 29 MESH DESCRIPTOR Endoscopy EXPLODE ALL AND CENTRAL:TARGET 30 MESH DESCRIPTOR Surgical Procedures, Operative EXPLODE ALL AND CENTRAL:TARGET 31 (surg*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 32 (endoscop* or uncinectomy or antrostomy or antrotomy or ethmoidectomy or sphenoidotomy):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 33 (sinus* near surg*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 34 (ess):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 35 #29 OR #30 OR #31 OR #32 OR #33 OR #34 36 #28 AND #35 37 MESH DESCRIPTOR Sinusitis EXPLODE ALL WITH QUALIFIER SU AND	1 (trans and (cyclohexanecarboxylic or "cyclohexane carboxylic")):AB, EH, KW, KY, MC, MH, TI, TO AND INREGISTER 2 (tranexamic or AMCHA or AMCA or Anvitoff or Cyclo-F or Cyklokapron or Espercil or Exacyl or Femstrual or Lysteda or Spotof or Transamin* or Transcam* or TXA or Traxyl or Ugurol or "KABI 2161" or spotof or Amchafibrin* or Antifibrinolytic* or "Anti fibrinolytic*" or Anti-fibrinolytic* or Antifibrinolysin* or Aminocaproic*): AB, EH, KW, KY, MC, MH, TI, TO AND INREGISTER 3 (plasma near inhibitor*): AB, EH, KW, KY, MC, MH, TI, TO AND INREGISTER 4 #1 OR #2 OR #352 #46 AND #51

Ovid MEDLINE	Ovid Embase
1 exp Sinusitis/	1 exp sinusitis/
2 Rhinitis/	2 rhinitis/
3 exp Rhinitis, Atrophic/	3 exp atrophic rhinitis/
4 exp Rhinitis, Vasomotor/	4 exp vasomotor rhinitis/
5 Paranasal Sinus Diseases/	5 paranasal sinus disease/
6 exp Paranasal Sinuses/	6 exp paranasal sinus/
7 (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis).ab,ti.	7 (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis).ab,ti.
8 (kartagener* adj6 syndrome*).ab,ti.	8 (kartagener* adj6 syndrome*).ab,ti.
9 (inflamm* adj6 sinus*).ab,ti.	9 (inflamm* adj6 sinus*).ab,ti.
10 ((maxilla* or frontal*) adj6 sinus*).ab,ti.	10 ((maxilla* or frontal*) adj6 sinus*).ab,ti.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp Chronic Disease/	12 exp chronic disease/
13 exp Recurrence/	13 exp recurrent disease/
14 (chronic or persis* or recurrent*).ab,ti.	14 (chronic or persis* or recurrent*).ab,ti.
15 12 or 13 or 14	15 12 or 13 or 14
16 11 and 15	16 11 and 15
17 ((sinusitis or rhinitis) adj6 (chronic or persis* or recurrent*)).ab,ti.	17 ((sinusitis or rhinitis) adj6 (chronic or persis* or recurrent*)).ab,ti.
18 (CRSwNP or CRSsNP or ARS or RARS or ARR).ab,ti.	18 (CRSwNP or CRSsNP or ARS or RARS or ARR).ab,ti.
19 16 or 17 or 18	19 16 or 17 or 18
20 exp Nasal Polyps/	20 exp nose polyp/
21 exp Nose/	21 exp nose/
22 exp Nose Diseases/	22 exp nose disease/
23 21 or 22	23 21 or 22
24 exp Polyps/	24 exp polyp/
25 23 and 24	25 23 and 24
26 ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj6 (papilloma* or polyp*)).ab,ti.	26 ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj6 (papilloma* or polyp*)).ab,ti.
27 rhinopolyp*.ab,ti.	27 rhinopolyp*.ab,ti.
28 19 or 20 or 25 or 26 or 27	28 19 or 20 or 25 or 26 or 27
29 exp Endoscopy/	29 exp endoscopy/
30 exp Surgical Procedures, Operative/	30 exp surgery/
31 surg*.ab,ti.	31 (endoscop* or uncinectomy or antrostomy or antrotomy or ethmoidectomy or sphenoidotomy).ab,ti.
32 (endoscop* or uncinectomy or antrostomy or antrotomy or ethmoidectomy or sphenoidotomy).ab,ti.	32 surg*.ab,ti.
33 (sinus* adj6 surg*).ab,ti.	33 ess.ab,ti.
34 ess.ab,ti.	34 (sinus* adj6 surg*).ab,ti.
35 29 or 30 or 31 or 32 or 33 or 34	35 29 or 30 or 31 or 32 or 33 or 34
36 28 and 35	36 28 and 35
37 exp Sinusitis/su [SURGERY]	37 exp sinusitis/su [Surgery]
38 Paranasal Sinus Diseases/su [SURGERY]	38 exp paranasal sinus/su [Surgery]
39 exp Paranasal sinuses/su [SURGERY]	39 paranasal sinus disease/su [Surgery]
40 exp Rhinitis/su [SURGERY]	40 exp rhinitis/su [Surgery]
41 exp Nasal Polyps/su [SURGERY]	41 exp nose polyp/su [Surgery]
42 (endoscop* adj6 sinus* adj6 surg*).ab,ti.	42 (endoscop* adj6 sinus* adj6 surg*).ab,ti.
	43 (sinonasal* and surg*).ab,ti.

[continued on next page]

Appendix 1. *[continued]*

CENTRAL:TARGET
38 MESH DESCRIPTOR Paranasal Sinus Diseases WITH QUALIFIER SU AND CENTRAL:TARGET
39 MESH DESCRIPTOR Paranasal sinuses EXPLODE ALL WITH QUALIFIER SU AND CENTRAL:TARGET
40 MESH DESCRIPTOR Rhinitis EXPLODE ALL WITH QUALIFIER SU AND CENTRAL:TARGET
41 MESH DESCRIPTOR Nasal Polyps EXPLODE ALL WITH QUALIFIER SU AND CENTRAL:TARGET
42 (endoscop* near sinus* near surg*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
43 (sinonasal* and surg*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
44 (FESS):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
45 (((paranasal or nasal) near sinus*) and surg*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
46 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
47 MESH DESCRIPTOR Antifibrinolytic Agents EXPLODE ALL AND CENTRAL:TARGET
48 (tranexamic or AMCHA or AMCA or Anvitoff or Cyclo-F or Cyklokapron or Espercil or Exacyl or Femstrual or Lysteda or Spotof or Transamin* or Transcam* or TXA or Traxyl or Ugurol or "KABI 2161" or spotof or Amchafibrin* or Antifibrinolytic* or "Anti fibrinolytic*" or Anti-fibrinolytic* or Antifibrinolysin* or Aminocaproic*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
49 (trans and (cyclohexanecarboxylic or "cyclohexane carboxylic")):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
50 (plasma near inhibitor*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
51 #47 OR #48 OR #49 OR #50

Web of Science (Web of Knowledge	**ClinicalTrials.gov**
#1 TOPIC: (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis) #2 TOPIC: (kartagener* near/6 syndrome*) #3 TOPIC: (inflamm* near/6 sinus*) #4 TOPIC: (((maxilla* or frontal*) near/6 sinus*)) #5 #4 OR #3 OR #2 OR #1 #6 TOPIC: (chronic or persis* or recurrent*) #7 #6 AND #5	**via CRS Web** 1 (trans and (cyclohexanecarboxylic or "cyclohexane carboxylic")) AND ALL:CRSTYPE AND CENTRAL:TARGET 2 (tranexamic or AMCHA or AMCA or Anvitoff or Cyclo-F or Cyklokapron or Espercil or Exacyl or Femstrual or Lysteda or Spotof or Transamin*

43 (sinonasal* and surg*).ab,ti. 44 FESS.ab,ti. 45 (((paranasal or nasal) adj6 sinus*) and surg*).ab,ti. 46 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 47 exp Antifibrinolytic Agents/ 48 (tranexamic or AMCHA or AMCA or Anvitoff or Cyclo-F or Cyklokapron or Espercil or Exacyl or Femstrual or Lysteda or Spotof or Transamin* or Transcam* or TXA or Traxyl or Ugurol or "KABI 2161" or spotof or Amchafibrin* or Antifibrinolytic* or "Anti fibrinolytic*" or Anti-fibrinolytic* or Antifibrinolysin* or Aminocaproic*).ab,ti. 49 (trans and (cyclohexanecarboxylic or "cyclohexane carboxylic")).ab,ti. 50 (plasma adj6 inhibitor*).ab,ti. 51 47 or 48 or 49 or 50 52 46 and 51	44 FESS.ab,ti. 45 (((paranasal or nasal) adj6 sinus*) and surg*).ab,ti. 46 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 47 exp antifibrinolytic agent/ 48 (tranexamic or AMCHA or AMCA or Anvitoff or Cyclo-F or Cyklokapron or Espercil or Exacyl or Femstrual or Lysteda or Spotof or Transamin* or Transcam* or TXA or Traxyl or Ugurol or "KABI 2161" or spotof or Amchafibrin* or Antifibrinolytic* or "Anti fibrinolytic*" or Anti-fibrinolytic* or Antifibrinolysin* or Aminocaproic*).ab,ti. 49 (trans and (cyclohexanecarboxylic or "cyclohexane carboxylic")).ab,ti. 50 (plasma adj6 inhibitor*).ab,ti. 51 47 or 48 or 49 or 50 52 46 and 51 53 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 54 (control* adj group*).tw. 55 (trial* and (control* or comparative)).tw. 56 ((blind* or mask*) and (single or double or triple or treble)).tw. 57 (treatment adj arm*).tw. 58 (control* adj group*).tw. 59 (phase adj (III or three)).tw. 60 (versus or vs).tw. 61 rct.tw. 62 crossover procedure/ 63 double blind procedure/ 64 single blind procedure/ 65 randomization/ 66 placebo/ 67 exp clinical trial/ 68 parallel design/ 69 Latin square design/ 70 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 71 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 72 exp human/ 73 71 not 72 74 70 not 73 75 52 and 74
ICTRP	**Other**
tranexamic* AND sinus* OR tranexamic* AND nasal OR tranexamic* AND nose OR tranexamic* AND paranasal OR tranexamic* AND rhinitis OR tranexamic* AND rhino* OR tranexamic* AND sinonasal OR tranexamic* AND FESS OR tranexamic* AND ESS OR tranexamic* AND CRS* OR Antifibrinolytic* AND sinus* OR Antifibrinoly* AND nasal OR Antifibrinoly* AND nose OR Antifibrinoly*	**LILACS** TW:tranexamic* OR TW:Antifibrinoly* OR (TW:"plasma inhibitor*") OR TW:Antiplasmin* AND Controlled Clinical Trial **CNKI (via Google Scholar)** site:en.cnki.com.cn (tranexamic OR Antifibrinolytic AND Antifibrinolytics OR "plasma inhipitor") (fess OR (sinus

[continued on next page]

Appendix 1. *[continued]*

#8 TOPIC: ((sinusitis or rhinitis) near/6 (chronic or persis* or recurrent*)) #9 TOPIC: (CRSwNP or CRSsNP or ARS or RARS or ARR) #10 TOPIC: ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) near/6 (papilloma* or polyp*)) #11 TOPIC: (rhinopolyp*) #12 #11 OR #10 OR #9 OR #8 OR #7 #13 TOPIC: (endoscop* or uncinectomy or antrostomy or antrotomy or ethmoidectomy or sphenoidotomy or surg*) #14 TOPIC: (sinus* near/6 surg*) #15 TOPIC: (ess) #16 #15 OR #14 OR #13 #17 #16 AND #12 #18 TOPIC: ((endoscop* near/6 sinus* near/6 surg*)) #19 TOPIC: (sinonasal* and surg*) #20 TOPIC: (FESS) #21 TOPIC: ((((paranasal or nasal) NEAR/6 sinus*) and surg*)) #22 #21 OR #20 OR #19 OR #18 OR #17 #23 TOPIC: ((tranexamic or AMCHA or AMCA or Anvitoff or Cyclo-F or Cyklokapron or Espercil or Exacyl or Femstrual or Lysteda or Spotof or Transamin* or Transcam* or TXA or Traxyl or Ugurol or "KABI 2161" or spotof or Amchafibrin* or Antifibrinolytic* or "Anti fibrinolytic*" or Anti-fibrinolytic* or Antifibrinolysin* or Aminocaproic*)) #24 TOPIC: ((trans and (cyclohexanecarboxylic or "cyclohexane carboxylic"))) #25 TOPIC: (plasma near/6 inhibitor*) #26 #25 OR #24 OR #23 #27 #26 AND #22	or Transcam* or TXA or Traxyl or Ugurol or "KABI 2161" or spotof or Amchafibrin* or Antifibrinolytic* or "Anti fibrinolytic*" or Anti-fibrinolytic* or Antifibrinolysin* or Aminocaproic*) AND ALL:CRSTYPE AND CENTRAL:TARGET 3 (plasma near inhibitor*) AND ALL:CRSTYPE AND CENTRAL:TARGET 4 #1 OR #2 OR #3 AND ALL:CRSTYPE AND CENTRAL:TARGET 5 (nct*):AU AND CENTRAL:TARGET 6 (nct*):SID,SN AND STUDY:CRSTYPE AND CENTRAL:TARGET 7 #5 OR #6 AND ALL:CRSTYPE AND CENTRAL:TARGET 8 #4 AND #7 AND ALL:CRSTYPE AND CENTRAL:TARGET **via www.clinicaltrials.gov** (tranexamic OR Antifibrinolytic OR "Anti fibrinolytic" OR AMCHA OR AMCA OR Anvitoff OR Cyclo-F OR Cyklokapron OR Espercil OR Exacyl OR Femstrual OR Lysteda OR Spotof OR Transamin OR transmins OR Antifibrinolysin* OR Aminocaproic* OR TXA OR Traxyl OR Ugurol OR "KABI 2161" OR spotof OR Amchafibrin* OR (trans AND cyclohexanecarboxylic) OR (trans AND "cyclohexane carboxylic" OR Antifibrinolytics) OR "plasma inhipitor") AND (fess OR (sinus AND surgery) OR ESS OR (nose AND surgery) OR (nasal AND surgery) OR (paranasal AND surgery) OR rhinitis OR rhinosinusitis OR sinusitis OR crs OR crswnp OR crssnp OR (nasal polyp) OR (sinonasal AND surgery)) Study Type: Interventional

AND paranasal OR Antifibrinoly* AND rhinitis OR Antifibrinoly* AND rhino* OR Antifibrinoly* AND sinonasal OR Antifibrinoly* AND FESS OR Antifibrinoly* AND ESS OR Antifibrinoly* AND CRS* OR “Anti fibrinoly*” AND sinus* OR “Anti fibrinoly*” AND nasal OR “Anti fibrinoly*” AND nose OR “Anti fibrinoly*” AND paranasal OR “Anti fibrinoly*” AND rhinitis OR “Anti fibrinoly*” AND rhino* OR “Anti fibrinoly*” AND sinonasal OR “Anti fibrinoly*” AND FESS OR “Anti fibrinoly*” AND ESS OR “Anti fibrinoly*” AND CRS* OR Antiplasmin** AND sinus* OR Antiplasmin* AND nasal OR Antiplasmin* AND nose OR Antiplasmin* AND paranasal OR Antiplasmin* AND rhinitis OR Antiplasmin* AND rhino* OR Antiplasmin* AND sinonasal OR Antiplasmin* AND FESS OR Antiplasmin* AND ESS OR Antiplasmin* AND CRS*	surgery) OR ESS OR (nasal surgery) OR (paranasal surgery) OR rhinitis OR rhinosinusitis OR sinusitis OR (nasal polyp) OR (sinonasal surgery))

Appendix 2. Summary of data collection

We extracted the following information using a data collection form.

- General information: publication type, year, country, author contact details.
- Study eligibility: type of study, participants, types of interventions, comparisons and outcomes.
- Study methods: design, unit of allocation, start and end dates, duration of participation, ethical approval, funding, possible conflicts of interest.
- Participants: population description, setting, inclusion and exclusion criteria, method of recruitment, informed consent, total number randomised, clusters (if applicable), baseline imbalances, withdrawals and exclusions, age, sex, race/ethnicity, severity of illness, comorbidities, other relevant sociodemographics, measured and reported subgroups, confounders:
  - application of anti-Trendelenburg position (degrees?);
  - anaesthetic and vasoconstrictive agents administrated to prepare surgical field;
  - administration of total intravenous anaesthesia or inhalational agents;
  - mean arterial pressure;
  - surgical instruments applied (traditional, microdebrider);
  - presence of polyps, active infection and fungal rhinosinusitis.
- Intervention and comparison groups: tranexamic acid and comparison type, number randomised to group, duration of treatment, timing, delivery, dosage, providers, co-interventions, economic information, resource requirements, integrity of delivery, compliance.
- Outcomes: type of outcome, time points measured, time points reported, unit of measurement, scale, assumed risk estimate, power.
- Funding sources.
- Declarations of interest.
- Risk of bias assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other bias.
- Data and analysis: comparison, outcome, subgroup, time points, results, number of missing participants, reason missing, number of participants moved from another group, reason for move, unit of analysis, statistical method.
- Other information: key conclusions of the study, references to other relevant studies.

History

Protocol first published: Issue 11, 2017

Contributions of authors

Drafting the protocol: MJL Ravesloot, E Lourijsen, V Pundir, WJ Fokkens.
Obtaining copies of studies: E Lourijsen, K Avdeeva.
Selecting which studies to include: E Lourijsen, K Avdeeva, KL Gan.
Extracting data from studies: E Lourijsen, K Avdeeva.
Assessing risk of bias: E Lourijsen, K Avdeeva.

Entering data into RevMan: E Lourijsen.
Carrying out the analysis: E Lourijsen, K Avdeeva, WJ Fokkens.
Interpreting the analysis: E Lourijsen, K Avdeeva, WJ Fokkens.
Drafting the final review: E Lourijsen, WJ Fokkens.
Updating the review: E Lourijsen, K Avdeeva, WJ Fokkens.

Declarations of interest

E Lourijsen: none known.
K Avdeeva: none known.
V Pundir: none known.
KL Gan: none known.
WJ Fokkens: none known.

Sources of support

Internal sources

- Amsterdam Medical Research BV, Netherlands
  Salary

External sources

- National Institute for Health Research, UK
  Infrastructure funding for Cochrane ENT

Differences between protocol and review

We adapted the sources to search from those listed in the Methods section of the protocol (Ravesloot 2017) for the search run for the review. We did not search the following resources:

- PubMed (as a top up to searches in Ovid MEDLINE);
- EBSCO CINAHL (1982 to date);
- Ovid CAB abstracts (1910 to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (search to date);
- ISRCTN, www.isrctn.com (search to date);
- Google (search to date).

We decided to report all outcomes in the summary of findings table, instead of the four outcomes selected in the protocol.

Following methodological feedback, we have made some edits in Types of outcome measures to clarify our time points of interest and prioritisation of scoring systems for the surgical field bleeding score primary outcome. We have also defined our pre-planned subgroups as primary and secondary subgroups.

CHAPTER 9

ORAL AND INTRANASAL ASPIRIN DESENSITISATION FOR NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)-EXACERBATED RESPIRATORY DISEASE

E.Lourijsen, K. Avdeeva, K.L. Gan, W.Fokkens

Cochrane Database Syst Rev. (accepted for publication)

ABSTRACT

Background

NSAID-exacerbated respiratory disease (N-ERD) is a hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, accompanied by chronic rhinosinusitis (with or without nasal polyps) or asthma. The prevalence of hypersensitivity to NSAIDs is estimated to be 2%. The first line of treatment is the avoidance of NSAIDs. Another treatment option is aspirin treatment after desensitisation (ATAD). Desensitisation can be induced by repeated administration of aspirin at fixed time intervals. The clinical benefit of aspirin might occur through inhibition of interleukin 4 and a reduction in prostaglandin D2. This therapy can be useful for people who have progressive airway disease and are in great need of medical intervention (mostly systemic corticosteroids) or surgery. An up-to-date Cochrane review is vital to investigate the effects of this therapy.

Objectives

To assess the effectiveness of oral or intranasal aspirin desensitisation, as monotherapy or as adjunctive therapy, in adults with NSAID-exacerbated respiratory disease.

Search methods

The Cochrane Ear Nose and Throat (ENT) Information Specialist searched the Cochrane ENT and Airways Trials Registers; Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; International Clinical Trials Registry Platform and additional sources for published and unpublished trials. The date of the search was 10 February 2023.

Selection criteria

Randomised controlled trials that compared ATAD with placebo were eligible. We included studies of adults with NSAID-exacerbated respiratory disease (i.e. intolerance to NSAID established, e.g. by aspirin challenge test), with chronic rhinosinusitis or asthma, or both. Participants had to be followed up for at least three months.

Data collection and analysis

We used standard Cochrane methods. The primary outcomes were health-related quality of life, asthma control, and significant serious and non-serious adverse events. The secondary outcomes were changes in airway assessments, nasal endoscopy score, medication use, symptom scores, and chronic rhinosinusitis and asthma exacerbations (description of exacerbation for which systemic corticosteroid or sinus surgery was needed). We used the GRADE approach to rate the certainty of the evidence.

MAIN RESULTS

We included five studies with a total of 211 participants (146 analysed). All studies compared oral ATAD at different dosages with placebo and were performed in tertiary care centres. All participants had a diagnosis of chronic rhinosinusitis with nasal polyps. In four studies, participants also had a confirmed diagnosis of asthma and two studies reported that participants had previous surgery for nasal polyps. Outcomes were analysed at six and 36 months follow-up. However, only one study reported data for 36 months follow-up. All but one study reported source of funding.

Mid-term follow-up (six months, ATAD versus placebo)
ATAD may improve health-related quality of life, assessed with Sino-Nasal Outcome Test (SNOT) scores (mean difference (MD) –0.54, 95% confidence interval (CI) –0.76 to –0.31; 3 studies, 85 participants; minimum clinically important difference (MCID) 9.0 points for total score; low-certainty evidence). In this analysis, SNOT-22 scores were divided by 22 and SNOT-20 scores were divided by 20. The mean reduction (11.9 points) in SNOT score (based on SNOT-22) is larger than the MCID.

It is uncertain if asthma control may be improved after ATAD. Asthma control was measured using the Asthma Control Test (ACT) in one study and the Asthma Control Questionnaire (ACQ) in another study, so data were not pooled. The MD on the ACQ was –2.00 (total score 0 to 6) (95% CI –4.30 to 0.30; 1 study, 15 participants; MCID 0.5 points; very low-certainty evidence). The MD on the ACT was 5.90 (total score 5 to 25) (95% CI 2.93 to 8.87; 1 study, 30 participants; MCID 3 points; very low-certainty evidence).

All but one study reported on adverse events. Seven participants in the active treatment group developed a gastrointestinal disorder and dropped out (129 participants, very low-certainty evidence).

We are uncertain of the effect of ATAD on nasal airflow, measured by peak nasal inspiratory flow scores (MD 32.90 L/min, 95% CI –12.44 to 78.24; 1 study, 15 participants; very low-certainty evidence).

It is uncertain if the dosage of intranasal or inhaled corticosteroids may be reduced with ATAD (inhaled corticosteroids: –1197.60 µg, 95% CI –1744.93 to –650.27; intranasal corticosteroids: –120.50 µg, 95% CI –206.49 to –34.51; 1 study; 15 participants; very low-certainty evidence).

Symptom scores may not differ between ATAD and placebo, but the evidence is very uncertain (sneezing: MD –0.70, 95% CI –1.45 to 0.05; smell: MD –2.20, 95% CI –4.74 to 0.34; nasal blockage: MD –0.90, 95% CI –1.90 to 0.10; 1 study, very low-certainty evidence).

No study assessed nasal endoscopy at this time point.

Long-term follow-up (36 months, ATAD versus placebo)
ATAD may improve quality of life, as measured with the Rhinosinusitis Disability Index (RSDI) score (MD –18.10, 95% CI –32.82 to –3.38; 1 study; 31 participants; low-certainty evidence).

ATAD may result in little to no difference in the size of nasal polyps (MD –1.20, 95% CI –2.72 to 0.32; 1 study, 31 participants; very low-certainty evidence).

No adverse events were reported in either group over the total study period of 36 months (1 study; 31 participants; very low-certainty evidence).

Data on peak nasal inspiratory flow, changes in dosage of inhalation or intranasal corticosteroids and symptom scores were not reported at this time point.

Authors' conclusions

Aspirin treatment after desensitisation may improve health-related quality of life for people with N-ERD with a follow-up of six months. With respect to asthma control, adverse events, peak nasal inspiratory flow score, nasal endoscopy scores, changes in dosage of inhaled or intranasal corticosteroids, nasal and bronchial symptom scores, exacerbations or worsening of asthma and chronic rhinosinusitis (including the need for surgery), the evidence is inconclusive for the short-term and long-term. We did not find data on peak expiratory flow.

It is difficult to interpret the results adequately, due to the potential influence of use of any co-medications for chronic rhinosinusitis or asthma. Future research should emphasise longer duration of follow-up, report baseline disease characteristics and report on compliance and exacerbations for which additional medication or surgery is warranted.

PLAIN LANGUAGE SUMMARY

Is a procedure to induce tolerance for aspirin an effective treatment for adults with a hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs)?

Key messages

- Due to a lack of robust evidence, the benefits and harms of aspirin after desensitisation (ATAD) (a procedure to induce tolerance to aspirin by exposing an individual to the drug gradually) as a treatment option for people with a hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) remain unclear.
- Treatment with ATAD may lead to a better quality of life, although the evidence comes from small studies.
- Future studies should be large enough to demonstrate clear effects of aspirin treatment on the need for surgery and corticosteroid use.

What is NSAID-exacerbated respiratory disease?
NSAID-exacerbated respiratory disease (N-ERD) is a hypersensitivity to NSAIDs, such as aspirin or ibuprofen, accompanied by chronic rhinosinusitis (inflammation of the nose and sinuses that lasts 12 weeks or longer) with or without nasal polyps (benign swellings of the lining of the nose) or asthma. Using an NSAID for people with N-ERD leads to a runny nose, nasal blockage, shortness of breath or even swelling of the tongue or throat within 30 to 120 minutes. The symptoms can be mild or severe.

How is NSAID-exacerbated respiratory disease treated?
People with N-ERD often suffer from chronic rhinosinusitis or asthma (or both). Treatment with ATAD might be effective in reducing symptoms in people with severe chronic rhinosinusitis or asthma who need medicine (repeated courses of corticosteroids by mouth (powerful medicine that works to reduce inflammation, such as prednisone)) or have repeated surgery performed for chronic rhinosinusitis.

What did we want to find out?
We wanted to see whether ATAD could be an effective and safe treatment for people with N-ERD. We wanted to know whether ATAD could have an effect on quality of life or control of asthma, or result in less need for (oral) corticosteroids (such as prednisone, which may have unwanted effects) and less need for surgery in people with chronic rhinosinusitis.

What did we do?
We searched for studies that investigated aspirin (either given by mouth or sprayed directly into the nose) compared with a placebo (dummy pill). We were interested in adults with a confirmed diagnosis of aspirin intolerance with asthma or chronic rhinosinusitis, or both. We compared and summarised the results of the studies we found and rated our confidence in the evidence based on the amount and quality of the evidence found.

What did we find?
We found five studies with a total of 211 people. The studies, which were performed in specialist care centres, compared ATAD with placebo in people with a confirmed diagnosis of N-ERD. In all studies, treatment was given by mouth. All participants had chronic rhinosinusitis with nasal polyps. People in four studies also had asthma and two studies reported that participants had previous surgery for nasal polyps. Results were reported at six months after treatment, and one study reported data at 36 months. All but one study reported funding for the study.

We found that after six months of treatment, daily aspirin may result in better quality of life compared to placebo (based on three studies with 85 participants). It is unclear if the treatment has any effect on control of asthma, causes unwanted effects, affects the flow of air through the nose, changes the use of nasal sprays or asthma inhalers, or changes nasal or lung symptoms. No study reported on nasal polyps at six months.

One study reported that daily aspirin after 36 months may lead to a better quality of life, but may have little or no effect on the occurrence of any serious unwanted effects, size of nasal polyps and need for surgery. No unwanted effects were reported. The study did not report other results at 36 months.

We cannot conclude how often and for how long aspirin should be taken. People in these studies could use other medications for asthma and chronic rhinosinusitis, which could have a potential influence on the results.

What are the limitations of the evidence?
We have little confidence in the evidence for improved quality of life. We are very unclear about the evidence for aspirin controlling asthma or causing unwanted effects. It is possible that people in the studies were aware of which treatment they were getting. Further, the studies were relatively small.

