The treatment of patients with otosclerosis

From expert opinion to evidence-based practice

Arnold JN Bittermann

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The treatment of patients with otosclerosis

From expert opinion to evidence-based practice

De behandeling van patiënten met otosclerose
Van klinische ervaring naar zorg op basis van wetenschappelijk bewijs

(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General introduction

1.1 HEARING IMPAIRMENT

Hearing is an essential element within our society, important for normal personal functioning. In 2005, a survey among the Dutch population (18 years and older) showed that the prevalence of hearing impairment was 11%, equaling 1.4 million persons (1). According to a publication in 2012 from the Dutch Hearing Foundation concerning 'facts and figures' about hearing impairment, 650.000 persons were using a hearing aid (2). In the Netherlands, hearing impairment is the fifth most chronic disorder (3). Due to the major impact of hearing problems, different coordinating organizations concerning hearing problems, such as the Dutch Ear, Nose and Throat Association, the National Hearing Foundation and different university hospitals, initiated the development of a 'National Program Hearing Research' (3). This project should take place between 2013 and 2016 and will focus on 4 different domains about hearing impairment: 'treatment', 'rehabilitation', 'participation' and 'prevention'. With the start of the program, 444 persons with hearing complaints completed a questionnaire to find out what their needs are and what they expect from such a program. Resulting from this questionnaire, treatment of hearing complaints turned out to be the most important topic for persons with hearing complaints. Although hearing loss due to otosclerosis will represent a small amount of persons compared to the complete group of persons with hearing impairment, otosclerosis-induced hearing loss could be successfully treated with surgery, in most cases (4).

1.2 HEARING & OTOSCLEROSIS

1.2.1 The ear and normal hearing

An acoustic signal consists of sonic waves of a certain frequency. The pinna functions as a dish antenna and receives the sonic waves, which continue travelling through the auditory (external) ear canal and cause a vibration of the tympanic membrane. The middle ear accommodates three ossicles; malleus, incus and stapes. These ossicles make the ossicular chain and are part of the conductive system of the ear. They transfer the acoustic vibrations from the tympanic membrane to the inner ear (cochlea). The stapes is a vital link of this noise conduction system through the middle-ear cavity. Below the stapes footplate lies the cochlea. In a normal situation, sound waves are conducted through the middle-ear cavity via the ossicular chain. Then, movement of the stapes footplate generates fluid movements inside the cochlea. Through these fluid movements, intracochlear hair cells bend over and produce electric signals. These signals reach the brain via the cochlear nerve and final sound perception is a fact.

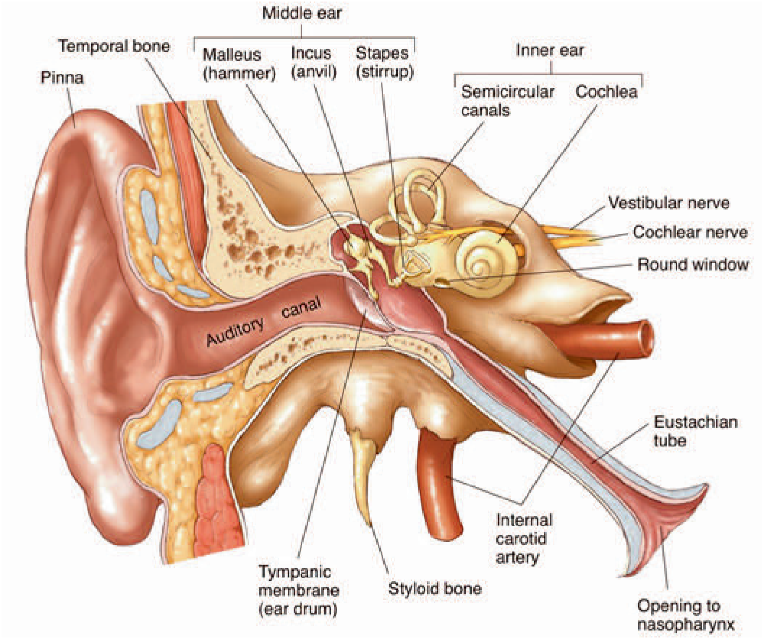


Figure 1 | Anatomy of the ear.

1.2.2 Otosclerosis

Otosclerosis is a syndrome, which disturbs the conductive qualities of the middle ear due to fixation of the stapes. Otosclerosis has been introduced in 1894 by an important pioneer within otology, Adam Politzer (5). In case of otosclerosis, osteoclasts remove mature lamellar bone and this bone is replaced by osteoblasts in bone of greater thickness and with increased cellularity and vascularity (6). This new spongy bone, also called otospongiosis, can be found around the otic capsule. The otic capsule (synonym for bony labyrinth) is a bony structure, surrounding the cochlear and vestibular system (7). The footplate of the stapes is located in the oval window of the otic capsule and is attached to the otic capsule by the annular ligament (8). When the otosclerotic foci are located on the otic capsule with a relation to the footplate of the stapes, this could result in fixation of the stapes. When the stapes is not able to move due to fixation, the acoustic vibrations cannot reach (in whole or in part) the cochlea and noise perception is limited, resulting in conductive hearing loss. Besides conductive hearing loss, otosclerotic foci could also affect the cochlea with sensorineural hearing loss as a result (9).

1.2.3 Audiometric findings in patients with otosclerosis

Figure 2 shows a typical audiogram of a patient with otosclerosis. The dotted line shows the bone-conduction threshold and is a measure to describe sensorineural hearing, in the cochlea. Bone-conduction means that the sound waves are transmitted through the bones of the skull directly into the cochlea. The sound conduction system in the outer and middle ear is avoided. In most otosclerosis patients, sensorineural hearing is intact, but minimally increased sensorineural hearing thresholds can be present due to normal ageing, noise-induced hearing deterioration or otosclerotic foci with a relation to the cochlea. Figure 2 shows a slightly decreased sensorineural hearing. The other line (below the dotted line) shows the air-conduction. The air-conduction reflects the process of transmitting sound waves to the cochlea via the noise conduction system through the outer and middle ear. Substantial increased hearing thresholds are present when the conduction system is affected and fixated by otosclerosis.

An air-bone gap indicates the differences between air- and bone-conduction thresholds on different frequencies. For example: the air-conduction threshold at 500 Hz is 45 dB and the bone-conduction threshold at 500 Hz is 25 dB. In this case, the air-bone gap at 500 Hz is 20 decibels (45 dB minus 25 dB). The most striking characteristic on an audiogram showing hearing loss due to otosclerosis is the so-called 'Carhart notch', which was first described by Carhart in 1950 (10). The Carhart notch shows increased bone-conduction hearing thresholds (dotted line in figure 1), mostly at or around 2000 Hz. It is not easy to explain the exact phenomenon of the Carhart notch, which is an artefact of perceptive neural hearing loss at that frequency. The footplate of the stapes is stiffened, resulting in an impedance change at the oval window causing a changed intracochlear fluid flow at a given sound loudness, with a reduction in perceptive hearing as a result (11,12). When removing the restriction of a stiffened stapes footplate by opening the inner ear with a fenestration, intracochlear fluid movement will recover and perceptive hearing will improve (artefact at or around 2000 Hz recovers) (11).

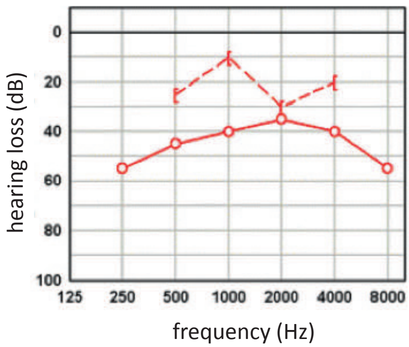


Figure 2 | Audiogram of an otosclerosis patient, including a Carhart notch at 2000 Hz.

1.2.4 Prevalence of otosclerosis

It can be difficult to diagnose the presence of otosclerosis. The 'gold standard' is a middle ear exploration. During this procedure, the stapes surgeon will open the middle ear to visualize the ossicles and to find out the cause of a conductive hearing loss. Other problems, resulting in conductive hearing loss, could be present, such as a discontinuity between the incus and the stapes, necrosis of the incus or mucosal adhesions. Following chapter 1.2.3 and chapter 4, a Carhart notch on an audiogram could indicate the presence of otosclerosis but it is certainly not the most sensitive diagnostic method. In an attempt to improve the preoperative diagnosis of otosclerosis (and thereby cost-effectiveness), high resolution CT imaging could be helpful with a sensitivity of 75% on axial coupes (13). It is important to realize that besides otosclerotic foci with hearing loss it also is possible that otosclerotic foci are present without clinical symptoms (subclinical otosclerosis). Declau et al. evaluated an unselected series of temporal bones from a national donor bank in Belgium and reported otosclerotic foci in 4 out of 119 autopsy cases (3.4%) (14). They also calculated the prevalence of clinical otosclerosis by extrapolation and suggested that the prevalence of clinical otosclerosis should be between 0.30 and 0.38% (14). Based on these results we calculated that the absolute numbers of patients with otosclerosis in the US and the Netherlands can subsequently be extrapolated to 860.000 and 50.000 respectively in 2009 (chapter 6). Hannula et al. reported a prevalence of clinical otosclerosis of 1.3% within an epidemiological study with a group of 850 native Finnish subjects (15).

1.2.5 Treatment of patients with otosclerosis

In case of hearing los due to otosclerosis, different treatment options are available (16). Patients could be fitted with a hearing aid, which is a simple treatment method without any surgical risks. In case of advanced otosclerosis, including severe sensorineural hearing loss due to cochlear otosclerotic foci, cochlear implantation could also be considered. However, in most cases with conductive hearing loss and limited perceptive hearing loss, stapes surgery will be the primary treatment option resulting in an effective restoration of conductive hearing. In case of stapes surgery, the suprastructure of the fixated stapes will be removed and replaced with a prosthesis. The main goal of stapes surgery is a reduction of the air-bone gap by replacing the malfunctioning stapes with a prosthesis and thereby improving the air-conduction. Surgical techniques have changed over the years. Surgery changed from the first stapedectomy technique towards the stapedotomy technique. In case of a stapedectomy, the complete stapes, including the stapes footplate, is removed from the oval window and a prosthesis is connected to the incus and placed into the oval window. In case of a stapedotomy the stapes is partially removed. The footplate remains in situ while the suprastructure of the stapes is removed. The prosthesis will be attached to the incus and placed in a small fenestration (0.5-0.7 mm diameter) in the footplate. Figure 3 shows the middle ear with the incus and stapes. The stapes is removed in figure 4A and a small fenestration is made in the footplate. Finally, a prosthesis is positioned inside the fenestration and connected to the incus (figure 4B). In this specific case, a vein graft is positioned between the fenestration and the prosthesis. The benefit of the application of a vein graft will be discussed in chapter 8.

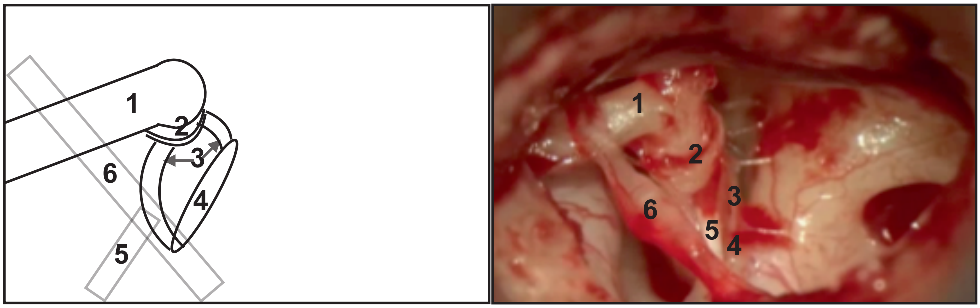


Figure 3 | Normal middle ear anatomy. (picture from dr. R. Vincent)
1: incus 2: junction between the incus and the stapes suprastructure
3: stapes suprastructure 4: stapes footplate
5: stapes tendon 6: chorda tympani (nerve)

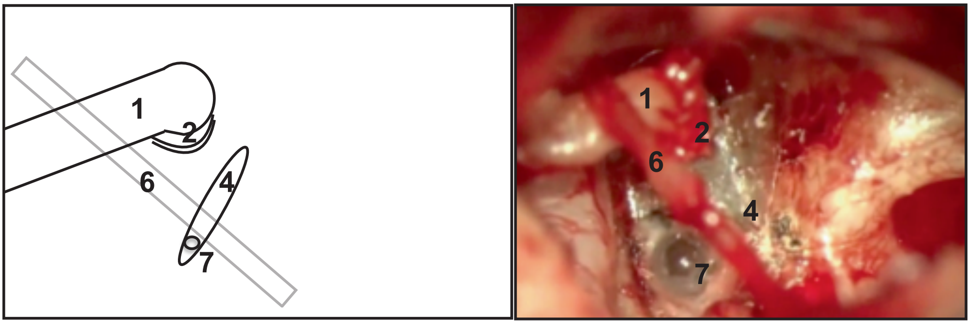


Figure 4A | The suprastructure of the stapes has been removed and a fenestration in the footplate has been created. (picture from dr. R. Vincent)
1: incus 2: junction between the incus and the stapes suprastructure
4: stapes footplate 6: chorda tympani (nerve)
7: fenestration

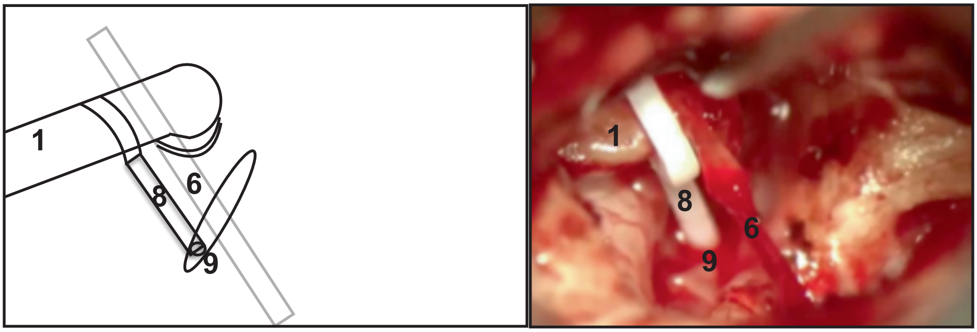
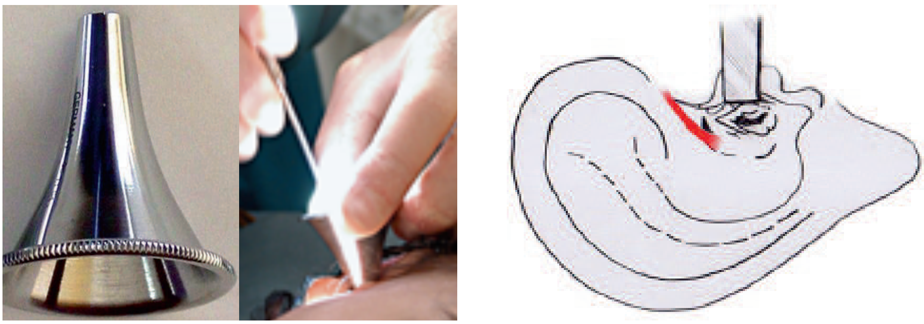


Figure 4B | A Teflon prosthesis has been placed in the fenestration and connected to the incus. (picture from dr. R. Vincent)

1: incus
6: chorda tympani (nerve)
8: Teflon prosthesis
9: prosthesis positioned in the fenestration (in this case including a vein graft)

1.2.6 Critical steps during stapes surgery

During stapes surgery, there are different techniques available to perform the procedure. It is possible to perform the procedure under local or general anesthesia (chapter 3). The middle ear can be approached using a transcanal or an endaural approach. In case of a transcanal approach, the surgeon inserts a speculum in the external ear canal and performs the surgical procedure through this speculum (figure 5A). An endaural approach includes an incision to enlarge the external ear canal (figure 5B). Following this incision a retractor will be used to keep the ear canal open during surgery.



A B

Figure 5 | A: Transcanal approach. **B**: Endaural approach.

After the middle ear has been opened (using either approach) and it is possible to visualize the ossicular chain (figure 3), there are different ways to remove the stapes suprastructure. A micro instrument could be used to fracture and remove the suprastructure of the stapes (figure 6). However, before fracturing, a drill or a laser could be used to weaken or completely cut the arch (crura) of the suprastructure, limiting the forces needed to safely perform this part of the procedure.

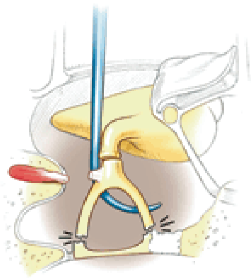


Figure 6 | Using a micro instrument to fracture and remove the suprastructure of the stapes. (Stanford School of Medicine, designed by Robert Jackler and Chris Gralapp)

Once the stapes suprastructure has been removed, there are different ways to create a fenestration in the footplate. Figure 7 demonstrates how a potassium titanyl phosphate laser (KTP) has been used to create a so-called rosette in the footplate. In this figure, the fenestration is not completed yet, such as in figure 4A. The surgeon could use the laser alone to complete the fenestration. It is also possible to complete the fenestration with a drill or micro instrument. In case there is no laser available the fenestration is created with a drill and/or micro instrument.

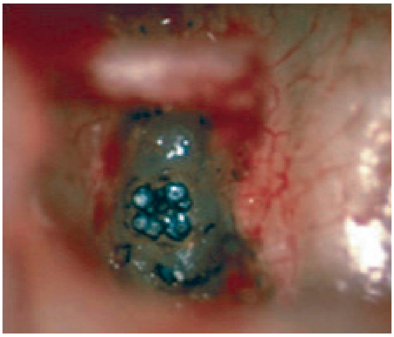


Figure 7 | A laser has been used to create rosette in the footplate (the fenestration is not completed yet). (picture from dr. R. Vincent)

After the fenestration has been created, some surgeons will position a small piece of venous blood vessel (vein graft) between the fenestration and the prosthesis (figure 8), while many surgeons do not use this vein graft interposition and place the prosthesis directly through the fenestration. Chapter 8 will attempt to compare these two surgical techniques (with and without a vein graft).

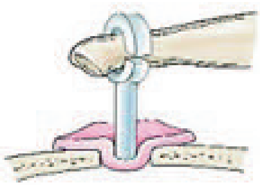
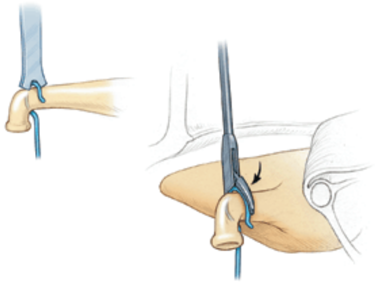


Figure 8 | A vein graft has been positioned between the fenestration and the prosthesis.

When looking at the prosthesis, differences in length/diameter, different materials and different insertion techniques are available. Figure 9A shows the titanium K-Piston with a loop (Heinz Kurz GmbH Medizintechnik). After this prosthesis has been connected to the incus, the surgeon needs to close the loop with an instrument (figure 9B). In figure 4B, a Teflon prosthesis has been inserted. The loop of this prosthesis is opened before insertion and closes around the incus automatically.



A **B**

Figure 9 | A: Titanium K-Piston with Loop (Heinz Kurz GmbH Medizintechnik). **B**: The surgeon must close the loop of this prosthesis.
(Stanford School of Medicine, designed by Robert Jackler and Chris Gralapp)

Figure 10 summarizes the potential variation in surgical steps. The surgeon has the possibility to choose an extensive amount of different pathways to complete the surgical procedure. It is likely that these differences may influence postoperative outcome.

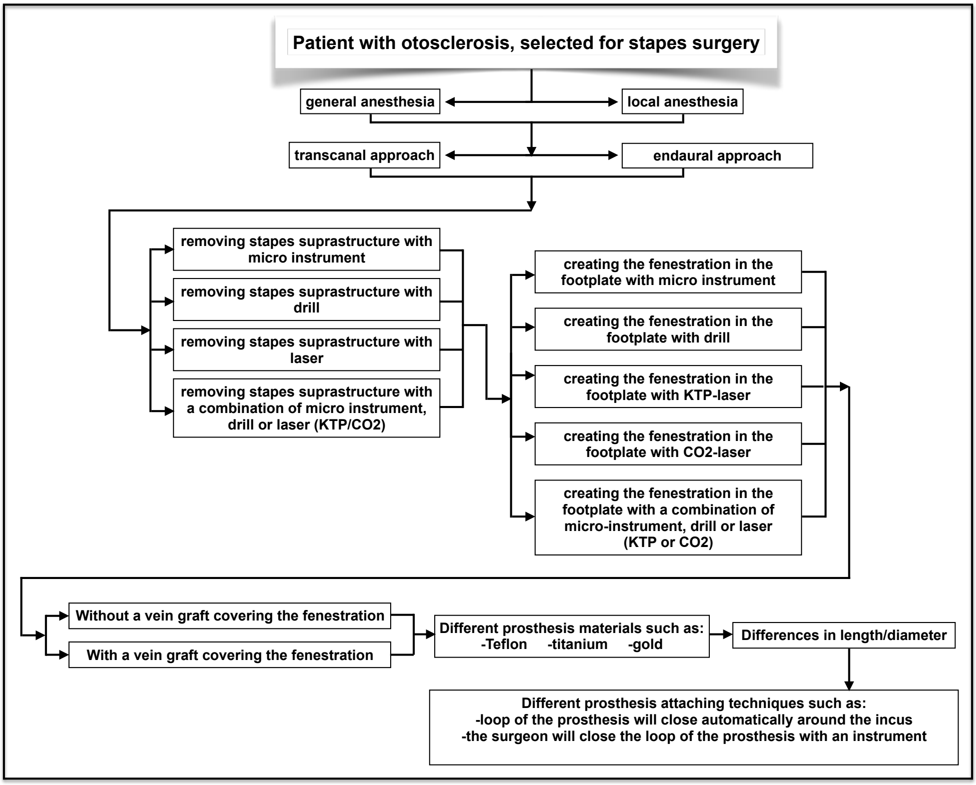


Figure 10 | Illustrating the potential variation in surgical steps that may influence the postoperative outcome.

1.3 PRESENT STATE OF AFFAIRS

Currently, the department of Otolaryngology, University Medical Center Utrecht (the Netherlands) performs around 80 to 100 stapes surgeries each year. In our publication comparing surgery with and without a vein graft (chapter 8) we found that the success percentage of patients from our clinic in Utrecht, with a mean postoperative air-bone gap closed to 10 dB or less, was 72.1%. The patients treated in France (Jean Causse Ear Clinic, Béziers) had a mean postoperative air-bone gap closed to 10 dB or les in 93.2% of the cases (chapter 8). The details of this study and its population are available in chapter 8, however it illustrates one of the most challenging topics regarding the surgical treatment of patients with otosclerosis: postoperative results differ among clinics due to differences in factors such as surgeons and surgical techniques, but also its postoperative evaluation. In an attempt to overcome the diversity and to improve postoperative results, we found that we had to initiate guideline devolvement and to look at promising preoperative counseling methods and different surgical techniques.

1.4 CLINICAL PRACTICE GUIDELINES (CGPs) AND ITS IMPLICATION

Due to differences in surgical techniques it is questionable if each individual patient will receive the best surgical treatment. Patients are in the hands of diversity due to the clinic they attend. Each individual stapes surgeon has his own approach of treatment, mostly based on expert opinion. This will not mean that the patient will experience the wrong treatment, but it is possible that the treatment could be improved. In order to reduce differences, the availability of clinical practice guidelines (CPGs) is essential. CPGs are expected to reduce untoward variation in practice and thereby improve quality of care. They are tools for efficiently sharing knowledge on best practice for groups of practitioners with a mutual interest in the optimal management of patients. In case it is not possible to develop or complete a guideline, due to a lack of reliable evidence, this indicates which focus future research should have. Within healthcare it is important to set limits to the costs of a specific treatment. Finally, the aim is to reduce or prevent harm for the patient, to maximize the benefits and to keep the costs as low as reasonable and achievable. Especially this balance between harm and benefits, keeping the costs in mind, will play a key role during guideline development.

1.5 AIM AND OUTLINE OF THIS THESIS

Keeping in mind that hearing loss due to otosclerosis could be treated successfully with surgery and the fact that treatment of hearing problems has top priority for persons suffering from hearing loss, it is essential to aim for the most optimal treatment option. This thesis provides an answer on how to reduce the unwanted variety among surgical treatment of patients with otosclerosis and how to aim for the most optimal balance between harm and benefits.

First we provide an instruction manual about how to create a clinical guideline, which is presented in **chapter 2**. Following this, two chapters will answer two important clinical questions based on available literature. **Chapter 3** indicates if patients with otosclerosis should be treated under local or general anesthesia. **Chapter 4** presents the clinical relevance of preoperative audiometry during clinical decision-making. **Chapter 5** is the ‘bridge’ between the instructional part and the clinical part of the thesis. It goes back to the basis and shows the significance of a genetic predisposition in patients with otosclerosis. In **chapter 6** we present a prognostic model, which could be used during the preoperative assessment of a patient with otosclerosis. Differences and their implications in surgical techniques are discussed in **chapter 7 and 8** in which we show if changing the type of laser during surgery and the way the stapes prosthesis is positioned will influence postoperative outcome. Finally, a general discussion in **chapter 9** will provide the overall implications of this thesis and recommendations.

The thesis is completed with a summary in English and Dutch.

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Chapter 2

Clinical practice guidelines on the management of patients with common otologic pathology toward European consensus: outline of approach

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Otology & Neurotology. 2013 October;34(8):1367-71

ABSTRACT

Objective: To achieve a European consensus about the best – evidence informed – management of patients with common otologic-related problems.

