Bone Conduction Devices

Reviewing the past, evaluating the present, considerations for the future

Ivo Kruyt

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I.J. Kruyt

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Chapter 1

Introduction

1. Introduction

As people go through their daily life, perception of sound is of paramount importance. Our auditory system enables us to detect, locate, and identify sounds, whether it is a fast-approaching car, the rustling of leaves, or glass breaking nearby. Moreover, and most importantly, hearing makes it possible for humans to perceive and recognize spoken language.

Despite the essential role hearing plays in our daily life, it is rarely recognised for its exceptionality, while its performance is extraordinary in several ways. Firstly, the extent of sensitivity of our auditory system is so exceptional that we can detect sound waves that cause the tympanic membrane to vibrate by about a picometre. To put this in perspective, the diameter of a hydrogen atom is 37 times larger.[1] Simultaneously, sounds of 100dB can also be perceived without resulting in loudness discomfort or direct damage to the hearing organ, despite containing 100.000 times more acoustic energy than sounds of 0dB. In addition, the auditory system is able to detect and interpret frequencies ranging from 20Hz to 20.000Hz; yet the frequency resolution of our auditory system makes it possible to distinguish nuances in sound one-thirtieth of the interval between adjacent keys on a piano.[2, 3]

Unfortunately, not everyone is born with normal-hearing, and others may lose their ability to hear during life, resulting in difficulties in detecting, locating, and identifying sounds and impairing verbal communication. People suffering from hearing loss (HL) have reported lower quality-of-life compared to their normal-hearing peers.[4, 5] Fortunately, hearing is one of the few bodily functions that can be improved after its deterioration, namely by using hearing aids, implants, or reconstructive surgery. As such, hearing rehabilitation improves quality-of-life.[5]

This thesis focuses on one of these hearing rehabilitation options: bone conduction devices.

2. Anatomy and physiology of the auditory system

The human ear consists of three segments: the outer ear, the middle ear, and the inner ear (figure 1). Each of these segments contributes to auditory perception, but all in their distinct way. The outer ear is composed of the pinna (or auricle), the external auditory meatus with the adjacent canal, and the lateral, epithelial surface of the tympanic membrane. The pinna is formed of irregularly shaped cartilage covered by perichondrium and skin. This characteristic shape funnels sound waves towards the external auditory meatus and furnishes spectral cues used for sound localization.[6, 7] However, the relative immobility of the pinna in humans limits this latter function. The external auditory canal is approximately 3 cm long and directs sound waves towards the tympanic membrane,

causing it to vibrate. In summary, the primary function of the external ear components altogether is to funnel external sound waves towards the middle ear.

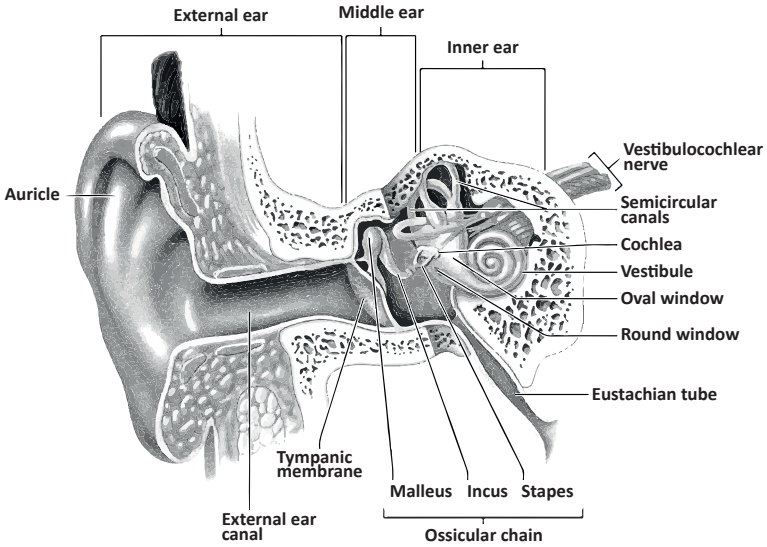

Figure 1. The anatomy of the ear

The tympanic membrane and attached ossicular chain are located in the middle ear. The tympanic membrane converts sound waves into mechanical vibrations, which are transmitted via the ossicular chain to the inner ear. The ossicular chain consists of three small bones (ossicles), i.e. malleus, incus, and stapes. The malleus is attached to the tympanic membrane and incus, which in turn is connected to the stapes. The ossicular chain is connected to the oval window of the inner ear's vestibule via the footplate of the stapes. Due to the shape and configuration of the tympanic membrane and its attached ossicular chain in the middle ear, mechanical vibrations are amplified before reaching the vestibule of the inner ear. Altogether, the middle ear converts sound waves, funnelled in the external ear, in amplified mechanical vibrations and transmits these to the inner ear.

The inner ear consists of the vestibule, the cochlea, and the semi-circular canals. The description of the latter system and its function, i.e. balance, is beyond the scope of this thesis. The vestibule of the inner ear is a chamber where mechanical vibrations of the middle ear are presented to the inner ear via an opening, called the oval window. The vestibule is filled with perilymph, which is incompressible; however, due to presence of a second window in the cochlea, i.e. the round window, if the stapes footplate moves into the oval window, the membrane of the round window moves out, allowing fluid

movement within the cochlea (figure 2). Mechanical vibrations of the stapes are thus converted to longitudinal pressure waves in the perilymph, travelling from the oval window of the vestibule towards the round window of the cochlea. The cochlea is a spiral-shaped, tube-like structure of approximately 33mm long and 2mm in diameter, resembling the shell of a snail.[8] The cochlea is divided into three ducts called scalae (Latin for 'stairway'), which are wrapped around the conical bony modiolus of the cochlea like a spiral staircase. The upper duct (scala vestibuli), runs from the vestibule to the apex of the cochlea (helicotrema) where it is connected to the lower duct (scala tympani), which runs to the round window membrane. The two scalae are a continuation of the vestibule, and, therefore, contain perilymph. In between these scalae, the scala media is situated. The scala media contains endolymph instead and is separated from the scala vestibuli by the Reissner's membrane and from the scala tympani by the basilar membrane, resulting in an electrical gradient.

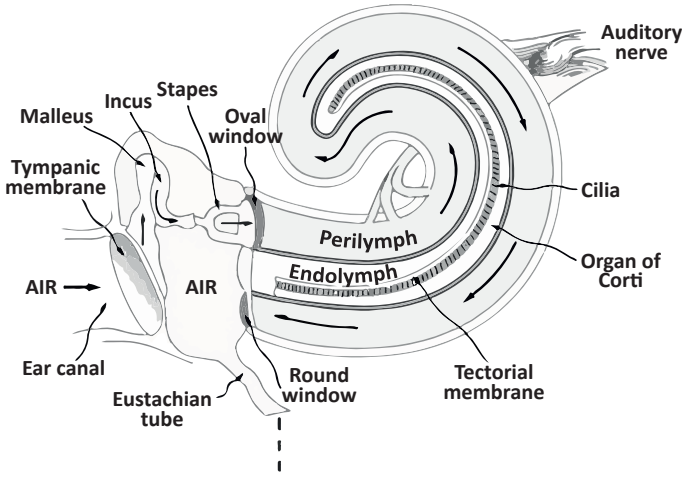

Figure 2. Anatomy of the cochlea and the transmission of sound through the ear.

On the basilar membrane, the organ of Corti is positioned. This organ is a complex structure composed of two types of mechanosensory hair cells, i.e. outer hair cells (OHC) and inner hair cells (IHC).[9] The function of OHC's is hypothesized to amplify sounds non-linearly.[10, 11] The IHC's are caudally attached to the basilar membrane and contain stereocilia on its apical surface, which are attached to the tectorial membrane. When sound waves reach the inner ear, the longitudinal pressure waves cause the basilar membrane to vibrate. As a result, the stereocilia of the IHC deflect, resulting in depolarisation. The following release of neurotransmitters causes an increased action

potential firing rate in the cochlear nerve traveling towards the auditory centres in the brain. In these centres, these action potentials are interpreted as sound.[12]

3. Hearing loss

Hearing impairment can be divided into three groups based on the localisation of the dysfunction: sensorineural hearing loss (SNHL), conductive hearing loss (CHL), and mixed hearing loss (MHL). SNHL is the most common type of hearing loss and is mainly caused by dysfunction in the cochlea, e.g. presbycusis or noise-induced HL. However, dysfunction of the vestibulocochlear nerve (e.g. vestibular schwannoma) or a structure located along the tract to the auditory centres in the brain (e.g. infarction) can also cause SNHL. CHL origins in the outer and/or middle ear structures which conduct sound towards the cochlea. CHL can be caused by the absence, malformation, or malfunction of any of these structures. MHL is defined as hearing loss with both a conductive and sensorineural component. The causes of hearing loss can either be of congenital origin, acquired during life, or a combination. In addition, hearing loss can occur unilaterally or bilaterally and may vary from mild to moderate in case of CHL, from mild to profound in MHL, and from mild to complete deafness in SNHL. Rehabilitation options depend on the type and grade of hearing loss.

4. Physiology of bone conduction hearing

In addition to hearing by means of sound waves reaching the inner ear (air conduction, AC), sound waves can also reach the cochlea through bone conduction (BC). Von Békésy was the first to report that mechanical vibrations directly applied to the temporal bone also result in longitudinal fluid waves in the cochlea (embedded in the petrous portion of the temporal bone), stimulating the basilar membrane in a similar way air conducted sound does.[13, 14]

Despite extensive research, the BC pathway is not yet fully understood. In 1966, Tonndorf postulated multiple contributing factors in BC hearing based on animal research.[15] A decade ago, Stenfelt and Goode published an updated review of the five identified factors significantly contributing to BC hearing: 1. The sound radiated in the external auditory canal; 2. The inertia of the cochlear fluids; 3. The inertia of the middle ear ossicles; 4. The compression of the cochlear walls; and 5. The pressure transmission from the cerebrospinal fluid.[16] The inertia of the cochlear fluids is considered the most important contributor to BC hearing. Cochlear fluid is deemed to be incompressible. However, skull vibrations (BC stimulation) result in a pressure gradient between the round and oval window in the cochlea. This pressure gradient causes longitudinal fluid waves in the

scalae, causing the basilar membrane to vibrate. Fluid inertia mainly contributes to BC hearing for sounds with a frequency below 4 kHz.[16] Nonetheless, the bone conduction route is less efficient for stimulating the basilar membrane compared to the air conduction route.[17]

5. Bone conduction devices (BCDs)

In the 17th century, John Bulwer and George Sibscota applied the phenomenon of bone conduction as an aid for impaired hearing.[18] In the following centuries, various instruments were developed using BC for sound transmission to the inner ear mechanically applied to either the teeth or mastoid bone. In the early 20th century, the carbon-electric microphone and the magnetic receiver were developed. These inventions initiated the construction of the first electric bone conduction device (BCD). This BCD was applied to the mastoid bone and remained in place via a steel spring band.[19] Meanwhile, these inventions also initiated the development of conventional air conduction hearing aids (ACHAs). Due to the unfavourable cosmetics and pressure-related discomfort caused by the steel spring band of BCDs, ACHAs were preferred by most patients.[20] However, not all patients suffering from hearing loss were able to benefit from ACHAs, such as patients with microtia, atresia of the ear canal, chronic middle ear or external ear canal infections.

To overcome the pressure-related issues encountered with conventional, transcutaneous (i.e. BC through intact skin) BCDs and to be able to provide a suitable treatment option for these patients, a different, more direct route for applying BC to the skull was needed. In experimental clinical studies, Brånemark and Albrektsson found that the upper arm skin could be permanently penetrated by an implant, without eliciting hazardous problems, provided the implant was manufactured from tissue tolerant metal, such as titanium, and movements of the skin were limited.[21, 22] Based on the promising outcomes of dental implant research that followed this observation, Tjellström and co-workers developed a percutaneous, i.e. skin-penetrating, titanium BCD that could be directly coupled to the mastoid bone: the Bone-Anchored Hearing Aid (BAHA®).[23-25] The registered name BAHA® was used for all these implants until a second manufacturer introduced a similar implant. Nowadays, the name Bone Conduction Device (BCD) is used.

A percutaneous BCD consists of three elements: a titanium implant and skin-penetrating abutment, onto which an externally worn sound processor is coupled (figure 3). In 1977, the first fourteen patients with hearing impairment were fitted with this system. It was found that percutaneous instead of the transcutaneous application of vibrations to the skull resulted in 15dB more favourable hearing thresholds.[25] More research followed; in a study of Håkansson et al., all ten patients reported to prefer the percutaneous BCD to their old conventional BCD, because of improved wearing comfort, aesthetic appearance, and sound quality.[26] The first long-term study concluded percutaneous

BCDs could remain seated for over five years without adverse tissue reactions, e.g. infection or inflammation.[27]

Figure 3. A BCD (Wide Ponto® from Oticon Medical™) consisting of a titanium implant, skin penetrating abutment, and externally worn sound processor. Image provided by Oticon Medical™.

In 1988, after the BCD became commercially available, prof. dr. C.W.R.J. Cremers operated the first patient to receive such an implant in our clinic. Nowadays, almost 2000 patients have been treated with a percutaneous BCD in Nijmegen. Many of these patients have participated in research - evaluating the developments in implant design, surgical technique, and sound processors - in our clinic, contributing to the improved clinical outcomes of BCD seen in the last decades. The current thesis is the 10th PhD thesis on BCD originating from Nijmegen.

6. Implant surgery

Besides providing optimal maximum power output (MPO) with the correct sound processor, successful BCD implant surgery requires firm anchorage of the titanium implant in the temporal bone, combined with low skin-related complication rates postoperatively. Several surgical techniques have been proposed in the literature, all driven with the aim to optimize soft tissue handling as well as the requirements for osseointegration.

6.1. Osseointegration and implant stability

In the early 1960s, Per-Ingvar Brånemark discovered that titanium implants inserted in living bone become more rigidly fixed over time and called this natural process osseointegration.[24] Osseointegration is a dynamic process in which implant characteristics, e.g. material, surface properties, and design, play a role in cellular behaviour modulation and result in a direct interface between an implant and bone, without intervening soft tissue.[28]

In 1987, Albrektsson and Jacobsson described six factors of importance to obtain osseointegration.[29] Firstly, the material of the fixture to be implanted; commercially pure titanium is known to integrate into the surrounding bone without causing adverse effects. In addition, other metals are also known to integrate to a certain degree, e.g. hydroxyapatite, vanadium, tantalum, certain ceramics, and aluminium hydroxide. Secondly, the geometry of the implant; screw-shaped implants often display good initial (primary) stability, whereas cone-shaped implants are more prone to be lost due to initial micro-movements and therefore have poorer stability. The third factor is the implant's microstructure: implants with a relatively smooth surface, e.g. original Brånemark implant, will result in poor integration, but with minor resorption. In contrast, an implant with a very rough surface will result in rapid integration, but the secondary inflammation and bone resorption can jeopardize its long-term integration.[30] Fourthly, the quality of the bone bed where the fixture is installed; bone quality matures during life. As a result, children have relatively soft and immature bone compared to adults. Furthermore, bone disease, e.g. osteoporosis, results in a lesser degree of integration, hence higher implant loss rates.[31] In addition, patients previously treated with radiation therapy have an altered texture of bone that will reduce the ability to integrate fixtures.[32, 33] Another factor of importance is the surgical technique for implantation. Surgery should be non-traumatic, without causing the bone temperature to rise by more than a few degrees due to the drilling. The titanium implant should only be handled by titanium instruments and not been touched by surgery gloves. Furthermore, the surgical field must be protected from powder, fibres, and other substances that might compromise osseointegration.[27] Finally, the load of the fixture should preferably be in a longitudinal direction. Even very high loads can be endured during many years of function, when forces on the implant are distributed in a longitudinal direction. However, even once the implant has osseointegrated, rotational and cantilever forces should be avoided.[34]

6.2. Developments in surgical techniques

Apart from a firmly osseointegrated implant, a successful system also requires the abutment to be tolerated by the soft tissue it penetrates. In the pursuit of minimising soft tissue complication rates, several types of incisions and soft tissue handling techniques have been advocated since the BCD was introduced. Initially, implant surgery was performed in two stages. In the first stage, the implant was surgically placed in the

temporal bone by elevating both the skin and periosteum via a curved incision. The skin was then closed, and the implant was left for 3-6 months for it to osseointegrate in the bone fully. In the second stage, the abutment was attached to the implant, and either a free skin graft or a U-shaped flap thinned with a surgical blade or dermatome was used to remove all subcutaneous tissue and hair follicles of the peri-implant area.[35, 36] It was thought this so-called skin-thinning would reduce the skin mobility around the implant, as well as avoid the accumulation of debris, thereby reducing the risk of inflammation and implant loss, and avoiding skin overgrowth over the abutment.[25, 37, 38] In 1989, the surgical technique was simplified by reducing the two-stage surgical procedure to a one-stage procedure, without compromising implant survival.[39, 40] However, for the implant to successfully osseointegrate, the time till sound processor loading was extended. In the early nineties, the Nijmegen linear incision technique was introduced. This straight incision aimed to facilitate soft tissue reduction as illustrated in figure 4.[41]

This technique was found to be superior in terms of healing, surgery time, and soft tissue complications compared to previously described techniques.[42, 43] Nonetheless, adverse skin reactions, osseointegration failure, and the need for skin revision surgery still occurred.[44] Furthermore, skin-thinning still inflicted extensive surgical trauma and compromised blood flow, hampering an optimal immune response during an infection, and neural structures around the implant, causing numbness.[45]

The abutment shape has also changed over time. The first titanium abutment was cylinder-shaped but was later modified to a cone-shape (figure 4F) due to skin reactions. In 2003, an 8.5mm abutment became available, providing extra distance from skin to the rim of the abutment compared to the standard 5.5mm abutment. This extension showed to be beneficial in managing soft tissue problems and preventing revision surgery, without resulting in higher implant loss rates. It also showed to be of value in patients with a thick scalp that interfered with sound processor coupling.[46] However, despite this additional benefit, surgeons remained reluctant to use this longer abutment as standard clinical practice. In 2010, a wider 4.5-mm-diameter implant was introduced. The larger implant diameter, providing a larger bone–implant contact surface, was thought to improve osseointegration. In addition, the abutment shape was changed from cone-shaped, having a relatively broad surface overlying the skin, to a bell-shaped abutment. Based on the improved implant survival rates of this implant, longer abutments were more often used as primary abutment as well, since the modified abutment shape also provided superior soft tissue tolerability.[47, 48]

In 2011, after the introduction and the demonstrated benefit of wider diameter implants and longer abutments, Hultcrantz reported outcomes of a modified linear incision technique without skin-thinning. By preserving the soft-tissue, and therefore inflicting less surgical trauma, it was hypothesized that this technique would result in shorter surgery times, faster wound healing, less scar tissue formation and numbness, cosmetic advantages, and possibly fewer skin infections.[49] A recent systematic review

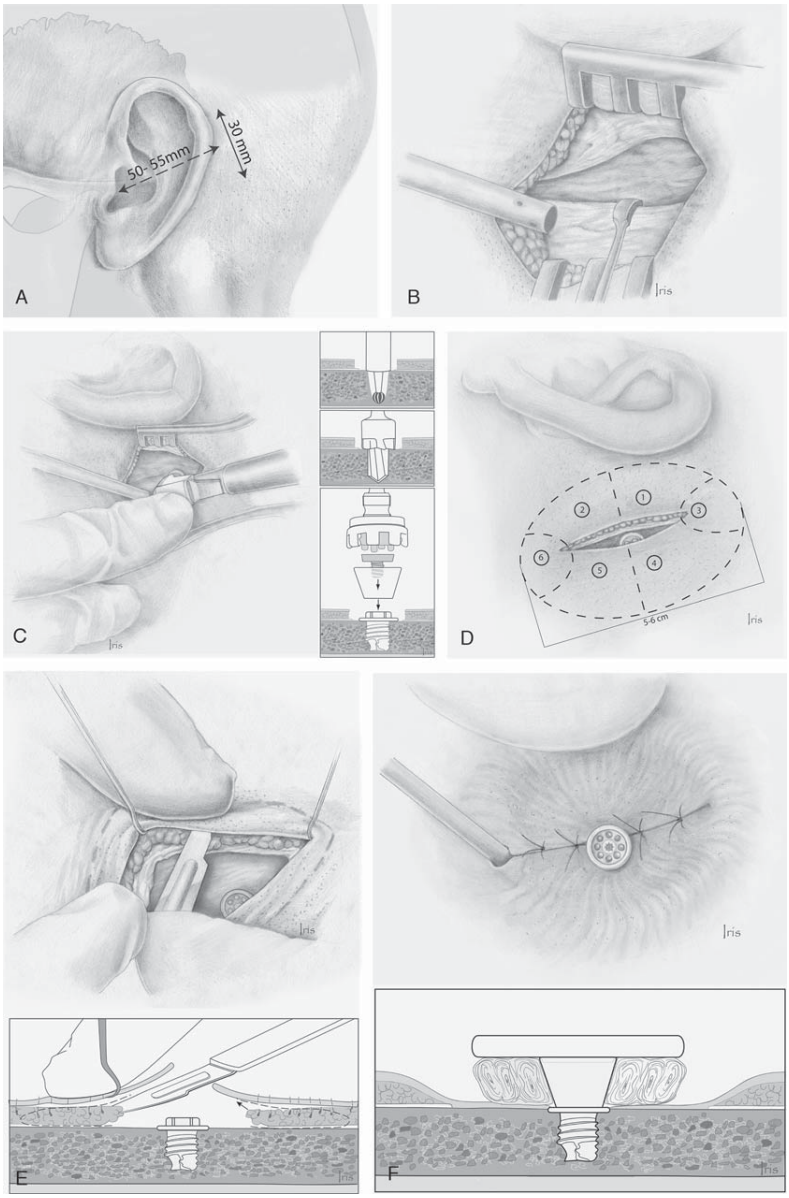

Figure 4. The simplified Nijmegen linear incision technique with soft tissue reduction for BCD surgery. A. Implant location. B. Opening the different layers and exposing the periosteum. C. Different steps in drilling procedure and implant instalment. D. Area of peri-implant subcutaneous soft tissue reduction. E. Subcutaneous soft tissue reduction procedure. F. Healing cap and position of the Yankauer to remove subcutaneous blood. (figure originally published by De Wolf et al.[41])

concluded that surgical techniques without skin-thinning indeed limited postoperative skin complication rates and required less surgical time compared to the skin-thinning techniques. However, since different surgical techniques were used in most comparative studies, no firm conclusions could be drawn on which technique, i.e. skin preservation or skin reduction, was superior.[50] The short-term evaluation of Den Besten et al. comparing the linear incision techniques found that the tissue preservation technique resulted in favourable sensibility scores, scar appearance, and shorter surgery time. However, more adverse skin reactions were observed.[51] In **chapter 3**, the long-term outcomes are evaluated to determine which technique is superior.

In 2012, a new abutment was introduced. This abutment has a hydroxyapatite coating, which is thought to facilitate tight integration between surrounding soft tissues and the abutment, possibly improving soft-tissue outcomes. Until now, no beneficial long-term effect from the hydroxyapatite coating on soft tissue complications has been demonstrated, while in the short term, a slight increase in adverse reactions was observed.[52, 53] Hence, the bell-shaped titanium abutment without coating currently remains the standard practice in our clinic.

7. Evaluation of complications

7.1. Intra-operative complication

Intraoperative complications seldom occur. The most common issue arising intraoperatively is bleeding originating from either the scalp, emissary veins, or the temporalis muscle. Although bleeding is easily controlled with bipolar electrocautery, extra care is needed to avoid compromising the blood supply of the thinned skin flap when using a skin-thinning technique.[54] Exposure of the dura mater may also occur, especially in children (up to 70%), although it does not seem to have any clinical consequences.[55-58] However, two case reports have described a subdural hematoma in a 65-year-old woman and an epidural hematoma directly after implantation in a 15-year-old girl.[59, 60]

7.2. Soft tissue tolerability

Soft tissue complications directly after implant surgery include hematoma, persistent bleeding, wound dehiscence, and pain. All these complications are rarely observed. Skin flap necrosis is a more severe complication which has been observed more frequently in the past.[61-63] However, the introduction of the single linear incision technique inflicting minimal soft tissue trauma by not using a skin flap eliminated this particular issue.[41]

Regardless of the surgical technique used, the skin-piercing abutment of a percutaneous BCD implies a continuous breach in the mechanical defensive barrier of the skin, forming a potential entry point for micro-organisms which can cause soft tissue infection. To compensate for this breach, immunological mechanisms in the subcutaneous tissue surrounding the

abutment become more active.[64, 65] Despite these changes in immunological activity, daily hygienic care around the abutment is needed to avoid the accumulation of debris potentiating infection. Nevertheless, skin infections do occur and remain one of the disadvantages of percutaneous implants. A grading system to standardize the reporting of soft tissue reactions around percutaneous implants for BCDs was introduced by Holgers et al. in 1988 (table 1).[66]

Table 1. Holgers score

Grade	Clinical description
0	No irritation: epithelial debris removed if present
1	Slight redness: temporary local treatment indicated
2	Red and slightly moist; no granulation tissue present: Local treatment; extra controls
3	Reddish and moist; sometimes granulation tissue: Revision surgery is indicated
4	Removal of skin-penetrating implant necessary due to infection
R	Removal of implant for reasons not related to skin problems

Although this scale is currently the standard for reporting skin status, it was originally designed to evaluate the skin three months after implantation and onwards. It is, therefore, unable to describe complications in early wound healing, such as (often minimal) dehiscence. Secondly, the scale lacks one of the most critical signal functions: pain. Pain can result from skin infection but may also be caused by peri-implantitis, as is seen in dental implants. Thirdly, skin height is not incorporated in the Holgers scale. This is relevant when a soft tissue preservation technique is applied, as the skin can thicken around the abutment without infection signs, which can result in the inability to couple the sound processor, which may ultimately require abutment change or skin revision. In addition, the scale would become more useful in daily practice if it also included a standardized treatment advice. Finally, the Holgers scale is not usable in patients with transcutaneous BCDs. It can be concluded that a standardized assessment scale for evaluating skin complications in these patients is lacking. To overcome all these shortcomings, a new standardized scoring system for evaluating skin status is proposed in **chapter 7**.

7.3. Implant survival

As previously mentioned, adequate osseointegration of the implant in the recipient's bone is a prerequisite for implants to sustain a patient's lifetime. If no adequate osseointegration is obtained, it will eventually result in implant loss. Some patients are more prone to spontaneous implant loss. Children, for example, have a lower bone quality compared to adults. In addition, patients who smoke are also significantly more at risk, and a trend for

higher implant loss rates has been observed in patients with cardiovascular disease or diabetes mellitus type 2.[67-69] Nevertheless, spontaneous implant losses can also occur in healthy, non-smoking adult patients. In addition, implant loss can also occur due to a severe (untreated) peri-implant infection or trauma, especially in children. Numerous studies have analysed the implant survival rates of percutaneous BCDs; however, reported implant loss rates vary significantly. A meta-analysis of these studies, evaluating more than 2300 implants, reported implant loss rates of 1.6-17.4% in adult and mixed populations and 0.0-25% in paediatric patients.[44] However, it should be noted that all included studies were published up until 2011, while in the last decade, many new developments in implant design have been introduced. For example, the more recent wide-diameter implants have reported loss rates of <5% after five years of follow-up.[70] Two other new implant designs and their loss rates are evaluated in **chapter 2** of this thesis.

7.4. Resonance frequency analysis

Resonance frequency analysis was introduced as an objective technique to measure dental implant stability.[71] It measures the implant resonance frequency with electromagnetic pulses via a transducer (SmartPeg) attached to the implant. The SmartPeg contains a small magnet in its tip which is stimulated by electromagnetic pulses produced by a handheld electronic device. Based on the frequency, the Implant Stability Quotient (ISQ) is automatically calculated, ranging from 1 to 100, with a higher frequency resulting in a higher ISQ.[72] ISQ is reported as two values, i.e. ISQ-low and ISQ-high obtained by perpendicular measurements, reflecting the lowest and highest recorded value.

The introduction of abutments with a compatible coupling to attach a SmartPeg has resulted in the applicability of this measurement in percutaneous BCD's as well. However, as extensively discussed by Nelissen et al., ISQ outcomes are determined by three main factors: the design of the SmartPeg and the implant-transducer interface; the stiffness of the implant-bone interface (reflecting the level of osseointegration); and the total distance the between bone level and tip of the SmartPeg (e.g. different abutment lengths). Due to these differences, absolute ISQ-values from single measurements provide little information. However, trends in ISQ values within a single patient or population over time are currently deemed most clinically relevant.[73]

8. Transcutaneous alternatives

Due to the aforementioned complications observed in percutaneous implants, the concept of transcutaneous coupling remained attractive, as an intact skin avoids an entry point for micro-organisms and, hence, could potentially prevent skin infections and loss of the implant. In addition, the transcutaneous system could be considered to be cosmetically appealing, as there are no visible parts if the sound processor is not worn. As such, two

new passive transcutaneous implants for bone-conduction hearing were introduced in 2011 (Sophono® Alpha 1, and later Alpha 2; (Medtronic plc™, N Jacksonville, Florida, USA) and 2013 (BAHA® Attract; Cochlear Bone Anchored Solutions AB™, Mölnlycke, Sweden) respectively. Both devices consist of either one (BAHA® Attract) or two internal magnets (Sophono® Alpha 1) fixed in the temporal bone and an external magnet, onto which the sound processor is attached.[74, 75] The magnets have to provide sufficient retention force for the sound processor to remain seated. However, a too high static pressure towards the skin could cause pressure-related complications, which was previously seen in the transcutaneous implant Xomed Audiant developed by Hough et al. in 1986.[76] This implant was withdrawn from the market soon after its introduction due to these pressure-related complications combined with insufficient amplification. One of the strategies to overcome pressure-related complications is to attach a soft pad to the external magnet of the BAHA® Attract to distribute the pressure evenly over the underlying skin (figure 5). This system is studied in more detail in **chapter 4** of this thesis. Previous studies have shown that passive transcutaneous systems provide lower functional gain (especially at high frequencies) compared to the percutaneous system due to dampening by the soft tissue layer between the magnets. Comparable to the application of a passive transcutaneous device via a headband or testband, the magnet coupling results in dampening of 15-20 dB for the frequency range from 1 to 4 kHz.[77-80]

More recently, the first active (electromagnetic) transcutaneous system (The Bonebridge®, BB, Med-El™, Innsbruck, Austria) was launched, while a second system is currently being evaluated in clinical trials (Osia® Cochlear BAS, Gothenburg, Sweden)(ClinicalTrials.gov Identifier: NCT03086135). The latter system contains a piezo-electrical transducer with potentially higher output at higher frequencies. In the near future, yet another active electromagnetic transcutaneous system will be launched (Sentio®, Oticon Medical AB™, Askim, Sweden). These transcutaneous partially implantable systems have, in contrast to passive transcutaneous systems, an implanted actuator instead of an external actuator, thereby

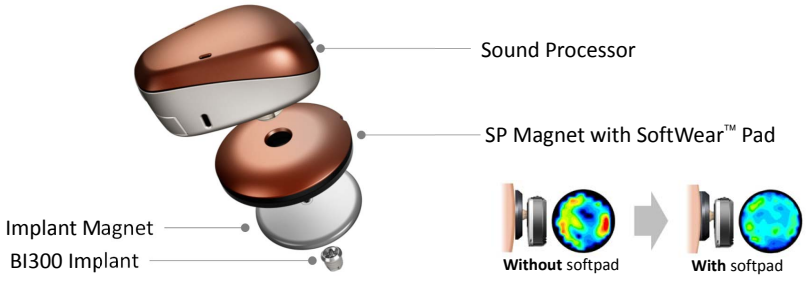

Figure 5. The BAHA® Attract system (left). On the right, displaying the pressure distribution on the skin without and with a soft pad attached to the external magnet. Image provided by Cochlear™

overcoming the dampening by the skin. The audiological benefit of the Bonebridge® system seems similar or slightly lower compared to percutaneous systems.[80, 81] However, more long-term, prospective, comparative research is needed to determine the benefit of these active transcutaneous systems and including optimal indications per implant type.

9. Outline of this thesis

The current thesis consists of two parts. The aim of the first part (**chapter 2-4**) is to evaluate the clinical safety and long-term effectiveness of developments in percutaneous and transcutaneous implant designs and clinical outcomes of a different surgical technique. The aim of the second part (**chapter 5-7**) is to review previously published studies critically and to determine future directions for BCD research.

In **chapter 2,** two new percutaneous implant designs from Oticon Medical™ are evaluated. **Chapter 2.1** reports the three-year implant stability, survival, and soft tissue tolerability of the new Wide Ponto® implant (diameter 4.5mm) compared to the previous generation Ponto® implant (diameter 3.75mm) in a prospective randomized controlled clinical trial. **Chapter 2.2** describes the clinical evaluation of the new laser-ablated wide Ponto BHX® implant. This multicentre study was designed as a retrospective chart review approximately one year after implantation of patients who previously participated in a completed 4-week controlled market release (CMR) testing performed in three different hospitals. The main outcomes are implant survival, adverse skin reaction rates, and ISQ.

In **chapter 3,** the linear incision surgery with soft tissue preservation for percutaneous implants is compared to the soft tissue reduction technique in a long-term evaluation, using the same type of implant (Wide Ponto® from Oticon Medical™) in both groups. The outcomes of interest are the influence of skin handling during surgery on post-operative skin sensibility, soft-tissue status, ISQ, skin height, implant survival, revision surgery rates, scar assessment, and hearing thresholds.

Chapter 4 presents the 2-year results of a multicentre study evaluating a new passive transcutaneous implant for bone conduction devices: the BAHA® Attract from Cochlear BAS™. Various clinical, audiological, and patient-reported outcomes are reported and discussed.

In **chapter 5**, the first chapter of the second part of this thesis, we attempt to elucidate whether the potentially improved performance (i.e. decline in complications) of new BCDs outweighs the increasing costs of these new implant models. A cost-benefit analysis, using a mathematical model, was performed to evaluate and compare the total costs of implant treatment over a 10-year period with selected previous and current generation implants.

Chapter 6 encompasses a systematic review of the published literature on the efficacy of BCDs in the paediatric population. The recent developments in implant width,

soft tissue handling technique, and single-stage implant surgery have reduced the post-operative complication rates in adults. However, since most research on these developments has been performed in adult populations, surgeons remain more cautious of applying these new developments in children. This review, therefore, aims to evaluate the efficacy of BCDs in children and to clarify the usage and outcomes of new surgical techniques and implants in this specific population.

In **chapter 7**, we critically review the gold standard for reporting post-operative percutaneous peri-implant soft tissue status: the Holgers' score. Based on its shortcomings, e.g. neither evaluating pain and skin height, nor providing treatment advice, and its lack in evaluating peri-implant soft tissue status in patients with a transcutaneous BCD, we propose a new soft tissue assessment scale. The IPS-scale can be used for both percutaneous and transcutaneous implants for bone conduction devices.

In **chapter 8,** we have provided an overview and an elaborate discussion of the current evidence, with suggestions for clinical practice and considerations for future research in the field of BCD.

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Abbreviations used in this paper: ISQ = implant stability quotient, AUC = area under the curve, RFA = resonance frequency analysis

Chapter 2.1

Three-year outcomes of a randomized controlled trial comparing a 4.5mm-wide to a 3.75mm-wide titanium implant for bone conduction hearing

I.J. Kruyt[1], R.C. Nelissen[1], E.A.M. Mylanus[1], M.K.S. Hol[1]

[1] Department of Otorhinolaryngology, Donders Center for Neurosciences, Radboud university medical centre, Nijmegen, The Netherlands

Abstract

Objective: To compare 3-year implant stability, survival, and tolerability of a 4.5mm-wide (test) and a 3.75mm-wide (control) percutaneous titanium implant for bone-conduction hearing, loaded with the sound processor after 3 weeks.

Methods: Sixty implants were allocated in a 2:1 ratio (test-control) in 57 adult patients included in this prospective randomized controlled clinical trial. Follow-up visits were performed at 7, 14, 21, and 28 days; 6 and 12 weeks; 6 months; and at 1, 2, and 3 years after implantation. During these visits, the Implant Stability Quotient (ISQ) was measured by means of resonance frequency analysis (RFA). The peri-abutment soft tissue status was assessed according to the Holgers classification. Skin height around the abutment was evaluated.

Results: The mean area-under-the-curve (AUC) of ISQ-low was statistically significantly higher for the test implant (65.7 versus 61.4, p=0.0002). Both implants showed high survival rates (97.4% versus 95.0% , p=0.6374). Adverse soft tissue reactions were observed sporadically, with no significant inter-group differences. Skin thickening was seen in the majority of the patients, but no correlation with adverse soft tissue reactions or implant type was observed.

Conclusion: The 4.5mm-wide implant provides significantly higher ISQ values during the first 3 years after surgery compared to the previous generation 3.75mm-wide implant. Both implants showed high survival rates and good tolerability. These long-term results indicate that the wider implant, loaded with a sound processor at 3 weeks, is a safe and well-performing option for hearing rehabilitation in specific types of hearing loss.

1. Introduction:

Since its introduction in 1977[1], the most frequently observed complications of percutaneous titanium implants for bone-conduction hearing are implant loss (1.6%-17.4%) and adverse soft tissue reactions (2.4-38.1%).[2, 3] Over the years, modifications in surgical technique and implant design have been made, aiming to reduce these complications.[4-7]

Based on improved outcomes of wider titanium implants seen in dental research[8], the design of titanium implants for bone-conduction devices has been modified as well. These wider implants have a diameter of 4.5mm compared to the 3.75mm-wide previous generation implants. This increase results in an enlarged contact area between implant and bone, resulting in a higher implant stability quotient (ISQ).[9, 10] It was also advocated that higher levels of initial stability allow for earlier loading of the implant with the sound processor, hence, starting hearing rehabilitation quicker. Loading titanium implants 3 weeks after surgery has been reported to be safe.[10-13]

The current randomized controlled clinical trial (RCT) investigated the 3-year outcomes of a 4.5mm-wide (test) implant in comparison to the previous generation 3.75mm-wide (control) implant on longer-term implant survival, ISQ, and soft tissue tolerability. This study is a continuation of the previously published study that presented clinical results with a follow-up period of 6 months.[11, 14] We studied the intra-subject ISQ-trends in order to gain additional understanding of how implant stability evolves over time. Finally, we assessed the long-term safety of loading both test and control implants at three weeks after implantation.

2. Materials & Methods

2.1. Patients and implants

Patients, indicated for a percutaneous bone conduction device in our tertiary referral centre, had to be at least 18 years of age, to have a bone thickness of at least 4 mm at the implant site, and to provide written informed consent to be eligible for inclusion. Exclusion criteria were as follows: a >6mm abutment needed; the inability to participate in follow-up visits or presumed doubt, for any reason, that the patient would not be able to attend all follow-up visits; a history of psychiatric diseases or mental disabilities; and the presence of diseases or a history of treatments known to compromise bone quality at the implant site (e.g., radiation therapy, osteoporosis, diabetes mellitus).

The test implant was the Wide Ponto implant (diameter 4.5mm, length 4mm) with a 6mm abutment, and the control implant was the previous generation Ponto implant (diameter 3.75mm, length 4mm) with an identical 6mm abutment. All implants and abutments are manufactured by Oticon Medical AB (Askim, Sweden).

The current study was performed in accordance with the guidelines established in the Declaration of Helsinki (Washington 2002), ISO 14155, Good Clinical Practice (International Conference on Harmonization Good Clinical Practice) and was approved by the local ethical committee (registration number 2011/497; NL nr.38556.091.11).

2.2. Study Design

The primary objective of this RCT was to demonstrate superiority in implant stability, measured in ISQ-low values, of the test implant compared to the control implant during 3-year follow-up.

The secondary objectives were to observe trends in ISQ over all visits and to compare ISQ-high values, implant survival, postoperative complications, and soft tissue tolerability.

A power calculation was conducted to determine the sample size based on the primary outcome parameter.[11] Based on data from a similarly designed study, [15] an expected difference of 4.5 in the mean area under the curve (AUC) of the ISQ-low values of the test and the control groups, with unequal standard deviations of 2.8 and 5.5, respectively, were used to determine the sample size. Due to unequal variance in the standard deviations, a 2-sided t-test with Satterthwaite's correction was performed. With a randomized implant allocation in a ratio of 2:1 (test:control), a total of 60 implants was needed to reach a statistical power of 90% (alpha = 0.05).