How up to date is the evidence?
The evidence is up to date to February 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (mid-term, 6 months of follow-up)

Oral or intranasal aspirin treatment after desensitisation versus placebo for adults with NSAID-exacerbated respiratory disease			
Patients or population: adults with NSAID-exacerbated respiratory disease			
Setting: tertiary hospitals			
Intervention: oral or intranasal aspirin treatment after desensitisation			
Control: placebo			
	Absolute effects* **(95% CI)**		**Relative effect (95% CI)**
Outcomes	**Risk with placebo**	**Risk with ATAD**	
Health-related quality of life *Assessed with:* Sino-Nasal Outcome Test-20 or 22 (scores divided by 20 or 22 for this analysis respectively)	The mean health-related quality of life ranged from 1.63 to 1.85.	The mean health-related quality of life was **0.54 points lower** (0.76 lower to 0.31 lower).	—
Asthma control *Assessed with:* Asthma Control Questionnaire (ACQ, scale 0 (well-controlled) to 6 (extremely poorly controlled) or Asthma Control Test (ACT, scale 5 (poor control of asthma) to 25 (complete control of asthma))	1 RCT (15 participants) reported the ACQ and 1 RCT (30 participants) reported the ACT. Studies could not be pooled because the outcomes are different in direction (lower points on the ACQ indicate better control, lower points on the ACT indicate less control). ACQ: mean 2.2 in placebo group; MD 2.00 lower (4.30 lower to 0.30 higher) in ATAD group ACT: mean 14.6 in placebo group; MD 5.90 higher (2.93 to 8.87 higher) in ATAD group		
Significant serious and non-serious adverse events: gastrointestinal disturbance, including nausea and vomiting, diarrhoea, abdominal pain	Study population		Risk ratio 3.71 (0.67 to 20.47)
	0/52	7/77	
Airway assessment (change in peak nasal inspiratory flow (PNIF, L/min) and change in peak expiratory flow (PEF))	The mean airway assessment (change in PNIF) was 53.2 L/min.	The mean PNIF was **32.90 L/min higher** (12.44 lower to 78.24 higher).	—
Nasal endoscopy score (i.e. Modified Lund Kennedy, Hadley's clinical scoring)	—	—	—

Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
85 (3 RCTs)	⨁⨁◯◯ **Low**[a,b]	ATAD may decrease the SNOT score. When converted to mean SNOT-22 scores, the score in the ATAD group was 11.9 points lower compared to placebo (scale 0 to 110), which is larger than the minimum clinically important difference of 9.0 points.
45 (2 RCTs)	⨁◯◯◯ **Very low** [a,c]	We are uncertain whether ATAD changes asthma control.
129 (4 RCTs)	⨁◯◯◯ **Very low**[c,d]	We are uncertain whether ATAD changes the risk of significant adverse events up to 6 months of treatment.
15 (1 RCT)	⨁◯◯◯ **Very low**[c,e]	We are uncertain whether ATAD changes PNIF values. None of the studies reported on PEF.
—	—	None of the included studies reported on this outcome.

[continued on next page]

Summary of findings 1. *[continued]*

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)
	Risk with placebo	Risk with ATAD	
Medication use (change in dosage of nasal corticosteroid spray or inhaled corticosteroids)	The mean medication use (change in dosage of nasal corticosteroid spray) was 89 µg.	The mean medication use (change in dosage of nasal corticosteroid spray) was **120.50 µg lower** (206.49 lower to 34.51 lower).	—
	The mean medication use (change in dosage of inhaled corticosteroids) was 539.3 µg.	The mean medication use (change in dosage of inhaled corticosteroids) was **1197.60 µg lower** (1744.93 lower to 650.27 lower).	—
Symptom scores (nasal and bronchial symptoms) Assessed with a VAS scale 0 to 10	The mean smell symptom score using a VAS was 8.4 points.	The mean smell symptom score using a VAS was **2.20 points lower** (4.74 lower to 0.34 higher).	—
	The mean nasal blockage symptom score using a VAS was 2.9 points.	The mean nasal blockage symptom score using a VAS was **0.90 points lower** (1.90 lower to 0.10 higher).	—
	The mean sneezing symptom score using a VAS was 0.75 points.	The mean sneezing symptom score using a VAS was **0.70 points lower** (1.45 lower to 0.05 higher).	—

The risk in the intervention group (and the 95% CI) is based on the risk in the control group and the **relative effect** of the intervention (and the 95% CI).

ATAD: aspirin treatment after desensitisation; **CI:** confidence interval; **MD:** mean difference; **NSAID:** non-steroidal anti-inflammatory drug; **RCT:** randomised controlled trial; **SD:** standard deviation; **SNOT-22** Sino-Nasal Outcome Test 22; **VAS:** visual analogue scale
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
15 (1 RCT)	⊕⊖⊖⊖ **Very low**[c,f]	We are uncertain whether ATAD changes medication use (dosage of intranasal corticosteroids).
15 (1 RCT)	⊕⊖⊖⊖ **Very low**[c,f]	We are uncertain whether ATAD changes medication use (dosage of inhaled corticosteroids).
15 (1 RCT)	⊕⊖⊖⊖ **Very low**[c,g]	We are uncertain whether ATAD changes the smell symptom score.
15 (1 RCT)	⊕⊖⊖⊖ **Very low**[c,g]	We are uncertain whether ATAD changes the nasal blockage symptom score.
15 (1 RCT)	⊕⊖⊖⊖ **Very low**[c,g]	We are uncertain whether ATAD changes the sneezing symptom score.

[a]Downgraded one level due to risk of bias: unclear allocation concealment and incomplete outcome data.
[b]Downgraded one level due to imprecision: limited number of participants.
[c]Downgraded two levels due to imprecision: limited number of participants and wide confidence interval.
[d]Downgraded one level due to risk of bias: three of four included studies had a high risk of bias that seriously weakens confidence in the results.
[e]Downgraded one level due to high risk of bias: PEF values were not reported and incomplete outcome data (25% loss to follow-up) in the single study included.
[f]Downgraded one level due to risk of bias: high risk of bias in the single study included- (25% loss to follow-up).
[g]Downgraded two levels due to risk of bias: very high risk of bias in reported results - selected symptoms were reported, which might be the symptom scores with the largest effect. Furthermore, 25% loss to follow-up in the study.

Summary of findings 2. Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID) -exacerbated respiratory disease (long-term, 36 months of follow-up)

Oral or intranasal aspirin desensitisation for non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (long-term, 36 months of follow-up)			
Patients or population: adults with NSAID-exacerbated respiratory disease			
Setting: tertiary hospitals			
Intervention: oral or intranasal aspirin treatment after desensitisation			
Control: placebo			
	Absolute effects* **(95% CI)**		**Relative effect (95% CI)**
Outcome	**Risk with placebo**	**Risk with ATAD**	
Health-related quality of life *Assessed with:* Rhinosinusitis Disability Index Questionnaire for German-speaking countries (RSDI, scale 30 to 150)	The mean health-related quality of life, using disease-specific health-related quality of life scores, was 68.4 points.	The mean health-related quality of life was **18.10 points lower** (32.82 lower to 3.38 lower).	—
Asthma control *Assessed with:* Asthma Control Questionnaire (ACQ, scale 0 (well-controlled) to 6 (extremely poorly controlled) or Asthma Control Test (ACT, scale 5 (poor control of asthma) to 25 (complete control of asthma))	—	—	—
Significant serious and non-serious adverse events: gastrointestinal disturbance, including nausea and vomiting, diarrhoea, abdominal pain	Not estimable (zero events)	Not estimable (zero events)	Not estimable
Airway assessment (change in peak nasal inspiratory flow (PNIF, L/min) and change in peak expiratory flow (PEF))	—	—	—
Nasal endoscopy score (i.e. Modifiek Lund Kennedy, Hadley's clinical scoring)	The mean nasal endoscopy score was 2.2 points.	The mean nasal endoscopy score was **1.20 points lower** (2.72 lower to 0.32 higher).	—
Medication use (change in dosage of nasal corticosteroid spray or inhaled corticosteroids)	—	—	—
Symptom scores (nasal and bronchial symptoms using a VAS scale 0 to 10)	—	—	—

The risk in the intervention group (and the 95% CI) is based on the risk in the control group and the **relative effect** of the intervention (and the 95% CI).
ATAD: aspirin treatment after desensitisation; **CI:** confidence interval; **RCT:** randomised controlled trial; **VAS**: visual analogue scale
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be

	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	31 (1 RCT)	⊕⊕⊖⊖ **Low**[a]	ATAD may decrease the RSDI score, since the difference in score is larger than the minimum clinically important difference of 10.35.
	—	—	None of the included studies reported on this outcome.
	31 (1 RCT)	⊕⊕⊖⊖ **Low**[a]	The evidence suggests that ATAD results in little to no difference in adverse events.
	—	—	None of the included studies reported on this outcome.
	31 (1 RCT)	⊕⊕⊖⊖ **Low**[a]	ATAD may have little to no effect on nasal polyp size.
	—	—	None of the included studies reported on this outcome.
	—	—	None of the included studies reported on this outcome.

close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels due to imprecision: limited number of participants and wide confidence interval.

BACKGROUND

Description of the condition

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is the coexistence of hypersensitivity to NSAIDs with underlying inflammatory disease of the upper and lower airways. Most people with N-ERD suffer from severe refractory eosinophilic chronic rhinosinusitis (with nasal polyps) and severe persistent asthma (Kowalski 2019). Ingestion of an NSAID (e.g. aspirin, ibuprofen, naproxen, diclofenac) by people with N-ERD leads to watery rhinorrhoea (runny nose), nasal congestion, chest tightness and progressive bronchial obstruction within 30 to 120 minutes. The severity ranges from mild symptoms to life-threatening reactions (Szczeklik 2000). Extrabronchial symptoms can be present and include ocular symptoms, urticarial lesions, angioedema or gastrointestinal discomfort (Kowalski 2019).

The terminology NSAID-exacerbated respiratory disease (N-ERD) has recently been proposed for the disease (Kowalski 2019). Diagnosis of N-ERD is based on a reliable history of reactions to NSAID and simultaneous presence of chronic rhinosinusitis (CRS) with nasal polyps with or without asthma. In case of any uncertainty of history or diagnosis of asthma/CRS, an oral, bronchial or intranasal aspirin challenge is advised to confirm the diagnosis of N-ERD (Kowalski 2019). Provocation challenges with aspirin are the most reliable method used to confirm the diagnosis of N-ERD. Oral, bronchial (inhaled) and nasal aspirin challenge tests can be used according to European and American guidelines (Kowalski 2019; White 2013). The oral aspirin challenge is the gold standard for confirming hypersensitivity, with a sensitivity of 90% compared to clinical diagnosis (Kowalski 2019).

The prevalence of hypersensitivity to NSAIDs is estimated to be 2% in the general European population (Kowalski 2019). A recent meta-analysis found a mean prevalence of 7.1% in adults with asthma, based on history (Rajan 2015). The prevalence of N-ERD increases with the severity of the underlying airway disease, reaching 14.9% in people with severe asthma and 9.7% in people with chronic rhinosinusitis with nasal polyps (CRSwNP), again based on history (Philpott 2018; Rajan 2015). However, the prevalence in adults with asthma rises to 21% when NSAID hypersensitivity is determined by provocation (Kowalski 2019). N-ERD is very rare in children.

Hypersensitivity to NSAIDs is attributed to inhibition of cyclooxygenase 1 (COX-1), which is an important enzyme in the lipoxygenase pathway of arachidonic acid metabolism. This inhibition triggers respiratory symptoms with local and systemic generation of cysteinyl leukotrienes due to deprivation of the protective prostaglandin E2 expression and upregulation of LTC_4 synthase enzyme genes (Kowalski 2019; Sokolowska 2022).

People with a history or diagnosis of hypersensitivity will need to strictly avoid all NSAIDs with moderate or strong cyclooxygenase inhibitory activity (COX-1 inhibitors; e.g. aspirin,

naproxen). People could be advised to use COX-2 inhibitors for pain relief instead, if necessary (e.g. celecoxib, meloxicam). However, another management option is desensitisation, which can be induced by repeated administration of aspirin.

Description of the intervention

Aspirin desensitisation involves repeated administration of small doses of aspirin at fixed time intervals. Different protocols exist for oral aspirin desensitisation; however, it generally takes place over two consecutive days, with increasing doses of oral aspirin with time intervals of at least 1.5 to 2 hours. The initial dose is usually between 20 mg and 40 mg and is increased until the goal of tolerating 325 mg of aspirin is reached. Since desensitisation will likely induce symptoms in a person with N-ERD, desensitisation is performed under the guidance of a desensitisation protocol to mitigate the risks inherent to the provocation. There are no reported cases of anaphylaxis to aspirin itself; therefore, it is safe to use for desensitisation compared to other COX-1 inhibitors. Spirometry and symptoms are monitored at regular intervals during the desensitisation protocol. Whenever a reaction occurs, symptoms are treated with medication and the procedure resumes. The dose that forced the reaction is repeated until the person no longer reacts to it. Desensitisation can take place in an outpatient setting or an inpatient setting. However, close medical supervision is necessary (Kowalski 2019; Stevens 2021; Stevenson 1984; Waldram 2016; White 2013). To maintain desensitisation, people can be treated with a long-term maintenance dose that ranges from a total of 300 mg to 1300 mg per day in one or two doses (Berges-Gimeno 2003; Comert 2013; Kowalski 2019; Stevens 2021; Stevenson 2007; White 2018). Desensitisation can also be performed with topical nasal aspirin (lysine aspirin) until an equivalent to 75 mg to 100 mg of aspirin is reached (Howe 2014; Pendolino 2022).

Aspirin treatment after desensitisation (ATAD), as monotherapy or adjunctive therapy, is useful for people with N-ERD who present with progressive airway disease despite medical or surgical intervention, since long-term treatment with aspirin following desensitisation can improve the symptoms of rhinosinusitis and asthma (Kowalski 2019; Rozsasi 2008; Swierczynska-Krepa 2014). Several studies conducted at the Scripps Clinic between 1980 and 2000 using aspirin maintenance therapy for up to six years noted a delayed need for sinus surgery even after the study (Berges-Gimeno 2003; Stevenson 1984; Sweet 1990; White 2013). Moreover, ATAD is useful for people with N-ERD who require antiplatelet treatment with aspirin for the treatment of other disorders, such as ischaemic heart disease or stroke (Kowalski 2019).

How the intervention might work

The exact mechanism of action of ATAD for treating NSAID-hypersensitive people remains unknown. Recent studies suggest that the clinical benefits of aspirin desensitisation may occur through direct inhibition of tyrosine kinases and the signal transducer and activator of transcription 6 pathway, with resultant inhibition of interleukin 4 production. A reduction in prostaglandin D2 (PGD2), as a consequence of aspirin desensitisation, may also produce clinical benefit for people with N-ERD by precluding recruitment of PGD2 responsive effector

cells to the airways (Cousins 2023; Hill 2016; Sehanobish 2021). Several studies, including observational and placebo-controlled trials, have shown promising results in the improvement of chronic rhinosinusitis and asthma symptoms, and the reduction of intranasal corticosteroid use, nasal polyp recurrence and the need for revision surgery (Esmaeilzadeh 2015; Fruth 2013; Stevenson 1984; Swierczynska-Krepa 2014). These therapeutic effects can be observed as early as one month after aspirin desensitisation treatment of 650 mg twice a day (White 2013).

The incidence of adverse events related to the intake of aspirin ranges from 0% to 34%. These are mostly gastrointestinal symptoms and some centres advocate the use of preventive measures such as *Helicobacter pylori* eradication, proton-pump inhibitors and H2 blockers during the treatment period to counteract the adverse events associated with aspirin treatment (Kowalski 2019).

Why it is important to do this review

N-ERD is associated with refractory chronic rhinosinusitis with nasal polyps and severe or poorly controlled asthma, with the need for repeated surgery and a substantial requirement for systemic corticosteroids. Any intervention that can significantly improve quality of life, asthma control and overall symptoms and decrease the need for (oral) corticosteroids and sinus surgery would be of clinical benefit. In recent years, very promising results have been seen with biologics for improving symptoms; however, these agents are very expensive and not available to every person with N-ERD (Hellings 2021; Oykhman 2022). According to the latest European Academy of Allergy and Clinical Immunology (EAACI) position paper, aspirin treatment after desensitisation is an alternative management strategy for people with N-ERD (Kowalski 2019). Several placebo-controlled, double-blind trials have demonstrated favourable outcomes of aspirin desensitisation therapy for people with N-ERD (Esmaeilzadeh 2015; Fruth 2013; Mortazavi 2017; Swierczynska-Krepa 2014). Although treatment with a variety of biologicals for chronic rhinosinusitis and asthma is emerging, this is still a very costly option and not suitable for each person. Thus, an up-to-date Cochrane Review is vital to address the question of whether aspirin treatment after desensitisation is beneficial in terms of quality of life, symptom reduction and tolerability for people with N-ERD. It will be of added value in evidence-based practice.

OBJECTIVES

To assess the effectiveness of oral or intranasal aspirin desensitisation, as monotherapy or as adjunctive therapy, in adults with NSAID-exacerbated respiratory disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies with the following design characteristics:

- randomised controlled trials (RCTs), including cluster-randomised trials and quasi-randomised trials; and
- participant follow-up of at least three months, to reflect the importance of focusing on long-term outcomes for a chronic condition.

We included studies irrespective of publication status, date of publication or language.

Types of participants

We included trials that enrolled adults with NSAID-exacerbated respiratory disease (N-ERD), i.e. confirmed intolerance to NSAID (e.g. established by the aspirin challenge test according to Nizankowska-Mogilnicka 2007), with chronic rhinosinusitis or asthma, or both.

We excluded studies that included people with:

- chronic rhinosinusitis (with or without polyps) without N-ERD;
- asthma without proof of N-ERD;
- cystic fibrosis (CF) (as the disease is often refractory to standard non-CF CRS treatment due to the genetic mutation);
- antrochoanal polyps (benign polyps originating from the mucosa of the maxillary sinus);
- malignant polyps;
- primary ciliary dyskinesia (disease is often refractory to standard non-CF CRS treatment due to the genetic mutation);
- a history of surgery for nasal polyps within six weeks of entry to the study; and
- allergic fungal rhinosinusitis/eosinophilic fungal/mucinous rhinosinusitis (different pathologic entity of primary CRS).

If only a subset of participants were eligible in a study, we included it if at least 70% (arbitrary cut-off) of the participants fulfilled the inclusion criteria. In all other cases, we excluded the study.

Types of interventions

The treatment of interest was:

- aspirin treatment after desensitisation.

We included studies irrespective of the dose, duration or method of administration of aspirin.
The comparison was:

- aspirin treatment after desensitisation versus placebo.

We allowed co-interventions (i.e. inhaled/intranasal corticosteroids) as long as they were administered equally in each group.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies.

Primary outcomes

- Health-related quality of life, assessed using disease-specific health-related quality of life scores, such as the Sino-Nasal Outcome Test 20 or 22 (SNOT 20 or 22; Hopkins 2009), Rhinosinusitis Outcome Measures-31 (RSOM-31; Piccirillo 2002).
- Asthma control, measured with the Asthma Control Questionnaire (ACQ; Juniper 1999; Juniper 2005) or Asthma Control Test (ACT) (Schatz 2009)
- Significant serious and non-serious adverse events: gastrointestinal disturbance, including nausea and vomiting, diarrhoea, abdominal pain. Adverse events, reported as: adverse events during desensitisation and adverse events during maintenance therapy, with a maximum of 12 months follow-up.

Secondary outcomes

- Airway assessment (change in peak nasal inspiratory flow (PNIF) and change in peak expiratory flow (PEF) (Starling-Schwanz 2005)).
- Nasal endoscopy score (i.e. modified Lund-Kennedy, Hadley's clinical scoring and other appropriate scoring systems (Meltzer 2006; Psaltis 2014)).
- Medication use (changes in dosage of inhaled/intranasal corticosteroids).
- Symptom scores (nasal and bronchial symptoms using a visual analogue scale (VAS)).
- Chronic rhinosinusitis and asthma exacerbations, including the need for surgery.

In general, we only extracted the longest available data within the time intervals of interest. We defined three time intervals: short-term (3 to 6 months follow-up), mid-term (6 to 12 months follow-up) and long-term (› 12 months follow-up). For example, if a study reported data after four months and after six months, we only extracted the data after six months.

Search methods for identification of studies

The Cochrane Ear Nose and Throat (ENT) Information Specialist conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the search was 10 February 2023.

We contacted the original authors for clarification and further data if trial reports were unclear, and we arranged translations of papers where necessary.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Trials Register (via the Cochrane Register of Studies; searched 10 February 2023);
- the Cochrane Airways Trials Register (via the Cochrane Register of Studies; searched 10 February 2023);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2023, Issue 2) (searched via the Cochrane Register of Studies to February 2023);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 10 February 2023);
- Ovid EMBASE (1974 to 10 February 2023);
- Web of Knowledge, Web of Science (1945 to 10 February 2023);
- ClinicalTrials.gov (via the Cochrane Register of Studies; searched 10 February 2023);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (via the Cochrane Register of Studies; searched 10 February 2023)
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to 10 February 2023); and
- CNKI (China National Knowledge Infrastructure; via Google Scholar; searched to 10 February 2023).

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (Lefebvre 2022). Search strategies are provided in Appendix 1.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We did not perform a separate search for adverse events. We considered adverse events described in the included studies only.

DATA COLLECTION AND ANALYSIS

In successive sections, we only report the methods we used. Please refer to the previously published protocol (Gan 2019) and Differences between protocol and review for preplanned but unused methods.

Selection of studies

Two review authors (KLG and EL) independently screened the titles and abstracts of all the potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports and three review authors (KLG, EL, KA) independently screened the full-text reports and identified studies for inclusion; they also identified and recorded the reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third author (WJF). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021) and the Characteristics of excluded studies section.

Data extraction and management

Two review authors (KA and EL) independently extracted data from each study using a standardised data collection form (see Appendix 2).

Whenever a study had more than one publication, we retrieved all the publications to ensure complete extraction of data. Where there were discrepancies in the data extracted by different review authors, we checked these against the original reports and resolved differences by discussion and consensus, with the involvement of a third author (WJF) or a methodologist where appropriate. We contacted the original study authors for clarification or for missing data whenever possible. If differences were found between publications of a study, we contacted the original authors for clarification. We used data from the main paper(s) if no further information was found.

We included key characteristics of the studies, such as study design, setting, sample size, population and how outcomes were defined or collected in the studies. In addition, we also collected baseline information on prognostic factors or effect modifiers. For this review, it included:

- presence or absence of nasal polyps;
- baseline nasal polyp score;
- whether the participant has had previous sinus surgery; and
- presence or absence of a diagnosis of asthma.

For the outcomes of interest in the review, we extracted the findings of the studies on an available case analysis basis; i.e. we included data from all participants available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether participants had received the treatment as planned.

In addition to extracting prespecified information about study characteristics and aspects of methodology relevant to risk of bias, we extracted the following summary statistics for each trial and each outcome.

- For continuous data: the mean values, standard deviations and number of participants for each treatment group. If endpoint data were not available and the study reported only the baseline value and change from baseline, we extracted these values. We analysed data from measurement scales such as SNOT-22 as continuous data.
- For binary data: the number of participants experiencing an event and the number of participants assessed at the time point.
- For ordinal scale data: if the data appeared to be approximately normally distributed or if the analysis that the investigators performed suggested parametric tests were appropriate, then we treated the outcome measures as continuous data.

We prespecified three time intervals of interest for the outcomes in this review (see Types of outcome measures). We only extracted and analysed the data for the longest available time point within each time interval.

Extracting data from figures

Where values for primary or secondary outcomes were shown as figures within the paper, we contacted the study authors to try to obtain the raw values. When the raw values were not provided, we extracted information from the graphs using an online data extraction tool (automeris.io/WebPlotDigitizer/), using the best-quality version of the relevant figures available.

Assessment of risk of bias in included studies

At least two review authors independently assessed the risk of bias in each included study (Higgins 2017). We used the original Cochrane risk of bias tool (RoB 1) to assess the risk of bias across the six domains below in RevMan 5.3 (Review Manager 2020):

- sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective reporting; and
- other sources of bias.

We described each of these domains as reported in the trial and then assigned a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* in judging the overall risk of bias for each outcome (Higgins 2017), which contributed to our GRADE assessment (Schünemann 2022b).

Measures of treatment effect

We summarised the effects of dichotomous outcomes as risk ratios (RR) with confidence intervals (CIs). For the key outcomes that we presented in the summary of findings table, we

also expressed the results as absolute numbers based on the pooled results and compared these to the assumed risk.

For continuous outcomes, we expressed treatment effects as a mean difference (MD) with standard deviation (SD).

Unit of analysis issues

We determined appropriate units of analysis from the included studies.

Multi-armed trials

When analysing multi-armed trials, we combined all relevant experimental intervention groups in the study into a single group and all relevant control intervention groups into a single control group. If we considered one of the arms to be irrelevant, we excluded it from analysis.

We did not find any relevant cluster-RCTs.

Dealing with missing data

We planned to contact study authors via email whenever the outcome of interest was not reported and the methods of the study suggested that the outcome had been measured. We planned to do the same if not all data required for meta-analysis had been reported, unless the missing data were standard deviations. If standard deviation data were not available, we approximated these using the standard estimation methods from P values, standard errors or 95% CIs if these were reported (Deeks 2023). We extracted and analysed all the data using the available case analysis method. If standard deviation data were not available, we approximated these using standard estimation methods: from P values, standard errors or 95% CIs if these were reported (Deeks 2023). Where it was impossible to estimate these, we contacted the study authors.

Assessment of heterogeneity

We assessed clinical diversity (which may be present even in the absence of statistical heterogeneity) and examined the included studies for potential differences between them in the types of participants recruited (including age of participants), interventions or controls used and the outcomes measured. We assessed methodological diversity by studying the differences in outcome measurements and risk of bias before pooling results (Deeks 2023). We assessed statistical heterogeneity by visually inspecting the forest plots and by considering the Chi^2 test (with a significance level set at $P < 0.10$) and the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with a value over 50% suggesting substantial heterogeneity (Deeks 2023).

Assessment of reporting biases

We assessed reporting bias as between-study publication bias and within-study outcome reporting bias.

Outcome reporting bias (within-study reporting bias)

We assessed within-study reporting bias by comparing the outcomes reported in the published report against the study protocol, whenever this could be obtained. If the protocol was not available, we compared the outcomes reported to those listed in the methods section. If results were mentioned but not reported adequately in a way that allowed analysis (e.g. the report only mentioned whether the results showed evidence of a difference or not), bias in a meta-analysis was likely to occur. We sought further information from the study authors. If no further information could be found, we noted this as being a 'high' risk of bias. If there was insufficient information to judge the risk of bias, we noted this as an 'unclear' risk of bias (Higgins 2017).

Data synthesis

We conducted all meta-analyses using Review Manager 5.4 (Review Manager 2020) and RevMan (RevMan 2024). For dichotomous data, we analysed treatment differences as a risk ratio (RR), calculated using the Mantel-Haenszel methods. For continuous outcomes, as all the data were on the same scale, we pooled the mean values obtained at follow-up with the change from baseline outcomes and reported this as a mean difference (MD).

When statistical heterogeneity is low, random-effects versus fixed-effect methods yield trivial differences in treatment effects. However, when statistical heterogeneity is high, the random-effects method provides a more conservative estimate of the difference. In both scenarios, we chose the random-effects method, under the assumption that the studies are not all estimating the exact same intervention effect (Deeks 2023).

If meta-analysis could not be performed (for instance, there was only one study that evaluated the outcome of interest), we provided a narrative description of the result.

Subgroup analysis and investigation of heterogeneity

In cases of substantial heterogeneity, we were unable to explore possible causes through prespecified subgroup analyses as planned, since there were too few studies.

Sensitivity analysis

We carried out sensitivity analyses to determine whether the findings were robust to the decisions made in the course of identifying, screening and analysing the trials. We conducted sensitivity analysis for the following factors, whenever possible:

- risk of bias of included studies: excluding studies with a high risk of bias (we defined these as studies that had a high risk of allocation concealment bias and a high risk of attrition bias (overall loss to follow-up of 20%, differential follow-up observed); and
- how outcomes were measured: we planned to investigate the impact of including data where the validity of the measurement was unclear.

If any of these investigations found a difference in the size of the effect, or heterogeneity, we mentioned this in the Effects of interventions section.

Summary of findings and assessment of the certainty of the evidence

Two independent authors (EL and KA) used the GRADE approach (Schünemann 2022b) to rate the overall certainty of evidence using GRADEpro GDT (GRADEpro GDT).

The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct, and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high-certainty evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very-low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We created two summary of findings tables for the comparison of aspirin treatment after desensitisation versus placebo in RevMan (Review Manager 2020; RevMan 2024). We presented only the seven top-priority outcomes for mid-term (6 months) and long-term (36 months) time points where available (health-related quality of life, asthma control, significant serious and non-serious adverse events, airway assessment, nasal endoscopy score, changes in medication use and symptom scores).

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The searches up to February 2023 identified 760 records; we found no records from searching other sources. After removing duplicates, we screened 687 titles and abstracts and removed 666 clearly irrelevant records. We assessed 21 full-text reports for eligibility and excluded 13 individual studies (see Excluded studies). We included five individual trials from eight reports. Two reports were poster abstracts for the included studies Esmaeilzadeh 2015 and Świerczyńska-Krępa 2014. One report was the EUDRA Clinical Trial Registration for the included study Fruth

2013 (EUCTR2005-004437-18-DE 2006). We identified one study that is awaiting assessment (IRCT2015061522531N2). This study should already be completed. However, no full-text report could be found.

A flow chart of study retrieval and selection is provided in Figure 1.