Design: Consensus process, supported by the 'European Academy of Otology & Neuro-Otology' (EAONO).

Setting: The 'European Academy of Otology & Neuro-Otology' (EAONO)

Methods: A guideline of a specific disease should include evidence-informed recommendations about questions relating to treatment, prognosis and diagnosis. A standardized method to design guideline questions, to search for evidence and to grade the quality of available evidence results in an overview of the best available literature. Experts achieve a consensus on best practice and articulate recommendations on evidence-based actions to be taken in patient care accordingly. The assets of such evidence-based consensus usually are the opinion of experts and arguments on availability, transferability, applicability and affordability.

Discussion: The volume of new information increases at a staggering pace. As a result there is an increasing demand for consistent systematic management of the available evidence. Systematic filtering of available evidence will help clinicians to find and apply best available and latest evidence efficiently and quickly.

Conclusion: Despite the otologic line of approach, the present paper provides a step-by-step 'guideline development instruction manual,' which could be used within other medical specialties.

INTRODUCTION

Nowadays, physicians increasingly rely on clinical practice guidelines (CPGs): systematically developed documents including evidence-based and consensus-based statements that assist physicians and patients in decisions about appropriate health care for specific circumstances (1).
Research findings from published literature provide the cornerstone for recommendations in CPGs. However, the published literature does not always provide complete information regarding the necessary or relevant details of clinical practice. To overcome this shortage, consensus methods are used to reach agreement. The 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) Working Group has developed a transparent approach to grading quality of evidence and strength of recommendations (2-4). The 'Appraisal of Guidelines for Research and Evaluation' (AGREE) Collaboration provides an instrument for the evaluation and development of well-structured and transparent guidelines (5-7).
Although during the last decade CPGs have gained popularity, only a small number of diseases are currently being covered by guidelines and available guidelines on similar topics are not always univocal (8,9).
The 'American Academy of Otolaryngology – Head and Neck Surgery' (AAO-HNS) published several otologic guidelines (10,11). Nonetheless, daily clinical practice shows a lack of general consensus among otologists (12). To overcome the diversity in the treatment of common otologic diseases, the 'European Academy of Otology & Neuro-Otology' (EAONO) initiated the development of guidelines concerning cholesteatoma, otosclerosis, Meniere's disease, vestibular schwannoma, cochlear implantation and the facial nerve, which are not only evidence-based but also consensus-based.
The present paper provides an insight in the standardized method used to design clinical practice guidelines.

METHODS

The development of a CPG should follow a rigorous step-by-step plan (Figure 1)

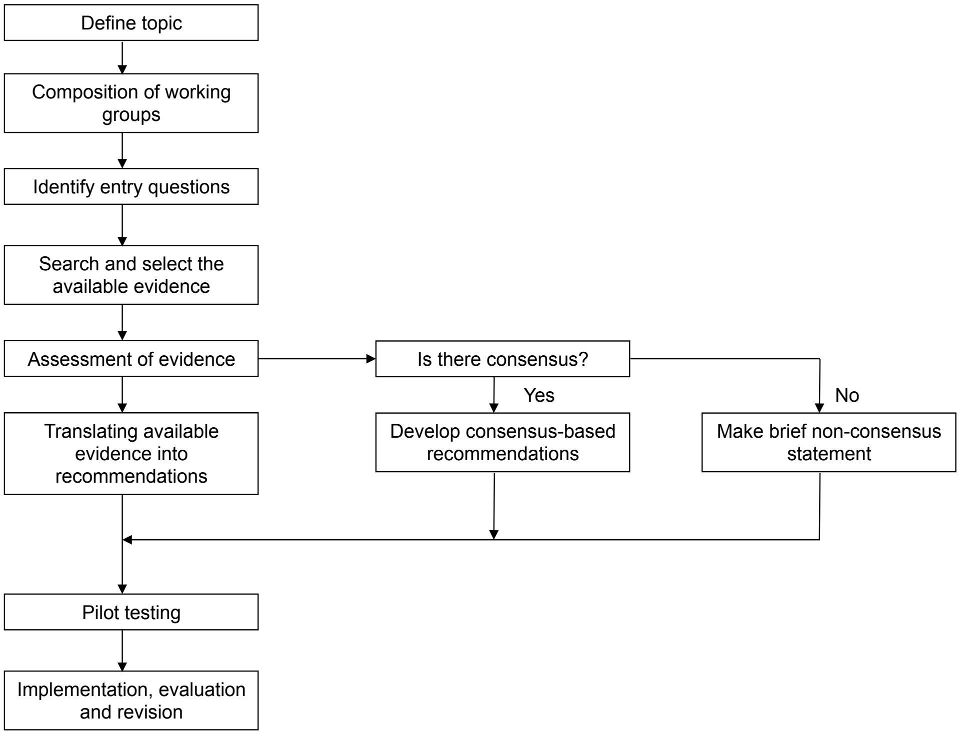

Figure 1 | Overview of the processes involved in developing clinical practice guidelines.

Working groups

Each guideline project starts with the composition of working groups with experts of the specific disease.

Entry questions

CPGs should focus on important outcomes such as survival and cure rates or quality-of-life and well-being. The working group should, in advance, specify what conditions and clinical problems will be covered and which entry questions regarding treatment, prognosis and diagnosis of the disease should be answered. These entry-questions are designed according the 'PICO' system (13). 'PICO' is an abbreviation for 'Patient/Population', 'Intervention', 'Control' and 'Outcome'. The 'P', 'I' and 'O' should always be included in a clinical guideline entry question. The 'C' is included in case a question includes a comparator. Not every question should include a comparator.

Table 1 shows example questions designed according to the 'PICO' system.

Table 1 | Examples of questions, using the PICO system.

Therapy/treatment effect question What is the effect of the **I** [for feature investigated] on the **O** [for outcome variables] at **T** [duration or time of follow-up] in patients with **P** [for target population] as compared to **C** [for comparator]? Example: *What is the effect of treatment with sodium fluoride on the progression of hearing loss at two years follow-up in patients with otosclerosis as compared to no treatment?*
Prognostic accuracy question What is the added value of **I [**feature investigated] for ruling in or ruling out the **O** [outcome variables] at **T** [duration or time of follow-up] in patients with **P** [target population]? Example: *What is the predictive value of postoperative tinnitus for ruling in or ruling out the presence of tinnitus at five years follow-up in patients who underwent stapes surgery for otosclerosis?*
Diagnostic accuracy question What is the added value of **I** [feature questioned] for ruling in or ruling out the **O** [outcome variables] in patients with **P** [target population]? Example: *What is the added value of high resolution CT for ruling in or ruling out otosclerosis in patients with progressive hearing loss?*
P: The target Population of the (study) question **I: The feature(s) that is questioned or Investigated** **C: Sometimes a treatment effect question may include a C for Comparator.** **O: The Outcome(s) variable of the (study) question**

Comprehensive evidence retrieval: search and select the evidence

PubMed, Embase and the Cochrane Library should be searched for available evidence, using a systematic search containing synonyms for the disease and the outcome. An example is shown in table 2 where synonyms for “otosclerosis” and “etiology” are used in title and abstract fields to find articles on the etiology of otosclerosis.

Table 2 | Systematic search example, on the etiology of otosclerosis.

Database	Search strategy for studies on the etiology of otosclerosis (search date: October 4th 2012)	Hits
PubMed	otosclerosis[Title/Abstract] OR otosclerotics[Title/Abstract] OR otosclerotic[Title/Abstract] OR otospongiosis[Title/Abstract] OR otospongioses[Title/Abstract] OR otospongiotic[Title/Abstract] OR otospongeotic[Title/Abstract] OR stapedotomies[Title/Abstract] OR stapedotomy[Title/Abstract] OR stapedectomies[Title/Abstract] OR stapedectomy[Title/Abstract] OR (stapes[Title/Abstract] AND (surgery[Title/Abstract] OR surgeries[Title/Abstract] OR mobilization[Title/Abstract] OR mobilisation[Title/Abstract])) OR (ossicular[Title/Abstract] AND (replacement[Title/Abstract] OR replacements[Title/Abstract])) AND causality[Title/Abstract] OR causalities[Title/Abstract] OR causation[Title/Abstract] OR causations[Title/Abstract] OR cause[Title/Abstract] OR causing[Title/Abstract] OR caused[Title/Abstract] OR causes[Title/Abstract] OR (causal[Title/Abstract] AND (factor[Title/Abstract] OR factors[Title/Abstract])) OR (causative[Title/Abstract] AND (factor[Title/Abstract] OR factors[Title/Abstract])) OR enable[Title/Abstract] OR enabling[Title/Abstract] OR enabled[Title/Abstract] OR enables[Title/Abstract] OR reinforce[Title/Abstract] OR reinforcing[Title/Abstract] OR reinforced[Title/Abstract] OR reinforces[Title/Abstract] OR (risk[Title/Abstract] AND (factor[Title/Abstract] OR factors[Title/Abstract])) OR environment[Title/Abstract] OR environmental[Title/Abstract] OR precipitate[Title/Abstract] OR precipitating[Title/Abstract] OR precipitated[Title/Abstract] OR precipitates[Title/Abstract] OR pathogenesis[Title/Abstract] OR pathologic[Title/Abstract] OR pathological[Title/Abstract] OR pathomechanical[Title/Abstract] OR etiopathogenesis[Title/Abstract] OR etiopathologic[Title/Abstract] OR etiopathological[Title/Abstract] OR etiology[Title/Abstract] OR etiologies[Title/Abstract] OR etiologic[Title/Abstract] OR etiologics[Title/Abstract] OR (etiological[Title/Abstract] AND (factors[Title/Abstract] OR factor[Title/Abstract])) OR aetiology[Title/Abstract] OR aetiologies[Title/Abstract] OR aetiologic[Title/Abstract] OR aetiologics[Title/Abstract] OR (aetiological[Title/Abstract] AND (factors[Title/Abstract] OR factor[Title/Abstract])) OR (epidemiologic[Title/Abstract] AND (factor[Title/Abstract] OR factors[Title/Abstract])) OR (epidemiological[Title/Abstract] AND (factor[Title/Abstract] OR factors[Title/Abstract]))	**922**
Embase	otosclerosis:ab,ti OR otosclerotics:ab,ti OR otosclerotic:ab,ti OR otospongiosis:ab,ti OR otospongioses:ab,ti OR otospongiotic:ab,ti OR otospongeotic:ab,ti OR stapedotomies:ab,ti OR stapedotomy:ab,ti OR stapedectomies:ab,ti OR stapedectomy:ab,ti OR (stapes:ab,ti AND (surgery:ab,ti OR surgeries:ab,ti OR mobilization:ab,ti OR mobilisation:ab,ti)) OR (ossicular:ab,ti AND (replacement:ab,ti OR replacements:ab,ti)) AND causality:ab,ti OR causalities:ab,ti OR causation:ab,ti OR causations:ab,ti OR cause:ab,ti OR causing:ab,ti OR caused:ab,ti OR causes:ab,ti OR (causal:ab,ti AND (factor:ab,ti OR factors:ab,ti)) OR (causative:ab,ti AND (factor:ab,ti OR factors:ab,ti)) OR enable:ab,ti OR enabling:ab,ti OR enabled:ab,ti OR enables:ab,ti OR reinforce:ab,ti OR reinforcing:ab,ti OR reinforced:ab,ti OR reinforces:ab,ti OR (risk:ab,ti AND (factor:ab,ti OR factors:ab,ti)) OR environment:ab,ti OR environmental:ab,ti OR precipitate:ab,ti OR precipitating:ab,ti OR precipitated:ab,ti OR precipitates:ab,ti OR pathogenesis:ab,ti OR pathologic:ab,ti OR pathological:ab,ti OR pathomechanical:ab,ti OR etiopathogenesis:ab,ti OR etiopathologic:ab,ti OR etiopathological:ab,ti OR etiology:ab,ti OR etiologies:ab,ti OR etiologic:ab,ti OR etiologics:ab,ti OR (etiological:ab,ti AND (factors:ab,ti OR factor:ab,ti)) OR aetiology:ab,ti OR aetiologies:ab,ti OR aetiologic:ab,ti OR aetiologics:ab,ti OR (aetiological:ab,ti AND (factors:ab,ti OR factor:ab,ti)) OR (epidemiologic:ab,ti AND (factor:ab,ti OR factors:ab,ti)) OR (epidemiological:ab,ti AND (factor:ab,ti OR factors:ab,ti)) AND [embase]/lim	**821**
The Cochrane Library	otosclerosis OR otosclerotics OR otosclerotic OR otospongiosis OR otospongioses OR otospongiotic OR otospongeotic OR stapedotomies OR stapedotomy OR stapedectomies OR stapedectomy OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements)) AND causality OR causalities OR causation OR causations OR cause OR causing OR caused OR causes OR (causal AND (factor OR factors)) OR (causative AND (factor OR factors)) OR enable OR enabling OR enabled OR enables OR reinforce OR reinforcing OR reinforced OR reinforces OR (risk AND (factor OR factors)) OR environment OR environmental OR precipitate OR precipitating OR precipitated OR precipitates OR pathogenesis OR pathologic OR pathological OR pathomechanical OR etiopathogenesis OR etiopathologic OR etiopathological OR etiology OR etiologies OR etiologic OR etiologics OR (etiological AND (factors OR factor)) OR aetiology OR aetiologies OR aetiologic OR aetiologics OR (aetiological AND (factors OR factor)) OR (epidemiologic AND (factor OR factors)) OR (epidemiological AND (factor OR factors))	**4**

An example of a systematic search on the etiology of otosclerosis, conducted in the PubMed, Embase and Cochrane databases from the inception of the databases to October 4 2012, by using the search "otosclerosis" and "etiology in the title and abstract fields

Figure 2 shows an overview of the search process and reveals records of publications, which are potentially useful to answer the clinical question. After exclusion of duplicates, title and abstract of the remaining articles need to be screened by two independent group members, using predefined inclusion criteria that match the 'PICO' elements of the entry question and specific exclusion criteria. Examples of exclusion criteria are editorials, commentaries, case reports, animal studies, publication language and secondary reports on research data. Subsequently, the full text of all potentially eligible publications is assessed in more detail, again using predefined selection criteria. For each phase of this stepwise selection procedure, the two screening group members resolve discrepancies in their judgment by discussion until they reach agreement. Finally, the initial search is completed with cross-reference searches in Scopus and Web of Science, related publications checks in PubMed and manual screening of the reference lists of the selected publications.

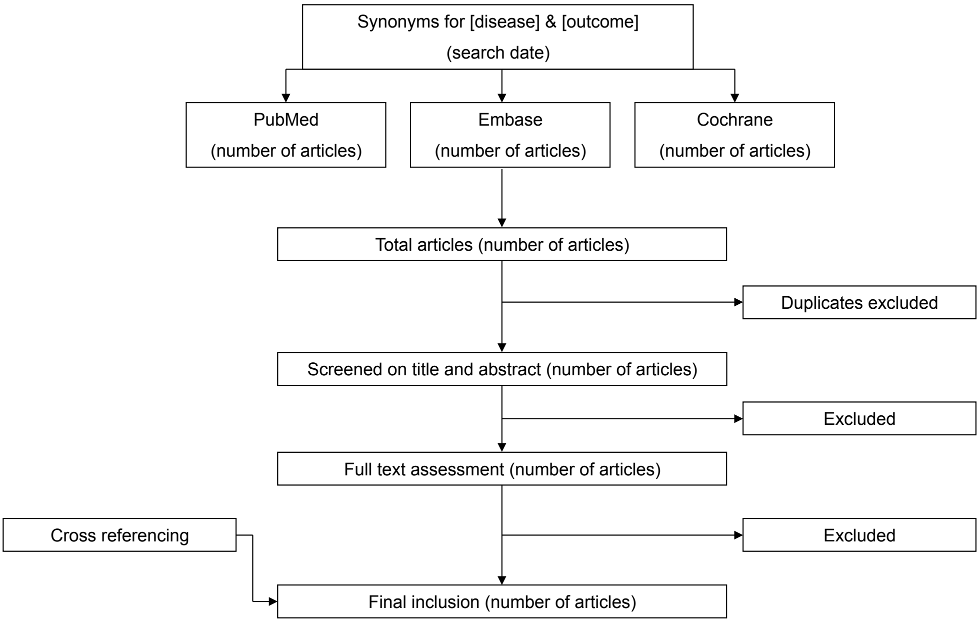

Figure 2 | Search and selection procedure.

Explicit and transparent (reproducible) retrieval (search and selection) and quality assessment should avoid inclusion of only a random or (worse) a selective portion of the best available evidence. To control for such bias, this part of the process is conducted not only by task force members, but also in collaboration with independent clinical librarians and experts in systematic review methods.

Assessment of evidence

The assessment and rating of evidence quality provides an indication for the reliability of the data. Available original studies are assessed for:

- The directness of the evidence, i.e. the extent to which research findings are applicable and transferable to other settings and patients.
- The risk of biased outcomes because of flaws in the design, conduct and reporting of a study.

Evidence can be used to answer the entry question when the assessment of available studies shows risk of bias to be low enough and the directness of evidence to be high enough. Studies with low directness and high risk of bias will be excluded from contributing to answering of the entry question.

Extracting the data

Reported raw risks from study samples for important time points on crucial, important and other outcomes should be extracted from the original studies in a standardized manner. Meta-analyses (pooling of data across studies) can be used in synthesizing the outcome data from the studies. To avoid biased and spurious findings, such data pooling should be restricted to studies with the highest directness and lowest risk of bias.

Translating evidence into recommendations

When an overview of the best evidence is available to answer the entry question, experts convene for stating recommendations on evidence-based actions to be taken in patient care. To translate the evidence-based answer to the entry question into actionable recommendations for patient care they need to achieve consensus. Differences in organization of health care among clinics and countries, and arguments on availability, applicability, transferability and affordability, may complicate consensus in stating recommendations for patient care. It is crucial, however, that evidence is explicitly separated from opinions and judgments, although it is very important for the clinical usefulness of CPGs that judgments, additional arguments and reasoning involved in arriving at recommendations are transparently and explicitly reported.

The GRADE Working Group has developed a system and tools that are extremely helpful in rating the quality of evidence, translating evidence into recommendations and grading the strength of recommendations (2-4).

Recommendations included in CPGs should be based on the (quality-rated) best available evidence and graded for their strength. In translating evidence in recommendation, there should be room for opinion and consensus when there is moderate to weak evidence. However, in arriving at a recommendation, strong evidence on a clear balance between benefit and harm should always be favored above opinion. To arrive at a strong recommendation, explicit and transparent methods should be followed and several sources of information need to be taken into consideration, notably a comprehensive evidence retrieval, reporting quality of available original studies, the direction, size and precision of effects and their consistency across studies and the overall balance between benefits and harms. Problems that may complicate the interpretation of findings, in particular selective inclusion, publication and reporting, should be explicitly considered and mentioned. Moreover, it should be kept in mind that large and precise effects with low risk of bias are more likely to be real, whereas those with high directness of evidence are more likely to be clinically important.

DISCUSSION

The volume of new information increases at a staggering pace. In the ENT field, the number of publications has increased exponentially over the last decades resulting in one publication per hour (14). Through this, there is an increasing demand for consistent systematic management of the available evidence. This is not only the clinician's priority, but also that of health insurers. Guidelines ensure a measurable standard of care and may be helpful in identifying evidence gaps.

If guidelines are to be relevant, those who are expected to use them or to benefit from their use should play a part in their conception and development. It is important to note that guidelines should be flexible and adaptable to varying local conditions and available resources. They should include evidence relevant to different target populations and geographic and clinical settings, take into account costs and constraints, and make provision for accommodating the different values and preferences of patients.

The present paper does not include economic considerations. However, guidelines should be developed keeping resource constraints in mind. They should incorporate an economic appraisal, which may be helpful for choosing between treatment options.

Finally, guidelines are developed to be disseminated and implemented, taking into account their target audiences. They should also be disseminated in such a way that practitioners and consumers become aware of them and use them.

The development of a specific guideline will not end at the moment of first publication. It is essential that the implementation and impact of guidelines will be evaluated and that literature will be monitored regularly to identify new, relevant evidence. New evidence could lead to a change of mind and could have major influence on guideline recommendations.

The guideline working group has the responsibility to ensure a long-term schedule, which includes deadlines for evaluation and revision.

CONCLUSION

Despite the otologic line of approach, the present paper provides a step-by-step ‘guideline development instruction’, which could be used within other medical specialties.

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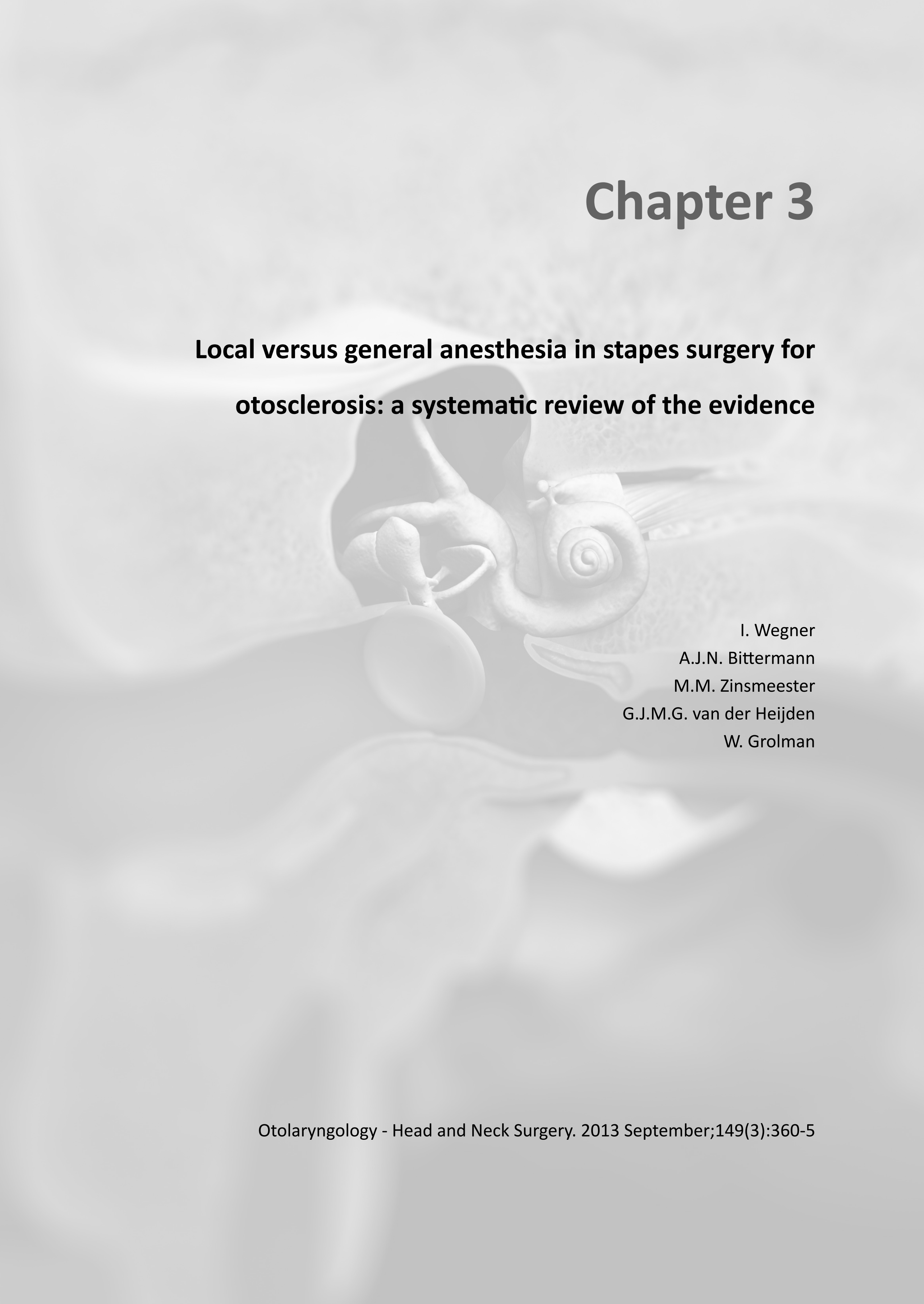

Chapter 3

Local versus general anesthesia in stapes surgery for otosclerosis: a systematic review of the evidence

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ABSTRACT

Objective: To assess hearing results following primary stapes surgery in patients with otosclerosis, comparing local and general anesthesia.

Data sources: PubMed, Embase, the Cochrane Library, CINAHL and Scopus.

Review methods: A systematic search was conducted, followed by assessment of directness of evidence and risk of bias. Studies reporting original data on the effect of local anesthesia, compared to general anesthesia, on closure of air-bone gap in patients undergoing stapes surgery for otosclerosis were included.

Results: A total of 257 unique studies were retrieved, of which three (including 417 procedures) satisfied the eligibility criteria. Assessment showed that all studies carried high risk of bias and only one study provided direct evidence.

Conclusion: There is no difference in postoperative air-bone gap, worsening of sensorineural hearing loss and postoperative vertigo between the two groups. A statistically significant increased risk of immediate dead ear following stapes surgery performed under general anesthesia was reported in one study.

CLINICAL QUESTION

A 50-year-old female is referred to the Ear, Nose and Throat (ENT) department with progressive hearing loss. Otologic examination shows left-sided conductive hearing loss, which is confirmed by pure-tone audiometry (PTA). CT images show bony deposits around the oval window. The diagnosis otosclerosis is made. The ENT-surgeon suggests treating the patient with stapes surgery. However, the patient has a fear of general anesthesia and would rather have the surgery done under local anesthesia.