Randomization was realized by computer-generated random allocation, by means of numbered, sealed envelopes. Both investigator and patient were blinded until the actual implantation. Continuation of blinding was not feasible, because of observable differences in implant design. In our hospital, surgically placed implants are automatically recorded in the electronic patient file, which is also used for reporting during follow-up visits making post-operative blinding not feasible. Blinding of patients was also not feasible, because most patients were implanted under local anesthesia and could have overheard which type of implant was being installed.

All implants and abutments were placed in a single-stage surgical procedure, using the, in our clinic at that time standardly applied, linear incision technique with subcutaneous soft tissue reduction.[7] Surgery was performed between June 2012 and January 2014. Test and control implants were both loaded with the sound processor three weeks after surgery (range, 19-24 days).

Follow-up visits were scheduled at 7, 14, 21, and 28 days; 6 and 12 weeks; 6 months; and at 1, 2, and 3 years after implantation. During these visits, the ISQ was objectively measured by means of resonance frequency analysis (RFA), using a handheld Osstell® ISQ device (Ostell AB, Göteborg, Sweden) and a SmartPeg (type 55) attached to the abutment. Perpendicular measurements result in two values, where the lowest and highest values are recorded as an ISQ-low value and an ISQ-high value, respectively. Peri-abutment skin status was assessed according to the Holgers classification.[16] The skin height was evaluated in relation to the abutment (figure 1).

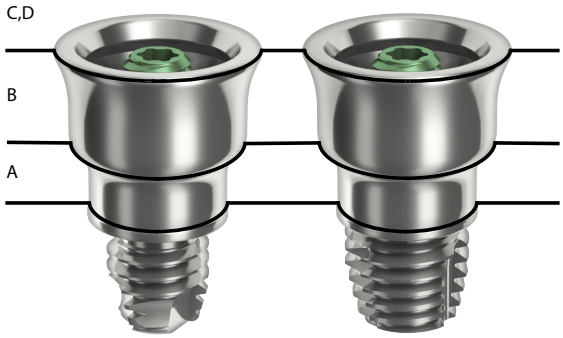

Figure 1. Skin height in relation to the abutment of the test implant (right) and control implant (left). A: Skin remains under the shoulder of the abutment; B: skin reaches between shoulder and rim of the abutment; C: skin is partially overgrowing the rim of the abutment; D: complete skin overgrowth of the abutment.

2.3. Data analysis

Data management and statistical analysis were executed according to a predefined statistical analysis plan, and were performed by independent external data managers and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden).

For comparisons between the test and control group, Mann–Whitney U tests were used for all continuous variables, Mantel–Haenszel chi-square tests were used for all ordered categorical variables, Fisher's exact test was used for all dichotomous variables, and chi-square tests were used for all non-ordered categorical variables. Repeated measures analyses were done for changes over time. The Wilcoxon signed rank tests were used for continuous variables, and sign tests were used for order categorical variables and dichotomous variables. Groups were compared according to the intention-to-treat principle. In case subjects were lost to follow-up, the last-observation-carried-forward method was used for ISQ measurements in the AUC calculations. Bilaterally implanted patients who received both a control and a test implant were included in both analyses for implant variables. Patients who received 2 test or 2 control implants were represented by the mean of the 2 measurements for continuous variables or the worst value for categorical variables. For patient variables, bilaterally implanted patients who received both control and test implants were included in descriptive statistics but excluded in analyses on the patient level.

All tests were two-tailed and conducted at 0.05 significance level. All analyses were performed using SAS® v9.4(Cary, NC).

3. Results

3.1. Patients

A total of 60 implants were consecutively placed in 57 patients. Three patients were implanted bilaterally in a single session; one of these patients received two test implants, and two patients received both a test and a control implant. Hence, in the analysis, the test group consisted of 39 implants and the control group consisted of 20 implants.[14] All patients received their allocated treatment. No major perioperative complications were observed. Demographics and baseline characteristics are summarized in table 1 and showed no statistically significant differences.[14]

Two patients were withdrawn from the study. The first patient lost the implant spontaneously (control implant) after 31 months. The second patient had the implant (test implant) electively removed in another hospital after 24 months due to severe tinnitus, which was thought to improve by performing a stapedotomy and afterwards fitting a normal air-conduction hearing aid.

Five follow-up visits, in five different patients, were missed or performed outside the defined visit window.

Table 1. Baseline characteristics

Variable	4.5mm implant group (n=39)	3.75mm implant group (n=20)	p-value
Gender			
Male	15 (38.5%)	9 (45.0%)	
Female	24 (61.5%)	11 (55.0%)	0.86
Age	53.7 (SD 12.0; range, 23.0; 83.0)	53.0 (SD 16.4; range, 19.0; 74.0)	0.50
Smoking	6 (15.4%)	6 (30.0%)	0.28
Type of hearing loss			
Acquired cond./mixed	26 (66.7%)	16 (80.0%)	0.37
Congenital conductive	1 (2.6%)	1 (5.0%)	1.00
Single sided deafness	13 (33.3%)	3 (15.0%)	0.27
Bilateral	3 (7.7%)	2 (10.0%)	1.00
Number of implants			
Single implant	36 (92.3%)	18 (90.0%)	
Two identical implants	1 (2.6%)	0 (0.0%)	
Two different implants	2 (5.1%)	2 (10.0%)	1.00

3.2. Implant stability quotient

The mean AUC for ISQ-low was 65.7 (SD 3.4; range 54.3-71.3) for the test implant (n=39) and 61.4 (SD 4.2; range 51.4-67.6) for the control implants (n=20). The inter-group difference of 4.32 ISQ-low points (range 2.28-6.35; p=0.0002) was statistically significant. The mean AUC for ISQ-high over the same period was 67.0 (SD 3.3; range 56.9-72.8) for the test implant (n=39) and 63.7 (SD 4.6; range 52.5-70.8) for the control implants (n=20). The inter-group difference of 3.29 ISQ-high points (range 1.22-5.35; p=0.006) was also statistically significant. Both results are displayed in figure 2A&B. The mean increase in ISQ-low from baseline is statistically significant for both groups during all follow-up visits. For the test implant, however, both ISQ-low and high increased statistically significantly more from baseline than for the control implant, but only during the first six months. During the 12-36 months visits, no ISQ-low and high inter-group differences in change between baseline were observed. When analyzing ISQ-trends, both implants showed increasing ISQ values up to 12 months, followed by period in which the ISQ remained stable until 2 years after surgery. Between the 2-year and 3-year visit, however, a statistically significant decrease was observed in the test group for both ISQ-high (0.72 ISQ-points, p=0.013) and low (0.78 ISQ-points, p=0.032). In the control group, no statistically significant decrease was observed in ISQ-low.

3.3. Implant survival

No statistically significant difference in 3-year implant survival was observed (test 97.4% versus control 95.0%)., One implant was electively removed in the test group, and one spontaneous implant failure was reported in the control group, 31 months after surgery. The loss occurred in a 21-year-old woman, a week after visiting our clinic because of progressive pain around the implant for months without signs of skin infection during any of her visits (Holgers 0).

3.4. Soft tissue tolerability and complications

Three patients needed revision surgery of the soft tissue surrounding the implant; 2 in the test group (5.1%) and 1 in the control group (5.0%). Two patients presented with thickened skin around the abutment resulting in persistent, unsolvable feedback issues six weeks, respectively 9 months after surgery. The third patient (control), who suffered from psoriasis, presented with insufficient skin healing after 28 days.

Figure 3 presents an overview of soft tissue reactions per visit. Across all visits, Holgers grade 0 was observed in 84.5% (test) and 84.8% (control) of the visits; Holgers grade 1 in 14.0% (test) and 12.3% (control) of the visits; Holgers grade 2 in 1.5% (test) and 2.4% (control) of the visits; Holgers grade 3 in 0.0% (test) and 0.5% (control); and no Holgers grade 4 were observed during any of the visits. Adverse skin reactions (Holgers grade 2-4) were observed in 15.4% of the test implants and in 20% of the control implants. Neither these differences nor the analysis of other postoperative complications showed significant

differences between implants: bleeding or hematoma in 2.6% (test) versus 4.9% (control); pain or numbness in 15.4% (test) versus 15.0% (control); and skin dehiscence in 7.7% (test) versus 10% (control).

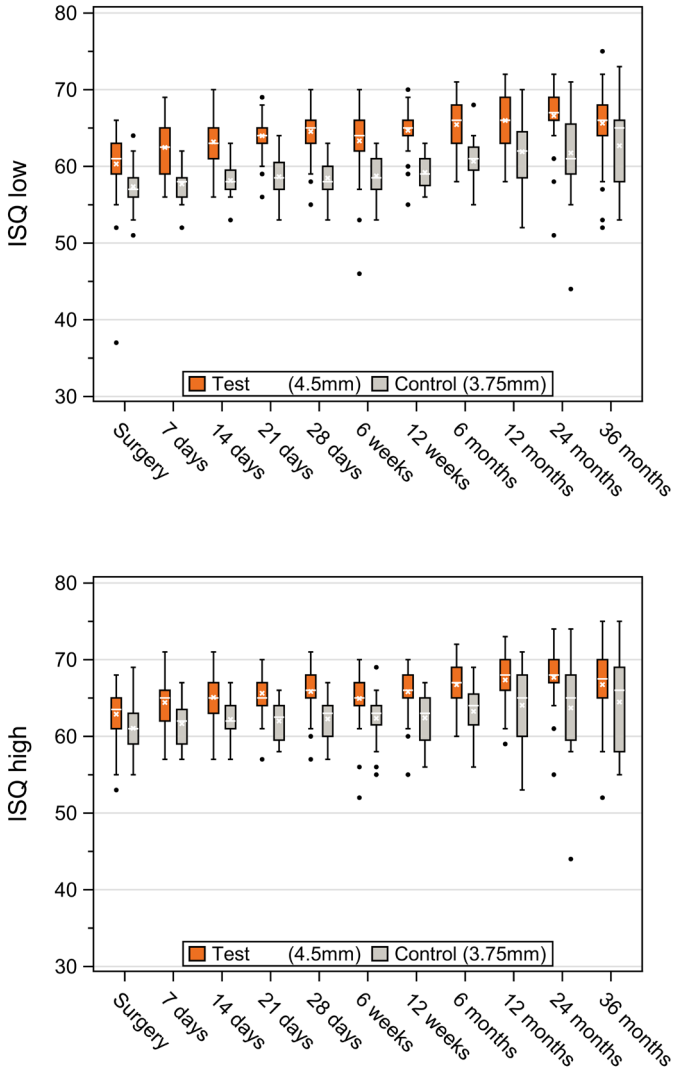

Figure 2. A. Box-and-whisker plots of ISQ-low per implant (left); B. Box-and-whisker plots of ISQ-high values per implant (right)

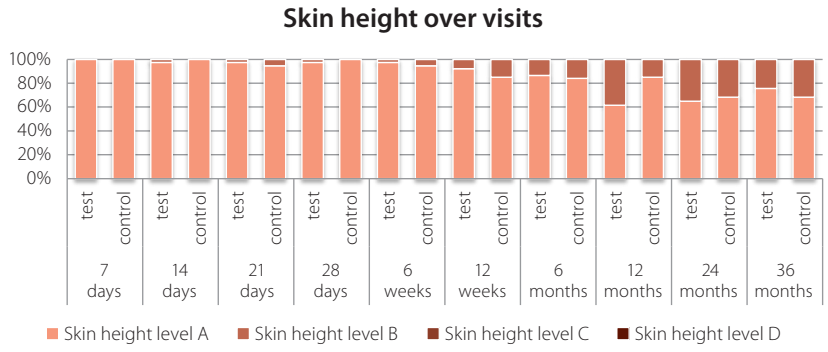

Figure 3. Skin height per implant across visits

Neither skin height during any of the follow-up visits, nor the maximum skin level across visits differed between groups (figure 4). However, in 55.9% of the implants (22 test implants and 11 control implants), skin height increased over time. No skin height levels C or D were observed. No difference in skin height was observed in patients who suffered from adverse skin reactions (Holgers grade 2-4) compared to those without adverse skin reactions.

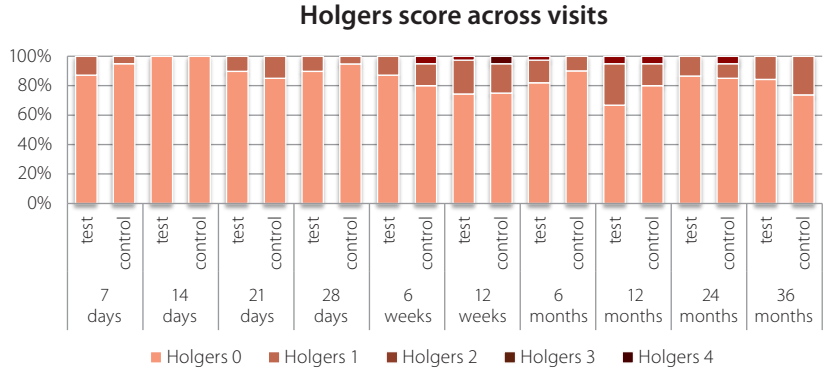

Figure 4. Holgers score per implant across visits

4. Discussion

The current study, a continuation of a previously published 6-month report[11], is the first RCT comparing long-term outcomes of this specific wide diameter percutaneous bone-anchored hearing implant to the previous generation implant, both loaded with the sound processor at three weeks after surgery. These long-term outcomes encompassed implant stability and survival, ISQ-trend, and complications.

The current study has shown that during all visits, significantly higher ISQ-values were recorded for the test implant compared to the control implant. However, no differences in implant survival or soft tissue reactions were observed between implants. These outcomes confirm data from previous studies showing that wider diameter implants have significantly higher ISQ values, suggesting a higher implant stability. Therefore, earlier loading, i.e. after 3 weeks, could be advocated safe, as it does not influence survival rates of both implants.[11, 13]

Despite the extensive use of ISQ measurements in research, clinical and therapeutic consequences of absolute values are yet to be determined. For instance, a minimum ISQ-value to safely start loading the implant is lacking[17], although McLarnon et al.[18] adhered to a minimum of 60 ISQ points to safely load another wide-diameter implant, resulting in no spontaneous implant losses in the 4-month follow-up. However, ISQ itself is not a measurement of osseointegration, since multiple other factors - e.g. geometry of the implant and abutment, bone quality, and SmartPeg type - influence ISQ. This attributes to the difficulty of interpreting absolute ISQ values.[17, 19] Most of these factors were kept identical in both our study groups and remained unchanged during follow-up. Therefore, differences in mean absolute ISQ values for the groups as a whole could be attributed to the primary, or mechanical, stability and osseointegration of the implant itself.

In the test group a minor decrease in ISQ was observed at the last follow-up, without clinically observed instability. Interestingly, a decreasing ISQ was also observed in two studies assessing a different wide-diameter implant. In the first study, the decrease occurred two years after surgery, but was overcome a year later.[13] In the second study, a decrease occurred at the 3-year follow-up, but was also overcome at the 5-year visit.[9, 20] The dips were also minor and have not corresponded to clinically observed instability or implant loss. Thus, the clinical implication of the decrease in this study is to be determined by extending the follow-up of our patients.

With only one implant failure observed in each study group, the survival of both implants in this study was high at 97.4% (test) and 95.0% (control), respectively; moreover, only the implant failure reported in the control group occurred spontaneously, a week after an extra visit for pain around the implant progressing for months. Interestingly, the mean ISQ of this specific patient gradually decreased from 59 (at surgery) to 44 (2-year follow-up), after which the implant was lost. Remarkably, this decreasing ISQ was observed without clinical signs of instability or skin infection. Nevertheless, no correlations between

ISQ and implant loss could be made due to limited number of implant losses. Noticeably, during the physical examination at this subjects' last follow-up visit, manipulation of the abutment (tightening of or tapping on the abutment) resulted in significant increase of pain. These symptoms might suggest peri-implantitis, which is reported in dental implant literature.[21] To our best knowledge, no report of peri-implantitis in bone-anchored hearing implants has been published. However, we did not assess whether loss of supporting marginal bone, defining peri-implantitis, was present in this patient. In addition, the biological mechanisms involved in late implant failures are obscure, particularly in the field of bone-anchored hearing implants. Future research is needed to unravel these mechanisms.

The implant loss rates of the test implant have previously been assessed by 4 prospective case studies with 1-year follow-up. Two studies used similar surgical techniques as in this study, while the two other studies used a tissue preservation technique. In none of the four studies, implant loss was observed.[10, 12, 22, 23] These are relatively short-term results; however more than 50% of implant failures generally occur during the first year after surgery.[2] These previous studies, therefore, cover this critical period.

The current study is the first RCT comparing the previous generation implant with the wide-diameter implant after 3 years of follow-up. Therefore, only studies assessing another wide-diameter implant with similar follow-up length can be used for comparison. This implant differs from our wide-diameter test implant by also having a moderately roughened surface and different abutment design. Two prospective studies reported equally high 3-year implant survival of 96.2% and 97% for these implants.[9, 13] It can be thus be concluded that the new generation wide-diameter implants show excellent implant survival.

The loading of both implants at three weeks after surgery seemed safe, as ISQ-trends increased, and few implant losses were observed. Similar results with another wide-diameter implant have also been reported with loading times of 1 week[24], 2 weeks[25], and 3 weeks[12, 13], confirming the safety of earlier loading with the sound processor.

Adverse skin reactions (Holgers ≥2) were observed sporadically and were equally distributed over both groups. This was expected since the implant diameter is not believed to significantly influence skin outcomes; It has previously been reported that the abutment shape, the angle between skin and abutment and the used surgical technique, together with personal characteristics (as hygiene, skin type, skin disease and age) do influence these skin outcomes to a certain extent. The current set-up of the study is unique, since the only parameter changed is the diameter of the implant. The abutment itself is identical in both groups. All adverse skin reactions were successfully treated with a topical antibiotic/steroid ointment.

Other studies found similar low adverse skin reaction rates observed in patients with the same test implant. Foghsgaard et al.[10] and Wazen et al.[12] observed adverse skin reactions in 2.6%, respectively 0.6% of the visits with a follow-up of 1 year. Mowinckel et

al.[22] and Hultcrantz[23] reported adverse skin reactions in 8%, respectively 2.5% of the visits with a follow-up of 1 year. In addition, Den Besten et al.[26] reported adverse skin reactions in 7.5% of the visits with a 6-month follow-up. However, in these three studies a different soft tissue handling technique was applied during surgery, i.e., soft tissue preservation instead of soft tissue reduction technique in current study.[22, 23, 26] Two other studies using a different wide-diameter implant reported equally low adverse skin reaction rates of 1.8% and 0.9% after three years.[9, 13] It can be thus be concluded that the soft tissue tolerability of the new generation wide-diameter implants and abutments in combination with the applied surgical technique, personal characteristics and after care is excellent.

As mentioned above, in many hospitals the tissue reduction technique has been replaced by the tissue preservation technique, due to shorter surgery time, cosmetic advantages, less numbness around the abutment, and similar or less skin complications.[27] However, a single study also suggest a higher rate of adverse skin reactions for the tissue preservation technique in the first six months.[26] Interestingly, when looking across the first 12 months follow-up in the same study, there was no longer any significant difference in adverse skin reactions between these techniques (unpublished data). Three-year data will be available soon. This underlines the need for long-term comparative research to evaluate evolvements in surgical techniques.

To our best knowledge, this is the first study analyzing skin height after bone-anchored hearing implantation. Two patients underwent revision surgery for persisting, unsolvable feedback issues due to thickened skin touching the snap coupling, without partial overgrowth (skin height level B). Normally, we would have switched to a longer abutment. However, changing abutment length would have influenced ISQ data (our primary outcome) significantly. We therefore preferred skin revision. Both patients were informed and consented with revision surgery. Independent of the implant type used, skin thickened around the fixture in 55.9% of the patients. All patients have been operated using the linear incision with tissue reduction.[7] Interestingly, skin thickening was only sporadically observed in the first six weeks (<4%), in 10% of the implants after 12 weeks, in 14% after 6 months, but it was observed around 27-34% of the implants after 12-36 months. No correlation with adverse skin reactions was observed. It could be possible that thickening of the skin reflects the restoration of normal soft tissue after soft tissue reduction performed during surgery. It could also be the result of more active immunological mechanisms to compensate for the continuous breach in the mechanical defensive barrier of the skin implied by the skin-penetrating implant, regardless of surgical technique.[28] In this light, the first 6-month evaluation of tissue preservation surgery versus tissue reduction surgery with this test implant reported no difference in skin height between groups.[26] As previously discussed, however, most skin thickening in current study was observed after 6 months follow-up. Future, long-term research is, therefore, needed to investigate whether skin thickening differs between soft tissue reduction and tissue preservation surgery for bone-anchored hearing implantation. Nevertheless,

the introduction of longer abutments in the past years will help to overcome possible problems with skin height.[29]

The results of the current study are considered to reliably reflect clinical outcomes of both implants, due to the study design and data quality. The study design included a large population with adequate statistical power over a long-term follow-up period, only differing a single parameter between groups, i.e., implant design. Data quality is very high, with no patients lost-to-follow-up (except withdrawn patients) and 5 visits outside the predefined visit window. However, the non-blinded follow-up is a limitation, but a common trait of most implant studies. As discussed in the method section, continuation of blinding was not feasible, because of observable differences in implant design during surgery.

5. Conclusion

In patients operated with the linear incision and soft tissue reduction technique, the 4.5mm-wide test implant provides significantly a higher implant stability quotient (ISQ) compared to the previous generation 3.75mm-wide implant after 3-year follow-up. Both test and control implant showed excellent survival rates. Adverse soft tissue reactions occurred sporadically, with no significant inter-group differences. Skin thickening occurred in the majority of the patients in both groups, but did not correlate with adverse soft tissue reactions. These long-term results of this prospective RCT indicate that the wide-diameter implant, for hearing rehabilitation in specific types of hearing loss, loaded with a sound processor at 3 weeks, is a safe and well-performing.

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Chapter 2.2

Clinical evaluation of a new laser-ablated titanium implant for bone-anchored hearing in 34 patients: 1 year experience

I.J. Kruyt[1], R.Banga[2], A.Banerjee[3], E.A.M. Mylanus[1], M.K.S. Hol[1]

[1] Department of Otorhinolaryngology, Donders Center for Neurosciences, Radboud university medical centre, Nijmegen, The Netherlands
[2] Department of Otorhinolaryngology, Queen Elizabeth Hospital, Birmingham, United Kingdom
[3] Department of Otorhinolaryngology, James Cook University Hospital, Middlesbrough, United Kingdom

Key points

- In specific patient groups, i.e. children or patients with compromised bone quality, the incidence of implant loss of for bone conduction hearing implants is much higher; further implant optimization is, therefore, needed.
- The new laser-ablated titanium implant for bone-anchored hearing implantation has an enlarged contact area for osseointegration compared to the standard implant, aiming to improve implant loss rates.
- This retrospective multicenter study is the first to assess the performance of this implant in healthy adults 1 year after surgery.
- With excellent survival rates, good soft tissue tolerability, and few complications, the implant is safe to use in healthy adults.

1. Introduction

Successful bone-anchored hearing implantation requires good osseointegration of the titanium implant in the temporal bone and low skin-related complication rates. The introduction of wider diameter implants, providing an enlarged bone-implant interface and thus a larger interface for osseointegration, have resulted in up to three-year survival rates of >96% in healthy adult patients.[1-3] Despite the low incidence of implant loss in healthy adults, in certain patient groups, i.e. patients with compromised bone quality or in children, the incidence is much higher, varying between 3.5-10.5% even with these wider diameter implants.[4-6] To improve implant survival in these populations as well, further optimization of implant material, design, and surgical technique remains needed.

Based on dental research, modifications of the implant surface, e.g. physical topography and chemical properties, could play a pivotal role in further optimizing the integration in the recipient's bone.[7] As such, a new implant for bone conduction hearing was developed in 2015. This implant is, in contrast to currently used implants, selectively laser-ablated within the thread valley. Combined with modified chemical properties, this has shown improved biomechanical anchorage in pre-clinical animal testing.[8] In our clinical practice, before this implant is tested in patients with a higher risk of implant loss, it first has to be proven effective to use in healthy adults. This study, therefore, assesses retrospectively the performance of the new laser-ablated implant by reviewing implant survival, stability, and soft tissue tolerability in healthy adults one year after surgery.

2. Methods

2.1. Ethical considerations

The ethics committee has passed a positive judgment on the study.

2.2. Study population

The study was designed as a retrospective chart review approximately 1 year after implantation of patients who previously participated in a completed 4-week controlled market release (CMR) testing conducted at Radboudumc (Nijmegen, The Netherlands), Queen Elizabeth University Hospital (Birmingham, England), and James Cook University Hospital (Middlesbrough, England). In these centres, patients eligible for bone-anchored hearing implantation test all available hearing restoration options in daily life situations to determine which system they prefer. Patients preferring the Ponto system were then asked whether they would like to participate in a CMR-testing of the new laser-ablated implant.

To be included in the CMR-testing, patients had to be ≥18 years old and have no disease or treatment known to compromise the bone quality at the implant site. Exclusion

criteria included inability to follow investigational procedure and any factor, at the discretion of the investigator, that was considered to contraindicate participation. As such, 34 healthy adult patients consented and received the laser-ablated implant between September 2015 and January 2016. In all patients a single-stage surgical procedure using a linear incision technique was performed under either local or general anaesthesia. Subcutaneous soft tissue reduction during surgery was applied in one hospital, whilst subcutaneous soft tissue was preserved in the other two hospitals.

2.3. Implant

The implant used was the wide Ponto BHX implant (diameter, 4.5mm; length, 3 or 4mm) (Oticon Medical AB Askim, Sweden). This implant is, in contrast to traditional Brånemark type machined titanium implant surface, selectively laser-ablated within the thread valley to produce a microtopography with a superimposed nanotexture and a thickened surface oxide layer. Premounted Ponto abutments of lengths 6, 9, and 12mm were used, in case of tissue preservation depending on skin thickness measured during surgery.

2.4. Follow-up evaluations and outcomes

Standard follow-up visits were performed 1 week, 4-6 weeks, and approximately 1 year after implantation. An additional standard 3-month visit was performed in one of the 3 participating hospitals. Implant survival and the degree of adverse skin reactions, according to the Holgers scale[9], were noted at each visit. Holgers ≥2 were considered as adverse skin reactions, in which medical treatment was needed. Extra visits, revision surgery, and, if available, stability over time measured as Implant Stability Quotient (ISQ) were also noted. ISQ was assessed using resonance frequency analysis (RFA) at abutment level, using the Osstell ISQ and a SmartPeg (type 55) (Osstell AB, Göteborg, Sweden).[10] The highest and lowest value obtained from perpendicular measurements were recorded.

2.5. Statistical Analyses

All data was analyzed using Descriptive Statistics in the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp), version 22.0. For continuous variables means and ranges are reported; for dichotomous variables frequencies are reported. For comparison over time, the Wilcoxon signed rank test was used for continuous variables. A significance level of 0.05 was adopted.

3. Results

All 34 subjects were eligible for review. However, in three patients the last visit was performed by phone due to travelling issues. For these visits, only implant survival data were used in the analysis. Demographics and baseline characteristics are summarized in table 1. Only one patient needed a 3mm implant due to insufficient bone thickness for placing a 4mm implant and did not experienced complications during the follow-up. In the entire cohort, no major perioperative complications were observed. The median clinical follow-up was 15 months (range: 7-17 months); only one patients had less than 12 months of follow-up.

In this one patient, a spontaneous implant loss occurred three months after surgery, but the patient did not present until almost 5 months after the event. No clinical signs of infection were reported to be present prior to the implant loss. The patient was re-implanted shortly after, outside this study. Data from the patient up to the moment of implant loss were included in the analysis. For the entire cohort, a median 15-month

Table 1. Demographics and baseline characteristics (N = 34)

Parameter	Number (%)
Gender:	
Male	16 (47.1%)
Female	18 (52.9%)
Age group:	
18-49 years	11 (32.4%)
50-74 years	17 (50.0%)
>75 years	6 (17.6%)
Hospital:	
Radboudumc	14 (41.2%)
James Cook University hospital	10 (29.4%)
Queen Elizabeth University hospital	10 (29.4%)
Surgical technique:	
Tissue reduction	14 (41.2%)
Tissue preservation	20 (58.8%)
Implant length	
3mm	1(2.9%)
4mm	33 (97.1%)
Abutment length:	
6mm	6 (17.6%)
9mm	21 (61.8%)
12mm	7 (20.6%)

implant survival of 97% was observed. Another patient spontaneously lost an abutment after three months, whilst being abroad. On the patient's return, the skin had grown over the remaining implant necessitating a skin punch to reinsert a new abutment. No other skin revision surgery was performed.

Figure 1 presents an overview of soft tissue reactions per visit. Overall, Holgers grade 0 was observed in 72.4% of the visits; Holgers grade 1 in 23.3% of the visits; Holgers grade 2 in 3.4% of the visits; Holgers grade 3 in 0.1%. No Holgers grade 4 was observed. During follow-up, an adverse skin reaction (Holgers grade 2-4) was observed in 4 (8.8%) subjects. Interestingly, all events were observed in the tissue preservation group. All have been successfully treated with locally applied medication.

Pain was reported by 9 subjects (27%) during any of the visits. In 2 patients, this was reported at the first visit one week after surgery without signs of infection and was resolved at the second visit. In 5 other patients, pain was reported combined with certain signs of infection (Holgers >0), but was resolved at the next visit. The last two patients reported pain at the latest visit without any signs of infection (Holgers=0). Numbness was also reported by 9 subjects (27%) during any of the visits. In 8 patients, it resolved during the follow-up; the other patient reported numbness at the latest visit, however without

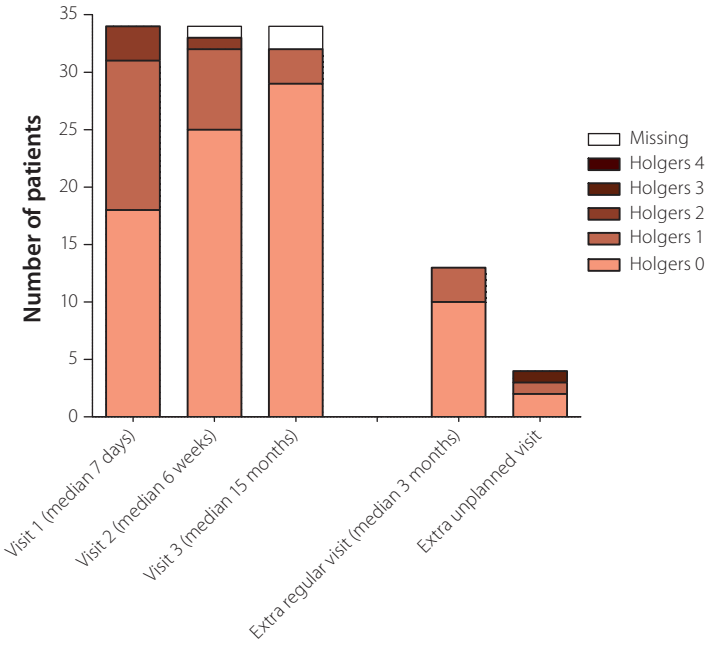

Figure 1. Holgers' score per visit. The median follow-up for each visit (entire cohort) is stated in the round brackets. Missing data was caused by visits performed by phone or implant loss prior to visit.

prior reported numbness. The presence of pain and numbness were independent of surgical techniques being used, i.e. tissue reduction or preservation.

ISQ was measured in two hospitals, resulting in 23 patients with complete ISQ-data. ISQ over time can be observed in figure 2. Overall, a significant decrease of 3.4 ISQ-Low points was observed at the first visit compared to at surgery. ISQ-low significantly increased thereafter until the last visit. At this visit, ISQ-low surpassed per-operative values by a significant 2.1 points. No clinical instability was observed during the ISQ-dip.

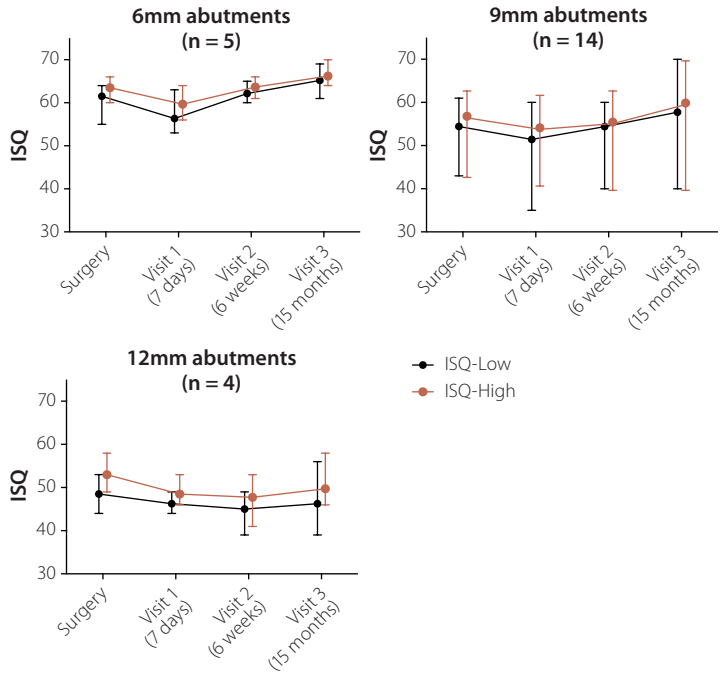

Figure 2. ISQ-low & -high over time per abutment length. The median follow-up for each visit (entire cohort) is stated in the round brackets.

4. Discussion

4.1. Synopsis of key/new findings & strengths of the study

The current study is the first to report clinical outcomes and performance data – i.e. implant survival, ISQ, soft tissue tolerability, and other complications – of the new laser-ablated titanium wide diameter implant for bone-conduction hearing. With only one spontaneous implant loss, the laser-ablated implant displays an excellent (median) 15-month implant survival in this patient group. The soft tissue tolerability is good with

only few adverse skin reactions observed. Due to this population size, the multicenter nature of the study, and no loss-to-follow-up outcomes can be considered reliable.

4.2. Comparisons with other studies

Implant survival and soft tissue tolerability seem comparable to the standard wide-diameter implants used in healthy adults. [1-3] However, due to the retrospective, multi-center nature of this study, using multiple surgical techniques, caution is needed in drawing conclusions especially regarding soft tissue tolerability.

The use of ISQ to measure osseointegration has been discussed extensively and remains questionable.[10] If we compare 1-year ISQ of the 5 patients in this cohort with a 6mm abutment to patients with the standard wide-diameter implant and identical 6mm abutment, using the same surgical technique, no differences seem present (66.0 versus 66.0).[Kruyt et al. submitted at O&N, under review] This was also found in pre-clinical animal testing of this implant, however, removal torque measurements showed a 153% higher biomechanical anchorage of the laser-modified implants.[8] This underlines that ISQ might not reliably reflect actual osseointegration, and that this implant might be beneficial for using in high-risk patients.

4.3. Clinical applicability of the study

Despite these excellent results in terms of survival, prospective, long-term comparative research, using only one surgical technique, is needed to determine clinical usefulness of this implant. In addition, incremental cost-effectiveness has to be assessed, since the (head)room for improving implant survival compared to the standard wide-diameter implants seems to be limited. However, more headroom is present in high-risk patient groups. The current (retrospective) study does suggest that this implant is safe to use in healthy adults. Based on these outcomes, in our clinical practice we believe it justified to test this implant in higher-risk patients and concomitantly assess the possible additional benefit in this specific patient group.

5. Conclusion

The new laser-ablated titanium implant for bone-anchored hearing implantation showed excellent survival rates and soft tissue tolerability, with few complications. These results indicate that the new implant is safe to use in healthy adults.

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Abbreviations used in this paper: ISQ = implant stability quotient, AUC = area under the curve, RFA = resonance frequency analysis, BC = bone conduction, BCD = bone conduction device, SD = standard deviation

Chapter 3

Three-year clinical and audiological outcomes of percutaneous implants for bone conduction devices: comparison between tissue preservation technique and tissue reduction technique

I.J. Kruyt[1], H. Kok[1], A.J. Bosman[1], R.C. Nelissen[1], E.A.M. Mylanus[1], M.K.S. Hol[1]

[1] Department of Otorhinolaryngology, Donders Center for Neurosciences, Radboud university medical centre, Nijmegen, The Netherlands

Abstract

Objective(s): To evaluate the three-year clinical and audiological outcomes of soft-tissue preservation compared to soft-tissue reduction in linear incision surgery for percutaneous implant for bone conduction devices.

Methods: Twenty-five patients (25 implants) were enrolled in a prospective cohort for implant surgery with linear incision and tissue preservation. The control-group consisted of 25 patients (25 implants) from a previous randomized controlled trial in which a linear incision with soft-tissue reduction was applied. Follow-up visits were scheduled at 7 and 21 days (fitting of sound processor); 12 weeks; 6 months; and at 1, 2, and 3 years after implantation. Main outcome measures were skin sensibility, soft-tissue status, Implant Stability Quotient (ISQ), skin height, implant survival, revision surgery, scar assessment, and hearing thresholds (BC in-situ between 250Hz-8kHz with BCD on testband & abutment, and BC thresholds at 250Hz-4kHz with a B71 boneconductor).

Results: Tissue preservation resulted in superior sensibility (mean percentage correct responses 99.7% [SD 1.7] versus 92.0% [SD 9.2], p=0.0001). No spontaneous implant loss occurred in either group. The abutment was removed in two test and in one control patient. Two control patients needed skin revision surgery. Although not statistically significant, more adverse soft-tissue reactions (Holgers ≥2) were observed in the test-group (n=9 [36%] versus n=3 [12%], p=0.095). ISQ increased significantly more in the test group compared to the control group (7.64 [SD 4.05] versus 4.29 [SD 3.93]). Skin thickening, scar assessment, and hearing outcomes were comparable.

Conclusion: Tissue preservation demonstrated superior skin sensibility compared to tissue reduction while other clinical outcomes were comparably excellent.

1. Introduction

Over the last decades, the surgical technique for inserting percutaneous titanium implants in the temporal bone, onto which bone conduction devices (BCDs) can be coupled, has evolved, driven by the aim to reduce post-operative complications, e.g. adverse skin reactions and implant loss. Until 2011, surgical implantation was always combined with peri-implant soft-tissue reduction, called skin-thinning. The rationale behind skin-thinning was that by reducing the skin mobility around the implant, the risk of inflammation and implant loss is reduced, and skin overgrowing the abutment is avoided.[1-3] At the same time, however, skin-thinning inflicts more surgical trauma and compromises both blood flow, thus hampering an optimal immune response during an infection, and neural structures around the implant, causing numbness.[4] In addition, skin-thinning prolongs the surgical procedure. In the past, different incision techniques with skin-thinning have been described, such as the U-shaped flap, dermatome, and linear incision technique.[5-7] Although several studies indicate the linear incision to be superior regarding clinical outcomes,[8, 9] adverse skin reactions, osseointegration failure, and the need for skin revision surgery still occur.[10]

In 2011, after the introduction of wider diameter implants and longer abutments, Hultcrantz described a modified linear incision technique without soft-tissue reduction. By preserving the soft-tissue, hence inflicting less surgical trauma, it was hypothesized that this technique would result in less scar tissue formation and numbness, cosmetic advantages, shorter surgery times, faster wound healing, and possibly fewer skin infections.[11] A recent systematic review concluded that surgical techniques with soft tissue preservation indeed have limited postoperative skin complication rates and require less surgical time compared to the skin-thinning techniques. However, because different surgical techniques were used in most comparative studies, no conclusions could be drawn on which technique, i.e. skin preservation or skin reduction, is superior.[12] The current study, a continuation of the previously published 6-month follow-up study, wherein short term and other data, such as surgery duration, is reported,[13] investigated the 3-year clinical and audiological outcomes of the linear incision surgical technique with soft-tissue preservation compared to soft-tissue reduction.