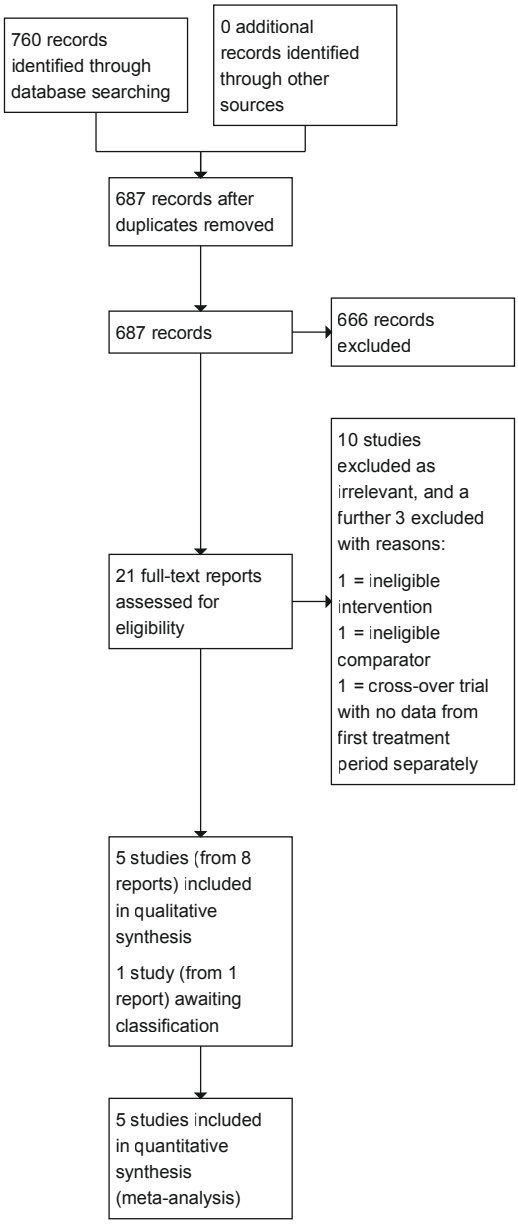


Figure 1. Process for sifting search results and selecting studies for inclusion

Included studies

We included five completed RCTs: Arshi 2021; Esmaeilzadeh 2015; Fruth 2013; Mortazavi 2017; Świerczyńska-Krępa 2014. See Characteristics of included studies. We contacted the study authors of Świerczyńska-Krępa 2014 for additional information about the provided data on airway assessment. We received a response, and they provided us with additional data. However, we could not use it for our analysis.

Design

All studies were parallel-group, double-blind randomised controlled trials and evaluated aspirin desensitisation with a placebo group as control. One study compared aspirin desensitisation with placebo both in aspirin-intolerant participants and aspirin-tolerant participants (Świerczyńska-Krępa 2014). We excluded the group of aspirin-tolerant participants given the scope of this review. No studies were stopped early.

Sample sizes

The studies randomised a total of 211 aspirin-intolerant participants and analysed 146 participants. Sample sizes in the included studies varied between 20 (Świerczyńska-Krępa 2014) to 70 participants (Fruth 2013).

Participants

In Arshi 2021 and Świerczyńska-Krępa 2014, all participants had an oral aspirin challenge test (according to the EAACI/GA2LEN guideline; Nizankowska-Mogilnicka 2007), to confirm the diagnosis of N-ERD. In Esmaeilzadeh 2015 and Mortazavi 2017, all participants had an intranasal challenge test with Ketorolac combined with a modified oral aspirin challenge test. In these four studies, a positive result was established if forced expiratory volume in one second (FEV_1) was decreased by 20% or decreased ‹ 20% combined with evident naso-ocular or bronchial symptoms. Fruth 2013 used a combination of clinical symptoms/participant history of complaints with the functional in vitro eicosanoid test to confirm the diagnosis of N-ERD.

Only adults (age › 17 years) were included in the five studies. In total, 41% to 66% of the participants in the active groups were female.

In four studies, participants also had a confirmed diagnosis of asthma. Two studies reported that participants had previous surgery for nasal polyps.

In Arshi 2021, Esmaeilzadeh 2015 and Mortazavi 2017, all participants had chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma. The studies did not provide a baseline nasal polyp score. It was unclear if participants had previous sinus surgery.

In Fruth 2013, all participants had CRSwNP. All participants had to present with symptoms of intrinsic asthma or NSAID-triggered hypersensitivity to fulfil the diagnosis of N-ERD. It is unclear if all participants had an actual asthma diagnosis. A baseline nasal polyp score was

not provided. All participants had surgery performed at least twice. All participants underwent a revision sinus surgery six weeks before inclusion in the study.

In Świerczyńska-Krępa 2014, all participants had CRSwNP and asthma. A baseline nasal polyp score was not provided. All but three participants had undergone previous polypectomies (a median of twice) at unknown previous times.

Settings

All studies were performed in university hospitals/tertiary medical centres. Three studies were conducted in Iran (Arshi 2021; Esmaeilzadeh 2015; Mortazavi 2017), one in Poland (Świerczyńska-Krępa 2014) and one in Germany (Fruth 2013).

Interventions

All studies compared active oral aspirin treatment after desensitisation (ATAD) with placebo. All studies described a desensitisation period and a maintenance period. Different treatment regimens were used in the active group. All participants could use standard medications (intranasal corticosteroids, inhalation corticosteroids, nasal saline, antihistamines) to control respiratory or nasal symptoms. It is unclear how many participants used these, since only Fruth 2013 mentioned that all participants used intranasal corticosteroids during the course of the study. In Arshi 2021, participants had to stop leukotriene antagonists seven days before the aspirin challenge test; antihistamines three days before; long-acting beta-agonists, tiotropium bromide and theophylline 48 hours before, and short-acting beta-agonists and ipratropium bromide eight hours before the aspirin challenge test. Esmaeilzadeh 2015 reported that participants had to stop all standard medications 48 hours before the aspirin challenge test. Świerczyńska-Krępa 2014 reported that dosages of standard medications were kept stable during the aspirin challenge and acute desensitisation.

Main comparison: aspirin desensitisation versus placebo

Desensitisation took place in an inpatient setting, ATAD in an outpatient setting.

Arshi 2021 compared two different dosages of oral aspirin (100 mg and 325 mg) once daily versus placebo. Two studies compared oral aspirin 650 mg twice daily in the first month and 325 mg twice daily versus placebo, with a six-month follow-up (Esmaeilzadeh 2015; Mortazavi 2017). One study compared oral aspirin 624 mg once daily versus placebo with a six-month follow-up (Świerczyńska-Krępa 2014). One study compared oral aspirin 100 mg once daily versus placebo with a 36-month follow-up (Fruth 2013).

Outcomes

Outcomes below were analysed at 6 and 36 months of follow-up, though only one study reported data at 36 months of follow-up.

1. Health-related quality of life, using disease-specific health-related quality of life scores
Three studies reported disease-specific health-related quality of life with SNOT-20 or SNOT-22 (Esmaeilzadeh 2015; Mortazavi 2017; Świerczyńska-Krępa 2014). Fruth 2013 reported the Rhinosinusitis Disability Index (RSDI) score. It consists of 30 questions concerning nasal and paranasal symptoms. Symptom severity is rated on a scale from 1 to 5 (1 = very rare, 2 = rare, 3 = sometimes, 4 = often, 5 = very often); the highest possible score is 150. The minimal clinically important difference (MCID) is 10.35 (Chen 2005). SNOT-20 consists of 20 questions with a score of 0 to 5 for each question (range from 0 to 100). The clinically meaningful difference is 0.8 (16 points) (Piccirillo 2002). SNOT-22 has 22 questions with a score of 0 to 5 for each question (range 0 to 110). The MCID is 8.9 points (Hopkins 2009). In the analyses, mean question scores from SNOT-20 and SNOT-22 were taken for assessment (i.e. SNOT-22 scores were divided by 22 and SNOT-20 scores were divided by 20).

2. Asthma control
Asthma control was measured by Arshi 2021 and Świerczyńska-Krępa 2014. The Asthma Control Questionnaire (ACQ) is based on seven items, being the most important for determining the adequacy of asthma control, on a seven-point scale (0 = no impairment, 6 = maximum impairment, total score 0 to 42). The items are equally weighted and the ACQ score is the mean of the seven items, so it ranges from 0 (well controlled) to 6 (extremely poorly controlled) (Juniper 1999; Juniper 2005). A score of ≤ 0.75 means fully controlled asthma, › 0.75 to ‹ 1.5 means partially controlled asthma, and ≥ 1.5 means inadequately controlled asthma. The Asthma Control Test (ACT) is a questionnaire that includes five items. Each item includes five response options with values that range from 1 to 5. The individual responses are summed to yield a score ranging from 5 (poor control of asthma) to 25 (complete control of asthma).

3. Significant serious and non-serious adverse events
All studies reported adverse events and withdrawal due to adverse events during maintenance therapy, except for Mortazavi 2017. Arshi 2021 only reported adverse events that were a reason for study withdrawal. Fruth 2013 and Esmaeilzadeh 2015 reported on gastrointestinal disturbance (bleeding). Świerczyńska-Krępa 2014 reported on all possible adverse events. No studies reported on adverse events during the aspirin challenge.

4. Airway assessment
We assessed the airway with peak nasal inspiratory flow (PNIF) and change in peak expiratory flow (PEF). PEF is a reliable and quick monitor of asthma symptoms and can be used unsupervised, in contrast to spirometry (GINA 2024). One study reported PNIF values (Świerczyńska-Krępa 2014). The same study mentioned reporting PEF values. However, we did not retrieve these values after contacting the study authors (although they provided us with the raw study data, which included PNIF values). Four included studies reported on FEV_1 during spirometry (Arshi 2021; Esmaeilzadeh 2015; Mortazavi 2017; Świerczyńska-Krępa 2014); however, we did not include this as an outcome parameter in our meta-analysis.

5. Nasal endoscopy score

Only Fruth 2013 reported on nasal polyp size, and used a scoring sytem from 0 to 3 for each side of the nose (maximum score of 6). Recurrence of nasal polyps was indicated by a score of 1 or more.

6. Medication use (changes in dosage of inhaled/intranasal corticosteroids)

Three studies reported on this outcome, but it was not reported by Arshi 2021 or Fruth 2013. Świerczyńska-Krępa 2014 reported change in dosage of inhaled and intranasal corticosteroids at one and six months of follow-up. The Świerczyńska-Krępa 2014 study did not report medication scores, whereas Esmaeilzadeh 2015 and Mortazavi 2017 reported no actual dosages, but did report medication scores (defined as local medication (both nasal sprays and eye-drops: 1 point for use of each one) and systemic medications (systemic antihistamines, inhaled beta-2-agonists, inhaled corticosteroids and theophylline; 2 points for use of each one). Scores were multiplied by two in the case of a maximum dose.

7. Nasal and bronchial symptom scores

Esmaeilzadeh 2015 and Mortazavi 2017 reported total symptom scores using a score of 0 to 3 for nasal complaints, eye complaints and bronchial complaints (0 no symptoms, 3 severe symptoms). Fruth 2013 evaluated four main (para-)nasal symptoms, which were scored from 0 to 4, and two secondary symptoms, which were scored from 0 to 2, and derived a total symptom score (0 to 20). In Świerczyńska-Krępa 2014, scores were derived from diaries for nasal and bronchial complaints using a VAS (0 to 10). We extracted the data from a figure. Arshi 2021 did not report symptom scores.

8. Chronic rhinosinusitis and asthma exacerbations

Fruth 2013 reported the number of chronic rhinosinusitis exacerbations that required revision sinus surgery. Esmaeilzadeh 2015 and Mortazavi 2017 reported exacerbations of asthma. Esmaeilzadeh 2015 reported the number of asthma exacerbations (not further defined) whereas Mortazavi 2017 reported the number of episodes of asthma attacks (not further defined). The other studies did not report on this outcome.

Funding sources

Three studies were supported by a university grant. Świerczyńska-Krępa 2014 received funding from three sources (see Characteristics of included studies). Mortazavi 2017 did not report any information about funding sources.

Excluded studies

After reviewing 21 full texts, we excluded 10 studies as clearly irrelevant. We excluded a further three studies which we reported in the Characteristics of excluded studies table. One study used an ineligible intervention (Sowerby 2021), the second study used an ineligible comparator (no placebo group was used and a direct comparison of different dosages of aspirin was performed; Celik 2017). The study by Parikh 2005 was a cross-over trial comparing intranasal

lysine-aspirin with placebo. The study did not report data separately for the two treatment periods. After contacting the study authors, we did not obtain a response to the request for additional data for the first treatment period (four participants in total).

Studies awaiting classification

For one study, no published full-text report could be found. It is categorised as awaiting classification (IRCT2015061522531N2).

Risk of bias in included studies

We included five studies in this review (Characteristics of included studies). Overall, the risk of bias was low or unclear for most domains. See Figure 2 for the risk of bias graph and Figure 3 for the risk of bias summary.

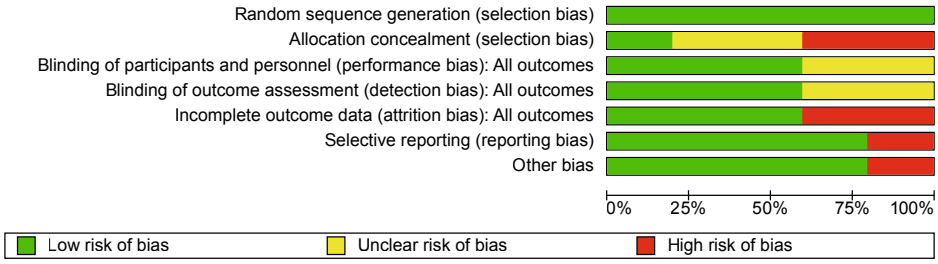


Figure 2. Review authors' judgements about each risk of bias item presented as percentages across all included studies

Allocation

The risk of selection bias was low in all studies for randomisation sequence generation, since all studies described a random component in sequence generation (use of block randomisation for Arshi 2021; Esmaeilzadeh 2015; Fruth 2013; Mortazavi 2017; use of a random numbers table for Świerczyńska-Krępa 2014).

Arshi 2021 did not describe their methods of allocation concealment; however, no important baseline characteristic imbalances were present, except gender. Therefore, we considered this study to have an unclear risk of bias in this domain. Esmaeilzadeh 2015 conducted randomisation using a computer-generated random list in block sizes of four. The randomisation was performed by the study director, who also supervised the trial. Together with the baseline imbalances between the intervention and placebo group, we scored it as high risk of bias for allocation concealment. Fruth 2013 used central allocation concealment by the institutional centre for clinical research, so we rated it at low risk of bias. Allocation concealment was not described in the Mortazavi 2017 study and because of significant baseline imbalances for relevant factors (SNOT-22, Lund-Mackay, medication scores), we rated it to be at high risk of bias. Świerczyńska-Krępa 2014 used a random numbers table but did not report allocation concealment methods. We assumed the risk of bias to be unclear for allocation concealment, since no baseline imbalances were present.

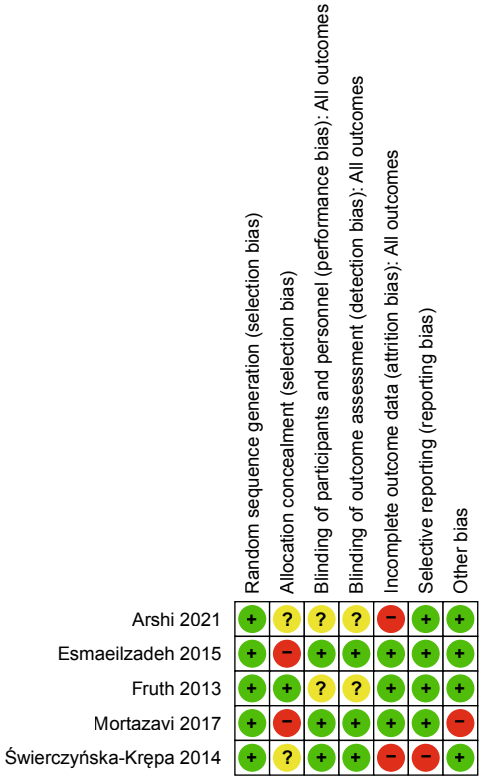


Figure 3. Review authors' judgements about each risk of bias item for each included study

Blinding

Arshi 2021 and Fruth 2013 did not mention blinding specifically in the text; however, they mentioned that the study was ‹double-blinded›. Therefore, we rated these studies as having an unclear risk of bias.

Esmaeilzadeh 2015 mentioned that all participants and investigators were blinded to the assigned treatment group, so we rated the study to be at low risk of bias.

In Mortazavi 2017, practising clinicians were blinded to the study intervention and, due to the mention of 'double-blinded' RCT, we assumed that participants were blinded too and assigned a low risk of bias.

Świerczyńska-Krępa 2014 reported that all participants were evaluated during visits by a blinded physician. Since the study was double-blinded, we assumed that the participants were blinded too. We considered this study to have a low risk of bias.

Incomplete outcome data

Arshi 2021 reported 35% loss of participants after randomisation, and these were not included in the primary analysis. Reasons for dropout or loss to follow-up were: lack of participant compliance, adverse events or unreported reasons. The losses were probably related to the interventions and outcomes and no sensitivity analyses were performed; therefore, there is a high risk of bias.

In Esmaeilzadeh 2015, 32 of 34 participants completed the study; two did not manage to complete the study due to adverse events. We considered the study to be at low risk of attrition bias.

Fruth 2013 reported having lost 44% of participants during 36 months of follow-up. Reasons for discontinuing the study were reported and were balanced between intervention groups. No withdrawals were attributed to adverse events. Two participants in the aspirin group versus six participants in the placebo group had revision surgery during the follow-up period. We rated this study at low risk of attrition bias.

For Mortazavi 2017, outcome data were available for almost all participants (three participants were lost during the trial), so we rated the study at low risk of attrition bias.

Świerczyńska-Krępa 2014 reported that 33% of participants (4 out of 12) withdrew from the aspirin-intolerant aspirin group due to adverse events. One participant in the aspirin-intolerant placebo group dropped out due to lack of improvement (16.7%). No sensitivity analysis was performed. We considered this study to be at high risk of bias.

Selective reporting

Arshi 2021 reported all outcomes previously published in the trial registration protocol, except for a description of specific adverse events (no separation between bleeding and gastrointestinal disorders). Therefore, there are minimal concerns regarding reporting bias, and we rated the study as low risk of bias for this domain. Esmaeilzadeh 2015 reported all primary and secondary outcomes, so we rated this study to be at low risk of reporting bias. Fruth 2013 reported primary and secondary outcomes fully as mentioned, so we rated the study as having a low risk of bias (although secondary outcomes were not reported at 6, 9, 12 and 18 months). For Mortazavi 2017, all data mentioned in the methods section were reported and analysed according to protocol. Therefore, the study is at low risk of bias. Świerczyńska-Krępa 2014 described primary and secondary outcomes; however, they did not report actual peak expiratory flow values (primary outcome) in the text or supplementary material, nor did they report all individual symptom scores. The study reported that the values remained unaltered or were insignificant. Therefore, there are considerable concerns regarding selective outcome reporting (high risk of bias).

Other potential sources of bias

Mortazavi 2017 did not provide a sample size calculation and did not report prespecified primary or secondary outcome parameters. Therefore, we rated the study as at a high risk of bias. We had no additional concerns about the remaining studies, so rated them as having a low risk of bias (Arshi 2021; Esmaeilzadeh 2015; Fruth 2013; Świerczyńska-Krępa 2014).

Effects of interventions

See Summary of findings table 1 and Summary of findings table 2 for the main comparison.

Aspirin desensitisation versus placebo

All participants had asthma and chronic rhinosinusitis with nasal polyps (CRSwNP). Subgroup analyses for method of administration, setting of aspirin administration or use of concomitant medication could not be performed.

Primary outcome measures

Health-related quality of life

Mid-term (6 months follow-up)

Three studies could be meta-analysed (n = 95 randomised participants, n = 85 analysed, 89%). Two studies used the SNOT-22 (Esmaeilzadeh 2015; Mortazavi 2017) and one study used the SNOT-20 (Świerczyńska-Krępa 2014). The mean difference (MD) in SNOT score after six months of follow-up was –0.54 (95% confidence interval (CI) –0.76 to –0.31; P < 0.001; $Chi^2 = 0.49$, P = 0.78, $I^2 = 0\%$; minimum clinically important difference (MCID) 9.0 points for total score; low-certainty evidence), in favour of aspirin treatment after desensitisation (ATAD); Analysis 1.1). For this analysis, the mean SNOT-22 scores were divided by 22 and the SNOT-20 scores were divided by 20. It shows a mean reduction in SNOT score of 11.9 points (based on SNOT-22) for ATAD compared to placebo.

At six months follow-up, the sensitivity analysis excluding studies with high risk of bias resulted in no clear difference between treatment groups (based on Świerczyńska-Krępa 2014: MD –0.77, 95% CI –1.65 to 0.11; 15 participants; Analysis 1.2).

Long-term (> 12 months follow-up)

Fruth 2013 (n = 31) showed less impairment of quality of life with ATAD compared to placebo after 36 months of follow-up (Analysis 1.3). The MD in the Rhinosinusitis Disability Index (RSDI) score was –18.10 (95% CI –32.82 to –3.38; low-certainty evidence).

Asthma control

The small study by Świerczyńska-Krępa 2014 (15 participants) reported control of asthma. After six months of follow-up, the MD in the ACQ score was –2.00 (95% CI –4.30 to 0.30; total score 0 to 6; MCID 0.5 points; very low-certainty evidence), in favour of ATAD (Analysis 1.4).

Arshi 2021 (n = 30) reported an MD in asthma control, measured with the Asthma Control Test, of 5.90 points (95% CI 2.93 to 8.87; total score 5 to 25; MCID 3 points; very low-certainty evidence), in favour of ATAD after six months of follow-up (Analysis 1.5).

Since these test scores run in different directions, we could not pool the data from these studies.

Significant serious and non-serious adverse events: gastrointestinal disturbance, including nausea and vomiting, diarrhoea, abdominal pain

Except for Mortazavi 2017, all studies reported on adverse events during maintenance therapy.

Arshi 2021 reported briefly on adverse events as a reason for dropout. No dropout due to adverse events occurred in the placebo group. In the active treatment group, one participant developed a skin rash and dropped out, and two participants developed a gastrointestinal disorder and dropped out. Other adverse events that did not lead to dropout were not reported in this study.

In Esmaeilzadeh 2015, one participant in the ATAD group experienced severe gastrointestinal bleeding, for which he discontinued the study. In Świerczyńska-Krępa 2014, four participants in the ATAD group had dyspepsia, for which they discontinued the study. One participant in the ATAD group developed a transient skin rash.

A meta-analysis of four studies (n = 129) showed a risk ratio (RR) of 3.71 (95% CI 0.67 to 20.47; P = 0.13; $Chi^2 = 0.22$, P = 0.90, $I^2 = 0\%$; very low-certainty evidence) during ATAD up to six months of follow-up for gastrointestinal disturbance, with little to no clear evidence of a difference (Analysis 1.6).

In Fruth 2013 (n = 31), no adverse events were reported in either group, over the total study period of 36 months (low-certainty evidence). The number needed to treat for an additional adverse event could not be calculated.

A sensitivity analysis excluding all studies with high risk of bias, leaving only the Fruth 2013 study (n = 31), could not provide an estimable risk ratio, since there were zero events in both study groups (analysis not shown).

Secondary outcome measures

Airway assessment

Only Świerczyńska-Krępa 2014 (n = 15) reported on PNIF scores. After six months of follow-up, the MD in mean change-from-baseline PNIF scores was 32.90 L/min, with no clear evidence of a difference in treatment effect (95% CI –12.44 to 78.24; very low-certainty evidence; Analysis 1.7).

No sensitivity analysis could be performed.

Nasal endoscopy score

Only one study reported this outcome after 36 months of follow-up (Fruth 2013, n = 31). The MD in nasal polyp scores was –1.20 (95% CI –2.72 to 0.32; low-certainty evidence), with no clear evidence of a difference in treatment groups (Analysis 1.8).

No sensitivity analysis could be performed.

Medication use (changes in dosage of inhaled/intranasal corticosteroids)

Only Świerczyńska-Krępa 2014 (n = 15) reported changes in the use of actual inhaled and nasal corticosteroids. The MD in the change in inhaled corticosteroid dosage from baseline was –1197.60 µg (95% CI –1744.93 to –650.27; very low-certainty evidence), in favour of ATAD (Analysis 1.9). The MD in the change in intranasal corticosteroid dosage from baseline was –120.50 µg (95% CI –206.49 to –34.51; very low-certainty evidence), in favour of ATAD (Analysis 1.10).

The studies of Esmaeilzadeh 2015 and Mortazavi 2017 could be meta-analysed (n = 70) at six months follow-up. There was an MD in medication score of –4.14 in favour of ATAD (95% CI –4.72 to –3.56; P < 0.001; $Chi^2 = 1.56$, P = 0.21, $I^2 = 36\%$; Analysis 1.11).

Nasal and bronchial symptom scores

Esmaeilzadeh 2015, Fruth 2013 and Mortazavi 2017 reported no VAS symptom scores and were not included.

Only Świerczyńska-Krępa 2014 reported individual VAS scores for smell, nasal blockage and sneezing at six months follow-up (n = 15). The individual MDs were: smell –2.20 (95% CI –4.74 to 0.34); nasal blockage –0.90 (95% CI –1.90 to 0.10); sneezing –0.70 (95% CI –1.45 to 0.05), all indicating little to no clear evidence of a difference between treatment groups (all very low-certainty evidence; Analysis 1.12). This study did not show individual values for rhinorrhoea, postnasal drip, nasal itching, cough and dyspnoea. In the methods section of the study, it was stated that only significant results were reported.

No sensitivity analysis could be performed.

Chronic rhinosinusitis and asthma exacerbations

This outcome is not part of the Summary of findings table 1 or Summary of findings table 2. Exacerbations were defined as a need for step-up in medical treatment (e.g. systemic corticosteroid) or sinus surgery during treatment.

Mid-term (6 months follow-up)
Two studies reported specifically on asthma exacerbations (Esmaeilzadeh 2015; Mortazavi 2017; n = 70). The RR was 0.53 (95% CI 0.27 to 1.02; P = 0.06; $Chi^2 = 0.02$, P = 0.88, $I^2 = 0\%$; Analysis 1.13) in favour of ATAD. Świerczyńska-Krępa 2014 (n = 15) only mentioned that no hospitalisations were caused by asthma exacerbations; however, this information could not be used in the meta-analysis.

No studies reported on chronic rhinosinusitis exacerbations at this time point.

No sensitivity analysis could be performed.

Long-term (> 12 months follow-up)
Fruth 2013 reported on chronic rhinosinusitis exacerbations for which revision sinus surgery was performed up to 36 months of follow-up (n = 31). Two events were reported in the ATAD group and six events in the placebo group. The RR was 0.24 in favour of ATAD (95% CI 0.06 to 1.01; Analysis 1.14).

No other studies reported on this outcome at this time point.

DISCUSSION

Summary of main results

See Summary of findings table 1 and Summary of findings table 2 for an overview of the results.

The primary outcomes for this review were health-related quality of life, assessed using disease-specific health-related quality of life scores; asthma control; and significant serious and non-serious adverse events with respect to gastrointestinal disturbances. We also reported on secondary outcomes: airway assessment (change in peak nasal inspiratory flow (PNIF) and change in peak expiratory flow (PEF)); nasal endoscopy score (i.e. modified Lund-Kennedy, Hadley's clinical scoring and other appropriate scoring systems); medication use (changes in dosage of inhaled/intranasal corticosteroids); symptom scores (nasal and bronchial symptoms, using a visual analogue scale (VAS)).

We identified five randomised controlled trials (RCTs) that all compared oral aspirin treatment after desensitisation (ATAD) with placebo for non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (211 aspirin-intolerant participants).

No studies reported outcomes in the short term (three to six months follow-up).

Outcomes at six months follow-up (mid-term)

Health-related quality of life could be meta-analysed by combining data from three studies (85 participants), all using the Sino-Nasal Outcome Test (SNOT) score. We found low-certainty

evidence that ATAD may result in a better health-related quality of life (an improvement in SNOT score of 11.9 points). This is a large improvement and clinically relevant, considering that the minimum clinically important difference is 8.9 points (Hopkins 2009).

Asthma control may be improved, but the evidence is very uncertain and derived from two small studies. Asthma control was measured with the Asthma Control Test in one study after six months of follow-up (30 participants) and with the Asthma Control Questionnaire in another study (15 participants). Since these test scores run in different directions, we could not pool the data from these studies. Arshi 2021 (30 participants) reported a larger improvement of approximately six points in asthma control compared to placebo. This finding, in itself, is clinically relevant, based on a minimum clinically important difference of three points (Schatz 2009). Most participants' asthma was well-controlled after ATAD, compared to still poorly controlled after placebo. Świerczyńska-Krępa 2014 (15 participants) used the Asthma Control Questionnaire and reported a 2-point lower score for ATAD compared to placebo, which in light of the minimum clinically important difference of 0.5 points is noteworthy; however, the confidence interval included both benefit and no clear benefit.

There is very low-certainty evidence (four studies, 129 participants) that aspirin desensitisation results in little to no difference in the occurrence of any serious gastrointestinal adverse events. No events occurred in the placebo group. Seven events were seen in the active treatment group, of which one was severe gastrointestinal bleeding, and these participants left the study. However, the participant numbers are too small to draw robust conclusions based on these studies. It is well known that ATAD is associated with (gastrointestinal) adverse events; the incidence of adverse symptoms related to aspirin intake ranges from 0% to 34% and is a frequent cause of stopping ATAD (Berges-Gimeno 2003; Forer 2011; Kowalski 2019). In a 10-year survey of people who underwent aspirin desensitisation at the Scripps Clinic (response rate 92 participants), 38% of people with N-ERD reported discontinuing aspirin treatment predominantly because of adverse reactions (26%) (Walters 2018). A careful review of individual risk factors for gastroduodenal toxicity from aspirin before initiating maintenance aspirin treatment could be relevant.

We do not know the effect of ATAD on peak nasal inspiratory flow (very low-certainty evidence, based on one small study, with 15 participants).

We are uncertain if medication use (dosage of intranasal corticosteroid spray or inhaled corticosteroids) may be substantially reduced with aspirin desensitisation (one study, 15 participants, very low-certainty evidence).

We are uncertain about the effect on symptom scores (individual smell, nasal obstruction and sneezing scores) (one study, 15 participants; very low-certainty evidence).