BACKGROUND

Otosclerosis is characterized by abnormal sponge-like bone growth in the middle ear, causing progressive hearing loss (1). It mainly affects the ossicular chain and can be treated surgically by removing (part of) the stapes and replacing it with a prosthesis (stapedotomy and stapedectomy). Although stapes surgery has proven to be a safe and effective treatment option for otosclerosis (2), permanent sensorineural hearing loss (SNHL) can occur and is the most dreaded complication of stapes surgery. The incidence of this complication following primary stapes surgery was less than 1% in large series (3,4).

Stapes surgery can be performed using both local and general anesthesia. Local anesthesia is preferred by some surgeons because of the possibility to test hearing immediately after placement of the prosthesis with early recognition of possible worsening of sensorineural hearing loss or dead ear. Moreover, vertigo caused by prosthesis displacement is immediately recognized and the surgeon can act accordingly, minimizing major complications. One could hypothesize that local anesthesia is safer and more beneficial than general anesthesia in stapes surgery. The ENT surgeon decides to circumstantiate this hypothesis with the available evidence and tries to find out the answer to the following clinical question: '*What is the effect of local anesthesia, compared to general anesthesia, on recovery of hearing loss as measured by postoperative air-bone gap at one year follow-up in patients undergoing primary stapes surgery for otosclerosis*?'

METHODS

A systematic search in PubMed, Embase, the Cochrane Library, CINAHL and Scopus was conducted, using synonyms for stapes surgery and anesthesia and relevant MeSH terms (see table 1).

Table 1 | Search for studies on the effect local anesthesia, compared to general anesthesia, in patients undergoing primary stapes surgery for otosclerosis (date of search: March 11th 2013).

Database	Search	Field
PubMed	(stapedect* OR stapedot* OR poststapedect* OR poststapedot* OR otoscler* OR otospongio* OR stapes OR stapedial OR ossicular OR footplate) AND (anast* OR anest* OR anaest* OR sedat* OR narco*)	Title/ Abstract
	(stapedectomy OR otosclerosis OR stapes) AND (anesthesia)	MeSH Terms
Embase	(stapedect*:ti,ab OR stapedot*:ti,ab OR poststapedect*:ti,ab OR poststapedot*:ti,ab OR otoscler*:ti,ab OR otospongio*:ti,ab OR stapes:ti,ab OR stapedial:ti,ab OR ossicular:ti,ab OR footplate:ti,ab) AND (anast*:ti,ab OR anest*:ti,ab OR anaest*:ti,ab OR sedat*:ti,ab OR narco*:ti,ab)	Title/ Abstract
	(stapedectomy/exp OR stapedotomy/exp OR otosclerosis/exp OR otospongiosis/exp OR stapes/exp) AND (anesthesia/exp OR anaesthesia/exp OR sedation/exp OR narcosis/exp)	Emtree
The Cochrane Library **CINAHL** **Scopus**	(stapedect* OR stapedot* OR poststapedect* OR poststapedot* OR otoscler* OR otospongio* OR stapes OR stapedial OR ossicular OR footplate) AND (anast* OR anest* OR anaest* OR sedat* OR narco*)	Title/ Abstract

Two independent assessors (IW and MZ) screened the titles and abstracts of the retrieved records for inclusion and duplicates were excluded. Only records reporting original study data on the effect of both local anesthesia and general anesthesia in patients undergoing stapes surgery for otosclerosis were included (see figure 1 for selection criteria).

Systematic reviews, opinion papers, animal studies and case reports were excluded. Related publications were searched in PubMed, while Scopus and Web of Science were used for cross-reference checking for studies not identified by the initial literature search. Selected articles, related reviews, meta-analyses and guidelines were hand searched for relevant cross-references.
Predefined criteria were used for assessment of the directness of evidence and risk of bias of the selected articles (see table 2). Initial discrepancies were discussed until consensus was reached. All studies with both low directness of evidence and high risk of bias were excluded from further review. Studies were classified as having high, moderate or low directness of evidence if they complied with all three, two or one of these criteria respectively. If studies complied with all, three or one criteria used to assess risk of bias, they were classified as having a low, moderate or high risk of bias respectively.

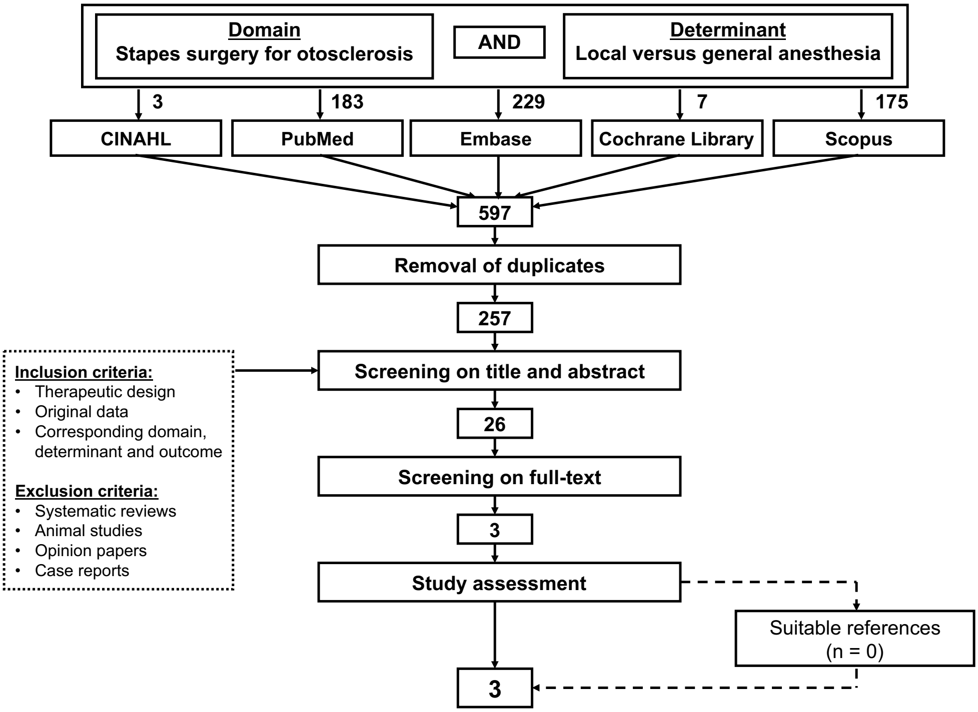

Figure 1 | Flowchart for selection of studies on the effect of local anesthesia, compared to general anesthesia, in patients undergoing primary stapes surgery for otosclerosis.

Outcome data of the included studies were extracted and calculated by two independent authors (IW and MZ). The primary outcome measure was closure of the air-bone gap to within 10 decibels or less, which is generally considered a successful outcome of stapes surgery in the literature (4-7). According to the Committee on Hearing and Equilibrium, follow-up should be at least one year for this outcome measure since results change over time and long-term results provide a more realistic prognosis (8). Secondary outcome measures were worsening of sensorineural hearing loss; defined as changes in pure-tone audiometry exceeding 5 decibels or more, vertigo and other complications. Preferably absolute risks were extracted or calculated. If these were not given or could not be calculated, the outcome measure as used in the article was reported.

Table 2 | Study assessment of studies on the effect local anesthesia, compared to general anesthesia, in patients undergoing primary stapes surgery for otosclerosis.

Study (PubMed ID**)**	**Sample size of study**	**Study design**	**Directness of evidence**			**Risk of bias**				
			Patients	**Treatment**	**Outcome**	**Treatment allocation**	**Blinding**	**Standardization (T)**	**Standardization (O)**	**Complete data**
Vital (18206328)[9]	268	RCS	●	●	●	○	?	?	●	●
Mathews (9917040)[10]	71	RCS	○	●	●	?	?	?	●	?
Babighian (19716020)[11]	78	RCS	○	●	●	?	?	?	●	○

Legend:

Study Design
-RCS = retrospective case series

Directness of evidence
-Patients: ● = primary stapedotomy or stapedectomy for otosclerosis; ○ = revision surgery for otosclerosis, nonotosclerotic stapes surgery, other.
-Treatment: ● = local anesthesia compared with general anesthesia; ○ = other.
-Outcome: ● = recovery measured by closure of air-bone gap; ○ = other.

Risk of bias
-Treatment allocation: ● = randomized or concealed; ○ = neither randomization nor concealment; ? = unclear, no information provided.
-Blinding of anesthesia method during postoperative pure-tone audiometry and interpretation of audiometry: ● = patients and clinicians blinded; ○ = only patients blinded or no blinding; ? = unclear, no information provided.
-Standardization (T) of anesthesia method and Standardization (O) of outcome measure: ● = yes; ○ = no; ? = unclear, no information provided.
-Completeness of outcome data for primary outcome: ● = below 10% missing data; ○ = 10% or more missing data; ? = unclear, no information provided.

RESULTS

A total of 597 titles were retrieved, of which 257 were unique studies (see figure 1; date of last search was March 11th 2013). After selection based on title and abstract, and subsequent full text screening, three articles (9-11) were considered eligible for answering our question. Of four articles, that could not be excluded based on their title (12-15), no abstracts or full texts were available, despite an extensive search in the available literature databases, university networks and Google Scholar. We judge it highly unlikely that original study data are reported in these articles. Cross-reference checking revealed no additional articles. The selected studies included in total 417 procedures in 397 patients. All studies were case series. Assessment of their reported methods showed that only one study (9) provided direct evidence (see table 2). Important limitations in the directness of evidence were found in the other two studies, notably inclusion of patients who had undergone revision stapes surgery (10,11) or stapes surgery for other reasons than otosclerosis (10). Revision stapes surgery is associated with an increased risk of postoperative sensorineural hearing loss and hearing outcome is less favorable when compared to primary surgery (16). Furthermore, revision is technically far more challenging than primary stapes surgery and the technique of repair is usually determined by the surgical findings at the time of revision (16). Therefore, studies reporting the results of revision stapes surgery do not provide direct evidence for answering the clinical question. These two studies were included for further analyses nonetheless. The risk of bias was high in all studies. None of the studies were performed in a randomized fashion, nor was treatment allocation concealed. No information was provided regarding blinding or standardization of treatment in all studies. It is unlikely that both audiometrists and interpreters were blinded for the used anesthesia method, since audiometric results are often interpreted by the surgeon performing the procedure.

The extracted data of the included studies are described in table 3 and table 4. There are major dissimilarities between studies regarding type of surgery, type of surgeon and follow-up duration. As to be expected there are large differences in the size of the reported absolute effects of both local and general anesthesia between studies reporting on effects in (mainly) patients undergoing primary stapes surgery (9,10) compared to patients undergoing revision surgery (11).

The difference in postoperative air-bone gap between local and general anesthesia is minimal in all studies with clinically irrelevant risk differences of around 1%. The percentage of sensorineural hearing loss in both groups is similar. However, Vital et al. did report a statistically significant difference in the occurrence of immediate dead ear; three patients (1.9%) in the general anesthesia group versus none (0%) in the local anesthesia group (9).
Data on potential adverse effects of local and general anesthesia, other than sensorineural hearing loss, were systematically collected by Vital et al (9). Mild postoperative vertigo was reported in both groups with a risk difference slightly in favor of local anesthesia. No other adverse effects of either or both local and general anesthesia were reported.

Table 3 | Study descriptives of studies on the effect of local anesthesia, compared to general anesthesia, in patients undergoing primary stapes surgery for otosclerosis.

Study (year)	**Local anesthesia**	**General anesthesia**	**Type of stapes surgery**	**Type of surgeon**	**Pure-tone audiometry**	**Follow-up duration**
Vital (2008)[9]	1% lidocaine with 1:100,000 epinephrine (n = 160)	Method unknown (n = 108)	Primary stapedectomy (n = 268)	ENT specialist (n = 1)	Air- and bone-conduction pure-tone thresholds at 500 Hz, 1, 2 and 3 kHz	Postoperative PTA showing best hearing within one year of surgery
Mathews (1999)[10]	1% or 2% lidocaine with 1:100,000 epinephrine, augmented by intravenous sedation and analgesia (n = 38)	Endotracheal intubation, intravenous narcotic agents and inhaled agents (n = 33)	Primary stapedectomy (n = 60) Revision stapedectomy (n = 7) Nonotosclerotic stapedectomy (n = 4)	Resident surgeons in fourth or fifth postgraduate year (n = 10)	Air- and bone-conduction pure-tone thresholds at 500 Hz, 1 and 2 kHz	Between 6 and 12 weeks postoperatively
Babighian (2009)[11]	Method unknown (n = 35)	Method unknown (n = 43)	Revision stapedotomy following primary stapedotomy (n = 78)	ENT specialist (n = 1)	Air- and bone-conduction pure-tone thresholds at 500 Hz, 1, 2, 3 and 4 kHz	1 month, 3 months and every 6 months after revision surgery. Last hearing test available was used in this study.

n = number of procedures/surgeons

Table 4 | Results of studies on the effect of local anesthesia, compared to general anesthesia, in patients undergoing primary stapes surgery for otosclerosis.

Study (year)	**Group size**		**Follow-up duration**	**Air-bone gap closure to within 10 dB**			**Secondary outcome measures**			
	Local anesthesia	**General anesthesia**		**Local anesthesia***	**General anesthesia***	**Risk difference***	**Outcome measure**	**Local anesthesia***	**General anesthesia***	**Risk difference***
Vital (2008)[9]	n = 160	n = 108	Best PTA within one year	93.2 (90.2; 96.2)	91.7 (88.4; 95.0)	1.5 (0.04; 3.0)	SNHL	5.4 (2.7; 8.1)	6.2 (3.3; 9.1)	1.2 (-0.1; 2.5)
							Dead ear	0	1.9 (0.3; 3.5)	1.9 (0.3; 3.5) #
							Vertigo	3.7 (1.4; 6.0)	4.4 (1.9; 6.9)	0.7 (-0.3; 1.7)
Mathews (1999)[10]	n = 38	n = 33	6-12 weeks	86.8 (78.9; 94.7)	87.9 (80.3; 95.5)	-1.1 (-3.5; 1.3)	SNHL	0	0	-
Babighian (2009)[11]	n = 35	n = 43	Every 6 months	54.3 (43.3; 65.4)	53.5 (42.4; 64.6)	0.8 (-1.2; 2.8)	-	-	-	-

When risk difference is positive, this favors local anesthesia.
n = number of procedures
* = % (95% confidence interval)
# = p-value < 0.05
PTA = pure tone average
SNHL =sensorineural hearing loss

TRANSLATING EVIDENCE INTO PRACTICE

The amount of available studies on the effect of local anesthesia compared to general anesthesia on postoperative air-bone gap in patients undergoing stapes surgery is limited. Most of these studies provide indirect evidence and carry high risk of bias. They all show no difference in hearing in both groups, except for a statistically significant difference in incidence of dead ear favoring local anesthesia in one study (9). Since there is only a small difference in clinical effect, it would be interesting to compare the benefits and costs of both types of anesthesia. Unfortunately, no data were available on the cost-effectiveness of any of the treatment options and it was not possible to perform a cost-benefit analysis.

As mentioned previously, local anesthesia enables the surgeon to test hearing and recognize vertigo during the procedure. The surgeon can act accordingly immediately, thereby minimizing major complications. This anesthesia method seems to be safer and more beneficial to the patient when compared to general anesthesia. However, the available evidence shows no difference in hearing outcome between the two groups. On the other hand the use of general anesthesia provides substantial advantages during teaching of residents. The patient is immobile and there is no limitation in the duration of anesthesia, enabling the surgeon to operate at a more relaxed and controlled pace and thereby making it possible for residents to complete the entire procedure. Furthermore, the patient is not disturbed by verbal communication among staff and residents during the surgery.

The following needs to be taken into consideration when interpreting these findings. First, the risk of bias is high in all studies. None of the studies were performed in a randomized fashion, nor was treatment allocation concealed. No information was provided regarding blinding or standardization of treatment. Second, the sample sizes are rather small, with the exception of one study (9). In total we were able to report on a total of 417 procedures. Third, the design of the included studies largely differed in their approach to the surgical intervention, amount and experience of surgeons and follow-up duration. Therefore, the reported effects cannot simply be compared between studies.

To date the evidence is weak and therefore no evidence-based recommendations can be provided. Based on the evidence, patients can be informed that it seems as though there is no difference in hearing outcome between local and general anesthesia and there seems to be an increased risk of immediate dead ear following stapes surgery under general anesthesia. The decision will be largely based on patient preference and experience of both surgeons and anesthesiologists with either method.

CONCLUSION AND RECOMMENDATION

The available studies on the effect of local anesthesia, compared to general anesthesia, on postoperative air-bone gap in patients undergoing stapes surgery carry substantial high risk of bias. This precludes firm conclusions. All of the studies show no difference in postoperative air-bone gap, sensorineural hearing loss and postoperative vertigo between the two groups. One study, with high directness of evidence and high risk of bias, reported an increased risk of immediate dead ear following stapes surgery under general anesthesia. Taking into consideration the risk of immediate dead ear and the patient's wishes, it was decided to perform stapes surgery under local anesthesia in this patient.

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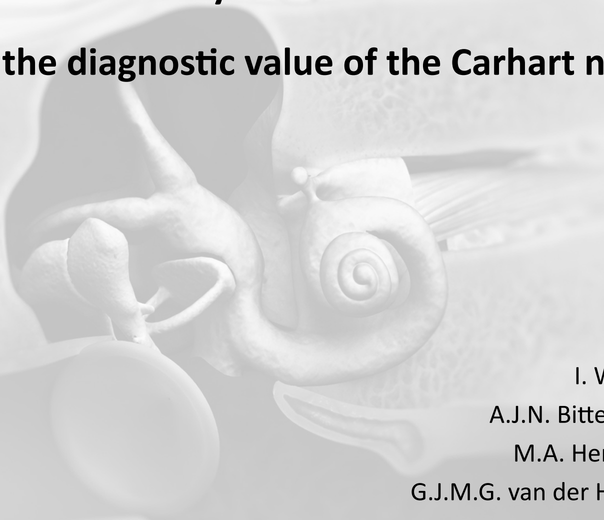
Chapter 4

Pure-tone audiometry in otosclerosis: insufficient evidence for the diagnostic value of the Carhart notch



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ABSTRACT

Objective: To evaluate whether the Carhart notch on pure-tone audiometry is reliable as a diagnostic test for predicting otosclerosis in patients with conductive hearing loss.

Data sources: PubMed, Embase, the Cochrane Library, CINAHL and Scopus.

Methods: A systematic search was conducted. Studies reporting original study data were included. After assessment of directness of evidence and risk of bias of the selected articles, the prevalences and the positive and negative predictive values were extracted.

Results: A total of 1402 unique studies were retrieved. Three of these satisfied the eligibility criteria. One study provided direct evidence, while all studies carried moderate to high risk of bias. One study with moderate directness of evidence and high risk of bias was not further analyzed. In a study with a high directness of evidence, a high risk of bias and a low prevalence of otosclerosis (8%) in patients with conductive hearing loss, the presence of a Carhart notch at 2,000 Hz increased the risk of otosclerosis with 33%. In a second study with moderate directness of evidence, moderate risk of bias and a high prevalence of otosclerosis (72%) in patients with a surgically confirmed congenital ossicular anomaly or otosclerosis, the presence of a Carhart notch at 2,000 Hz increased the risk of otosclerosis with 2%.

Conclusion and recommendation: Although there is insufficient high quality evidence regarding the diagnostic value of the Carhart notch, it seems it is a useful hint for the presence of otosclerosis, but it cannot be used to confirm a diagnosis of otosclerosis.

CLINICAL QUESTION

A 50-year-old female is referred to the Ear, Nose and Throat (ENT) department with progressive hearing loss. Otological examination shows left-sided conductive hearing loss, which is confirmed by pure-tone audiometry (PTA). There is an air-bone gap typical for otosclerosis and a Carhart notch is clearly visible at 2,000 Hz. The mean pure-tone air-conduction hearing threshold at 500, 1,000 and 2,000 Hz is 55 dB HL. Most likely her clinical signs and symptoms are the result of otosclerosis. The ENT surgeon wonders whether it is possible to establish this diagnosis based on this particular notch on pure-tone audiometry.

BACKGROUND

An increase in bone-conduction threshold with a peak at 2,000 Hz in patients with otosclerosis was first described by Carhart in 1950 (1). The depression ranges in frequency from 500 to 4,000 Hz and can therefore also be called the Carhart effect. Although studies suggest that a Carhart notch can also originate from various other disorders of the middle ear, such as otitis media with effusion, chronic otitis media and congenital ossicular anomalies (2-6), a Carhart notch on pure-tone audiometry is generally believed to hint for the presence of otosclerosis in patients with conductive hearing loss (7). The objective of this systematic review is to evaluate whether the presence of a Carhart notch adds information for an accurate diagnosis of otosclerosis in patients with conductive hearing loss.

METHODS

A systematic search in PubMed, Embase, the Cochrane Library, CINAHL and Scopus was conducted, combining relevant synonyms for pure-tone audiometry and for otosclerosis (see table 1).

Table 1 | Search for studies on the diagnostic value of the Carhart notch in diagnosing otosclerosis in patients with conductive hearing loss (date of search: March 25th 2013).

Database	Search	Search field
PubMed **The Cochrane Library** **CINAHL** **Scopus**	((bone AND conduction) OR (air AND conduction) OR PTA OR audiogr* OR audiomet* OR audiolog* OR carhart OR carhart's OR (air AND bone AND gap) OR ABG) AND (otoscler* OR otospong* OR stapedot* OR stapedect* OR (middle AND ear AND inspection) OR ((surgery OR surgeries OR procedure OR procedures OR operation OR operations OR fixation OR fixations) AND stapes))	Title/ Abstract
Embase	((bone:ti,ab AND conduction:ti,ab) OR (air:ti,ab AND conduction:ti,ab) OR PTA:ti,ab OR audiogr*:ti,ab OR audiomet*:ti,ab OR audiolog*:ti,ab OR carhart:ti,ab OR "carhart/s":ti,ab OR (air:ti,ab AND bone:ti,ab AND gap:ti,ab) OR ABG:ti,ab) AND (otoscler*:ti,ab OR otospong*:ti,ab OR stapedot*:ti,ab OR stapedect*:ti,ab OR (middle:ti,ab AND ear:ti,ab AND inspection:ti,ab) OR ((surgery:ti,ab OR surgeries:ti,ab OR procedure:ti,ab OR procedures:ti,ab OR operation:ti,ab OR operations:ti,ab OR fixation:ti,ab OR fixations:ti,ab) AND stapes:ti,ab))	Title/ Abstract

Two independent assessors (IW and MH) screened title and abstract of the retrieved records for inclusion and duplicates were excluded. Studies on the diagnostic accuracy of the Cahart notch in patients with conductive hearing loss were selected when pure-tone audiometry was performed prior to middle ear inspection for otosclerosis. Only reports of original study data on the added value of the Carhart notch on pure-tone audiometry in diagnosing otosclerosis were included; systematic reviews, opinion papers, animal studies, postmortem studies and case reports were excluded (see figure 1 for selection criteria). Related publications were searched in PubMed, while Scopus and Web of Science were used for cross-reference checking for studies not identified by the initial literature search. Selected articles, related reviews, meta-analyses and guidelines were hand searched for relevant cross-references.

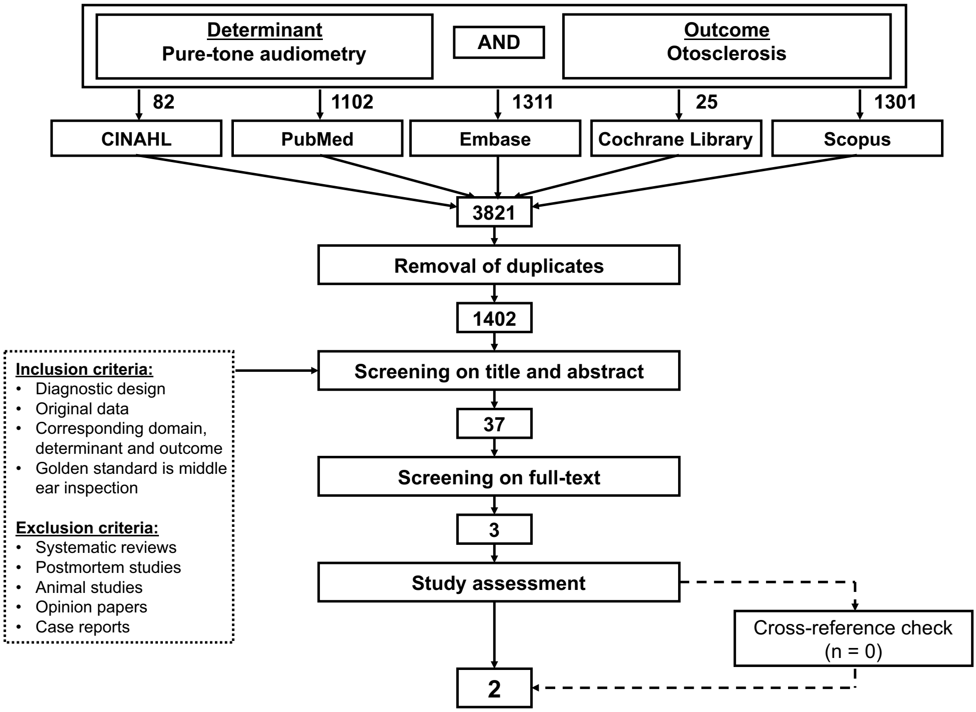

Figure 1 | Flowchart for selection of studies on the diagnostic value of the Carhart notch in diagnosing otosclerosis in patients with conductive hearing loss.