2. Materials & Methods

2.1. Ethical considerations

The current study was performed in accordance with the guidelines established in the Declaration of Helsinki (Washington 2002, ISO 14155), Good Clinical Practice (International Conference on Harmonization Good Clinical Practice), and was approved by the local ethical committee. The current study was registered as NCT02064478 at www.Clinical-Trials.gov.

2.2. Study design & patients

The current study was designed as a prospective clinical trial on soft-tissue preservation in implant surgery for BCDs (test population) compared to a historical control population in which soft-tissue reduction was performed. To be eligible for participation, patients indicated for a percutaneous BCD in our tertiary referral centre had to be ≥18 years and provide written informed consent. Exclusion criteria were (i.) bone thickness of <4mm at the implant site; (ii.) skin thickness of >10mm; (iii.) inability to participate in follow-up visits; (iv.) history of psychiatric diseases or mental disabilities; and (v.) having a disease or treatment known to compromise bone quality at the implant site (e.g., diabetes mellitus, radiation therapy, osteoporosis). These eligibility criteria were identical for test and control group, except for the exclusion criteria skin thickness of >10mm (in the test group) and the need for >6mm abutment (in the control group).

The primary outcome of this study, skin sensibility around the implant, was used as an outcome in a study on these implants for the first time, therefore, no data was available for statistical sample size calculations. Sample size was instead determined pragmatically by the investigators' experience, as well as on practical feasibility. Twenty-five patients consented and were consecutively included in the test group between February and September 2014. The historical control group consisted of the last 25 patients (having received 25 implants) of a previously published randomized controlled clinical study implanted between March 2013 and January 2014. These patients received the same implant, placed using the same incision technique, but with soft-tissue reduction instead of tissue preservation.[14] Two senior surgeons (EM & MH) performed all surgeries in both groups.

2.3. Surgical techniques, implants, and follow-up

The same type of Wide Ponto implant (diameter 4.5mm, length 4mm) with selected abutment was placed in a single-staged surgical procedure using a standard linear incision technique, with either soft-tissue preservation (test), as originally described by Hultcrantz[11], or soft-tissue reduction (control), as described by De Wolf et al.[7] In the test-group, abutment length was determined based on skin thickness measured at the start of surgery before injection of local anesthetics (0.5-3mm skin thickness = 6mm abutment; 3-6mm = 9mm; 6-10mm = 12mm). In the control group, all patients underwent soft-tissue reduction with placement of a 6mm abutment.[14] All implants and abutments were developed by Oticon Medical AB (Askim, Sweden).

Follow-up visits in test group were scheduled at 7 and 21 days (fitting of sound processor); 12 weeks; 6 months; and at 1, 2, and 3 years after implantation. Follow-up visits in the control group were scheduled at identical time points, with additional visits at 14 and 28 days, and 6 weeks. Additional assessments, intended for the current study, were included at the 12-month follow-up visit and onward for control patients.

2.4. Outcome measures

The primary objective of this study was to compare skin sensibility around the abutment in the test group compared to the control group. Sensibility was determined at 6 standardized locations (figure 1A) using a broken wooden cotton swab to determine gnostic (cotton side) and vital (sharp wooden side) sensibility and was reported as a percentage of correct answers. In addition, subjective numbness was measured on a Visual Analogue Scale (VAS) – from 0 (no numbness) to 10 (complete numbness) – and by the patient reported diameter (centimeters) of the numb area.

The secondary objectives were to investigate implant stability over time (measured as Implant Stability Quotient, ISQ) and to compare soft-tissue tolerability, skin height, implant survival, the need for revision surgery, and scar assessment. ISQ was objectively measured by means of resonance frequency analysis (RFA), using a handheld Osstell® ISQ device (Ostell AB, Göteborg, Sweden) and a SmartPeg (type 55) attached to the abutment. Perpendicular measurements result in two values, recorded as an ISQ-low value and an ISQ-high value, respectively. Soft-tissue tolerability was assessed according to the Holgers' classification[15], in which a Holgers grade 2 or higher was considered an adverse skin reaction. Skin height was evaluated in relation to the abutment (figure 1B). Scar assessment was performed by means of the Patient and Observer Scar Assessment Scale (POSAS) v2.0.[16] The POSAS consists of a patient and an observer scale, containing six categories

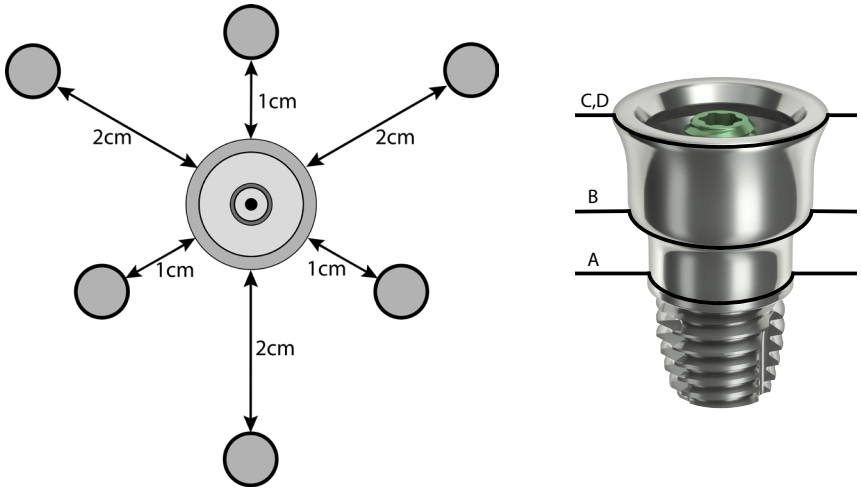

Figure 1. A, Sensibility test locations: at all locations both vital (broken, sharp wooden side) and gnostic (cotton side of wooden cotton swab) sensibility were tested in a random fashion (left). B, Skin height relative to abutment (A - under the shoulder of the abutment; B - above the shoulder of the abutment; C - partial overgrowth; D - complete overgrowth) (right).

with response options from 1 (normal skin) to 10 (worst imaginable). The total score ranges from 6 to 60 for both scales. The patient and the observer additionally score their overall opinion (not included in the total scores).

To investigate a potential sound dampening effect of the preserved soft-tissue surrounding the abutment, bone conduction (BC) in situ thresholds were measured both with the patients' sound processor on abutment and on a testband. Furthermore, audiometric BC thresholds (Interacoustics Equinox audiometer fitted with a B71 transducer, Interacoustics, Assens, Denmark) were used to check stability of the BC thresholds over time.

2.5. Data analysis

Data management and statistical analyses were performed by independent external data managers and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) and executed according to a predefined statistical analysis plan.

For comparisons between groups, Fishers nonparametric permutation test was used for numbness variables, Mantel–Haenszel chi-square tests were used for all ordered categorical variables, Fisher's exact test was used for all dichotomous variables, and Mann–Whitney U tests were used for all continuous variables. Implant survival was analyzed with the Log-rank survival test between the two groups. Repeated measures analyses were done for changes over time, using the Wilcoxon signed rank tests for continuous variables and Sign test for categorical and dichotomous variables. Due to differences in abutment length in the test group, for ISQ values and functions of ISQ values the adjusted analyses between the two groups was performed with analysis of covariance (ANCOVA). Groups were compared according to the intention-to-treat principle. The number of visits varied between test and control-groups. Therefore, only data from follow-up visits available for both groups were included in the analysis of visit-based data; for cumulative variables all visits, including extra visits, were included. All tests, performed by using SAS® v9.4 (Cary, NC), were two-tailed and conducted at 0.05 significance level.

3. Results

3.1. Patients and follow-up

The test population consisted of 25 patients with the same number of implants. The historical control population consisted of 25 patients with 25 implants. Demographics and baseline characteristics showed no statistically significant differences between these study groups (table 1). No major perioperative complications were observed in either group. In total, 45 patients (46 implants) completed the 3-year follow-up. Three patients were withdrawn from the test group. The first patient had his abutment electively removed after 30 months due to persisting pain and minimal bleeding at the implant site despite extensive antibiotic treatment and pain medication. The second patient wanted his abutment removed after

26 months due to the burden of fast progressing lewy-body dementia. The third patient was lost to follow-up, after missing multiple scheduled visits. His last visit was performed 6 months after surgery, during which he stated to only use the sound processor a few hours per month. In the control group, one patient had his abutment electively removed after 24 months in another hospital due to disabling tinnitus, which was hoped to improve by performing a stapedotomy combined with a normal air-conduction hearing aid.[14] For all these patients, data was included in the analysis up until the moment of withdrawal. Besides these withdrawn patients, only four follow-up visits, in four different patients (two test patients and two control patients), were missed or performed outside the predefined visit window.

Table 1. Baseline characteristics

Variable	Tissue Preservation group (n=25)	Tissue reduction group (n=25)	p-value
Gender			
Male	15 (60.0%)	10 (40.0%)	
Female	10 (40.0%)	15 (60.0%)	0.26
Age	51.5 (SD 13.4; range, 18.0; 73.0)	53.9 (SD 12.2; range, 30.0; 83.0)	0.55
Smoking	4 (16.0%)	4 (16.0%)	1.00
Indication			
Acquired cond./mixed	21 (84.0%)	18 (72.0%)	0.50
Congenital conductive	1 (4.0%)	0 (0.0%)	1.00
Single sided deafness	3 (12.0%)	7 (28.0%)	0.29

3.2. Skin sensibility

The cotton swab sensibility test showed a significant difference in median total sensibility (percentage of correct answers): 99.7% (Range 91.7-100%) in the test-group versus 92.0% (Range 66.7-100%) in the control-group (p=0.012) 36 months after surgery. (See table, supplemental digital content 1, which reports sensibility scores for each group per visit) Moreover, 4% of the test patients experienced numbness to some extent, compared to 52% of the control patients. In line with this, subjective numbness (VAS 0 [SD 0] versus VAS 0.9 [SD 1.6]) and patient reported diameter of the numb area (0cm [SD 0] versus 0.4cm [SD 0.7]) also differed significantly in favour of the test group. Skin sensibility at 12 and 36 months is displayed in figure 2.

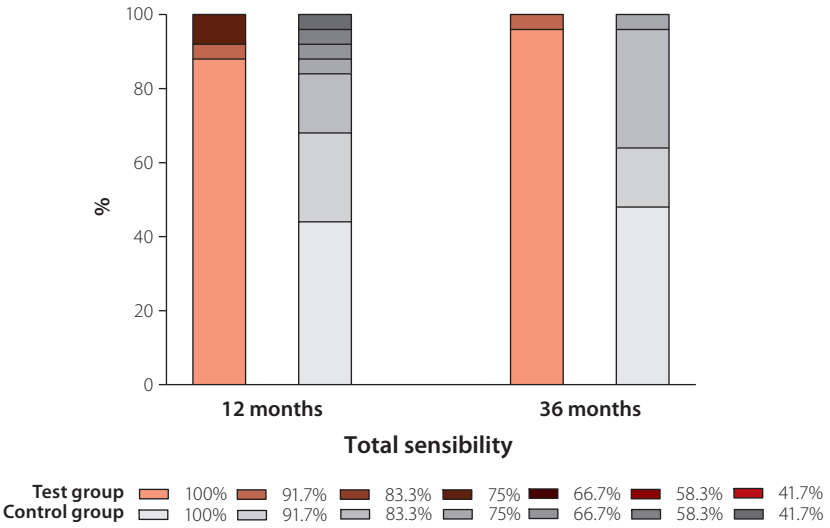

Figure 2. Total skin sensibility test results at 12 and 36 months.

3.3. Soft tissue tolerability and complications

Figure 3 presents an overview of soft tissue reactions per planned visit and all visits combined (including extra visits). Across all visits, adverse skin reactions (Holgers 2-4) were observed in 36.0% of the test patients and in 12.0% of the control patients, which were all successfully treated with locally applied ointment for 14 days. Neither adverse skin reactions (p=0.10) nor other postoperative complications were significantly different between groups: bleeding or hematoma (0% versus 0%;(p=1.0); and skin dehiscence (0% versus 8% (all healed 3 weeks after surgery);p=0.49).

Thickening of the skin was observed in 56% (test) and 64% (control) of the patients, not statistically correlating with the presence of an adverse skin reaction (Holgers grade 2-4). Neither the maximum skin height observed at all visits, nor skin height during any of the follow-up visits differed between groups. Skin height per visit is displayed in figure 4. Only two control patients needed revision surgery (6 weeks and 9 months after surgery, respectively), both due to thickened skin (level B) around the abutment without inflammation, resulting in feedback issues.[14]

3.4. POSAS

At 1-year follow-up, none of the categories on the patient and observer scale exceeded scores of 4. The patient categories thickness (p=0.031), irregularity (p=0.03), mean total patient score (p=0.01), and overall opinion (p=0.003) differed significantly in favour of the

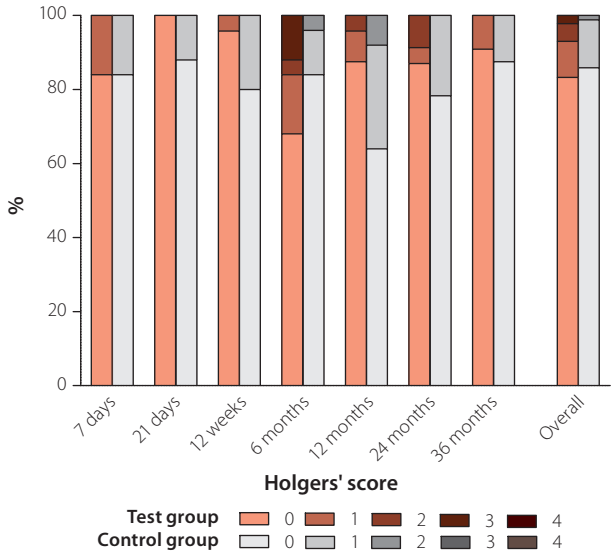

Figure 3. Skin reactions (Holgers grade) at each visit and overall. The overall data also contain observations during unplanned extra visits.

test group. The observer categories vascularity (p=0.012), relief (p=0.004), surface area (p<0.0001), mean total observer score (p=0.0025), and overall opinion (p=0.0004) differed significantly in favour of the test group.

At 3-year follow-up, none of the categories on the patient and observer scale exceeded scores of 3. The patient category stiffness significantly (p=0.041) differed in favour of the control group. The observer categories relief (p=0.0037), and overall opinion (p=0.027), differed significantly in favour of the test-group. (See table, supplemental digital content 1, which reports the POSAS data per visit)

3.5. Implant and abutment survival

No implants were lost in either group. No statistically significant difference in 3-year abutment survival was observed between groups (test 92% versus control 96%): two abutments were electively removed in the test group and one in the control group (see section 'patients and follow-up'). The implant itself remained seated in all three patients.

3.6. ISQ

As expected with differences in abutment length, the mean 36-month AUC for ISQ-low was significantly higher in the control-group compared to the test-group (p<0.001). In both groups a significant increase in ISQ-low is observed over time (p<0.001), however,

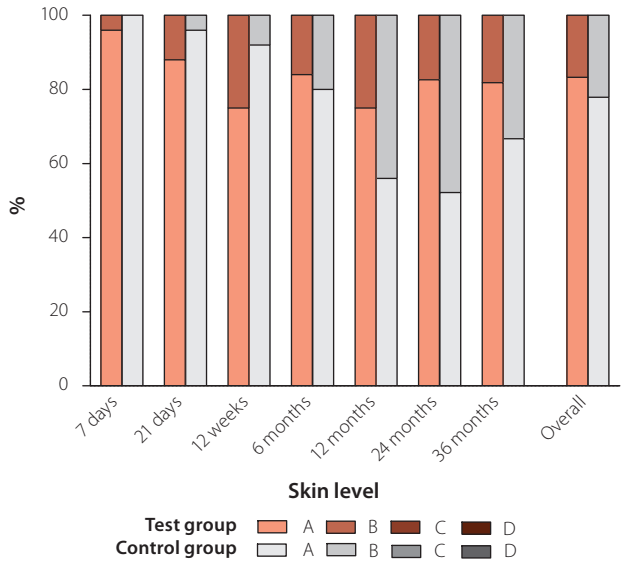

Figure 4. Skin height relative to abutment by visit and overall per group. The overall data also contain observations during unplanned extra visits.

this increase is significantly higher in the test group compared to the control group (7.64 (SD4.1) versus 4.29 (SD3.9); p=0.0068) For ISQ-high, similar results were observed, with absolute numbers 1 to 2 points higher on average and slightly less increase over time. ISQ data are displayed in figure 5.

3.7. Audiology

After 36 months, no significant differences (p>5%) were seen for thresholds measured with testband and B-71 audiometric boneconductor when averaged across all frequencies, indicating essentially similar hearing thresholds. Also, BC-in-situ (*i.e.* on abutment) thresholds averaged across 250Hz-8kHz showed no difference between test and control group (mean, 27.5dB [SD 12.3] versus 27.1dB [SD 14.0] p=0.81). However, the 1000-Hz thresholds on testband were statistically significantly different (mean 34.5dB [SD 13.8] versus 25.0dB [SD 14.4] p=0.015). When comparing individual thresholds on testband, abutment, and B71 between test and control group *B71* and abutment were not significantly different, but at 1000 Hz a significant group effect was observed for the differences between abutment and testband thresholds (mean, -17.6dB [SD 10.2] versus -9.0dB [SD 6.1] p=0.0016).

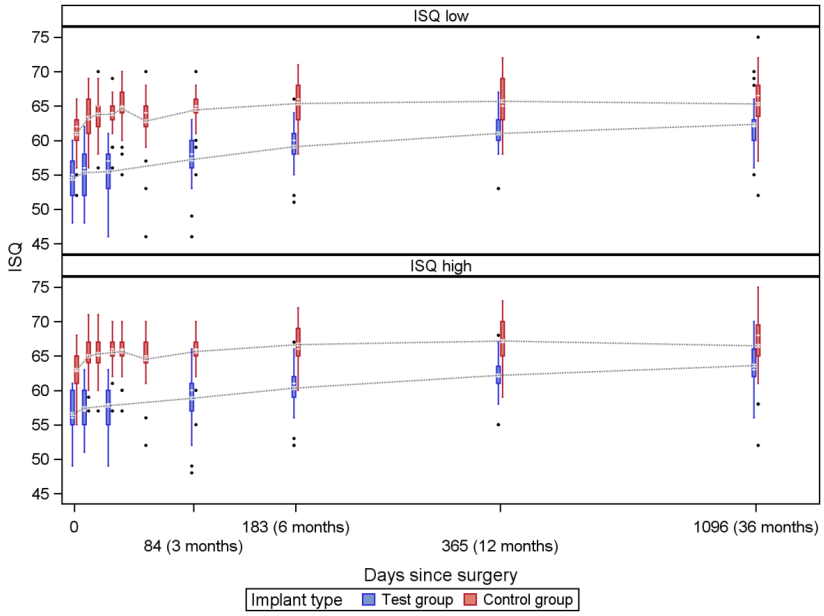

Figure 5. Boxplot of ISQ Low and ISQ High over time

4. Discussion

4.1. Synopsis of key/new findings

In current study, we compared the long-term clinical outcomes of two different surgical techniques for placing a percutaneous titanium implant for BCDs in the temporal bone: the linear incision with soft tissue reduction and the linear incision with soft tissue preservation. Based on our primary outcome measure, i.e. skin sensibility 3 years after surgery, patients operated with tissue preservation experienced significantly less numbness at the implant site compared to the tissue reduction group. No differences were observed in the total POSAS-scores, soft tissue tolerability, skin height around the abutment, implant survival, and audiological performance.

4.2. Strengths & limitations of the study

The current study is the first to compare long-term clinical outcomes of two groups with tissue preservation or reduction as the only variable. In addition, data quality is considered very high, with only one patient lost-to-follow-up and 4 visits outside the predefined visit window.

At the study's inception, skin sensibility was measured for the first time in relationship to these surgical techniques. A sample size could therefore not be calculated, thus, was empirically chosen. In addition, by using a historical control group randomization was not possible. However, for both groups the same eligibility criteria were applied, baseline characteristics were comparable, and all data were gathered prospectively. Blinded follow-up was not feasible, since the implant site appearance differs between surgical techniques and longer abutments were used in the test group.

Another limitation could be the difference in follow-up visits. In the first 6 months of follow-up, patients in the control-group had three additional visits compared to the test group. This might have influenced the quality of the soft-tissue care, since more than half of adverse soft-tissue reactions in the test group were observed at the 6-month visit, and 77% of all reactions occurred in the first 6 months after surgery. Nonetheless, no difference in soft tissue reactions was observed at the 1-year interim analysis and over the entire follow-up.

4.3. Comparisons with other studies

Post-operative numbness is evaluated in only two other studies. [17, 18] In these studies the linear incision technique with tissue preservation is compared to the dermatome technique with tissue reduction. In line with our observations, both studies reported significantly less numbness at the implant site for the tissue preservation group. However, caution is needed since a different skin thinning technique was used. [17, 18]

A recent systematic review on soft tissue preservation techniques concluded that postoperative skin complication rates were low and that overall complication rates were comparable with skin-thinning techniques, while the duration of the surgery was significantly shorter.[12] However, in only one comparative study, the same incision technique, i.e. linear incision, was applied in both skin-thinning group and tissue preservation group.(18) Despite the relatively high incidence of Holgers≥2 at 1 week (64% versus 67%), no significant differences in cutaneous reactions after 1 year of follow-up were found between groups,(18) which is in line with the observations in the current study.

4.4. Clinical applicability of the study

The primary outcome, i.e. skin sensibility, differed significantly in favour of the tissue preservation technique. However, also patients operated with the reduction technique reported good sensibility scores and low subjective numbness scores (VAS) in small corresponding areas, which all improved over time. In addition, no difference in subjective numbness was observed at 12 months despite significantly differing sensibility scores. The significant differences on the POSAS after 12 months, in favour of the tissue preservation technique, were overcome at the 3-year follow-up; especially the total patient score in the control group improved (from 18.9 to 9.1). It is worth noting, however, that many patients reported difficulties answering the POSAS questions because of limited visibility and the

lack of interest in the appearance of the scar. Due to the position of the implant, sensibility and appearance seem to be of limited importance to patients, especially in the long-term.

In the previous 6-month evaluation, significantly more soft tissue reactions were observed in the tissue preservation group.[13] At the following visits, however, no differences in soft tissue reactions were observed. As such, over the entire follow-up, no significant difference in adverse skin reactions were noticed between surgical techniques.

Skin thickened in more than half of the patients, regardless of the surgical technique. The skin height per visit did not differ between groups. At the 36-month follow-up skin thickening was observed in 18.2% (test) and 33.3% (control) patients. This suggests that skin thickening is often only temporary. The previous hypothesis that thickening of the skin reflects the restoration of normal soft tissue after soft tissue reduction seems unlikely since skin thickening is also observed after tissue preservation surgery.[14] The hypothesis that skin thickening could be the result of more active immunological mechanisms to compensate for the continuous breach of the skin implied by the skin-penetrating implant, seems more likely. However, we did not observe any correlation with adverse skin reactions. Future research, therefore, remains needed.

The difference in absolute ISQ scores (both low and high) between groups was expected, since longer abutments were used in the test group. Interestingly, the ISQ-scores over time increased significantly more in the tissue preservation group compared to the tissue reduction group. Although this observation could suggest that tissue preservation leads to a more rigid bone-implant interface, we deem it unlikely that soft tissue handling significantly influences osseointegration. Perhaps, the stronger increase in ISQ could be assigned to measurement error caused by the difference in abutment length, which emphasizes the importance of not comparing ISQ values of implants with different abutment lengths.[19] These results should be repeated by future studies with similar protocols to affirm these assumptions.

The two statistically significant differences in frequency specific BC thresholds between groups (BC-in-situ threshold for 1000Hz on testband and the difference between the BC-in-situ threshold on abutment and testband) were also, and to the same extent, observed in the 6-month evaluation.[13] These differences can be most likely attributed to differences in resonance frequency of the sound processor in the transcutaneous conditions.[13, 20] Nonetheless, since no differences were observed between groups on the average thresholds measured on testband, B71, and abutment, these indicate that the preservation of soft tissue around the abutment has no sound dampening effect.

5. Conclusion

A linear incision with soft-tissue preservation for the implantation of percutaneous implants for BCDs is superior in terms of skin sensibility and scar appearance, without influencing audiological outcomes, compared to soft-tissue reduction. Both surgical techniques have comparable implant survival and soft tissue tolerability. Also taking into account the shorter surgery time, we advocate using the soft-tissue preservation technique.

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Supplemental digital content 1

Table: Sensibility outcomes, reported as percentage of correct answers, and scar assessment by means of the Patient and Observer Scar Assessment Scale (POSAS) at 12 and 36 months. The POSAS consists of a patient (P) and an observer (O) scale, containing six categories with response options from 1 (normal skin) to 10 (worst imaginable). The total score ranges from 6 to 60 for both scales. The patient and the observer additionally score their overall opinion (not included in the total scores).

Variable		Tissue Preservation group Mean (SD)	Tissue reduction group Mean (SD)	p-value
12 months		**N = 24**	**N = 25**	
Numbness	Total sensibility (%)	97.6 (7.2)	89.0 (15.0)	0.049
	Vital sensibility (%)	95.1 (14.3)	89.3 (17.9)	0.18
	Gnostic sensibility (%)	100.0 (0.0)	88.7 (18.5)	0.0016
	Subjective numbness (VAS)	1.64 (2.27)	1.69 (2.44)	0.76
	Area of numbness (cm)	1.08 (2.15)	0.892 (1.391)	0.88
POSAS	P - Pain	1.79 (1.61)	2.44 (1.96)	0.089
	P - Itching	1.88 (1.12)	2.84 (2.53)	0.35
	P - Color	2.75 (1.67)	3.88 (2.51)	0.12
	P - stiffness	2.04 (1.49)	2.60 (1.80)	0.21
	P - thickness	2.33 (1.97)	3.48 (2.20)	0.031
	P - Irregularity	2.38 (2.00)	3.64 (2.20)	0.030
	P - Total score	13.2 (7.1)	18.9 (9.7)	0.0097
	P - Overall score	2.00 (1.50)	3.36 (1.87)	0.0029
	O - Vascularity	2.83 (0.76)	3.64 (1.25)	0.012
	O - Pigmentation	2.38 (0.49)	2.76 (1.16)	0.54
	O - Thickness	2.79 (0.88)	3.32 (1.63)	0.33
	O - Relief	2.54 (0.88)	3.56 (1.53)	0.004
	O - Pliability	2.63 (0.71)	2.76 (1.23)	0.98
	O - Surface area	2.17 (0.38)	3.32 (1.31)	<0.0001
	O - Total score	15.3 (2.8)	19.4 (6.3)	0.0025
	O - Overall opinion	2.63 (0.71)	3.76 (1.30)	0.0004

Variable		Tissue Preservation group Mean (SD)	Tissue reduction group Mean (SD)	p-value
36 months		**N = 22**	**N = 24**	
Numbness	Total sensibility (%)	99.7 (1.7)	92.0 (9.2)	0.012
	Vital sensibility (%)	100.0 (0.0)	91.0 (13.0)	0.0016
	Gnostic sensibility (%)	99.2 (3.6)	93.1 (13.8)	0.082
	Subjective numbness (VAS)	0.00 (0.00)	0.913 (1.632)	0.0036
	Area of numbness (cm)	0.00 (0.00)	0.364 (0.727)	0.020
POSAS	P - Pain	2.00 (1.90)	1.43 (1.12)	0.26
	P - Itching	1.68 (1.21)	2.22 (1.88)	0.37
	P - Color	1.40 (0.89)	1.60 (0.99)	0.67
	P - stiffness	1.59 (1.05)	1.05 (0.22)	0.041
	P - thickness	2.05 (1.89)	1.33 (0.91)	0.24
	P - Irregularity	1.77 (1.41)	1.38 (0.97)	0.32
	P - Total score	11.0 (7.2)	9.11 (3.56)	0.86
	P - Overall score	1.73 (1.52)	1.85 (0.88)	0.13
	O - Vascularity	2.09 (0.75)	2.68 (1.04)	0.067
	O - Pigmentation	1.91 (0.61)	2.14 (0.89	0.46
	O - Thickness	2.27 (0.83)	2.50 (1.10)	0.61
	O - Relief	2.05 (0.72)	2.95 (1.36)	0.0037
	O - Pliability	1.82 (0.59)	2.14 (0.99)	0.30
	O - Surface area	2.00 (0.53)	2.41 (0.85)	0.068
	O - Total score	12.1 (3.2)	14.8 (5.1)	0.093
	O - Overall opinion	2.00 (0.53)	2.57 (0.98)	0.027

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Abbreviations used in this paper: CHL = conductive hearing loss; MHL = mixed hearing loss; SSD = single sided sensorineural deafness; HRQoL = health-related quality of life, SNR = signal-to-noise-ratio, APHAB = Abbreviated Profile of Hearing Aid Benefit, SSQ = Speech, Spatial and Qualities of Hearing Scale; HUI3 = The Health Utilities Index Mark 3
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Chapter 4

Results of a two-year prospective multicentre study evaluating long-term audiological and clinical outcomes of a transcutaneous implant for bone conduction hearing

I.J. Kruyt[1]; P. Monksfield[2]; P.H. Skarzynski[5,6]; K. Green[3]; C. Runge[4]; A.J. Bosman[1]; J.I. Blechert[7]; S. Wigren[7]; E.A.M. Mylanus[1]; M.K.S. Hol[1]

[1] Department of Otorhinolaryngology, Donders Center for Neurosciences, Radboud university medical centre, Nijmegen, The Netherlands
[2] Department of Otorhinolaryngology, Queen Elizabeth Hospital, Birmingham, England
[3] Department of Otorhinolaryngology, Manchester Royal Infirmary, Manchester, England
[4] Department of Otorhinolaryngology, Medical College of Wisconsin, Milwaukee Wisconsin, United States of America
[5] Department of Otorhinolaryngology, World Hearing Center, Institute of Physiology and Pathology of Hearing, Warsaw/Kajetany, Poland
[6] Department of Heart Failure and Cardiac Rehabilitation, Medical University of Warsaw, Poland
[7] Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden

Abstract

Objective(s): To evaluate two-year audiological and clinical outcomes of a transcutaneous implant for bone conduction hearing of a previously published 6-month evaluation.
Design: Fifty-four unilaterally implanted adult patients with conductive or mild mixed hearing loss or single-sided sensorineural deafness were included in this prospective multicentre study. Follow-up visits were scheduled post-surgery at 10 days; 4, 6, and 12 weeks; 6, 12, and 24 months. Main outcomes were audiological benefit, patient-reported outcomes (PROs), soft tissue status, pain, numbness, implant survival, and daily usage.
Results: In the study population, the transcutaneous implant resulted in statistically significant improvement in objective hearing test compared to the unaided situation as well as improvements in PROs. Soft tissue complications were observed in 4.6% of the patients per visit. Pain/discomfort and numbness were initially reported in the majority of the patients, but declined over time; approximately 9% of patients reported some degree of numbness and 15% (slight) pain/discomfort after 2 years. During the 24-month period, two implant magnets were removed (3.7%), while two other implants were converted to the percutaneous counterpart (3.7%). At the final visit, 89.6% (n=42 out of 47) of the patients used their sound processor, with a median daily usage of 6h/day(range 0-18h/day).

Conclusions*:* After 24 months, the transcutaneous implant provided statistically significant mean improvement in objective and subjective hearing performance as well as PROs compared to the pre-operative unaided condition and had a low soft tissue complication rate in the studied population. The test device could be considered as an alternative treatment option for appropriately selected and counselled patients.

1. Introduction

Traditional percutaneous implants for bone conduction hearing consist of a titanium fixture surgically placed into the temporal bone and a skin-penetrating abutment, onto which a sound processor is coupled. These implants have shown to be an effective hearing rehabilitation option in patients suffering from either conductive (CHL) or mixed hearing loss (MHL), or single-sided sensorineural deafness (SSD). Despite its audiological success and good levels of patient satisfaction, the skin-penetrating abutment of percutaneous implants implies an entry point for microorganisms potentially causing complications, e.g. recurrent skin infections and implant loss. [1, 2]

In 1986, Hough et al. developed a transcutaneous system, the Xomed Audiant, using magnets instead of a skin-penetrating abutment to transmit the sound vibrations to the skull. [3] As a result, the skin remained intact postoperatively, thus avoiding an entry point for microorganisms and, hence, potentially preventing skin infections and loss of the implant. For the sound processor to remain seated, the magnets had to provide sufficient retention force. However, the necessary retention force resulted in too high static pressure towards the skin causing pressure related complications. Combined with insufficient amplification, the transcutaneous device was withdrawn from the market.

Although recent modifications in percutaneous implant design and surgical techniques have resulted in a reduction of adverse skin reactions (observed in <6.3% of the visits) [4-7] and implant loss rates (occurring in approximately 4.2% of patients with up to 5-year follow-up) [8-10], the concept of transcutaneous coupling remained attractive, as the intact skin could potentially further diminish skin reactions and could be considered to be cosmetically appealing. As such, a new passive transcutaneous implant for bone conduction hearing was introduced in 2013. This device consists of an internal magnet fixed in the temporal bone and an external magnet, onto which the sound processor is coupled. To reduce pressure related complications, a soft pad is attached to the external magnet to distribute the pressure evenly over the underlying skin.

The primary aim of this multicentre study was to evaluate efficacy in terms of hearing performance of a transcutaneous implant for bone conduction hearing after six months of follow-up, as previously reported by den Besten et al.[11] The aim of this paper was to evaluate the long-term audiological and clinical performance after a total of two years of follow-up in the same population, and to compare patient-reported outcomes (PROs) over time.

2. Methods

2.1. Implant & Study design.

The device was a Baha Attract System, consisting of: 1. a BI300 implant (osseointegrating implant fixture), 2. an attached BIM400 implant magnet, and 3. an external sound processor magnet (SP magnet) with a soft pad to distribute the pressure more evenly over the skin. Together, the magnets constitute the transcutaneous coupling. A sound processor can be attached to the SP magnet via a snap coupling. All parts were manufactured by Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden).

The study was designed as an international multicentre, open, prospective clinical investigation with a primary evaluation after 6 months and a secondary evaluation after 24 months of follow-up. The participating centres were Radboudumc (Nijmegen, The Netherlands), Queen Elizabeth University Hospital (Birmingham, United Kingdom), Manchester Royal Infirmary (Manchester, United Kingdom), Medical College of Wisconsin (Milwaukee, Wisconsin, USA), and World Hearing Center, Institute of Physiology and Pathology of Hearing (Warsaw, Poland). All patients eligible for a bone-conduction device were fully informed about the different percutaneous and transcutaneous options. All patients preferring the transcutaneous option were informed about the trial. The patients then attended a screening and baseline visit, during which eligibility criteria (table 1) were evaluated, medical history was collected, and baseline hearing tests were performed for the unaided hearing condition as well as with a sound processor on a Baha Softband (same sound processor type as to be used on the implant).

The baseline visit was followed by a period of softband trial prior the surgical intervention. Follow-up visits were scheduled at 10 days; 4, 6, and 12 weeks; 6, 12, and 24 months after surgery. The sample size was calculated for improvement in audiometric thresholds pure tone average PTA4 (mean of 500, 1000, 2000, and 4000Hz) compared to the pre-operative unaided hearing condition for the whole study population; for details, see den Besten et al. [11] Furthermore, a subgroup analysis per type of hearing loss (CHL/MHL and SSD) was performed. Audiological outcomes, i.e. free-field hearing thresholds (PTA4 and per frequency 250-8000Hz), adaptive speech recognition in noise, and speech recognition in quiet (at 50, 65, and 80dB SPL) were compared to the unaided situation and to preoperative performance with a softband. In case of significantly better hearing in the contralateral ear, data was obtained with the better ear blocked. Audiometric methods are described in detail in den Besten et al.[11]

In addition to audiological outcomes, the focus of the current manuscript was to evaluate long-term safety and usability of the test implant regarding implant survival, soft tissue tolerability, pain/discomfort after sound processor loading, skin numbness, retention difficulties, and daily usage of the sound processor. Soft tissue tolerability encompassed the presence of signs of infection, inflammation, skin necrosis and/or scar hypertrophy.

Table 1. Eligibility Criteria

- Age ≥ 18 years
- Conductive or mixed hearing loss in the ear to be implanted with a PTA4[a] bone conduction (BC) threshold of <30dBHL
- Single-sided sensorineural deafness with a PTA4[a] bone conduction threshold of <30dBHL in the contralateral ear[b]
- no previous bone conduction hearing implant on the implant site
- Unilateral implant surgery
- ≥3mm soft tissue thickness at planned implant site
- Have no condition that could jeopardize osseointegration or skin healing, e.g. osteoporosis, psoriasis, radiation therapy, uncontrolled diabetes, and use of systemic corticosteroids
- Able to follow investigational procedures (e.g. to complete quality of life scales)
- No participation in another investigation with pharmaceuticals and/or medical device

[a] Mean of 500, 1000, 2000, 4000 Hz.
[b] For US ≤20 dB hearing level AC in the good ear or indication for an AC CROS but cannot or will not use an AC CROS

The level of pain/discomfort was classified as follows: 0 = no pain/discomfort (normal daily usage SP); 1 = slight pain/discomfort (not significantly affecting daily usage SP); 2 = Discomfort/pain (reducing daily usage SP); 3 = Excessive pain/discomfort (preventing usage SP). Skin sensibility was assessed at randomly picked locations in and around the implant area, i.e. within and beyond 2 cm from the centre of the implant magnet, and was tested on both gnostic (cotton swab) and vital (pin prick) sensibility. The following scale was used: 0 = no numbness; 1 = numbness within 2cm from the implant centre; 2 = numbness within and beyond 2cm from the implant centre. Daily usage encompassed the average use of the sound processor in hours per day during the last month prior to the study visit as reported by the patient. Non-use was defined as wearing the sound processor on average 0 hours a day.

Patient-reported outcomes were measured using the health-related quality of life (HRQoL) questionnaire Health Utilities Index (HUI3)[12] as well as the hearing specific questionnaires Abbreviated Profile of Hearing Aid Benefit (APHAB)[13] and Speech, Spatial, and Qualities of Hearing Scale (SSQ)[14]. HUI3 is a multi-attribute health-status classification system which consists of 15 individual questions on eight HRQoL attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each category is scored from 0.00 (highest degree of impairment or disability) to 1.00 (no impairment). A comprehensive health state attribute is calculated from these separate attributes. The APHAB is a 24-item inventory to evaluate the amount of difficulty the patient experiences in daily life listening

conditions. All items are scored on a 7-point scale indicating the frequency of difficulties experienced, ranging from 1 to 99%, with higher scores indicating more frequently occurring difficulties. Items are grouped and reported on the four domains ease of communication, reverberation, background noise, and aversiveness, as well as a global score.

The SSQ is composed of 49 questions that are scored on a visual analogue scale ranging from 0 (complete inability) to 10 (complete ability/no effort). The questionnaire measures auditory disability across the three subscales speech recognition (in a variety of contexts), spatial hearing (segregation, direction, distance, and movement of sound), and hearing qualities (ease of listening, naturalness, and clarity). For each subscale a mean score is calculated.

2.2. Ethical considerations

The current study was performed in accordance with the guidelines established in the Declaration of Helsinki (Washington 2002), ISO 14155:2011 Good Clinical Practice, and was approved by all local ethics committees. The current study was registered at www.ClinicalTrials.gov under identifier NCT02022085.

2.3. Data analysis

Monitoring at the four European sites was performed by external monitors (Factory-CRO, Bilthoven, The Netherlands), while at the US site monitors at Cochlear Americas (Denver, CO, USA) performed the monitoring. Data management and statistical analysis were performed by independent external data managers and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) according to a predefined statistical analysis plan. For comparison over time, Fisher's non-parametric permutation test for paired observations was used for continuous variables. For paired analysis of dichotomous and ordered categorical variables the Sign test was used. All data is reported according to the intention-to-treat principle. All tests were two-tailed, conducted at 0.05 significance level, and performed using SAS® v9.4 (Cary, NC).