The evidence suggests that ATAD slightly reduces sudden attacks of worsening of asthma (two studies, 70 participants). We are unaware if this also indicates a lower need for systemic corticosteroids, since the two studies did not report their definition of worsening of asthma.

No studies reported data on peak expiratory flow changes. Świerczyńska-Krępa 2014 mentioned that there was no "statistically significant" change after ATAD, but did not report the data (and we were unable to obtain these data).

No studies reported on nasal endoscopy scores at this time point.

Outcomes at ≥ 12 months follow-up (long-term)

One study presented long-term results up to 36 months of follow-up (Fruth 2013; 31 participants). There is low-certainty evidence that ATAD may result in a large, clinically relevant improvement (› 18 points) in health-related quality of life, measured with the modified Rhinosinusitis Disability Index (RSDI) score, compared to placebo, after 36 months (based on a minimal clinically important difference of ≥ 10.35 points for the RSDI; Benninger 1997; Chen 2005). No adverse events were reported in either of the groups up to 36 months follow-up, and no robust conclusions can be drawn. There is low-certainty evidence that ATAD results in little to no difference in the size of nasal polyps. ATAD may reduce sudden worsening of chronic rhinosinusitis slightly, which implies less revision sinus surgery. Two revision sinus surgeries were reported in the active treatment group and six in the placebo group. Other outcomes were not reported at long-term follow-up.

Overall completeness and applicability of evidence

We were able to include five placebo-controlled trials. Placebo-controlled studies are inherently difficult to perform in people with N-ERD. First, desensitisation cannot easily be blinded because symptoms will develop on ingestion of aspirin, but not placebo. Second, people in whom a desensitisation took place will lose their desensitised status after a period of placebo treatment. This could be an impediment (Stevens 2021).

All five studies included adults treated in university medical centres in an outpatient setting for ATAD (aspirin desensitisation was carried out in an inpatient setting). All participants had proven NSAID-exacerbated respiratory disease with chronic rhinosinusitis with nasal polyps. In four of the five studies, participants had an actual diagnosis of asthma. No studies reported the severity of nasal polyps except Fruth 2013. In this study, all participants had sinonasal surgery six weeks before randomisation. For the other studies, we do not know if or when participants had previous surgery, although it is recommended before initiating ATAD (Kowalski 2019; Stevens 2021). Furthermore, it is unclear if the participants were compliant in taking the medications.

We were unable to draw robust conclusions on the efficacy of ATAD, since all the evidence is of low or very low-certainty. For four secondary outcomes, data were only available from one or other of two small trials ((Fruth 2013; Świerczyńska-Krępa 2014), leading to imprecision).

Regrettably, the benefit-over-harm profile remains uncertain. A meta-analysis of large, double-blind, placebo-controlled studies in cardiovascular disease (135,043 participants) with a median of 5.0 (interquartile range 4.7 to 6.7) years of follow-up, demonstrated that low-dose (50-100 mg) aspirin increases the risk of gastrointestinal bleeding in people with a low cardiovascular risk profile (hazard ratio 1.54 95% CI 1.35 to 1.76) (Zheng 2019). It is important to demonstrate the risk profile more clearly in N-ERD, since we usually prescribe higher daily dosages of aspirin to individuals when following the common guidelines (Kowalski 2019).

Our included studies illustrate the variation in prescribing dosages for ATAD. Four different treatment regimens were used in the active group, varying from aspirin 100 mg once daily to 325 mg twice daily. We were unable to conclude whether there might be a preferential dose. The dosing of 100 mg per day in the study of Fruth 2013 might be too low to establish an effect. Current guidelines advise the use of at least 300 mg per day (Kowalski 2019).

We did not identify eligible studies that evaluated intranasal treatment with lysine-aspirin. We identified one randomised cross-over trial in which intranasal lysine-aspirin was compared to placebo (22 participants, intranasal lysine-aspirin or placebo for six months, followed by crossover). In total, 11 participants were analysed in this study after dropouts. Unfortunately, the study did not report data separately for both periods of treatment. We contacted the corresponding author for additional data for the first period. However, no response was obtained (first period data consisted of four participants in total). The study authors concluded that there was no benefit in the use of intranasal lysine-aspirin (Parikh 2005).

In our included studies, all participants could use standard medications (intranasal corticosteroids, inhalation corticosteroids, nasal saline, antihistamines) to control respiratory or nasal symptoms. It is unclear how many participants used these in the included studies, which might influence the effect of ATAD. Only Fruth 2013 mentioned that all included participants used nasal corticosteroids.

No studies reported outcomes during the first months of therapy, and only one study reported long-term outcomes after 36 months of follow-up (Fruth 2013). This was also the only study, as far as we know, in which participants underwent surgery for nasal polyps six weeks before randomisation. Results could have been influenced by this surgery, although we could assume a wash-out effect for sinus surgery to occur before 36 months of follow-up. Moreover, it is in general advised to perform sinus surgery before starting ATAD to enhance potential effects (Kowalski 2019). There is a lack of studies looking into the need for revision surgery during treatment, as it was only reported in the study of Fruth 2013. In general, most outcomes were only available for six months of follow-up. It would be preferential to have data with longer follow-up for most outcomes.

For the five included studies, no statistical methods were used to impute potential missing data. We considered the high dropout rates of 35% in Arshi 2021, 44% in Fruth 2013 and 25% in Świerczyńska-Krępa 2014 as a problem for interpretation; the studies were probably underpowered.

Certainty of the evidence

In this review, we rated the overall evidence for ATAD versus placebo as low or very low certainty using the GRADE classification, downgrading for risk of bias or imprecision (Schünemann 2022b). In four of the five included studies there was attrition bias with baseline imbalances or lack of (adequate description of) allocation concealment, which made us downgrade the evidence.

We downgraded one level for risk of bias in the following outcomes at mid-term follow-up: health-related quality of life (unclear allocation concealment and incomplete outcome data); asthma control (unclear allocation concealment and incomplete outcome data); significant serious and non-serious adverse events (three of the four included studies were at high risk of bias for either allocation concealment or attrition); airway assessment (PEF values were not reported and there was incomplete outcome data (25% loss to follow-up) in the single study included); change in dosage of medication use (high risk of bias in the single study included due to 25% loss to follow-up).

We downgraded two levels for risk of bias for symptom scores at mid-term follow-up. Selected symptoms were reported, which might be the symptom scores with the largest effect. Furthermore, there was 25% loss to follow-up.

We downgraded mid-term health-related quality of life and long-term significant serious and non-serious adverse events by one level for imprecision, due to the limited number of participants. We downgraded the following outcomes by two levels for imprecision, due to the limited number of participants and wide confidence intervals: mid-term asthma control, significant serious and non-serious adverse events, airway assessment, change in dosage of medication use and symptom scores, as well as long-term health-related quality of life and nasal endoscopy.

No studies assessed nasal endoscopy at mid-term follow-up, or asthma control, airway assessment, medication use and symptoms scores at long-term follow-up.

We did not create funnel plots to identify any other chances of publication bias since we included too few studies.

Potential biases in the review process

This review was based on a published protocol (Gan 2019). We feel that there is likely to be complete identification of studies for this review as we performed a comprehensive search multiple times. The last search date could be viewed as a limitation, but there were no ongoing studies

identified that may introduce bias, so the search is considered up to date. The methodology of the review is unlikely to have introduced any bias into the review process. We were unable to assess publication bias through examination of funnel plots, because we only included up to four trials in the meta-analyses.

Agreements and disagreements with other studies or reviews

The EPOS 2020 evidence-based position paper for people with chronic rhinosinusitis and nasal polyps suggests that oral ATAD can be a treatment for people who have N-ERD and chronic rhinosinusitis with nasal polyps (CRSwNP), whenever there is confidence in the individual›s compliance. This advice compares partially to our findings, which demonstrate that ATAD may result in a clinically relevant improvement in health-related quality of life, although we are unsure whether it results in less use of asthma or CRS medications, either topical or systemic, or gives a greater improvement in control of disease or symptoms. Also, there is a risk of dropout due to adverse events. EPOS 2020 does not recommend the use of intranasal lysine-aspirin as a treatment option for people with N-ERD.

Chu 2019 conducted a systematic review of people with N-ERD and compared aspirin desensitisation with placebo or no aspirin treatment. They concluded that aspirin desensitisation should be considered to improve clinical outcomes and delay or prevent future sinus surgery. ATAD meaningfully reduced the symptoms of rhinosinusitis and improved quality of life, but resulted in a significant increase in adverse events. Five trials were included in that review (including Stevenson 1984, which we excluded because it is not a randomised trial) and two case-control studies. The evidence was rated to be of moderate to high certainty, in contrast to the certainty ratings in our review. Chu 2019 reported that all included trials had a low risk of bias in each domain (sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting and other sources of bias), which is in disagreement with our assessment. There is no explanation given for the rating provided for each domain. We do believe there are considerable risks present in allocation concealment and incomplete outcome data.

Oykhman 2022 conducted a systematic review and network meta-analysis of the efficacy and safety of biologics and ATAD in people with CRSwNP. They compared trials of seven different biologics and five trials of ATAD. Comparable to us, they concluded that there were positive effects of ATAD: they found that ATAD improves health-related quality of life, sinusitis symptoms, smell and nasal polyp size, and decreases rescue nasal polyp surgery. With respect to adverse events, they stated that the seven biologics (2321 participants) are not clearly different in risk compared to each other and to placebo; however, they stated that there is likely an increased risk of adverse events with ATAD (233 participants) compared to biologics. We feel that this cannot be stated firmly, considering the finding is based on similar small participant numbers.

AUTHORS' CONCLUSIONS

Implications for practice

Most of the evidence in this review is limited to six months of follow-up and only one study of low quality described a few long-term outcomes.

The low-certainty evidence available suggests that aspirin treatment after desensitisation (ATAD) may lead to a clinically relevant improvement in health-related quality of life after six months of follow-up, as well as after 36 months of follow-up. ATAD may also result in clinically relevant better control of asthma, although this evidence is very uncertain. The evidence suggests that ATAD may result in little to no difference in significant gastrointestinal adverse events after six months and 36 months of follow-up, although no robust conclusions can be drawn due to the small patient numbers and dropouts (30%). This implies there is a risk of discontinuation during treatment and this should be kept in mind when selecting individuals for this treatment.

The evidence is very uncertain about the effect of ATAD on peak nasal inspiratory flow (PNIF) scores, nasal endoscopy scores, change in use of inhaled or intranasal corticosteroids for chronic rhinosinusitis or asthma and symptom scores (sneezing, smell and nasal obstruction).

The limited evidence available suggests that ATAD reduces exacerbations or worsening of asthma and reduces sudden worsening of chronic rhinosinusitis. However, whether it actually reduces oral corticosteroid use or revision sinus surgery remains unclear.

We could not draw any conclusions about the optimal dosage or dosing frequency of aspirin.

The extent to which the individual's compliance and comorbidities affect outcomes remains unclear.

Implications for research

There is a clear need for larger, better designed randomised controlled trials with adequate power. Blinding will be very difficult due to the development of symptoms after ingesting aspirin.

It should be made clear in future studies what the severity of asthma or chronic rhinosinusitis is in all participants before the start of therapy, and whether participants underwent sinus surgery. In the current review, we included only one study that mentioned previous sinus surgery and revision surgery during ATAD.

We need studies with longer follow-up periods to see if any treatment effect persists over time and if (and after how much time) adverse events develop, which might eventually lead to discontinuation of treatment. In the included studies, 30% of participants dropped out, which challenges the feasibility of this treatment option for people who have CRS with N-ERD. Dropouts

might have shown poor adherence, experienced a lack of effect or developed adverse events for which they stopped. Besides compliance, adequate documentation on the co-medications used or prescribed for asthma and chronic rhinosinusitis during treatment should be guaranteed to allow interpretation of identified treatment effects. One important unanswered question is whether ATAD leads to a corticosteroid-sparing effect or prevention of repetitive sinus surgery. Furthermore, data on cost-effectiveness are both lacking and needed.

Acknowledgements

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT to the end of March 2023. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Evidence Synthesis Programme, NIHR, NHS or the Department of Health.

We acknowledge the authors of the suite of Cochrane Reviews on the medical management of chronic rhinosinusitis for the use of some protocol methods text, as directed by the Cochrane ENT editorial base.

One of the review authors, KLG, would also like to acknowledge the support given by the European Academy of Allergology and Clinical Immunology (EAACCI) in undertaking this project.

We are grateful to Elizabeth Stovold, Information Specialist with Cochrane Airways, for providing peer-review comments on the draft search methods.

Editorial and peer-reviewer contributions

Cochrane ENT supported the authors in the development of this intervention review. The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Robert Boyle, National Heart & Lung Institute, Section of Inflammation and Repair, Imperial College London, London
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Joanne Duffield, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Andrea Takeda, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Elina Jerschow, MD, MSc, Professor of Medicine and Immunology Allergy Division Chair, Mayo Clinic, 200 First Street, S.W. Rochester, MN 55905, www.mayoclinic.org (clinical review); Felipe Valdés, Clinical Immunologist; Academic at the Pontifical Catholic University of Chile; Immunology Consultant at Red UC Christus and Barros Luco Hospital (clinical review); Dorien Van Broeck, Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, KU Leuven, Belgium (clinical review); Dr Andrej

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arshi 2021

Study characteristics	
Methods	**Design:** parallel-group randomised controlled trial **Duration of study:** 6 months follow-up **Study dates:** February 2014 to February 2015
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Allergy Department, Hazrat Rasoul-E-Akram Hospital, Iran University of Medical Sciences, Tehran **Sample size:** N = 65 (no sample size calculation provided), of which 51 were eligible **Number randomised:** N = 46 (15 in placebo group A, 15 in active treatment group B, 16 in active treatment group C) **Number analysed:** N = 30 (8 in placebo group A, 9 in active treatment group B, 13 in active treatment group C) **Participant baseline characteristics** Presence or absence of nasal polyps: all patients had CRSwNP Baseline nasal polyp score: not mentioned Previous sinus surgery: not mentioned Presence or absence of a diagnosis of asthma: all patients had asthma Other baseline characteristics Female sex: Group A 37.5%, Group B 89%, Group C 69.2% Age (mean years, SD): Group A 44.9 (9.5), Group B 39 (10.2), Group C 39.6 (12.7) FEV_1 (mean L/sec, SD): Group A 64.6 (9.1), Group B 71.6 (7.9), Group C 70.8 (9.5) Asthma Control Test (mean score, SD): Group A 13 (4.8), Group B 14.6 (3.3), Group C 15.8 (3.0) **Inclusion criteria** Ages of 18 to 65 years Moderate to severe asthma and CRSwNP Diagnosis of aspirin hypersensitivity: decrease of at least 20% in FEV_1 after oral aspirin challenge or decrease of more than 15% in FEV_1, in association with severe extra-bronchial symptoms including nasal stuffiness and rhinorrhoea **Exclusion criteria** People with serious systemic diseases (including bleeding disorders, gastrointestinal diseases, rheumatologic diseases, malignancies, renal diseases, cardiac diseases, hepatic diseases, psychological diseases and mastocytosis) Pregnancy or breast-feeding History of life-threatening anaphylactic reactions precipitated by NSAIDs Forced expiratory volume in 1 second (FEV_1 less than 70% of predicted at the time of aspirin challenge) People receiving warfarin, beta-blockers and angiotensin-converting enzyme inhibitors

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Arshi 2021 *[continued]*

Study characteristics	
Interventions	**Group A (n = 15):** oral placebo after aspirin challenge **Group B (n = 15)**: oral aspirin 100 mg/day after aspirin challenge **Group C (n = 16):** oral aspirin 325 mg/day after aspirin challenge **Additional interventions:** participants with moderate to severe asthma were treated with a combination of inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA), a short course (maximum 5 days) of oral corticosteroid, if needed, and leukotriene receptor antagonist (LTRA) for 3 months. Concurrent reflux disease and rhinosinusitis were also treated. Drug withdrawal before the oral aspirin challenge included LTRA, 1 week; short-acting antihistamines, 3 days; LABA, tiotropium bromide and theophylline, 48 hours; and short-acting beta-agonists and ipratropium bromide, 8 hours.
Outcomes	**Outcomes:** No primary or secondary outcomes were reported separately. Monthly: Clinical findings Possible adverse events Treatment adherence At 6 months follow-up: Asthma Control Test (scale 5 (poor control of asthma) to 25 (complete control of asthma)) FEV_1 (L/sec)
Funding sources	The study was funded by the Vice Chancellor for Research, Iran University of Medical Sciences, Tehran.
Declarations of interest	None
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study used block randomisation.
Allocation concealment (selection bias)	Unclear risk	Unclear if the block sizes were fixed and what size the blocks were. Allocation might have been predictable. One baseline imbalance between the analysed intervention groups (gender), probably due to loss of follow-up and to chance.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was a double-blind study. However, it was not clearly stated who was blinded and who was not blinded during and after the assignment of interventions.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study did not report who performed the outcome assessments.

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Arshi 2021 *[continued]*

Risk of bias		
Incomplete outcome data (attrition bias) All outcomes	High risk	Almost 35% loss of participants after randomisation, who were not included in the analysis. Reasons for dropout or loss to follow-up were: lack of compliance or adverse events, or unreported reasons. Could have been related to interventions and outcome.
Selective reporting (reporting bias)	Low risk	Study protocol/trial design published before data analyses and writing the paper. The only deviation from this was that adverse events were not separated into bleeding or gastro-intestinal disorder, but combined. We consider this a low risk of bias.
Other bias	Low risk	No other obvious issues.

Esmaeilzadeh 2015

Study characteristics	
Methods	**Design:** parallel-group randomised controlled trial **Duration of study:** 6 months follow-up **Study dates:** not reported
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Rasool-e-Akram Hospital, Iran University of Medical Sciences **Sample size:** no sample size calculation provided **Number randomised:** N = 34 (18 in active group, 16 in placebo group) **Number analysed:** N = 32 (16 in active group, 16 in placebo group) **Participant baseline characteristics** Presence or absence of nasal polyps: all participants had CRSwNP Baseline nasal polyp score: not mentioned Previous sinus surgery: not mentioned Presence or absence of a diagnosis of asthma: all participants had asthma Other baseline characteristics Age (mean years, SD): 31 ± 4.3 (NSAID), 27 ± 5.5 (placebo) Female sex: N = 13 (72%) (NSAID), N = 10 (62%) (placebo) Lund-Mackay score (mean, SD): 15.1 ± 0.7 (NSAID), 12.4 ± 0.3 (placebo) Medication score (mean, SD): 13.1 ± 0.3 (NSAID), 11.5 ± 0.6 (placebo) Symptom score (mean, SD): 14.5 ± 1.1 (NSAID), 11.3 ± 0.9 (placebo) SNOT-22 score (mean, SD): 52.8 ± 4.1 (NSAID), 37.6 ± 2.7 (placebo) FEV_1 (% of predicted mean L/sec, SD): 79.1 ± 1 (NSAID), 83.8 ± 2.0 (placebo) **Inclusion criteria** CRSwNP in accordance with endoscopic and CT findings Stable asthma with no increase in baseline glucocorticoids for at least 3 months or no asthma attack in at least the last 6 months Aspirin hypersensitivity confirmed by a positive Intranasal Ketorolac test and positive modified oral aspirin challenge test 18 years or over Both sexes were eligible to participate

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Esmaeilzadeh 2015 *[continued]*	
Study characteristics	
Participants *[continued]*	**Exclusion criteria** Smoking Pregnancy or current breastfeeding History of bleeding diathesis and gastrointestinal bleeding History of ischaemic heart disease, stroke and diabetes History of abnormal liver function Uncontrolled hypertension
Interventions	**Aspirin desensitisation (n = 18):** aspirin desensitisation according to protocol. Desensitisation was initiated by administrating intranasal ketorolac spray and aspirin capsules for 2 consecutive days. Day 1: 4 increasing doses of Ketorolac spray at 30-minute intervals, 2 x 60 mg aspirin at 90-minute intervals Day 2: 2 increasing dosages of aspirin from 150 mg to 325 mg at 180-minute intervals, depending on the reaction to 60 mg on day 1 Maintenance: twice-daily 650 mg aspirin for 1 month, followed by aspirin 325 mg twice daily for 5 months Method of administration of aspirin (nasal versus oral/systemic): oral Setting of aspirin administration (outpatient or inpatient): aspirin desensitisation in hospitalised setting **Placebo treatment (n = 16):** the placebo arm followed the same protocol as the active arm. Day 1: placebo sprays containing normal saline at 30-minute intervals 2 x glucose capsules at 90-minute intervals Day 2: 2 glucose capsules at 180-minute intervals Maintenance: twice-daily glucose capsules for 6 months **Additional interventions:** Standard medications to control respiratory and naso-ocular symptoms were allowed. Antihistamines, beta-agonists and corticosteroids were discontinued for at least 48 hours prior to aspirin challenge test.
Outcomes	**Primary outcomes** Effect of aspirin desensitisation on disease-specific health-related quality of life (SNOT-22; SNOT-22 has 22 questions with a score of 0 to 5 for each question (range 0 to 110)). Effect of aspirin desensitisation on anti-inflammatory cytokines (IL-10), TGF-beta, IFN-gamma **Secondary outcomes** Effect of aspirin desensitisation on symptom scores Effect of aspirin desensitisation on Lund-Mackay Score (CT finding: this score ranges from 0 (complete lucency of all sinuses) to 24 (complete opacity of all sinuses)) Effect of aspirin desensitisation on lung function (FEV1) Effect of aspirin desensitisation on medication needs (medication scores for local and systemic medication) Outcomes were measured after 1 month and 6 months follow-up
Funding sources	Grant from Tehran University of Medical Sciences, grant number of 92-01-119-20728
Declarations of interest	The authors declare no conflict of interest.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer-generated list of random numbers; block randomisation.
Allocation concealment (selection bias)	High risk	Randomisation was implemented by an unblinded study director. Baseline imbalances.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and investigators were blinded to the assigned treatment group. Neither participants nor investigators were aware of the arm assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were not aware of the arm assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 of 34 participants completed the study; 2 did not manage to complete the study due to adverse events.
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome parameters as mentioned in the protocol are reported.
Other bias	Low risk	No other obvious issues.

Fruth 2013

Study characteristics	
Methods	**Design:** parallel-group randomised controlled trial **Duration of study:** 36 months **Study dates:** individuals undergoing sinus surgery between 2006 and 2008
Participants	**Location:** Germany, 1 site **Setting of recruitment:** Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center of the Johannes Gutenberg University, Mainz **Sample size:** with N = 70 participants, a recurrence rate below 10% in the active group could be established at the 5% level with a power of 80%, assuming a base recurrence rate of 40% in the placebo group **Number randomised:** N = 70 (36 in active group, 34 in placebo group) **Number analysed:** N = 31 (18 in active group, 13 in placebo group) **Participant baseline characteristics** Presence or absence of nasal polyps: all participants had CRSwNP Baseline nasal polyp score: not mentioned Previous sinus surgery: at least twice Presence or absence of a diagnosis of asthma: all participants had asthma Other baseline characteristics Age (mean years, SD): 44.9 (11.3) (NSAID), 45.9 (10.4) (placebo) Male sex: N = 19 (53%) (NSAID), N = 20 (59%) (placebo)

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Fruth 2013 *[continued]*

Study characteristics	
Participants *[continued]*	**Inclusion criteria** Individuals suffering from CRSwNP and AERD, who have at least twice undergone previous sinus surgery. AERD was diagnosed by combining clinical symptoms of the participant with a functional in vitro eicosanoid test. **Exclusion criteria** Pregnancy Haemorrhagic diathesis Chronic gastric or duodenal ulcers Glucose-6-phosphatedehydrogenase deficiency Renal diseases Liver diseases Individuals who took anticoagulant medication
Interventions	All participants underwent surgery. After 6 weeks, randomisation took place. **Aspirin desensitisation (n = 36)** Day 1: 180 mg aspirin cumulative Day 2: 800 mg aspirin cumulative Day 3 and on: 100 mg aspirin Method of administration of aspirin (nasal versus oral/systemic): oral. Time intervals of aspirin administration unclear on days 1 and 2 Setting of aspirin administration (outpatient or inpatient): desensitisation was hospitalised, maintenance therapy at home **Placebo (n = 34):** followed the same steps as aspiring desensitisation. Placebo medication consisted of lactose, magnesium stearate, cellulose powder and microcrystalline cellulose. **Additional interventions:** inhaled steroids and nasal saline washing were allowed. All participants used nasal steroids during the study period.
Outcomes	**Primary outcome** Recurrence of nasal polyps, defined as a polyp score of 1 or more **Secondary outcome** Sense of smell, quality of life (Rhinosinusitis Disability Index (rated on a scale from 1 to 5 (1 = very rare, 2 = rare, 3 = sometimes, 4 = often, 5 = very often); the highest possible score was 150), symptom score Measurements were performed after 6, 9, 12, 24 and 36 months.
Funding sources	Supported by the research program of the University of Mainz, Germany (MAIFOR)
Declarations of interest	There is no conflict of interest to declare.
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation was performed.
Allocation concealment (selection bias)	Low risk	Computer randomisation at the institutional centre of clinical research (central allocation concealment).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study medication was produced by the institutional pharmacy. We can assume they are the only ones aware of the randomisation, although it is not specifically stated in the text, apart from mentioning "double-blinded" in the introduction.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The method of blinding is not clear, although the study is double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow of participants through the study was adequately described. No exclusions were mentioned, although 39 participants had discontinued the study after 36 months of follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the 'Methods section' were reported in Table 1 of the publication.
Other bias	Low risk	No other obvious issues.

Mortazavi 2017

Study characteristics	
Methods	**Design:** parallel-group randomised controlled trial **Duration of study:** 6 months follow-up **Study dates:** May 2015 to January 2017
Participants	**Location:** Iran, 2 sites **Setting of recruitment:** 2 referral centres for immunology and allergy, affiliated to the Shiraz University of Medical Sciences in South Iran and Shadid Beheshti University of Medical Sciences in Central Iran **Sample size:** not reported **Number randomised:** N = 41 (22 in active group, 19 in placebo) **Number analysed:** N = 38 (19 in active group, 19 in placebo group) **Participant baseline characteristics** Presence or absence of nasal polyps: all participants had CRSwNP Baseline nasal polyp score: not mentioned Previous sinus surgery: not mentioned Presence or absence of a diagnosis of asthma: all participants had asthma Other baseline characteristics Age (mean years, SD): 33 (2) (NSAID), 29 (1) (placebo) Male sex: N = 13 (59%) (NSAID), N = 10 (53%) (placebo) SNOT-22 score (mean, SD): 53.95 (14.4) (NSAID), 41.53 (9.9) (placebo), P = 0.011 Lund-Mackay score (mean, SD): 14.74 (3) (NSAID), 12.42 (1.1) (placebo), P = 0.014 Symptom score (mean, SD): 15.37 (4.8) (NSAID), 12.42 (3.9) (placebo), P = 0.063 Medication score (mean, SD): 13.05 (1.3) (NSAID), 11.47 (2.2) (placebo), P = 0.021 **Inclusion criteria** Aspirin hypersensitivity confirmed by a positive Intranasal Ketorolac test and positive modified oral aspirin challenge test **Exclusion criteria** History of anaphylactic or type-1 hypersensitivity reaction to aspirin History of gastrointestinal bleeding or bleeding incontinence Liver dysfunction Pregnancy
Interventions	**Aspirin desensitisation (n = 22)** Day 1: intranasal ketorolac spray in 2-fold increasing dosage at an interval of 30 minutes, followed by 2 dosages of 60 mg aspirin at 90-minute intervals Day 2: 160 mg and 325 mg of aspirin at 180-minute intervals Maintenance: 650 mg of aspirin twice every day for 1 month; 325 mg of aspirin twice every day for 5 months Method of administration of aspirin (nasal versus oral/systemic): oral Setting of aspirin administration (outpatient or inpatient): not reported **Placebo (n = 19)** Day 1: intranasal ketorolac spray in 2-fold increasing dosage at an interval of 30 minutes, followed by 2 dosages of placebo at regular intervals of 90 minutes Day 2: 160 mg and 325 mg of placebo at 180-minute intervals

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Mortazavi 2017 *[continued]*

Study characteristics	
Interventions	Maintenance: 650 mg of placebo twice every day for 1 month; 325 mg of placebo twice every day for 5 months **Additional interventions:** allowed to take standard medications to control asthma or nasal symptoms
Outcomes	**Outcomes:** no primary or secondary outcomes were reported separately Asthma attacks Recurrence of nasal polyposis FEV_1 (L/sec) Symptom score Medication need scores SNOT-22 (SNOT-22 has 22 questions with a score of 0 to 5 for each question (range 0 to 110)). Lund-Mackay score (CT finding: this score ranges from 0 (complete lucency of all sinuses) to 24 (complete opacity of all sinuses)) Levels of interleukin 4 and 5 Baseline visit, 1-month and 6-month follow-up measurements
Funding sources	Unreported
Declarations of interest	Unreported
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random computer-generated division in block size.
Allocation concealment (selection bias)	High risk	No information on allocation concealment and multiple baseline imbalances between intervention groups.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The aspirin and placebo capsules were prepared by a pharmacy student, who was not engaged in visiting the participants. Practising clinicians were blind to the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Practising clinicians were blind to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 43 randomised participants, 3 discontinued (1 lost to follow-up, 1 pregnant, 1 had gastrointestinal bleeding). The rest were analysed. No significant risk of bias.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	No sample size calculation provided. No primary or secondary outcome parameters specified.