Predefined criteria were used for assessment of selected studies for their directness of evidence and the risk of bias (see table 2). Studies were classified as having high, moderate or low directness of evidence if they complied with all three, two or one of these criteria respectively. If studies complied with five to six, three to four or none to two of the criteria used to assess risk of bias; they were classified as having a low, moderate or high risk of bias respectively. Initial discrepancies between independent reviewers were resolved by discussion and reported results are based on full consensus. Studies with either or both low directness of evidence and high risk of bias were excluded from further review.

Table 2 | Study assessment of studies on the diagnostic value of the Carhart notch in diagnosing otosclerosis in patients with conductive hearing loss.

Study (PubMed ID**)**	**Sample size of study (n)**	**Study design**	**Directness of evidence**			**Risk of bias**					
			Patients	**Index test**	**Outcome**	**Reference test**	**Blinding (I)**	**Blinding (R)**	**Standardization (I)**	**Standardization (R)**	**Complete data**
Yasan (16995960)[10]	315	CS	●	●	●	●	?	?	●	?	?
Kashio (21422306)[8]	153	CS	○	●	●	●	?	?	●	?	●
Perez (18957900)[9]	150	CS	○	●	●	●	?	?	?	?	○

Legend:

n = number of procedures

Study Design
-CS = cross-sectional design

Directness of evidence
-Patients: ● = patients suffering from conductive hearing loss; ○ = patients diagnosed with otosclerosis, other.
-Index test: ● = presence of Carhart notch at 2,000 Hz on pure-tone audiogram; ○ = other.
-Outcome: ● = otosclerosis as determined by middle ear inspection or during stapes surgery; ○ = other.

Risk of bias
-Reference test: ● = middle ear inspection or stapes surgery performed in all patients; ○ = reference test not performed in all patients, reference test other than middles ear inspection or stapes surgery; = unclear, no information provided.
-Blinding (I) of patients and surgeon for results of index test (Carhart notch on pure-tone audiometry) and Blinding (R) of patients and interpreter of pre-operative audiogram for results of reference test (middle ear inspection or stapes surgery): ● = adequate blinding of patients and clinicians; ○ = only patients blinded or no blinding; ? = unclear, no information provided.
-Standardization (I) of index test (Carhart notch on pure-tone audiometry) and Standardization (R) of reference test (middle ear inspection or stapes surgery) ● = yes; ○ = no; ? = unclear, no information provided.
-Completeness of outcome data: ● = below 10% missing data; ○ = 10% or more missing data; ? = unclear, no information provided.

Outcome data of the included studies were extracted and calculated by two independent authors (IW and MH). The true positive, false positive, true negative and false negative test results were extracted in order to be able to calculate the prevalence and the positive and negative predictive values (PPV and NPV respectively). If these were not given or could not be calculated, the findings as reported in the article were presented.

RESULTS

A total of 3821 titles were retrieved, of which 1402 were unique studies (see figure 1; date of last search was March 25th 2013). After selection based on title and abstract, and subsequent full text screening, three articles (8-10) were considered eligible for answering our question. Papers published in Chinese (11) and Polish (12,13) were excluded. Cross-reference checking revealed no additional articles. The three included cross-sectional diagnostic accuracy studies included in total 582 patients with 618 examined ears.

Assessment of their reported methods showed that only one study (10) provided direct evidence (see table 2). The other two studies included patients with a priori surgically confirmed congenital ossicular anomalies (8) or otosclerosis (8,9) only. Yasan et al. (10) excluded patients from their data analysis that were unsuccessfully operated, without reporting the number of patients and ears excluded for this reason. The risk of bias was moderate in one study (8) and high in the other two (9,10). Standardization of the index test was achieved in two studies (8,10). None of the included studies provided information about either blinding of the index test and the reference test or standardization of the reference test. For one study (9) a large amount of outcome data was missing. Its risk of bias was too high and directness of evidence was too low, and therefore this study (9) was excluded from further review.

The extracted data of the remaining two studies are described in table 3 and table 4. Both studies report on the Carhart notch if, in comparison to 1,000 and 4,000 Hz, a depression of bone-conduction threshold of at least 10 dB was observed at 2,000 Hz on pure-tone audiometry. Definite criteria for the depth of the bone-conduction threshold dip at 2,000 Hz have not yet been established. Reported means in depth have ranged from 2.4 to 12.5 dB (8, 14-16).

Table 3 | Study descriptives of studies on the diagnostic value of the Carhart notch in diagnosing otosclerosis in patients with conductive hearing loss.

Study	Sample size (n)	Patients	Reference test	Definition of Carhart notch	Timing of pure-tone audiometry
Yasan (2007)[10]	315	Patients with conductive hearing loss due to various types of middle-ear pathology	Stapes surgery not otherwise specified	Depression in bone-conduction threshold of at least 10 dB	Three days preoperatively
Kashio (2011)[8]	153	Patients with a surgically confirmed congenital ossicular anomaly or otosclerosis	Stapes surgery not otherwise specified	Depression of bone-conduction threshold of at least 10 dB	On various days preoperatively

n = number of procedures

Table 4 | Results of studies on the diagnostic value of the Carhart notch at 2,000 Hz in diagnosing otosclerosis in patients with conductive hearing loss.

Study	Sample size (n)	Prevalence*	PPV*	NPV*	Added diagnostic value	
					To rule in	To rule out
Yasan (2007)[10]	315	8 (6-12)	41 (26-57)	97 (94-98)	33%	5%
Kashio (2011)[8]	153	72 (64-79)	74 (59-86)	29 (20-39)	2%	1%

n = number of procedures, PPV = positive predictive value, NPV = negative predictive value.
* = % (95% confidence interval)

In the study by Yasan et al. (10), including patients with conductive hearing loss, the prior probability (prevalence) of otosclerosis was low (8%). This leaves sufficient room for a Carhart notch to add for ruling in otosclerosis. Its presence at 2,000 Hz increased the risk of otosclerosis with 33% (risk difference for ruling in otosclerosis: PPV minus prevalence). In its absence the risk of otosclerosis decreases with 5% (risk difference for ruling out otosclerosis: NPV minus 1-prevalence). The prevalence of otosclerosis in patients with a surgically confirmed congenital ossicular anomaly in the study by Kashio et al. (8) is, as to be expected, rather high (72%). This leaves little to add for a Carhart notch in diagnosing otosclerosis, and so the added value of its presence or absence is very small, respectively 2% and 1%. Major differences in type of patients between the two studies precluded pooling of data.

DISCUSSION

Although the presence of a Carhart notch in patients with conductive hearing loss is generally considered a useful finding in diagnosing otosclerosis, this systematic review shows that to date evidence supporting such belief is lacking. Although a 33% increase to 41% in the presence of a Carhart notch on pure-tone audiometry increases diagnostic certainty for ruling in otosclerosis may appear as a considerable additional value, it should be noted that these data come from a population with a low prevalence in a study that carries a high risk of bias. Given this weak evidence the ENT surgeon may to date explain to the patient that the presence of the Carhart notch may be one of the signs hinting to a diagnosis otosclerosis, especially in combination with the presence of low-frequency conductive hearing loss.
In interpreting the findings the following considerations need to be taken into account. First, in real life, diagnostic decisions are by definition of multivariate nature. However, to date the diagnostic value of a Carhart notch has been evaluated only as a stand-alone diagnostic tool, and studies have thus far failed to evaluate the diagnostic value of a Carhart notch by a multivariate design of study. Second, although both studies included a series of consecutive patients, the sample sizes varying from 153 to 315 ears, are rather small. Third, both studies carry a moderate to high risk of bias due to lack of blinding of observations, large amount of missing data and poorly standardized test procedures. Fourth, pure-tone audiometry is not solely used as a diagnostic tool for otosclerosis, but also for monitoring severity and progression of disease. Audiologic parameters are taken into consideration when deciding whether to perform stapes surgery and are used in establishing success rates of stapes surgery. Moreover, for medico-legal reasons pre- and postoperative audiograms are obtained from every patient undergoing middle ear surgery.

CONCLUSION AND RECOMMENDATION

Although the Carhart notch is in general believed to be an indicator for otosclerosis, as yet sufficient evidence to support such belief is lacking. Moreover, the diagnostic value of the presence of the Carhart notch to rule in or in its absence to rule out otosclerosis in patients with conductive hearing loss is not supported by low risk of bias studies. The highest diagnostic value was witnessed in a study with a low prevalence of otosclerosis (8%) and a high risk of bias, where the presence of a Carhart notch at 2,000 Hz increased the risk of otosclerosis with 33%.

TRANSLATING EVIDENCE INTO PRACTICE

For arriving at a diagnosis for the 50-year-old female with progressive hearing loss and left-sided conductive hearing loss, the ENT surgeon decided not to rely solely on the findings of the Carhart notch during pure-tone audiometry. During the staff meeting prior to informing her, he explained that until results of sufficiently large low risk of bias diagnostic accuracy study providing high directness of evidence become available, the presence of a Carhart notch cannot be used to confirm a diagnosis of otosclerosis in patients with conductive hearing loss.

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Chapter 5

An introduction of genetics in otosclerosis: a systematic review

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ABSTRACT

Objective: To present an easy to read systematic review concerning the genetic etiology of otosclerosis to help health care providers in counseling otosclerosis patients more accurately.

Data sources: PubMed, Embase, CINAHL and the Cochrane Library.

Review methods: Studies on the genetic etiology of otosclerosis were selected. Association studies and family-based studies were included for further review. After quality assessment (risk of bias), data were extracted from the included studies. When available, odds ratios were presented. In case of corresponding genetic anomalies between the studies, it was the aim to combine results.

Results: The number of available studies with low risk of bias is limited to two association studies and one family-based study. These high-quality studies show that otosclerosis in Japanese patients is not linked to the NOG gene and that a polymorphism in the Sp1 binding site located on the COL1A1 gene is associated with otosclerosis as well as OTSC1. Association and family-based studies with moderate risk of bias show a statistically significant association with the ACE gene, AGT gene, OTSC2, RELN gene, TGFB1 gene, 11q13.1, OTSC2, OTSC5, OTSC8 and OTSC10. These results may be spurious associations due to their bias and low statistical power.

Conclusion: The present systematic review shows that there is scattered evidence of limited quality and a lack of replication studies. It is not possible to point out one or more responsible genes, which play a key role within the genetic pathophysiologic mechanism of otosclerosis.

INTRODUCTION

Hearing loss due to otosclerosis is caused by disordered bone remodeling in the region of the otic capsule (1). Although its exact etiology remains unknown, over the years quite a few theories have been suggested. Endocrine factors, immune disorders, viral involvement, connective tissue disorders and genetic factors have been proposed as potential causes of otosclerosis (1).

At the moment, treatment usually comprises the use of a hearing aid or replacement of the affected stapes with a prosthesis: stapedotomy. Stapedotomy has proven to be a safe and effective treatment option for hearing loss caused by otosclerosis (2,3). However, it would be advantageous to know more about the disease mechanism in order to develop treatment options that tackle the origin of the disease thereby preventing the disease from progressing or even developing at all.

Otosclerosis often occurs within large families and therefore a genetic cause seems obvious (1). During the past decades multiple loci have been identified that are associated with otosclerosis. These so-called monogenic otosclerosis loci are, among others, OTSC1 (chromosome 15q25-26), OTSC2 (chromosome 7q34-36), OTSC3 (chromosome 6p21.3-22.3), OTSC4 (chromosome 16q21-23.2), OTSC5 (chromosome 3q22-24) and OTSC7 (chromosome 6q13-16.1) (4). Monogenic otosclerosis is relatively rare and in most patients, otosclerosis occurs without a clear familial background or with only a few affected family members, suggesting the involvement of both genetic and environmental factors (5). Genes associated with this complex form of otosclerosis include COL1A1, TGFB1 and RELN.

Even though there is an extensive amount of articles available on the genetic etiology of otosclerosis, an easy to read overview is lacking. The aim of this article is to provide a systematic review concerning the genetic etiology of otosclerosis.

METHODS

Search Strategy and Study Selection

A systematic search was conducted on May 1st 2013 in PubMed, Embase, CINAHL and the Cochrane Library, using synonyms for otosclerosis, etiology and genetic in the title and abstract fields. A complete overview of all search terms used, is presented in table 1. Three independent authors (AB, IW and BN) screened the titles and abstracts of the retrieved records for inclusion and duplicates were removed. Articles reporting original study data on the genetic etiology of otosclerosis were selected. Association studies with a case-control, cohort or cross-sectional design and family-based studies were included for further review. An association study typically examines associations between single-nucleotide polymorphisms (SNPs) and traits such as otosclerosis. Usually their design is case-control: DNA of patients with the disease is compared to DNA of similar participants without the disease. In family-based studies, unaffected family members are usually used as controls and therefore their design can be considered case-control as well. Articles written in languages other than English, German, French or Dutch, non-human studies and papers discussing the genetics of otosclerosis in children were excluded (see figure 1 for selection criteria). Disagreement was resolved by discussion. Related publications were searched in PubMed, while Scopus and Web of Science were used for cross-reference checking for studies not identified in the initial search strategy. Selected articles, related reviews, meta-analyses and guidelines were hand searched for relevant cross-references.

Table 1 | Systematic search for studies on the genetic role in the etiology of otosclerosis (date of search: May 1st 2013).

Database	Search	Field	Hits
PubMed	(otoscler* OR otospongio* OR stapedot* OR stapedect* OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements))) AND (caus* OR ((risk OR epidemiologic OR epidemiological) AND (factor OR factors)) OR enabl* OR reinforc* OR environment OR environmental OR precipitat* OR pathogenesis OR pathologic OR pathological OR pathomechanical OR etiopatho* OR etiolog* OR aetiolog* OR genetic* OR gene OR heredit* OR chromosom* OR locus)	Title/ abstract	**1075**
Embase	(otoscler*:ti,ab OR otospongio*:ti,ab OR stapedot*:ti,ab OR stapedect*:ti,ab OR (stapes:ti,ab AND (surgery:ti,ab OR surgeries:ti,ab OR mobilization:ti,ab OR mobilisation:ti,ab)) OR (ossicular:ti,ab AND (replacement:ti,ab OR replacements:ti,ab))) AND (caus*:ti,ab OR ((risk:ti,ab OR epidemiologic:ti,ab OR epidemiological:ti,ab) AND (factor:ti,ab OR factors:ti,ab)) OR enabl*:ti,ab OR reinforc*:ti,ab OR environment:ti,ab OR environmental:ti,ab OR precipitat*:ti,ab OR pathogenesis:ti,ab OR pathologic:ti,ab OR pathological:ti,ab OR pathomechanical:ti,ab OR etiopatho*:ti,ab OR etiolog*:ti,ab OR aetiolog*:ti,ab OR genetic*:ti,ab OR gene:ti,ab OR heredit*:ti,ab OR chromosom*:ti,ab OR locus:ti,ab) AND [embase]/lim	Title/ abstract	**946**
CINAHL	TI ((otoscler* OR otospongio* OR stapedot* OR stapedect* OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements))) AND (caus* OR ((risk OR epidemiologic OR epidemiological) AND (factor OR factors)) OR enabl* OR reinforc* OR environment OR environmental OR precipitat* OR pathogenesis OR pathologic OR pathological OR pathomechanical OR etiopatho* OR etiolog* OR aetiolog* OR genetic* OR gene OR heredit* OR chromosom* OR locus)) OR AB ((otoscler* OR otospongio* OR stapedot* OR stapedect* OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements))) AND (caus* OR ((risk OR epidemiologic OR epidemiological) AND (factor OR factors)) OR enabl* OR reinforc* OR environment OR environmental OR precipitat* OR pathogenesis OR pathologic OR pathological OR pathomechanical OR etiopatho* OR etiolog* OR aetiolog* OR genetic* OR gene OR heredit* OR chromosom* OR locus))	Title/ abstract	**64**
The Cochrane Library	(otoscler* OR otospongio* OR stapedot* OR stapedect* OR (stapes AND (surgery OR surgeries OR mobilization OR mobilisation)) OR (ossicular AND (replacement OR replacements))) AND (caus* OR ((risk OR epidemiologic OR epidemiological) AND (factor OR factors)) OR enabl* OR reinforc* OR environment OR environmental OR precipitat* OR pathogenesis OR pathologic OR pathological OR pathomechanical OR etiopatho* OR etiolog* OR aetiolog* OR genetic* OR gene OR heredit* OR chromosom* OR locus)	Title/ abstract	**9**

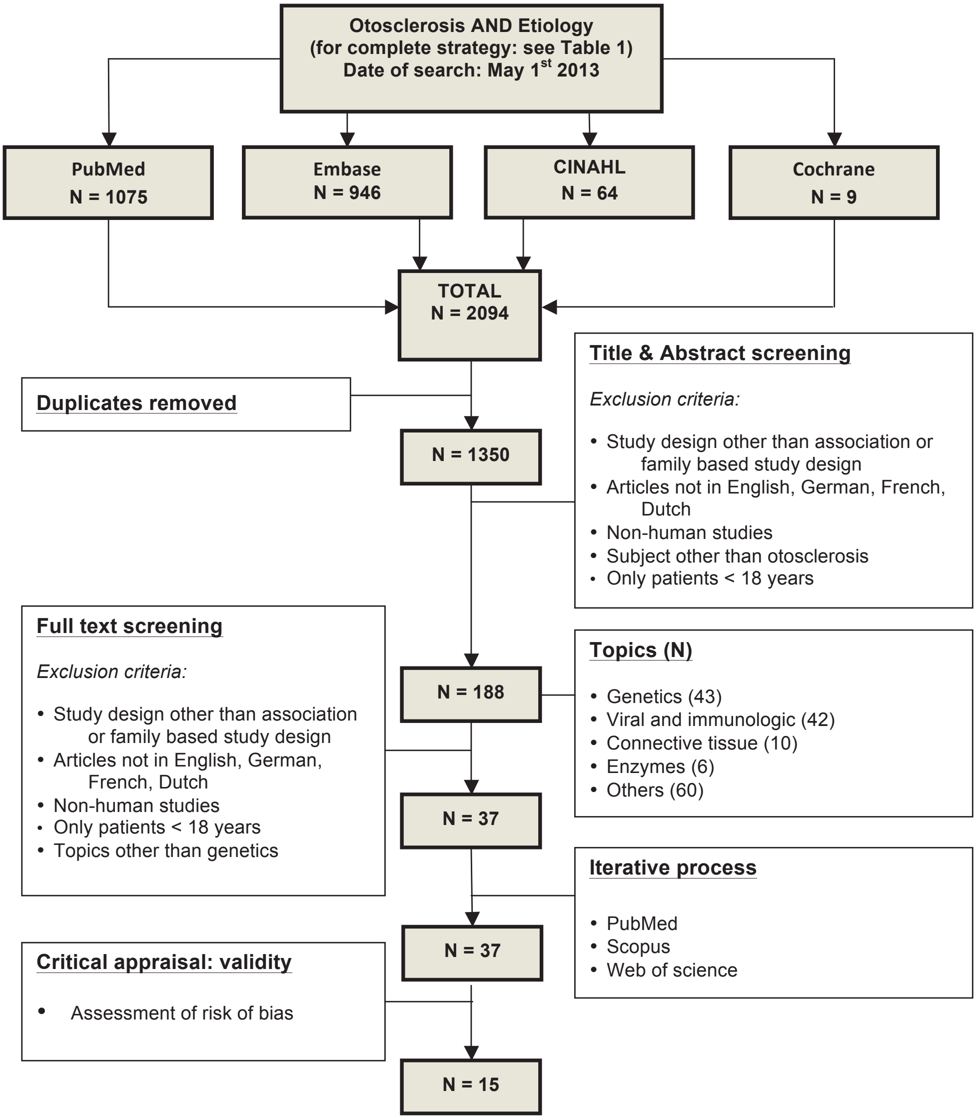

Figure 1 | Flowchart for selection of studies on the genetic role in the etiology of otosclerosis.

Quality assessment

Predefined criteria were used for the assessment of the risk of bias of the selected articles (see table 2). Three authors (AB, IW and BN) independently assessed the quality of included studies using these predefined criteria. Initial discrepancies were discussed until consensus was reached. In case of unresolved issues, a fourth author (GH) decided. Risk of selection bias was assessed using the following four criteria: "similarity in study-participant selection" (case and control patients were selected in the same standardized method), "similarity in participant outcome risk" (case and control participants were drawn from the same source population), "completeness of analysed data" (missing data not exceeding 15%) and "missing data pattern" (difference in proportion of missing data between cases and controls below 5%). Risk of information bias was assessed using the following three criteria: "similarity of data collection" (outcome data for cases and controls were collected in the same standardized manner), "observer blinding for exposure" and "observer blinding for outcome" (considered blinded when exposure/outcome status was masked for the outcome assessor). Similarity in outcome risk avoids potential confounding effects of population stratification. Since this criterion covers the issue of population stratification, there is no need to further score impact of confounding. Each item was classified as either adequate or inadequate. If an item was not reported in the article, it was classified as uncertain.

Studies that did not meet the similarity in study-participant criterion or the similarity in participant outcome risk criterion were excluded from further review. Remaining studies were classified as having low, moderate or high risk of bias if they complied with six or seven, three to five, or none to two criteria respectively. Studies with high risk of bias were also excluded from further review.

Table 2 | Risk of bias assessment of included case-control and family-based studies.

Study	Design	No. of patients	No. of controls	Participant selection	Participant outcome risk	Completeness of data	Missing data pattern	Data collection	Observer blinding	Impact of missing data
Usami (2012)[9]	Case-control	33	192	+	+	+	+	+	?	+
El Gezeery (2012)[8]	Case-control	160	100	+	+	+	+	+	?	+
Tomek (1998)[19]	Family-based	14	10	+	+	+ (3% missing)	+	+	?	+
Van den Bogaert (2004)[15]	Family-based	10	8	+	+	+ (10% missing)	-	+	?	?
Khalfallah (2011)[11]	Case-control	159	155	+	+	?	?	+	?	?
Khalfallah (2010)[14]	Case-control	149	152	+	+	?	?	+	?	?
Schrauwen (2011)[10]	Family-based	7	14	+	+	?	?	+	?	?
Schrauwen (2010)[13]	Case-control	24	26	+	+	?	?	+	?	?
Schrauwen (2009b)[12]	Case-control	591	550	+	+	?	?	+	?	?
Bel Hadj Ali (2008)[4]	Family-based	7	12	+	+	- (33%)	?	+	?	?
Bel Hadj Ali (2007)[7]	Family-based	16	21	+	+	- (34%)	?	+	?	?
Rodriguez (2004)[16]	Case-control	100	100	+	+	?	?	+	?	?
Van den Bogaert (2002)[17]	Family-based	53	25	+	+	-(34%)	?	+	?	?
Van den Bogaert (2001)[18]	Family-based	17	8	+	+	-(19%)	?	+	?	?
Imauchi (2008)[20]	Case-control	186	526	+	+	-(28%)	-	+	?	?

+ adequate, - inadequate, ? uncertain
-*Participant selection* : Considered adequate when case and control participants are selected in the same standardized, predetermined method.
-*Participant outcome risk*: Considered adequate when case and control participants are drawn from the same source population (inception cohort).
-*Completeness of analyzed data* : If analysis is on incomplete data: provide total proportion of missing data. Assess missing data pattern when total proportion of missing data exceeds 15%.
-*Missing data pattern*: Considered adequate when difference in proportion of missing data between case and control participants remained below 5%.
-*Data collection*: Considered adequate when outcome data for case and control participants are obtained in the same, standardized manner.
-*Observer blinding*: Considered blinded (adequate) when outcome status of participants is masked during accrual of exposure data.
-*Impact of missing data* : Considered appropriate (adequate) when findings of sensitivity analysis for missing data are reported using appropriate (best and worst case) assumptions.

Data extraction and analysis

Outcome data of the included studies were extracted and calculated by three independent authors (AB, IW and BN). Preferably, odds ratios or natural logarithm of odds scores (LOD scores) were extracted or calculated. The LOD score is a statistical test often used for linkage analysis in human and animal populations (6). The LOD score compares the likelihood of obtaining the test data if two loci are indeed linked to the likelihood of observing the same data purely by chance. A positive score favors linkage, whereas a negative score indicates linkage is less likely. A LOD score greater than 3.0 is considered evidence for linkage (7). It indicates that the likelihood of actual linkage is 1000 (10^3) greater than the likelihood of the linkage occurring by chance (6). If odds ratios, LOD scores or both were not given or could not be (re)calculated, the results as reported in the article were reported.

Outcome data were extracted for all single nucleotide polymorphisms (SNPs) or short tandem repeat polymorphism (STRPs) examined. A single nucleotide polymorphism is a difference in a single nucleotide in a DNA sequence between two persons or paired chromosomes in a human. SNPs are coded and usually start with 'rs'. Short tandem repeat polymorphisms are polymorphisms in a repeated sequence of two to six base pairs of DNA.

Although a quantitative analysis had been planned, the genes that were reported in the included studies hardly corresponded and pooling was not possible. Therefore, a descriptive analysis was used: the data of each individual study were summarized

RESULTS

Search results

A total of 2094 records were retrieved following the database search (see figure 1, date of last search was May 1st 2013). After removing duplicates, 1350 unique articles remained. After selection, based on title and abstract, a total of 188 articles concerning the etiology of otosclerosis were identified. Full-text screening resulted in the identification of 37 articles that were considered eligible for answering the research question. Cross-reference checking revealed no additional articles.

Risk of bias assessment

A total of 37 articles were selected for risk of bias assessment. Fifteen of these selected case and control participants in the same standardized method, drew their case and control participants from the same source populations and carried either moderate or low risk of bias (see table 2) (4,7-20). Eight of these were association studies, which all had a case-control design (8,9,11-14,16,20) and seven of these were family-based studies (4,7,10,15,17-19). The selected studies included in total 1526 otosclerosis patients and 1899 controls.