3. Results

3.1. Patients and follow-up

In total, 54 patients were included in the study and implanted unilaterally; 39 of the patients had CHL or mild MHL and 15 patients had SSD. Baseline and surgery characteristics as well as choice of sound processor are displayed in table 2. Seven patients discontinued the study prematurely: two patients had their transcutaneous system converted to a percutaneous system (after 7 and 13 month, respectively; see section implant survival); in two patients the implant magnet was removed (after 75 days and 25 months, respectively; see section implant survival); one patient was unable to attend the last visit due to being

Table 2. Patient characteristics and demographics

Parameter	Number (%)
Gender :	
Male	21 (38.9%)
Female	33 (61.1%)
Hospital:	
Nijmegen	23 (42.6%)
Manchester	4 (7.4%)
Birmingham	12 (22.2%)
Milwaukee	1 (1.9%)
Warsaw	14 (25.9%)
Nicotine use:	
Does not smoke	40 (74.1%)
<10 cig/day	5 (9.3%)
11-20 cig/day	7 (13%)
21-40 cig/day	2 (3.7%)
Type of hearing loss	
Conductive/mixed hearing loss	39 (72.2%)
Single-sided sensorineural deafness	15 (27.8%)
Age at implantation	
Years	42.1 (SD 13.6; range 18.3-70.3)
Soft tissue thickness (surgery)	
Millimetre	5.83 (SD 1.3; range 4.0-10.0)
Surgery time (incision to last suture)	
Minutes	38.7 (SD 10.7; range 17.0-68.0)
Soft tissue thinning performed	
Yes	12 (22.2%)
No	42 (77.8%)
Bone Polishing/removal performed	
Yes	11 (20.4%)
No	43 (79.6%)
Implant length	
4mm	54 (100%)
Sound processor	
Baha BP110	23 (42.6%)
Baha 4	28 (51.9%)
Other	3 (5.6%)

abroad; one patient passed away during the study (after 14 months); and one patient chose to discontinue participation after the 12-month visit due to non-usage of the device; the patient reported persistent pain at the last attended visit. Data for these patients up until the moment of discontinuation were included in the analysis. Furthermore, in one patient, the 24-month visit was partly performed by phone, since the patient was not using the sound processor anymore due to Ménière attacks; hence, only implant survival, pain/discomfort, retention, and daily usage were collected at this visit.

3.2. Audiology

For the total cohort, the statistically significant improvement in audiological outcomes recorded at 6 months of follow-up as reported by den Besten et al.[11] was maintained also at 12 and 24 months and was numerically similar to the 6-month results. The mean

Table 3. Mean change in audiometric results from to the preoperative Unaided and Softband test situation to the postoperative Aided situation. For PTA and SNR, a negative value for the mean change indicates an improvement. The table shows the results for the subgroup of patients with CHL/MHL and SSD. For all outcomes, standard deviation, range, and sample size are reported.

	CHL/MHL			
Variable	**Mean change from Unaided to 6 months Aided**	**Mean change from Unaided to 12 months Aided**	**Mean change from Unaided to 24 months Aided**	**Mean change from Softband to 24 months Aided**
Free-field hearing thresholds, PTA4* (dB)	**-20.8** SD 9.8 (-38.8 to 5.0) n=39, p=<.0001	**-21.2** SD 9.3 (-41.3 to 7.5) n=38, p=<.0001	**-21.1** SD 8.0 (-45.0 to -3.8) n=36, p=<.0001	**0.0** SD 7.2 (-12.5 to 21.3) n=36, p=1.00
Adaptive speech in noise, Signal to noise ratio SNR (dB)	**-5.02** SD 6.2 (-23.9 to 5.1) n=25, p=<.0001	**-5.3** SD 6.7 (-26.3 to 3.9) n=24, p=<.0001**	**-5.90** SD 6.4 (-25.2 to 1.3) n=22, p=<.0001**	**-1.84** SD 3.8 (-11.5 to 4.1) n=24, p=0.025
Speech in quiet, 50dB SPL (% correctly repeated words)	**53.8** SD 27.6 (-24.0 to 100.0) n=39, p=<.0001	**53.5** SD 27.0 (-21.0 to 95.0) n=38, p=<.0001	**39.3** SD 29.0 (-50.0 to 90.0) n=36, p=<.0001	**-11.1** SD 33.2 (-95.0 to 50.0) n=36, p=0.053
Speech in quiet, 65dB SPL (% correctly repeated words)	**44.5** SD 31.7 (-3.0 to 100.0) n=39, p=<.0001	**46.7** SD 32.0 (-20.0 to 100.0) n=38, p=<.0001	**44.3** SD 30.3 (-10.0 to 90.0) n=36, p=<.0001	**-5.97** SD 18.3 (-55.0 to 30.0) n=36, p=0.059
Speech in quiet, 80dB SPL (% correctly repeated words)	**13.8** SD 22.7 (-20.0 to 80.0) n=39, p=<.0001	**13.6** SD 23.6 (-20.0 to 85.0) n=38, p=0.0001	**15.0** SD 22.4 (-7.0 to 71.0) n=36, p=<.0001	**-0.44** SD 8.4 (-20.0 to 30.0) n=36, p=0.77

* Mean of 500, 1000, 2000 and 4000 Hz

** The Fisher non-parametric permutation test for paired observations failed to approximate the p-value so Wilcoxon signed-rank test was used instead.

improvement from baseline unaided PTA4 to the aided value at 24-month was -21.5 dB (SD 8.3, range -45.0 to -3.8 dB, n=46, p≤.0001). The mean improvement in speech recognition in noise at 24 months was -4.47 dB signal-to-noise ratio SNR (SD 6.11, range -25.2 to 4.20, n=31, p≤.0001); data from two sites were excluded from the analysis due to invalid results for this specific test, as elaborated in Den Besten et al.[11] In speech tests in quiet the Mean improvement in % correctly repeated words from unaided to 24-month aided hearing was 40.4% at 50 dB SPL (SD 33.3, range -65.0 to 90.0, n=46, p≤.0001), 43.3% at 65 dB SPL (SD 29.9, range -10.0 to 90.0, n=46, p≤.0001) and 14.0% at 80 dB SPL (SD 20.7, range -10.0 to 71.0, n=46, p≤.0001). In line with the 6-month results, for the total study cohort no significant differences were observed at 24 months compared to baseline softband tests in terms of PTA4, speech recognition in noise, and speech in quiet at 80 dB SPL. However, while the improvements in speech recognition at 50- and 65-dB SPL compared

	SSD			
Variable	**Mean change from Unaided to 6 months Aided**	**Mean change from Unaided to 12 months Aided**	**Mean change from Unaided to 24 months Aided**	**Mean change from Softband to 24 months Aided**
Free-field hearing thresholds, PTA4* (dB)	**-21.6** SD 12.2 (-50.0 to 0.0) n=15, p=<.0001	**-20.0** SD 13.5 (-50.0 to 8.8) n=13, p=0.0005	**-23.0** SD 9.5 (-45.0 to -7.5) n=10, p=0.0008	**-0.6** SD 3.1 (-5.0 to 6.3) n=10, p=0.63
Adaptive speech in noise, Signal to noise ratio SNR (dB)	**-2.66** SD 3.9 (-7.2 to 3.8) n=11, p=0.051	**-3.7** SD 5.0 (-10.6 to 6.4) n=11, p=0.041	**-0.98** SD 3.72 (-7.40 to 4.20) n=9, p=0.47	**2.2** SD 3.6 (-4.1 to 7.6) n=9, p=0.11
Speech in quiet, 50dB SPL (% correctly repeated words)	**47.5** SD 33.6 (-20.0 to 90.0) n=15, p=0.0005	**42.5** SD 38.2 (-60.0 to 78.0) n=13, p=0.0044	**44.5** SD 47.4 (-65.0 to 90.0) n=10, p=0.023	**-13.2** SD 32.3 (-70.0 to 27.0) n=10, p=0.25
Speech in quiet, 65dB SPL (% correctly repeated words)	**40.7** SD 31.8 (0.0 to 96.0) n=15, p=0.0005	**42.0** SD 30.5 (-6.0 to 78.0) n=13, p=0.0013	**40.1** SD 29.4 (-10.0 to 76.0) n=10, p=0.0060	**-4.6** SD 7.3 (-16.0 to 9.0) n=10, p=0.094
Speech in quiet, 80dB SPL (% correctly repeated words)	**12.0** SD 14.6 (-10.0 to 43.0) n=15, p=0.0059	**14.8** SD 12.8 (-5.0 to 39.0) n=13, p=0.0023	**10.6** SD 12.9 (-10.0 to 39.0) n=10, p=0.023	**-1.6** SD 7.6 (-20.0 to 6.0) n=10, p=0.66

to softband were not statistically significant at 6 months, the results at 24 months were statistically significantly better than softband scores.

The audiological outcomes per subgroups of patients with CHL/MHL and SSD, respectively, are displayed in table 3. For the CHL/MHL group, the improvements compared to the unaided situation was statistically significant for all audiological tests at all time points (6, 12 and 24 months). Compared to softband tests, the 24-month data showed statistically significant improvements for speech recognition in noise. For the smaller subgroup of patients with SSD, the improvement in all audiological tests compared to unaided hearing reached statistical significance or near-significance at all time points (6, 12, 24 months), except for speech recognition in noise at 24 months. No statistically significant differences compared to softband were recorded in this patient group at any time point.

3.3. Soft tissue tolerability

Over the entire follow-up, signs of inflammation, e.g. swelling or erythema or infection were observed in 4.6% (mean) of the patients per post-operative visit: in 1.8% (mean) of the patients per visit prior to fitting the external magnet/sound processor and of 5.8% (mean) of the patients per visit after fitting (6 weeks until 24 months; range mean 3.8-7.7%). Besides a patient who underwent implant magnet removal due to infection shortly after implantation (see section implant survival), all other observations were minor soft tissue inflammations or infections which resolved by local treatment.

3.4. Pain/discomfort & skin numbness

The presence of pain/discomfort and skin numbness per visit are displayed in figure 1. Skin numbness was seen in 19.2% (vital sensibility) and 17.3% (gnostic sensibility) of the patients at the 6-month follow-up visit, most of whom had a numb area exceeding 2cm in diameter. In the following 18 months, skin numbness declined steadily, and at the 24-month visit, numbness was reported in four patients (out of 46 patients, 8.7%), with only one patient having a numb area exceeding 2cm in diameter.

At the 6-month follow-up, five patients (out of 53 patients, 9.4%) experienced pain which significantly reduced daily use. Similar to the skin numbness outcomes, in the following 18 months, pain decreased steadily over time. At the last visit, three patients (out of 47 patients, 6.4%) experienced pain which significantly affected daily use.

3.5. Implant survival

No spontaneous implants loss occurred, and all patients had their osseointegrated implant in position, resulting in a two-year implant survival of 100%. However, two patients (3.7%) had their implant magnet surgically removed (osseointegrated implant remained seated): in one patient due to persisting pain resulting in non-use, and the other due to infection shortly after surgery. In addition, two other patients (3.7%) had their transcutaneous

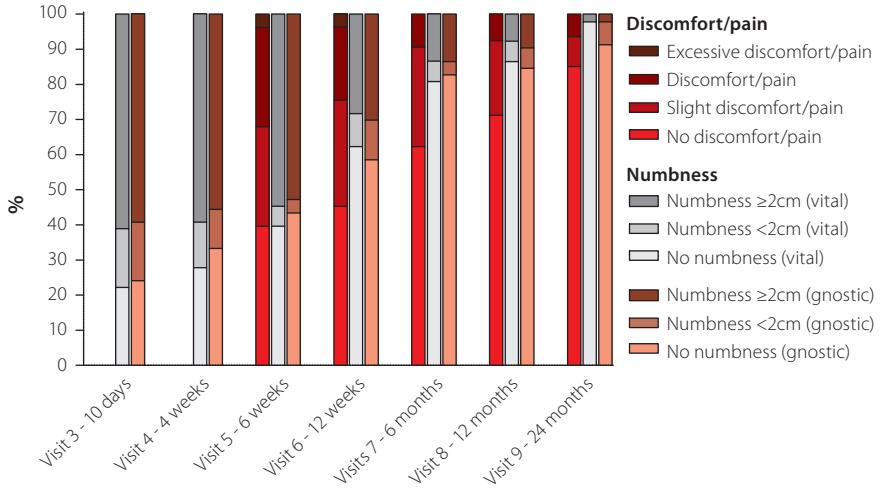

Figure 1. Stacked bar-chart displaying the percentage of patient with pain and its severity, as well as numbness per visit around the implant site i.e. within and beyond 2 cm from the centre of the implant magnet. The latter was tested on both gnostic (cotton swab) and vital (pin) sensibility. Pain data was collected at visits after sound processor loading.

system surgically converted to a percutaneous system. One of the conversions was performed due to insufficient audiological benefit experienced by the patient, and the other due to persisting pain combined with the sound processor frequently falling off. Conversion encompassed replacing the implant magnet with a skin-penetrating abutment, onto the seated osseointegrated implant.

3.6. Sound processor usage, retention difficulties & device deficiency

Of the patients that attended the 24-month visit, 89.6% (n=42 out of 47) used their sound processor on the transcutaneous implant. Grouped per indication, 97.2% (n=35 out of 36) of the CHL/MHL patients used their sound processor, while 2.8% became a non-user (n=1; due to insufficient benefit of the system). In contrast, 63.6% (n=7 out of 11) of the SSD patients used their sound processor at the last follow-up, while 36.4% were non-users (n=4; one due to pain and feedback issue, one due to pain/discomfort, one due to subjectively eliciting Ménière attacks, and one due to insufficient benefit). The daily usage of the sound processor per visit is displayed in figure 2. The median daily sound processor usage after 24 months was 6h/day (range 0-18h/day) for the entire cohort (n=47), 8h/day (range 0-18h/day) in patients with CHL/MHL (n=36), and 3h/day (range 0-17h/day) in patients with SSD (n=11). For patients that used their sound processor at the last visit, the

median daily usage was 7.5h/day for the total cohort (n=42), 8h/day for patients with CHL/MHL (n=35), and 6h/day for patients with SSD (n=7).

At 6 weeks (first visit after sound processor loading), in 35.8% of the patients the sound processor fell off at least once a week (mean 4.53 times a week, range 0-80). For the following visits it was reported as follows: 12 weeks - 32.1% (mean 1.79 times a week, range 0-30); 6 months - 35.8% (mean 1.87 times a week, range 0-50); 12 months - 17.3% (mean 0.63 times a week, range 0-10); 24 months - 6.2% (mean 0.19 times a week, range 0-7). Twenty-four device deficiencies occurred during the 24-month follow-up period, of which almost all encompassed a broken snap coupling or battery door on the sound processor.

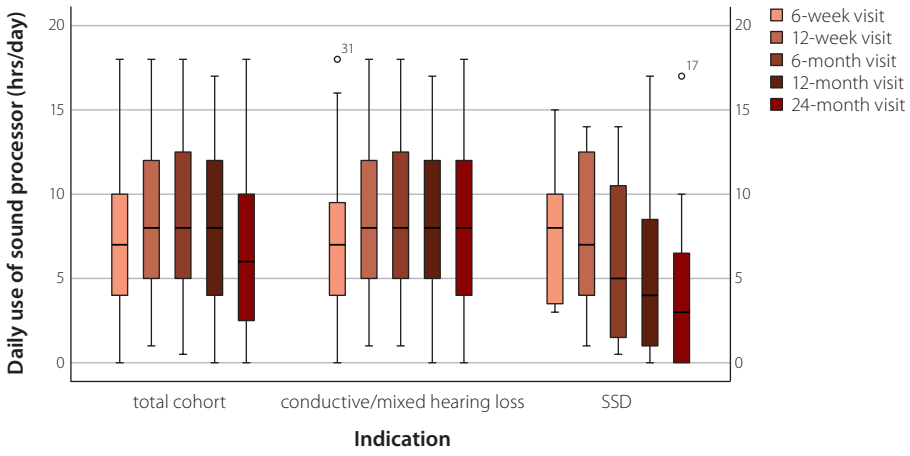

Figure 2. Daily use of sound processor per visit for the total cohort as well as per indication. The median (horizontal bar) is defined within each plot, boxes represent interquartile range, whiskers represent 95% range and dots represent outlier values.

3.7. Patient-reported outcomes

In the studied population, the transcutaneous system resulted in statistically significant improvement on the HUI3 attributes hearing, speech, and pain, the APHAB domains ease of communication, background noise, reverberation, and global score, and on all SSQ scales at the 24-month follow-up compared to the baseline situation. For the subgroup of patients with CHL/MHL a significant improvement was also reported on the HUI3 attribute Comprehensive Health State (table 4). For patients with SSD, the statistically significant improvements seen at 6 months for APHAB (background noise, reverberation, global score) and SSQ (all subscales) were no longer statistically significant at 24 months; all HUI3

attributes failed to show improvements for the SSD population. No significant differences were found in either group comparing the aided situation at the 6-month visit to the 24-month visit, except for a significant deterioration on the SSQ quality scale in SSD patients (-1.05; p=0.008).

4. Discussion

4.1. Synopsis of key/new findings

In the current multicentre study, we evaluated the two-year audiological and clinical performance of a new transcutaneous implant for bone conduction hearing, as well as patient-reported outcomes (by means of HRQoL and hearing specific questionnaires). The transcutaneous system provided significant improvement in all audiometric and patient-reported hearing outcomes compared to the unaided situation as well as in HRQoL. No implants were lost, although in four patients the implant magnet was either removed or replaced with an abutment due to complications or insufficient audiological benefit. The majority of the patients initially reported to experience both some degree of pain/discomfort and numbness; however, these complication rates declined over the following visits and were reported only sporadically at the last follow-up. In the subgroup analysis, the transcutaneous system provided both significant improvement in hearing outcomes compared to the unaided baseline condition as well as regarding PROs in patients with CHL/MHL. For patients with SSD, the transcutaneous system provided statistically significant or near-significant improvement compared to the unaided condition in all audiometric tests throughout the 24-month follow-up, except for speech recognition in noise at the 24-month visit. However, the statistically significant improvements in APHAB and SSQ recorded at 6 months were no longer present at 24 months. HUI failed to show statistically significant improvement at any time point in this small subgroup. At the last follow-up, 97.2% of the patients with CHL/MHL with the transcutaneous implant in place used their sound processor, compared to 63.6% of the SSD patients.

4.2. Strengths & limitations of the study

The results of the current study are considered to reliably reflect clinical outcomes of the transcutaneous system due to the prospective multicentre study design and data quality. The study design included one of the largest populations with the longest follow-up period to date with this device type. The study was designed as a within-subject evaluation with audiological benefit after 6 months compared to the unaided situation as primary outcome variable. The current long-term follow-up study, evaluating the clinical outcomes after 24 months, therefore, had the same within-subject design. The transcutaneous system was developed as an alternative to the percutaneous system, which is currently the gold standard in terms of transmission efficiency. While the high frequency sound

transmission is less effective, passive transcutaneous devices are thought to offer other advantages in terms of non-audiological clinical outcomes. A direct comparison of such clinical outcomes (i.e. numbness, pain/discomfort, soft tissue tolerability, daily use, implant loss, and health-related quality of life) would have been desirable. Until now, prospective studies objectively comparing the clinical outcomes of the two systems are lacking. Another point that should be taken into consideration, is that the study was not powered for the subgroup analysis; hence, no firm conclusions could be drawn on these subgroup analyses, especially in the SSD population which at the 24-month visit only included ten patients (nine patients for the speech in noise test). However, as discussed by den Besten et al., since pooling of the data was not optimal due to differences between indications, the choice was made to also report data per indication.[11] Last, a significant percentage of our implant recipient were smokers, which could have influenced complication rates. However, we did not include an analysis regarding the influence of smoking on post-operative complications in our predefined statistical analysis plan.

4.3. Comparisons with other studies & clinical applicability

In the current study, we observed signs of inflammation or infection with a mean of 5.8% of the patients per visit after sound processor loading. These were most likely the result of the constant pressure the magnets apply to the skin, since the prevalence was lower prior to loading (1.9%). Furthermore, almost all events resolved after switching to a weaker SP magnet. As aforementioned, soft tissue outcomes should ideally be compared to the percutaneous counterpart; however, accurate comparison to these implants is impossible due to differences in reporting soft tissue status and the nature of skin complications, i.e. infection-related versus pressure-related. Moreover, until recently, no systematic soft tissue scoring system for transcutaneous implants was available.[15] This makes comparison to other studies evaluating the transcutaneous system difficult as well, since complications are not uniformly reported across studies.

However, previous studies have also reported on pressure-related issues: a too strong magnet resulted in pain and erythema, while a too weak magnet resulted in retention difficulties. The occurrence of various degrees of pain or discomfort in the first months after surgery varied across studies, ranging between 14.8 and 60% of the patients with the same transcutaneous system.[16-19] In line with our observation, a general trend was seen that pain was most frequently reported in the first months after surgery, but declined over time. Retention difficulties were reported in 83% of the patients in Powell et al. and in 20% of the patients in Carr et al.[18, 20] As a result, finding the optimal magnet strength often required additional visits to the clinic, but was eventually almost always achieved. The issue, whether it was pain or retention difficulties, most often resolved once switched to a different magnet strength.[17, 18, 20, 21] Based on our experience, great attention should be given to carefully selecting a magnet strength that suits each individual patient. A too

week magnet may fall off, and a too strong magnet may result in discomfort or skin soreness. It is important to regularly check the magnet, and change magnet strength when indicated due to insufficient retention or discomfort/soreness. In addition, patients should change the softpad regularly to warrant optimal pressure distribution and to avoid discomfort. Last, patients should be advised to use a safety line to avoid losing or damaging the sound processor in case it falls off.

The high rate of skin numbness after surgery followed by a decline over time was also reported in two other studies. Briggs et al. reported skin numbness in 62.9% of the patients immediately following sound processor fitting and in 22.2% of the patients nine months after surgery. [17] Godbehere et al. reported slightly lower skin numbness rates: in 48.1% of patients following surgery, and in 29.6% six months post-operatively.[22] In the current study, skin numbness declined from 77.8% (vital sensibility) and 66.7% (gnostic sensibility) of the patients at 10 days post-operatively, to 19.2% (vital sensibility) and 17.3% (gnostic sensibility) at 6 months, and finally to 2.2% (vital sensibility) and 8.7% (gnostic sensibility) at 24 months. In both studies, the same anterior based C-shaped incision was used as in the current study. Modifications to the incision technique to optimize soft tissue handling during surgery might play a pivotal role in improving clinical outcomes, and should therefore be further explored. [23] From a clinical perspective, until then, patients should be informed prior to surgery, that the majority of patients will, to some extent, experience post-operative skin numbness, but that this will most likely resolve entirely over time.

In line with previous observations 6 months after implantation [11], the 12-month outcomes of the three PRO questionnaires showed that the transcutaneous implant system continues to provide significant improvement in subjective hearing benefit and HRQoL also over the longer term in the total studied population. At the 24-month follow-up, hearing and health-related PROs remained stable in CHL/MHL patients; in patients with SSD, however, no significant benefit could be seen in terms of HRQoL, and statistically significant improvements in terms of subjective hearing outcomes seen at 6 months were no longer statistically significant.

The daily usage of the transcutaneous system was previously presented by Briggs et al. (follow-up of 6 months) and Gawecki et al. (follow-up of 9 months). For patients with CHL/MHL, daily sound processor usage seems comparable to our study at 6 months (8.3h/day versus 7.6h/day[17] and 10h/day[19]). For patients with SSD the daily use recorded in the present study was slightly lower than in patients with CHL/MHL, but comparable to the other studies (6.5h/day versus 6h/day[17] and 9h/day[19]). Furthermore, no patients in either of the two studies were non-users at the last follow-up. In our study, all patients used their sound processor to some extent at 6 months; however, among the patients with SSD who had the transcutaneous system in place, four stopped using the device for

different reasons (including one case of insufficient benefit) and average daily usage declined to 3h/day (including non-users) at 24 months. A diminished usage over time have also been observed in SSD patients with percutaneous systems.[24, 25] It should, however, be noted that patients with SSD may have sufficient hearing for normal communication, but typically experience difficulties with speech intelligibility in noise and sound localization.[26] It has been suggested that these difficulties are challenging to overcome by means of any bone conduction device.[27] In addition, since the start of current study new, more powerful sound processors have been developed. Future research is needed to determine the effect of a more powerful hearing device on daily use, PROs and audiological benefit.

5. Conclusion

The current multicentre study showed that after 24 months of follow-up, the transcutaneous implant for bone conduction hearing is safe to use and provides statistically significant improvement in hearing performance and patient-reported outcomes compared to the pre-operative unaided condition in studied patients with CHL, mild MHL or SSD. The transcutaneous test device did not necessitate daily skin care, although the magnetic coupling did result in pressure related symptoms, e.g. pain/discomfort and signs of inflammation. However, these symptoms were almost always relieved after switching to a weaker magnet strength. For the subgroup of patients with SSD, the improvement in speech understanding in noise and patient-reported outcomes was less outspoken than for patients with CHL/MHL and the percentage of non-users was higher. Since the sample size in the SSD group was too small to draw statistically supported conclusions, further research on a larger population is needed. Until then, for SSD patients an extra careful selection procedure may be needed. Based on the current results, the transcutaneous test device could be considered as an alternative treatment option for appropriately selected and counselled patients.

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Abbreviations used in this paper: BAHI: Bone Anchored Hearing Implant

Chapter 5

Economic evaluation of percutaneous titanium implants for bone conduction hearing: a cost-benefit analysis

I.J. Kruyt[1], M.R.W. Bours[1,2], M.M. Rovers[2,3], M.K.S. Hol[1], J.Rongen[2,4]

[1] Department of Department of Otorhinolaryngology, Donders Center for Neurosciences, Radboudumc
[2] Department of Operating rooms, Radboud Institute of Health Sciences, Radboudumc
[3] Department of Health Evidence, Radboud Institute of Health Sciences, Radboudumc
[4] Clinical Science & Medical Affairs, Image-Guided Therapy Systems, Philips, The Netherlands

Abstract

Introduction: Developments in bone-anchored hearing implants have resulted in fewer complications, and, thus, lower complication-related costs. However, a weighing of the potential clinical benefits with higher implant purchase price is lacking.

Methods: A mathematical Markov model was used to evaluate the total costs (complication costs, implant purchase price, and standard costs) of three widely used current generation implants with expected similar outcomes, compared to a previous generation implant in adult patients over a ten-year time horizon from a healthcare perspective. Parameter estimates were derived from published clinical literature. Missing parameter estimates were based on expert opinion. Implant costs were derived from manufacturer catalogues, while standard and complication costs related to the BAHI were derived from a Dutch University Hospital and Dutch guideline for cost-effectiveness research.

Results: The average total costs of the treatment with a previous generation implant was €4.967(SD±€134) per patient over a ten-year time horizon, compared to €4.678(SD±€83) with a current generation implant. This implant type is potentially up to €506 more beneficial per patient over a ten-year horizon. By further improving implant survival, an additional €645(SD± €86) per patient could be saved over ten years.

Conclusion: Despite a higher initial purchase price, the current generation implants are potentially cost-beneficial compared to previous generation implants. More data on current generation implants is needed to be able to determine which of the newer implants is most cost-beneficial. Focussing future developments on improving implant survival is likely to have more impact on costs compared to developments on improving soft tissue tolerability.

1. Introduction

The bone-anchored hearing implant (BAHI) is a semi-implantable type of hearing aid based on bone conduction. The BAHI offers a solution for patients with hearing loss that cannot benefit from conventional hearing aids (e.g. patients with conductive hearing loss, chronic ear infections, or anatomically unable to wear conventional hearing aids).[1]

The BAHI consists of three parts: a fixture, an abutment, and a sound processor. In the last decade new BAHI models have been introduced with modifications in abutment and fixture design. These modifications aimed to improve clinical outcomes. Indeed, fewer complications (i.e. skin reactions, skin overgrowth, and implant loss) have been reported with the new BAHI models.[2-4] However, over the past years an increase in purchase prices of these newer BAHI models has also been observed. This raises the question as to whether the potential improved performance of the BAHIs (i.e. decline in complications) outweighs the increasing costs of the new BAHI models. To answer this question, we performed a cost benefit analysis, using a mathematical model, to evaluate and compare total costs of BAHI treatment over a 10-year period with selected previous and current generation implants.

2. Methods

This report was written conform the guidelines for Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[5]

2.1. Population and implants

The target population consisted of patients (≥16 years of age) with either uni- or bilateral conductive or mixed hearing loss, or unilateral single sided deafness eligible for a BAHI. This study focused on the fixtures and abutments only, and excluded any modifications to the sound processor, as it is not associated with clinical complications. Four widely used BAHI's were included in the study. Three implants (Flange Fixture, BIA300 and BIA400) from Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden), and one implant (Wide Ponto) from Oticon Medical AB (Askim, Sweden) (Figure 1A).

2.2. Setting and timeframe

This economic evaluation was performed adopting a Dutch healthcare perspective. The cost related to the BAHI treatment were evaluated over a ten-year time horizon. This period was empirically chosen, based on the CHEERS guidelines, which states the time horizon —how far into the future outcomes are modelled—is dictated by the problem scope. In our case, we expected the majority of the patients to have the implant in place at least 10 years after surgery, while complications could occur anytime in this

time frame. In addition, we chose the 10-year timeframe since we deemed it long enough to capture all meaningful differences with respect to complications between both groups of implants.

2.3. Comparators and outcomes

The aim of the analysis was to evaluate whether the improved performance of the new BAHI models outweighed the increased purchase cost. Therefore, we compared the previous generation Flange Fixture implant, further referred to as the reference implant, with the three current generation implants (BIA300, BIA400 and Wide Ponto). These three

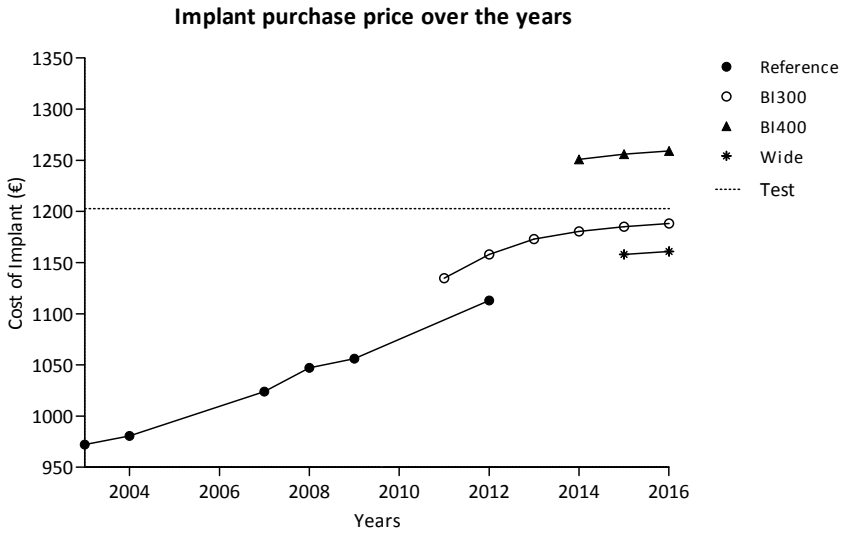


Figure 1. A, BAHI's used in the analyses: A. Flange Fixture*, B. BIA300*, C. BIA400* and D. Ponto Wide implant**. *Implant of Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden). **Implant of Oticon Medical AB (Askim, Sweden) (above). **B,** Overview of the purchase price of implants over the years from 2003 to 2017. The dotted line represents the price used for the test implant (below).

implants combined are referred to as the test implant group and all share a wider implant diameter (4.5mm diameter), compared to the smaller diameter previous generation implant (3.75mm diameter) From a clinical perspective they are expected to have similar outcomes.

2.4. Measurement of outcomes

Clinical outcomes of interest were implant related complications, including adverse skin reactions, implant survival, and skin overgrowth. We systematically searched the literature to identify original articles reporting on the prevalence of these clinical outcomes with respect to the type of implant in patients who underwent BAHI surgery. Abstracts were screened independently by two researchers, followed by a full text screening if deemed eligible. Data on skin reactions, skin overgrowth, and implant survival were systematically extracted from the studies. The detailed search strategy and screening procedure has been provided in Supplemental Digital Content I and II. The inclusion criteria were as follow: (1) patients ≥16 years of age with a BAHI, (2) adverse skin reactions (Holgers' classification ≥2)[6], (3) implant survival, (4) skin overgrowth, (5) retro- or prospective studies, (6) clear definition of implant type used, (7) follow-up time stated, and (8) implant received after 1988. The selection was independent of type of surgical technique, loading time or abutment length. Furthermore, reference lists of eligible studies and of studies citing the eligible studies were cross checked for additional studies.

Proportions of clinical outcomes reported in individual studies were pooled by applying a random intercept logistic regression model, taking inter- and intra- study differences of the clinical outcomes into account. Estimates were categorized per implant type and follow-up.

2.5. Costs and discounting

Standard costs and complication costs related to the BAHI were derived from the ENT department of the Radboudumc (Nijmegen, The Netherlands). Standard costs included all actions related to inserting and evaluating the implant (e.g. implant surgery and outpatient clinical visits). Costs that were not available were derived from the Dutch guideline for cost-effectiveness research.[7]

Implant purchase prices were obtained from the catalogues of the two manufacturers over the period ranging from 2003 to 2017 (figure 1B). The most recent implant price was used in the analysis. For the test implants we used the average purchase price of the three implants. Standard procedures for treating complications were aligned and verified with clinical experts (BAHI specialist).

Since all studies were published in or before 2016, all costs were presented in 2016 Euros, and if necessary cost were inflated to 2016 cost by using the Dutch consumer price index.[8] A cost overview is provided in table 1. As recommended by the Dutch guidelines for economic evaluations in healthcare, costs were discounted using a 4.0 % discount rate.[7]

Table 1. Overview of treatments and related costs

Action	Information	Costs (€)	Volume
Standard costs/Initial treatment costs			
Implant surgery			
*First consultation**	per intake consult	248,00	1 consult
*Operating Room**	Implant surgery per hour; Care/bed/(local)anaesthesia	700,00	1 hour
*Surgeon**	per hour	200,00	1 hour
*Operating room nurse**	per hour	50,00	1 hour
*Healing cap**	per unit	36,45	1 unit
Terra-Cortil®: Hydrocortisone, Oxytetracycline & Polymyxin B ●	per unit	8,52	1 unit
	Total	**1.242,97**	
Check-up: first year			
First check-up + Terra Cortil (1 week) □●	Regular outpatient visit + 1 unit	171,52	10 min
Second check-up (3 month) □	Regular outpatient visit	163,00	10 min
Third check-up (1 year) □	Regular outpatient visit	163,00	10 min
	Total	**497,52**	
Check-up: following years			
Yearly check-up □	Regular outpatient visit	163,00	10 min
	Total	**163,00**	
Treatment of complications			
Adverse skin reactions			
Terra-Cortril® ●	per unit	8,52	1 unit
Consult □	Regular outpatient visit	163,00	10 min
	Total	**171,52**	
Implant loss			
*New implant surgery**	Implant surgery with normal consult instead of intake consult, per hour	1.157,97	1 hour
New implant°	See figure 2	Dependent on implant	
First additional check-up + Terra-Cortil® (1 week) □●	Regular outpatient visit + 1 unit	171,52	10 min
Second additional check-up (3 month) □	Regular outpatient visit	163,00	10 min
	Total	**1.492,49 + new implant**	

Table 1. Continued

Action	Information	Costs (€)	Volume
Treatment of complications			
Skin overgrowth			
Skin revision surgery:			
Consultation □	Regular outpatient visit	163,00	10 min
*Operating Room**	Implant surgery per hour; Care/bed/(local)anaesthesia	700,00	1 hour
*Surgeon**	per hour	200,00	1 hour
*Operating room nurse**	per hour	50,00	1 hour
*Healing cap**	per unit	36,45	1 unit
Terra-Cortil®: Hydrocortisone, Oxytetracycline & Polymyxin B ●	per unit	8,52	1 unit
	Total	**1.157,90**	

* ENT Department, Radboud University Medical Centre (Nijmegen, Netherlands)
° Catalogue with price list from implant manufacturers
□ National Health Care Institute Manual
● https://www.medibib.be/producten/terra-cortril-huidzalf-15-gram

2.6. Choice of model

A mathematical Markov cohort model was used to evaluate the total costs over a ten-year time horizon (see figure, Supplemental Digital Content III, displaying the schematic overview of the Markov model for a single year).

2.7. Model description

The Markov model captures the course of the BAHI treatment and potential complication pathways over time. The model compared two strategies, a strategy in which a patient cohort received a reference implant, and a strategy in which a cohort received a test implant. Besides implant and surgery costs, each year there is a risk of developing any of the given complications, followed by a designated treatment, which results in complication related costs. The risk of developing complications varied between implant types and over time. The model simulated ten cycles of one year.

2.8. Model assumptions

Some assumptions had to be made due to a lack of published data. All assumptions were made in consultation with two clinical BAHI experts.

The first assumption was that patients could only develop one complication per year, and that every complication was treated successfully within that same year. Second, it was assumed that no skin overgrowth could be observed in the test implant group due to availability of abutments with an increased length. Third, if data was limited, we assumed that the incidence of complications decreased over time (Table 2).[2, 9]

2.9 Analytic methods

2.9.1. Base-case and threshold analysis

We applied a probabilistic Monte Carlo simulation, repeated over 5,000 samples, taking into account the relevant (2nd-order) uncertainty related to the sampling distribution of all input parameters. The cost for both strategies (reference implant vs. test implant) and the difference in outcome between the two were calculated.

In addition, a threshold analysis was performed to evaluate from which year the test implant will be equivalent in terms of cost compared to the reference implant.

2.9.2. Sensitivity analysis

A sensitivity analysis was performed wherein several variables were separately varied to determine their overall influence on the outcome. This was done as a series of one-way sensitivity analyses, i.e., only one parameter was varied at a time. All parameter estimates of complications were varied between the extreme values of its confidence interval. In addition, an extra analysis was performed to measure the effect of having multiple complications per year over the first three years. In this analysis, the patients could either develop a maximum of two or three skin reactions or an implant loss followed by a skin reaction.

2.9.3. Headroom analysis

A headroom analysis was performed to provide an estimation of the potential maximum cost savings of the test implant compared to the reference implant over ten years. This analysis provides information whether room for improvement is present for future implants, and if so, which component has the potential to save most costs. As such, a full headroom analysis and two scenario analyses were performed. In the first scenario, the patient did not have a risk of developing a skin reaction. In the second scenario, the patient did not have a risk of losing the implant.