Świerczyńska-Krępa 2014

Study characteristics	
Methods	**Design:** parallel-group randomised controlled trial **Duration of study:** 6 months follow-up **Study dates:** not reported
Participants	**Location:** Poland, 1 site **Setting of recruitment:** Division of Pulmonology, Jagiellonian University School of Medicine, Krakow **Sample size:** N=20 aspirin-intolerant participants, no sample-size calculation provided **Number randomised:** N=34 **Aspirin-intolerant participants (AIA):** N = 20 (12 active group, 8 placebo) **Aspirin-tolerant participants (ATA):** N = 14 (6 active group, 8 placebo) We excluded the ATA group in this review and focussed on AIA participants. **Number analysed AIA:** N = 15 (8 active group, 7 placebo group) **Participant baseline characteristics (AIA)** Presence or absence of nasal polyps: all participants had CRSwNP Baseline nasal polyp score: not mentioned Previous sinus surgery: 17/20 underwent previous polypectomy Presence or absence of a diagnosis of asthma: all participants had asthma Other baseline characteristics (AIA) Age (median years, IQR): 48.5 (SD 18) (NSAID), 39.5 (SD 27) (placebo) Male sex: N = 3 (25%) (NSAID), N = 2 (25%) (placebo) Asthma Control Questionnaire (median, IQR): 1.2 (2.0) (NSAID), 1.4 (1.1) (placebo) Medication score (median, IQR): 800 (600) (NSAID), 800 (650) (placebo) Baseline PEF (median, IQR): 445 (148) (NSAID), 405 (110) (placebo) SNOT-20 (median, IQR): 1.9 (0.8) (NSAID), 1.8 (1.2) (placebo) FEV_1 (mean % of predicted L/sec, SD): 84.6 (23.0) (NSAID), 93.9 (14.2) (placebo) **Inclusion criteria** Aged 18 to 65 years Asthma diagnosed in compliance with applicable guidelines CRSwNP as evidenced by medical records and endoscopic findings, computed tomographic (CT) findings, or both Positive history of a prior reaction to aspirin, other NSAIDs, or both, confirmed by a positive response to oral aspirin challenge for the participants with AIA **Exclusion criteria** History of life-threatening anaphylactic reactions precipitated by NSAIDs Uncontrolled asthma or FEV_1 of less than 70% of predicted value, or both Autoimmune diseases Severe diseases of the heart or digestive, urinary or neurologic systems, or any other clinical condition that could potentially influence the study outcome Neoplasm Pregnancy
Interventions	**Aspirin group in AIA participants (n = 12)** Day 1: maximal dose of aspirin tolerated during aspirin challenge. If asymptomatic, increased administrations, 90 minutes apart, until 624 mg reached.

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Świerczyńska-Krępa 2014 *[continued]*

Study characteristics	
Interventions *[continued]*	Day 2: starting dose that provoked a reaction on day 1. The day of desensitisation was the day on which a participant could ingest 624 mg of aspirin in the morning without any reaction. Maintenance: 624 mg for 6 months Method of administration of aspirin (nasal versus oral/systemic): oral Setting of aspirin administration (outpatient or inpatient): not reported **Placebo group in AIA participants (n = 8):** placebo administration for 6 months **Use of additional interventions:** Doses of inhaled corticosteroids and nasal corticosteroids were kept stable throughout the aspirin challenge and acute desensitisation. Afterwards, dosages could vary.
Outcomes	**Primary outcomes** Changes in the scores for the clinical symptoms (VAS), PNIF, FEV_1 and PEF values Absolute reductions in corticosteroid doses **Secondary outcomes** Changes in uLTE4, p9a, 11b-PGF2, or both levels Monthly follow-up (30 ± 7 days) for 6 months for measurements We contacted the study authors for data on PEF values, since these data were not reported in their published article. We received a table with raw study data. However, no information on PEF values was found.
Funding sources	University grant
Declarations of interest	Research support from the Ministry of Science and Higher Education of Poland in association with Collegium Medicum Jagiellonian University (grant no. K/ZDS/000362) A grant from Switzerland through the Swiss Contribution to the enlarged European Union (PSPB-072/2010) A grant from Iceland, Liechtenstein and Norway through the European Economic Area (EEA) U-BIOPPRED, EU, and EFPIA within the Innovative Medicines Initiative (IMI)
Notes	**Participants lost to follow-up:** n = 6

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Authors used a random numbers table.
Allocation concealment (selection bias)	Unclear risk	No report of concealment provided. No baseline imbalances.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Aspirin and placebo were prepared by a hospital pharmacy in the form of identical, powder-packed gelatin capsules.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were evaluated during visits by a blinded physician.
Incomplete outcome data (attrition bias) All outcomes	High risk	In total, 5 participants (25%) withdrew from the study, and this differed per intervention group. In total, 4 participants withdrew due to adverse events in the active group.
Selective reporting (reporting bias)	High risk	Full reporting on clinical symptoms missing: 3 were selected and reported: smell, nasal blockage and sneezing score (rhinorrhoea, postnasal drip and nasal itching; bronchial: cough and dyspnoea missing). PEF values were not reported at 6 months.
Other bias	Low risk	No other obvious issues.

AERD: aspirin-exacerbated respiratory disease
AIA: aspirin-intolerant asthma
CRSwNP: chronic rhinosinusitis with nasal polyps
CT: computed tomography
EFPIA: European Federation of Pharmaceutical Industries and Associations
EU: European Union
FEV_1: forced expiratory volume in one second
ICS: inhaled corticosteroid
IFN: interferon
IL-10: interleukin 10
IQR: interquartile range
LABA: long-acting beta-agonist
LTRA: leukotriene receptor antagonist
NSAID: non-steroidal anti-inflammatory drug
N/n/no.: number
PEF: peak expiratory flow
PNIF: peak nasal inspiratory flow
SD: standard deviation
SNOT-20: Sino-Nasal Outcome Test-20
SNOT-22: Sino-Nasal Outcome Test-22
TGF: transforming growth factor
uLTE4: urine leukotriene E4
VAS: visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Celik 2017	Ineligible comparator (aspirin maintenance 300 mg versus 600 mg)
Parikh 2005	Cross-over trial comparing intranasal lysine-aspirin and placebo (22 participants). Did not obtain first period treatment data (4 participants).
Sowerby 2021	Ineligible intervention (no aspirin desensitisation)

Characteristics of studies awaiting classification *[ordered by study ID]*

IRCT2015061522531N2

Methods	**Design:** parallel-group randomised controlled trial **Duration of study:** 6 months of follow-up **Study dates:** possibly July 2015 to December 2015
Participants	**Location:** Iran, 1 site **Setting of recruitment:** Allergy department of Rasool-e-Akram Hospital **Sample size:** N = 60 **Inclusion criteria** Age 18 to 65 years Achieving a course of three months of conventional treatment before aspirin challenge Presence of symptoms of chronic rhinosinusitis with nasal polyposis confirmed by CT scan **Exclusion criteria** Presence of any serious underlying disease including haemorrhagic; gastrointestinal; rheumatologic; malignant; cardiovascular; renal; hepatic and psychological disorders History of IgE-mediated reactions to aspirin or other nonsteroidal antiinflammatory drugs First second expiratory volume of less than 70% of predicted at the time of aspirin challenge Pregnancy Nursing Use of topical or systemic beta blockers Warfarin and its derivates Angiotensin converting enzyme inhibitors People with poor cooperation or treatment adherence People with carriers with high risk of trauma and accidents
Interventions	**Group 1:** aspirin desensitisation and aspirin 325 milligrams daily added to conventional treatment, including intranasal beclomethasone, one puff per nostril twice a day, nasal rinsing with 5 ml saline three times a day, 10 mg montelukast tablet once daily, 10 mg cetirizine tablet once daily **Group 2:** aspirin desensitisation and aspirin 100 mg daily added to conventional treatment, including intranasal beclomethasone, one puff per nostril twice a day, nasal rinse with 5 ml saline three times a day, 10 mg montelukast tablet once daily, 10 mg cetirizine tablet once daily

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IRCT2015061522531N2 *[continued]*

Interventions *[continued]*	**Group 3:** aspirin desensitisation and placebo tablet once daily, added to conventional treatment, including intranasal beclomethasone, one puff per nostril twice a day, nasal rinse with 5 ml saline three times a day, 10 mg montelukast tablet once daily, 10 mg cetirizine tablet once daily
Outcomes	**Outcomes:** before intervention, 3 months and 6 months after intervention **Primary** Severity of symptoms of chronic rhinosinusitis with nasal polyposis (SinoNasal Outcome Test and sinus CT scan) **Secondary** Complications of aspirin, including gastrointestinal discomfort, epigastric pain or burning, nausea, vomiting, gastro intestinal bleeding, easy bruising, bleeding with minor trauma
Notes	Unable to find full text, but could be included if study has been completed. **Funding:** Vice chancellor for research, Iran University of Medical Sciences

CT: computed tomography; IgE: immunoglobulin E; N: number.

DATA AND ANALYSES

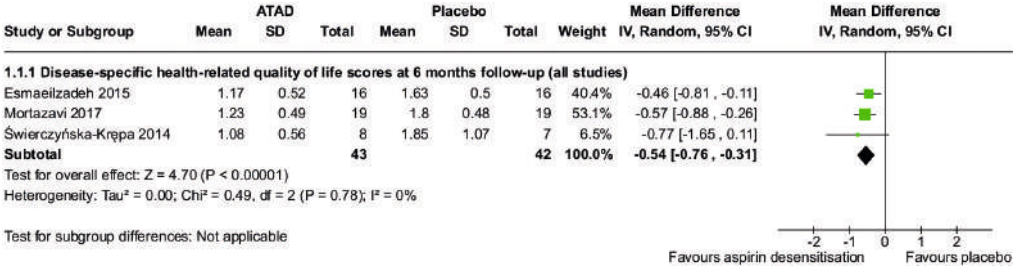
Comparison 1. Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Disease-specific health-related quality of life scores at 6 months follow-up (SNOT-score)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 Disease-specific health-related quality of life scores at 6 months follow-up (all studies)	3	85	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.76, -0.31]
1.2 Disease-specific health-related quality of life scores at 6 months follow-up (SNOT-score) (excluding high risk of bias studies)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.1 Disease-specific health-related quality of life scores at 6 months follow-up (excluding high risk of bias studies)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3 Disease-specific health-related quality of life scores at 36 months follow-up (Rhinosinusitis Disability Index) (all studies)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4 Asthma control at 6 months follow-up (Asthma Control Questionnaire)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

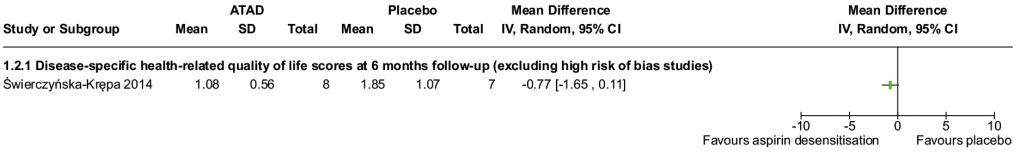
[continued on next page]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Asthma control at 6 months follow-up (Asthma Control Test)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6 Significant adverse events during maintenance therapy up to 6 months follow-up	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Significant adverse events during maintenance therapy up to 6 months follow-up (all studies)	4	129	Risk Ratio (M-H, Random, 95% CI)	3.71 [0.67, 20.47]
1.7 Mean change from baseline in peak nasal inspiratory flow (PNIF) at 6 months follow-up (L/min)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.8 Nasal endoscopy score at 36 months follow-up (Lildholdt score)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9 Change in dosage of inhaled corticosteroids at 6 months follow-up (µg)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10 Change in dosage of nasal corticosteroids at 6 months follow-up (µg)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11 Change in medication score at 6 months follow-up (dosage of inhaled/ intranasal corticosteroid)	2	70	Mean Difference (IV, Random, 95% CI)	-4.14 [-4.72, -3.56]
1.12 Symptom score after 6 months follow-up	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.12.1 Smell score	1	15	Mean Difference (IV, Random, 95% CI)	-2.20 [-4.74, 0.34]
1.12.2 Nasal blockage	1	15	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.90, 0.10]
1.12.3 Sneezing	1	15	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.45, 0.05]
1.13 Asthma exacerbations after 6 months follow-up	2	70	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.27, 1.02]
1.14 Chronic rhinosinusitis exacerbations after 36 months follow-up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

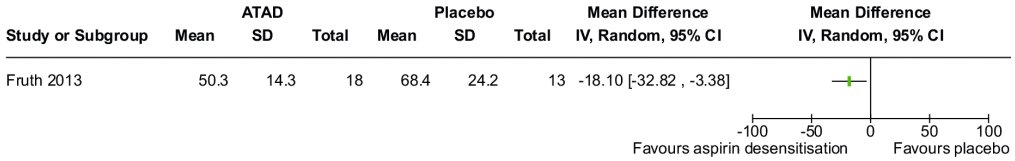
Analysis 1.1. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 1: Disease-specific health-related quality of life scores at 6 months follow- (SNOT-score)



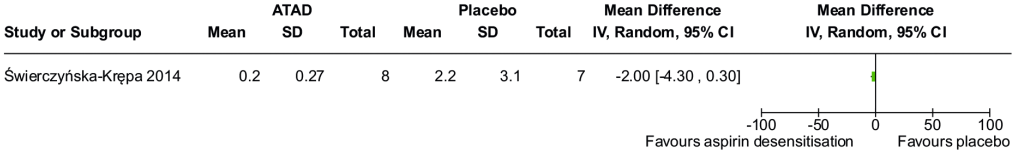
Analysis 1.2. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 2: Disease-specific health-related quality of life scores at 6 months follow- (SNOT-score) (excluding high risk of bias studies)



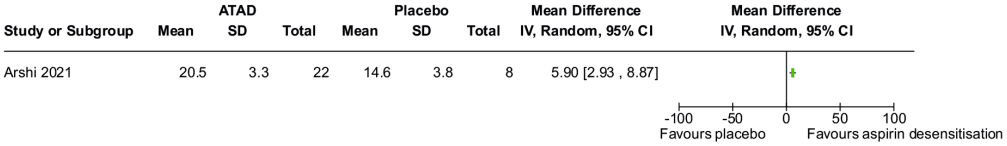
Analysis 1.3. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 3: Disease-specific health-related quality of life scores at 36 months follow- (Rhinosinusitis Disability Index) (all studies)



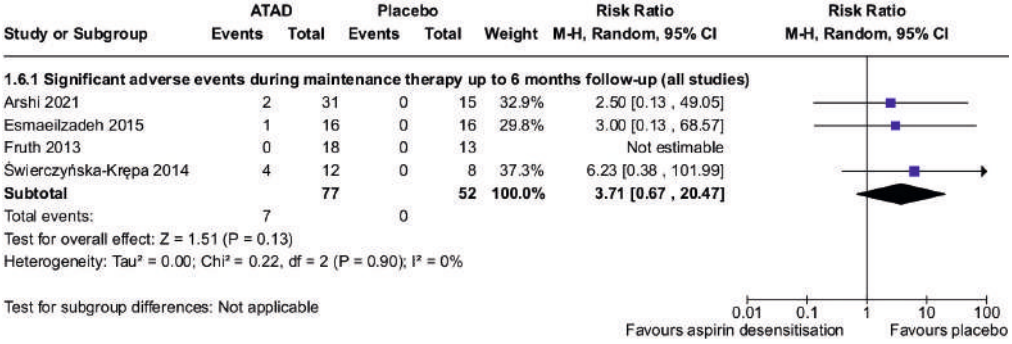
Analysis 1.4. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 4: Asthma control at 6 months follow-up (Asthma Control Questionnaire)



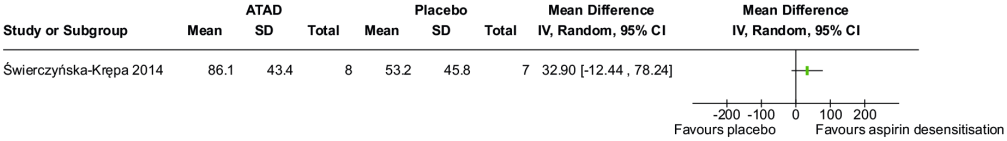
Analysis 1.5. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 5: Asthma control at 6 months follow-up (Asthma Control Test)



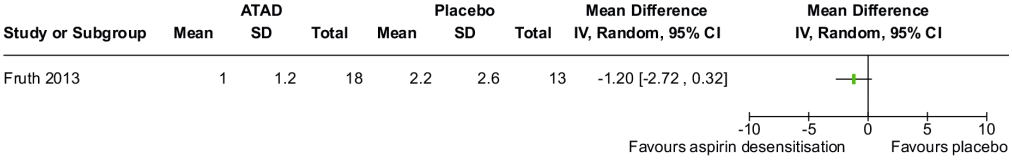
Analysis 1.6. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 6: Significant adverse events during maintenance therapy up to 6 months follow-up



Analysis 1.7. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 7: Mean change from baseline in peak nasal inspiratory flow (PNIF) at 6 month follow-up (L/min)

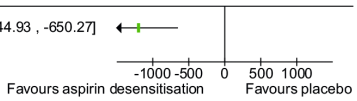


Analysis 1.8. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 8: Nasal endoscopy score at 36 months follow-up (Lildholdt score)



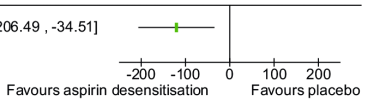
Analysis 1.9. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 9: Change in dosage of inhaled corticosteroids at 6 months follow-up (µg)

Study or Subgroup	ATAD Mean	ATAD SD	ATAD Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Random, 95% CI
Świerczyńska-Krępa 2014	-658.3	284.9	8	539.3	689.1	7	-1197.60 [-1744.93 , -650.27]



Analysis 1.10. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 10: Change in dosage of nasal corticosteroids at 6 months follow-up (µg)

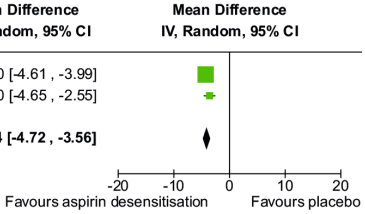
Study or Subgroup	ATAD Mean	ATAD SD	ATAD Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Random, 95% CI
Świerczyńska-Krępa 2014	-31.5	65.3	8	89	98.7	7	-120.50 [-206.49 , -34.51]



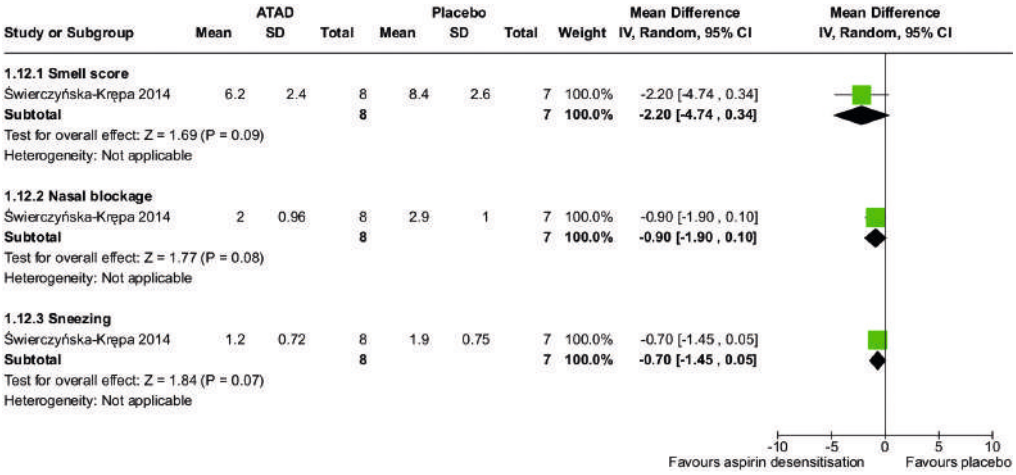
Analysis 1.11. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 11: Change in medication score at 6 months follow-up (dosage of inhaled/intranasal corticosteroid)

Study or Subgroup	ATAD Mean	ATAD SD	ATAD Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Esmaeilzadeh 2015	-3.8	0.36	16	0.5	0.51	16	77.0%	-4.30 [-4.61 , -3.99]
Mortazavi 2017	-3.6	1.3	19	0	1.95	19	23.0%	-3.60 [-4.65 , -2.55]
Total			**35**			**35**	**100.0%**	**-4.14 [-4.72 , -3.56]**

Test for overall effect: Z = 14.05 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.09; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%



Analysis 1.12. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease, Outcome 12: Symptom score after 6 months follow-up



Analysis 1.13. Comparison 1: Oral and intranasal aspirin desensitisation versus placebo for non-steroidal anti-inflammatory drug (NSAID)- exacerbated respiratory disease, Outcome 13: Asthma exacerbations after 6 months follow-up

APPENDICES

Appendix 1. Search strategies

Cochrane ENT Trials Register (CRS)	Cochrane Airways Trials Register (CRS)	CENTRAL (CRS)
1 MESH DESCRIPTOR Respiratory Tract Diseases EXPLODE ALL AND INREGISTER 2 MESH DESCRIPTOR Aspirin EXPLODE ALL WITH QUALIFIER AE AND INREGISTER 3 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL WITH QUALIFIER AE AND INREGISTER 4 MESH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL AND INREGISTER 5 #2 OR #3 OR #4 AND INREGISTER 6 #1 AND #5 AND INREGISTER 7 MESH DESCRIPTOR Asthma, Aspirin-Induced EXPLODE ALL AND INREGISTER 8 ((aspirin OR ASA) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 9 ((Acetylsalicylic OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 10 (NSAID* NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv*or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER	1 (AST):MISC1 AND AIRWAYS:INREGISTER 2 MESH DESCRIPTOR Respiratory Tract Diseases EXPLODE ALL AND AIRWAYS:INREGISTER 3 MESH DESCRIPTOR Aspirin EXPLODE ALL WITH QUALIFIER AE AND AIRWAYS:INREGISTER 4 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL WITH QUALIFIER AE AND AIRWAYS:INREGISTER 5 MESH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL AND AIRWAYS:INREGISTER 6 #3 OR #4 OR #5 7 #1 OR #2 8 #6 AND #7 9 MESH DESCRIPTOR Asthma, Aspirin-Induced EXPLODE ALL AND AIRWAYS:INREGISTER 10 ((aspirin OR ASA) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND AIRWAYS:INREGISTER 11 ((Acetylsalicylic OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND AIRWAYS:INREGISTER	1 MESH DESCRIPTOR Respiratory Tract Diseases EXPLODE ALL AND CENTRAL:TARGET 2 MESH DESCRIPTOR Aspirin EXPLODE ALL WITH QUALIFIER AE AND CENTRAL:TARGET 3 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL WITH QUALIFIER AE AND CENTRAL:TARGET 4 MESH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL AND CENTRAL:TARGET 5 #2 OR #3 OR #4 AND CENTRAL:TARGET 6 #1 AND #5 AND CENTRAL:TARGET 7 MESH DESCRIPTOR Asthma, Aspirin-Induced EXPLODE ALL AND CENTRAL:TARGET 8 ((aspirin OR ASA) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 9 ((Acetylsalicylic OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 10 (NSAID* NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

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Appendix 1. *[continued]*

Cochrane ENT Trials Register (CRS)	Cochrane Airways Trials Register (CRS)	CENTRAL (CRS)
11 ((non-steroid* NEAR (antiinflammatory or anti-inflammatory)) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,-TO AND INREGISTER 12 ((nonsteroid* NEAR (antiinflammatory or anti-inflammatory)) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,-TO AND INREGISTER 13 (AERD OR N-ERD or AIA):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 14 #6 OR #7 OR #8 OR #10 OR #11 OR #12 OR #13 AND INREGISTER 15 MESH DESCRIPTOR Desensitization, Immunologic EXPLODE ALL AND INREGISTER 16 MESH DESCRIPTOR Aspirin EXPLODE ALL WITH QUALIFIER IM AND INREGISTER 17 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL WITH QUALIFIER IM AND INREGISTER 18 MESH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL WITH QUALIFIER IM AND INREGISTER 19 (Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)): AB,EH,KW,KY,MC,MH,TI,-TO AND INREGISTER 20 #15 OR #16 OR #17 OR #18 OR #19 AND INREGISTER 21 #20 AND #14 AND INREGISTER 22 * AND CENTRAL:TARGET 23 #21 NOT #22	12 (NSAID* NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv*or hyper-responsiv*)): AB,EH,KW,KY,MC,MH,TI,TO AND AIRWAYS:INREGISTER 13 ((non-steroid* NEAR (antiinflammatory or anti-inflammatory)) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)): AB,EH,KW,KY,MC,MH,TI,-TO AND AIRWAYS:INREGISTER 14 ((nonsteroid* NEAR (antiinflammatory or anti-inflammatory)) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)): AB,EH,KW,KY,MC,MH,TI,-TO AND AIRWAYS:INREGISTER 15 (AERD OR N-ERD or AIA): AB,EH,KW,KY,MC,MH,TI,TO AND AIRWAYS:INREGISTER 16 (AST): MISC1 AND AIRWAYS:INREGISTER 17 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv*): AB,EH,KW,KY,MC,MH,TI,TO AND AIRWAYS:INREGISTER 18 #16 AND #17 19 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #18 20 MESH DESCRIPTOR Desensitization, Immunologic EXPLODE ALL AND AIRWAYS:INREGISTER 21 MESH DESCRIPTOR Aspirin EXPLODE ALL WITH QUALIFIER IM AND AIRWAYS:INREGISTER 22 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL WITH QUALIFIER IM AND AIRWAYS:INREGISTER	11 ((non-steroid* NEAR (antiinflammatory or anti-inflammatory)) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,-TO AND CENTRAL:TARGET 12 ((nonsteroid* NEAR (antiinflammatory or anti-inflammatory)) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)):AB,EH,KW,KY,MC,MH,TI,-TO AND CENTRAL:TARGET 13 (AERD OR N-ERD or AIA):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 14 #6 OR #7 OR #8 OR #10 OR #11 OR #12 OR #13 AND CENTRAL:TARGET 15 MESH DESCRIPTOR Desensitization, Immunologic EXPLODE ALL AND CENTRAL:TARGET 16 MESH DESCRIPTOR Aspirin EXPLODE ALL WITH QUALIFIER IM AND CENTRAL:TARGET 17 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL WITH QUALIFIER IM AND CENTRAL:TARGET 18 MESH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL WITH QUALIFIER IM AND CENTRAL:TARGET 19 (Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 20 #15 OR #16 OR #17 OR #18 OR #19 AND CENTRAL:TARGET 21 #20 AND #14 AND CENTRAL:TARGET

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Appendix 1. *[continued]*

Cochrane ENT Trials Register (CRS)	Cochrane Airways Trials Register (CRS)	CENTRAL (CRS)
	23 MESH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL WITH QUALIFIER IM AND AIRWAYS:INREGISTER 24 (Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)): AB,EH,KW,KY,MC,MH,TI,TO AND AIRWAYS:INREGISTER 25 #20 OR #21 OR #22 OR #23 OR #24 26 #19 AND #25	

MEDLINE (Ovid)	EMBASE (Ovid)	Web of Science (Web of Knowledge)
1. exp Respiratory Tract Diseases/ci or exp Respiratory Hypersensitivity/ or Respiratory Tract Diseases/ 2. exp Aspirin/ae [Adverse Effects] 3. exp Anti-Inflammatory Agents, Non-Steroidal/ae [Adverse Effects] 4. exp Drug Hypersensitivity/ 5. 2 or 3 or 4 6. 1 and 5 7. exp Asthma, Aspirin-Induced/ 8. ((aspirin or ASA) adj5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*)).ab,ti. 9. ((Acetylsalicylic or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetysal) adj5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*)).ab,ti. 10. (NSAID* adj5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv*)).ab,ti.	1 exp respiratory tract disease/ 2 exp acetylsalicylic acid/ae [Adverse Drug Reaction] 3 exp nonsteroid antiinflammatory agent/ae [Adverse Drug Reaction] 4 exp drug hypersensitivity/ 5 2 or 3 or 4 6 1 and 5 7 exp aspirin exacerbated respiratory disease/ 8 ((aspirin or ASA) adj5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*)).ab,ti. 9 ((Acetylsalicylic or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetysal) adj5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*)).ab,ti. 10 (NSAID* adj5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv*)).ab,ti.	#1 TOPIC: ((aspirin or ASA) near/5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #2 TOPIC: ((Acetylsalicylic or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetysal) near/5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #3 TOPIC: (non-steroid* near/5 (antiinflammatory or anti-inflammatory) near/5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #4 TOPIC: (nonsteroid* near/5 (antiinflammatory or anti-inflammatory) near/5 (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provok* or hyperresponsiv* or hyper-responsiv*))

[continued on next page]

Appendix 1. *[continued]*

MEDLINE (Ovid)	EMBASE (Ovid)	Web of Science (Web of Knowledge)
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MEDLINE (Ovid)	EMBASE (Ovid)	Web of Science (Web of Knowledge)
	36 Latin square design/ 37 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 38 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 39 exp human/ 40 38 not 39 41 37 not 40 42 19 and 41	
Trial Registries	**LILACS**	**CNKI (via Google Scholar)**
Clinicaltrials.gov and ICTRP via CRS 1 (aspirin OR ASA) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND CENTRAL:TARGET 2 (aspirin OR ASA) NEAR (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND INREGISTER 3 (Acetylsalicylic OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal) AND (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND INREGISTER	(TW:aspirin OR TW:ASA OR TW:NSAID OR TW:AERD or TW:N-ERD or TW:AIA) AND (TW:sensitiv* OR TW:exacerbat* OR TW:induced OR TW:intolerence) AND (TW:desensitiz* OR TW:desensitis* OR TW:hyposensitis* OR TW:hyposensitiz*) AND (TW:Non-steroid* OR TW:non-steroid*) AND (TW:antiinflammatory or TW:anti-inflammatory) AND (TW:desensitiz* OR TW:desensitis* OR TW:hyposensitis* OR TW:hyposensitiz*)	site:cnki.com.cn (aspirin OR NSAID OR Acetylsalicylic OR (non-steroidal anti-inflammatory) OR (nonsteroidal antiinflammatory) OR AERD or N-ERD or AIA) (desensitization OR hyposensitization or sensitivity OR exacerbated OR induced OR intolerence)

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Trial Registries	LILACS	CNKI (via Google Scholar)
4 (Acetylsalicylic OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal) AND (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND CENTRAL:TARGET 5 (non-steroid* NEAR (antiinflammatory or anti-inflammatoryl)) AND (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND CENTRAL:TARGET 6 (non-steroid* NEAR (antiinflammatory or anti-inflammatoryl)) AND (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND INREGISTER 7 (nonsteroid* NEAR (antiinflammatory or anti-inflammatoryl)) AND (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperresponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND INREGISTER 8 (nonsteroid* NEAR (antiinflammatory or anti-inflammatoryl)) AND (sensitiv* or exacerbat* or induced or intoleran* or hypersensitiv* or provoke* or hyperre		

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Trial Registries	LILACS	CNKI (via Google Scholar)
sponsiv*or hyper-responsiv* or Desensitiz* or Desensitis* or Hyposensitiz* or hyposensitis* or (Allergen NEAR Immunotherap*)) AND CENTRAL:TARGET 9 AERD OR N-ERD or AIA AND CENTRAL:TARGET 10 AERD OR N-ERD or AIA AND INREGISTER 11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 AND INREGISTER 12 http*:SO AND INREGISTER 13 http*:SO AND CENTRAL:TARGET 14 (NCT0* or ACTRN* or ChiCTR* or DRKS* or EUCTR* or eudract* or IRCT* or ISRCTN* or JapicCTI* or JPRN* or NTR0* or NTR1* or NTR2* or NTR3* or NTR4* or NTR5* or NTR6* or NTR7* or NTR8* or NTR9* or SRCTN* or UMIN0*):AU AND CENTRAL:TARGET 15 (NCT0* or ACTRN* or ChiCTR* or DRKS* or EUCTR* or eudract* or IRCT* or ISRCTN* or JapicCTI* or JPRN* or NTR0* or NTR1* or NTR2* or NTR3* or NTR4* or NTR5* or NTR6* or NTR7* or NTR8* or NTR9* or SRCTN* or UMIN0*):AU AND INREGISTER 16 #12 OR #13 OR #14 OR #15 AND INREGISTER 17 #11 AND #16 AND INREGISTER **Clinicaltrials.gov** (aspirin OR ASA OR NSAID OR Acetylsalicylic or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetysal) AND (sensitivity OR exacerbated OR induced OR intolerence) OR (desensitization OR desensitisation OR hyposensitisation OR hyposensitization) OR		

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Trial Registries	LILACS	CNKI (via Google Scholar)
(Non-steroidal OR nonsteroidal) AND (antiinflammatory or anti-inflammatory) AND (sensitivity OR exacerbated OR induced OR intolerence) AND (desensitization OR desensitisation OR hyposensitisation OR hyposensitization) OR (AERD or N-ERD or AIA) AND (desensitization OR desensitisation OR hyposensitisation OR hyposensitization) **ICTRP** aspirin AND desensiti* OR NSAID AND desensiti* OR non-steroid* AND anti-inflammatory AND desensiti* OR nonsteroid* antiinflammatory AND desensiti* OR AERD AND desensiti* OR N-ERD AND desensiti* OR AIA AND desensiti* OR NSAID AND desensiti*		

Google Scholar
(aspirin OR NSAID OR Acetylsalicylic OR (non-steroidal anti-inflammatory) OR (nonsteroidal antiinflammatory) OR AERD or N-ERD or AIA) (desensitization OR desensitisation OR hyposensitisation OR hyposensitization or sensitivity OR exacerbated OR induced OR intolerence)

Appendix 2. Summary of data collection

We extracted the following information using a data collection form.