Important limitations in risk of bias were found in twelve of the fifteen included studies. Completeness of data was not achieved in four family-based studies (4,7,17,18) and one association study (20). Completeness of data was unclear in one family-based study (10) and five association studies (11-14,16). When data on disease status is missing in family-based studies, while otherwise completeness of data has been achieved, participants for whom information on disease status is missing cannot be categorized into case or control. Therefore the pattern of missing data in these studies is unknown. The pattern of missing data was dissimilar in one family-based study (15) and one association study (20), with a difference in proportion of missing data between case and control participants greater than 5 percent in both studies. Observer blinding was not reported in any of the studies.
Three studies carried low risk of bias. Two of them were case-control studies (8,9) and one publication was a family-based study (19). We put most trust in their results.

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Association studies
A total of eight association studies were identified (8,9,11-14,16,20). All had a case-control design. The results of these studies are summarized in table 3.
We put most trust in the data of the two association studies that provided direct evidence and carried low risk of bias (8,9). Usami et al. showed that otosclerosis in Japanese patients is not associated with the NOG gene (9). El Gezeery et al. showed a statistically significant association between G to T nucleotide polymorphism in the Sp1 binding site and otosclerosis (8). The polymorphisms discussed in these two studies were not examined in any of the other included studies.
Statistical significance was reached in moderate-quality studies examining the association between otosclerosis and the ACE gene (20), the AGT gene (20), OTSC2 (13), the RELN gene (12,14), the TGFB1 gene (11) and 11q13.1 (14). All of the reported significant results are very likely to be spurious findings due to the risk of bias and low statistical power of these studies.
The RELN gene was examined in two studies (12,14). Three of the six SNPs that were associated with otosclerosis in the study performed by Schrauwen et al. (2009b) (12) were found to be significantly associated with otosclerosis by Khalfallah et al. (2010) as well (14) (see table 3 and table 4).
Rodriguez et al. (16) reported no association of the COL1A1 and the COL1A2 gene with otosclerosis. However, it is not clear which SNPs were examined in their study. Furthermore, studies examining the association between otosclerosis and the AT1R gene (20) and the COL1A1 gene (11) did not reach statistical significance.

Table 3 | Results of included case-control and family-based studies.

Gene	SNP/STRP-interval	Studies	Design	No. of cases	No. of controls	Ethnicity	OR (95% CI)	P-value	Maximum multipoint LOD score
ACE	I/D polymorphism	Imauchi (2008)[20]	Case-control	101	526	French	**1.30 (1.04-1.63)**	**0.031**	-
AGT	M235T polymorphism	Imauchi (2008)[20]	Case-control	186	511	French	**1.87 (1.25-2.81)**	**0.002**	-
AT1R	A1166C polymorphism	Imauchi (2008)[20]	Case-control	87	425	French	1.12 (0.70-1.77)	> 0.05	-
COL1A1 (17.q21.33)	SP1 binding site	El Gezeery (2012)*[8]	Case-control	160	100	Egyptian	-	-	-
	rs1107946	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	0.958 (0.614-1.494	0.851	-
	rs11327935	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	1.395 (0.985-1.974)#	0.059	-
	rs2269336	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	0.865 (0.576-1.298)	0.482	-
	rs1800012	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	1.267 (0.922-1.741)	0.143	-
	?	Rodriguez (2004)[16]	Case-control	100	100	Spanish	Negative	> 0.05	
COL1A2 (7q22.1)	?	Rodriguez (2004)[16]	Case-control	100	100	Spanish	Negative	> 0.05	
NOG	?	Usami (2012)[9]	Case-control	33	192	Japanese	Negative	-	-
OTSC1 (15q25-26)	D15S652-D15S657	Tomek (1998)[19]	Family-based	14	10	Indian	-	-	**3.4**
	D15S652-D15S657	Van den Bogaert (2002)[17]	Family-based	53	25	Belgian and Dutch	-	-	Negative
OTSC2 (7q34-36)	?	Schrauwen (2010)$[13]	Case-control	24	26	Belgian	-	**0.004**	
	D7S2560-D7S2513	Van den Bogaert (2001)[18]	Family-based	17	8	Belgian	-	-	**3.54**
	D7S2560-D7S2513	Van den Bogaert (2002)[17]	Family-based	53	25	Belgian and Dutch	-	-	1.91

OTSC3 (6p21.3-22.3)	D6S1660-D6S1680	Ben Hadj Ali (2007)†[7]	Family-based	16	21	Tunisian	-	-	2.04
OTSC5 (3q22-24)	D3S1558-D3S1744	Van den Bogaert (2004)[15]	Family-based	10	8	Dutch	-	-	**3.46**
OTSC8 (9p13.1-9q21.11)	?	Bel Hadj Ali (2008)[4]	Family-based	7	12	Tunisian	-	-	**4.42**
OTSC10 (1q41-44)	D1S490-D1S404	Schrauwen (2011)[10]	Family-based	7	14	Dutch	-	-	**3.3**
RELN (7q22.1)	rs2299383	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	**0.798 (0.671-0.949)**	**0.010**	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	0.931 (0.670-1.293)	0.670	-
	rs39335	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	**0.571 (0.448-0.727)**	**< 0.001**	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	**0.575 (0.398-0.832)**	**0.003**	-
	rs39350	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	**1.263 (1.060-1.505)**	**0.009**	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	**1.513 (1.060-2.161)**	**0.021**	-
	rs39374	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	**1.200 (1.007-1.430)**	**0.041**	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	**1.529 (1.085-2.155)**	**0.014**	-
	rs39395	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	**0.797 (0.671-0.947)**	**0.010**	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	0.732 (0.532-1.018)	0.062	-
	rs7791481	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	0.952 (0.738-1.229)	0.707	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	0.692 (0.414-1.157)	0.156	-
	rs3914132	Schrauwen (2009b)[12]	Case-control	591	550	DE, I, CH, RO	**1.295 (1.034-1.1621)**	**0.024**	-
		Khalfallah (2010)[14]	Case-control	149	152	Tunisian	1.392 (0.984-1.967)	0.060	-

TGFB1 (19q13.2)	rs1982073	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	0.957 (0.670-1.365)	0.807	-
	rs1800472	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	**0.274 (0.098-0.762)**	**0.007**	-
	rs8179181	Khalfallah (2011)[11]	Case-control	159	155	Tunisian	1.077 (0.691-1.677)	0.743	-
Unknown (11q13.1)	rs670358	Khalfallah (2010)[14]	Case-control	149	152	Tunisian	0.586 (0.292-1.173)	0.127	-
	rs494252	Khalfallah (2010)[14]	Case-control	149	152	Tunisian	**3.015 (0.938-9.963)**	**0.049**	-
	rs627497	Khalfallah (2010)[14]	Case-control	149	152	Tunisian	1.330 (0.884-2.001)	0.169	-
	rs616322	Khalfallah (2010)[14]	Case-control	149	152	Tunisian	1.188 (0.782-1.803)	0.418	-

Legend:
-Results with P-values < 0.05 and LOD scores > 3.0 are in bold.
-SNP = single nucleotide polymorphism; STRP = short tandem repeat polymorphism; OR (95% CI) = odds ratio with 95% confidence interval; DE = German; I = Italian; CH = Swiss; RO = Romanian.
-* Significant association between G to T nucleotide polymorphism in the Sp1 binding site of the COL1A1 gene and otosclerosis (X^2 = 20.3, p-value < 0.0001)
-# Assuming a dominant-recessive model: OR (95% CI) = 3.988 (1.570-10.128) with a P-value of 0.001.
-$ Significantly lower expression of T-cell receptor beta locus messenger RNA in OTSC2-patients, compared to controls (exact difference in expression is unknown, p-value = 0.004).
-† Negative linkage in this family to OTSC1, OTSC2, OTSC4, OTSC5, COL1A1, COL1A2 and NOG.

Interestingly, two association studies confirmed sex-related associations with otosclerosis. One SNP of the COL1A1 gene was significant in female otosclerosis patients only (rs11327935), whereas another SNP was significant in male otosclerosis patients only (rs2269336) (11). A significant sex effect was found for the RELN gene (rs3914132), where the association was only significant in males (14).

Table 4 | Results of studies on the association of the RELN gene and otosclerosis.

Chromosome	Schrauwen et al. (2009b)[12] OR (95% CI)	Khalfalla et al. (2010)[14] OR (95% CI)
Chr7q22.1 (RELN) rs39335	0.571 (0.448-0.727) *	0.575 (0.398-0.832) *
Chr7q22.1 (RELN) rs39350	1.263 (1.060-1.505) *	1.513 (1.060-2.161) *
Chr7q22.1 (RELN) rs39374	1.200 (1.007-1.430) *	1.529 (1.085-2.155) *
Chr7q22.1 (RELN) rs3914132	1.295 (1.034-1.1621) *	1.392 (0.984-1.967)
Chr7q22.1 (RELN) rs39395	0.797 (0.671-0.947) *	0.732 (0.532-1.018)
Chr7q22.1 (RELN) rs2299383	0.798 (0.671-0.949) *	0.931 (0.670-1.293)
Chr7q22.1 (RELN) rs7791481	0.952 (0.738-1.229)	0.692 (0.414-1.157)

OR = Odds ratio, CI = confidence interval
* = statistically significant (p-value < 0.05)

Family-based studies
A total of seven family-based studies were included (4,7,10,15,17-19).
Only one family-based study provided direct evidence and carried low risk of bias (19). Tomek et al. (19) demonstrated linkage of OTSC1 and otosclerosis with a maximum multipoint LOD score of 3.4. One family-based study with moderate risk of bias could not replicate these results (17).
Maximum multipoint LOD scores of more than 3.0 were reached in five studies examining the association of otosclerosis with OTSC1 (19), OTSC2 (18), OTSC5 (15), OTSC8 (4) and OTSC10 (10). All of these studies carried moderate risk of bias. In one study examining OTSC2 (17) and one study examining OTSC3 (7), maximum multipoint LOD scores were lower than 3.0.

DISCUSSION

The number of available studies on the genetic etiology of otosclerosis with low risk of bias is limited to two association studies (8,9) and one family-based study (19). These high-quality studies show that otosclerosis in Japanese patients is not linked to the NOG gene (9) and that a polymorphism in the Sp1 binding site located on the COL1A1 gene is associated with otosclerosis (8) as well as OTSC1 (19).

Association studies with moderate risk of bias show a statistically significant association of otosclerosis with the ACE gene (20), the AGT gene (20), OTSC2 (13), the RELN gene (12,14), the TGFB1 gene (11) and 11q13.1 (14). Family-based studies of moderate quality show a statistically significant association of otosclerosis with OTSC2 (18), OTSC5 (15), OTSC8 (4) and OTSC10 (10). It is important to note that results from studies with moderate to high risk of bias may report spurious associations due to their bias and low statistical power.

To our knowledge, this is the first publication reviewing the genetic origin of otosclerosis in a systematic way. Strengths of this systematic review include the comprehensive and extensive search for evidence, inclusion of all known genetic variants related to otosclerosis, the independent quality assessment and a clear summary of associations between genetic variants and otosclerosis. Unfortunately the choice of investigated genetic variants seems rather arbitrary. As a result a wide range of genetic variations is investigated and most results are not reproduced in high-quality replication studies. Conclusions on the association of individual genes or loci with otosclerosis are therefore based on only one or two studies that met the assessment criteria.

In 2009, Little et al. presented the STrengthening the REporting of Genetic Association studies (STREGA) method (21). The STREGA method serves as a handle to improve transparency among genetic publications. STREGA recommendations comprise guidelines and suggestions about how to present a genetic association study. Although the STREGA method could result in standardized genetic publications, we were not able to detect STREGA-based coherence between the included articles. Naturally, articles published before 2009 do not adhere to the STREGA principle, but more recent articles did not use the STREGA guidelines either. Through this, it is difficult to pool the data between the articles and to perform a quantitative analysis. In the second place, replication of the presented data will be difficult.

Replication of initial findings is essential for establishing credibility of a genotype-phenotype association (22) and ruling out false-positive results. Initial findings often cannot be replicated. Population stratification, genetic heterogeneity, differences in patterns of interacting environmental exposures and clinical features between study populations, admixture of ethnicity and lack of power of replications studies can all contribute to the lack of reproducibility. There is a lack of replication of moderate- to high-quality association studies discussing the genetic etiology of otosclerosis. It seems as though the association of COL1A1 with otosclerosis is reported in an opposite direction by Rodriguez et al. (16) when compared with the positive association reported by Khalfallah et al. (2011) (11). However, it is not clear which polymorphisms were studied by Rodriguez et al. and therefore there is no way of knowing whether the study performed by Khalfallah et al. (2011) is in fact a replication study. The SNPs located on the RELN gene that were investigated by Schrauwen et al. (2009b) (12), on the other hand, were replicated by Khalfallah et al. (2010) and showed a similar effect (see table 4). Some of the SNPs investigated in these studies are associated with an increased risk of otosclerosis with odds ratios above 1, while others are associated with a reduced risk with odds ratios between 0 and 1 (see table 4). Replication lacks for all other loci and genes discussed in this review.

Interestingly, sex-specific association of COL1A1 to otosclerosis was found in one study (11). The same goes for the RELN gene (14). One SNP in the COL1A1 region was associated with female sex (odds ratio 1.395) and one SNP in the same region with male sex (odds ratio 0.865) (11). One SNP in the RELN gene was identified that was associated with male sex (odds ratio 1.392) (14). These findings suggest that both the COL1A1 and RELN gene association with otosclerosis might be influenced by sex.

CONCLUSION

The present systematic review shows that there is scattered evidence of limited quality and a lack of replication studies. Therefore it is not possible to assign one or more responsible genes that play a key role in the pathophysiological pathway that leads to otosclerosis. Even though the included studies imply a genetic influence, since there is no reliable and consistent evidence for genetic causation of otosclerosis, it is not possible to form evidence-based statements on this matter. In addition, it is difficult to clarify to what extent a potential otosclerosis gene influences the development and progress of the disease. Clinicians could inform their patients about the idea of a potential genetic cause, but they should be reserved in giving a value judgment about the genetic etiology.

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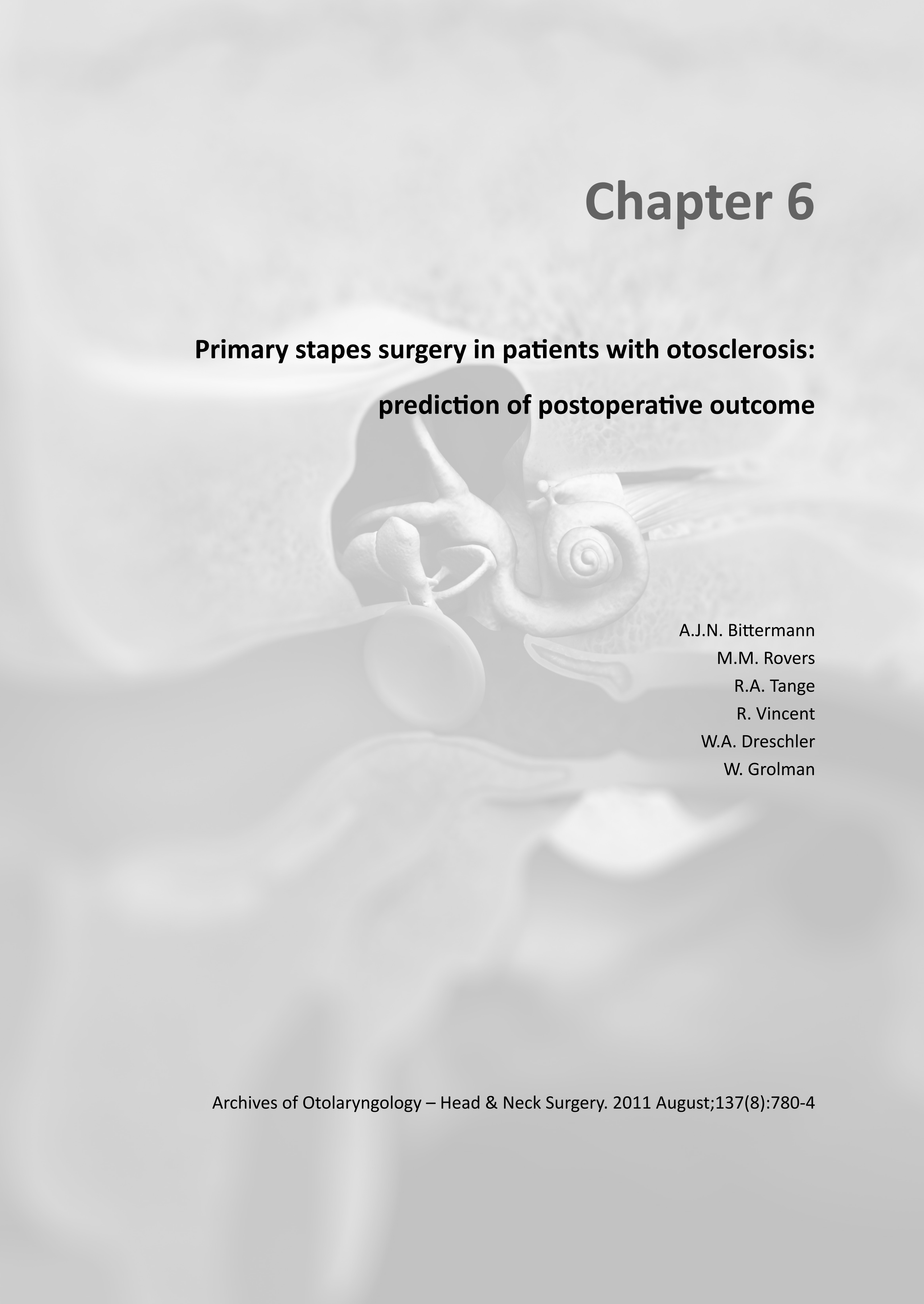

Chapter 6

Primary stapes surgery in patients with otosclerosis: prediction of postoperative outcome

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ABSTRACT

Objective: To evaluate the hearing results of primary stapes surgery in patients with otosclerosis and to determine predictors for both a postoperative air-bone gap (ABG) of 10 dB or less and a postoperative gain in air-conduction (AC) exceeding 20 dB.

Design: A retrospective cohort study.

Setting: Tertiary referral center in Utrecht (the Netherlands).

Patients: Nine hundred thirty-nine otosclerosis patients who underwent primary stapes surgery between January 1982 and February 2009.

Intervention: Primary stapes surgery.

Main outcome measures: Pre- and postoperative audiometric results were compared. Logistic regression analyses were performed to evaluate which factors (i.e. 'preoperative bone-conduction (BC), AC, ABG', 'sex', 'age at moment of surgery' and 'bilateral otosclerosis') independently contributed to the prediction of a postoperative ABG of 10 dB or less and a postoperative gain in AC exceeding 20 dB.

Results: The results show that 72% of the patients had a postoperative four-frequency (0.5, 1, 2, 4 kHz) ABG of 10 dB or less and 94% had a postoperative ABG of 20 dB or less. 'Age at surgery', 'preoperative four-frequency AC' and 'preoperative four-frequency ABG' were independent prognostic determinants. A patient older than 40 years with a preoperative four-frequency ABG of 30 dB or less has a chance of 78% to achieve a postoperative four-frequency ABG of 10 dB or less. A patient, with a preoperative four-frequency AC exceeding 50 dB and a preoperative four-frequency ABG exceeding 30 dB has a chance of 86% to achieve a postoperative gain in AC exceeding 20 dB.

Conclusion: It appears possible to predict both the postoperative ABG of 10 dB or less and the postoperative gain in AC exceeding 20 dB with accuracies of 62% and 80%, respectively. Clinicians can use this information to inform patients more explicitly about the expected postoperative hearing results.

INTRODUCTION

Otosclerosis is characterized by a disordered bone remodeling in the region of the otic capsule, mostly located between the cochlea and the vestibule, and just anterior to the footplate of the stapes (1,2). In 2001, Declau et al. studied an unselected series of temporal bones and calculated that clinical otosclerosis has a prevalence of 0.3% to 0.4% in the Caucasian population (3). The absolute numbers in the US, and the Netherlands can subsequently be extrapolated at 860.000 and 50.000 in 2009, respectively. It is important to distinguish histological otosclerosis (no symptoms) from clinical otosclerosis (symptoms such as hearing loss and vertigo). Histological otosclerosis is about 10 times more common compared to clinical otosclerosis (1). Stapes surgery is a treatment option for hearing loss resulting from otosclerosis and has proven to be an effective and safe intervention (4-8). However, postoperative results show large variability. Reported air-bone gap (ABG) closure, closed to 10 dB or less, varied from 94% (n = 2368) to 75% (n = 861) (6,7). Patient characteristics, surgical experience and intraoperative findings may be considered potential prognostic factors influencing postoperative hearing results. So far, many studies reported on the effectiveness of stapes surgery (4-7, 9-11); only two studies reported ten potential prognostic factors. However, both studies only investigated one factor at a time. Ueda et al. (10) reported that a small preoperative ABG resulted in a better postoperative ABG closure at frequencies less than 1 kHz. Gerard et al. (11) found no prognostic factors.

Given the variability among patients and in the etiology, presentation, and treatment of diseases and other health states, a single predictor or variable rarely gives an adequate estimate of prognosis. Physicians, implicitly or explicitly, use multiple predictors to estimate a patient's prognosis. Therefore, prognostic studies need to use a multivariate approach in design and analysis to determine the important predictors of the studied outcomes and to provide outcome probabilities for different combinations of predictors, or to provide tools to estimate such probabilities. These studies enable care providers to use combinations of predictor values to estimate an absolute risk or probability that an outcome will occur in an individual (12).

A postoperative ABG of 10 dB or less is considered the primary outcome measurement in stapes surgery literature (6,7,9) and should be included in a prognostic model evaluating stapes surgery. However, it is also important to include the postoperative gain in air-conduction (AC), because it reflects the degree of success with regard to restoration of middle ear hearing transmission function (5). A reduction of the ABG could reflect an improved AC, a deteriorated bone-conduction (BC), or a combination of the change in AC and BC. The preoperative factors 'preoperative BC', 'preoperative AC', 'preoperative ABG', 'sex', 'age at moment of surgery' and 'bilateral otosclerosis' were selected as potential predictors influencing the postoperative ABG and gain in AC. The selection of these factors was based on the knowledge from literature (10,13), clinical expertise, and available information from routine clinical practice.

Therefore, we performed a multivariate prognostic study among patients with otosclerosis who all underwent primary stapes surgery and determined predictors of two different postoperative outcome measurements: a postoperative ABG of 10 dB or less and a postoperative gain in AC exceeding 20 dB.

MATERIALS AND METHODS

Patients

We performed a retrospective cohort study in all patients (n = 939) that underwent primary stapedotomy surgery in a specialized tertiary referral center between January 1982 and February 2009.

Surgery

An endaural procedure was performed in all cases. A stapedectomy was performed in a minority of the cases (3%) compared to a small fenestra stapedotomy in the other cases. The fenestration was performed with the micro-pick technique described by Marquet (14) in most cases. The potassium titanyl phosphate (KTP) laser was introduced in our center in 2007. The surgeries were performed by two different surgeons (RT and WG). Various prostheses were used (table 1).

Audiometric assessment

Audiometric evaluation included preoperative and postoperative ABG thresholds, AC thresholds, and BC thresholds. Postoperative follow-up data were collected, three months after the surgery, which is the first regular follow-up moment at our institution. We used a four-frequency pure-tone average (PTA) for AC, BC and ABG thresholds. Four-frequency means 0.5, 1, 2, and 4 kHz. Audiometry was reported according to the American Academy of Otolaryngology—Head and Neck Surgery guidelines (15), except for thresholds at 3 kHz, which were substituted in all cases with those at 4 kHz. In our series, we focused on 0.5, 1, 2, and 4 kHz because of the availability of these data. It has been shown that the percentage of patients with a postoperative ABG of 10 dB or less will increase using the mean thresholds at frequencies 0.5, 1, 2 and 3 kHz, instead of 0.5, 1, 2, and 4 kHz (6).

Table 1 | Baseline characteristics.

	All primary stapes surgeries (n = 939)	Primary stapes surgeries with pre- and postoperative audio-metric data available (n = 666)
Mean age at surgery (Years (SD))	41.4 (11.5) (ranged from 9-74)	41.3 (11.2) (ranged from 10-72)
Sex (%)		
Female	63	62
Male	37	38
Left/Right ear surgery (%)		
Left ears	49	51
Right ears	51	49
Laser (KTP) surgery (%)	1.5	0.9
Surgeon (%)		
RT	85	83
WG	15	17
Bilateral cases (%)	31	31
Piston types (%)		
Titanium (4.5mm)	32.4	30.4
Titanium (4.75mm)	2.2	2.6
Titanium (5.0mm)	0.1	0.2
a Wengen (4.5mm)	8.6	10.8
a Wengen (4.75mm)	1.8	2.2
Causse 0.3 (Length manually fitted)	7.9	7.1
Causse 0.4 (Length manually fitted)	33.1	32.4
Shea Tefl cup/loop (Length manually fitted)	8.0	8.3
Gold piston (4.5mm)	3.8	4.5
Gold piston (4.75mm)	0.6	0.5
Other	1.5	1.2

-SD = standard deviation
-KTP = potassium titanyl phosphate
-Length manually fitted = surgeon adapted the length according to intraoperative findings

Outcome predictors

On the basis of knowledge from literature, clinical expertise, and the available information in routine clinical practice, the following baseline candidate predictors were selected: 'preoperative four-frequency BC', 'preoperative four-frequency AC', 'preoperative four-frequency ABG', 'sex', 'age at moment of surgery' and 'bilateral otosclerosis'. We aim to use the prognostic model during preclinical assessment; therefore, we only included predictors that were available at the time of diagnosis (12).