Table 2. Overview of used parameter estimates in the model analysis

		Value	95% CI		
Implant	**Year**	**Deterministic**	**-**	**+**	**Source**
Skin reaction					
Reference	1	*0,2631*	*0,0492*	*0,7112*	Meta-analysis
	2	*0,0231*	*0,0148*	*0,0359*	Meta-analysis
	3	*0,0313*	*0,006*	*0,1466*	Meta-analysis
	4-5	= year 3			Assumption*
	6-10	= 80% of year 3			Assumption*
Test	1	*0,1206*	*0,0764*	*0,1853*	Meta-analysis
	2	*0,0514*	*0,0164*	*0,1497*	Meta-analysis
	3	*0,0122*	*0,0017*	*0,0815*	Meta-analysis
	4-5	= year 3			Assumption*
	6-10	= 80% of year 3			Assumption*
Bi300	1	*0,1353*	*0,0548*	*0,297*	Meta-analysis
Bi400	1	*0,1642*	*0,0492*	*0,427*	Meta-analysis
Wide	1	*0,1033*	*0,0668*	*0,1562*	Meta-analysis
Implant loss					
Reference	1	*0,0228*	*0,0127*	*0,0329*	Meta-analysis
	2	*0,0101*	*0,005*	*0,015*	Single study
	3	*0,0206*	*0,008*	*0,03*	Single study
	4	0,0162	0,01	0,025	Single study
	5	0,0212	0,015	0,03	Single study
	6-10	= 50%/45%/40%/35%/30% of year 5			Assumption*
Test	1	*0,0166*	*0,0069*	*0,0391*	Meta-analysis
	2	0,0074	*0,001*	*0,015*	Assumption*
	3	0,0150	*0,005*	*0,025*	Assumption*
	4	0,0118	*0,005*	*0,025*	Assumption*
	5	0,0154	*0,005*	*0,025*	Assumption*
	6-10	= 50%/45%/40%/35%/30% of year 5			Assumption*
Skin overgrowth					
Reference	1	*0,0000*	*0*	*0*	Single study
	2	*0,0038*	*0,002*	*0,005*	Single study
	3	*0,0103*	*0,005*	*0,015*	Single study
	4	0,0090	0,004	0,012	Single study
	5	0,0105	0,005	0,015	Single study
	6-10	= 0			Assumption*
Test	1-10	= 0			Assumption*

* Assumption based on expert opinion

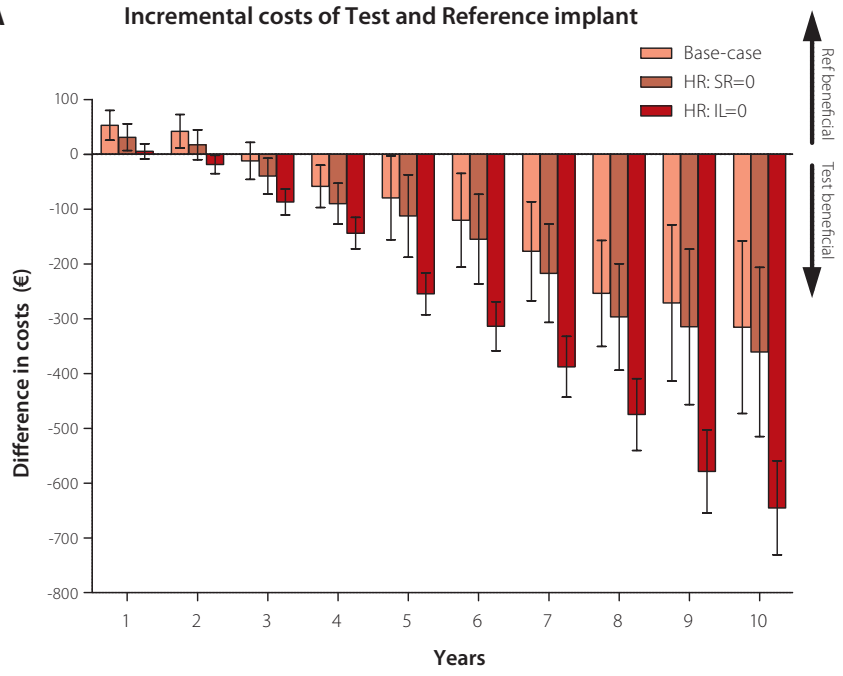
3. Results

The systematic search resulted in thirteen eligible studies (see table, Supplemental Digital Content IV).[2-4, 9-18] Two additional studies were identified by means of reference checking. All derived data was pooled in a meta-analysis (table 2). Based on this analysis, the test implants had both lower implant losses and skin reaction rates compared to the reference implant.

3.1. Base-case analysis & threshold analysis

The base-case analysis showed an average total cost of €4.678 (SD±€83) per patient for the test implant over a ten-year horizon, compared to €4.967 (SD±€134) per patient for the reference implant. Over a ten-year period, the test implant strategy was between €72 and €506 more cost-beneficial per patient than the reference implant strategy (figure 2A). The threshold analysis demonstrated that, compared to the reference implant, the test implant could be cost-beneficial as from the third year onward.

The total complication costs of both the reference and test implant are displayed in figure 2B. Costs for the treatment of skin reactions, skin overgrowth, and re-implantation were included in the costs of complications. Over ten years, complications from the test implant resulted in a mean cost of €384 (SD±€134) per patient compared to €785 (SD±€83) for the reference implant. The test implant thus saved €184 per patient in the worst-case scenario and €617 in the best-case scenario over ten years, confirming that the new introduced models have reduced complication-related costs.



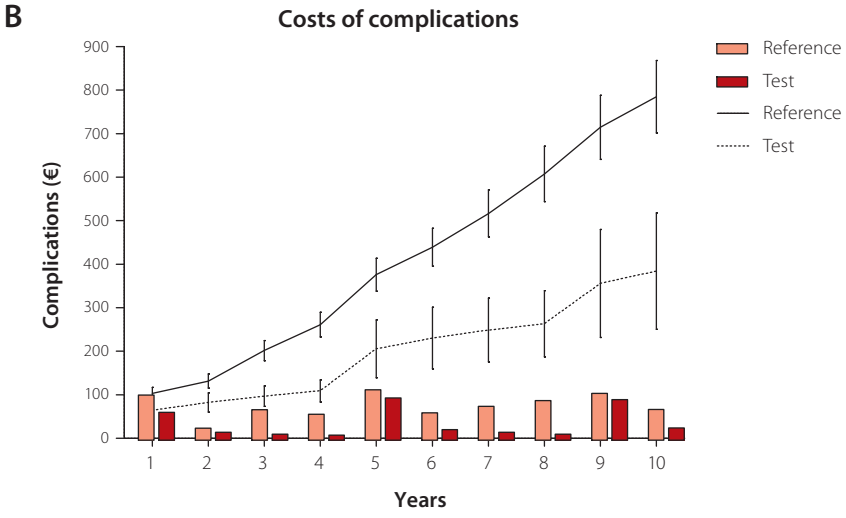


Figure 2. A (left), Analyses of the test implant compared to the reference implant. The cost difference between implants are represented over ten years. The total costs include the implant purchase price, costs of complications and standard costs. Base-case: Base-case analysis, HR:SR=0: Headroom analysis with hypothetical scenario without skin reactions, HR:IL=0: Headroom analysis with hypothetical scenario without implant losses. Positive bars indicate that the reference implant is cost-beneficial compared to the test implant. Negative bars indicate that the test implant is cost-beneficial compared to the reference implant. Whiskers represent range. **B** (right), Yearly and cumulative costs of complications of the reference and test implant. Implant loss, skin reactions, and skin overgrowth are taken into account. The bars represent the yearly costs of complications. The lines represent the cumulative costs related to complications over ten years. Reference: Flange fixture implant. Test: BIA300, BIA400 and Ponto Wide implant. Whiskers represent range.

3.2. Sensitivity analysis

The sensitivity analysis evaluated the effect of varying several variables on the model outcome. Although these variations had an (modest) effect on the absolute outcome, they did not influence the interpretation of the model outcome, namely that the test implant was cost-beneficial over a ten-year time horizon (Figure 3). Assuming that patients could develop more than one complication per year did also not influence the interpretation of the outcome.

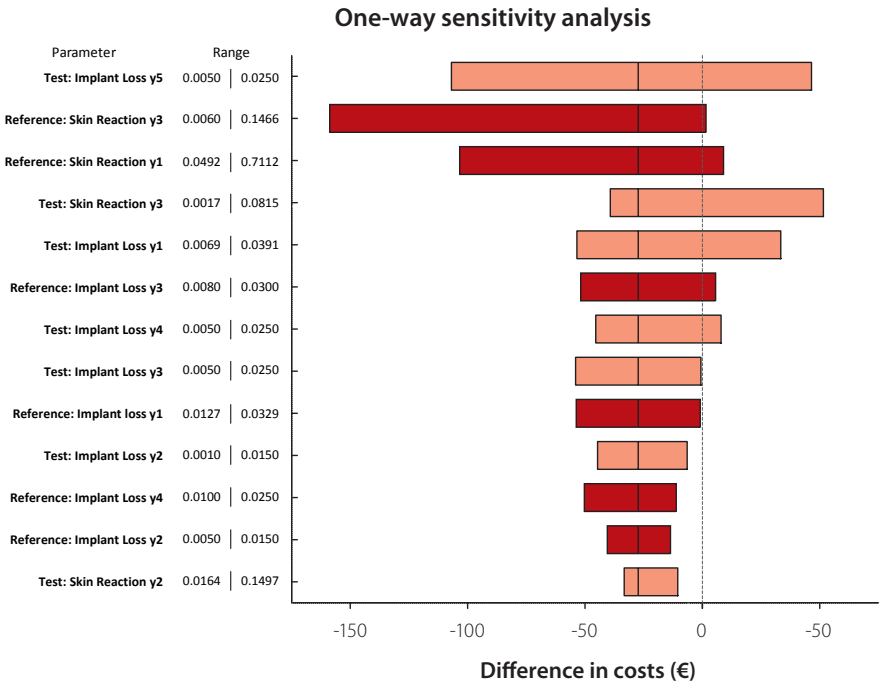


Figure 3. Multiple one-way sensitivity analysis on model outcome over ten years. Only parameters that affect the model outcome with more than €100.- are included. The variables are put in order from most effect to least effect. y1: parameter in year 1, y2: parameter in year 2 etc. The x-axis represents the difference in cost in favour of the test implant, i.e. larger difference is more favourable. The range reported on the y-axis per parameter is the range, i.e. confidence interval, over which the parameter is varied to determine its influence on the costs.

3.3. Headroom analysis

The headroom analysis showed a total potential cost savings between €590 and €756 per patient for the test implant compared to the reference implant over ten years (Figure 2A).

The two scenario analyses evaluated the potential maximum cost savings if either skin reactions or implant losses were completely prevented (figure 2A, grey and dark grey bar) compared to the reference implant. Completely preventing skin reactions (SR = 0) has the potential to save on average €361 (SD± €154) over a ten-year period. Completely preventing implant loss (IL = 0) has the potential to save on average €645 (SD± €86) over a ten-year period.

4. Discussion

The current study is the first to evaluate the current generation of widely used BAHI implants with the previous generation implant in an economic evaluation. This provided insight in costs over different generations of implants and allowed us to weigh cost and performance over the successive BAHI models.
Based on our meta-analysis and model outcome, the current generation implants seem to result in fewer complications and complication-related costs. Despite the higher purchase prices of the newer implants the improved performance led these implants to be cost-beneficial compared to the reference implant over a ten-year time period. The threshold analysis showed that the test implant could be cost-beneficial if used for at least three years. The headroom analyses showed that there is still room for reducing complication-related cost, in which future developments improving implant survival may be most attractive.

4.1 Limitations

Some potential limitations should be taken into consideration.

First, the availability of high-quality long-term data was limited. For the newer test implants follow-up data of more than three years were scarce. Next, follow-up data for the reference implant was only available from retrospective studies. To overcome this limitation, the data that was available was combined with expert opinion to make assumptions. These assumptions could potentially introduce bias. However, in health technology assessment it is best practice to use expert opinion in case of absence of high-level evidence. The interesting thing about these kind of modelling studies is that is allows for evaluating the impact of these expert opinions on the interpretation of the outcome. In our case, the sensitivity analyses evaluating the effect of these assumptions on the interpretation of the outcome demonstrated the effect to be limited. Nevertheless, prospective long-term data will be necessary in order to validate results, highlighting a need for registries.

Second, we assumed that a patient could only suffer one complication per year. In reality, patients may develop more than one complication per year. From a clinical perspective, however, multiple complications per year, necessitating additional outpatient visits, do not frequently occur. This questions the clinical relevance of including this pathway in a model. A sensitivity analysis evaluating the potential effect of this assumption demonstrated that it had no effect on the interpretation of the outcome.

Third, the reduced soft tissue complications rates could have been influenced by factors other than the implant updates. Modifications to the abutment design are more likely to have influenced soft tissue complication rates than the modification to a wider implant diameter. The influence of these abutment updates, however, are included in this review since these were updated within the new generation implants. However, since

both updates were introduced simultaneously it is impossible to determine its separate influence on the outcomes compared to the previous generation implant. The outcomes in this study, nonetheless, reflect the outcomes of both implant and abutment update.

Fourth, due to lack of data, we were not able to take different surgical techniques into account. Surgical techniques have changed over the years to reduce post-operative complication rates.[11, 13] This may have affected the risk of developing complications (i.e. skin complications rather than implant survival rates) and variations in surgery costs, and thus may have influenced the model outcomes. The potential effect would be that part of the (skin-related) benefits observed in our analysis are to be attributed to improvements in surgical procedures, rather than improvements in implants (abutment types). However, the systematic review by Verheij et al. concluded no statement could be made on which technique, skin preservation or skin reduction, or which technique of all skin preservation techniques, is superior.[19] Yet, based on tissue preservation techniques are suggested to have at least similar complications rates compared with skin thinning, although almost all included tissue preservation studies had a follow-up of 12 months or less. The long-term study comparing both techniques of Kruyt et al., which was not included in the review, underlines this outcome; both techniques were comparably excellent regarding implant survival and soft tissue tolerability.[20] Based on these studies, we believe the influence of tissue handling during surgery on clinical outcomes might not be a major factor for bias in our analysis. To overcome the potential influence of differences in surgical time between techniques on total costs, we decided to use the same surgical time in both groups to avoid the surgical time to influence the outcomes of our implant cost-benefit analysis. The minimal invasive Ponto surgery (MIPS) was not included in this evaluation as it was introduced in 2016, hence no data was yet available in our study period (2013-2017).

4.2. Comparison with other studies

This study is the first to compare the previous generation implant to multiple current generation implants, making the comparison with other studies difficult. Nonetheless, two studies evaluated the costs of the BAHI with the Flange Fixture implant (our reference implant).[21, 22] These studies were similar in methods. We found that the standard costs were different from our study (first year: €1.762 vs. £2640, following years: €163,- vs £72-). However, over ten years this difference has almost disappeared (€3069 vs.£3288). Costs of complications in these studies are higher for implant loss (€1577 vs. £2380) and lower for skin reactions (€171 vs £123). Differences in costs may be due to the costs from other countries, while the estimates from these studies were based from the UK healthcare system. However, the similarity in methods and setting may confirm our choice of types of included costs in our study.

4.3. Clinical implications and future perspectives

This modelling study provided a cost estimate of previous and current generation BAHI's, and provided insight into the effect of purchase prices to complication costs. Based on our results, our initial choice to use a 10-year time frame seems appropriate: a significant difference in total costs between groups was found. Taken together, these outcomes might be helpful in the decision-making concerning implant choices.

The current generation wide diameter implants, available since 2010, have shown superiority in terms of implant survival and skin reactions compared to the previous generation implant. However, maximum follow-up of the current generation is to date maximum 9 years, compared to 23 years follow-up of the previous generation (commercially available since 1988). Due to this and concomitant limited amount of published data of current generation implants, range estimates per implant are rather large and, thus, overlap each other, indicating clinical outcomes of the three current generation implants to be comparable. In current practice, patients are, therefore, offered a trial with devices of the different manufacturers on a headband at home. In this way, they are able to determine if, and which type of sound processor they prefer, before actual implant surgery will be performed. The patient then receives the implant compatible with this specific device.

However, more data on complication rates and more detailed information about surgical techniques and models used would allow for improved evaluations as well as to determine which of the three implants is most cost-beneficial. This may require setting up a(n) (inter)national database for collecting long-term clinical data of all current generation implants. We therefore propose a set of standards for reporting implant and surgery characteristics and outcomes after BAHI implantation that can help in future systematic reviews and cost-effectiveness studies (see table, Supplemental Digital Content V). Until that time, the Wide Ponto implant would be the most cost-beneficial implant choice within the test implants due to the lowest purchase price, whereas the BIA400 implant would be the least cost-beneficial implant with a purchase price that is almost €100,- higher.

5. Conclusions

The introduction of wide diameter implants for bone conduction hearing have resulted in fewer complication related cost, making them cost-beneficial compared to the previous generation BAHI model, despite their higher purchase prices. However, due to a lack of published data, no conclusions could be drawn on which of the wide diameter implants model is the most cost-beneficial. Therefore, more long-term data on current generation implants is necessary to further support in shared decision making. Furthermore, focussing future developments on improving implant survival is likely to save more costs compared to focussing on improving soft tissue tolerability of the implant.

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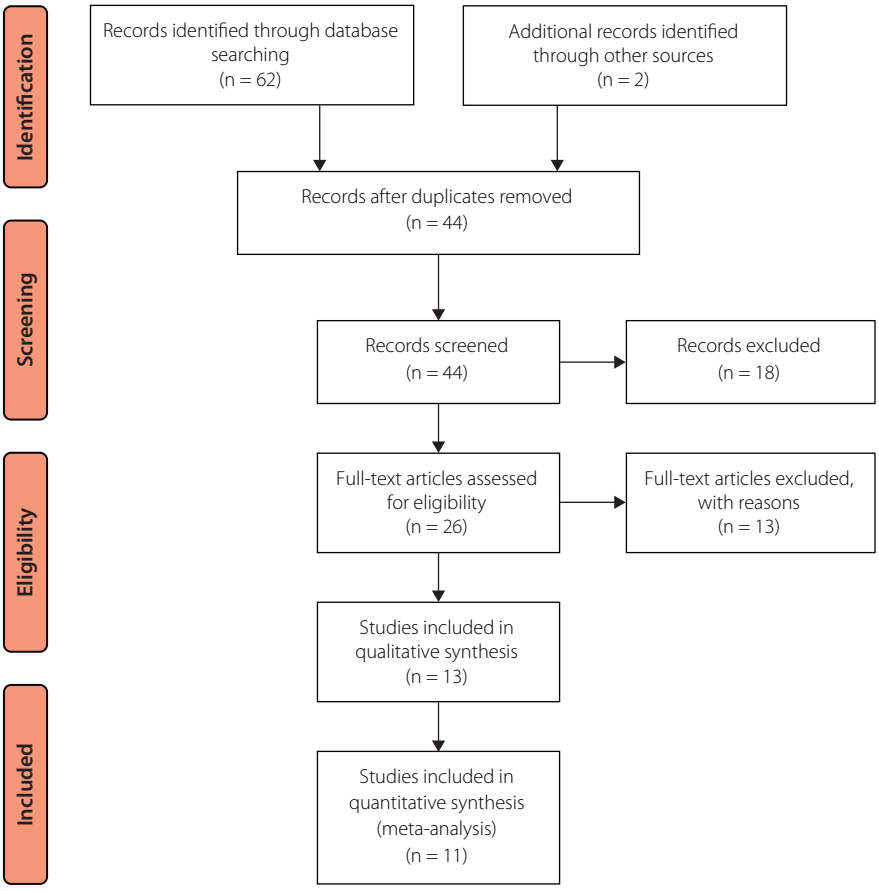
Supplemental Digital Content I: Search strategy

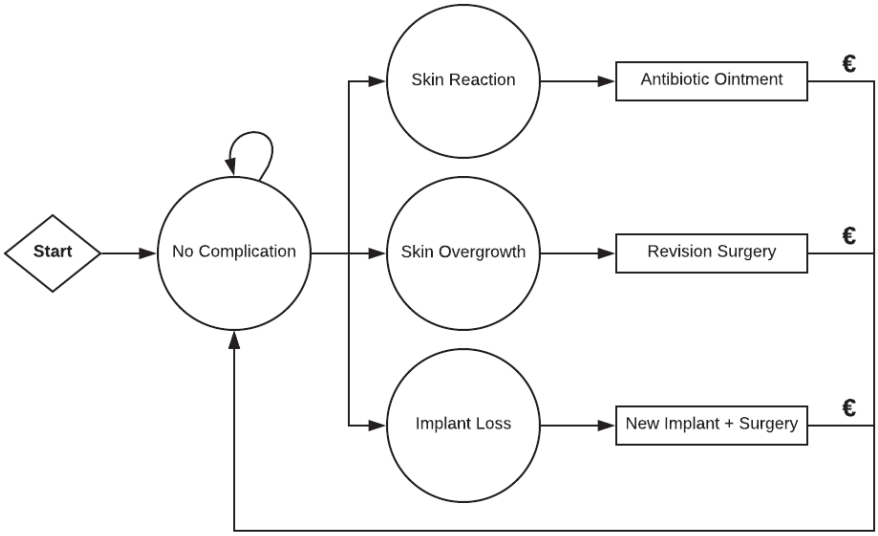
(((((surgery technique[Title/Abstract] OR linear incision technique[Text Word]) OR dermatome technique[Text Word]) AND skin thinning[Text Word]) OR tissue reduction[Text Word]) OR tissue preservation[Text Word]) OR ((((complication[Title/Abstract] OR complications[Title/Abstract]) OR soft tissue reaction[Title/Abstract]) OR soft tissue problem[Title/Abstract]) OR infection[Title/Abstract]) OR (((((revision surgery[Title/Abstract] OR implant loss[Title/Abstract]) OR fixture loss [Title/Abstract]) OR osseointegration[Title/Abstract]) OR osseointegration failure[Title/Abstract]) OR implant failure[Title/Abstract]) AND (((((Bone-anchored hearing aid[Title/Abstract] OR Bone-anchored hearing implant[Title/Abstract]) OR BAHA[Title/Abstract]) OR BAHI[Title/Abstract]) OR Bone conduction device[Title/Abstract]) OR BCD[Title/Abstract] OR Holgers [Tiab])

Supplemental Digital Content II: PRISMA Flow Diagram



Supplemental Digital Content III

A schematic overview of the Markov model for a single year. The patient has a risk of developing one of the complications, which changes each year. Each complication has a corresponding treatment and related costs. Each cycle represents one year. The model is run for ten cycles.



Supplemental Digital Content IV: Overview included studies

Study	Implant	Systematic search/ supplemented study
Dun 2012[9]	Flange Fixture	Additional study
Nelissen 2014[10]	Flange Fixture/BIA300	Systematic search
Høgsbro 2015[13]	BIA300	Systematic search
Nelissen 2015[2]	BIA300	Systematic search
Wilkie 2014[3]	BIA400	Systematic search
Høgsbro 2017[14]	BIA400	Systematic search
Foghsgaard 2014[15]	Ponto Wide	Systematic search
Caruso 2016[16]	Ponto Wide	Systematic search
Den Besten 2016[11]	Ponto Wide	Systematic search
Nelissen 2016[12]	Ponto Wide	Systematic search
Wazen 2016[17]	Ponto Wide	Systematic search
Mowinckel 2016[18]	Ponto Wide	Systematic search
Kruyt 2018[4]	Ponto Wide	Additional study

Supplemental Digital Content V: Proposed standards for reporting implant and surgery characteristics and outcomes after BAHI implantation

Type of implant (i.e. BI300, BI400, Wide Ponto Implant), including length of implant and abutment
Surgical technique (tissue reduction, tissue preservation, punch-only, other/specify)
State follow-up scheme and total follow-up duration in months*
Adverse skin reactions in absolute numbers*/** (reported according the Holgers score or the IPS-score)
Implant loss rate in absolute numbers*/** and state its cause (e.g. spontaneous, trauma or infection)
Skin revisions or abutment change in absolute numbers*/**

* reported per implant type and per surgical technique if more than one is reported in a study
** if possible reported per visit in case of a prospective study

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Chapter 6

The efficacy of Bone-Anchored Hearing Implant Surgery in children: a systematic review

I.J. Kruyt[1], K.H.E. Bakkum[1], C.J.I. Caspers[1], M.K.S. Hol[1]

[1] Department of Otorhinolaryngology, Donders Center for Neurosciences, Radboud university medical centre, Nijmegen, The Netherlands

Abstract

Objective: To evaluate the efficacy of Bone-Anchored Hearing implants (BAHIs) in children and to elucidate the usage and outcomes of new surgical techniques and implants in this specific population.
Data Sources: Embase and PubMed.
Study Selection: We identified studies evaluating surgical outcomes of BAHIs in children. Retrieved articles were screened using predefined inclusion and exclusion criteria. Critical appraisal included directness of evidence and risk of bias. Studies that successfully passed critical appraisal were included.
Data Extraction: Outcome measures included patient demographics, follow-up time, surgical technique (one- versus two-stage surgery), tissue handling technique (reduction versus preservation), type of implant used, and complications.
Data Synthesis: We selected 20 articles published between 2000 and 2017 for data extraction, encompassing 952 implanted BAHIs. The overall mean age at implantation was 8.6 years (range, 2-21 years). Adverse soft-tissue reactions occurred in 251 of the 952 implants (26.4%; range 0% to 89% across studies). Revision surgery was performed in 16.8% (142 of the 845) of the implants. The total rate of implant loss, i.e. caused by OIF (n = 61), trauma (n = 33), recurrent infection (n = 15), elective removal due to insufficient benefit (n = 1), cosmetic reasons (n = 1), or unknown reason (n = 16), was 13.3% of the implants (127 out of 952; range 0% to 40% across studies). Differences are seen in the type of implants used; wide-diameter implants seem to be superior in terms of implant survival, and similar in terms of adverse skin reactions, while one-stage surgery and soft-tissue preservation do not seem to result in higher implant loss rates or increased adverse skin reactions based upon limited amounts of literature.
Conclusion: In general, BAHIs are a safe method for hearing rehabilitation in children, although large differences between studies are observed. The outcomes of new surgical techniques and implant designs in the paediatric population seem promising, but more research is needed before definitive conclusions can be drawn.

1. Introduction

Percutaneous bone-anchored hearing implants (BAHIs) consist of a titanium fixture surgically placed in the mastoid bone and a skin penetrating abutment onto which a sound processor is coupled.[1] BAHIs with a coupled sound processor can be used to rehabilitate patients with conductive hearing loss, mixed hearing loss, or single-sided deafness.[2]

Until two decades ago, all BAHI surgery was performed in two stages in both children and adults. In the first stage, a 3.75mm diameter implant was placed in the mastoid bone. The second stage was performed approximately three months later to provide sufficient time for the implant to osseointegrate. In this stage, a skin-penetrating abutment was attached to the implant, combined with peri-implant soft-tissue removal, since the latter was hypothesized to reduce the occurrence of postoperative skin infections. Over the last two decades, however, both implant design and surgical techniques have evolved based on clinical research performed in adult BAHI-recipients. Nowadays, BAHI surgery in adults is safely performed in one stage, using previously smaller and later wider diameter implants, i.e. 4.5mm, and is nowadays combined with longer and differently shaped abutments and soft-tissue preservation instead of soft-tissue reduction. These developments have reduced the post-operative complication rates, e.g. soft-tissue reactions and implant failure, and have, thus, become the gold standard in adult patients.[3-8] However, a proportion of BAHI recipients are children, and since most research on developments has been performed in adults, surgeons remain more cautious in applying these new developments, i.e. surgical techniques, in children. Since higher complication rates have been reported in this specific population, it can be argued that, by adopting the new developments, complication rates might decline in children as well.[9-12] The aim of the current systematic research was, therefore, to evaluate the efficacy of BAHIs in children and to elucidate the usage and outcomes of both new surgical techniques and implants in the paediatric population.

2. Methods

2.1. Search strategy

The current systematic review was registered in Prospero (CRD42017078285) and was conducted adhering to PRISMA recommendations.[13] With expert librarian support, we designed and performed a comprehensive search in the databases PubMed and Embase from inception until July 17th, 2017, with an update on July 24th, 2019. The search terms were related to BAHI surgery and treatment outcomes, as described in Appendix A. Furthermore, reference lists of eligible studies and studies citing the eligible studies were checked for unidentified studies.

Study selection, data extraction, and critical appraisal were independently performed by two review authors (I.K & K.B). Obtained results were compared at each stage of the PRISMA flowchart. Any disagreements were solved by discussion, if necessary with a third reviewer (M.H.).

2.2. Study selection

First, all identified articles were screened on title and abstract. Studies evaluating surgical outcomes of BAHIs in children, e.g. soft-tissue reactions, revision surgeries, implant stability, implant loss, pain, and/or numbness, were considered eligible. Next, the full texts of these articles were reviewed. Case reports, opinion papers, reviews, animal studies, *in vitro* studies, and congress abstracts were excluded. Authors of articles either written in languages other than English or Dutch or without available full texts were contacted for obtaining an English full text. If not available, the study was excluded. Other exclusion criteria were: 1) missing information regarding follow up; 2) a study population of five or fewer children (total study population); 3) an age-mixed study population without subanalysis; 4) and studies not evaluating clinical outcomes of percutaneous BAHIs. If the patient population or data was presented in multiple articles, only the article considered most relevant/comprehensive was included.

2.3. Data extraction

Demographic data, surgical technique, implant design, and surgical outcomes, e.g. soft-tissue reactions and implant loss, were extracted using predefined data extraction forms in Excel (Appendix B).

2.4. Critical appraisal

Eligible studies were critically appraised for the directness of evidence (DoE) and the risk of bias (RoB) on predefined criteria. The DoE was assessed using six criteria: study design, study population, indication for surgery, surgical procedure, outcome measures, and follow-up. The DoE was rated high in studies with positive scores on five or six criteria, as moderate in studies with positive scores on four criteria, and as low in studies with positive scores on less than four criteria. RoB was assessed using eight criteria: missing data, not standardized follow-up, risk of confounding, risk of selective reporting, risk of selection bias, risk of bias in measurements of outcomes, risk of bias in classification of interventions, and a study population of <10 children. The RoB was rated low in studies with positive scores on nil or one criterion, as moderate in studies with positive scores on two or three criteria, and as high in studies with positive scores on four or more criteria. Studies with high or moderate DoE and with low or moderate RoB were included in the data synthesis.

3. Results

3.1. Search results and critical appraisal

The study selection process is demonstrated in figure 1. After removing duplicates, a total of 2171 unique articles were identified in our primary search. After screening the title and abstract, 161 full texts were reviewed. Thirty-four articles were eligible for critical appraisal, of which 20 passed the quality assessment. The updated search resulted in 172 additional articles, of which only one did pass the screening and selection on full text, but not the critical appraisal.[14] For unclear reasons, one article did not appear in the PubMed search results but was identified in the reference list of another study. This identified study successfully passed the critical appraisal.[15] In total, 20 articles were included in the data

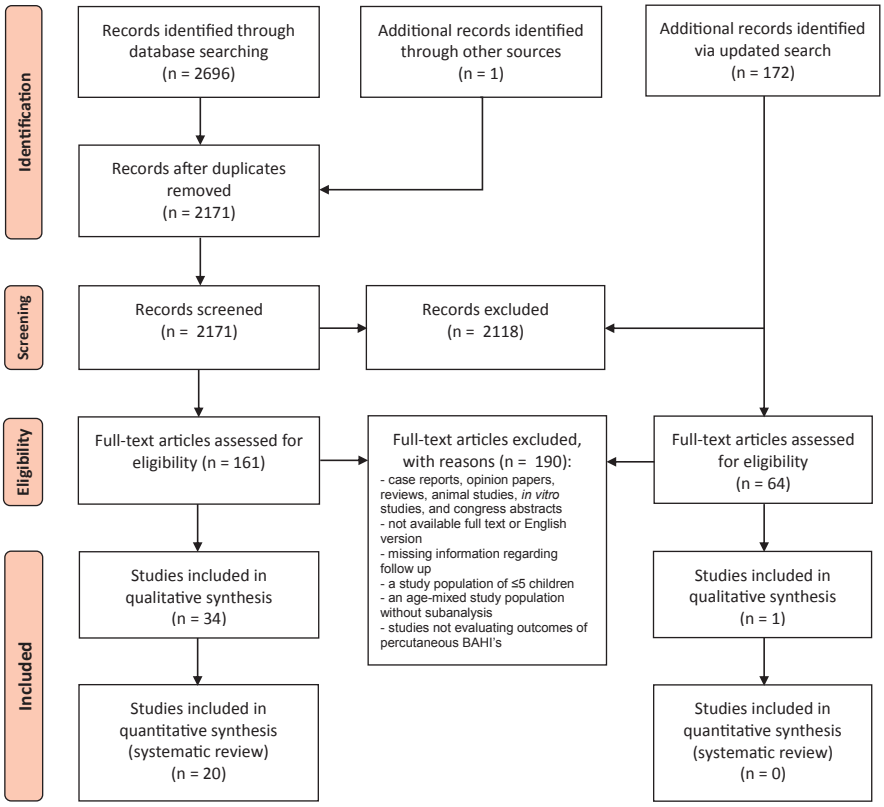

Figure 1. Flowchart demonstrating the study selection process. The initial search was performed on July 17th, 2017. Due to the large interval, the search was repeated on July 24th, 2019, to identify newly published articles.

Table 1. Critical appraisal of selected studies

		Directness of evidence (DoE)								Risk of bias (RoB)								
	Year	Study design	Study population	Indication for surgery	Surgical procedure	Outcome measures	Follow-up	DoE-score	Missing data	Standardization of follow-up	Confoun-ding	Selective reporting	Selection bias	Standardization of outcomes	Classification of intervention	>10 children	RoB-score
Ali *et al. [16]*	2009	PCS	●	●	●	○	○	M	●	⊖	●	●	●	○	●	●	L
Bejar- Solar *et al. [17]*	2000	PCS	●	●	●	●	●	H	●	●	●	●	○	●	●	●	L
Den Besten *et al. [23]*	2015	RCS	●	●	●	●	⊖	M	○	⊖	⊖	●	●	●	●	●	M
Felton *et al.[18]*	2014	PCS	⊖	●	⊖	●	⊖	M	●	○	●	●	●	●	⊖	○	M
Hultcrantz *et al.[19]*	2015	PCS	●	●	●	●	⊖	H	●	●	●	●	●	●	●	○	L
Kohan *et al.[24]*	2008	RCS	●	●	●	⊖	●	H	●	●	●	●	●	⊖	●	●	L
Kraai *et al.[25]*	2011	RCS	●	●	●	⊖	●	M	⊖	⊖	⊖	●	●	●	●	●	M
Lanis *et al.[26]*	2013	RCS	●	●	●	⊖	●	M	●	○	⊖	●	●	⊖	⊖	●	M
Lloyd *et al.[27]*	2007	RCS	●	●	●	⊖	●	M	●	⊖	●	●	●	⊖	⊖	●	M
Marsella *et al.[20]*	2012	PCS	●	●	●	●	⊖	H	●	●	⊖	●	⊖	●	⊖	○	M
Marsella *et al.[28]*	2012	RCS	●	●	●	●	●	H	●	⊖	⊖	●	●	●	●	●	L
Mazita *et al.[29]*	2009	RCS	●	●	●	⊖	●	M	●	○	●	●	○	⊖	●	●	M
McDermott *et al.[30]*	2009	RCS	●	●	●	⊖	●	M	●	○	⊖	●	⊖	⊖	⊖	●	M
McLarnon *et al.[21]*	2014	PCS	●	●	●	●	○	H	●	●	●	●	●	●	●	●	L
Mierzwinski *et al. [22]*	2015	PCS	●	●	●	●	○	H	●	⊖	⊖	●	●	●	●	●	L
Nelson *et al.[31]*	2016	RCS	⊖	●	●	⊖	●	M	⊖	⊖	●	●	●	○	⊖	●	M
Romo *et al.[35]*	2009	RCS	●	●	⊖	⊖	●	M	●	●	●	●	●	⊖	⊖	●	M

Rosa *et al.[33]*	2017	RCS	●	●	●	●	●	H	○	○	●	●	●	●	⊖	●	M
Saliba *et al.[34]*	2012	RCS	●	●	●	⊖	●	M	●	○	●	●	●	⊖	●	●	L
De Wolf *et al.[15]*	2008	RCS	●	●	●	●	●	H	●	○	⊖	●	●	●	●	●	L

Directness of evidence (DoE):
Study design: RCS indicates retrospective case study and PCS prospective case study; Study population (number of patients, age at surgery, sex): complete ●, not complete ⊖, not reported ○; Indication for surgery: clearly reported and complete ●, not clearly reported or incomplete ○; Surgical procedure: clearly reported and complete ●, Reported but not elaborated ⊖, not clearly reported or incomplete ○; Outcome measures on soft tissue reactions, revision surgeries, implant stability, implant loss, pain and numbness: clearly reported ●, reported but soft tissue reactions not according to Holgers or inconsistent data ⊖, not reported or unclear ○; Follow-up: minimum of >1 year ●, between 6 months and 1 year ⊖, less than <6 months or not reported ○
DoE score: High (H) ≥ 5 points, Moderate (M) 4 points, Low (L) < 4 points

Risk on Bias (RoB):
Missing data: no missing data or missing data are explained ●, missing data ○; Standardization of follow-up: Identical length and moments of follow-up for all patients ●, only identical length or moments of follow-up for all patients ⊖, no identical length and moments of follow-up for all patients or not reported ○; Risk on confounding: no risk on confounding, 1 other factor than surgical procedure, implant design and population could affect the outcomes ●, >1 other factors than surgical procedure ⊖, implant design and population could affect the outcomes ○; Risk on selective reporting: no selective reporting ●, selective reporting ○; Risk on selection bias: the included patients are representative for all children with indication for a BAHI ●, the patients are selectively included according to predefined inclusion and exclusion criteria ○; Standardization of outcome measures: standardization of skin reactions using the Holgers classification and standardization of implant stability with ISQ values ●, standardization of skin reactions using the Holgers classification or implant stability with ISQ values ⊖, no standardization of both skin reactions and implant stability or unclear outcome measures ○
Risk on bias in classification of interventions: standardization of surgical procedure, implant design and/or a subanalysis of outcomes for different surgical procedures and implant designs ●, differences in surgical procedures or implant designs without a subanalysis of outcomes ⊖, differences in both surgical procedures and implant designs ○ ; >10 children ●, ≤ 10 children ○

RoB score: Low (L) ≥ 7 points, Moderate (M) ≥ 5 < 7 points, High (H) < 5 points
Studies with H or M for DoE and L or M for RoB, were included.

synthesis (table 1): seven prospective cohort studies or case series [16-22] and thirteen retrospective cohort studies or case series [15, 23-34]. No randomized controlled trials (RCTs) were included.

3.2. Patient and implant characteristics

Patient and implant characteristics of the 20 studies are summarized in table 2. All studies combined encompassed 854 patients, of which 851 patients were aged 18 years or younger. The study of Nelson *et al.* contained two patients (2.9% of their study population) of 19 years old, while Marsella *et al.* contained one patient of 21 years old, both without a subanalysis.[28, 31] However, the large populations and expected minimal influence on outcome outweighed the exclusion of these studies. Slightly more males were included (406 versus 371; N/A in 77 patients). After excluding the 21-year-old patient from Mazita *et al.*[29], reporting outcomes per patient, and patients lost-to-follow-up, 825 patients were included in the data synthesis. The overall mean age at implantation was 8.6 years (range, 2-21 years). The most-reported indications for implantation were a conductive or mixed hearing loss caused by unilateral or bilateral aural atresia/microtia, chronic otitis media, recurrent otorrhoea, canal atresia or stenosis, or congenital craniofacial malformation. Forty-four percent of the patients had an underlying syndrome, e.g. Treacher Collins syndrome (105 patients), Goldenhar syndrome (70 patients), Down syndrome (44 patients), and CHARGE-association (19 patients).

Sixteen studies reported the number of implants installed, of which seven implants (number of patients unknown) were lost-to-follow-up, encompassing 850 implants. [15, 17-24, 26-28, 30, 31, 33, 35] The other four studies reported the number of patients instead, totalling 102 patients.[16, 25, 29, 34] Assuming these patients were implanted unilaterally, a total of 952 implants were installed. Of these, 274 implants were placed in one-stage surgery[15, 16, 18-24, 26, 28-31, 33-35] and 643 implants in two-stage surgery.[15, 17, 19, 23, 25-31, 33, 35] In 35 implants, no information on surgical instalment was available.[26] Soft-tissue reduction was performed in 868 implant instalments[15-18, 20-31, 33, 34], soft-tissue preservation in 62 implant instalments[19, 22, 23, 26], and in 22 implants the surgical technique was unknown.[35] Of all the implants used, 573 were small-diameter implants[15-17, 20, 24, 25, 27, 29-31, 35] compared to 219 wider diameter implants.[18-23, 31] In 160 implants, implant type was unknown.[26, 28, 33, 34] Duration of follow-up and follow-up moments varied widely between studies. The mean follow-up time ranged from 3 months to 6.4 years. However, 14 out of the 20 studies had a mean follow-up of at least one year[15, 17, 19, 24-31, 33-35], and the mean follow-up of 12 of these 14 studies was two years or more.[15, 17, 24-31, 34, 35] The mean interval between stages in two-stage surgery ranged from 2.8 to 6.8 months.[17, 19, 23, 25-30, 33, 35] The mean interval between abutment instalment surgery and processor loading in one-stage surgery ranged from 1.4 to 6 months.[16, 18, 20-24, 26, 28, 34] The mean interval between the second stage of two-stage surgery and processor loading ranged from 0.2 to 3 months.[17, 23, 26, 28]

3.3. Surgical outcomes

Surgical outcomes are summarized in table 2. It should be noted that complication rates were reported differently among studies: in the absolute number of patients, the absolute number of implants, or the absolute number of observations. For clarity purposes, all complications in table 3 are noted in the absolute number of implants, unless otherwise specified. The implant loss rate was evaluated in all studies.