- General information: publication type, year, country, author contact details.
- Study eligibility: type of study, participants, types of interventions, comparisons and outcomes.
- Study methods: design, unit of allocation, start and end dates, duration of participation, ethical approval, funding, possible conflicts of interest.
- Participants: population description, setting, inclusion and exclusion criteria, method of recruitment, informed consent, total number randomised, clusters (if applicable), baseline imbalances, withdrawals and exclusions, age, sex, race/ethnicity, severity of illness, comorbidities, other relevant sociodemographics, measured and reported subgroups, confounders:
    - o use of concomitant medications with known influence on airway symptoms (e.g. systemic corticosteroids);
    - o compliance with aspirin/NSAID use; and
    - o setting of aspirin administration (outpatient or inpatient).

- Intervention and comparison groups: aspirin desensitisation and placebo, number randomised to group, duration of treatment, timing, delivery, dosage, providers, co-interventions, economic information, resource requirements, integrity of delivery, compliance.
- Outcomes: type of outcome, time points measured, time points reported, unit of measurement, scale, assumed risk estimate, power.
- Funding sources.
- Declarations of interest.
- Risk of bias assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other bias.
- Data and analysis: comparison, outcome, subgroup, time points, results, number of missing participants, reason missing, number of participants moved from another group, reason for move, unit of analysis, statistical method.
- Other information: key conclusions of the study, references to other relevant studies.

History

Protocol first published: Issue 11, 2019

Contributions of authors

Conception of the review: WF.
Design of the review: KLG, WF.
Co-ordination of the review: WF.
Drafting the protocol: KLG, WF.
Searching other resources: EL.
Obtaining copies of studies: KLG, EL.
Selecting which studies to include: KLG, EL, KA.
Extracting data from studies: KA, EL.
Assessing risk of bias: KA, EL.
Entering data into RevMan: EL.
Carrying out the analysis: EL, WF.
Interpreting the analysis: EL, WF.
Assessing certainty of evidence: EL, KA.
Drafting the final review: EL, KA, WF.
Updating the review: EL, WF.
EL is the guarantor of the review.

Declarations of interest

Evelijn Lourijsen works as an ENT-resident at Amsterdam UMC and is a PhD candidate. She declares that she has no known conflicts of interest.

Klementina Avdeeva works as an ENT-resident at Amsterdam UMC and is a PhD candidate. She declares that she has no known conflicts of interest.

Kit Liang Gan works as an ENT-specialist at Mahkota Medical Centre, Malaysia. He declares that he has no known conflicts of interest.

Prof. Dr. Wytske Fokkens is a Professor in Otorhinolaryngology at the Amsterdam Academic Medical Centre, AMC. She declares grants from GSK and Sanofi (paid to institution, but WF benefitted/had access to/control of the funds) and advisory board fees from Dianosic, GSK, Novartis (all personal payments) and Sanofi (paid to institution, but WF benefitted/had access to/control of the funds).

The Department of Otorhinolaryngology, Amsterdam University Medical centre, AMC, received grants for research in Rhinology from: Novartis, EU, GSK, and Sanofi-Aventis.

Sources of support

Internal sources

- European Academy of Allergology and Clinical Immunology (EAACI), Netherlands Scholarship to KLG, which supported his work on the protocol for this review whilst employed at Amsterdam UMC.

External sources

- National Institute for Health Research, UK
  Infrastructure funding for Cochrane ENT up to the end of March 2023.

Differences between protocol and review

Data extraction and management

We did not need to convert ordinal scale data into binary data, since there were none.

Measures of treatment effects

We did not use the standardised mean difference (SMD) with confidence intervals, since no different scales had been used to measure the same outcome. If the SMD had to be used as an effect measure, we did not plan to pool change and endpoint data, because the SDs used in the standardisation reflect different variabilities (Deeks 2023).

We were not able to calculate the number needed to treat for an additional harmful outcome (NNTH) using the pooled results for (significant) adverse events. The number of studies was too low. Further, we did not present additional data based on the assumed baseline risk in a low-risk population and a high-risk population for the same reason. In future updates, should we find sufficient data, we will calculate the assumed baseline risk either by using the median of the risks of the control groups in the included studies, to represent a 'medium-risk population' or, alternatively, the average risk of the control groups in the included studies as the 'study population' (Schünemann 2022a).

Unit of analysis issues

Cluster-randomised trials

We did not identify cluster-randomised trials. If cluster-randomised trials were identified, we planned to analyse these based on the level of participant allocation (Higgins 2023).

Cross-over trials

If we had identified eligible cross-over trials, we would have analysed data from the first period for the allocated intervention only. Split-body trials were only to be included if correctly analysed and reported. If the trial correctly analysed and reported the data (analysis for paired outcomes), we would have used the mean values as a summary measure and made a two-group comparison.

Subgroup analysis and investigation of heterogeneity

Where data were available, we planned to conduct subgroup analyses regardless of whether statistical heterogeneity was observed, as these are widely suspected to be potential effect modifiers. However, we were not able to conduct any subgroup analyses due to the few studies that we found. For this review, the planned subgroup analysis included the following.

- Method of administration of aspirin (nasal versus oral/systemic); however, in this review all participants used oral aspirin.
- Different dosages (aspirin challenge starts from 20 mg to 40 mg in escalating doses on day one with at least 1.5- to 2-hour time intervals until 325 mg is reached on day two; an oral maintenance dose of aspirin ranges from 300 mg to 1300 mg daily); however, in this review all five studies used a different maintenance dosage.
- Time intervals of aspirin administration (escalating dose intervals are between two and three hours; maintenance therapy can be daily or twice daily); however, in this review, three studies used once daily and two studies used twice daily.
- Setting of aspirin administration (outpatient or inpatient); however, in this review all maintenance therapy was in an outpatient setting.
- Use of concomitant medication with known influence on airway symptoms (e.g. systemic corticosteroids) during aspirin desensitisation; however, in this review most studies did not report on concomitant medication during aspirin treatment.

Dealing with missing data

We conducted no imputations for missing data.

Publication bias (between-study reporting bias)

We planned to assess funnel plots if sufficient studies (more than 10) were available for an outcome. If we had observed asymmetry of the funnel plot, we would have conducted a more formal investigation using the methods proposed by Egger 1997. However, we did not include enough studies in any analysis for funnel plots to be created.

Summary of findings and assessment of the certainty of evidence
Instead of one summary of findings table, we created two summary of findings tables to present the seven main outcomes, to improve readability and interpretation: one table for mid-term follow-up (6 to 12 months) and one for long-term follow-up (› 12 months).

In case of differences in opinion with respect to certainty of the evidence, this would have been discussed and a definitive choice made. However, this was not necessary.

CHAPTER 10

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

As outlined in this thesis, chronic rhinosinusitis (CRS) is a prevalent disease. Its treatment is focussed on optimal suppression of mucosal inflammation, aiming for a state of controlled symptoms, with minimal side effects of necessary treatment including endoscopic sinus surgery (ESS).

When (functional) ESS was introduced in the '80s of the last century, its primary goal was to clear disease from the anterior ethmoid, thus providing drainage and ventilation. The idea was that once the ethmoidal focus was cleared, the dependent larger sinuses usually would heal without having been touched – even if their mucosal pathologies seemed almost irreversible. This idea did not 'survive' data gathered in the following decades as many patients, although exact figures are unknown, remained symptomatic. More and more, CRS was viewed as a chronic *inflammatory* condition, much like asthma in the lower airways. Consequently, in most of these patients, persistent anti-inflammatory treatment appeared necessary. The availability of then new intranasal corticosteroids would aid in the reduction of mucosal inflammation, preventing or solving the vicious circle of swelling, blockage and more extensive inflammation of the sinuses. From this historical development of treatment modalities, current guidelines and position papers on the treatment of CRS unanimously advise a combination of appropriate medical treatment with (when necessary) appropriate surgery. However, there is very little data on the what and when of these treatment options, as is easily reflected in the complementary guidelines of EPOS2020 and ICAR-RS-2021 (Figure 1 and 2, (1, 2)).

This thesis focuses on treatment modalities of CRS and their outcomes. Its main question is when to add surgery to appropriate medical treatment, in addition to what medical treatment should be coined "(most) appropriate". The answer to this question cannot be viewed separately, but should include the larger picture of this disease in relation to society as a whole: how prevalent is the disease and what burden does it harbour in terms of costs?

Epidemiology of CRS

The prevalence of CRS is a crucial factor in understanding its overall impact on society. CRS generally presents with a variety of nasal- and extranasal symptoms, which may differ between patients (1, 3). International guidelines and position papers define four 'cardinal' symptoms of CRS that are present for a period of at least 3 months. These entail nasal blockage, anterior or posterior nasal discharge, reduced sense of smell, and facial pain/pressure (1, 2, 4). Using these symptoms, a symptom-based diagnosis of CRS can be constructed and used in questionnaire-based studies.

In the GA2LEN cohort, which represents a large cross-sectional survey on upper and lower airway symptoms including over 50.000 European participants, 12% of the participants fulfilled the criteria for symptom-based CRS with the afore-mentioned symptoms present for at least 3 months in the past year (5). Later, similar data were found in other areas such as the US and China (6, 7). Within these symptom-based evaluations, a large geographical variation can be observed, from 5% in Brazil, to 29% in some parts of Europe (7-9).

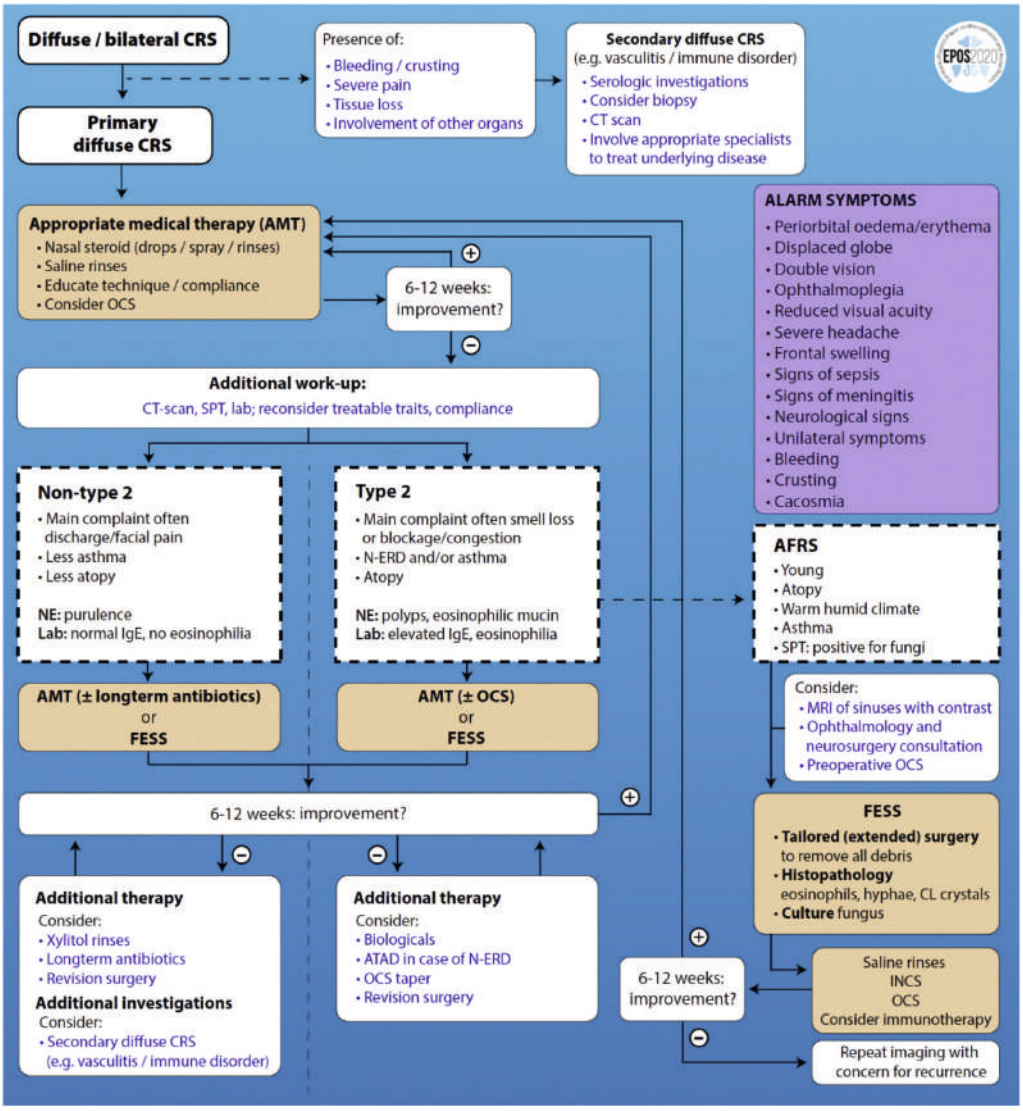

Figure 1. **EPOS 2020 treatment scheme for CRS.** Reproduced with permission from the authors. AFRS, allergic fungal rhinosinusitis; ATAD, aspirin treatment after desensitization; CL, Charcot Leyden; CRS, chronic rhinosinusitis; CT, computed tomography; FESS, functional endoscopic sinus surgery; INCS, intranasal corticosteroid; MRI, magnetic resonance imaging; NE, nasal endoscopy; N-ERD, nonsteroidal anti-inflammatory drug exacerbated respiratory disease; OCS, oral corticosteroids; SPT, skin prick test.

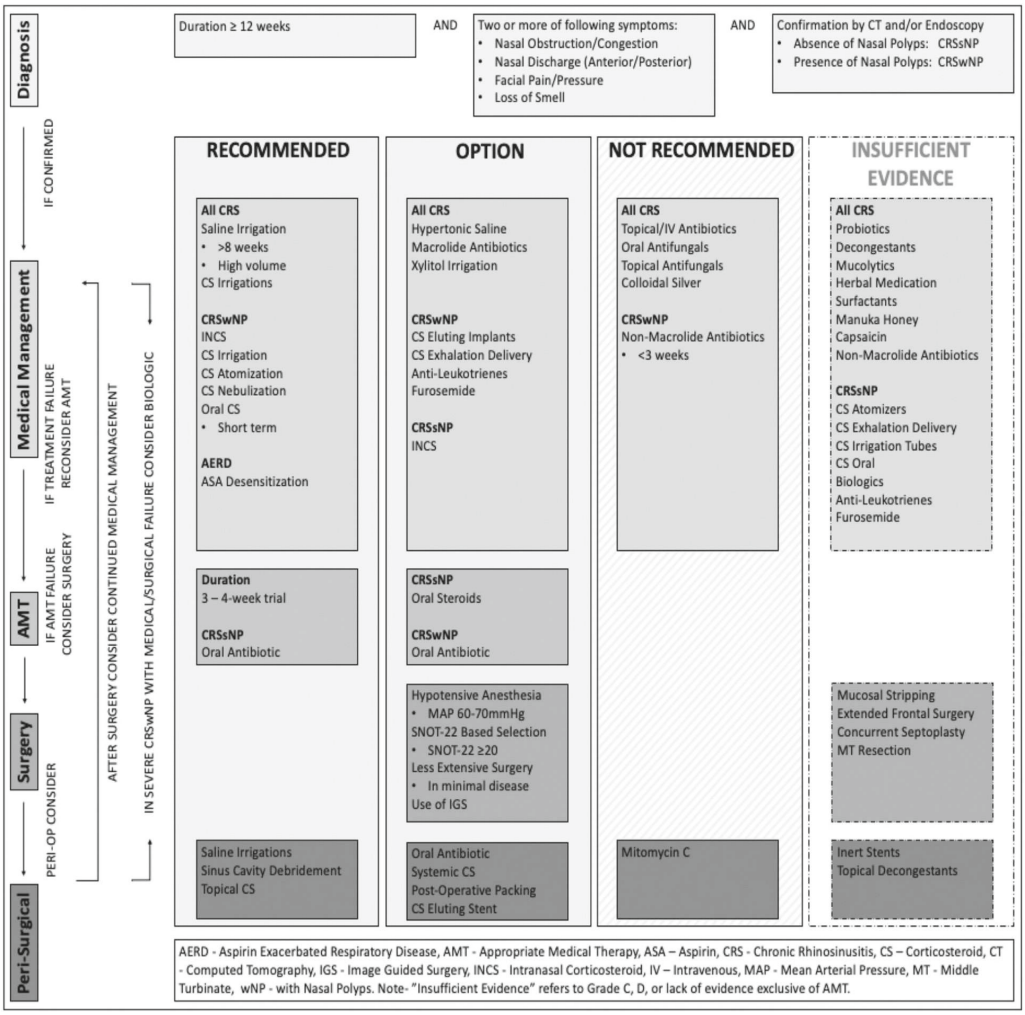

Figure 2. ICAR-RS-2021 treatment scheme for CRS. Reproduced with permission from the authors.
ICAR-RS, International Consensus Statement on Allergy and Rhinology - Rhinosinusitis; SNOT-22, Sinonasal Outcome Test-22.

The reasons for this variation are largely unknown. One possible explanation is that the shared symptomatology of CRS with other common upper respiratory diseases, such as (non)-allergic rhinitis, complicates the appraisal of the prevalence of CRS. This is especially applicable when using questionnaires, and, thus, only symptoms to diagnose CRS.

For a correct (clinical) diagnosis, additional physician-reported signs of disease, either by nasal endoscopy or by CT scan of the sinuses, are paramount (1, 3). Nasal endoscopy can help to differentiate CRS from other upper airway diseases once nasal polyps, oedema in the middle meatus and/or purulence are found. When nasal endoscopy is performed in a population of

patients fulfilling the criteria for symptom-based CRS, more than one third of the patients (38%) do not show any abnormalities pointing to the diagnosis of CRS (10).

It can be presumed that these patients most likely have other forms of upper airway disease like persistent (allergic) rhinitis, presenting with similar symptomatology.

Alternatively, radiology can show abnormalities indicating (chronic) sinus disease. In analogy with the application of nasal endoscopy to symptom-based CRS patients, we wondered whether radiology of the paranasal sinuses would show similar results. Because it is not possible, due to ethical and/or financial reasons, to randomly perform radiologic examinations in a large group of the general population fulfilling the symptom-based criteria for CRS, we decided to perform the study the other way around. We asked patients that needed CT or MRI imaging of the head to complete the GA2LEN questionnaire, excluding those patients with a rhinologic indication for imaging. Similar to what we previously found in the Dutch general population, 12.8% of patients met the criteria for symptom-based CRS (8). However, only half of these patients had any signs of sinus disease on radiology (Lund-Mackay score › 0). When using a cut-off Lund-Mackay score of ≥ 4 (often considered the minimum score pointing to CRS) only 3% met the criteria for clinical CRS %. To complicate matters further, abnormalities at radiology were found in comparable percentages in subjects that did not report upper airway symptoms. Our results have recently been confirmed by others (8, 11-13).

For the moment, it is unclear whether the patients with no indications of disease at nasal endoscopy and imaging are the same patients, or whether the combination of both modalities would even lower the prevalence further. In either case, it is clear that utilizing symptom-based CRS to calculate prevalence, is likely to give an overestimation. Still, the number of patients with a clinical diagnosis of CRS is 3% – 6.4% of the general population, and consequently represents a large and relevant group of people.

The observed drop in prevalence between symptom-based and clinical CRS highlights the discrepancy between reported symptoms and nasal endoscopy or radiological examination. This can have many (clinical) implications. For example, it is currently unknown what percentage of patients fulfilling symptom-based CRS criteria in the general population seek care from a health professional, what diagnosis these patients get and what treatment is started. Also, in general practice, the differentiation between chronic rhinitis and CRS cannot be made, frustrating the choice for appropriate treatment. Even though treatment for both diseases in the general practice is partly overlapping, it could hamper timely and effective referral to an otorhinolaryngologist for further diagnosis and management. Matters become even more difficult when patients present e.g. with headache/facial pain, nasal obstruction and/or loss of smell, where the differential diagnosis encompasses a large variety of neurological diseases, from migraine to brain tumour.

At this moment, a golden diagnostic tool for CRS is missing, hampering epidemiological studies. The discrepancy between symptoms and radiological findings forces us to reconsider our current diagnostic construct of CRS. Studies showing its shortcomings are abundant, however we lack those advancing our precision to diagnose CRS without additional procedures (endoscopy or imaging). There are some pointers to help us, though.

Current epidemiological EPOS 2020 criteria for CRS include the presence of the specified cardinal symptoms, however these are one on one exchangeable (i.e. have the same weight). Another approach to augment epidemiological disease criteria could be to further explore the clustering of (questionnaire-based) nasal symptoms or associated extranasal symptoms that constitute CRS, to subsequently enhance or reduce the chance of clinical CRS. At least 5 combinations of distinct symptoms were found to be interconnected in patients with CRS. The used questionnaire in this study auxiliary included severity, frequency and degree of bother of the symptoms and seem to be a useful evolution to modify the construct of CRS (14) . The challenge for such new constructs to be validated is the application in large population-based series with additional endoscopy or imaging, representing a considerable cost.

If we were to successfully address the diagnostic construct of CRS, it would help clinicians and researchers to correctly identify patients with clinical CRS and to treat them accordingly in advance of obtaining a sinus CT-scan. For research purposes regarding prevalence, we need appropriate constructs to understand differences between continents or nations and within studies. On a larger economic scale, it is important to differentiate between patients with and without CRS, to regulate healthcare costs worldwide and to guard against misdiagnosis and subsequent waste of costly treatment in patients without CRS. In addition, policymakers need reliable CRS prevalence numbers for health guidelines and health insurance matters. Consequently, correct information on effectiveness of various treatments could further shape policy development.

CRS treatment, evaluation of daily practice

CRS was originally characterised into CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP), for which antibiotics and/or surgery were prescribed in the former and systemic corticosteroids and/or surgery in the latter (1). More recently, a new classification for CRS has been proposed (see introduction). This classification differentiates primary from secondary CRS. Secondary CRS is CRS secondary to another disease, like cystic fibrosis, primary ciliary dyskinesia, vasculitis, or immunodeficiencies. The management of secondary CRS is outside the scope of this thesis.

The new classification of primary CRS has significant consequences for its management. The classification is based on two aspects: localised versus diffuse disease and the prominent endotype. Localized disease is usually limited to one or two sinuses and the treatment is generally surgical. The much more prevalent diffuse disease is divided into a non-type 2 or type-2 endotype, in which the type-2 more typically presents with more severe disease.

Also, type-2 patients more often have comorbidities such as asthma or NSAID-exacerbated respiratory disease (N-ERD) (1). The endotypes expose a different pattern of inflammation with consequences for management. Recently, the development of anti-type-2 inflammatory biologicals, has given a boost to the importance of classifying diffuse CRS. However, most of the available literature, until very recently, does not make a difference between different endotypes of CRS, although for literature from Europe and the USA we can assume that the majority of the CRSwNP is type-2 inflammation (1, 15, 16).

The basic anti-inflammatory therapy for CRS is corticosteroids. Since the end of the 1970, corticosteroids are available in local formulations for treatment of upper and lower airway inflammation. Nasal corticosteroids have been shown to be effective in a considerable percentage of the patients with CRS, with and without nasal polyps (1, 17, 18). The term 'appropriate medical treatment' was adopted in the EPOS 2020 document as more guidance to diminish pharmacotherapeutic variation in practice (1). What appropriate medical treatment exactly encompasses has not been defined. It commonly consists of a form of nasal corticosteroids and saline rinsing. Often the choice is made to rinse with a solution of saline combined with nasal corticosteroids, although the data to show superiority over separate rinsing with saline and nasal corticosteroid sprays or drops is limited (19-21). When this local anti-inflammatory treatment is insufficient, most guidelines relating to the treatment of CRSwNP propose systemic corticosteroids (SCS) and/or (F)ESS (1, 2). In addition, in the USA drug eluting stents are used in attempt to increase the local corticosteroid dose, without systemic consequences (22, 23). However, direct comparisons between nasal sprays and these more sophisticated methods of delivery are limited (24, 25).

Bursts of SCS as step-up treatment for type-2 CRS is a modality frequently chosen by specialists to control inflammation, if necessary, several times a year (5). SCS are effective on the short-term in improving disease-specific quality of life (QoL), nasal symptoms, and reduce nasal polyp size, with the effect generally lasting 3-6 months at best (26, 27).

We evaluated in this thesis the beneficial effect of (F)ESS over medical treatment alone, which often consisted of treatment with (repeated courses) of SCS. We showed a small, but significant better effect of (F)ESS over medical treatment based on the Sinonasal Outcome Test-22 (SNOT-22), but the magnitude of the effect did not touch the minimal clinically important difference (MCID) (28). One might conclude from this limited additional effect that (F)ESS has insufficient effect to outweigh the "cost" both for the patient and for society. In the short run, one may indeed conclude that at least for society (F)ESS is not cost-effective. However, it has become increasingly clear that, in the long run, the (financial) consequences of repeated short courses of SCS are much larger than expected. The EPOS 2020 criteria advise clinicians not to prescribe more than two courses of SCS per year, because of the risk of cumulative toxicity (1), but this may still be far too much. In this thesis, we performed a systematic literature review on the benefits and harm of SCS for upper airway disease, and demonstrated beneficial effects for both allergic rhinitis and CRSwNP. We also disclosed that the risk of SCS-related adverse

events (AE's) in upper airway disease could not be assessed properly, as these are portrayed in multiple (inflammatory) diseases, with mixed duration of treatment, dosing and follow-up. In the asthma literature a dose-response relationship for cumulative SCS exposure with most AE's has been found to emerge at cumulative exposures of 1.0 – ‹2.5 gram (g) and for some outcomes like e.g. diabetes mellitus and hypertension starts already at a cumulative exposure of only 0.5 – ‹1 g, equivalent to four lifetime short SCS courses (29-33).