Statistical analyses

To evaluate the effect of primary stapes surgery in patients with otosclerosis, pre- and postoperative audiometric results were compared, using a paired samples *t*-test.

The association between each prognostic factor and the presence of a postoperative ABG of 10 dB or less or a postoperative gain in AC exceeding 20 dB was examined with univariate logistic regression analyses. Predictors that were associated with the outcome in univariate analyses (p <0.10) were included in multivariate logistic regression analyses. The model was reduced through exclusion of predictors with p values of >0.05. The predictive accuracy of the models was estimated on the basis of their reliability using the Hosmer-Lemeshow goodness-of-fit test (16). The model's ability to discriminate between patients was estimated as the area under the receiver operating characteristic curve of the model (17). The receiver operating characteristic curve area is a suitable parameter to summarize the discriminative or predictive value and can range from 0.5 (no discrimination, like a flip of a coin) to 1.0 (perfect discrimination). In addition, we calculated the absolute risks of a postoperative ABG of 10 dB less or a postoperative gain in AC exceeding 20 dB across combinations of independent predictors.

Missing values

Information was available for 82% of the predictor variables and for 71% of the outcome variables. Data are seldom missing at random; it has been shown that removal of subjects with a missing value for one of the predictors studied (complete case analysis) commonly leads to biased results and certainly to loss of power (18,19). To decrease bias and to increase statistical efficiency, it is better to impute missing data than to perform a complete case analysis (20,21). Accordingly, we imputed the missing data for each trial using multiple imputation in SPSS 17.0 for Windows (SPSS, Chicago, IL). Such imputation is based on the correlation between each variable with missing values and all other variables, as estimated for the set of complete subjects.

RESULTS

Between March 1982 and January 2009, 939 patients were operated. Pre- and postoperative audiometric data were available for 666 patients. The mean age was 41 years and ranged from 9 to 74 years (SD 11.5), with a sex ratio of 37% male and 63% female. The division between left ears and right ears was 49% and 51%, respectively. The introduction of the KTP laser, in 2007, resulted in 1.5% laser surgeries. Eighty-five percent of the patients were operated on by RT and 15% of the patients were operated on by WG. Otosclerosis was bilateral in 31% percent of patients. Table 1 shows the characteristics of all patients (n = 939) and those with pre- and postoperative audiometric data available (n = 666), i.e. those without missing values. No large differences between both groups were found.

Pre- and postoperative audiometric evaluation (n = 666)

Pre- and postoperative audiometric data are summarized in table 2. The mean BC, AC, and ABG improved by 0.6 dB (95% CI: -0.04 to 1.21), 21.0 dB (95% CI: 19.96 to 22.04), and 20.4 dB (95% CI: 19.60 to 21.23), respectively.

Table 2 | Pre- and postoperative audiometric evaluation.

Audiometry	Preoperative (PTA in dB (SD))	Three months postoperative (PTA in dB (SD))	Improvement/deterioration (PTA in dB (95% CI))		p-value
BC 0.5 kHz	15.9 (10.4)	16.9 (11.6)	-1.0	(-1.79 to -0.27)	0.008
BC 1 kHz	18.5 (10.5)	17.6 (12.6)	+0.9	(0.06 to 1.68)	0.035
BC 2 kHz	29.7 (12.2)	25.0 (14.2)	+4.7	(3.95 to 5.56)	< 0.001
BC 4 kHz	25.8 (16.1)	28.1 (18.3)	-2.3	(-3.14 to -1.39)	< 0.001
Mean four-frequency BC	*22.5 (9.8)*	*21.9 (11.9)*	+0.6	(-0.04 to 1.21)	0.068
AC 0.5 kHz	56.1 (13.2)	29.3 (14.9)	+26.8	(25.64 to 28.02)	< 0.001
AC 1 kHz	52.9 (14.0)	27.0 (14.8)	+25.9	(24.69 to 27.07)	< 0.001
AC 2 kHz	47.8 (15.0)	28.8 (15.5)	+19.0	(17.91 to 20.14)	< 0.001
AC 4 kHz	49.6 (20.8)	37.3 (21.2)	+12.3	(10.95 to 13.57)	< 0.001
Mean four-frequency AC	*51.6 (13.5)*	*30.6 (14.4)*	+21.0	(19.96 to 22.04)	< 0.001
ABG 0.5 kHz	40.2 (12.0)	12.3 (10.9)	+27.9	(26.76 to 28.96)	< 0.001
ABG 1 kHz	34.4 (10.8)	9.4 (9.5)	+25.0	(24.00 to 26.02)	< 0.001
ABG 2 kHz	18.1 (11.2)	3.8 (7.0)	+14.3	(13.34 to 15.20)	< 0.001
ABG 4 kHz	23.8 (13.3)	9.2 (10.5)	+14.6	(13.40 to 15.66)	< 0.001
Mean four-frequency ABG	*29.1 (9.3)*	*8.7 (7.4)*	+20.4	(19.60 to 21.23)	< 0.001

SD: Standard deviation
BC: Bone-conduction
AC: Air-conduction
ABG: Air-bone gap
PTA: Pure-tone average
dB: Decibels
+: Improvement
-: Deterioration

Prognostic model; based on a postoperative four-frequency ABG of 10 dB or less

Out of 666 patients, 72.1% (n = 480) had a postoperative four-frequency ABG of 10 dB or less and 93.8% (n = 625) had a postoperative four-frequency ABG of 20 dB or less.

Univariate predictors of a postoperative ABG of 10 dB or less were 'preoperative four-frequency AC', 'age at surgery' and 'preoperative four-frequency ABG', which were also independent predictors of a postoperative ABG of 10 dB or less.
The prognostic model showed a good fit (Hosmer-Lemeshow goodness-of-fit test, p = 0.972), and the 'area under the curve' (AUC) was 0.62 (95% CI: 0.57– 0.67).
Table 3 shows the absolute risks of a postoperative ABG ≤10 dB with certain combinations of independent predictors. The chance a patient, aged over 40 years with a preoperative four-frequency ABG exceeding 30 dB, will achieve a postoperative four-frequency ABG of 10 dB or less is 68%, whereas a patient aged 40 years or less with an ABG exceeding 30 dB has a chance of 61%.
Analyzing the data using multiple imputation showed similar results.

Table 3 | Absolute risks, based on a postoperative four-frequency ABG of 10 dB or less.

	Postoperative four-frequency ABG of 10 or less (n = 480)	**Postoperative four-frequency ABG exceeding 10 (n = 186)**
≤40 Year and FF ABG >30 dB	60.6%	39.4%
≤40 Year and FF ABG ≤30 dB	76.3%	23.7%
>40 Year and FF ABG >30 dB	67.9%	32.1%
>40 Year and FF ABG ≤30 dB	77.6%	22.4%

Year: Age at surgery in years
ABG: Air-bone gap
dB: Decibels
FF: Four-frequency (0.5, 1, 2, 4 kHz)

Prognostic model; based on a postoperative four-frequency gain in AC exceeding 20 dB

A postoperative gain in AC exceeding 20 dB was achieved in 56% (n = 372) of the patients, compared to 44% (n = 294) of the patients who had a postoperative gain in AC of 20 dB or less.
Univariate predictors of a postoperative gain in AC exceeding 20 dB were 'preoperative four-frequency AC', 'preoperative four-frequency BC' and 'preoperative four-frequency ABG'. Independent predictors of a postoperative gain in AC exceeding 20 dB were 'preoperative four-frequency AC' and 'preoperative four-frequency ABG'.
The prognostic model showed a good fit (Hosmer-Lemeshow goodness-of-fit test, p = 0.338), and the 'area under the curve' (AUC) was 0.80 (95% CI: 0.77-0.83).

Table 4 shows the absolute risks of a postoperative gain in AC exceeding 20 dB with certain combinations of independent predictors. The chance a patient, with a preoperative four-frequency AC exceeding 50 dB and a preoperative four-frequency ABG exceeding 30 dB will achieve a postoperative gain in AC exceeding 20 dB is 86%, whereas a patient with a

preoperative four-frequency AC of 50 dB or less and a preoperative four-frequency ABG exceeding 30 dB has a chance of 69%.
Analyzing the data using multiple imputation showed similar results.

Table 4 | absolute risks, based on a postoperative four-frequency gain in AC exceeding 20 dB.

	Postoperative gain in four-frequency AC exceeding 20 dB (n = 372)	**Postoperative gain in four-frequency AC of 20 dB or less (n = 294)**
FF AC ≤50 dB and FF ABG >30 dB	69.0%	31.0%
FF AC ≤50 dB and FF ABG ≤30 dB	34.0%	66.0%
FF AC >50 dB and FF ABG >30 dB	86.2%	13.8%
FF AC >50 dB and FF ABG ≤30 dB	50.5%	49.5%

AC: Air-conduction
ABG: Air-bone gap
dB: Decibels
FF: Four-frequency (0.5, 1, 2, 4 kHz)

DISCUSSION

Our results show that 72% and 94% of the patients had a postoperative four-frequency (0.5, 1, 2, 4 kHz) ABG of 10 dB or less and a postoperative four-frequency (0.5, 1, 2, 4 kHz) ABG of 20 dB or less (three months after surgery), respectively. 'Age at surgery' and 'preoperative four-frequency ABG' were independent prognostic determinants, to achieve a postoperative four-frequency ABG of 10 dB or less. 'Preoperative four-frequency AC' and 'preoperative four-frequency ABG' were independent prognostic determinants, to achieve a postoperative four-frequency gain in AC exceeding 20 dB.
Our results were in agreement with Kisilevsky et al. who reported a mean postoperative four-frequency ABG of 10 dB or less in 75.2% (n = 861) of the cases, using the mean thresholds at frequencies 0.5, 1, 2 and 4 kHz (6). Nevertheless, Kisilevsky et al. (6) reported a mean follow-up of 16.4 months (range from 0.25 – 117 months), compared to a mean follow-up of three months in our series. Our results were, however, not in agreement with the results of Vincent et al., who reported a postoperative four-frequency ABG closed to 10 dB or less in 95.5% (n = 1.838) of the cases with a follow-up exceeding 1 year (range from 3-11 months), based on the mean thresholds at frequencies 0.5, 1, 2 and 4 kHz (7). Vincent et al. also reported the long-term hearing results, divided in years and showed that the percentage of patients with a postoperative ABG of 10 dB or less remained balanced around 96% (7). The mean postoperative ABG of 10 dB or less was 95.6% (n=800) at 1 year follow-up (range from 12-18 months) (7). It is obvious that there is a large variability in surgical outcome. Possible explanations for these differences are surgical technique and surgical experience

(22,23). For example, Vincent et al. (7) used a vein graft interposition (24) between the fenestration and the prosthesis and published one of the largest samples with otosclerosis patients within otosclerosis literature.

Our prognostic model is in agreement with the results of Marchese et al., who also found that age and preoperative ABG were the strongest predictors of postoperative success (13). The difference, however, is that they evaluated prognostic factors influencing the ABG gain, which is something different than the actual postoperative ABG. Both outcome measurements are related to each other, but an improved gain in ABG does not automatically result in a postoperative four-frequency ABG of 10 dB or less. Our finding that a smaller preoperative ABG increases the chance of a better postoperative ABG closure is also supported by the findings of Ueda et al. (10). In 2003, Welling et al. also published an article about predictive factors in stapes surgery, but they focused on pediatric patients only (25). Our results (table 3) showed that older patients (>40 years) experienced a slight advantage of their age compared to younger patients (≤40 years) in terms of the chance on a postoperative ABG of 10 dB or less. This finding is the opposite of Marchese et al. who reported that older patients (≥50 years) had a lower probability of a good functional outcome (13). It is obvious that there is a correlation between the age of the patient and the disease advancement of the otosclerosis. However, based on the present results we are not able to explain the exact mechanism between age of the patient and the pathologic mechanism of the otosclerosis.

The major strength of our study is that we were able to identify independent prognostic factors influencing postoperative outcome by means of the postoperative four-frequency ABG of 10 dB or less or a postoperative AC gain exceeding 20 dB. These prognostic factors were combined and translated into absolute risks for the individual patient. It is important to note that the cut off points in table 3 and 4 (age, preoperative ABG and preoperative AC) were only used to make absolute risk tables applicable to our own clinic during preclinical assessment. The mean age was 41 years; and we therefore used 40 years as a round cutoff for age at surgery. A preoperative ABG of 30 dB was used because it makes a patient eligible for hearing revalidation with a hearing aid. In other words; a patient with primary otosclerosis and an ABG of 30 dB could choose between otosclerosis surgery and a hearing aid. The mean preoperative AC was 52 dB; and we therefore used 50 dB as a round cutoff for preoperative AC. The actual prognostic model (multivariate logistic regression analysis) was not influenced by cutoff points and only shows which factors significantly influence the chance on a postoperative ABG of 10 dB or less and a postoperative gain in AC exceeding 20 dB. To our knowledge, this is the first publication focusing on such a prognostic model and its related absolute risks in primary stapes surgery.

Some possible limitations should also be discussed. First, about 18% of the predicting variables and 29% of the outcome variables were missing, which might lead to bias and a loss of power (18,19). However, the results after using multiple imputation were in agreement with the complete case analyses. Second, since other surgeons may operate on slightly different patients, use other techniques, and surgical skills between surgeons might also differ, our results may not be directly applicable to other clinics and surgeons. Besides the surgical variation it is important to note that the way of reporting audiometry in stapes surgery could influence the final results (9).

We expect that the results of this study will improve understanding of prognostic characteristics among patients with otosclerosis who undergo primary stapes surgery.

CONCLUSION

In conclusion, it appears possible to predict both the postoperative ABG of 10 dB or less and the postoperative gain in AC exceeding 20 dB with accuracies of 62% and 80%, respectively. The chance of a postoperative ABG of 10 dB or less was 1.3 times higher in patients over 40 years of age with a preoperative ABG of 30 dB or less, compared with patients aged 40 years or less with a preoperative ABG exceeding 30 dB. The chance of a postoperative gain exceeding 20 dB was 2.5 times higher in patients with a preoperative four-frequency AC exceeding 50 dB and a preoperative four-frequency ABG exceeding 30 dB, compared to patients with a preoperative four-frequency AC of 50 dB or less and a preoperative four-frequency ABG of 30 dB or less. Clinicians can use these factors to inform patients more explicitly about the expected postoperative hearing results.

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Chapter 7

KTP versus CO2 laser fiber stapedotomy for primary otosclerosis: results of a new comparative series with the otology-neurotology database

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ABSTRACT

Objective: To compare the 3-month postoperative hearing results after laser stapedotomy using a flexible potassium titanyl phosphate (KTP) or CO_2 laser fiber in patients with primary otosclerosis.

Study design: Prospective nonrandomized clinical study

Setting: Tertiary referral center, 862 stapedotomies were performed in 818 study patients between November 2006 and July 2011.

Methods: Otosclerotic stapes fixation was treated with flexible KTP laser fiber in 410 patients (431 stapedotomies) and with flexible CO_2 laser fiber in 408 patients (431 stapedotomies). Their pre- and postoperative audiometric results were compared.
Logistic regression analyses were performed to evaluate the main effect of laser fiber type and the effect after adjustment for independent predictors of a postoperative air-bone gap (ABG) of 10 dB or lower.

Results: In the KTP laser group the mean postoperative ABG was 4.3 dB compared with 3.1 dB in the CO_2 group (difference: 1.1, 95% confidence interval (CI): 0.4-1.9). In 90.4% of the patients in the KTP group the postoperative ABG was 10 dB or lower, as compared with 96.5% in the CO_2 group. The mean postoperative ABG at 4 kHz was 5.4 dB with KTP and 2.2 dB with CO_2 (difference: 3.2, 95% CI: 2.2-4.2). Sensorineural hearing loss was reported by 1 patient with KTP laser (0.3%) and by none with CO_2 laser. 'Type of laser' and 'sex' were independent predictors of an ABG of 10 dB or lower. The chance to achieve a postoperative ABG of 10 dB or lower for male subjects is 95% when treated with CO_2 laser and 85% when treated with KTP laser. For female subjects, these chances are 97% and 94% respectively.

Conclusion: The use of the CO_2 laser fiber may be associated with better hearing results than the KTP laser fiber, regarding the ABG closure within 10 dB.

INTRODUCTION

Argon laser stapedotomy was introduced by Perkins in 1979 (1) with the intent to minimize the risk of mechanical trauma to both middle and inner ears and potassium titanyl phosphate (KTP) laser stapedotomy was then employed in the mid-1980's (2). In 1989, Lesinski and Palmer (3) published new developments of the CO_2 laser system, which enabled it to be used for stapes surgery. KTP laser is a visible light laser (λ = 0.532 microns), which delivers energy by means of a fiber optic and can be used with a microhandpiece. KTP lasers can potentially have thermal effects on deeper structures as they are easily transmitted through perilymph with risk of injury to inner ear structures (3). Conversely, the CO_2 wavelength (λ = 10.6 microns) is well absorbed by water and the heat generated is dissipated to the labyrinthine fluids before reaching the vestibular membrane (4).

For the past 30 years, the long wavelength of the CO_2 laser could not be transmitted by fiber optic cable and had to be coupled to the microscope using a micromanipulator. This delivery system can be associated with risk of missing the target and causing damage to adjacent structures if the aiming beam is not precisely aligned with the CO_2 laser beam (4). For this reason, we have always preferred to use a handheld KTP laser to perform stapedotomy (5,6). The introduction of the new OmniGuide handheld CO_2 laser fiber combines the safety of the CO_2 laser, in respect of inner ear structures, with the precision offered by a handheld delivery system.

In 2010, Vincent et al. (7) reported a preliminary comparative series of KTP and CO_2 laser stapedotomy for primary otosclerosis performed on 214 ears in 214 patients between January 2008 and January 2009. They concluded that the use of the CO_2 laser fiber appeared to be associated with slightly better hearing results than the KTP laser fiber, especially when assessed at the 4-kHz frequency. All other differences were small and did not have enough power to show significance. Since 2009, another 46 stapes operations have been performed with the KTP laser and 324 stapes operations with the CO_2 laser and OmniGuide system at the Causse Clinic. Between November 2006 and January 2008, 278 stapes operations have been performed with the KTP laser.

The aim of this paper is to compare the results of primary stapes surgery performed with the KTP laser and the CO_2 laser in patients treated for otosclerosis.

MATERIALS AND METHODS

Patients

This is a prospective study of 818 patients who underwent 862 primary surgeries for otosclerosis with stapes fixation. All patients treated between November 2006 and July 2011 were included in the study and were operated on by the same surgeon using the same technique (stapedotomy with vein graft interposition) as previously described (6,7). Patients were divided in two groups according to the type of laser fiber used for stapedotomy. The first 410 patients (50%) were operated with the flexible KTP laser fiber (KTP laser fiber group) from November 2006 to March 2010, whereas the last 408 patients (50%) were operated with the flexible CO2 laser fiber (CO2 laser fiber group) from August 2008 to July 2011. Patients with obliterative otosclerosis and/or simultaneous malleus ankylosis or eroded incus were excluded. Obliterative otosclerosis was defined as presence of hard new bone filling the oval fossa, requiring an oval window drill out for an excessively thick footplate. This affected fourteen patients in the KTP laser fiber group (eleven patients had obliterative otosclerosis (2.5%), two patients had a simultaneous malleus ankylosis (0.5%) and one patient had a simultaneous eroded incus (0.2%)). This resulted in a total of 417 cases in the KTP laser fiber group included in the final analysis. In the CO2 laser fiber group there were four cases of obliterative otosclerosis (1%), 3 cases of simultaneous malleus ankylosis (0.7%) and two cases of simultaneous incus erosion (0.4%) and were therefore excluded from the final analysis, giving a total of 422 cases in the CO2 laser fiber group in the final analysis. Hearing status was assessed at three months after surgery.

All data were prospectively tabulated using the Otology Neurotology Database (ONDB©) (AS Multimedia Inc, Cassagne, France) (6). This is a commercially available software package developed at our center, designed to comply with the American Academy of Otolaryngology Guidelines for reporting clinical and audiometric results (8).

Surgery

All procedures were performed by the same surgeon (RV). In all cases, a transcanal procedure was undertaken and laser stapedotomy was performed using either the flexible KTP or CO2 laser probes followed by vein graft interposition (6,7). The surgical technique was similar in both groups and was described in detail in our previous paper (7). After a rosette was created on the footplate with the laser, a stapedotomy was performed with the Skeeter microdrill using a 0.7 mm diameter diamond dust burr. In both groups, a 0.4-mm-diameter Teflon piston of appropriate length was routinely used in all cases.

The Novus-Spectra™ KTP laser (Lumenis Inc., Salt Lake City, UT, USA) was delivered via the Gherini Endo-Otoprobe™ fiber (Lumenis Inc., Salt Lake City, UT, USA), which enabled a 200-micron spot size as previously described by the author (9).

The CO_2 laser used in this study was the BeamPath® OTO, fiber-enabled CO_2 laser system (OmniGuide Inc., Cambridge, MA, USA). The fiber technology has been described in detail previously (10-13). It is a hollow-core photonic band-gap waveguide that enables flexible delivery of the 10.6-micron CO_2 laser wavelength. The 130-cm-long fiber has a 250-micron spot size, is coupled to a CO_2 laser source (in this series, Sharplan 20C, Lumenis Inc., Yokneam, Israel), and terminates distally in a stainless-steel tip. A gentle flow of inert gas (Helium) at an input pressure of 10 PSI (pounds per square) cools the fiber as it is passed through the fiber's hollow core and prevents build-up of debris.

Audiometric assessment

Audiometric evaluation included preoperative and postoperative air-bone gap (ABG), air-conduction (AC) thresholds, and bone-conduction (BC) thresholds. Only AC and BC results that were obtained at the same time postoperatively were used for calculation of ABG and pure-tone averages (PTAs). We used a four-frequency PTA for AC and BC thresholds (0.5, 1, 2 and 4 kHz) obtained at 3 months follow-up. The preoperative and postoperative BC and AC levels at 4 kHz were also assessed. Audiometry was reported according to American Academy of Otolaryngology-Head and Neck Surgery Guidelines (8) except for thresholds at 3 kHz, which were substituted in all cases with those at 4 kHz. A postoperative ABG of 10 dB or lower could be considered as the primary outcome measurement among stapes surgery literature (6) and is included in the model evaluating the effect of the laser.

Statistical analyses

To evaluate the effect of stapes surgery performed with the KTP laser or the CO_2 laser, in patients with primary otosclerosis, pre- and postoperative audiometric results were compared, using an independent samples T-test.

In a univariate logistic regression analysis, the effect of the type of laser on the postoperative ABG (up to versus above 10 dB) was evaluated. The effect of laser type was adjusted for potential prognostic factors. Those that were associated in univariate analyses ($p < 0.10$) with the postoperative ABG (up to versus above 10 dB) were included in multivariate logistic regression analyses (14). The model was reduced through exclusion of predictors with p values greater than 0.05. The predictive accuracy of the multivariate models was estimated on the basis of the goodness of fit using the Hosmer-Lemeshow tests (15). The model's ability to discriminate between patients was estimated as the area under the receiver operating characteristic curve of the model (16). The receiver operating characteristic curve area is a suitable parameter to summarize the discriminative or predictive value and can range from 0.5 (no discrimination, like a flip of a coin) to 1.0 (perfect discrimination).

We calculated the crude absolute risks for a postoperative ABG of 10 dB or lower for treatment with the KTP laser and the CO2 laser and the adjusted absolute risks for subgroups of independent predictors. All analyses were performed using SPSS (version 15.0; SPSS Inc., Chicago IL, USA).

RESULTS

Patient characteristics

Of the 417 patients in the KTP laser group, 334 had audiologic data available at 3 months follow-up. Of the 422 patients in the CO2 laser group, 315 had audiologic data available at 3 months follow-up. Because many of our patients travel long distances for care at our center, onsite follow-up care is sometimes not possible. Table 1 shows the preoperative patient characteristics for the two groups. In the KTP and CO2 groups, 65% and 68%, respectively, were female and the mean age was 47.4 and 48.9 years, respectively. There were 25 senior patients (age ≥ 65 yr) and three children (age ≤ 18 yr) in the KTP laser group. There were 30 senior patients in the CO2 laser group and no children. The mean preoperative BC threshold was 22.4 (standard deviation (SD) 10.5) dB in the KTP laser group and 22.0 (SD 9.5) dB in the CO2 laser group. The mean preoperative AC threshold was 49.4 (SD 13.3) dB in the KTP laser group and 46.8 (SD 12.3) in the CO2 laser group. The preoperative ABG was 27.0 (SD 7.6) dB in the KTP laser group and 24.8 (SD 6.5) dB in the CO2 laser group.

Table 1 | Preoperative patients characteristics in 334 patients operated with the flexible KTP laser fiber and 315 patients operated with the flexible CO2 laser fiber.