3.3.1. Soft-tissue reactions

In 13 studies, soft-tissue reactions were scored according to Holgers classification - ranging from Holgers 0 (no soft-tissue reaction) to Holgers 4 (extensive soft-tissue reaction necessitating revision surgery or explantation).[15, 17-19, 21-23, 25-28, 33, 36] A Holgers Grade ≥2 was observed in 25.8% of the implants (151 of 585), while a Holgers 4 was reported in 5.1% of the implants (30 of 585). [15, 17-23, 25-28, 33, 36]] Holgers ≥2 are considered clinically relevant since these necessitate medical treatment.[36] The other seven studies did not report skin status according to the Holgers score. However, in these studies, adverse soft-tissue reactions were defined as a skin complication necessitating treatment and occurred in 25.3% of the implants (93 of 367). [16, 24, 29-31, 34, 35] Combining the data, adverse soft-tissue reactions occurred in 251 of the 952 implants (26.4%; range 0% to 89% across studies).[15-31, 33-35]

3.3.2. Revision surgeries

Revision surgery was performed in case of skin or bony overgrowth. Revision surgeries rates were reported in 16 studies and ranged from 0% to 44.4% of the implants. In total, revision surgery was performed in 16.8% (142 of the 845) of the implants. Furthermore, 3.7% of the abutments (31 of the 845 implants) were changed to overcome skin overgrowth. [15, 16, 20-30, 33-35]

3.3.3. Osseointegration failure and implant loss

Osseointegration failure (OIF), i.e. spontaneous implant loss without an identifiable cause, occurred in 6.4% of the implants (61 of the 952, range 0-21.6% across studies). The total rate of implant loss, i.e. caused by OIF (n = 61), trauma (n = 33), recurrent infection (n = 15), elective removal due to insufficient benefit (n = 1), cosmetic reasons (n = 1), or unknown reason (n = 16), was 13.3% of the implants (127 out of 952; range 0% to 40% across studies). [15-17, 19-31, 33-35]

3.3.4. Persistent postoperative pain & skin numbness

Two studies evaluated post-operative pain. In these studies, persistent postoperative pain was reported in 1.4% of the patients (1 out of 72).[26, 34] Skin numbness was evaluated in 2 studies and was reported in 26.1% (12 out of 46) of the implants 12 months after surgery. [19, 26]

Table 2. Data extraction and complications

	Factors affecting outcomes													Complications			
						Tissue handling technique		Surgical technique		Implant type							
	No. of patients in data analysis	Mean age at surgery (years)	No. of implants in data analysis	Mean follow-up time (range) in months	Follow-up schedule	Tissue reduction (n*)	Tissue preservation (n*)	One-stage surgery (n*)	Two-stage surgery (n*)	Small diameter (n*)	Wide diameter (n*)	Mean interval between stages (months)**	Mean time till loading (months)	Adverse skin reaction (n*)	Revision surgery (n*)	OIF (n*)	Implant losses (n*)
Ali *et al. [16]*	30	9.1 (range 3-15)	30	N/A (…-96)	2w, 4-6w, 6m, 12m	30	0	30	0	30	0	N/A	2.3-2.8	4 (13.3%)	0 (0%)	0 (0%)	2 (6.7%)
Bejar- Solar *et al. [17]*	11	10.0? (range 5-17)	11	24	1m, 2m, 4m, 6m, 12m, 18m, 24m	11	0	0	11	11	0	>3	0.5	4 (36.4%)	N/A	1 (9.1%)	1 (9.1%)
Den Besten *et al. [23]*	79	9.4 (range 3-17)	115	11.7 (0.2-30.2)	1w, 1-12w pre-loading, 3m, 6m, 9m, 12m post-loading in Birmingham and 3m, 9m, 12m in Nijmegen	80	35	22	93	0	115	2.8	1.4-2.8 (OS); 0.2-0.9 (TS)	32 (27.8%)	33 (28.7%)	3 (2.6%)	4 (3.5%)
Felton *et al. [18]*	9	9.4 (range 4-13)	10	9.5 (0.8- 19)	Not standardized	10	0	10	0	0	10	N/A	3.3	1 (10%)	N/A	0 (0%)	0 (0%)
Hultcrantz *et al. [19]*	10	5.1 (range 2-15)	10	12	1w, 3m, 6m, 12m	0	10	7	3	0	10	3	0.9-1.4	8 (80%)	N/A	2 (20%)	4 (40%)
Kohan *et al. [24]*	16	9.4 (range 6-13)	18	24.2 (11.25-41)	1-2w, 3-4m, annually	18	0	18	0	18	0	N/A	4	3 (16.7%)	2 (11.1%)	0 (0%)	0 (0%)
Kraai *et al. [25]*	27	8.2 (range 1-16)	27	33.6 (6-96)	Every 4-6m	27	0	0	27	27	0	3-6	N/A	23 (89%)	12 (44.4%)	3 (11.1%)	3 (11.1%)
Lanis *et al. [26]*	33	6.5 (range 2-15)	35	76.8 TR, 15.6 TP	1w, then N/A	25	10	N/A	N/A	N/A	N/A	3	1.4 (OS); 3 (TS)	10 (30.3%)	6 (17.1%)	5 (14.3%)	6 (17.1%)
Lloyd *et al. [27]*	71	8.7 (range 3-17)	85	54	3w, 3m, 6m, every 6m	85	0	0	85	85	0	6.8	N/A	26 (30.6%)	36 (42.4%)	6 (7.1%)	22 (25.9%)

Marsella *et al. [20]*	10	7.8 (range 3-11)	10	6	1w, 2w, 1m, 2m, 3m, 4m, 5m, 6m	10	0	10	0	5	5	N/A	6	2 (20%)	1 (10%)	0 (0%)	0 (0%)
Marsella *et al. [28]*	47	8.0 (range 1-21)	47	36 (1-168)	1w, 2w, 1m pre-loading 1m, 6m, 12m, 18m, 24m, annually	47	0	15	32	N/A	N/A	4	6 (OS), 3 (TS)	3 (6.4%)	1 (2.1%)	0 (0%)	2 (4.3%)
Mazita *et al. [29]*	15	8.1 (range 3-16)	15	54.4 (4-84)	N/A	15	0	4	11	15	0	4.1	>1	5 (33.3%)	4 (26.7%)	1 (6.7%)	1 (6.7%)
McDermott *et al. [30]*	165	6.8 (range 2-15)	182	(48-156)	4-8d, 3m, 12m, then N/A	182	0	8	174	182	0	4.7	N/A	34 (18.6%)	14 (7.7%)	19 (10.4%)	32 (17.6%)
McLarnon *et al. [21]*	22	9.0 (range 2-16)	30	3.7	4w, 16w	30	0	30	0	0	30	N/A	1.4	0 (0%)	0 (0%)	0 (0%)	3 (10%)
Mierzwinski *et al. [22]*	22	9.8 (range 5-16)	24	3	Pre-loading: 1-2w, 1-4m Post-loading: 2-4 w, 3m	17	7	24	0	0	24	N/A	1.7	9 (37.5%)	0 (0%)	0 (0%)	0 (0%)
Nelson *et al. [31]*	68	11.0 (range 5-19)	74	59 (11-74) (SDI), 32 (7-50) (WDI)	1-2w, 6m, 12m, annually	74	0	23	51	49	25	N/A	N/A	39 (52.7%)	N/A	5 (6.8%)	16 (21.6%)
Romo *et al. [35]*	19	9.4 (range 6-14)	22	35 (6-60)	Every 6 months	N/A	N/A	14	8	22	0	4	0.7-1.4	5 (22.7%)	5 (22.7%)	1 (4.5%)	2 (9.1%)
Rosa *et al.[33]*	52	10.6 (range 4-17)	52	>12	N/A	52	0	12	40	N/A	N/A	4.5	N/A	12 (23.1%)	5 (9.6%)	3 (5.8%)	6 (11.5%)
Saliba *et al.[34]*	26	8.5 (range 5-17)	26	26.5	N/A	26	0	26	0	26	0	N/A	4	3 (11.5%)	1 (3.8%)	0 (0%)	2 (7.7%)
De Wolf *et al.[15]*	93	9.0 (range 3-16)	129	30 (0-159)	Every 4m, later every 6m, finally every 12m	129	0	21	108	129	0	4.3	4.3	28 (21.7%)	22 (17.1%)	12 (9.3%)	21 (16.3%)
Total	**825**	**8.6 (2-21 years)**	**952**	**-**	**-**	**868 (91.2%)**	**62 (6.5%)**	**274 (29.9%)**	**643 (70.1%)**	**599 (72.3%)**	**219 (26.4%)**	**-**	**-**	**251 (26.4%)**	**142 (16.8%)**	**61 (6.4%)**	**127 (13.3%)**

OS = One-stage surgery; TS = two-stage surgery; OIF = Osseointegration failure; N/A = Not available; SDI = Small-diameter implants; WDI = Wide-diameter implants

* Number of implants **Mean interval between stages in case of two-stage surgery

3.4. Comparisons

3.4.1. One-stage versus two-stage surgical techniques

In seven studies, only one-stage surgery was applied [16, 18, 20-22, 24, 34] while three studies only applied two-stage surgery.[17, 25, 27] In the other ten studies, both one-stage and two-stage surgery were used, although in only four, data was presented per surgical technique.[15, 28, 29, 35] None of the studies were designed to compare one-stage surgery to two-stage surgery. In total, clinical outcomes were available of 202 implants (21.2%) installed in one-stage surgery, compared to 283 (29.7%) implants instalments in two-stage surgery.[15-31, 33-35] Implant loss, OIF, revision surgery, and soft-tissue reactions occurred in 5.0%, 1.0%, 3.2%, and 15.0%, respectively, of the implants placed in one-stage surgery, compared to 17.0%, 6.7%, 33.3%, and 41.6%, respectively, of the implants placed in two-stage surgery (table 3).

3.4.2. Tissue reduction versus tissue preservation

Three studies compared surgical outcomes of the soft-tissue reduction and preservation techniques (table 4).[22, 23, 26] In a subgroup analysis, Den Besten *et al.* observed few implant losses in both groups but more soft-tissue complications in the tissue reduction group. Eighteen abutments were changed in the reduction group, compared to 3 in the preservation group. Some of these implants required both soft-tissue revision and abutment change performed simultaneously in one revision surgery.[23] In den Besten *et al.* and Lanis *et al.*, the rate of revision surgeries was higher in the soft-tissue reduction group.[23, 26] Lanis *et al.* reported a higher soft-tissue reaction rate in the tissue reduction technique group, while in Mierzwinski *et al.,* the rate of soft-tissue reactions was comparable between techniques.[22, 26] In Lanis *et al.*, a higher implant loss rate was observed in the soft-tissue reduction group compared to the preservation group.

Furthermore, Lanis *et al.* reported persistent postoperative pain in 1/35 (3.0%) implants and numbness in 12/35 (36.4%) implants, all placed using the soft-tissue reduction technique.[26]

3.4.3. Small versus wide-diameter implants

Small-diameter implants were used in 11 studies (573 implants) [15-17, 20, 24, 25, 27, 29-31, 35], while in 7 studies a wide-diameter implant was used (219 implants).[18-23, 31] In 4 studies, implant type was not specified (160 implants).[26, 28, 33, 34] Only two studies compared the surgical outcomes of small-diameter implants (3.75mm) to wide-diameter (4.5mm) implants. [20, 31] In Marsella *et al.*, the main outcome, mean primary (intra-operatively) implant stability quotient (ISQ), was significantly higher in patients with the wide-diameter implant(8.6 ISQ units) compared to the small-diameter implants. However, no implant failures occurred in either group.[20] In Nelson *et al.*, significantly more OIF and implant losses were observed in the small-diameter implant group, while no differences were observed in soft-tissue reactions.[31]

Table 3. Comparison of surgical outcomes between one-stage and two-stage surgery

One-stage surgery	Mean age Years (range)	Implants (n)	Soft tissue reactions (n)	Revision surgery (n)	OIF (n)	Implant loss (n)
Ali et al.[16]	9.1 (3-15)	30	4	0	0	2
Felton et al.[18]	9.4 (4-13)	10**	1	N/A	0	0
Marsella et al.[20]	7.8 (3-11)	10**	2	1	0	0
McLarnon et al.[21]	9 (2-16)	30**	0	0	0	3
Mierzwinski et al.[22]	9.8 (5-16)	24**	9	0	0	0
Kohan et al.[24]	9.4 (6-13)	18	3	2	0	0
Saliba et al.[34]	8.5 (5-17)	26	3	1	0	2
Marsella et al.[28]	11 (4-?)	15***	N/A	0	0	0
Mazita et al.[29]	15 (14-16)	4	1	1	0	0
Romo et al.[35]	9.4 (6-14)*	14	N/A	N/A	0	0
De Wolf et al.[15]	9.0 (3-16)*	21	N/A	N/A	2	3
Total	9.3 (2-17)	202	23/153 (15%)	5/157 (3%)	2/202 (1%)	10/202 (5%)

Two-stage surgery	Mean age Years (range)	Implants (n)	Soft tissue reactions (n)	Revision surgery (n)	OIF (n)	Implant loss (n)
Bejar-Solar et al.[17]	10 (5-17)	11	4	N/A	1	1
Kraai et al.[25]	8.2 (1-16)	27	23	12	3	3
Lloyd et al.[27]	8.7 (3-17)	85	26	36	6	22
Marsella et al.[28]	6.5 (3-?)	32***	N/A	1	0	2
Mazita et al.[29]	5.5 (3-9)	11	4	3	1	1
Romo et al.[35]	9.4 (6-14)*	8	N/A	N/A	1	2
De Wolf et al.[15]	9.0 (3-16)*	108	N/A	N/A	N/A	18
Total	8.3 (1-17)	283	57/137 (42%)	52/156 (33%)	12/178 (7%)	49/289(17%)

* mean age for the entire cohort, i.e. both one-stage and two-stage surgery combined; **Wide diameter implant; ***Implant type unknown

Table 4. Surgical outcomes of the soft-tissue reduction technique versus soft-tissue preservation technique

Tissue preservation	Mean age Years (range)	Implants (n)	Soft tissue reactions (n)	Revision surgery (n)	OIF (n)	Implant loss (n)
Mierzwinski et al.[22]	9.8 (5-16)*	7**	3	0	0	0
Den Besten et al.[23]	9.4 (3-17)*	24**	5/11****	1	2****	2****
Lanis et al.[26]	5.3 (2-15)	10***	1	0	0	1
Total	-	41	9/28 (32%)	1/41 (2%)	2/41 (5%)	3/41 (7%)
Tissue reduction	**Mean age Years (range)**	**Implants (n)**	**Soft tissue reactions (n)**	**Revision surgery (n)**	**OIF (n)**	**Implant loss (n)**
Mierzwinski et al.[22]	9.8 (5-16)*	17**	6	0	0	0
Den Besten et al.[23]	9.4 (3-17)*	45**	15/21****	15	1****	1****
Lanis et al.[26]	7 (2-15)	25***	9	6	4	5
Total	-	87	30/63 (48%)	21/87(24%)	5/87 (6%)	6/87 (7%)

* mean age for the entire cohort, i.e. both soft tissue preservation and soft tissue reduction combined;**Wide diameter implant; ***Implant type unknown, **** data obtained via personal communication

Overall, implant loss, OIF, revision surgery, and soft-tissue reactions occurred in 5.9%, 2.3%, 19.5%, and 29.2%, respectively, of the wide-diameter implants, compared to 17.1%, 8.4%, 18.5%, and 27.7%, respectively, of the small-diameter implants (table 5).

Table 5. Surgical outcomes of small-diameter implants versus wide-diameter implants

Small diameter implant	Mean age Years (range)	Implants (n)	Soft tissue reactions (n)	Revision surgery (n)	OIF (n)	Implant loss (n)
Ali et al.[16]	9.1 (3-15)	30	4	0	0	2
Bejar-Solar et al.[17]	10 (5-17)	11	4	N/A	1	1
Kohan et al.[24]	9.4 (6-13)	18	3	2	0	0
Kraai et al.[25]	8.2 (1-16)	27	23	12	3	3
Lloyd et al.[27]	8.7 (3-17)	85	26	36	6	22
Marsella et al.[20]	8.0 (6-11)	5	1	0	0	0
Mazita et al.[29]	8.1 (3-16)	15	5	4	1	1
McDermott et al.[30]	6.8 (2-15)	182	34	14	19	32
Nelson et al. [31]	11.0 (5-19)*	49	26	N/A	5	14
Romo et al.[35]	9.4 (6-14)	22	5	5	1	2
De Wolf et al.[15]	9.0 (3-16)	129	28	22	12	21
Total	8.4 (2-19)	573	159/573 (28%)	95/513 (19%)	48/573 (8%)	98/573 (17%)

Wide diameter implant	Mean age Years (range)	Implants (n)	Soft tissue reactions (n)	Revision surgery (n)	OIF (n)	Implant loss (n)
Den Besten et al.[23]	9.4 (3-17)	115	32	33	3	4
Felton et al.[18]	9.4 (4-13)	10	1	N/A	0	0
Hultcrantz et al.[19]	5.1 (2-15)	10	8	N/A	2	4
Marsella et al.[20]	7.4 (3-11)	5	1	1	0	0
McLarnon et al.[21]	9 (2-16)	30	0	0	0	3
Mierzwinski et al.[22]	9.8 (5-16)	24	9	0	0	0
Nelson et al.[31]	11.0 (5-19)*	25	13	N/A	0	2
Total	9.3 (2-19)	219	64/219 (29%)	34/174 (20%)	5/219 (2%)	13/219 (6%)

* mean age for the entire cohort, i.e. both small and wide diameter implant combined

4. Discussion

The current review aimed to evaluate the surgical outcomes of BAHIs in the paediatric population and to outline the use and outcomes of new surgical techniques and implants in this specific patient group. Although the clinical outcomes have improved in adults since adopting these new developments [3-8], many surgeons remain reluctant to apply these new developments in children, because of the limited evidence for this specific group. Yet, the higher complication rates observed in children combined with the proven safety of new developments in adults emphasizes the need for more research in children. However, some institutions have already implemented the new techniques and implant types in the paediatric population based on the improved results seen in adults. This literature review, therefore, provided an overview of the available evidence, guiding future research and clinical practice in children.

The interpretation of the results of this review is subject to certain limitations. First, the quality of the included studies was relatively poor. No randomized controlled clinical trials were available, while only 7 out of the 20 included studies scored high on level of evidence and low on risk on bias. [15, 17, 19, 21, 22, 24, 28] Second, most studies were of retrospective nature of which many entailed small sample sizes with substantial missing data. [15, 23-31, 35] Third, the majority of studies only reported descriptive data without a statistical comparison of outcomes between surgical techniques or implant types. [16, 17, 19, 21, 23, 24, 29, 30, 35] Last, a high level of heterogeneity in age, comorbidity, e.g. syndromes, surgical procedures, implants, study design, and follow-up duration was observed among studies. Since these clinical characteristics are likely to have influenced implant survival and soft-tissue outcomes, a meta-analysis of all studies would have been useful. Yet, due to this heterogeneity, a meta-analysis was not possible.

Due to the limitations mentioned above, it is challenging to formulate definite conclusions on outcomes after BAHI surgery in children, especially on the new developments. Yet, this review suggests that BAHI surgery is safe in children, since implant loss rates ≤20%, reported by 17 out of 20 studies included, are deemed acceptable, while skin complications are usually minor and easy to treat. Furthermore, new surgical techniques and wide-diameter implants in the paediatric population seem to have at least comparable, and perhaps, more favourable outcomes when compared to previous surgical procedures and implant types.

4.1. Surgical outcomes

The overall implant loss rate was 13.3% among reviewed studies with both small and wide-diameter implants (127 out of 952).[15-31, 33-35] This rate is comparable to the implant loss rate (15.2%) in children, as observed in the largest series from our clinic.[10] In this specific series, however, the implant loss rate (15.2%) of only small-diameter implants in children is significantly higher than the same type of implants in adults (7.3%).[10]

Several factors might explain this difference. One of the risk factors for implant loss in children is the higher incidence of head trauma. [30, 40] In the current review, 26% (33 out of 127) of the implant losses was caused by trauma. If implant losses due to trauma are excluded, the implant loss rate in children drops to 10.2% (94 out of 919), which, however, is still higher than the implant loss rate in adults. Another risk factor might be the thinner calvarial bone. Especially in young children, the implant length frequently exceeds bone thickness. The implant used in children is, therefore, often shorter than the implant used in adults, i.e. 3mm instead of 4mm. McDermott *et al.* reported a mean implant loss rate of 40% for children younger than five years, 8% for children between 5 and 10 years, and 1% for children above ten years. In addition, 78% of the implant losses observed in their cohort were 3mm implants.[30] However, De Wolf *et al.* and Lloyd *et al.* observed no significant difference in implant loss rates between children with 3mm implants and those with 4mm implants. [15, 27] Based on these partially contradicting observations, it difficult to determine which of the two is a risk factor; hence, more research is needed to draw firm conclusions.

Another factor that could explain the higher implant loss in children is that 44% of the patients in this review had an underlying syndrome. Craniofacial abnormalities and developmental delay of the mastoid bones resulting in thinner cortical bone have been reported in Treacher Collins syndrome and in Goldenhar syndrome, which together accounts for 18.4% of the patients in this review.[41, 42]

Last, a higher implant loss rate in children might be explained by differences in wound care and hygiene. Children rely upon their caretakers for help with peri-implant hygiene, which could be even more difficult, especially in syndromic children. In this review, 15 of out 127 implant losses were caused by infection (Holgers 4).

Based on the results of this review, the implant loss rate in children does seem higher compared to adults, regardless of traumatic losses being included or not. However, for most children, no other hearing rehabilitation options than bone-anchored hearing implants are available, while good hearing is necessary to reach adequate speech development; therefore, the higher implant loss rates in children are generally accepted. As a consequence, a spare fixture (a so-called "sleeper") is often implanted during the initial procedure. If the primary implant is lost, the sleeper can immediately be loaded, since it has already osseointegrated, thus avoiding another surgery. Hearing rehabilitation can then be resumed as quickly as possible.

The adverse soft-tissue reaction rate (Holgers≥2) was 25.8% (151/585 implants), ranging from 0-89% among studies. [15, 17-23, 25-28, 33, 34] Many factors could have influenced these outcomes. Besides differences in surgical technique and follow up, postoperative care and patient/skin characteristics are likely to play a role in complication rates as well. Kraai *et al.* reported that both patients with obesity or low socioeconomic status are likely to have a higher risk of soft-tissue hypertrophy requiring revision surgery. [25] Behavioural disorders do not seem to result in higher complication rates, as was observed by Kubala *et al.*[43]

The adverse soft-tissue reaction rate mentioned above is higher compared to the study of Dun *et al.*, in which adverse soft-tissue reactions were reported in 7.8% of the children. In this latter study, the rate of adverse soft-tissue reactions in adults (4.3%) was significantly lower when compared to the paediatric cohort.[10] Differences in wound care and hygiene might explain this difference. In addition, children in puberty have an increased number of active hypertrophied sebaceous glands and moving skin due to skull growth; both are suspected of making them more prone to adverse soft-tissue complications compared to adults. Another possible influencing factor is that soft-tissue reactions are usually only recorded during routine check-ups, so adverse events that occur at home are often not identified. Differences in the interval between check-ups might have contributed to the large differences in adverse soft-tissue reaction rates between studies. Last, all patients in the study of Dun *et al.* underwent implantation with the same linear incision with soft-tissue reduction compared to different techniques used in the studies in this review.

4.2. One-stage and two-stage surgery

One-stage surgery has several advantages over two-stage surgery: it avoids a second surgical procedure, hence, reducing anaesthetic exposure since surgery in children is performed under general anaesthesia, and it allows for earlier hearing rehabilitation. Early hearing rehabilitation in children is important for optimal language and speech development and aiding the child to reach his or her full socially and educationally potential. Lanis *et al.* reported that in a two-stage procedure with soft-tissue reduction, the interval between showing interest in an implant and being able to use the device often is up to 9 months. In a one-stage procedure without soft-tissue reduction, however, the waiting time is minimized to as little as two months, displaying a great benefit for the patient.[26] A possible advantage of two-stage surgery is that it provides sufficient time for the implant to osseointegrate before the abutment is attached. In one-stage surgery, the implant is more at risk before complete osseointegration in case a trauma to the head occurs.

When comparing outcomes to two-stage surgery, a lower incidence of soft-tissue reactions, revision surgeries, OIF, and implant loss was observed in favour of the one-stage surgery.[15-18, 20-22, 24, 25, 27-29, 34, 35] However, none of the studies were designed to compare the two surgery types. In addition, the mean age in the one-stage surgery group (9.3 years) was slightly higher compared to the mean age in the two-stage surgery group (8.3 years). Yet, no OIF occurred in children aged five or younger who underwent one-stage surgery.[16, 18, 20-22, 28, 34] It should, however, be noted a wide-diameter implant was used in at least 37% of the one-stage surgery patients compared to 0% in the two-stage surgery group. In addition, the follow-up duration between groups could have influenced these outcomes, since the follow-up in four studies using one-stage surgery was less than ten months, while all studies using two-stage surgery had a follow-up of at least 24 months. Despite these serious limitations, the currently available results seem to indicate

that one-stage surgery does not result in higher implant loss rates compared to two-stage surgery.

4.3. Soft-tissue reduction and soft-tissue preservation

Soft-tissue preservation surgery in adults has shown to result in a shorter surgical time, faster wound healing, less numbness, and improved cosmetic results.[8] In the current review, three studies compared outcomes after soft-tissue reduction to soft-tissue preservation.[22, 23, 26] Although both groups encompassed a rather small sample size, outcomes regarding revision surgeries, soft-tissue reactions, numbness, and pain were either comparable or favourable for the tissue preservation technique. Lanis *et al.* reported a significant difference in revision surgery due to excessive bone growth around the implant in favour of soft-tissue preservation group.[26] The soft-tissue reduction may irritate the osteoclasts because of direct contact between the periosteum and the skin. This irritation may stimulate bone growth and scar tissue formation, consequently resulting in raised skin around the abutment.[26] However, the shorter follow-up of children with soft-tissue preservation might have influenced outcomes. Yet, the tissue preservation technique has already shown superiority in adults [3-5, 8] and seems to at least be non-inferior in the paediatric population as well.

4.4. Wide and small-diameter implants

Wide-diameter implants have an increased contact surface between the temporal bone and the implant. This increase has resulted in higher primary and secondary stability, with superior implant survival rates compared to small-diameter implants in adults.[44, 45] It could be hypothesized the same mechanism applies in children.

In the current review, the overall implant loss rate in children for small-diameter implants was 17.1% compared to 5.9% for wide-diameter implants. Furthermore, spontaneous osseointegration failure rates for small and wide-diameter implants were 8.4% and 2.3%, respectively. Although the mean age at implantation in the small-diameter group (8.4 years) was slightly lower compared to the wide-diameter group (9.3 years), the difference in OIF and the overall implant loss rate is quite large. Also, the two studies designed to compare both implants underline the excellent outcomes of wide-diameter implants.[20, 31] Marsella *et al.* observed no implants losses in either group.[20] In contrast, Nelson *et al.* reported a significant reduction in both OIF and overall implant loss rates in the wide-diameter group.[31] These outcomes suggest that the wide-diameter implants are superior in terms of implant survival compared to small-diameter implants in the paediatric population.

4.5. Future perspective

The wide heterogeneity in study design, population, and reporting of complications among the studies reviewed prevented the appropriate statistical analyses to draw firm

conclusions. More high-powered, prospective comparative research wherein only one parameter differs between groups, and with uniform reporting of complications are needed. We therefore propose a set of standards for reporting implant and surgery characteristics and outcomes after BAHI implantation in children that can help in future comparison between studies and systematic reviews (table 6). Subsequently, it would be possible to draw broader conclusions in children specifically, regarding the superiority of one-stage surgery, tissue preservation, and wide-diameter implants. Especially research on surgical outcomes of the one-stage procedure is needed since it poses a major advantage of avoiding a second surgery in children.

Table 6. Proposed standards for reporting implant and surgery characteristics and outcomes after BAHI implantation in children

Age at time of implantation
Underlying syndrome
Type of implant (i.e. BI300, BI400, Wide Ponto Implant), including length of implant and abutment
One-stage or two-stage surgery
Tissue handling/Surgical technique (tissue reduction, tissue preservation, punch-only, other/specify)
State follow-up scheme and total follow-up duration in months*
Adverse skin reactions in absolute numbers and state how many patients experienced an adverse skin reaction */** (reported according the Holgers score or the IPS-score)
Implant loss rate in absolute numbers*/** and state its cause (e.g. spontaneous, trauma or infection)
Skin revisions or abutment change in absolute numbers*/**

* reported per implant type and per surgical technique if more than one is reported in a study
** if possible reported per visit in case of a prospective study

5. Conclusion

BAHIs are a safe method for hearing rehabilitation in children set with the correct indication, mainly with conductive/mixed hearing loss, who are not able to benefit from conventional hearing aids, e.g. due to anotia, microtia, ear canal atresia, or recurrent infections. Despite many limitations, the outcomes of new surgical techniques and implant designs in the paediatric population seem promising; wide-diameter implants seem to be superior in terms of implant survival, while one-stage surgery and soft-tissue preservation do not seem to result in higher implant loss rates and adverse skin reactions. However, because of the heterogeneity of the available literature, no definite conclusions regarding superiority of these new developments can be drawn. More prospective, long-term comparative research, wherein only one parameter differs between groups is, therefore, needed.

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Appendix A

1. Important search terms

- Hearing Aids [MeSH:noexp]
- Hearing device*
- Bone-anchored hearing implant
- Bone-anchored hearing aid
- BAHA
- BAHAs
- BAHI
- BAHIs
- Bone conduction device
- BCD
- BCDs
- Percutaneous implant
- Percutaneous abutment
- Oticon
- Ponto
- BI300
- BIA300
- Bone anchored hearing
- Treatment outcome [MeSH]
- Complications [subheading]
- Reoperation [MeSH]
- Abutment loss*
- Abutment stability
- Complication*
- Fixture loss*
- Fixture stability*
- Holgers
- Implant failure
- Implant loss*
- Implant stability
- ISQ
- OIF
- Osseointegration
- Revision surger*
- Skin reaction*
- Skin infection*
- Soft tissue infection*
- Soft tissue reaction*
- Stability

2. Search strategy in Embase:

(Hearing aids or hearing device* or bone-anchored hearing implant or bone-anchored hearing aid* or baha or bahas or bahi or bahis of bone conduction device* or bcd or bcds or percutaneous implant* or percutaneous abutment* or oticon or ponto or bi300 or flange fixture or bi400 or BIA400 or bone-anchored hearing).ab. AND (Treatment outcome OR Complications OR Reoperation OR Abutment loss* OR Abutment stability OR Complication* OR Fixture loss* OR Fixture stability OR Holgers OR Implant failure* OR Implant loss* OR Implant stability OR ISQ OR OIF OR Osseointegration OR Revision surger* OR Skin reaction* OR Skin infection* OR Soft tissue infection* OR Soft tissue reaction* OR Stability).ab.

3. Search strategy in PubMed:

(("Hearing Aids"[Mesh:noexp] OR Hearing device*[tiab] OR Bone-anchored hearing implant[tiab] OR Bone-anchored Hearing Aid*[tiab] OR BAHA[tiab] OR BAHAs[tiab] OR BAHI[tiab] OR BAHIs[tiab] OR Bone Conduction Device*[tiab] OR BCD[tiab] OR BCDs[tiab] OR Percutaneous implant*[tiab] OR Percutaneous abutment*[tiab] OR Oticon[tiab] OR Ponto [tiab] OR flange fixture [tiab] OR BI300[tiab] OR BIA300[tiab] OR BI400 [tiab] or BIA400[tiab]OR Bone anchored hearing[tiab])) AND (Treatment outcome[MeSH] OR Complications[subheading] OR "Reoperation"[Mesh] OR Abutment loss*[tiab] OR Abutment stability[tiab] OR Complication*[tiab] OR Fixture loss*[tiab] OR Fixture stability[tiab] OR Holgers[tiab] OR Implant failure*[tiab] OR Implant loss*[tiab] OR Implant stability[tiab] OR ISQ[tiab] OR OIF[tiab] OR Osseointegration[tiab] OR Revision surger*[tiab] OR Skin reaction*[tiab] OR Skin infection*[tiab] OR Soft tissue infection*[tiab] OR Soft tissue reaction*[tiab] OR Stability[tiab])

Appendix B

Data extraction from studies:

- Author
- Year of publication
- Title
- Journal
- Reason for inclusion
- Inclusion period
- Study design
- Follow-up duration
- Follow-up moments
- Mean age at intervention
- Mean age at evaluation
- Sex (m/f)
- Sample size
- Indications for surgery
- Number of participants in analysis
- Number of implants
- Lost-to-follow-up
- Main outcomes
- Soft tissue reactions
- Revision surgery
- Osseointegration failure (OIF)
- Implant stability
- Implant loss
- Pain
- Numbness
- Tissue preservation technique
- Tissue reduction technique
- One-stage surgery
- Two-stage surgery
- Mean time till second stage
- Small diameter implant
- Wide diameter implant
- Time till processor loading

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Chapter 7

The IPS-scale: A new soft tissue assessment scale for percutaneous and transcutaneous implants for bone conduction devices

I.J. Kruyt[1]; R.C. Nelissen[1]; M.L. Johansson[2,3]; E.A.M. Mylanus[1]; M.K.S. Hol[1]

[1] Department of Otorhinolaryngology, Donders Centre for Neurosciences, Radboudumc, Nijmegen, The Netherlands.
[2] Oticon Medical AB, Askim, Sweden
[3] Department of Biomaterials, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Key points

- Developments in the design of percutaneous implants/abutments for bone conduction devices, as well as surgical techniques, have resulted in other parameters becoming important in reporting soft tissue status.
- Transcutaneous BCDs do not result in a permanent breach of the mechanical barrier of the skin. Nonetheless, soft tissue complications have been reported.
- To date, a standardized assessment scale for skin complications after transcutaneous BCD implantation is lacking.
- The new IPS-scale is a complete assessment scale for reporting soft tissue status in patients with either percutaneous or transcutaneous implants for BCDs.
- Standardized treatment advice is provided, based on the IPS-scale.

1. Introduction

Percutaneous titanium implants for bone conduction devices (BCDs) have offered, since 1977, a solution for patients with hearing loss not treatable by conventional hearing aids, such as patients with chronic ear infections or microtia and/or ear canal atresia.[1] Percutaneous implants imply a continuous breach in the mechanical defensive barrier of the skin. To compensate for this breach, immunological mechanisms in the subcutaneous tissue surrounding the implant become more active.[2] Nonetheless, in a study, adverse skin reactions around the abutment were reported in 2.4 to 38.1% of patients.[3] A grading system to standardize the reporting of soft tissue reactions around percutaneous implants for BCDs was introduced by Holgers et al. [4] Recently, surgical techniques for soft tissue handling have evolved and have become less invasive. With new implant/abutment designs, this has resulted in fewer adverse skin reactions. Moreover, other parameters are becoming important in reporting soft tissue status.[5-7] Furthermore, BCDs not relying on percutaneous coupling have been developed, where the vibrations are transferred through the intact skin to the skull. Although this transcutaneous coupling does not cause a permanent breach of the skin's mechanical barrier, soft tissue complications have been reported.[8] To date, a standardized assessment scale for skin complications after transcutaneous BCD implantation is lacking. We, therefore, propose a new consistent, uniform, and easy assessment scale for both percutaneous and transcutaneous implants for BCDs. Furthermore, we have attempted to determine standardized treatments based on this scale.

2. Methods

Ethical considerations: Ethical committee approval was not required for this evaluation. With the widely used Holgers scale as reference, we interviewed surgeons and health-care professionals experienced in post-operative care for BCD-implant recipients within our tertiary referral centre. First, we evaluated the current suitability of the Holgers scale, identifying its strengths and weaknesses concerning current percutaneous implants. Second, we identified clinical signs and symptoms relevant in the follow-up of percutaneous BCDs that are not encompassed by the Holgers scale. Third, we designed a soft tissue assessment scale for transcutaneous implants, which is currently lacking. Finally, we aimed to create a similar structure for assessing percutaneous and transcutaneous implants with standardized clinical treatment decisions, while retaining the ease of use, reliability, and a standardized measurement.

3. Results and discussion

3.1. Evaluation of the Holgers scale for percutaneous implants

The Holgers scale is determined solely based on observations made by health-care professionals. It consists of serial observations regarding severity with a dichotomous outcome, i.e., present/not present. The scale can be used to indicate treatment, e.g., topical treatment for Holgers grade 2 or revision surgery for Holgers grade 4; however, these treatment decisions are not standardized worldwide. The advantages of the currently used Holgers scale are its ordinal scale and overall simplicity that result in its high usability. The Holgers scale has three disadvantages, in addition to being subject to personal interpretations in indicating treatment. First, the current scale was originally developed to start evaluating the skin three months after implantation. It, therefore, lacks the ability to describe complications in wound healing, such as (often minimal) dehiscence. Second, the scale lacks possibly the most important signal function, namely pain. Pain can result from skin infection, but may be caused by peri-implantitis, as is seen in dental implants.[9] Third, skin height is not incorporated in the Holgers scale. This is relevant in case a soft tissue preservation technique is applied, as skin can thicken around the abutment without infection signs, which can result in the inability to couple the sound processor, in the worst-case requiring abutment change or skin revision.

3.2. Requirements for a scale for transcutaneous implants

We evaluated possible pressure-related signs and symptoms based on our experience with post-operative skin inspection of patients with transcutaneous BCDs. Observations regarding skin integrity, colour, and oedema were found to suggest intervention, such as reducing magnet strength. In addition, reporting of pain and numbness of the surgical flap area were found to be important factors influencing daily usage and patient satisfaction.

3.3. Introduction of the IPS-scale

We aimed to incorporate all elements that are essential in soft tissue grading around implants into a new scale with three parts, namely I-scale (Inflammation-scale), P-scale (Pain-scale), and S-scale (Skin height/numbness-scale). These abbreviations have a different meaning based on implant type being scored, i.e. percutaneous or transcutaneous. A higher score reflects a more severe complication. The whole scale is presented in Figure 1 and is clarified below.

For percutaneous implants (the pIPS-scale), the Inflammation-scale ranges from 0 to 4, comprising four dichotomous objective observations made by health-care professionals, namely skin integrity, erythema, oedema, and granulation tissue. The latter three are derived from the Holgers scale, however, skin integrity was added. Skin integrity encompasses the observation of a blood crust or persistent minimal blood loss at the

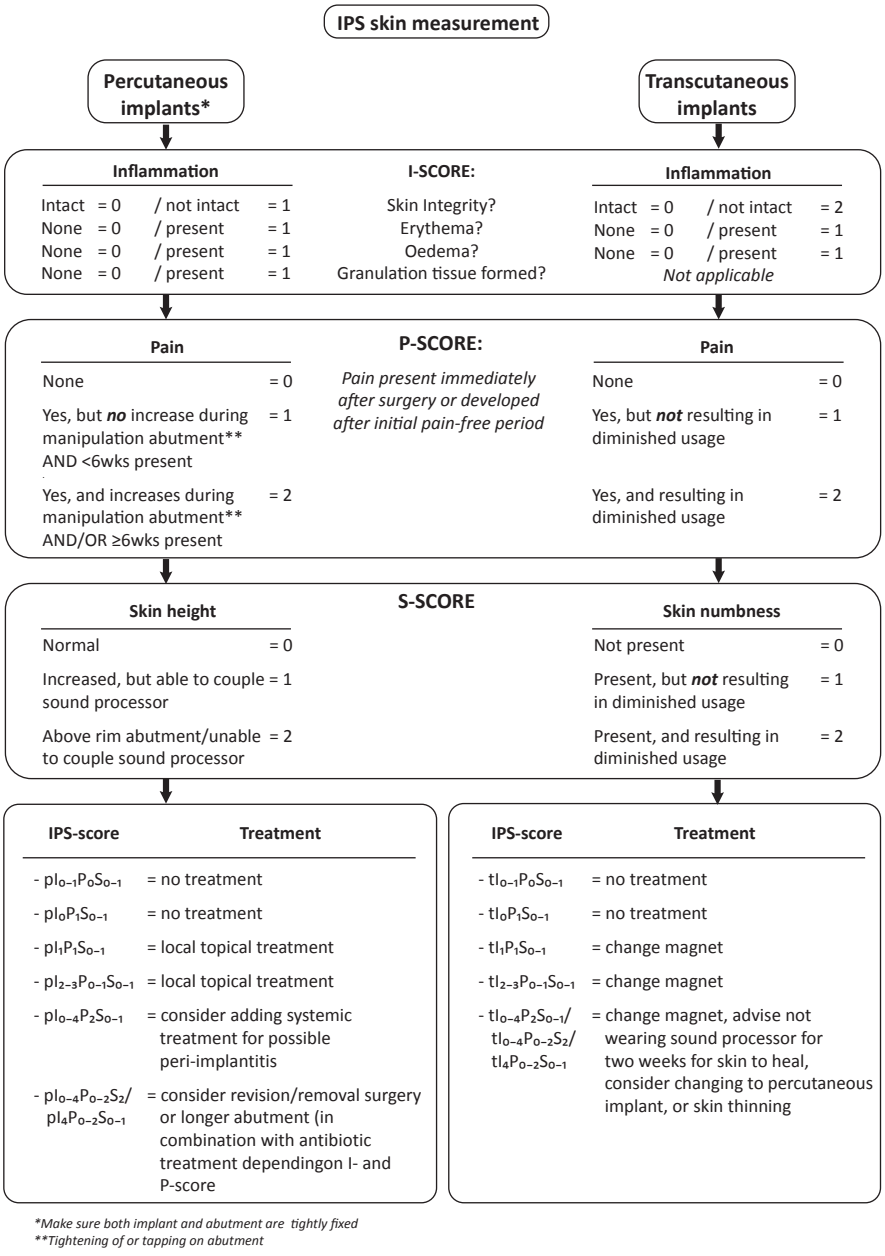

Figure 1. Flow chart of the IPS-scale and treatment advice

skin-abutment junction. These breaches of mechanical barrier function could make the peri-abutment soft tissue more prone to infections and should be included.