In these asthma studies, patients with continuous need for SCS were included, which does not happen frequently in the management of patients with CRSwNP, creating a potential bias. However, very recently, a database study from the UK showed that even in asthma patients merely receiving intermittent courses of SCS, risks of AE's were significantly increased (34). This way of utilizing SCS represents a very similar fashion to what usually occurs in the treatment of CRSwNP, strongly suggesting the same results might apply to CRSwNP patients. In asthmatic patients alleged shadow costs of SCS-toxicity have been investigated. A UK cross-sectional study estimated the additional healthcare costs associated with steroid-induced AE's and appraised direct annual SCS-induced costs from £224 for mild/moderate asthma to £1310 for severe asthma (35). Strikingly, it was previously shown that more than 60% of patients taking SCS are not monitored for AE's (36).

In routine clinical practice, there is a significant heterogeneity in prescribing SCS for the treatment of CRSwNP in terms of type, dosage, and treatment duration, partially explained by the lack of universally accepted modes of prescribing SCS over the years (4, 37-39).

For now, with increasing evidence of the significant consequences of even limited amounts of SCS, undoubtedly in the long run, we are hesitant to advise regular use of SCS over (F)ESS. The better understanding of the consequences of systemic corticosteroid use in CRSwNP, and thus the guidance in the use of SCS is an urgent need for further studies.

A first step, providing that CRS healthcare professionals keep prescribing SCS, would be to closely monitor AE's to mitigate their impact and associated costs, so-called steroid-stewardship (40). A challenge for such studies will be that most of the serious AE's only manifest many years later (33, 41). Furthermore, comorbidities might give rise to additional SCS prescriptions and should be monitored closely. It would not be surprising to find that the long-term AE's of SCS use are much larger than usually considered and this would be an extra reason to explore more advanced strategies to deliver corticosteroids locally, such as = drug-eluting stents.

In our study evaluating (F)ESS over medical therapy (MT), we wanted to remain as close to daily practice as possible. In daily practice, both appropriate MT and (extent of) surgery are not standardized, as the patient naturally is not standardized either. This automatically results in significant variation both in severity of disease as in the treatment of choice. The variation in the SCS already shortly mentioned above was anything from a seven-day course of 3 mg prednisolone-equivalent to a long-term tapering dose treatment starting with 2 weeks 30 mg

with a reduction over a period of weeks-months for patients with very severe disease that otherwise needed frequent revision surgery.

There are no studies comparing different courses of SCS in CRSwNP. In the asthma literature, no convincing evidence of differences in outcomes was found either between a higher dose or longer course, and a lower dose or shorter course of prednisolone or dexamethasone, nor between prednisolone and dexamethasone in the treatment of asthma exacerbations (42). In CRSwNP, courses up to 3 weeks with a decreasing dose of 32-8 mg once daily, result in limited benefit of a few months at best (43). Clinical experience shows that tapering to doses of sometimes 5 mg every other day can keep patients well with good olfactory function for long periods. Whether this outweighs the significant risk of AE's is a discussion that with the new possibilities of biologics should be answered negatively.

Also, for the (extent of) surgery, there is very little data to guide the clinician. Outcomes may depend on the skills of the surgeon, the extent of the surgery, and per-operative challenges to complete surgery. There is no (little) evidence that in primary surgeries a more complete ESS, targeting all sinuses, leads to better results. There are a few paradigms that are brought up in discussions regarding extent of ESS: 1) ESS should be aimed at creating access for local therapy (corticosteroids) to the paranasal sinuses (21, 44, 45); 2) ESS should be aimed at removing remodelled mucosa (i.e., polyps) as 'de-remodelling' is not likely to occur after AMT has failed to do so (46-50); 3) ESS should be aimed at removing as much diseased mucosa as possible (51, 52). Especially the third paradigm is a matter of strong debate. A complete removal of mucosa is also termed 'reboot' surgery and was introduced by Jankowski already in 1994 (51, 53). More recently, equally 'aggressive' procedures have been published on (54-63). A complete removal of the mucosa from the paranasal sinus is virtually impossible and at least requires extended surgical procedures such as a Draf III to be able to reach (most of) the frontal sinuses (63). Some authors describe mucosal grafting after such procedures (64). The idea would be to introduce healthy mucosa in the otherwise diseased sinuses. However, the actual data underlying these procedures is limited in terms of patient numbers and scientific quality (65). Prospective (randomized) direct comparisons with a long-term follow-up are lacking. Although the current data on such approaches are relatively good, one should also consider the possible drawbacks, such as a risk of scar tissue formation / non-functional mucosal lining of the sinuses, the risk for olfactory functioning, and other irreversible changes to the anatomy and functionality of the paranasal sinuses. Especially with the advent of biological therapy), these extensive procedures are expected to be less needed or not indicated at all. A less aggressive approach to the third paradigm would be to tailor the extent of surgery to the extent of disease, i.e., accessing diseased sinuses only.

In our own study, most of our patients underwent a quite complete ESS (sometimes termed 'full house FESS') entailing a maxillary antrostomy, total ethmoidectomy, and Draf IIA, with or without sphenoidotomy (51.4%). This is not surprising, as most patients underwent revision surgery and most patients were included in tertiary centres. Our sample size was not built to

evaluate the impact of the extent of surgery. Future research evaluating the role of the extent of surgery, both in primary and revision surgery, on symptomatology, Health-related Quality of Life (HRQoL), and revision figures is needed. For now, we advise a pragmatic approach in which the extent of disease dictates the extent of surgery needed, especially when considering one of the major goals of ESS, namely to create access to the paranasal sinuses for local therapy.

For our study, the variation both in MT as in surgical treatment and the uncertainty about the consequences of these variations, is a good reflection of daily practice but results in a significant uncertainty about the optimal treatment of our patients.

We observed a substantially improved disease-specific HRQoL after ESS in addition to MT, although the difference between treatment groups did not reach clinical significance after 12 months follow-up when juxtaposed to a MCID of 9 points, as mentioned before. Our findings compare to prospective observational studies, which predominantly provided insight in the appropriateness of surgery until now (66-69). A UK-study group is conducting a direct comparison of long-term antibiotics versus ESS in adults with non-type 2 and type-2 CRS, to investigate symptomatic improvement and costs at 6 months follow-up. This study is currently recruiting and will contribute to our comprehension of surgery versus MT in CRS (70).

The mean period of recurrent need for SCS or revision surgery is 3-6 months (SCS) and 3-5 years (revision surgery) respectively (26, 27, 71). One could argue that an optimal trial would need an evaluation period of at least 3-5 years. Unfortunately, such a follow-up period has not been proven fundable. We have preliminary 2-year results ready from our own study pointing HRQoL to remain stable in the ESS group throughout the second year of follow-up. Also, HRQoL improved a little further in the MT group between the first and second year of follow-up, although without a clinically or statistically significant difference between MT and ESS. These findings are independent of in-or excluding cross-overs to ESS (11% between 1 and 2 years of follow-up). The use of ongoing concomitant medications, such as intranasal corticosteroids and repeated courses of SCS, as well as the introduction of the new endotype-driven biologics as treatment option after one year of follow-up, all might have maintained the HRQoL to be stable in the MT group. Another potential explanation lies in a higher compliance of rinsing and nasal corticosteroids due to monitoring and frequent contact moments with the study team.

In addition to our primary chosen patient-reported outcome measurement (PROM) to evaluate the effect of both treatments, we discovered that surgically treated patients reported less general nasal symptoms and symptoms of nasal obstruction (as measured with a Visual Analogue Scale), developed a better control of CRS, suffered from smaller nasal polyps, and consumed less volumes of SCS. We particularly emphasize the observed difference in SCS prescribed, considering the potential risks as described earlier (29): we presented a between-group difference of 316 mg (95% CI -468 to -166), easily converted to one 10-day course of 30 mg prednisolone.

Preliminary 2-year data show that between 1 and 2 years follow-up, 35% of MT patients needed at least one short course of prednisolone-equivalent, compared to 22% of ESS patients. Besides, after ESS patients used 35% fewer courses of SCS between 1 and 2 years follow-up, compared to the MT group. Hence, ESS can be viewed as having a steroid-sparing effect that lasts up to two years after surgery. This information is functional in the shared-decision making process with patients, as to make a deliberate choice for either surgery or continuous MT.

Even though control of disease improved more after ESS, (partially) controlled disease was acquired in only 50% of patients, based on the EPOS 2020 criteria for disease control (1). Strikingly, adequate and sustained improvement of olfactory function appears to be unachievable at group level with either treatment option, since most patients were still hyposmic or anosmic. It is well recognized that impairment of smell and taste can have a profound negative influence on quality of life and perception of health (72, 73). Our finding highlights an important unmet need for patients with our current 'standard' treatment options.

Despite optimal medical treatment, recurrent SCS, and surgery, a significant group of patients with CRS (especially type-2 CRS) remains uncontrolled (67, 74).

Until quite recently, the therapeutic options for this patient group were limited. Part of these patients display an intolerance to non-steroidal anti-inflammatory drugs (NSAID), or better: a non-IgE mediated reaction to inhibitors of the cyclooxygenase-1 pathway. This results in NSAID-Exacerbated Respiratory Disease (N-ERD), which clinically usually presents as a severe form of diffuse type-2 disease with CRSwNP and late onset asthma (75, 76), requiring frequent treatment with SCS (77). Widal *et al*. first recognized the apparent existence of a refractory period after a hypersensitivity reaction to aspirin intake in 1922, in which respiratory symptoms improved (78). It formed the basis of the development of desensitisation protocols for patients with N-ERD with repeated increasing doses of oral aspirin at fixed time intervals to induce tolerance (79, 80). To maintain tolerance, daily aspirin intake is needed, so-called aspirin treatment after desensitisation (ATAD) (76, 80, 81). Through a systematic review, we showed in this thesis the additional value of ATAD in (difficult-to-treat) patients with N-ERD, likely resulting in improved disease-specific HRQoL, and might lead to a better control of their asthma**.** The treatment is very cheap and can therefore be attractive, especially in less privileged parts of the world. However, we found no data on whether ATAD also results in a SCS or surgery sparing effect. Furthermore, the treatment has significant AE's leading to frequent discontinuation of the treatment. A recent retrospective real-world study in Finland showed that 63% of patients stopped ATAD due to AE's or lack of effect after 2 years of using ATAD. Revision rates for ESS or bursts of SCSs (median 0-1 / year) were not different from patients with N-ERD not using ATAD (82). Attempts with local application of aspirin (lysine), although resulting in less AE's, has never been shown to be equally effective in a RCT (1, 83).

Therefore, we scrutinize that a beneficial effect for patients with acceptable side-effect profile is perceivable with ATAD, however which patient will profit most remains unclear, nor do we

understand the preferred dose, frequency or duration of ATAD. In addition, data on cost-effectiveness is lacking. It is possible that the success of ATAD depends on a certain endotype of patients with N-ERD and this requires adequate patient selection. Previous studies point to a more beneficial effect when receiving ESS before starting ATAD (84); however, our review included studies that lacked to report on this topic. Our general advice is that clinicians propose ATAD if a patient is willing and capable to use it diurnal.

With the recent advent of biological therapies for patients with CRSwNP, the management of the disease in severe cases has radically changed. Biologics present the field with a safe and very effective treatment option in patients with type-2 CRS. This has been shown in phase III trials for the three currently available biologics in the Netherlands (dupilumab, mepolizumab, omalizumab (85-89)) and is further corroborated by real-world evidence (90-94). Due to the high cost of treatment, strict selection/indication and evaluation criteria exist (1, 4, 95), thus targeting severe uncontrolled CRSwNP patients. Albeit the encouraging effects of biologicals, not every patient with type-2 CRS with or without N-ERD is eligible for biologicals in the near future. Naturally, as with any other treatment, ATAD is not suitable for each patient due to comorbidities, such as anaphylaxis precipitated by NSAID or uncontrolled asthma. For these patients, biologicals might be the better advisable option.

Economic burden of CRS

Contrary to the US, where a considerable number of health economic studies have been performed in patients with CRS (96-101), there is a striking lack of data on direct and indirect costs of CRS in Europe. The study we performed was the first (one of the two first) European studies evaluating direct and indirect costs of CRS in Europe. With mean annual direct medical costs per patient of at least €1501 and mean indirect costs of at least €5659, costs were significantly higher than costs of e.g. asthma, a disease with comparable prevalence. European data on the (direct and indirect) costs of asthma show a mean individual patient cost of €1583/year increasing to €2281/year (indirect costs 63%) when the patient is uncontrolled and these costs depend on the level of control of disease (102).

The total costs for CRSwNP are higher than we previously expected, and is still an underestimation since we did not measure all cost components. For instance, we did not take into account medication prescriptions. One caveat is that mean cost results are an estimate based on the Dutch healthcare system and mean costs are derived from Dutch cost data and data sources, which might be different in other countries, subsequently limiting comparability. A socioeconomic study in the UK taking into account direct CRS costs from out of pocket expenditures, healthcare resource utilisation, and absenteeism showed a yearly cost of £4844, with indirect costs £1567. In comparison, this study has a likely underestimation of indirect costs, since full productivity losses were not computed (103).

Our results correspond well to the previous findings from the USA, indicating indirect costs to be $7182 per patient per annum (37, 98).

Our cost study in CRSwNP patients did not control for the severity of CRS disease based on HRQoL or other patient symptoms, but we know that a substantial part of the patients in this study was uncontrolled.

One might wonder why there has been so little interest in the obviously high costs of such a prevalent disease as CRS. It seems that the loss of productivity in (most) CRSwNP patients should be explored further, especially to show whether our current treatment strategies are able to reduce these indirect costs.

Cost-effectiveness of treatment strategies in CRS

We encased a cost-effectiveness analysis parallel to our RCT comparing the addition of ESS to MT alone, which is not part of this thesis. If ESS, apart from clinical effectiveness, is shown to be a cost-effective treatment compared to MT, it also helps to guide decision-making in practice. A previous Markov decision-tree economic evaluation of ESS versus MT demonstrated ESS to be the most cost-effective treatment option, although this was an observational study, not based on accurate patient costs and effects (104). Especially on the short-term, it is unlikely that ESS is more cost-effective than MT alone, given the relatively small additional benefit in terms of patient outcomes (SNOT-22) and the relatively high costs of surgery in the first year compared to the mostly very affordable MT.

An Italian study using a Markov Model has shown Dupilumab to be a cost-effective add-on treatment option compared to regular care of CRSwNP (105). Contrary to the Italian findings, a study in the United States has shown that ESS was the more cost-effective treatment as opposed to Dupilumab (106). Adequate patient selection will be the precarious issue in light of the new costly biologicals. As more real-life studies will appear and we will have more perception on the best dosing regimens for biologicals, the treatment paradigm may change, such as is suggested by studies on dupilumab tapering (91).

Nowadays, a treatment that starts with appropriate medical therapy 'AMT', followed by a course of SCS or direct yield to ESS after failure of AMT, seems to be justified in the context of the more beneficial results found after ESS plus MT and the (long-term) sequelae of SCS. To overcome the hiatus of what constitutes 'failure of AMT', surgical criteria were developed by a CRS expert panel, defining a minimal threshold to consider ESS a treatment option (107). We believe that if a patient does not respond to SCS, ESS should be considered, instead of repeated attempts of SCS with longer duration, considering the presumed high-risk profile (29, 34). If ESS is not feasible or patients already had revision surgery, especially when having N-ERD, biologics emerge. Preliminary 2-year data from our RCT indicate that 3.5% of patients started a biological (mepolizumab or dupilumab) between 1 and 2 years after ESS, as opposed to 7% after MT only. Given the limitations of MT and/or ESS in these patients, our findings highlight the justified emergence of these biologicals, which in particular seem to have an astounding effect on smell, which is an impactful, if not the most debilitating symptom in patients with CRSwNP (108).

Despite an extensive treatment potential, we probably still face a situation in which even an acceptable controlled state of disease for each individual CRS patient is out of reach, let alone remission or cure (109). Identifying factors that contribute to control of disease is an important topic for future research (110).The impact of these factors and their treatments on cost-effectiveness is a second large research need for the coming years.

Lessons learned

The Dutch Society of Otorhinolaryngology (ORL) has a long-standing successful history of multi-centre trials evaluating the most common surgical procedures in our field (111-113). Many of these trials, although eventually reaching target, were hampered by "slow recruiting". Our trial has not been an exemption.

Already at the start of the trial, the time between METC approval in Amsterdam and the last local chief hospital board approving the trial was 6 months. Because we learned from earlier ORL trials, we fully relied on a dedicated research team that frequently visited the participating clinics to relieve the administrative burden as much as possible. Moreover, we facilitated participating patients as much as we could with maximal flexibility in contact moments. Ultimately, we were able to reach the anticipated 238 patients with an acceptable loss-of-follow up and adequate power, but with a disproportional inclusion of patients in our own institute. In the years since the design of this trial, a substantial improvement has been achieved in the digitalisation of trials, with apps, SMS-reminders, and direct insertion of all trial data in a digital form. This results in significantly reduced administrative burden than we encountered with part of the data still acquired on paper. One has to realize however, that the use of electronics may bias inclusion by scaring off patient with less digital skills.

Apart from the administrative burden, we realized the extreme importance of communication with colleagues who could include patients in the trial. We encountered all possible "bears on the road": colleagues being afraid of the administrative burden, worried about the time it would take to explain the trial to the patient, reservations about the production, believe in the superiority of surgery over medical treatment (I cannot do that to my patient….), fears about contributing to a negative trial with impact on production in the future, etc. Communication to all stakeholders has been of great importance. Communication with colleagues about the importance of the trial and the potential risk of being accused by the health care payers of performing surgery with unproven efficacy, the minimal time and effort that we would ask of them and the responsibility to inform their patients on the trial was communicated regularly in meetings, by phone, and by personal visits. Furthermore, we invested heavily in the communication with the supporting site staff, by explaining the importance of the trial, helping with administrative tasks, being always easily reachable, thanking them with little presents for their effort and regular updates about the progress of the trial, and, thus, we tried to maximally involve them. Moreover, we "advertised" to patients in the waiting rooms of clinics that participated in the trial, explaining the relevance of the trial.

Another stage of a study is that of finalizing the data management and reporting to the subsidiary party. It should not be underestimated how much time and effort is involved with getting a study sponsored, and wrapping up all the sponsor-required documentation at the end. This time and effort are often 'invisible' and not calculated in study budgets or hours.

The same is basically true for our patients. Here again, adequate compensation is very hard to realize. We could not have achieved such interesting results without their ongoing support and willingness to invest their time and effort. Naturally, patients stand to benefit from trials like ours, but the 'gains' of new knowledge are future promises that are not always made reality for those participating in trials currently.

Future needs and perspectives

As discussed previously, we need solid data on what extent of surgery leads to the best improvement in symptoms and QoL. The current hypothesis that more extensive surgery leads to better results in patients with severe disease or recalcitrant disease should be proven in high-quality studies (54, 60). It would be very interesting to compare outcomes on extent of surgery with the currently developed Amsterdam Classification of Completeness of Endoscopic Sinus Surgery (ACCESS) scoring system for uniformity in future trials (114).

One thing stands out in our evaluation of regular treatment outcomes: our current treatments have limitations in their effectiveness and we desperately need to improve our treatment results, either with the currently available drugs and surgical options, or with new drugs that target specific endotypes. Until now, there will remain symptoms in CRS that will not improve largely with either MT or surgery. We showed that hyposmia/anosmia needs attention, since most patients will keep suffering from this very incapacitating symptom with all consequences (73).

In addition, overall full control over CRS in the perception of patients is poor with either regular treatment strategy. The latest promising developments with novel treatment options such as distinct biologicals are a great success for the majority of patients with type-2 CRS. In the future, we need to determine which patients have a good response pattern and what the adequate dosing, timing and duration is of these biologicals.

Furthermore, insight in the cost-effectiveness of our treatments is needed. In our analysis of ESS in addition to MT versus MT alone, we will determine in the near future whether the benefit of ESS compares against the costs. In addition, more data must appear on the cost-effectiveness of biologicals in direct comparison to ESS, for these medications to become part of current treatment pathway of type-2 CRS. As we showed, indirect costs form the majority of costs, therefore implementing these costs in socio-economic evaluations seems critical. Since we are still unaware of the role of the level of control of CRS on total costs, future studies should also answer the question if people with uncontrolled CRS are more likely to be unemployed, miss more days of work, and experience more limitations in their activities. Finally, studies

should ascertain if the savings of less indirect costs and less uncontrolled CRS (far) outweigh the additional cost of any management strategy.

Concluding remarks

This thesis focused on answering the question whether ESS is beneficial over MT, and what MT is appraised appropriate, both in light of the impact of CRS on patients and society. Although accurate diagnosis of clinical CRS is challenging without a CT-scan of the sinuses or nasal endoscopy, the prevalence of CRS is significant and imposes financial strain on society, where the common and unmeasured 'hidden' costs are the chief contributing factors.

We outlined that ESS has a small beneficial effect over MT in terms of HRQoL, despite the trivial difference in SNOT-22 scores (based on the MCID) after 12 months of follow-up. The demonstrated considerable variation, practised both in MT as in the extent of surgery, and the uncertainty about the clinical effects of these variations, results in an ambiguity of the most 'appropriate' treatment for our patients. Although it is highly unlikely that ESS is the cheaper treatment option on the short-term compared to affordable drug therapy, the SCS-sparing effect of surgery is a paramount finding and prompts the justification to merit prioritization of ESS over repeated courses of SCS, given the potential broad range of adverse events related to SCS and accompanying (shadow-) costs. We advise a surgical approach that meets the level of disease, instead of more aggressive sinus surgery until proven otherwise.

Another profitable step-up treatment option in uncontrolled type-2 CRS with comorbid N-ERD is ATAD, in lieu of revision surgery or SCS, although it is unclear if and for how long it results in precluding SCS or (revision) surgery. Furthermore, there is a very substantial risk of the development of concomitant side-effects and successive discontinuation of treatment during ATAD, which implies a less enticing treatment option. However, for patients that have a severe form of uncontrolled disease, in which SCS or surgery is undesirable, it forms a cheap treatment option if the patient is thought to be therapy-compliant.

Both medical and surgical therapy comprise high (patient) costs, the former in terms of potential acute or long-term adverse events with associated costs, the latter due to the high direct costs of the surgery itself. Moreover, an acceptable state of disease control for all CRS patients, regardless of surgery or MT, has unfortunately shown to be elusive, as are the treatment results on olfaction.

The development of new endotype-driven treatment options such as biologicals, form a justified emergence for uncontrolled (type-2) CRS patients, contributing to fulfilling unmet patient needs with a presumed acceptable risk profile. However, since the ongoing high direct costs of biologicals, surgery and conventional medication will currently still form the mainstay treatment option for most CRS patients. This emphasizes the need for future research that directly compares biologicals with standard treatment in terms of clinical and cost-effectiveness. With time we will know if we reach a paradigm shift from surgery to biologicals. What is most

prominent, is that we will keep trying to find factors and/or treatments that can enhance patient control and serve their needs, with a balanced cost-effectiveness for society.

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APPENDICES

SUMMARY

Chronic rhinosinusitis (CRS) is a prevalent inflammatory disease of the nose and paranasal sinuses. It is often associated with comorbidities such as asthma, allergic rhinitis, or hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs). Primary CRS refers to sinus inflammation without an evident underlying cause (e.g. cystic fibrosis or immunodeficiencies). The current primary CRS classification moves away from the traditionally used CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP), which does not account for the presumed underlying inflammatory mechanisms. Primary CRS is now classified as type-2 or non-type 2 inflammation, for which a management strategy based on this subdivision is advocated (endotype-driven treatment).

Treatment of CRS encompasses optimal suppression of inflammation, aiming for a controlled state of symptoms, with minimal side effects of (appropriate) medical treatments or endoscopic sinus surgery. There is, however, very little data on the extent and timing of these treatment options.

This thesis focuses on an appraisal of both an "appropriate" medical and surgical management option, in particular when to add surgery to medical treatment. This will be explored in a broader light of the burden of CRS, in terms of prevalence and costs. The prevalence of CRS is a crucial factor in understanding its overall impact on society.

In **Chapter 2** we explored the prevalence of CRS in the general population applying both symptoms with imaging (CT or MRI). In epidemiological research, most often questionnaire-based, the shared symptomatology of CRS with other common upper respiratory diseases complicates the appraisal of the actual prevalence of CRS. In the study we found that 12.8% of patients met the criteria for symptom-based CRS (defined by the criteria as formulated in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012), comparable to previous studies using the GA2LEN questionnaire. However, after combining symptom-based diagnosis with imaging results (CT or MRI), the prevalence of CRS was 3% (based on Lund-Mackay score ≥ 4). A comparable reduction in prevalence was also seen when combining symptoms with nasal endoscopy. It is unclear what the prevalence would be with a combination of CT and nasal endoscopy.

In **Chapter 3** the total costs of CRSwNP were investigated in a cohort of Dutch patients. We aimed to see what societal burden CRS bears in terms of costs, both direct and indirect. We showed that the main costs are indirect, such as loss of productivity at home or work and absenteeism. Total costs were higher than expected and this forms a substantial burden to society as a whole and needs future attention in evaluating treatment outcomes.

In **Chapter 4** we performed a systematic review of beneficial and harmful effects of systemic corticosteroids (SCS) for distinct upper airway diseases. SCS are a frequently chosen treatment

option, usually as (repeated) short courses, due to its well-known anti-inflammatory properties. We created a consensus document to provide practical recommendations for their use. Despite beneficial effects on symptoms in CRS, especially CRSwNP, there is a risk of significant adverse events on both the short- and long-term. Ensuing research in the field of asthma show comparable results. These findings in combination with the development of the corticosteroid-sparing biologics, strengthen our hesitation to advise the use of repeated courses of SCS.

In **Chapter 5** and **Chapter 6** we presented the study methods and statistical analysis plan for the Dutch randomised, controlled, pragmatic, multicentre trial, set up to determine the effectiveness of endoscopic sinus surgery (ESS) in patients with CRswNP compared to medical therapy (MT). Our primary outcome was the disease-specific health-related quality of life (HRQoL) measured with the Sinonasal Outcome Test (SNOT)-22, after 12 months of follow-up.

In **Chapter 7** we demonstrated the results of the randomised controlled trial (RCT), which included 238 patients in 15 hospitals in the Netherlands. After 12 months of follow-up, we discovered a (limited) better improvement in SNOT-22 scores with ESS, although the difference between ESS and MT did not reach the minimal clinically important difference. After ESS, patients had a better appraisal of nasal obstruction, reported more general control of CRS, and showed smaller nasal polyps. Moreover, ESS demonstrated a steroid-sparing effect, which is an important finding in the light of increasing evidence of the detrimental consequences of SCS.

In **Chapter 8** we performed a systematic review and meta-analysis of RCTs on the role of tranexamic acid (TXA) in ESS for CRS. Visibility of the surgical field is important for patient safety and for the ability to complete surgery. We found evidence that TXA reduces the surgical field bleeding score and intraoperative blood loss. However, the risk of thrombo-embolic events in the first 24 hours after surgery remains unclear.

In **Chapter 9** we performed a systematic review and meta-analysis of RCTs to assess the effectiveness of oral or intranasal aspirin treatment after desensitisation (ATAD), as an alternative treatment for patients with more difficult to treat CRS as part of NSAID-exacerbated respiratory disease (N-ERD). We showed additional value of ATAD in patients with N-ERD, as it showed significant improvements in disease-specific HRQoL and better asthma control. However, the treatment can have considerable adverse events leading to frequent discontinuation of ATAD.

In **Chapter 10** we summarised the results presented in this thesis, discussed our findings and provided future research recommendations.

This thesis revealed that ESS is a corticosteroid-sparing treatment option with a small beneficial effect over MT in terms of HRQoL, which warrants precedence over repeated courses of SCS. In selected cases ATAD could be helpful. When considering therapy, both medical and surgical treatments involve different cost aspects. Unfortunately, achieving a controlled state of CRS with reasonable costs remains a therapeutic challenge.

SAMENVATTING

Chronische rhinosinusitis (CRS) is een inflammatoire ziekte van de neus en neusbijholten. CRS gaat regelmatig gepaard met co-morbiditeit zoals astma, allergische rhinitis en een overgevoeligheid voor niet-steroïdale anti-inflammatoire middelen (NSAID's). Wanneer er geen onderliggende oorzaak is voor CRS (zoals bijvoorbeeld taaislijmziekte of een afweerstoornis), dan spreken we van primaire CRS. Als er sprake is van primaire CRS, wordt er verder een onderverdeling aangebracht op basis van het onderliggende ontstekingsmechanisme (inflammatoir endotype; type2 of non-type2). De huidige behandelstrategieën voor primaire CRS zijn uitgesplitst naar het endotype. Daarmee ligt er tegenwoordig veel minder nadruk op de aanwezigheid van neuspoliepen, op basis waarvan voorheen een onderscheid werd gemaakt tussen CRS met neuspoliepen (CRSwNP) en CRS zonder neuspoliepen (CRSsNP).

Centraal in de behandeling van CRS staat het onderdrukken van de ontsteking van het neusslijmvlies om zo controle te krijgen over de symptomen van de ziekte. Tegelijkertijd dient er gestreefd te worden naar zo weinig mogelijk bijwerkingen. Hiertoe kan men medicamenteuze behandeling inzetten, al of niet aangevuld met endoscopische neusbijholtenchirurgie. Helaas is er maar weinig data beschikbaar om de uitgebreidheid en de timing van deze behandelopties te onderbouwen in de praktijk.

Dit proefschrift evalueert de medicamenteuze behandelopties van CRS en de rol van endoscopische neusbijholtenchirurgie daarbij. Deze evaluatie kan niet los gezien worden van de ziektelast van CRS in termen van prevalentie en kosten. De prevalentie van CRS is immers een cruciale factor om de impact op onze samenleving op waarde te schatten.