Variable	KTP Laser	CO2 Laser	Differences (95% CI)	P-value	Association between prognostic factor and the chance on a postoperative ABG <=10 dB (*Univariate*)	Association between prognostic factor and the chance on a postoperative ABG <=10 dB (*Multivariate*)
Laser type (number of patients)	334	315			0.003	0.010
Age – yrs ((SD) min-max)	47.4 ((12.2) 8-75)	48.9 ((11.3) 19-78)	-1.5 (-3.3 ; 0.3)	0.103	0.179	----
Sex (% female)	65.0	67.6	3 (-4.6 ; 9,9)	0.475	0.006	0.007
Mean BC – dB (SD)	22.4 (10.5)	22.0 (9.5)	0.4 (-1.1 ; 2.0)	0.586	0.673	----
Mean AC – dB (SD)	49.4 (13.3)	46.8 (12.3)	2.7 (0.7 ; 4.6)	0.008	0.299	----
Mean ABG – dB (SD)	27.0 (7.6)	24.8 (6.5)	2.2 (1.1 ; 3.3)	0.000	0.203	----
BC at 0.5 kHz – dB (SD)	16.6 (8.3)	13.9 (6.8)	2.6 (1.5 ; 3.8)	0.000	0.334	----
BC at 1 kHz – dB (SD)	20.8 (10.1)	18.6 (9.3)	2.2 (0.7 ; 3.7)	0.005	0.915	----
BC at 2 kHz – dB (SD)	27.5 (13.8)	27.2 (12.7)	0.3 (- 1.8 ; 2.3)	0.790	0.648	----
BC at 4 kHz – dB (SD)	24.8 (15.9)	28.1 (15.1)	-3.4 (-5.7 ; -1.0)	0.006	0.876	----
AC at 0.5 kHz – dB (SD)	49.2 (12.7)	48.4 (11.0)	0.9 (-1.0 ; 2.7)	0.351	0.376	----
AC at 1 kHz – dB (SD)	51.6 (13.2)	48.6 (11.5)	3.0 (1.0 ; 4.9)	0.003	0.713	----
AC at 2 kHz – dB (SD)	49.0 (14.7)	45.5 (14.6)	3.5 (1.3 ; 5.8)	0.002	0.505	----
AC at 4 kHz – dB (SD)	48.0 (19.3)	44.7 (19.0)	3.3 (0.4 ; 6.3)	0.028	0.137	----
ABG at 0.5 kHz – dB (SD)	32.6 (9.9)	34.4 (8.0)	-7.8 (-3.2 ; -0.4)	0.013	0.737	----
ABG at 1 kHz – dB (SD)	30.8 (9.5)	30.0 (7.6)	0.8 (-0.5 ; 2.1)	0.244	0.682	----
ABG at 2 kHz – dB (SD)	21.5 (9.1)	18.2 (7.7)	3.2 (1.9 ; 4.5)	0.000	0.660	----
ABG at 4 kHz – dB (SD)	23.2 (12.3)	16.6 (10.8)	6.7 (4.9 ; 8.5)	0.000	0.032	0.194

SD: Standard deviation BC: Bone-conduction AC: Air-conduction
ABG: Air-bone gap dB: Decibels (pure-tone average) Means were calculated with 0.5, 1, 2, 4 kHz

Postoperative audiometric assessment at 3 months follow-up

Sensorineural hearing loss (SNHL) was defined as change in the BC PTA of 15 dB or more. None of the patients had postoperative SNHL in the CO2 laser group, whereas there was one case of SNHL in the KTP laser group (0.3%). Postoperative hearing results are shown in table 2. In the KTP laser group, the postoperative four-frequency average ABG was 4.3 (SD 5.4) dB compared to 3.1 (SD 4.6) dB in the CO2 laser group (mean difference 1.1 dB, 95% CI: 0.4-1.9). The postoperative ABG was closed to 10 dB or less in 302 cases (90.4%) in the KTP laser group, compared with 304 cases (96.5%) in the CO2 laser group (mean difference 6%, 95% CI: 23-98). The postoperative mean AC was 25.8 (SD 11.8) dB in the KTP laser group compared with 23.7 (SD 10.3) dB in the CO2 laser group (mean difference 2.1 dB, 95% CI: 0.4-3.8) The postoperative gain in AC threshold was 23.6 (SD 10.8) dB in the KTP laser group compared with 23.0 (SD 8.9) dB in the CO2 laser group (mean difference 0.6 dB, 95% CI: -0.9 to 2.1). The postoperative change in BC threshold was negligible in both groups (+0.8 (SD 5.1) dB in the KTP laser group and +1.3 (SD 4.6) dB in the CO2 laser group) and overclosure (postoperative improvement of BC >10 dB) occurred in nine cases in the KTP laser group (2.6%) and in twelve cases in the CO2 laser group (3.8%). At 4 kHz, the postoperative ABG was 5.4 (SD 8.1) dB in the KTP laser group and 2.2 (SD 4.6) dB in the CO2 laser group (mean difference 3.2, 95% CI: 2.2-4.2). The postoperative gain in AC at 4 kHz was 16.4 (SD 13.4) dB in the KTP laser group compared with 14.0 (SD 13.2) dB in the CO2 laser group (mean difference 2.4, 95% CI: 0.3-4.4), whereas the BC threshold deterioration at 4 kHz was 1.4 (SD 8.2) dB in the KTP laser group compared with 0.4 (SD 8.9) dB in the CO2 laser group (mean difference -1.1 dB, 95% CI: -2.4 to 0.3).

Univariate & multivariate analysis

The last two columns of table 1 show the association between each of the potential preoperative prognostic factors and the chance to achieve a postoperative ABG of 10 dB or lower, which was determined by calculating the rate difference of each prognostic factor between both groups and by applying univariate logistic regression analysis. In univariate analysis, the factors ‘laser-type’, ‘sex’ and ‘preoperative ABG at 4 kHz’ significantly influence the chance on a postoperative ABG of 10 or lower. However, in a multivariate logistic regression analysis only the factors ‘laser type’ and ‘sex’ remained significant and the factor ‘preoperative ABG at 4 kHz’ did not significantly influence the chance on a postoperative ABG of 10 dB or lower ($p = 0.194$).

Table 2 | Hearing results at 3-months follow-up according to the type of flexible laser fiber used.

Variable	KTP Laser (n = 334)	CO2 Laser (n = 315)	Difference (95% CI)	P-value
ABG ≤ 10dB (%)	90.4	96.5	6 (2.3 ; 9.8)	0.002
Mean BC – dB (SD	21.6 (10.1)	20.6 (9.0)	0.9 (-0.6 ; 2.4)	0.218
Mean AC – dB (SD)	25.8 (11.8)	23.7 (10.3)	2.1 (0.4 ; 3.8)	0.017
Mean ABG – dB (SD)	4.3 (5.4)	3.1 (3.7)	1.1 (0.4 ; 1.9)	0.002
Mean BC at 4 kHz – dB (SD)	26.2 (16.0)	28.5 (16.1)	-2.3 (-4.8 ; 0.2)	0.071
Mean AC at 4 kHz – dB (SD)	31.6 (17.9)	30.7 (17.1)	0.9 (-1.8 ; 3.6)	0.497
Mean ABG at 4 kHz – dB (SD)	5.4 (8.1)	2.2 (4.6)	3.2 (2.2 ; 4.2)	0.000
Mean *change* in BC – dB (SD)	0.8 (5.1) improvement	1.3 (4.6) improvement	-0.5 (-1.3 ; 0.2)	0.189
Mean *change* in AC – dB (SD)	23.6 (10.8) improvement	23.0 (8.9) improvement	0.6 (-0.9 ; 2.1)	0.449
Change in BC at 4 kHz – dB (SD)	-1.4 (8.2) deterioration	-0.4 (8.9) deterioration	-1.1 (-2.4 ; 0.3)	0.113
Change in AC at 4 kHz – dB (SD)	16.4 (13.4) improvement	14.0 (13.2) improvement	2.4 (0.3 ; 4.4)	0.023

SD: Standard deviation BC: Bone-conduction AC: Air-conduction
ABG: Air-bone gap dB: Decibels (pure-tone average) Means were calculated with 0.5, 1, 2, 4 kHz
SNHL: Sensorineural hearing loss

Adjusted analyses for the effect of the type of laser

Out of 315 patients treated with the CO2 laser, 97% had a postoperative ABG of 10 dB or lower compared with 91% of the 334 patients treated with the KTP laser (mean difference 6%, 95% CI: 2.3%-9.8%). Sex was an independent predictor of a postoperative ABG of 10 dB or lower.

Out of 102 male patients treated with the CO2 laser, 95% had a postoperative ABG of 10 dB or lower compared with 85% of the 117 male patients treated with the KTP laser (mean difference 11%, 95% CI: 3%-20%). Out of 213 female patients treated with the CO2 laser, 97% had a postoperative ABG of 10 dB or lower compared with 94% of the 217 female patients treated with the KTP laser (mean difference 4%, 95% CI: -0.3% to 8%). Table 3 shows the absolute risks of a postoperative ABG of 10 dB or lower with certain combinations of independent predictors.

The chance a male patient, treated with the CO2 laser, will achieve a postoperative ABG of 10 dB or lower is 95%, whereas a male patient, treated with the KTP laser, has a chance of 85%.

After adjustment for sex, the multivariate model for the effect of laser type showed a good fit (goodness-of-fit test) (15), (p = 0.862) with an ‘area under the curve’ (AUC) of 0.68 (95% CI: 0.59-0.76).

Table 3 | The effect of the type of laser: absolute risks for an outcome of ABG of 10 dB or lower.

	CO2 laser	KTP laser	Difference (95% confidence interval)	P-value
All	304/315 (97%)	302/334 (90%)	6% (2% ; 10%)	0.002
Male	97/102 (95%)	99/117 (85%)	11% (3% ; 20%)	0.002
Female	207/213 (97%)	203/217 (94%)	4% (-0.3% ; 8%)	0.073

DISCUSSION

The current study presents the second part of the consecutive Causse Ear Clinic comparative series of stapedotomy with KTP and CO2 handheld laser. The first part of that series regarded 214 ears between 2008 and 2009 (7). Since 2009, another 324 stapes operations have been performed with the CO2 laser and Omniguide system at the Causse Clinic and 46 stapes operations with the KTP laser. Between November 2006 and January 2008, the KTP laser was used in 278 stapes operations. Therefore, this second comparative study concerns 862 stapes operations. The authors use a drill to complete the stapedotomy cases of CO2 and KTP laser. As the drill may be more traumatic to the inner ear in comparison to laser, this may effectively negate any more substantial differences that would exist between the two techniques. However, the same technique of drilling was routinely used by the same surgeon for all patients in both groups using the same material (skeeter drill with a 0.7 mm diameter diamond dust burr). For this reason also, patients with obliterative otosclerosis requiring an oval window drill out for an excessively thick footplate were excluded. The author performed the first half of the cases with KTP and the second half with CO2; the difference may be complicated by the accrual of experience in the procedure. However, as previously stressed, this technique of laser stapedotomy with vein graft interposition is routinely used by the author in the same tertiary referral center since 1991. Both current series were performed from November 2006 to July 2011 and the same technique was used in both groups.

The present study confirms the efficacy of both the KTP and CO2 laser for primary stapedotomy (1,17-19) as mean hearing thresholds improved in both groups. However, there was no case of SNHL in the CO2 laser group compared with one case (0.3%) in the KTP laser group, which is similar to the 0.5% incidence of SNHL, which was reported in our large series of 3,050 KTP laser stapedotomies (6). However, our comparative analysis supports the use of the new handheld CO2 laser, which is associated with a higher success rate than the KTP laser. The ABG closure to within 10 dB was 90.4% with the handheld KTP laser as compared with 96.5% with the CO2 handheld laser (mean difference 6, 95% CI: 2.3-9.8). The postoperative ABG at 4KHz was 5.4 dB in the KTP and 2.2 dB in the CO2 group (mean difference 3.2, 95% CI: 2.2-4.2). In our previous comparative study, the CO2 laser fiber was significantly associated with better hearing results than the KTP laser fiber only for the postoperative mean ABG at 4 kHz (7). Similar findings at 4 kHz were reported by Vernick (18) in his comparative study of stapedotomy with KTP laser and CO2 laser both delivered via a microscope-mounted micromanipulator system, but their study did not have enough power to show significance. Currently, no explanation could be given by the authors as to why a CO2 laser would be more effective than KTP in reducing the conductive hearing loss.

Lasers have become widely used for stapedotomy since their introduction into otosclerosis surgery by Perkins in 1980 (1), and their use has increased markedly over the last decade. Experimental and theoretical concerns regarding differential tissue absorption characteristics between the visible (Argon and KTP) and infrared (CO2) light laser systems have introduced controversy regarding the safety of this technique for otosclerosis surgery. Using both animal and experimental models, several authors have emphasized concerns about excessive heating of perilymph and the potential risk of injury of the inner ear structures both with visible and infrared lasers (3,17). However, clinical studies have shown the safety and efficacy of both types of lasers (6).

When a laser is directed by a micromanipulator coupled to the operating microscope, the laser beam is restricted to the visual axis of the microscope with the potential risks of incorrect aiming and laser beam misalignment. This might increase the difficulty of the surgical procedure in case of specific anatomical conditions such as dehiscence of the facial nerve, abnormal position of the nerve or a facial nerve overhang narrowing the oval window. The anterior crus of the stapes is often difficult to visualize and this may prevent vaporization, thus requiring fracture towards the promontory with the potential risk of footplate fracture, mobilization or floating footplate. Conversely, the anterior crus can usually be palpated and vaporized with a handheld laser probe.

We have routinely used a handheld laser using a pulsed mode either in primary or revision stapes surgery in our center (6,19). The handpiece is used to vaporize the posterior and anterior crus directly, avoiding fracturing or mobilization of the anterior segment. We used a combination of a Skeeter microdrill and a handheld laser to perform a calibrated stapedotomy. The fiberoptic probe carbonizes and fenestrates the footplate with little or no bleeding, whereas the microdrill allows a precisely calibrated stapedotomy. The same technique was also used with the flexible CO2 laser fiber in this series and we have defined our own working and safety parameters for vaporization of the stapes crus and footplate using the OmniGuide system.

Several previous studies also reported the results of the Argon, KTP and CO2 lasers individually (1,6,17). The power of the few studies that did compare Argon or KTP to CO2 laser stapedotomy (18,20) was, however, too low to draw firm conclusions. Furthermore, in these earlier studies, the CO2 laser was delivered via a micromanipulator in all cases while

the Argon and KTP lasers were delivered by way of a micromanipulator (18) or a handheld fiber (20). In our study we used a direct comparison by using equivalent modes of delivery and using a flexible laser fiber in both groups.
This is a short-term follow-up comparative study and longer follow-up may show further sensorineural hearing loss, especially at 4kHz.
Third, because we did not perform a randomized trial, confounding, external effects and information bias cannot be completely precluded. As previously described by Bittermann et al. (14), it was possible to identify prognostic characteristics, influencing the chance on a postoperative ABG of 10 dB or lower, using a multivariate logistic regression. However, different factors were found. Our results show that laser type (KTP or CO2) has an effect on the postoperative ABG of 10 dB or lower; CO2 laser has the largest positive effect. It showed that patient sex had a marked influence on this effect, as an independent predictor of the postoperative ABG: the effect of stapedotomy in female patients is somewhat higher. Potential prognostic factors such as 'age at surgery', 'preoperative AC', 'preoperative BC' and 'preoperative ABG' had no major effect on postoperative ABG. There is a risk of bias due to confounding because of the absence of randomized allocation. Hence, in a randomized comparison, different results may be found.
Unfortunately, other potential confounders like comorbidity and ENT history could not be taken into account. External effects were minimized by treating all patients in a similar way. Information bias, e.g. a time trend or measurement errors might have occurred because the first 107 patients were operated with the flexible KTP laser and the subsequent 107 patients with CO2. On the other hand, the surgeon was already very experienced at the start of the study and similar audiometric equipment was used in all patients.

Because of the results of our previous article (7) and the present study reinforces the superiority of the CO2 with the OmniGuide Handheld system, we have progressively abandoned the KTP laser in favor of the CO2 laser, which is now routinely used in all our primary and revision stapes operations. However, there is a significant cost differential of the single-use probe for each system, which is in favor of the KTP laser.
We recommend a large randomized trial to ensure the comparability and validity of the data, and in which other important outcomes, such as tinnitus or dizziness and quality of life can also be studied.

CONCLUSION

The results of this study indicate that both lasers (with regard to both wavelength and delivery system) seem to be equally safe, but the CO_2 laser fiber seems to perform better than the KTP laser for primary otosclerosis surgery, regarding the ABG closure within 10 dB as 90.4% of patients treated with KTP laser achieved ABG closure to less than 10 dB compared with 96.5% of patients treated with CO_2 laser.

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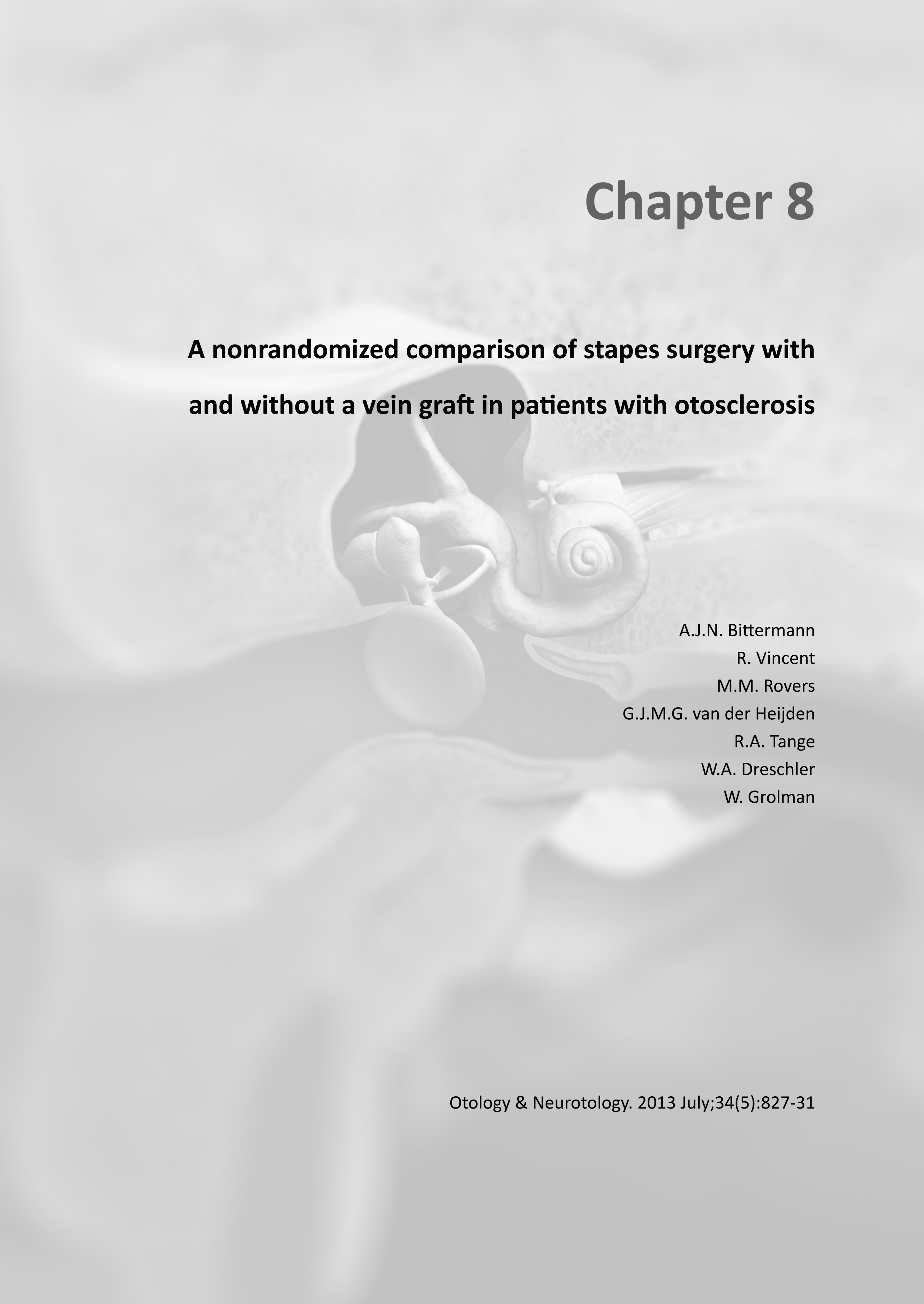

Chapter 8

A nonrandomized comparison of stapes surgery with and without a vein graft in patients with otosclerosis

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ABSTRACT

Objective: To evaluate the effectiveness of primary stapes surgery with and without a vein graft in patients with otosclerosis and to determine the differences in the postoperative gain in air-bone gap (ABG) and air-conduction (AC).

Study Design: A nonrandomized multicenter clinical evaluation.

Setting: Two tertiary referral centers in the Netherlands and France.

Patients: Otosclerosis patients that underwent primary stapedotomy surgery.

Intervention: Primary stapedotomy surgery without a vein graft (n=939, first center) compared with primary stapedotomy surgery with a vein graft (n= 3691, second center).

Main Outcome Measures: Pre- and postoperative audiometric results were compared. An analysis of variance (ANOVA) was performed to evaluate differences in postoperative ABG and AC gains between surgeries with and without a vein graft, adjusted for potential confounders.

Results: The postoperative ABG was 10 dB or less in 72.1% of the patients without a vein graft and in 93.2% of patients with a vein graft. After adjustments for differences at baseline, the mean gain in ABG was 18.6 dB (95% CI: 18.1-19.1) in the group without vein graft, compared with 24.2 dB (95% CI: 23.9–24.6) in the group with vein graft (mean difference 5.6 dB, 95% CI: 5.0–6.2). The mean gain in AC was 19.5 dB (95% CI: 18.7–20.3) in the group without vein graft, compared to 24.3 dB (95% CI: 23.7–24.7) in the group with vein graft (mean difference 4.8 dB, 95% CI: 3.8–5.7).

Conclusion: Patients with otosclerosis undergoing primary stapes surgery may benefit more from a vein graft interposition.

INTRODUCTION

Otosclerosis is characterized by a disordered bone remodeling in the region of the otic capsule, mostly located between the cochlea and the vestibule and just anterior to the footplate of the stapes (1,2). In 2001, Declau et al. (1) studied unselected series of temporal bones and found that clinical otosclerosis has a prevalence of 0.3% to 0.4% in the Caucasian population. The absolute numbers in the US, and the Netherlands can subsequently be extrapolated to 86.000 and 50.000 in 2009, respectively. It is important to distinguish histological otosclerosis (no symptoms) from clinical otosclerosis (symptoms such as hearing loss and vertigo). Histological otosclerosis is about 10 times more common, compared to clinical otosclerosis (2). Stapes surgery is the treatment of choice for clinical otosclerosis and is frequently applied in different countries, although a hearing aid is also a feasible alternative.

During the last 50 years, surgical treatment for hearing loss due to otosclerosis has changed dramatically. The technique altered from stapedectomy to stapedotomy (3) and the interposition of a vein graft to cover the fenestration was introduced (4-6). The purpose of a vein graft is to create an effective continuation of the sound conduction system including a reduced risk of fistulas or intracochlear damage (4-7). Theoretically, the application of a vein graft in otosclerosis surgery is an ideal method to perform a stapedotomy, which could result in better postoperative hearing outcomes, in terms of the postoperative air-bone gap (ABG) (8). Earlier studies showed mean four-frequency (0.5, 1, 2, 4 kHz) postoperative ABGs closed to 10 dB or less in 94.2% (n = 2.368) of patients treated with a vein graft (8), as compared with 75.2% (n = 861) patients treated without a vein graft (9). However, due to methodological differences and limitations, it is difficult to compare literature evaluating stapes surgery. Furthermore, most studies performed so far have focused on the application of different types of laser (10), different piston types (11), stapedotomy versus stapedectomy (12) or different audiometric parameters (13). Others (14,15) showed that a vein graft has an advantage over other sealing methods (blood seal and tragal perichondrium seal), but so far, no publications are available comparing patients with and patients without a vein graft. We therefore compared the results of primary stapes surgery with and without a vein graft interposition in patients treated for otosclerosis.

MATERIALS AND METHODS

The results of two different specialized tertiary referral centers were compared. In the first center (center of the last author; the Netherlands), all patients were treated without a vein graft. In the second center (center of the second author; France), all patients were treated with a vein graft.

Patients treated without a vein graft (first center)
All patients (n = 939) that underwent primary stapedotomy surgery from 1982 till 2009 were evaluated. A transcanal procedure was undertaken in all cases. A stapedectomy was performed in a minority of the cases (3%) compared with a small fenestra stapedotomy in the other cases. The fenestration was performed with the micro-pick technique described by Marquet (16) in most cases. The potassium titanyl phosphate (KTP) laser was introduced in our center in 2007. The surgeries were performed by two different surgeons (RT and WG). No vein graft was positioned between the prosthesis and the fenestration. Different prostheses were used and are summarized in table 1.

Patients treated with a vein graft (second center)
All patients (n = 3691) that underwent primary stapedotomy surgery between January 1991 and May 2010 were evaluated. In all cases, a transcanal procedure was undertaken. A laser stapedotomy followed by a vein graft interposition was performed in all cases. The KTP laser was used in a majority of the cases (93%), at settings of 2 W, 0.5-second pulse duration for the stapes crura and 1 W, 0.2-second pulse duration for the stapes footplate. After a rosette was created on the footplate with the laser, a stapedotomy was performed with the Skeeter microdrill using a 0.7-mm-diameter diamond dust burr. A 0.4-mm-diameter Teflon piston of appropriate length was routinely used in most cases. The Novus-Spectra KTP-laser (Lumenis Inc., Salt Lake City, UT) was delivered via the Gherini Endo-Otoprobe fiber (Lumenis Inc.), which enabled a 200-µm spot size as previously described (17). Different prosthesis and lasers, which were used, are summarized in table 1.

Audiometric assessment
Audiometric evaluation included preoperative and postoperative ABG, air-conduction (AC) thresholds, and bone-conduction (BC) thresholds. Only AC and BC results that were obtained at the same time postoperatively were used for calculation of ABG and pure-tone averages (PTAs). We used a four-frequency PTA for AC and BC thresholds (0.5, 1, 2 and 4 kHz) obtained at 3 months follow-up. The preoperative and postoperative BC and AC levels at 4 kHz were also assessed. Audiometry was reported according to the American Academy

of Otolaryngology—Head and Neck Surgery guidelines (18), except for thresholds at 3 kHz, which were substituted in all cases with those at 4 kHz.