The Pain-scale reflects pain around the implant, developed immediately after surgery or after an initial post-operative pain-free period. The Pain-scale ranges from 0 to 2 and is scored based on the presence, duration, and increase of pain during abutment manipulation i.e., tightening of or tapping on the abutment. If increase of pain is observed after an initial post-operative pain-free period, it could indicate possible peri-implantitis, as seen in dental implants.[10] Early detection is crucial, because immediate treatment is necessary to avoid implant loss or elective removal because of chronic pain.

The introduction of soft tissue preservation surgery has resulted in an additional possible complication, i.e., skin thickening around the abutment without infection signs. The S-scale, therefore, represents skin height in relation to the abutment. It ranges from 0 to 2 and is scored based on the presence of skin thickening and the ability or inability to couple the sound processor onto the abutment, possibly requiring an abutment change or skin revision.

For transcutaneous implants (tIPS-scale), the Inflammation-scale ranges from 0 to 4 and comprises three observations, i.e., skin integrity, erythema, and oedema. Granulation tissue cannot be observed in these implants. To retain similarity to the pIPS-scale, skin integrity weighs for two points, because lacerated skin is the result of prolonged excessive pressure, requiring immediate treatment. Erythema and oedema weigh in for one point, because the observation of one of these two does not make treatment necessary per se.

The Pain-scale refers to pain at the implant site and ranges from 0 to 2. It is scored, unlike the pIPS-scale, based on the presence of pain together with the normal or diminished usage of the BCD. In our experience with transcutaneous implants, pain severity is closely related to a change in daily usage.

The S-scale refers, in transcutaneous implants, to the presence of skin numbness instead of skin height, but also ranges from 0 to 2. Skin numbness is common in patients with a transcutaneous implant, possibly due to the c-shaped flap created during surgery. It can result in patients being unable to feel excessive pressure, compromising skin vascularisation and possibly resulting in necrosis. The S-scale is scored based on the presence of numbness and normal or diminished usage of the BCD.

Prior to IPS-scoring in patients with a transcutaneous implant (tIPS-scale), it is important to verify normal daily usage, because most complications are pressure-related. In patients wearing the sound processor only a few hours a day, development of minor signs is, hence, the result of exceedingly high skin pressure during usage.

Although not yet evaluated, the tIPS-scale might also be useful as a standardized assessment scale for skin complications in patients with a cochlear implant or middle ear implant.

3.4. Standardized treatment derived from the IPS-scale

In contrast to the Holgers scale, we propose a standardized treatment advice for each IPS-scale (see Figure 1), based on our expert opinion. In patients with a percutaneous implant, an I_{2-3} should be treated topically and for I_4, systemic treatment and/or removal surgery should be considered. However, if a P_1 is found, we advise commencing topical treatment for I_{1-3}. A P_2 (indicating possible peri-implantitis) should be treated with systemic antibiotics, regardless of the I-scale. However, it is important to distinguish between pain manifesting immediately after implantation or after a pain-free period. The first is unlikely to result from infection, but can be due to peri-operative occipital nerve trauma; hence, pain medication is sufficient. The second is probably infection-caused, requiring antibiotic treatment. An S_2 implies the necessity of revision surgery or changing to a longer abutment.

In patients with a transcutaneous implant, an I_{2-3} indicates unduly high skin pressure and should be treated by reducing magnet strength and by the non-use of the sound processor for two weeks. Like pIPS, if an P_1 is found, magnet strength change for I_{1-3} is advised. If pain or numbness results in diminished usage (thus P_2 or S_2) and/or I_4 is found, changing to a percutaneous implant should also be suggested. In case of chronic pain without signs of infection and/or antibiotic treatment does not result in improvement for either type of implant, advanced pain treatment, such as occipital nerve block, should be considered.

By adding standardized treatment, the IPS-score has another advantage, namely its usefulness in research. Much research has been undertaken for percutaneous and transcutaneous implants, however, comparison across studies and interventions is difficult, because of the different methods of reporting complications i.e. skin reactions or treatments administered.[3] By providing a standardized, easy-to-use, and objective reporting method for soft tissue status and treatment indications, the IPS-scale should result in higher reproducibility and comparability in future research.

4. Conclusion

The Holgers scale has become less useful as a single measure for reporting soft tissue status around percutaneous and non-useful for transcutaneous implants for BCDs. We have, therefore, proposed a new assessment scale, the IPS-scale comprising three parts: inflammation, pain, and skin height/skin numbness, with higher scores reflecting more severe complication. For transcutaneous BCDs, the tIPS-scale is the first standardized assessment scale for soft tissue assessment. Altogether, the IPS-scale is a complete assessment scale for reporting soft tissue status in combination with standardized treatment advice for each IPS-scale in patients with percutaneous or transcutaneous implants for BCDs.

5. Acknowledgement

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Chapter 8

General discussion

Since the first bone-anchored hearing implant was implanted in 1977, modifications to the original surgical technique and the implant itself have been evaluated in clinical research in order to achieve optimal survival rates and soft tissue tolerability. Especially in the last decade, developments in terms of implant devices and surgical techniques have taken flight. The current chapter provides a critical evaluation/an overview of the clinical outcomes of (recent) BCD developments, and discusses future directions for clinical practise.

1. Evaluating the present

1.1. Developments in percutaneous implant design

The first percutaneous BCDs were based on titanium implants similar to dental implants.[1-3] As a result, developments that proved beneficial in one field could also be utilised in the other. In dental research, it was observed that by widening the implant diameter implant, survival improved.[4] From a biomechanical standpoint, the use of a wider implant diameter provides more bone-to-implant contact for osseointegration, and hence, theoretically improved distribution of stress in the surrounding bone.[5, 6] Based on this improved outcome, the design of titanium implants for bone-conduction devices was modified as well. These new implants were designed with a diameter of 4.5mm compared with the 3.75mm-wide, previous generation implants. This enlarged contact area between implant and bone has resulted in a higher implant stability quotient (ISQ); however, long-term implant survival rates were yet to be evaluated.[7, 8]. **Chapter 2** of this thesis evaluated two new wide diameter percutaneous implant designs from Oticon Medical™.

Chapter 2.1 reported the three-year implant stability, survival, and soft tissue tolerability of the Wide Ponto® implant (diameter 4.5mm) compared to the previous generation Ponto® implant (diameter 3.75mm) in a prospective randomized controlled clinical trial. In this study, 60 patients were randomly allocated in a ratio of 2:1 (test:control). All implants and abutments were placed in a single-stage surgical procedure, using the, in our clinic at that time standardly applied, linear incision technique with subcutaneous soft tissue reduction.[9] The strength of this study lies in the fact that only a single parameter differed between groups, i.e. the implant diameter. Both implants displayed an increasing ISQ trend (both on ISQ low and high), whereas the wide diameter test implant showed a significantly higher mean absolute ISQ compared to the small-diameter implant. The sound processor loading of both implants at three weeks after surgery seemed safe, as ISQ-trends increased post-fitting. No statistically significant difference in 3-year implant survival was observed (test 97.4% versus control 95.0%). Adverse soft tissue reactions occurred sporadically, with no significant inter-group differences. Skin thickening occurred in the majority of the patients in both groups, but did neither correlate with adverse soft tissue reactions nor necessitated revision surgery or abutment change.

Dental research has also shown that modifications of the implant surface, including physical topography and chemical properties, could play a pivotal role in further optimizing the integration in the recipient's bone, hence improving implant survival.[10] **Chapter 2.2** described the clinical evaluation of the new laser-ablated 4.5mm-wide Ponto BHX® implant through a multicentre study. This implant is, in contrast to currently used implants including the Wide Ponto® implant (**chapter 2.1**), selectively laser-ablated within the thread valley with a modified thickened surface oxide layer. The addition of micron-level topography and roughened surface greatly enlarges the surface area and improves the mechanical adherence of bone to the implant surface.[10, 11] In preclinical animal testing, it was shown that the laser-ablated implant had an improved biomechanical anchorage compared to the standard titanium implant.[12]

The multicentre study was designed as a retrospective chart review approximately one year after implantation. In all patients, a single-stage surgical procedure using a linear incision technique was performed under either local or general anaesthesia. Subcutaneous soft tissue preservation during surgery was applied in two hospitals, whilst subcutaneous soft tissue was reduced in the other hospital. The main outcomes were adverse skin reaction rates, implant survival, and ISQ. In total, 34 subjects were included and reviewed. The median 15-month implant survival of 97% was considered excellent, with only one spontaneous implant loss. An adverse skin reaction (Holgers grade 2-4) was observed in only four (8.8%) subjects. Despite a significant decline in ISQ after seven days, ISQ was significantly higher at the last visit compared to per-operative ISQ. The ISQ decline did not result in clinically observed instability.

The results of **chapter 2.1** and **2.2** both indicate that ISQ for both types of wide-diameter implants are higher compared to small diameter implants. When we compare the 1-year ISQ of the patients with the same abutment length, using the same surgical technique (hence excluding patients implanted with the soft tissue reduction technique in the BHX-study) between studies, no differences seem present (66.0 vs. 66.0). This was also observed in preclinical animal testing; however, removal torque measurements in that study showed a 153% higher biomechanical anchorage of the laser-modified implants.[12] This underlines that ISQ might not reliably reflect actual osseointegration. On the other hand, the higher removal torque measurements in animals might not necessarily imply improved clinical implant survival in humans either. When comparing survival outcomes of the implant studies, the implant loss rate of the different type of wide implants does not seem to differ. Moreover, despite a significant difference in ISQ between small-diameter and wide-diameter implants, no significant difference in implant survival is observed either; all three implant types displayed excellent survival rates. This supports the conclusions drawn by Nelissen et al. regarding the limitations of ISQ in comparative research: ISQ values are currently most useful to construe a trend in the individual patient or a population over time.[13] However, the correlation between ISQ and actual clinical implant stability/higher implant survival rates is not yet established. Recently, a new

measurement system for evaluating implant stability has been developed (ASIST: advance system for implant stability testing). Based on a comparative in vitro study, the ASIST seems more sensitive to changes in bone-implant interface properties and displayed smaller variations due to changes in abutment length compared to ISQ.[14] However, the value of ASIST in monitoring implant stability of BCDs in patients and its correlation with clinical stability has yet to be determined.

Based on the outcomes of **chapter 2.1** and **2.2**, the Wide Ponto® implant has become the standard implant used when a patient prefers the Oticon™ system, since both implants were priced similarly. To determine a possible benefit of the BHX-implant over the standard Wide Ponto® implant in terms of implant survival, future prospective, long-term comparative research, using only one surgical technique is needed. In addition, incremental cost-effectiveness has to be assessed, since at the time of writing the economic evaluation, the BHX implant was much more expensive (+15%; +€177,-) compared to the standard implant. This higher implant cost is only warranted if it leads to significantly improved clinical outcomes. (**chapter 5**). However, since the headroom for improving implant survival is rather small, obtaining adequate statistical power to identify an actual difference in survival requires a sample size that is too vast to achieve (over 700 per group if implant survival, for instance, is expected to improve from 97 to 99%, if α=0.05 and β=0.2). In our centre, one of the largest in Europe regarding BCD implantation with almost 2000 BCD implantations, around 75 BCDs are implanted annually, illustrating the unfeasibility of such a prospective study. In addition, based on the higher costs of the BHX implant and the outcomes of **chapter 2.1 and 2.2**, the BHX® implant does not seem to be cost-effective compared to the standard Wide Ponto implant, and, therefore, should not be used as new standard implant in healthy adults, unless the implant becomes cheaper. However, more headroom is present in high-risk patient groups, such as patients with a compromised bone quality or children. The incidence of implant loss in these groups is significantly higher, varying between 3.5%-40% using wide-diameter implants.[15-17] The BHX® implant might prove beneficial in these populations. In addition, a prospective study in these populations requires significantly fewer patients; although obtaining sufficient patients may prove difficult due to smaller numbers of candidates.

1.2. Developments in surgical technique

Besides developments in implant design, modifications in surgical technique have also been investigated, with the aim to reduce postoperative complications. As more elaborately narrated in the introduction, until 2011, surgical BCD implantation was always combined with subcutaneous tissue reduction at the implant site. This technique was thought to reduce the risk of inflammation and implant loss, improve sound transmission, while avoiding skin overgrowth.[3, 18, 19] However, although the linear incision technique with skin thinning described by de Wolf et al. proved to be superior to previous surgical

techniques involving skin grafting regarding clinical outcomes, adverse skin reactions, implant loss, and skin overgrowth still occurred.[9, 20, 21] In 2011, after the introduction of wide-diameter implants and longer abutments which were able to span the entire soft tissue thickness at the implant site, Hultcrantz published the first short-term outcomes of a modified linear incision technique without soft-tissue reduction. Compared to the dermatome technique with soft tissue reduction, tissue preservation resulted in faster surgery and less numbness of the surrounding skin without increasing the frequency of implant losses and skin infections.[22] However, the dermatome technique is different from the linear incision technique.

We, therefore, performed the study described in **chapter 3.** In this study, the 3-year clinical and audiological outcomes of the linear incision surgical technique with soft-tissue preservation were compared to the linear incision technique with soft-tissue reduction. This prospective study entailed 50 patients: 25 patients in the test group and 25 patients of a historical control group **(chapter 2.1)**. The primary objective of this study was to compare skin sensibility around the abutment. The secondary objectives were to investigate ISQ over time and to compare soft-tissue tolerability, skin height, implant survival, the need for revision surgery, and scar assessment. Based on our primary outcome measure, i.e. skin sensibility three years after surgery, patients operated with tissue preservation experienced significantly less numbness at the implant site compared to the tissue reduction group. No differences were observed in the total scar assessment-scores, soft tissue tolerability, skin height in relation to the abutment, implant survival, and audiological performance.

The systematic review of Verheij et al. on soft tissue preservation techniques concluded that postoperative skin complication rates were low and that overall complication rates were comparable with subcutaneous tissue reduction techniques, while the surgery duration of the preservation techniques were significantly shorter.[23] However, only one included study used the same incision technique in both groups, and this 5-year study found favourable clinical outcomes in the tissue preservation group.[24] The recently published comparative study by Reznitsky et al. also used the same incision technique in both groups and found similar outcomes: higher ISQ values were noted in the group with tissue preservation compared with tissue reduction, while there were no differences in implant survival and adverse skin reaction rates.[25] All studies advocate opting for the tissue preservation procedure for future patients due to these improved clinical outcomes combined with the shorter surgery time, underlining our results. Nowadays, tissue preservation is the standard surgical technique for implanting BCDs.

Despite these excellent results, new, minimally invasive surgical techniques are emerging, focusing on the reduction of intraoperative soft tissue trauma. Hopefully this reduction will further improve clinical outcomes. These minimally invasive punch techniques do not entail a linear incision but use a 5mm punch to expose the bone at the implant site. The entire surgical procedure is performed via the created keyhole. Once the

implant is seated, the skin surrounds the implant closely; hence, no stitches are needed, and the formed scar is thought to be negligible.[26] However, the drawback of punch-only techniques is the limited surgical exposition, hampering adequate visualization and, possibly, sufficient cooling during drilling. The first may lead to an angulated drilling/implant placement, soft tissue entrapment, or incomplete insertion, while the second may lead to thermal damage leading to bone resorption and, hence, impaired osseo-integration with subsequent implant loss.[27, 28] Although several centres have already adopted this technique, the benefit of this technique based on the first published results remain equivocal. In two comparative studies, no significant differences between the punch technique and the linear incision techniques were observed regarding skin inflammation. The punch technique did result in statistically significantly improved cosmetic results and reduced surgical time. Furthermore, in one study, a statistically significant reduction in the loss of skin sensibility was observed, while in the other comparable excellent skin sensibility was reported. However, both studies reported a higher implant extrusion rate of 12.0% and 12.1% in the test group. Unfortunately, both were not powered for this outcome and therefore did not reach significance (p=0.079 and p=0.19).[Caspers et al. submitted and under review at Otology & Neurotology][29] Currently, new comparative punch technique studies are underway wherein modifications to the original punch-technique have been made to improve bone cooling during drilling. It will be interesting to see whether this modification will solve the higher implant loss rate. In addition, the extended evaluation of the comparative study in **chapter 3** is nearing completion, thus, possibly providing new insights as well. Based on the excellent results of the standard linear incision technique with soft tissue preservation, the headroom for improving clinical outcomes is again rather small causing previously mentioned difficulties in obtaining adequate statistical power to identify differences to also apply.

From a patient perspective, the surgical technique with the lowest risk of complications, in particular implant loss, takes preference. An implant loss is most burdensome, since it necessitates a new surgery, while the patient is temporarily unable to use the sound processor or has to wear a testband instead. The improved sensibility and cosmetic appeal of a punch technique are not likely to outweigh the higher implant loss rates. Furthermore, even if the higher implant loss rate is solved by modifying the technique, a punch technique still has several disadvantages which should be considered. Firstly, in children, it is common also to place a sleeper implant in the mastoid bone. Using a punch technique necessitates a second punch, which is not cosmetically appealing. Secondly, it is quite common that the bone surface at the intended implant site is not optimal, e.g. being angulated relative to the overlying skin or if a fissure is present. Using a linear incision technique does not result in any challenges since it is possible to adjust the intended drill site due to the extensive exposure. In contrast, if a punch technique is used, this is not a possibility since the drill site must be directly under the perpendicularly punched skin. Finally, another complication that can occur during drilling, especially in children with

CHARGE-syndrome, is excessive bleeding from an emissary vein.[30] If either of these two situations occurs, the surgeon needs to be able to convert the punch technique to an incision technique to obtain better visualisation and to deal with the situation accordingly. Since most surgeons are likely to perform BCD surgery only a few times a year, it would be advisable to adhere to a single surgical technique that can be used in all patients (including children) and is most useful in challenging situations, hence, advocating a linear incision technique with tissue preservation.

1.3. The passive transcutaneous alternative

The concept of passive transcutaneous coupling is an appealing alternative, as an intact skin avoids an entry point for micro-organisms and could, therefore, potentially prevent skin infections and implant loss observed in percutaneous implants. Because of this, we have seen a revival of passive transcutaneous systems in the last decades. In **chapter 4**, the results of a two-year prospective multicentre study evaluating long-term audiological and clinical outcomes of the Cochlear™ Baha Attract are presented. Fifty-four unilaterally implanted adult patients with conductive or mild mixed hearing loss (CHL/MHL), or single-sided sensorineural deafness (SSD) were included across five hospitals. The primary aim of this extended follow-up study was to evaluate the long-term audiological and clinical performance after a total of two years of follow-up and to compare patient-reported outcomes (PROs) over time. In the study population, the transcutaneous implant resulted in statistically significant improvement in objective hearing testing compared to the unaided situation as well as improvements in PROs. No significant differences were observed at two years compared to baseline softband tests in terms of the average aided threshold at 0.5, 1, 2, and 4kHz (PTA_4), speech recognition in noise, or speech in quiet at 80dB SPL. For speech in quiet at 50 and 65dB, the results for the transcutaneous implant were statistically significantly better than softband scores. Pain/discomfort and numbness were initially reported in the majority of the patients, but declined over time; approximately 9% of patients reported some degree of numbness and 15% (slight) pain/discomfort after 24 months. Soft tissue complications were observed in 4.6% of the patients per visit. During the 2-year study period, two implant magnets were removed (3.7%), while two other implants were converted to the percutaneous counterpart (3.7%). All four patients experienced either unsolvable complaints or insufficient audiological benefit. At conclusion of the study, 89.6% (42 out of 47) of patients with a transcutaneous system in place used their sound processor, with a median daily usage of 6h/day (range 0-18h/day).

Unfortunately, the study was not powered for a subgroup analysis, thus, prohibiting any definitive conclusions being drawn for different indications, such as the SSD population. However, some interesting observations could be made. At the 2-year follow-up, hearing and health-related PROs remained stable in CHL/MHL patients and were significantly higher compared to unaided situation; in patients with SSD, however, no significant benefit could be seen in terms of HRQoL compared to the unaided situation, and

statistically significant improvements in terms of subjective hearing outcomes seen at 6 months were no longer statistically significant. Coinciding with these findings, we found that at the last follow-up, 97.2% of the CHL/MHL group with the transcutaneous implant in place used their sound processor with a median daily use of 8h/day, compared to 63.6% of the SSD patients with a median daily use of 3h/day. This observation underlines the need for additional research.

Comparing clinical outcomes among studies evaluating the same transcutaneous system is difficult as complications are not uniformly reported across studies. Until recently, no systematic soft tissue complication scoring system for transcutaneous implants was available. In **chapter 7** we, therefore, propose a new a new assessment scale [31] By adopting this IPS-scoring system, future studies can be compared and merged in meta-analyses, providing more robust conclusions.

The high incidence of numbness, and especially pain/discomfort reported in the first few months after transcutaneous implant surgery observed in our study are noticeable. Although the exact cause of post-operative pain remains unclear, injuries to both macro and microcirculation of the implant site are known to compromise the vitality of skin flap, while damage to cutaneous nerves results in numbness.[32] Hence, the relatively sizeable C-shape incision located anterior to the intended internal magnet site that is suggested by manufacturer Cochlear might be an essential factor.[33] Perenyi et al. have shown the arterial pattern of the retro-auricular region was similar in all subjects, with larger arterial branches lying close to the auricle, i.e. the intended incision site. In contrast, the area posterosuperior to the intended implant site contains only small arteries.[34] By changing the incision location, numbness and pain might be reduced. Reddy-Kolanu et al. described a linear incision with tissue reduction similar to the technique previously used in percutaneous BCDs. No results are yet available. Although the incision is much smaller, it runs straight over the implant magnet.[35] As such, it can be hypothesized formed scar tissue between the magnets might result in retention difficulties and pain. Nonetheless, modifications to the surgical technique should be further explored.

1.4. Comparison of transcutaneous and percutaneous options

It would be interesting to compare skin-related clinical outcomes of transcutaneous implants to percutaneous implants, which is currently the gold standard in our centre. However, an accurate comparison of these implants is impossible due to differences in reporting soft tissue status and the nature of skin complications, including infection-related versus pressure-related injury. However, a possible solution is to focus on patient-reported outcome measures, such as hearing-related quality of life. However, randomization of patients is unlikely to be feasible, impeding comparability among study groups. On the other hand, one could question whether differences in outcome between systems is that important since the transcutaneous system offers a viable alternative to the percutaneous system if this is not indicated or accepted.

Nevertheless, if a patient is eligible for obtaining a BCD, he or she should be appropriately counselled on the different treatment options, explaining advantages and disadvantages of each system, before deciding on a transcutaneous or percutaneous system. The advantage of BCDs is that patients can experience the expected hearing benefit before implantation, i.e. via a pre-operative testband trial. As the results with a passive transcutaneous BCD are generally comparable to those with the testband. Hearing rehabilitation with a percutaneous BCD, however, provides significant lower, thus more beneficial, hearing thresholds of 5-20 dB for frequencies 1-4 kHz compared to a passive transcutaneous BCD. This difference results from a more efficient transmission of vibrations via the rigid abutment-implant-bone connection, avoiding the skin dampening in passive transcutaneous implants.[36, 37] When deciding on a particular treatment, longevity is one of the factors that should also be considered, taking into account the deterioration of the sensorineural hearing thresholds due to presbyacusis. Snik showed that in patients with conductive hearing loss and averagely progressing presbyacusis, sound processors on percutaneous implants can provide lifelong sufficient hearing. Deteriorating sensorineural hearing thresholds may cause a transcutaneous system to become insufficient at an advancing age, hence, converting to a different type of hearing device is most often needed.[38]

Over the last few years, more powerful sound processors have been introduced, extending the longevity of transcutaneous systems as well, although it has yet to be evaluated whether these are able to provide lifelong sufficient hearing amplification.

Furthermore, the type of hearing loss to be rehabilitated should also be taken into account. **Chapter 3** showed limited benefit in SSD patients, with a high rate of non-use over time. The diminished device use over time has also been observed in SSD patients with percutaneous systems.[39, 40] An explanation may be that the hearing of SSD patients is sufficient in most situations, but in challenging situations like speech in noise and sound localization, their device provides insufficient benefit.[41] For SSD patients an extra careful selection procedure with both BCDs and conventional CROS (Contralateral Routing Of Signals) devices in combination with a home trial is needed to identify patients that are most likely to obtain benefit with the system, consequently reducing the non-use rates.

The Dutch national guideline for bone conduction implants and devices recommends to always use a power device during the testband home trial, and in SSD patients with passive transcutaneous implants.[42] Future research should determine the effect of a more powerful hearing device with the aim to overcome the high rate of non-use observed in SSD patients using a passive transcutaneous implant.

Whilst the sound transmission is more efficient in percutaneous implants, passive transcutaneous devices are thought to offer other advantages in terms of non-audiological clinical outcomes. The post-operative intact skin could potentially prevent skin infections and loss of the implant observed in the percutaneous counterpart. The necessary daily skincare around the percutaneous implant is not needed in the transcutaneous recipients. In addition, the transcutaneous system is considered by patients to be cosmetically

appealing if no sound processor is used. However, when using the sound processor, the system is more visible due to the relatively large external magnet. Also, the transcutaneous system is prone to inflict pressure-related complications, such as pain and signs of inflammation. Based on our experience, we advise to regularly check the magnet, and to change the magnet strength when indicated due to insufficient retention or discomfort/soreness. In addition, patients should change the softpad regularly to warrant optimal pressure distribution and to avoid discomfort. However, patients should be aware the softpads and different magnets have to be paid by themselves. Last, if a patient chooses a Cochlear™ device, its percutaneous system can quite easily be converted to a passive transcutaneous system and vice versa if needed, e.g. persistent skin infection in the first case and insufficient audiological benefit in the latter. This is possible since both implant systems use a BI300 implant onto which either an internal magnet or abutment can be coupled. It does, however, entail another surgery.

Combining the advantages of percutaneous and transcutaneous implants has resulted in another group of BCDs: active transcutaneous BCDs. These partially implantable transcutaneous systems have an implanted actuator instead of an external actuator, thereby overcoming the dampening by the skin in passive transcutaneous BCDs, e.g. Baha Attract® and Sophono®. The effective audiological gain, i.e. aided threshold minus the bone conduction threshold, of active transcutaneous BCDs, e.g. Med-El™ Bonebridge®, Cochlear™ OSIA®, and Oticon™ Sentio®, may be similar or slightly lower compared to percutaneous systems.[43, 44] However, more long-term prospective comparative research is needed to determine benefit (once commercially available) and, consequently, optimal indications per implant type.

Last but not least, when informing a patient eligible for receiving a bone conduction device about the different options, magnetic resonance imaging (MRI) compatibility of the different implants should be taken into consideration. MRI compatibility of an implantable device depends on the interactions between ferromagnetic components and the magnetic field and the heating of an implant caused by radiofrequency energy during the exam.[45] These interactions can result in the displacement of the material, possibly causing damage to the surrounding soft tissue or to the implant itself.[46, 47]

The use of MRI as a diagnostic modality has dramatically increased over the last decades; between 1996 and 2010, the use of MRI has quadrupled.[48] In the latest published data by the Organisation for Economic Co-operation and Development (OECD), 49 MRI exams are performed per 1.000 inhabitants in the Netherlands, while in the US and Germany, this number is even much higher, namely 111 and 139 per 1.000, respectively.[49] This data implies that on average, everyone will undergo at least one, but most likely multiple MRI exams during their lifetime. In addition, although most hospitals use 1.5T (Tesla, representing the maximum strength of a magnetic field) MRI-scanners, nowadays, 3T MRI-scanners are being used more frequently (while even 7T MRI scanners are being used for scientific research). A stronger magnetic field, thus, implies stronger interactions with the implant.

All currently available percutaneous titanium implants for bone conduction devices, produced by Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden) and Oticon Medical AB (Askim, Sweden), are marked MRI-conditional for 3T.[50, 51] MRI-conditional implies the implant does contain metal, conducts electricity and/or heats up by the radiofrequency energy; however, it does not result in significant interaction if adhered to the specified MRI-conditions, i.e. not exceeding the maximum strength of the magnetic field, in this case, 3T.[52] Furthermore, the implant does produce a small image artefact of 1cm around the implant.[50, 51]

For both passive and active transcutaneous BCDs MRI compatibility is different. First, the Sophono® Alpha 1 & 2 (Medtronic plc, N Jacksonville, Florida, USA) are MRI-conditional for 3T, while the Baha Attract® (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) and the Bonebridge® (BB, Med-El, Innsbruck, Austria) are MRI-conditional for 1.5T.[53, 54] However, since passive transcutaneous BCDs contain either one or two implanted magnets, these implants produce a significant image artefact of up to 11cm around the implant, while for active transcutaneous BCDs the image artefact can reach up to 15cm.[53-55] As a result, the ipsilateral side of the head cannot be assessed with MRI in case of a passive system, while for active systems, almost the entire head cannot be assessed. Secondly, as almost all patients will need to undergo an MRI exam during their lifetime, the implant needs to be temporarily removed via surgery if the head has to be evaluated by means of MRI, as there is often no diagnostic alternative. Additionally, the internal magnet(s) demagnetizes by around 5% per exam; fortunately, this can be overcome by using a stronger external magnet.[53, 54]

Patients should, therefore, be fully aware of these differences between the different implant types before deciding which system they would like to receive. This is particularly the case in patients with a history of cholesteatoma or children with neurological comorbidities, since both active and passive transcutaneous implants cause standard follow-up by means of MRI to be impossible.[56] Currently, developments in customizing MRI sequences for metal artefact suppression are underway and show promising results in reducing image artefact, consequently improving diagnostic imaging quality.[57] If successfully adopted in clinical practice, these MRI considerations regarding percutaneous, and both passive and active transcutaneous BCDs may change or become obsolete.

All the mentioned considerations in counselling patients are also elaborated in the recent publication of the Dutch national guideline for bone conduction implants and devices.[42] This guideline is expected to help doctors in selecting appropriate candidates for BCDs. Furthermore, by including guidelines for pre-operative diagnostic processes, optimal surgical technique, and clinical and audiological follow-up, it will assist in providing optimized patient-centered healthcare.[58-60]

2. Reviewing the past, considerations for the future

2.1. Cost-effectiveness

In 2018, the Dutch *National Institute for Public Health and the Environment (RIVM)* published the updated Public Health Foresight Report. In this report, the RIVM stated that health care expenditures are increasing an average 2.9 percent per year, and are expected to reach 174 billion euros in 2040. When compared to the reported health care costs of 2015, health expenditures in 2040 will have doubled.[61] An obvious option to reduce costs is to improve the cost-effectiveness of health care. Between 2003 and 2017, the costs for the standard BCD implant have increased with €199-226, which is 23.5%. Compared to the standard implant, newer implants are even more expensive (Cochlear™ BIA400 €70 and Oticon™ BHX €177). Combined with the increased costs of sound processor replacement, taking place every five years, BCDs are an increasing financial burden on Dutch hospital budgets. In **chapter 4**, we described the first study to compare the current generation of widely used BAHI implants to the previous generation implant through an economic evaluation. This study provided insight into costs over different generations of implants and allowed us to compare costs and performance over the successive BAHI models. The current generation implants (Oticon™ Wide Ponto, Cochlear™ BIA300 and BIA400) all share a 4.5mm implant diameter, while the previous generation implant (flange fixture) was designed with a 3.75mm implant diameter. From a clinical perspective, the current generation implants were expected to have similar outcomes. The BHX implant **(chapter 2.2)** could not be included since no BHX data was available at the time of performing the analysis. It was concluded that despite their higher purchase prices, wide-diameter implants for bone conduction hearing have resulted in fewer complication-related costs, making them cost-beneficial (between €72 and €506) over a 10-year period compared to the previous generation BAHI model. The large-scale acceptance of 4.5mm diameter implants as standard clinical practice can, therefore, also be considered justified from an economic point of view. This study has also shown that when future developments focus on improving implant survival, it may result in more cost-saving than when focusing on improving soft tissue tolerability. More data on complication rates and more detailed information about surgical techniques and models used would allow for improved evaluations by reducing the number of assumptions as well as to determine which of the three implants is most cost-beneficial. The imminent commercial availability of active transcutaneous implants should also be evaluated, especially since they are expected to be much more expensive, with different complication-related costs, while the effective audiological gain is suggested to be similar or slightly lower compared to percutaneous systems. A cost-benefit analysis regarding audiological outcomes (using the most current processor for all systems), e.g. calculating dB gained per Euro for each system, would be interesting as well. Taken together, this underlines the need for more long-term clinical research; however, data can also be obtained without clinical trials, through setting up (inter-)national implant registries.

2.2. BCDs in children

Recent developments in surgical technique and implant design have reduced the post-operative complication rates and have, therefore, become the gold standard in adult patients.[22, 23, 62-65] However, a proportion of BAHI recipients are children. In this population, higher complication rates have been reported, caused by lower bone quality, a higher prevalence of underlying syndromes, more frequent head trauma, and differences in wound care and hygiene. However, since most research on developments has been performed in adults, surgeons remain more cautious in applying new developments in children. Nevertheless, it can be argued that, by adopting the new techniques in children, complication rates might also decline.[66-69] **Chapter 6** describes a systematic review aiming to evaluate the efficacy of BAHIs in children and to elucidate the usage and outcomes of new surgical techniques and implants in this specific population. The quality of the included studies was relatively poor, while the majority of studies only reported descriptive data without a statistical comparison of outcomes between surgical techniques or implant types. The review suggests that BCD surgery is safe in children since implant loss rates are deemed acceptable, while skin complications were usually minor and easy to treat. Furthermore, new implant designs and modifications in surgical technique in the paediatric population seem to have at least comparable, and perhaps, more favourable outcomes compared to previous implant types and surgical technique. Future studies are needed to draw broader conclusions regarding the superiority of one-stage surgery, tissue preservation, and wide-diameter implants. However, performing statistically powered, prospective comparative BCD research in children is hampered by specific challenges. First, local ethical committees often prohibit prospective clinical research in children if it can also be performed in adults, regardless of the non-generalizability of the outcomes. However, when modifications are adopted without specific assessment in children, this may lead to unexpected outcomes and, therefore, may even be harmful. On the other hand, withholding children from a proven superior treatment option in adults may also be difficult to justify. Second, in order to reach sufficient statistical power, an adequate number of patients need to be available. However, children only represent a small part of the total number of BCD recipients, which, in itself, is also a rather small niche. In order to reach sufficient numbers, the inclusion period needs to be extensive, which might result in the studied modification to become outdated before the results become available. Another option is for the study to have a multicentre study design, but this design has another set of limitations. Last, to evaluate the three developments, i.e. wide-diameter implant, tissue preservation, and one-stage surgery, three separate studies must be undertaken wherein only one parameter differs between groups. With the limited number of possible study participants, the research questions must be prioritized. We propose that focus should lay on one-stage surgery, as it has the potential to avoid a second surgery in all children, thereby halving the general anaesthetic exposure. In addition, Lanis et al. reported that hearing rehabilitation could start seven

months earlier if a one-stage surgery scheme is used, which is essential in children for optimal language and speech development and aiding the child to reach his or her full socially and educationally potential.[70]

2.3. Standardization of reporting soft tissue status

Soft tissue complications are one of the standard reported outcome measures in percutaneous BCDs research. Holgers et al. developed a grading system to standardize the reporting of soft tissue status around implants.[71] The Holgers scale was originally developed to start evaluating the skin three months after implantation, thus lacking the ability to describe early complications in wound healing, such as (often minimal) dehiscence. Second, the score is determined based on observation alone and, therefore, lacks one of the most essential signal functions: pain. Pain can result from skin infection or peri-implantitis.[72] Third, developments in the surgical technique have occasionally caused the skin around the implant to thicken, which could result in the inability to couple the sound processor, requiring an abutment change or skin revision. Skin height is also not incorporated in the Holgers scale. For transcutaneous systems, a standardized assessment scale for skin complications is lacking. The new soft tissue assessment scale described in **chapter 7** has incorporated these shortcomings and is the first standardized assessment scale to be used in patients with a transcutaneous implant. This IPS-scale comprises three parts: inflammation, pain, and skin height/skin numbness, with higher scores reflecting a more severe complication. For each score, a standardized treatment advice is provided. Systematic reporting outcomes via a standardized scale allows studies to be compared and included into a meta-analysis. As seen in the review in **chapter 6,** the lack of standardized reporting of outcomes was one of the reasons a meta-analysis was not possible. Other systematic reviews on either percutaneous or transcutaneous BCDs faced similar issues.[23, 73] At this moment, the IPS-scale is yet to be validated, but by providing a standardized, easy-to-use, and objective reporting method for soft tissue status and treatment indications, the widespread adoption of the IPS-scale is expected to result in higher reproducibility and comparability of future research.

2.4. Overcoming the research hiatus

The effective regulation of auditory implants is vital to the patient's safety. Recent scandals regarding other surgical implants, e.g. the metal-on-metal hip prosthesis and the Poly Implant Prosthesis (PIP) breast implant, have underlined the risks of not systematically gathering long-term clinical data on implants and their surgical outcomes.[74, 75]. Although there is a clear need for high-quality research on implants, it is important to consider the barriers in obtaining high-quality data, particularly by means of randomised controlled trials (RCT). First, RCTs are expensive, and due to their considerable costs and the growing numbers of implants, it is not feasible for RCTs to be performed for all implants.[76] Second, to cover these costs, a large number of RCTs are funded by the

industry, thereby resulting in possible conflicts of interest.[77] There is evidence which supports the association between research funded by the industry and statistically significant pro-industry findings.[78, 79] In addition, the industry is reluctant to finance research comparing their implants to that of different companies. Moreover, since most implant research is industry-funded, comparisons between implants of different companies are lacking. Third, RCTs assessing implant safety and its clinical outcomes and getting it published take considerable amounts of time to perform. The RCT comparing three-year outcomes of a wide-diameter implant to the previous generation small-diameter implant described in **chapter 2.1** started in June 2012 and was published in June 2018.[80] Given the rapidly advancing field of auditory implant surgery, the implant assessed may become outdated before high quality data is available, while the introduction of new options in the field of BCD also impede obtaining adequate number of participants for each option. Fourth, for surgical studies it is often impossible to blind treatment arms, thereby introducing bias.[81] Last, external validity of RCT is another key limitation. RCTs by nature are strictly controlled by means of in- and exclusion criteria, and therefore often only include healthy adults, which limits the generalisability of their findings.[76] For instance, patients with possibly compromised bone quality, e.g. due to radiation therapy, osteoporosis, or diabetes mellitus, are often excluded in BCD research, while, if eligible, they get implanted outside the controlled study. Another example are children. Local ethical committees often prohibit prospective research in the paediatric population, despite the fact that a substantial part of auditory implant recipients are children. For both these patient categories, information regarding best treatment options obtained from research in healthy adults do not necessarily apply to them, or it can only be based on low-quality retrospective research. The review in **chapter 6** underlines this observation: only a minority of the published research in children are prospective studies (however none designed as RCT), while these studies generally lack adequate statistical power. Performing a multicentre study is one way to generate larger studies with faster inclusion. However, multicentre studies have their own disadvantages. Multicentre studies need rigorous study protocols to ensure uniform data collection among centres. As a result, multicentre studies are more expensive and therefore require adequate funding. Furthermore, heterogeneity in clinical practice among centres may be a major confounding factor in interpreting the results of these studies. In order to overcome these research barriers, an option is setting up surgical implant registries, which have recently gained much attention across Europe due to these previous implant scandals.[82]

One may ask how implant registries can help in improving clinical outcomes and implant safety for patients. Over the last decades, hearing implants have been widely adopted to treat hearing loss, however, a Dutch registry data on patients with auditory implants is lacking. The exact number of annually implanted hearing devices in the Netherlands is currently unknown.[83] Furthermore, the range of available surgically-implanted devices is expanding; new active transcutaneous systems, e.g. OSIA® (Cochlear™)

and Sentio® (Oticon Medical™), are on the verge of becoming commercially available. However, new implants can become commercially available based on equivalence data of a similar existing implant, rather than on its own clinical outcomes.[84] In addition, recent systematic reviews conclude that high-quality evidence on clinical efficacy and cost-effectiveness of existing auditory implants is lacking.[44, 73, 85-87] This is in line with the cost-analysis in **chapter 5**, wherein due to a lack of published data, no conclusions could be drawn on which of the wide-diameter implants model is the most cost-beneficial. We believe an auditory implant registry could play a pivotal role in overcoming these issues.