In **Hoofdstuk 2** is de prevalentie van CRS in de algemene bevolking onderzocht. We gebruikten hiervoor een combinatie van symptomen die patiënten rapporteerden (vragenlijst) en beeldvorming (CT- of MRI-scan van de neusbijholten). Eén van de uitdagingen bij dit soort epidemiologisch onderzoek is namelijk dat andere, veel voorkomende bovenste luchtwegaandoeningen overlappende symptomen geven met CRS. Daardoor is het vaak lastig om tot een juiste diagnose- en prevalentiebepaling van CRS te komen. In onze studie vonden we dat 12.8% van de patiënten voldeed aan de criteria voor symptoom-gebaseerde CRS (gebaseerd op de gedefinieerde criteria uit de 'European Position Paper on Rhinosinusitis and Nasal Polyps 2012'), wat vergelijkbaar is met voorgaande onderzoeken die de GA2LEN vragenlijst gebruikten. Echter, na toevoegen van de informatie uit de beeldvorming (CT- en MRI-scans), reduceerde de prevalentie tot 3% (gebaseerd op een Lund-Mackay score ≥4). Een vergelijkbare reductie in prevalentie wordt ook waargenomen wanneer lichamelijk onderzoek (nasendoscopie) met symptomen wordt gecombineerd. Het is nog onduidelijk wat het effect zou zijn van het toevoegen van zowel nasendoscopie als beeldvorming om tot een prevalentiecijfer van CRS te komen.

In **Hoofdstuk 3** beschrijven we hoe we een indruk hebben verkregen van de ziektelast van CRSwNP voor de Nederlandse samenleving. Hiertoe werden de kosten van CRSwNP geanalyseerd in een

groep met Nederlandse CRS-patiënten, waarbij onderscheid werd gemaakt tussen directe en indirecte kosten. In deze studie hebben we aangetoond dat de voornaamste kosten indirect van aard zijn en bestaan uit verlies van productiviteit (thuis én op het werk) en werkverzuim. De totale kosten bleken hoger dan verwacht, wat een aanzienlijke last vormt voor onze samenleving als geheel. Dit verdient dan ook aandacht in toekomstige evaluaties van behandelingen voor CRS.

In **Hoofdstuk 4** hebben wij een systematische review uitgevoerd naar gunstige en ongunstige effecten van systemische corticosteroïden (SCS) bij verschillende aandoeningen van de bovenste luchtwegen. Vanwege hun welbekende en effectieve ontstekingsremmende eigenschappen worden SCS regelmatig gekozen als behandeling, meestal in de vorm van (herhaalde) korte kuren. In het door ons opgesteld consensusdocument geven we aanbevelingen voor het gebruik van SCS in de praktijk. Ondanks de gunstige effecten op de symptomen van CRS (met name CRS met neuspoliepen) bestaat er een risico op significante bijwerkingen, zowel op de korte als op de lange termijn. Meer recent onderzoek bij astmapatiënten laat vergelijkbare resultaten zien. Deze uitkomsten sterken ons in het advies om terughoudend te zijn met het regelmatig gebruik van SCS voor CRS, zeker nu er nieuwe medicijnen (biologicals) beschikbaar zijn die de noodzaak tot SCS-gebruik sterk terug kunnen brengen.

In **Hoofdstuk 5** en **Hoofdstuk 6** beschrijven wij het onderzoeksprotocol en het bijbehorende statistische analyseplan voor de gerandomiseerde, gecontroleerde, pragmatische, multicentrum studie om de effectiviteit van neusbijholtenchirurgie te bepalen in vergelijking met medicamenteuze behandeling bij patiënten met CRSwNP. Onze primaire uitkomstmaat was de ziekte-specifieke gezondheid gerelateerde kwaliteit van leven na 12 maanden follow-up, gemeten met een vragenlijst (de SinoNasal Outcome Test (SNOT)-22).

In **Hoofdstuk 7** presenteren wij de resultaten van deze gerandomiseerde gecontroleerde studie, waarbinnen 238 patiënten geïncludeerd werden in 15 Nederlandse ziekenhuizen.

Na 12 maanden follow-up zagen we een grotere verbetering in SNOT-22 scores na chirurgie, hoewel het verschil met alleen de medicamenteuze behandeling niet de minimaal klinisch relevante drempelwaarde bereikte. Na een neusbijholte-operatie gaven patiënten minder neusverstopping aan, beoordeelden zij de controle van CRS als beter, en waren de neuspoliepen kleiner. Tevens had chirurgie een corticosteroïd-sparend effect, wat een belangrijke bevinding is gezien de toenemende bewijslast voor de schadelijke gevolgen van SCS-gebruik.

In **Hoofdstuk 8** hebben wij een systematische review en meta-analyse van gerandomiseerde onderzoeken uitgevoerd naar de effectiviteit van tranexaminezuur (TXA) bij neusbijholtenchirurgie voor de behandeling van CRS. Een goed zicht op het operatieveld is cruciaal voor de veiligheid van de patiënt en voor het succesvol en volledig kunnen uitvoeren van de operatie. Wij stelden vast dat TXA inderdaad de zichtbaarheid verbeterde en het intra-operatieve bloedverlies verminderde. Het risico op trombo-embolische complicaties ‹24 uur postoperatief blijft echter onduidelijk.

In **Hoofdstuk 9** voerden we een systematische review en meta-analyse uit van gerandomiseerde onderzoeken naar de effectiviteit van orale of intranasale aspirine behandeling na desensibilisatie (ATAD). Dit is een alternatieve behandeling voor patiënten met moeilijk te behandelen CRSwNP in het kader van een overgevoeligheid voor NSAID's. Wij toonden aan dat ATAD toegevoegde waarde heeft in deze groep patiënten, met verbetering in ziekte-specifieke kwaliteit van leven en verbeterde astmacontrole. De behandeling kan echter aanzienlijke bijwerkingen hebben, die vaak leiden tot het staken ervan.

In **Hoofdstuk 10** hebben wij de resultaten uit dit proefschrift samengevat, onze bevindingen bediscussieerd en aanbevelingen gedaan voor toekomstig onderzoek.

Dit proefschrift heeft aangetoond dat neusbijholtenchirurgie een corticosteroïd-sparende behandelingsoptie is met een (beperkt) gunstiger effect ten opzichte van medicamenteuze behandeling op het gebied van ziekte-specifieke kwaliteit van leven. Neusbijholtenchirurgie verdient derhalve voorrang boven het herhaaldelijk gebruik van SCS kuren. In patiënten met een overgevoeligheid voor NSAID's kan een behandeling met ATAD een nuttig alternatief zijn. Zowel medicamenteuze behandelopties als chirurgie brengen verschillende relevante kostenaspecten met zich mee. Helaas blijft het behandeldoel, namelijk goed gecontroleerde CRS met een overzichtelijke kostenimpact, een aanzienlijke uitdaging.

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2019: Herregistratie Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers	(ECTS: 1.50)
2016: Clinical Epidemiology: Evaluation of Medical Tests	(ECTS: 0.90)
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2016: Practical Biostatistics	(ECTS: 1.40)
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2016: Citation Analysis and Impact Factors	(ECTS: 0.10)
2016: Clinical Epidemiology: Systematic Reviews	(ECTS: 0.70)
2015: Project Management	(ECTS: 0.70)
2015: Clinical Epidemiology: Randomized Clinical Trials	(ECTS: 0.60)
2015: Endnote	(ECTS: 0.10)
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2024 'Kinderluchtwegcasuïstiek, Bring your larynx'. *Oral presentation, KNO-vergadering,* May 2024, Kamerik (The Netherlands)	(ECTS: 0.50)
2023 'Opereren bij CRS - Medicatie vs Operatie'. *Oral presentation, refereeravond Amsterdam UMC*. January 2023, Amsterdam (The Netherlands)	(ECTS: 0.50)

2022 'Endoscopische neusbijholtenchirurgie als aanvulling op medicatie versus medicatie voor chronische rhinosinusitis met polyposis nasi: een multicenter gerandomiseerde trial'. *Key Lecture, KNO-vergadering*. May 2022, Nieuwegein (The Netherlands)	(ECTS: 0.50)
2022 'CATxTalks, Critically Appraised Topic, Systemische corticosteroïden bij kinderen met cellulitis orbitae, invited oral presentation OLVG, Maart 2022, Amsterdam (The Netherlands)	(ECTS: 0.50)
2021 ' Een losgeslagen carnaval'. *Oral presentation, Refereermiddag perifere opleidingsklinieken*, September 2021, Hoorn (The Netherlands)	(ECTS: 0.50)
2021 'The correlation of systemic corticosteroids with bone mineral density in patients with Chronic Rhinosinusitis with Nasal Polyps'. *Oral presentation, European Rhinologic Society (ERS) conference,* September 2021, Thessaloniki (Greece)	(ECTS: 0.50)
2021 'Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps – a randomised controlled multicentre trial'. *Oral presentation, European Rhinologic Society (ERS) conference,* September 2021, Thessaloniki (Greece) **(Clinical research prize)**	(ECTS: 0.50)
2021 'Direct and indirect costs of adult patients with Chronic Rhinosinusitis with Nasal Polyps'. *Oral presentation, European Rhinologic Society (ERS) conference, September 2021, Thessaloniki (Greece)*	(ECTS: 0.50)
2021 'Onverwachte bijwerkingen bij SLIT'. *Oral presentation, Refereeravond allergologie AMC*, May 2021, Amsterdam (The Netherlands)	(ECTS: 0.50)
2020 'CRS: nieuwe inzichten, nieuwe therapie'. *Oral presentation, KNO-vergadering,* November 2020, Online (The Netherlands)	(ECTS: 0.50)
2019 'Op grote hoogte loopt het water je uit de mond'. *Oral presentation, KNO-vergadering,* November 2019, Nieuwegein (The Netherlands)	(ECTS: 0.50)
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LIST OF PUBLICATIONS

1. **Lourijsen E**, Avdeeva K, Gan KL, Fokkens W. Oral and intranasal aspirin desensitisation for non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease. Cochrane Database Syst Rev. 2025 Jan 7;1:CD013476. doi: 10.1002/14651858.CD013476.pub2. PMID: 39775459.

2. **Lourijsen E**, Avdeeva K, Gan KL, Pundir V, Fokkens W.
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10. **Lourijsen ES**, Fokkens WJ. Geschiktheidscriteria voor endoscopische sinuschirugie bij volwassen patiënten met chronische rhinosinusitis: een RAND/UCLA-project. NTvAA. 2017 Sept 17; 17(3): 104-109.

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14. Pundir V, Pundir J, Lancaster G, Baer S, Kirkland P, Cornet M, **Lourijsen ES**, Georgalas C, Fokkens WJ. Role of corticosteroids in Functional Endoscopic Sinus Surgery - a systematic review and meta-analysis.Rhinology.2016 Mar; 54(1): 3-19.

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She moved to Bennekom with her parents and after graduating from the Marnix College in Ede (2006) she started studying medicine at the University of Leiden. During her medicine study she participated in a research project at the Otorhinolaryngology Department of the Haga Hospital, the Hague, the Netherlands. In 2013 she graduated and started working as a junior doctor in Otorhinolaryngology in the Haga Hospital, the Hague, the Netherlands.

As of November 2014 she started her PhD-project at the department of Otorhinolaryngology in the Amsterdam UMC, location AMC (prof. dr. W.J. Fokkens). In 2020 she started her specialist training in Otorhinolaryngology at the Amsterdam UMC, location AMC (prof. dr. F.G. Dikkers, prof. dr. P. Merkus) and continued to work on her PhD-project.

She plans to finish her specialist training in 2026.

DANKWOORD

De meest waardevolle afsluiter in een proefschrift: mijn enorme dank gaat uit naar zoveel verschillende vrienden, familie en collega's die mij op diverse manieren ondersteund en geholpen hebben tijdens deze bijzondere reis wat een promotie-traject heet.

Ik richt graag een woord tot een aantal in het bijzonder:

Allereerst dank aan de **patiënten** die meegedaan hebben aan de PolypESS studie en de overige onderzoeken van dit proefschrift. Daar was vanuit hen een tijdsinvestering mee gemoeid en velen hebben zich onderworpen aan het 'lot' van de dobbelsteen. Zonder deze patiënten zou er geen klinisch artikel noch verder wetenschappelijk inzicht over verschenen zijn.

Mijn promotor, **Prof. Dr. W.J. Fokkens**, beste Wytske, ik kan me nog goed het eerste gesprek in 2014 op locatie AMC herinneren en het daaropvolgende telefoontje waarin je je vertrouwen uitsprak en mij aan nam als promovendus. Je hebt me losgelaten op het project wat we redelijk 'from scratch' op papier en database moesten inrichten. Dank voor het vertrouwen mij dit promotie-traject te laten uitrollen, de samenwerking, je immer heldere mening en je klinische - en levensinzichten. Je hebt me veel geleerd. Je vertelde me ooit dat je pas echt efficiënt wordt wanneer je moeder bent. Ik moet je op dit punt absoluut gelijk geven.

Mijn copromotor, **Dr. S. Reitsma**, beste Sietze, toen ik al enige tijd gemoeid was met mijn promotie-traject kwam jij als rhinoloog werken binnen het AMC. Jij hebt je altijd betrokken en benaderbaar opgesteld, zonder jezelf op te dringen. Ik waardeer je kunde binnen wetenschap, je beschouwende vermogen, je kunst om hoofd- van bijzaken te onderscheiden, en je rustige aard en natuurlijke vriendelijkheid. Ik hoop nog veel te kunnen leren van je als rhinoloog in de kliniek.

Leden van de promotiecommissie, **Prof. dr. P.M.M. Bossuyt, Prof. dr. V.J. Lund, Prof. dr. A.H. Maitland-van der Zee**, **dr. L.B.L. Benoist en dr. V. Hox,** ik wil jullie allen van harte danken voor de bereidheid te willen deelnemen aan de beoordeling van mijn proefschrift en hiermee een positie in de promotiecommissie te hebben willen bekleden.

Dr. V. Hox, beste Valerie, wat hebben we een weg afgelegd sinds de start van de Task Force rondom bijwerkingen van systemische corticosteroïden. Heel wat zoekacties, overlegmomenten en wellicht wat grijze haren verder zijn we wel bijna 2 grote papers rijker. Dank voor de fijne samenwerking afgelopen jaren en je functie als kartrekker. Ik voel me enorm vereerd dat je in mijn promotiecommissie wilde deelnemen.

Dr L. Benoist, beste Linda, ik weet nog dat je als jong staflid het AMC binnen kwam. Dank voor je benaderbare houding en positieve instelling zowel in de kliniek als daarbuiten. Je hebt me al veel geleerd op het gebied van de rhinologie en ik kijk uit naar de differentiatie.

Mijn **mede auteurs**, natuurlijk komt jullie ook alle eer toe in het hebben kunnen opschrijven en publiceren van de artikelen in dit proefschrift. Heel veel dank voor de samenwerking.

My **co-authors**, of course, all the credit also goes to you for being able to write and publish the articles in this dissertation. Many thanks for the collaboration.

Alle **hoofdonderzoekers van de Polypess studie,** beste **Claire Bommeljé, Jan van der Borden, Jochen Bretschneider, Ed van Deelen, Wynia Derks, Robert van Haastert, Paul Nagtegaal, Edwin van Nieuwkerk, Susanne Reinartz , Maryvonne Sassen, Judith Schmidt, Liane Tan, Jaap Veldhuizen, Ward Videler en Marleen Vleming**, zonder jullie noeste arbeid om patiënten voor te lichten, te werven en te behandelen, zouden we de trial niet tot een goed einde gebracht hebben. Ik heb het altijd heel erg leuk gevonden als jonge arts om een kijkje bij jullie in de KNO-keuken te kunnen nemen. Dank voor de gastvrijheid om de data op locatie te kunnen verzamelen. We komen elkaar hopelijk nog regelmatig tegen in de toekomst!

Prof. Dr. M. M. Rovers, beste Maroeska, ik wil je bedanken voor de samenwerking en de fijne overleggen rondom het analyseren en opschrijven van de data van de Polypess studie. Jouw ervaring met dit type trials is van zeer veel waarde geweest.

Dr. G. Hannink, beste Gerjon, ontzettend bedankt voor de prettige samenwerking rondom de analyses van de Polypess studie. Ik kan me menig ad hoc app- en mail verkeer voor de geest halen rondom figuren, tabellen en interpretaties. Jouw relativering en humor maakten het voor mij een stuk gemakkelijker.

Prof. Dr. C. A. J. M. de Borgie, beste Corianne, ik wil je bedanken dat je me als klinisch methodologe geholpen hebt mijn eerste stappen als arts-onderzoeker in het AMC te zetten. Ik heb menig overleg moment als een mooi leermoment ervaren. Dank voor je sturing en uitleg bij de opzet en uitvoer van de Polypess studie.

Mijn huidige opleiders, **Prof dr. P. Merkus en dr. R. Rinkel**, beste Paul en Rico, dank jullie wel voor jullie inzet en toewijding in het begeleiden en ondersteunen van mijn leerproces als AIOS en de betrokkenheid bij mij als persoon.

Beste oud-opleider, **Prof. Dr. F. Dikkers**, dank voor het vertrouwen om mij als AIOS aan te nemen na de periode als arts-onderzoeker in het AMC.

Prof. dr. I. Terreehorst, Beste Ingrid, jij hebt mij als eerste wegwijs gemaakt binnen de AMC KNO-research afdeling en de organisatie van de (vele) mapjes op de schijf. Ook al hebben we verder qua wetenschappelijk inhoudelijk werk niet samengewerkt wil ik je danken voor je gezelligheid en humoristische anekdotes als buren.

Beste **Marije**, ik wil je bedanken voor je hulp binnen de statistiek. Het was heel fijn om de kennis in huis te hebben en te kunnen gebruiken.

Beste **Kees, Esther en Daniëlle van het KNO-research lab**, dank jullie voor de vriescapaciteit die ik kon gebruiken bij het opslaan van patiënten materiaal! Heel wat serumbuisjes zijn jullie kant op gegaan. Daarnaast waren jullie bezoekjes aan onze werkkamer voor een koffie altijd een waar genoegen!

Beste **Ibra, Annelot en Lywke**, jullie inzet werd enorm gewaardeerd met de enorme bak aan papier-, invoer- en kopieerwerk rondom de lopende studies. Soms misschien met wat vierkante ogen verder.

Beste oud collega's van **Spaarne Gasthuis** en **OLVG**, bedankt voor jullie moeite om mij een zet in de goede richting te geven als AIOS en voor de interesse rondom het promotieonderzoek! Ik heb bij jullie een hele fijne werktijd gehad.

Beste **doktersassistenten/doktersassistentes, secretaresses, planners**, wat is het fijn om je werkdag te starten of door te komen met een gezellig praatje en wat positiviteit. Het klimaat waarin je werkt maakt zo veel uit op energie-level.

Beste **Stafleden KNO Amsterdam UMC**, de meeste 'oud' AMC-artsen 'ken' ik inmiddels al 10 jaar. Ik heb veel zien gebeuren, ontwikkelen en ook zien veranderen sinds de fusie. Ik kan zeggen dat ik jullie allemaal individueel, met jullie eigen karakter, subspecialisatie en passie, enorm waardeer als opleiders. Dank voor jullie fijne samenwerking en vertrouwen, en ik hoop nog een jaar veel te kunnen leren.

Lieve **AIOS 2020-nu,** dankzij jullie is het werken dagelijks toch weer een klein feestje (geweest) met de nodige koffie, plein lunches en vrijdagmiddagborrels. Dit alles naast de dagelijkse klinische afwisselende en soms wat chaotische werkzaamheden op beide locaties van het AUMC. Ik ben heel blij dat we zo'n fijne groep vormen met een hoog gehalte aan collegialiteit en interesse in elkaar. Ik heb genoten van alle skireisjes en kerstdiners. Gelukkig nog een heel jaar vol sociale momenten voor de boeg, maar ik geniet erna ook graag nog mee!

Lieve **Inge, Yasmin, Iris**, ik denk dat wij met z'n allen een boek kunnen vullen over alle bijzondere, hilarische en spraakmakende momenten tijdens onze werkzaamheden binnen de KNO-research. Het was jaren werken op D2 met een lach en soms de nodige peptalks. Maar vooral hebben we het heel erg leuk gehad als team inclusief koffies, etentjes en sinterklaasvieringen. Zonder jullie tomeloze inzet bij het coördineren van onderzoek, mede-includeren van patiënten en invoeren van data zouden we veel niet tot een goed einde hebben kunnen brengen. **Inge** en **Yasmin**, ik ben blij dat we ook nu ik AIOS ben af en toe nog samen werken in de kliniek waar we dan ook 'onze' oude patiënten weer even samen tegenkomen! Ik hoop dat we nog een hele tijd samen mogen werken en daarna, regelmatig maar een etentje!

Lieve **Paranimfen, lieve Neal en Klementina,** ik kan geen beter team wensen ter support dan jullie. Mocht het echt niet meer gaan met deze dikke buik, dan weet ik zeker dat jullie een verhaal klaar hebben tijdens de verdediging!

Lieve **Neal**, als 'trophy wife' heb je menig rhinologisch congres en etentje meegepakt. Jij wilde dolgraag zien met wie ik mijn dagen doorbracht in het AMC. Ik heb door jou altijd kunnen doen wat ik wilde en moest doen voor werk. Ik heb je zelf gevraagd als Paranimf, maar jij vond zelf ook absoluut dat je recht op deze eretaak had. Wie zou er meer over neuspoliepen weten dan jij na al die jaren?!

Lieve **Klementina**, met jouw komst als fellow en daarna mede-promovenda op de KNO-research werd het voor mij een stuk gezelliger door het hebben van een sparringpartner met de nodige koffie dates. We hebben een hele tijd in hetzelfde schuitje gezeten en ik ben heel blij dat onze vriendschap zo ontstaan is. Ik heb enorme bewondering gehad voor je doorzettingsvermogen te gaan werken in een ander land en het leren van het Nederlands. Ik vind het geweldig dat we nu samen AIOS zijn en wederom in het zelfde schuitje zitten. Ik kan enorm goed met je lachen, je hebt altijd diepe interesse in alles op persoonlijk- en werkvlak, je staat altijd klaar, en je hebt een hele fijne heldere kijk op zaken. Ik hoop dat er nog vele jaren volgen waarin we samen werken, borrelen, eten en congressen bezoeken. Ik heb de vrijheid genomen dit stukje in het Nederlands te verwoorden, ook al spreken we uit macht der gewoonte altijd in het Engels.

Lieve **Rosemary**, jouw altijd aanwezige gastvrijheid en warme hart is mij zeer dierbaar. Bedankt voor je interesse alle afgelopen jaren. Neal en ik boffen enorm dat je zo veel tijd vrijmaakt voor ons en Marcus. Ik kan me geen betere schoonmoeder en Granny wensen.

Lieve **schoonfamilie Conijn**, lieve **Ron, Vincent, Karin, Maria, Elyse, Perry en Jona**, jullie zijn een heerlijk avontuurlijke groep schoonfamilie om erbij te hebben. Dank voor alle jaren aan enerverende weekendjes weg (dab), de Caribische vakantie en alle brunches/etentjes samen. Dit heeft me altijd enorm afgeleid van de nodig druk, stress of moeilijkere zaken in mijn werk. Ik ga ervan uit dat ik met het afronden van dit traject nu wel ga shinen in de 'snelle' spelletjes zoals de slimste mens.

Lieve **Lotte**, dankjewel voor je oprechte belangstelling in mijn promotietraject en je liefde voor Marcus samen met Koen. Je bent een hele lieve en betrokken schoonzus.

Lieve **Femke**, om maar op onze klassieke wijze te starten; wij hebben nooit wat, dus het zal toch niet dat het glas nu half vol en niet half leeg is?! Sinds onze middelbare schooltijd geniet ik volop van de belevenissen die we hebben. Variërend van uren praten, levensweggen, borrelen, uit eten, of het bezoek aan een bijzondere theatershow of film. Het laatste jaar is er meer gespreksstof over kinderen en ballen hoog houden bij gekomen. Je bent een geweldige vriendin en er is 1 ding zeker, een avondje met jou en ik kan er weer tegenaan, dankjewel hiervoor.

Daarnaast ben je een cruciale factor geweest in het kunnen plannen van de verdediging. Dank reddende Engel!

Lieve **Maaike**, sinds het Teddy Bear Hospital zijn we elkaar niet meer uit het oog verloren. We hebben van alles met elkaar meegemaakt de afgelopen 16 jaar, van ups tot downs in relatie, leven en werk. Ik bewonder je uitgesproken mening, je oog voor perfectie en doelen, en je avonturisme om ook elders op de wereld van het leven te proeven. Ik ben heel blij dat we ook na je terugkomst uit Nieuw-Zeeland op dezelfde voet verder gaan!

Lieve **Mariëlle**, van borrelend studeren in Leiden tot mom-life. Jij bent al jaren een geweldige vriendin met een hele fijne energie, flexibiliteit, het hart op de tong en een aanstekelijke lach. Dank voor je luisterend oor afgelopen jaren, de heerlijke hater-praat en de borrels. Ik hoop dat we nog vele mooie momenten gaan meemaken met elkaar en de kinderen!

Lieve **Anneline**, twee Vissen die elkaar gevonden hebben in ons huis aan de Groenesteeg in Leiden. Ik bewonder je analytisch vermogen en doorziende blik. Dankjewel voor je energie, je life-hacks en luisterend oor afgelopen jaren.

Lieve **Nienke**, je bent een fantastische vriendin bij wie ik altijd kan aankloppen, met een bak aan interesse. Dankjewel voor het luisteren. In jou schuilt een echte roeiersmentaliteit; je bent een keiharde positieve werker die de omstandigheden accepteert zoals ze zijn. Ik vind dat bewonderenswaardig en ik hoop dat we samen nog vele mooie momenten in het Limburgse of elders gaan meemaken.

Lieve **cordiaalgenoten**, lieve **Anne, Bernadette, Cecile, Lieke, Liset, Marielle, Nikki, Satya**, 18 jaar geleden begon het in Leiden en ik heb het vermoeden dat we zo nog 18 jaar door kunnen. Nog steeds elke maand met elkaar eten blijft een feest en ik bewonder ieders inzet om dit ondanks de drukte en waan van de dag te laten voortbestaan. Dank jullie wel voor jullie vriendschap.

Lieve **Kay**, zo blij dat jij het cover ontwerp wilde maken voor me, zelfs in je waardevolle tijd met Toma samen. Het is prachtig geworden, heel veel dank hiervoor.

Lieve **Annelot en Koen**, eindelijk iets tastbaarder dan een verzameling artikelen waar jullie vaak genoeg over gehoord hadden als ik (weer eens)moest werken. Ik wil jullie bedanken voor jullie interesse en begrip, onze hechte band als broer en zussen, en de weekendjes in Bennekom en vakanties samen als gezin. Jullie staan altijd klaar als het nodig is. Dank jullie wel voor de hulp bij en het plezier wat jullie Marcus in zijn leven geven als oom Koen en tante Anna. Dat is onbetaalbaar.

Lieve **pap en mam**, ik wil jullie bedanken voor alle mogelijkheden die ik gehad heb in mijn leven. Jullie hebben me altijd gesteund in de keuzes die ik gemaakt heb. Geneeskunde, een promotietraject en uiteindelijk de opleiding tot KNO-arts. ‘Het onderzoek’ is al jaren

gespreksonderwerp en ik ben heel blij dat ik jullie eindelijk in gebundelde vorm kan tonen waar ik me zoal druk om heb gemaakt. Mede dankzij jullie oppaskunsten voor Marcus heb ik dit proefschrift kunnen afronden. Daar zal ik jullie mijn hele leven dankbaar voor zijn. Lieve **mam**, jij bezit een inwendige levenskracht en een doorzettingsvermogen waar veel mensen een puntje aan kunnen zuigen. Ik ben dolblij dat je je leven samen met papa weer terug hebt na een bewogen jaar waarin het vooral ook spannend geweest is. Het is mij weer duidelijk geworden wat het belangrijkste is in het leven, dat is familie en gezondheid.

Lieve **Neal**, wat zijn wij beiden ongelofelijk blij nu dit 'levenswerk' afgerond is. Vanaf de eerste werkdag in 2015 tot nu heb je mijn hele tocht van dit soms vlakke maar vaak genoeg ook steile pad, door luwte en storm, eigenlijk mee afgelegd. Daar was jouw Santiago de Compostella tocht waarschijnlijk niets bij. Ik kan me goed heugen dat we mijn proefschrift op post-its zijn gaan uitwerken op de koelkast twee jaar geleden. Dank je wel voor wie je bent sinds het moment dat we elkaar ontmoetten in 2010; je geduld, je support om te kunnen doen wat ik soms moest doen op werkvlak, je daadkracht, je kritische of retorische vragen, je relativerende woorden, je gepaste (vaak genoeg ook ongepaste) humor en al je liefde voor mij. Het heeft me gebracht tot waar we nu staan. (Bijna) twee kinderen verder en het boek is af. Samen door naar een nieuw hoofdstuk in het leven, maar een die niet in een boekje vastgelegd hoeft te worden. Ik heb dit boek aan jou opgedragen.

Lieve **Marcus,** mijn kleine boefje, die mijn leven totaal veranderd heeft. Jouw vrolijke gekwetter is altijd een feest om bij thuis te komen. Jij bent voor mij het allerbelangrijkst in mijn leven samen met papa, en ik heb me vaak genoeg schuldig gevoeld over alle oppas die nodig geweest is om de afrondende fase door te komen. Mama kijkt uit naar alle heerlijke momenten die we samen nog gaan beleven.