In 2015, The Dutch Ministry of Health, Welfare and Sports (VWS) introduced the Dutch national implant registry (LIR). This registry aims to facilitate hospitals in identifying patients with a particular implant in case of a medical emergency, i.e. recall of implants due to safety issues.[88, 89] The LIR was piloted for orthopaedic, cardiac, gynaecological, and plastic surgery implants, while all other surgical implants will be enrolled over the upcoming years.[89] As such, it is recently decided that high-risk active hearing implants, i.e. cochlear implants, middle ear implants, and active transcutaneous bone conduction devices, will need to be registered starting the end of 2019. Lower risk hearing implants, e.g. percutaneous and passive transcutaneous bone conduction devices and new active transcutaneous implants, will be added later. However, since this LIR does not collect implant outcome data, it cannot be used to evaluate implant safety or detect medical emergencies. As such, the Dutch ENT society has taken the initiative to fill in this gap and to develop another, more functional registry: The Dutch Otologic Quality Registry. This registry aims to systematically collect clinical efficacy and cost-effectiveness data of all auditory implants in the Netherlands, as well as the impact of factors such as surgical technique, surgeon, hospital, and patient characteristics. Eventually, the aim is to expand the registry also to evaluate otologic surgeries.

Compared with clinical trials, registries require fewer resources and often collect data from the entire eligible population instead of only from healthy adults meeting the strict inclusion criteria of clinical research. The findings of a registry, thus, have a stronger external validity.[90, 91] Registries can also be of particular use in obtaining data from patient groups that are usually excluded from clinical trials, such as children **(chapter 6)**. They also frequently provide data on long-term outcomes that exceed the follow-up duration of a clinical trial. Moreover, registries make it possible to compare outcomes of devices from different manufacturers, in our case, BCDs from Oticon and Cochlear. Clinical trials evaluating devices are almost always funded by implant manufacturers. These companies are reluctant to fund comparative research between different implants.

Developing and maintaining an implant registry that collects all these data faces several challenges, e.g. long-term funding, clear objectives, governance, data completion, etc.[92] By adopting the methodological framework developed for the UK auditory implant registry, the Dutch Otologic Quality Registry is deemed able to overcome these

challenges, and will eventually improve patient safety and quality of care for the entire field of otologic surgery.

3. Concluding remarks

The question that remains is: Have we reached the limit of bone conduction devices? This thesis has shown the developments in implant design and surgical technique have reduced complications of percutaneous BCDs. Further improving clinical outcomes in the healthy adult population will be difficult due to the limited remaining headroom and the large sample sizes that are needed to evaluate the superiority of new developments. However, the paediatric population provides more room for clinical improvement. The developments already adopted in the adult population could play a pivotal role and need to be investigated in this particular group. For passive transcutaneous implants, more research is needed in optimizing surgical technique and determining the effect of a more powerful hearing device on daily use, PROs, and audiological benefit. Patient selection could be further optimized, while newer active transcutaneous systems might change the current BCD landscape.

In addition, the shift towards a patient-centred and individualized type care is underway. Future research should, therefore, also include patient-centred outcomes such as quality of life and patient perspectives on optimal sound processor loading times. Due to the relatively fast development of new options in the field of BCD, another important focus should be on improving cost-effectiveness, as the rising health care expenditures will increase the burden on Dutch hospital budgets and society. Finally, implant registries have the potential to aid future research and evaluation of current and prospective BCD implant devices, and may even become a cornerstone in the improvement of BCD implants and its surgery.

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Chapter 9

Summary

The current thesis on bone conduction devices (BCDs) consists of two parts. The first part (**chapter 2-4**) evaluates the clinical safety and long-term effectiveness of developments in percutaneous and transcutaneous implant designs and compare clinical outcomes of different surgical techniques. The second part (**chapter 5-7**) aims to critically review previously published studies, evaluate the cost-benefit of different implants, and to determine future directions in BCD research.

In **chapter 2,** two new percutaneous implant designs from Oticon Medical™ were evaluated. **Chapter 2.1** reports the three-year implant stability, survival, and soft tissue tolerability of the new Wide Ponto® implant (diameter 4.5mm) compared to the previous generation Ponto® implant (diameter 3.75mm) in a prospective randomized controlled clinical trial (RCT). In this study, 60 patients were randomly allocated in a ratio of 2:1 (test:control). All implants and abutments were placed in a one-stage surgical procedure using the at that time in our clinic standardly applied linear incision technique with subcutaneous soft tissue reduction. The study has shown the 4.5mm test implant provided significantly higher Implant Stability Quotient (ISQ) values compared with the 3.75mm control implant during all visits. No statistically significant differences in implant survival or soft tissue reactions were observed between implants; both implants showed high survival rates (97.4% versus 95.0%) and good soft tissue tolerability. Skin thickening was seen in the majority of the patients, although no correlation was observed with adverse soft tissue reactions or implant type. The long-term results of this prospective RCT indicate that the wide-diameter implant, loaded with a sound processor at three weeks, is a safe and well-performing option for hearing rehabilitation in specific types of hearing loss.

Chapter 2.2 describes the clinical evaluation of the 4.5mm-wide Ponto BHX® implant. This implant is, in contrast to traditional Brånemark type titanium implants, selectively laser-ablated within the thread valley combined with a modified thickened surface oxide layer. These modifications greatly enlarge the surface area and are hypothesized to improve the mechanical adherence of bone to the implant surface. Our multicenter study aimed to evaluate implant survival, adverse skin reaction rates, and ISQ of this laser-ablated implant. The study was designed as a retrospective chart review approximately one year after implantation and was the first to assess the performance of this implant. All 34 healthy adult patients previously participated in a short-term controlled market release (CMR) testing performed in three different hospitals. A one-stage surgical procedure using the linear incision technique was performed under either local or general anesthesia. Subcutaneous soft tissue preservation during surgery was applied in two hospitals, whilst subcutaneous soft tissue was reduced in the other hospital.

No major perioperative complications were observed. For the entire cohort, the median 15-month implant survival was 97%; only one spontaneous implant loss occurred. No signs of infections were observed prior to the implant loss. During follow-up, an adverse skin reaction (Holgers grade ≥2) was observed in four (8.8%) subjects, and all were successfully treated with locally applied medication. Interestingly, all adverse skin reactions were observed in the tissue preservation group. The excellent results of the implant indicate that the new implant is safe to use in healthy adults. As such, we deem it safe to evaluate this implant in higher-risk patients, e.g. children and patients with compromised bone quality, as well.

In **chapter 3,** a modification to the surgical technique was compared to the standard technique: linear incision surgery with soft tissue preservation compared to the soft tissue reduction technique. Twenty-five patients were enrolled in the test group of this prospective cohort study. The control group consisted of 25 patients from a previous randomized controlled trial (**chapter 2.1)**. In both groups, the same type of implant (Wide Ponto® from Oticon Medical™) and follow-up scheme was used. The outcomes of interest were the influence of skin handling during surgery on post-operative skin sensibility, soft-tissue status, ISQ, skin height, implant survival, revision surgery rates, scar assessment, and hearing thresholds. The new technique resulted in superior sensibility scores (99.7% versus 92%). No spontaneous implants loss occurred in either group. No significant differences were observed in skin thickening, adverse soft-tissue reactions, revision surgery rates, and scar assessment (total score). Furthermore, soft tissue preservation did not influence hearing outcomes. Based on these results, combined with the shorter surgery time, we advocated adopting soft-tissue preservation surgery as the standard technique.

Chapter 4 presents the 2-year results of a study evaluating a new passive transcutaneous implant for bone conduction devices, the BAHA® Attract from Cochlear BAS™. Fifty-four unilaterally implanted adult patients with conductive (CHL) or mild mixed hearing loss (MHL) or single-sided sensorineural deafness were included in this prospective multicenter study. The main outcomes were audiological benefit, patient-reported outcomes (PROs), soft tissue status, pain, numbness, implant survival, and daily use (h/day). The transcutaneous implant provided statistically significant improvement in the objective hearing test compared to the unaided situation as well as improvements in PROs. No significant differences in hearing outcomes were observed compared to the situation with a soundprocessor worn on a soft band. For the subgroup of patients with SSD, the improvement in speech understanding in noise and patient-reported outcomes was less outspoken than for patients with CHL/MHL. Soft tissue complications were observed in 4.6% of the patients per visit. The majority of the patients initially reported to experience both some degree of pain/discomfort and numbness; however, these complication rates declined over the following visits and were reported only sporadically at the last follow-up. Two implant

magnets were removed (3.7%), while two other implants were converted to the percutaneous counterpart (3.7%). At the final visit, 89.6% (n=42 out of 47) of the patients with their transcutaneous system in place used their sound processor, with a median daily usage of 6h/day (range 0-18h/day). The percentage of non-use was higher in the SSD-subgroup. Based on these results, the transcutaneous implant is safe to use and provides improvement in hearing performance and patient-reported outcomes compared to the unaided situation. Noticeable differences in outcomes between patients with conductive/mixed hearing loss and single-sided sensorineural hearing loss highlight the need for more research with larger populations.

In **chapter 5**, the first chapter of the second part of this thesis, we elucidated whether the potentially improved performance (i.e. decline in complications) of new BCDs weighs up against the increasing costs of these new implant models. A cost-benefit analysis, using a mathematical Markov model, was used to evaluate and compare total costs (complication costs, implant purchase price, and standard costs) of three widely used current generation implants compared to a previous generation implant in adult patients over a 10-year period. Complication data was obtained from published clinical literature. In the case of missing data, parameters were based on expert opinion. Implant costs were derived from manufacturer catalogues, while standard and complication-related costs were obtained from a Dutch University Hospital and Dutch guideline for cost-effectiveness research. Based on our meta-analysis and model outcome, current generation implants seem to result in fewer complications and complication-related costs. Despite the higher purchase prices of the newer implants, the improved performance led these implants to be cost-beneficial compared to the reference implant over a ten- year time period (potentially up to €506 per implant over ten years). However, due to a lack of published data, no conclusions could be drawn on which of the wide-diameter implant models is the most cost-beneficial. The threshold analysis showed the test implant could be cost-beneficial if used for at least three years. Based on the headroom analyses, focusing future developments on improving implant survival is likely to save more costs compared to improving soft tissue tolerability of the implant. To overcome a lack of data in future evaluations, we proposed a set of standards for reporting implant and surgery characteristics and outcomes in BCD research.

Chapter 6 presents a systematic review of the published literature on the efficacy of BCDs in the paediatric population. Furthermore, the use and outcomes of recent developments, i.e. implant width, soft tissue handling technique, and one-stage implant surgery, that have reduced the post-operative complication rates in adults are elucidated for the paediatric population. Outcome measures included patient demographics, follow-up time, surgical technique (one- versus two-stage surgery), tissue handling technique (reduction versus preservation), type of implant used, and complication rates.

Twenty articles were included, encompassing 952 BCDs. The overall mean age at implantation was 8.6 years (range, 2-21 years). Adverse soft-tissue reactions occurred in 26.4% (range 0% to 89% across studies) of the implants. Revision surgery was performed in 16.8% of the implants. The total implant loss rate was 13.3% (range 0% to 40% across studies). Based on these results, BCDs are a safe method for hearing rehabilitation in children set with the correct indication, although large differences between studies are observed. Based upon the limited amount of literature regarding recent developments, wide-diameter implants seem to be superior in terms of implant survival, and similar in terms of adverse skin reactions, while one-stage surgery and soft-tissue preservation do not seem to result in higher implant loss rates or increased adverse skin reactions. Yet more high-powered, prospective comparative research wherein only one parameter differs between groups, and with uniform reporting of complications are needed. We have, therefore, proposed a set of standards for reporting implant and surgery characteristics and outcomes after BCD implantation in children that can help in future comparisons between studies and in systematic reviews.

In **chapter 7**, we have critically reviewed the gold standard for reporting post-operative percutaneous peri-implant soft tissue status, the Holgers' score. Based on its shortcomings, e.g. neither evaluating pain and skin height, nor providing treatment advice, and the lack of a systematic scoring system for peri-implant soft tissue status in patients with a transcutaneous BCD, we have proposed a new soft tissue assessment scale for percutaneous and transcutaneous BCD implants: the IPS-scale. This IPS-scale consists of three parts: inflammation, pain, and skin height/skin numbness. A higher score reflects a more severe complication. In addition, the IPS-scale provides standardized treatment advice for each score, which can aid clinical practice.

In the current thesis, we have critically reviewed the past and evaluated modifications to the BCD implant design and surgical techniques. Further improving clinical outcomes in the healthy adults will be difficult due to the limited remaining headroom and the large sample sizes that are needed to evaluate the superiority of new developments. However, we have identified other areas that need to be investigated, such as new developments in children as well as more extensive cost-effectiveness studies. As such, this thesis also provides considerations for future research in the field of bone conduction devices.

9.1

Samenvatting

Dit proefschrift bestaat uit twee delen. Het eerste deel **(hoofdstuk 2-4)** evalueert de veiligheid en klinische langetermijn-uitkomsten van nieuwe ontwikkelingen in het ontwerp van percutane en transcutane beengeleidende hoorimplantaten (BCDs). Percutane BCDs bestaan uit een schroef die in het rotsbeen wordt geïmplanteerd (achter de oorschelp) met daarop een koppelstuk (abutment). Dit koppelstuk steekt door de huid, waardoor dit type percutaan wordt genoemd. Op het koppelstuk kan de geluidsprocessor worden gedragen. De geluidstrillingen van de geluidsprocessor worden hiermee via het koppelstuk en schroef overgebracht op het rotsbeen, waar zich het slakkenhuis in bevindt. De transcutane BCD die in dit proefschrift werd geëvalueerd heeft een soortgelijke schroef in het rotsbeen. Dit implantaat heeft echter in plaats van een koppelstuk een (inwendige) magneet op de schroef, waarover de huid gesloten wordt. De geluidsprocessor wordt gekoppeld aan een uitwendige magneet. De magnetische koppeling tussen de uit- en inwendige magneet zorgt ervoor dat de geluidstrillingen van de geluidsprocessor door de huid heen worden overgebracht op de schroef in het rotsbeen. Door deze manier van overdracht wordt dit type implantaat transcutaan genoemd. Verder worden in het eerste deel van dit proefschrift de klinische uitkomsten van verschillende chirurgische technieken voor het plaatsen van dergelijke implantaten met elkaar vergeleken. Het doel van het tweede deel **(hoofdstuk 5-7)** is om reeds gepubliceerde literatuur kritisch te evalueren, de kosten-baten van verschillende implantaten in kaart te brengen en aandachtsgebieden voor toekomstig BCD-onderzoek vast te stellen.

In **hoofdstuk 2** werden de uitkomsten van twee nieuwe percutane implantaatontwerpen van Oticon Medical™ geëvalueerd. **Hoofdstuk 2.1** beschrijft een prospectief gerandomiseerd onderzoek met controle groep (RCT) waarin de uitkomsten van het nieuwe wijd-diameter Ponto® implantaat (diameter 4.5mm) werden vergeleken met de, toen standaard gebruikte, smallere diameter Ponto® implantaat (diameter 3.75mm). De totale follow-up van de patiënten in dit onderzoek bedroeg 3 jaar. De belangrijkste uitkomstmaten waren de implantaatstabiliteit en -overleving en de mate van huidreacties. Zestig patiënten werden gerandomiseerd over twee groepen in de verhouding 2:1 (test groep: controle groep). Alle implantaten en koppelstukken (abutments) werden in één fase geplaatst, waarbij gebruik werd gemaakt van de toen in ons ziekenhuis standaard gebruikte lineaire incisie techniek met weefseluitdunning. De studie heeft aangetoond dat het 4.5mm testimplantaat gedurende de gehele follow-up een significant hogere Implantaat Stabiliteits Quotiënt (ISQ) had ten opzichte van het 3.75mm controle-implantaat. De mate van implantaatoverleving en huidreacties waren vergelijkbaar: beide implantaten hadden een hoge implantaatoverleving (97.4% versus 95.0%) en laag aantal klinisch relevante huidreacties (Holgers' score ≥2). Een verdikking van de huid rondom het implantaat (gemeten aan de hand van de afstand van huid tot de bovenrand van het koppelstuk) werd in de meerderheid van

de patiënten vastgesteld. Er werd echter geen correlatie gevonden met klinisch relevante huidreacties of het gebruikte implantaattype. De langetermijnresultaten van deze RCT hebben aangetoond dat het wijd-diameter implantaat met een geluidprocessor aangemeten op drie weken na de operatie een veilige, goed presterende optie is om het gehoor van BCD-kandidaten mee te rehabiliteren.

Hoofdstuk 2.2 omvat de klinische evaluatie van het 4.5mm-wijde Ponto BHX® implantaat. De schroefdraadgroeve van dit implantaat is in tegenstelling tot het traditionele Brånemark type titanium implantaat deels bewerkt met een laser. Daarnaast is de oxidelaag aan het implantaatoppervlak gemodificeerd. Door deze combinatie heeft het BHX-implantaat een veel groter contactoppervlakte dan zijn voorganger, waardoor hypothetisch de biomechanische verankering van het bot aan het implantaat zal verbeteren. Deze multi-centerstudie had derhalve als doel om als eerste de implantaatoverleving, huidreacties en ISQ van het laser-bewerkte implantaat te evalueren. De studie had een retrospectieve opzet waarbij de follow-up van alle patiënten ongeveer een jaar betrof. Alle 34 geïncludeerde gezonde volwassen patiënten hadden eerder deelgenomen aan de zogenoemde 'controlled market release (CMR) testing' welke was uitgevoerd in drie ziekenhuizen. Alle implantaten werden onder lokale of algehele anesthesie met de lineaire incisie techniek in één fase geplaatst. In twee ziekenhuizen werd dit gecombineerd met een weefselsparende techniek, terwijl in het derde ziekenhuis een weefselreducerende techniek werd toegepast. In de studie werden geen grote perioperatieve complicaties vastgesteld. De mediane 15-maanden implantaatoverleving van het gehele cohort betrof 97%, waarbij er slechts één spontaan implantaatverlies optrad. Dit werd niet voorafgegaan door tekenen van ontsteking. Gedurende de follow-up werden bij vier patiënten (8.8%) een klinisch relevante huidreactie (Holgers' score ≥2) vastgesteld. Alle huidreacties werden succesvol behandeld met antibiotica/corticosteroid-zalf. Opvallend genoeg traden alle huidreacties op bij patiënten bij wie een weefselsparende techniek was toegepast. Het verschil was echter niet statistisch significant. De uitmuntende resultaten geven aan dat het nieuwe BHX-implantaat veilig is om te gebruiken in gezonde volwassenen. Als zodanig achten wij het nu ook veilig om de uitkomsten van het implantaat te onderzoeken in patiënten met een hoger risico op implantaatverlies, zoals kinderen of patiënten met een verminderde botkwaliteit.

In **hoofdstuk 3** werden in een prospectieve cohort studie twee chirurgische technieken met elkaar vergeleken: de lineaire incisie waarbij het omringende onderhuidse weefsel behouden blijft (weefselsparende techniek) en de standaard lineaire incisie techniek waarbij het omringende weefsel onderhuids wordt uitgedund (weefselreducerende techniek). Vijfentwintig patiënten werden geïmplanteerd met de weefselsparende techniek. De controlegroep (weefselreducerende techniek) bestond uit 25 patiënten van een eerdere prospectieve gerandomiseerde klinische studie (**hoofdstuk 2.1**). In beide groepen werd hetzelfde type implantaat gebruik (Wide Ponto® van Oticon Medical™) en werd hetzelfde follow-upschema

gehanteerd. De uitkomsten waarin we het meest geïnteresseerd waren, waren de invloed van weefselbehandeling tijdens implantatie op postoperatieve sensibiliteit van de huid, klinisch relevante huidreactie (Holgers score ≥2), ISQ, huidhoogte, implantaatoverleving, noodzaak tot revisie chirurgie, beoordeling van het litteken en de invloed op de geholpen hoordrempels (met hoorimplantaat). De nieuwe weefselsparende techniek resulteerde in superieure sensibiliteit rondom het implantaat (99.7% versus 92%). In beide groepen traden geen spontane implantaatverliezen op. Er werden ook geen statistisch significante verschillen gevonden in huidhoogte, klinische relevante huidreacties, aantal revisies en cosmetische resultaat van het litteken (totale score). Ook bleek het behoud van het omliggende weefsel geen invloed te hebben op de geholpen hoordrempels. Op basis van deze uitkomsten in combinatie met een kortere operatieduur raden wij aan om de lineaire incisie met onderhuids weefselbehoud als standaard techniek te gebruiken.

Hoofdstuk 4 beschrijft een studie waarin de tweejaars-resultaten van een nieuwe passief transcutaan BCD implantaat (BAHA® Attract van Cochlear BAS™) werden geëvalueerd. Vierenvijftig volwassen patiënten met een eenzijdige implantatie vanwege geleidings-gehoorverlies (CHL), gemengd gehoorverlies (MHL) of eenzijdige doofheid (SSD) werden geïncludeerd in deze prospectieve multicenterstudie. De belangrijkste uitkomstmaten waren gehoorwinst, patiënt-gerapporteerde uitkomsten (PROs), post-operatieve huidstatus, pijn, gevoelloosheid, implantaatoverleving en dagelijks gebruik van de geluidprocessor. Uit de resultaten bleek dat het transcutane implantaat statistisch significante verbeteringen gaf op de verschillende hooruitkomsten ten opzichte van de ongeholpen situatie (zonder hoorimplantaat), maar ook in PROs. Er werden geen significant verschillen in hooruitkomsten gevonden ten opzichte van de situatie waarin de geluidsprocessor op een softband werd gedragen. In de subgroep van patiënten met SSD was de verbetering in spraak verstaan in rumoer en PROs minder uitgesproken dan in patiënten met CHL/MHL. Huidcomplicaties werden bij 4.6% van de patiënten per visite vastgesteld. Pijn/discomfort en gevoelloosheid werden aanvankelijk door de meerderheid van de patiënten gerapporteerd, maar deze namen af over de tijd. Tijdens de laatste, tweejaars-visite werden deze slechts bij een enkeling gerapporteerd. In totaal werden twee geïmplanteerde magneten verwijderd (3.7%) en werd in twee andere patiënten (3.7%) het transcutane systeem omgebouwd naar een percutaan systeem (verwijderen inwendige implantaat en vervangen door een koppelstuk/abutment). Tijdens de laatste visite gebruikte 89.6% (n=42 van de 47) van de patiënten met het implantaat in situ hun geluidsprocessor. De mediane gebruiksduur was 6u/dag (range 0-18u/dag). Het percentage patiënten die hun geluidprocessor helemaal niet meer droeg was hoger in de SSD-subgroep. Op basis van bovenstaande uitkomsten kan worden geconcludeerd dat de passieve transcutane BCD veilig is in het gebruik en dat het een significante verbetering geeft in hoorresultaten en PROs ten opzichte van de ongeholpen situatie. De opvallende verschillen in uitkomsten tussen patiënten met CHL/MHL en SSD onderstrepen dat meer onderzoek met grotere onderzoeksgroepen nodig zijn.

In **hoofdstuk 5,** het eerste hoofdstuk van het tweede gedeelte van deze thesis, onderzochten we of de potentieel verbeterde prestatie, oftewel afname in complicaties van nieuwe BCDs opwegen tegen de toegenomen kosten van deze nieuwe implantaatmodellen. Om dit te berekenen werd een kosten-baten-analyse uitgevoerd aan de hand van een mathematisch Markov-model. In dit model werden de totale kosten (complicatiegerelateerd, implantaatkosten en standaardkosten) van drie veelgebruikte, huidige generatie, 4.5mm BCDs berekend en vergeleken met een vorige generatie, 3.75mm BCD in volwassen patiënten over een periode van 10 jaar. Complicatiegerelateerde data werden aan de hand van een systematische review uit gepubliceerde literatuur verkregen. In het geval van ontbrekende data werden parameters geschat door twee BCD experts. Implantaatkosten werden verkregen uit de fabrikantcatalogi. De standaardkosten en complicatiegerelateerde kosten werden bepaald aan de hand van gegevens van een Nederlands Universiteitsziekenhuis en de Nederlands *Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg*. Op basis van onze meta-analyse en modeluitkomsten bleken de nieuwe generatie implantaten minder complicaties te geven en derhalve lagere complicatiegerelateerde kosten te genereren. Ondanks de hogere aanschafprijs van deze implantaten leiden de verbeterde prestaties ertoe dat de nieuwe generatie implantaten kosteneffectief zijn over een periode van 10 jaar (tot €506,- per implantaat over 10 jaar). Door een tekort aan gepubliceerde data kon geen uitspraak worden gedaan welke van de drie wijd-diameter implantaten het meeste kosteneffectief is. De drempelanalyse toonde aan dat de wijd-diameter implantaten kosteneffectief kunnen zijn bij een gebruik van ten minste drie jaar. Ook werd er een analyse uitgevoerd waarin gekeken werd naar de potentiele ruimte voor verbetering van nieuwe implantaten, een zogenaamde "headroom-analyse". De conclusie van deze analyse was dat ontwikkelingen die focussen op het verbeteren van implantaatoverleving waarschijnlijk tot een grotere kostenbesparing zullen leiden dan ontwikkelingen die focussen op het verminderen van huidcomplicaties. Om het tekort aan bruikbare data te verminderen hebben wij een standaardset van noodzakelijke implantaat- en operatiekarakteristieken en uitkomsten voorgesteld om te gebruiken in toekomstig wetenschappelijk onderzoek om zo nieuwe kostenevaluaties te faciliteren.

Hoofdstuk 6 beschrijft een systematisch literatuuronderzoek naar de doelmatigheid van BCDs in kinderen. Ook werd er gekeken naar de bewijsvoering voor het gebruik van recente ontwikkelingen, zoals het gebruik van wijd-diameter implantaten, weefselsparende chirurgie en één-fase-chirurgie bij kinderen, welke het optreden van postoperatieve complicaties in volwassenen reeds hebben doen verminderen. De uitkomstmaten waren demografische kenmerken, follow-upduur, chirurgische techniek (één- versus twee-fase-chirurgie), peroperatieve weefselbehandeling (weefselsparende versus weefselreducerende techniek), gebruikte type implantaat en mate van complicaties. In totaal werden 20 artikelen geïncludeerd welke in totaal 952 BCDs omvatten. De gemiddelde leeftijd ten

tijde van implantatie was 8.6 jaar (range 2-21 jaar). Relevante huidreacties traden op bij 26.4% (range 0-89%) van de implantaten. Revisie chirurgie was noodzakelijk bij 16.8% van de implantaten. De totale aantal implantaatverliezen was 13.3% (range 0-40%). Op basis van deze resultaten zijn BCDs een veilige methode om het gehoor mee te rehabiliteren in kinderen met een correcte indicatie. Er werden echter grote verschillen in uitkomsten gevonden tussen studies. Ondanks de beperkte hoeveelheid data ten aanzien van nieuwe ontwikkelingen lijkt het wijd-diameter implantaat superieur te zijn in implantaatoverleving en gelijkwaardig qua huidcomplicaties, terwijl één-fase-chirurgie en de weefselsparende techniek niet tot meer implantaatverliezen of huidreacties lijken te leiden. Om echter tot definitieve, statistisch onderbouwde conclusies te komen zijn er meer prospectieve, vergelijkende studies met adequate patiëntaantallen nodig waarin slechts één parameter wordt vergeleken. Daarnaast ontbrak een uniforme manier van het rapporteren van complicaties. Als zodanig hebben wij een voorstel gedaan voor een uniforme dataset voor het rapporteren van implantaat- en operatiekarakteristieken en complicaties wat noodzakelijk is voor toekomstige literatuuronderzoeken en meta-analyses om definitieve conclusies te formuleren.

In **hoofdstuk 7** hebben we de gouden standaard voor het rapporteren van post-operatieve huidstatus rondom een percutane BCD, de Holgers' score, kritisch geëvalueerd. Tekortkomingen van deze score waren het niet evalueren van pijn en huidhoogte, maar ook het ontbreken van een behandeladvies. Daarnaast was er tot op heden geen systematisch scoringssysteem voor het evalueren van de huidstatus in patiënten met een transcutane BCD. Als zodanig hebben wij op basis van deze tekortkomingen een nieuwe huidscore ontwikkeld. Deze IPS-score is een nieuw scoresysteem welke gebruikt kan worden om de huidstatus te beoordelen van patiënten met een percutane of transcutane BCD. De IPS-score bestaat uit drie delen: inflammatie, pijn en huidhoogte/ gevoelloosheid, waarbij een hogere score een ernstigere complicatie weerspiegelt. Daarnaast omvat de IPS-score een gestandaardiseerd behandeladvies voor elke score, waardoor deze ook behulpzaam kan zijn in dagelijkse praktijk.

In dit proefschrift hebben we kritisch gekeken naar de gepubliceerde literatuur en hebben we nieuwe ontwikkelingen in chirurgische techniek en implantaatontwerp geëvalueerd. Het nog verder verbeteren van klinische uitkomsten in gezonde volwassenen zal lastig worden door enerzijds de beperkte resterende verbeterruimte en anderzijds doordat er zeer grote patiëntgroepen nodig zijn om aan te tonen dat een aanpassing superieur/ inferieur is. We hebben echter ook gebieden geïdentificeerd waarin wel meer ruimte voor verder onderzoek is, zoals de in volwassenen reeds ingevoerde nieuwe ontwikkelingen toepassen bij kinderen en meer uitgebreide uitgebreide kosteneffectiviteitsstudies. Hiermee geeft deze thesis ook aanbevelingen voor toekomstig onderzoek in het veld van beengeleidende hoorimplantaten.

Chapter 10

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Chapter 11

Publication list

Published:

1. **Three-year outcomes of a randomized controlled trial comparing a 4.5mm-wide to a 3.75mm-wide titanium implant for bone conduction hearing**
   Authors: I.J. Kruyt; R.C. Nelissen; E.A.M. Mylanus; M.K.S. Hol
   Journal: Otology & Neurotology - Published 2018 Jun;39(5):609-615.
2. **Clinical evaluation of a new laser-ablated titanium implant for bone-anchored hearing in 34 patients: 1 year experience**
   Authors: I.J. Kruyt; R. Banga; A. Banerjee; E.A.M. Mylanus; M.K.S. Hol
   Journal: Clinical Otolaryngology - Published 2018 Apr;43(2):761-764.
3. **Three-year clinical and audiological outcomes of percutaneous implants for bone conduction devices: comparison between tissue preservation technique and tissue reduction technique**
   Authors: I.J. Kruyt; H. Kok, A.J. Bosman; R.C. Nelissen; E.A.M. Mylanus; M.K.S. Hol
   Journal: Otology & Neurotology - Published 2019 Mar;40(3):335-343.
4. **Results of a two-year prospective multicenter study evaluating long-term audiological and clinical outcomes of a transcutaneous implant for bone conduction hearing**
   Authors: I.J. Kruyt; P. Monksfield; P.H. Skarzynski; K. Green; C. Runge; A.J. Bosman; J.I. Blechert; S. Wigren; E.A.M. Mylanus; M.K.S. Hol
   Journal: Otology & Neurotology – In press
5. **Economic evaluation of percutaneous titanium implants for bone conduction hearing: a cost-benefit analysis**
   Authors: I.J. Kruyt; M.R.W. Bours, M.M. Rovers, M.K.S. Hol, J. Rongen
   Journal: Otology & Neurotology – Published 2020 Jan; doi: 10.1097/MAO.0000000000002616
6. **The efficacy of Bone-Anchored Hearing Implant Surgery in children: a systematic review**
   Authors: I.J. Kruyt, K.Bakkum, J.I. Caspers, M.K.S. Hol
   Journal: International Journal of Pediatric Otorhinolaryngology – Published 2020 Jan; doi.org/10.1016/j.ijporl.2020.109906
7. **The IPS-scale: A new soft tissue assessment scale for percutaneous and transcutaneous implants for bone conduction devices**
   Authors: I.J. Kruyt; R.C. Nelissen; M.L. Johansson; E.A.M. Mylanus; M.K.S. Hol
   Journal: Clinical Otolaryngology – Published 2017 Dec;42(6):1410-1413.
8. **On the evaluation of a superpower sound processor for bone-anchored hearing**
   Authors: A.J. Bosman; I.J. Kruyt; E.A.M. Mylanus; M.K.S. Hol; A.F.M. Snik
   Journal: Clinical Otolaryngology – Published 2018 Apr;43(2):450-455.

9. **Evaluation of an Abutment-level SuperPower Sound Processor for Bone-Anchored Hearing**
   Authors: A.J. Bosman; I.J. Kruyt; E.A.M. Mylanus; M.K.S. Hol; A.F.M. Snik
   Journal: Clinical Otolaryngology – Published 2018 Feb 16. doi: 10.1111/coa.13084.
10. **Gehoorimplantaten en MRI-compatibiliteit**
    Authors: I.J. Kruyt, E.A.M. Mylanus, J.J.S. Mulder, L.J.Th.O. van Erning, S.C.A. Steens, M.K.S. Hol
    Journal: Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde – Published 2017; 23e jaargang; nr. 2
11. **A controlled clinical trial on Minimally Invasive Ponto Surgery and the linear incision technique with tissue preservation for bone-anchored hearing implants: outcomes after 6 months**
    Authors: C.J.I. Caspers; I.J. Kruyt; E.A.M. Mylanus; M.K.S. Hol
    Journal: Otology & Neurotology – In press
12. **Kansen en uitdagingen van transcutane botimplantaten: een tweetal illustratieve casus**
    Authors: R.M. Strijbos; I.J. Kruyt; C.A. den Besten; A.J. Bosman; E.A.M. Mylanus; M.K.S. Hol
    Journal: Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde – Published 2016; 22e jaargang; nr. 4
13. **Gamma Knife radiosurgery for treatment of growing vestibular schwannomas in patients with neurofibromatosis Type 2: a matched cohort study with sporadic vestibular schwannomas**
    Authors: I.J. Kruyt; J.B. Verheul; P.E.J. Hanssens; H.P.M. Kunst
    Journal: Journal of Neurosurgery – Published 2018 Jan;128(1):49-59..
14. **Autologous versus prosthetic nasal and auricular reconstruction – patient, professional and laymen perceptions**
    Authors: J.P.J. Dings; M.A. Vijverberg; M.K.S. Hol; D.J.O. Ulrich; A.F.J. de Haan; G.W. Verhage-Damen; M.T.P. de Clonie Maclennan-Naphausen; I.J. Kruyt; H. Ghaeminia; G.B. Bruekers-Schipper; K.J.O.A. Ingels; G.J. Dicker; G.J. Meijer; M.A.W. Merkx
    Journal: International Journal of Oral & Maxillofacial Surgery – In press
15. **Patient' preferences in sound processor loading time after BAHI surgery**
    Authors: J.C.I. Caspers; I.J. Kruyt (shared first authorship); R.C. Nelissen; E.A.M. Mylanus; M.K.S. Hol
    Journal: Otology & Neurotology – in press

Scientific communications:

1. **Comment on "Baha Skin Complications in the Pediatric Population: Systematic Review with Meta-Analysis"**
   Authors: M.A. Vijverberg; C.J.I. Caspers; I.J. Kruyt; J.W. Wasmann; A.B. Bosman; E.A.M. Mylanus; M.K.S. Hol
   Journal: Otology & Neurotology – Published 2019 Jun;40(5):689-691.
2. **'Comment on - Original solution for MEI and Anesthetic-Surgical Management in a child with severe craniofacial dysmorphism'**
   Authors: I.J. Kruyt; A.L. McDermott; M.K.S. Hol
   Journal: Case reports of otolaryngology – Published 2016; 2859051.
3. **Letter to the Editor 'Verheij et al. - A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices'.**
   Authors: I.J. Kruyt; C.A. den Besten; R.C. Nelissen; M.K.S. Hol
   Journal: Otology & Neurotology – Published 2017 Jan;38(1):157-158.

Under review:

16. **Case Report – Ernstig hoofd- en halsletsel door particulier vuurwerk**
    Authors: S. de Bock; S. Bekkers; I.J. Kruyt; G.B. van den Broek
    Journal: Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde

17. **A clinical evaluation of Minimally Invasive Ponto Surgery with modified drills for inserting bone-anchored hearing implants**
    Authors: J.C.I. Caspers; I.J. Kruyt; E.A.M. Mylanus; M.K.S. Hol
    Journal: Otology & Neurotology

Chapter 12

Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit:
http://www.ru.nl/donders/graduate-school/phd/

Chapter 13

Curriculum Vitae

Ivo Joachim Kruyt werd op 26 oktober 1989 geboren te Utrecht. Als middelste telg groeide hij op samen met zijn twee broers en ouders in Zeist. Nadat hij in 2007 zijn atheneum-diploma had behaald aan het Montessori Lyceum Herman Jordan te Zeist, werd hij uitgeloot voor de studie geneeskunde. Hij begon daarop met de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. Het jaar erna werd hij alsnog ingeloot voor de studie Geneeskunde te Nijmegen, een stad die tot dan toe onbekend voor hem was. In de zomer van 2008, voor de aanvang van het collegejaar, besloot hij op kamers te gaan in Nijmegen. Na het afronden van zijn bachelor en in afwachting van de coschappen heeft hij samen met een vriend ruim 3 maanden door Zuidoost Azië gereisd. Tijdens de hierop volgende coschappen raakte hij geïnteresseerd in Keel-, Neus- en Oorheelkunde en besloot wetenschappelijk onderzoek te gaan doen binnen deze afdeling van het Radboudumc. Dit resulteerde in zijn eerste wetenschappelijk publicatie. Na het afronden van zijn keuze-coschappen op de afdeling Radiologie van het Radboudumc (toegespitst op de KNO), de afdeling KNO van het Radboudumc en de afdeling KNO van het Gelre ziekenhuis te Zutphen behaalde hij zijn artsenexamen in augustus 2015. In november 2015 begon Ivo met het onderzoekstraject dat heeft geleid tot dit proefschrift. Na een kleine tweeënhalf jaar voltijd aan zijn promotieonderzoek te hebben gewerkt begon hij in april 2018 met de opleiding tot KNO-arts. Na het eerste jaar in het Radboudumc te hebben doorlopen, volgde hij zijn tweede jaar in het Jeroen Bosch ziekenhuis te Den Bosch en het Canisius Wilhelmina ziekenhuis te Nijmegen. Ten tijde van de verdediging van dit proefschrift bevindt Ivo zich aan het begin van het derde jaar van zijn opleiding, opnieuw in het Radboudumc.

Bo Håkansson (Grondlegger van de BAHA)
& Ivo Kruyt op OSSEO '17

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