Statistical analyses

Preoperative findings were analyzed using descriptive statistics and compared between those with and without a vein graft with a chi-square or student's *t*-test.

The analysis of the postoperative gain in four-frequency ABG and AC were carried out using an analysis of variance (ANOVA), in which 'age at moment of surgery', 'sex' and 'preoperative four-frequency AC, BC and ABG' were entered as a covariate to adjust for differences at baseline. Mean estimates and mean differences between both groups regarding the postoperative gain in four-frequency ABG and AC, adjusted for covariates, were calculated with 95% confidence intervals.

All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL)

Table 1 | Baseline characteristics (without vein graft; first center vs with vein graft; second center).

	All primary stapes surgeries *without vein graft* (first center) (N=939)	Primary stapes surgeries *without vein graft* (first center), with pre- and postoperative audiologic data available (N=666)	All primary stapes surgeries *with vein graft* (second center) (N=3691)	Primary stapes surgeries *with vein graft* (second center), based on surgical technique (N=1593)
Mean age at surgery (Years (SD))	41.4 (11.5) (ranged from 9-74)	41.3 (11.2) (ranged from 10-72)	45.1 (11.5) (ranged from 7-75)	46.1 (11.8) (ranged from 8-75)
Sex (%)				
Female	63	62	66	66
Male	37	38	34	34
Laser surgery (%)				
KTP	1.5	0.9	93	100
CO2	--	--	4	--
Revolix	--	--	3	--
Surgeon (%)				
RT	85	83	--	--
WG	15	17	--	--
RV	--	--	100	100
Bilateral cases (%)	31	31	7	9
Piston types (%)				
Teflon 0.4 Bucket	--	--	5	--
Causse HA- Teflon TORP	--	--	1	--
Titanium (4.5mm)	32.4	30.4	--	--
Titanium (4.75mm)	2.2	2.6	--	--
Titanium (5.0mm)	0.1	0.2	--	--
a Wengen (4.5mm)	8.6	10.8	--	--
a Wengen (4.75mm)	1.8	2.2	--	--
Causse 0.3 (Length manually fitted)	7.9	7.1	--	--
Causse 0.4 (Length manually fitted)	33.1	32.4	94	100
Shea Teflon cup/loop (Length manually fitted)	8.0	8.3	--	--
Gold piston (4.5mm)	3.8	4.5	--	--
Gold piston (4.75mm)	0.6	0.5	--	--
Other	1.5	1.2	--	--

-SD = standard deviation
-KTP = potassium titanyl phosphate
-TORP = total ossicular replacement prosthesis
-Length manually fitted = surgeon adapted the length according to intraoperative findings

RESULTS

Surgeries without a vein graft (first center)

Nine hundred ninety-three primary otosclerosis patients were operated without a vein graft between 1982 and 2009. Pre- and postoperative audiometric data, 3 months after surgery, were available for 666 patients. The mean age was 41 years and ranged from 9 to 74 years (SD 11.5) and 63% was female. The introduction of the potassium titanyl phosphate (KTP) laser in 2007 resulted in 1.5% laser surgeries. Eighty-five percent of the patients were operated by RT and 15% of the patients were operated by WG. Thirty-one percent of the cases were bilateral. Table 1 shows the characteristics of all patients (n = 939) and those with pre- and postoperative audiometric data available (n = 666), i.e. those without missing values.

Surgeries with a vein graft (second center)

Three thousand six hundred ninety-one primary otosclerosis patients were operated with a vein graft between April 1991 and June 2010 by the same surgeon (RV). Seven percent of the cases were bilateral. The mean follow-up time was 48 months. Only postoperative audiometric data, 3 months after surgery, were included, which resulted in 1918 patients. The majority of these patients (n = 1593) were treated following the same surgical technique; KTP-laser and Skeeter microdrill with a 0.4-mm-diameter Teflon piston of appropriate length between the incus and the stapes footplate. There were no missing audiometric data for these patients. This homogenous group of 1593 patients was used to perform the comparison (surgeries with and without vein graft). The mean age was 46 years and ranged from 8 to 75 years (SD 11.8) and 66% was female. Table 1 shows the characteristics of all patients (n = 3691) and those with the same surgical technique (n = 1593).

Preoperative patient characteristics

Preoperative mean BC, AC and ABG are summarized in table 2. The mean preoperative BC was 22.5 dB (SD 9.8) in the group without vein graft, compared to 24.4 dB (SD 11.5) in the group with vein graft (mean difference 1.9 dB (95% CI: 1.0-2.8)). The mean preoperative AC was 51.6 dB (SD 13.5) in the group without vein graft, compared to 50.7 dB (SD 14.3) in the group with vein graft (mean difference -0.9 dB (95% CI: -2.1 to 0.3)). The mean preoperative ABG was 29.1 dB (SD 9.3) in the group without vein graft, compared to 26.3 dB (SD 7.8) in the group with vein graft (mean difference -2.8 dB (95% CI: -3.6 to -2.0)).

Table 2 | Preoperative patient characteristics (without vein graft; first center versus with vein graft; second center).

Variable	Without vein graft (first center) (N=666)	With vein graft (second center) (N=1593)	Differences (95% CI)
Age, yrs (min-max)	41 (9-74)	46 (8-75)	4.8 (3.8 to 5.9)*
Sex, % female	63	66	3% (-5.0 to 11.0)
Mean BC, dB (SD)	22.5 (9.8)	24.4 (11.5)	1.9 (1.0 to 2.8)*
Mean AC, dB (SD)	51.6 (13.5)	50.7 (14.3)	-0.9 (-2.1 to 0.3)
Mean ABG, dB (SD)	29.1 (9.3)	26.3 (7.8)	-2.8 (-3.6 to -2.0)

SD: Standard deviation
BC: Bone-conduction
AC: Air-conduction
ABG: Air-bone gap
dB: Decibels (pure-tone average)
+: Higher value in the 'with vein graft group', compared to the 'without vein graft group'
-: Lower value in the 'with vein graft group', compared to the 'without vein graft group'
Means were calculated with 0.5, 1, 2, 4 kHz

*The confidence intervals for 'age' and 'mean BC' exclude zero (0): they indicate that 'age' and the 'mean preoperative BC' significantly differ between the two groups at the conventional 5% level

Postoperative audiometric assessment at 3 months follow-up; differences between patients without and patients with a vein graft

The postoperative four-frequency ABG was closed to 10 dB or less in 72.1% of the patients without a vein graft and in 93.2% of the patients with a vein graft. In figure 1, the preoperative four-frequency ABG (dB) is plotted against the postoperative gain in four-frequency ABG (dB). This figure clearly shows that in patients with a vein graft, a similar preoperative four-frequency ABG resulted in a better postoperative gain in four-frequency ABG as compared to those without a vein graft.

Postoperative gain in ABG and AC, adjusted for differences at baseline

The postoperative gain in ABG and AC, adjusted for differences at baseline, are summarized in table 3.

After adjustment for 'age at moment of surgery', 'sex', 'preoperative four-frequency ABG', 'preoperative four-frequency AC' and 'preoperative four-frequency BC', the mean four-frequency gain in ABG was 18.6 dB (95% CI: 18.1–19.1) in the group without vein graft, compared to 24.2 dB (95% CI: 23.9–24.6) in the group with vein graft (mean difference 5.6 dB, 95% CI: 5.0–6.2)

After adjustment for 'sex', 'preoperative four-frequency ABG' and 'preoperative four-frequency AC, the four-frequency gain in AC was 19.5 dB (95% CI: 18.7–20.3) in the group without vein graft, compared to 24.3 dB (95% CI: 23.7–24.7) in the group with vein graft (mean difference 4.8 dB, 95% CI: 3.8–5.7).

Table 3 | Estimated means, adjusted for confounders; postoperative gain in four-frequency ABG and AC.

	Without vein graft (first center) (N=666)	With vein graft (second center) (N=1593)	Differences (95% CI)
Postoperative gain in FF ABG (95% CI) in dB*	18.6 (18.1 – 19.1)	24.2 (23.9 – 24.6)	5.6 (5.0 – 6.2)
Postoperative gain in FF AC (95% CI) in dB**	19.5 (18.7 – 20.3)	24.3 (23.7 – 24.7)	4.8 (3.8 – 5.7)

ABG: Air-bone gap
AC: Air-conduction
CI: Confidence interval
dB: Decibels (pure-tone average)
FF: Four-frequency (0.5, 1, 2, 4 kHz)
The gain in AC exceeds the gain in ABG which is the result of an improved postoperative bone-conduction (overclosure)

*Adjusted for "age at moment of surgery", "sex", "preoperative mean BC", "preoperative mean AC" "preoperative mean ABG"
** Adjusted for "sex", "preoperative mean AC", "preoperative mean ABG"

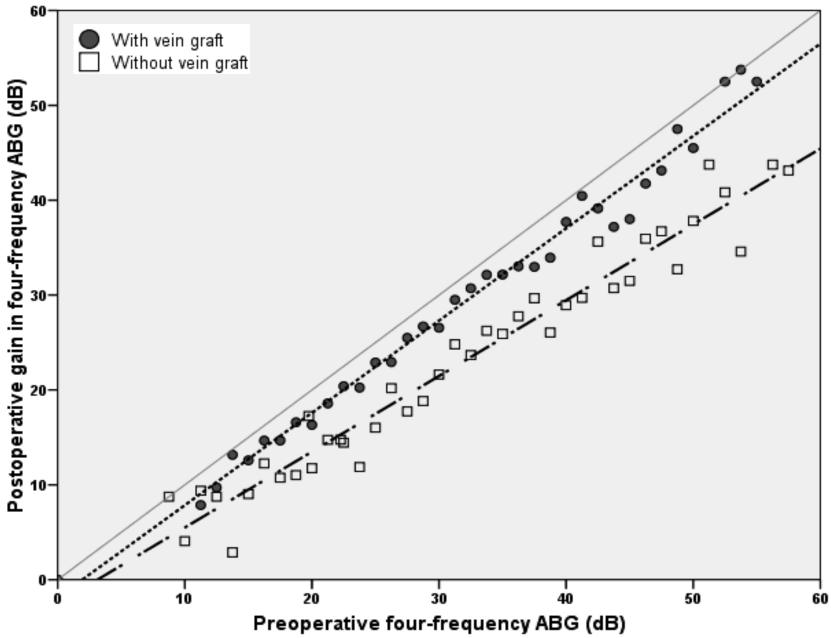

Figure 1 | Preoperative four-frequency ABG (dB) plotted against the postoperative gain in four-frequency ABG (dB).

Legend figure 1:

-Individual points represent mean postoperative gains in ABG which are linked to specific mean preoperative ABG's
-Diagonal solid line: Postoperative gain in four-frequency ABG is comparable to the preoperative four-frequency ABG
-Dotted line: (**.....**): Linear regression line; patients with a vein graft
-Dashed line: (**. _ .**): Linear regression line; patients without a vein graft
-ABG: Air-bone gap
-dB: Decibels (pure-tone average)
-Four-frequency: 0.5, 1, 2, 4 kHz
-Without vein graft: First center (the Netherlands)
-With vein graft: Second center (France)

DISCUSSION

Our results show that the postoperative four-frequency (0.5, 1, 2, 4 kHz) ABG was closed to 10 dB or less in 72.1% of the patients without a vein graft and in 93.2% of the patients with a vein graft. After adjustment for potential confounders, the postoperative gain in four-frequency (0.5, 1, 2, 4, kHz) ABG and AC were superior in patients with a vein graft compared with patients without a vein graft.

To our knowledge, we are the first comparing the results of a large number of stapes surgeries with and without a vein graft, using available statistical techniques to adjust for potential confounders.
Some possible limitations should also be discussed. First, factors like ‘surgeon’ and ‘piston type’ may interfere with the postoperative results. However, sensitivity analyses in which we studied homogenous groups, i.e. those operated by the same surgeon or those operated with the same piston type, showed similar results. Second, in the vein graft group, all patients were treated with the KTP-laser and Skeeter microdrill (8), whereas almost all patients in the without vein graft group, were treated with the micro-pick technique (16). Based on the literature (8,19,20), we believe that the positive results in those treated with a vein graft cannot completely be explained by these co-interventions. However, in theory the differences between the patients with vein graft and the patients without vein graft could be the result of the KTP-laser, the Skeeter microdrill or the micro-pick technique. Third, since all surgeons in our study were experienced, we do not believe that learning curves play a role. However, learning curves will influence the future applicability in clinical practice (21,22). Fourth, table 1 shows a large number of patients, who were not included in the final analysis. As has been shown by Eekhout et al. (23), when response percentages are not reported, this may hint to selectivity in reporting of outcome data and may give an untoward impression of the quality of any study. That is selectivity in reporting of outcome data and may seriously bias any study. Moreover, Eekhout et al. (23) showed that the non-selectivity of outcome data was seldom examined. Therefore, we compared baseline characteristics of patients that eventually were excluded from our data-analyses. This provides insight in the characteristics of the groups included and excluded from our analyses. When groups are similar, which is shown in table 1, this may rule out selective reporting of the outcome data. The absence of selectivity of reporting of outcome data supports the validity of our study results.
Our results show that patients with otosclerosis undergoing primary stapes surgery may benefit from a vein graft interposition. However, the causal inferences established in this nonrandomized study are judged weaker than those identified in a randomized controlled trial (RCT) (24). Furthermore, the effect of co-interventions could not be precluded in this nonrandomized study. We therefore believe that an RCT is necessary to establishing the safety and efficacy of the vein graft interposition (24).

CONCLUSION

Patients with otosclerosis undergoing primary stapes surgery may benefit more from a vein graft interposition.

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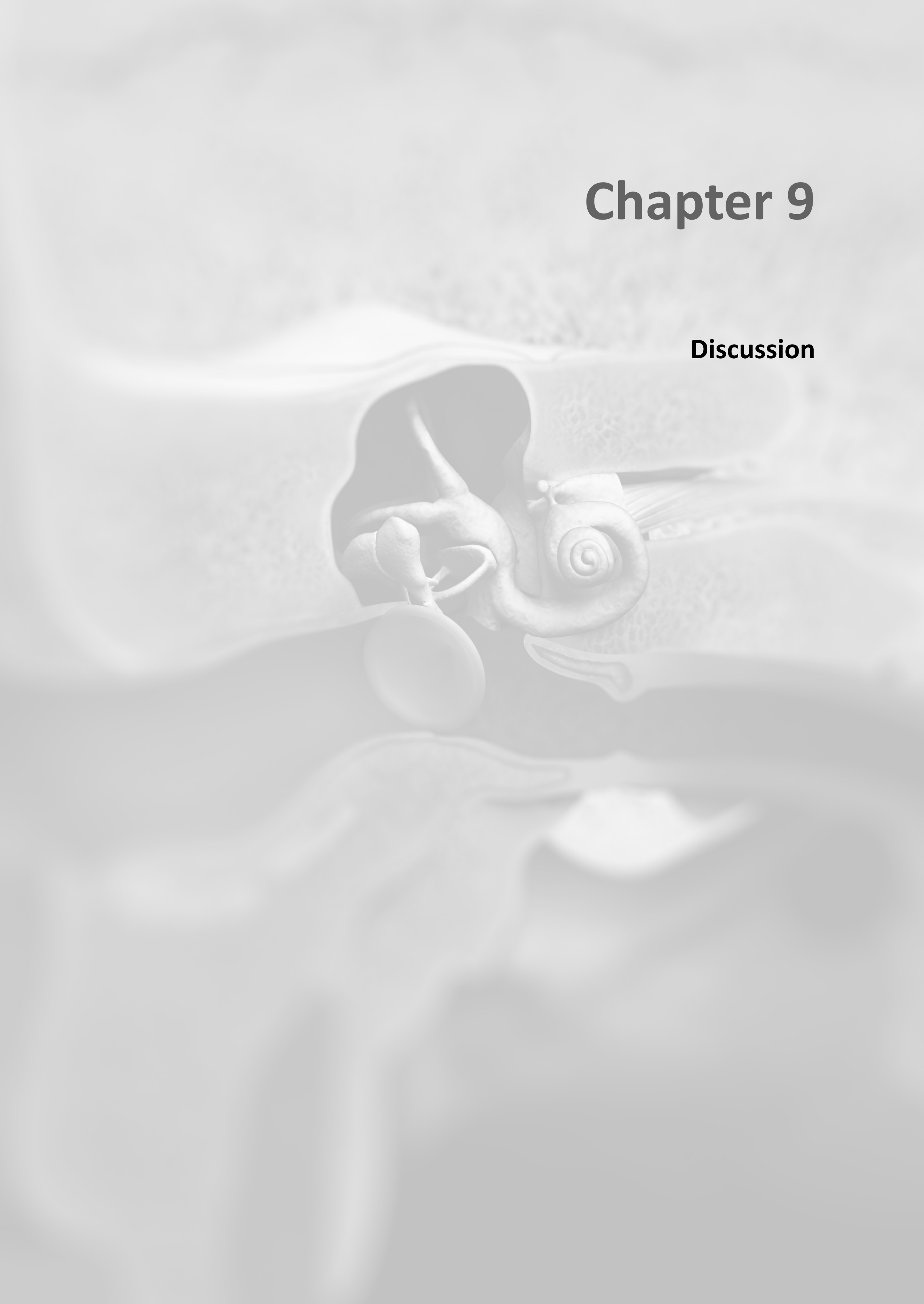
Chapter 9

Discussion



WHAT THIS THESIS CONTRIBUTES TO THE CURRENT KNOWLEDGE

In 2009, roughly 50.000 persons were suffering from otosclerosis in the Netherlands (chapter 6). While many patients with clinical otosclerosis will experience complaints such as hearing loss due to otosclerosis lesions, otosclerosis lesions without symptoms could be present and are often incorrectly labeled as histological otosclerosis, since all of these patients have histological otosclerosis (1). For such latter cases it is better to label them as subclinical otosclerosis. Subclinical otosclerosis is about 10 times more common than clinical otosclerosis (1). In 2009, approximately 5.000 persons had otosclerosis-related complaints, which is conductive hearing loss in most cases (chapter 6). For most patients with clinical otosclerosis, surgery is a good treatment option. It is important to realize that otosclerosis surgery is an elective treatment option carrying the risk of postoperative failures such as persistent conductive hearing loss, sudden sensorineural hearing loss, extrusion of the implanted prosthesis and complaints of vertigo (2). Without surgery, the otosclerosis patient will not be exposed to these potential complications and hearing could be improved with a conventional hearing aid. Besides the potential surgical complications, variation in postoperative hearing outcomes is a problem (3). As discussed in the introduction of this thesis, surgical treatment of otosclerosis entails different critical steps. The fenestration in the footplate could be made with a drill, a micro instrument or the laser. Literature suggests a potential increased risk of sensorineural hearing loss when using a drill or micro instrument, compared to a laser (4). However, the evidence remains rather weak and the authors suggest that the surgeon should use the technique he or she is most comfortable with (4). When looking at the application of the laser we could expect variation between different laser types. As presented in chapter 7, the application of the CO2 laser seems to result in better postoperative hearing outcomes (in terms of the postoperative air-bone gap), compared to the application of the potassium titanyl phosphate laser (abbreviation is KTP; kalium titanyl phosphate). When the fenestration is performed, the surgeon will position a prosthesis between the incus and the fenestration. As presented in chapter 6, the baseline characteristics of our study sample showed that 5 different prosthesis types were used. Following chapter 8, the fenestration could be covered with a vein graft before inserting the prosthesis, which also will influence postoperative hearing. Due to the aforementioned differences, variation in the balance between harm and benefits could be expected and it is unlikely that every otosclerosis patient will receive the best treatment available.

In most cases, the surgical procedure will be based on personal and local preferences within a clinic. Ultimately the stapes surgeon should aim for an optimal treatment procedure, preferably including a personalized approach. Although we realize that it will take a lot of time and effort to achieve a standardized 'best practice', this thesis provides a start.

A guideline instruction manual and the evidence-based case reports helped to identify and rate available evidence and to answer important clinical questions. Our preoperative prognostic model showed that it is possible to achieve a more personalized approach during preoperative counseling and it helps with patient selection. The clinical studies provided an answer on important clinical questions, which will help to identify the favorable critical steps during the surgical procedure.

AN EVIDENCE-BASED APPROACH IN OTOSCLEROSIS TREATMENT: CREATING GUIDELINES

As discussed in chapter 2, the amount of new literature is enormous and has increased at a staggering pace over the last decades. In the Ear, Nose and Throat field, the number of publications has increased from around 1,000 publications per decade before 1950 to about 90,000 in the last decade, equaling one publication every hour (5). It is impossible to keep up with this overload of information. However, without a solid overview of available publications the stapes surgeon will work according to his/her own experience, examples from direct colleagues and perhaps information from experts. It is generally recognized that the stapes surgeon will face a learning curve when starting with stapes surgery. It will take around 60 to 80 procedures to achieve steady postoperative results and to smooth down the learning curve (6).

Figure 1A illustrates a hypothetical learning curve. After a certain case load the optimal point of the learning curve will be reached. It will thereafter be difficult to detect improvements in the postoperative performance for individual cases. Each surgeon will achieve an individual maximum performance level, resulting in an asymptotic diagram. It is unlikely that the surgeon will reach a performance level without room for improvement. Furthermore, it also is a matter of practice. A period of time without surgeries could result in a decreased performance level (figure 1B). In case of a new innovation within the field or new evidence, the surgeon could change the surgical technique with a partially new learning curve as a result (figure 1B). It could, however, be slightly uncomfortable to abandon a specific surgical procedure that has been routine practice for some time. To maintain quality and to keep up with competence, one is expected to leave routine in certain situations, which are not rare.

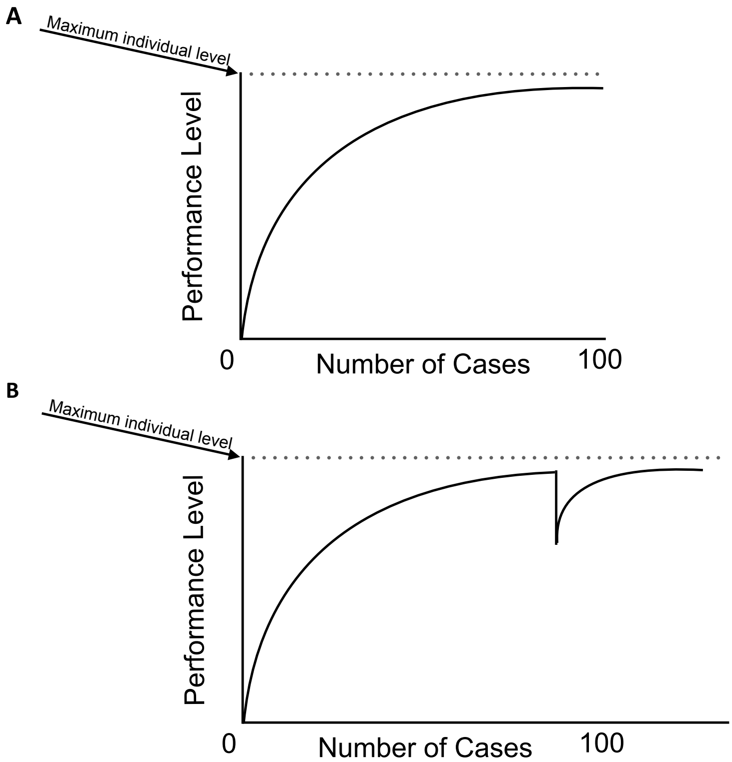


Figure 1A: Learning curve; an individual maximum performance level will be reached.
Figure 1B: Slightly decreased performance level with a partially new learning curve due to a period without surgeries or a new surgical technique.

Ultimately, a socially acceptable performance level should be determined. In the Netherlands, health insurers are increasingly focusing on the so-called ‘capacity norm’. This means that a certain hospital should treat a minimal number of patients with a specific disease, such as breast cancer, to become a contracting party (7) . Although, there is no ‘capacity norm’ for stapes surgery at the moment, this could be expected in the near future. Currently we do not know the minimal number of patients, which should be treated each year to maintain a medically acceptable performance level for this procedure. Also the exact determination of such a performance level is currently not available.
Guidelines can play an essential role within the quality improvement and maintenance process. Within the otosclerosis field, guidelines aim to overcome the lack of a general consensus among otologists and to ensure that patients with otosclerosis will not be treated according to a variety of opinions depending on the clinic they attend. It helps with evidence-informed best practice and provides an indication for the strength of evidence for or against specific practice and it should stop unnecessary and potential unwanted (harmful)

treatments. Development of guidelines is thereby expected, on the one hand to improve the quality of patient care and on the other hand to help identify targets for further research. Ultimately, we should aim for the highest benefit/harm ratio. Problem-based systematic filtering of relevant information from research will help the clinician to find and apply the best available and latest evidence efficiently and quickly. A guideline should be designed by a multidisciplinary group involving a range of generalist and specialist clinicians, supporting staff, experts in methodology and patients. This will improve the quality and continuity of care and make it more likely that the guidelines will be adopted in daily practice by the masses.

THE 'EUROPEAN ACADEMY OF OTOLOGY & NEURO-OTOLOGY' (EAONO)

In September 2012, the 'European Academy of Otology & Neuro-Otology' EAONO organized a meeting in Siena (Italy) with the aim to discuss and establish guidelines concerning different otologic pathologies, including otosclerosis. Experts from different European countries discussed relevant clinical questions concerning otosclerosis-related problems. Weeks before the meeting started, they were asked to complete an online questionnaire and provide clinical questions, which should be answered in the guideline. They were free to formulate and to prioritize questions regarding diagnosis, treatment, treatment outcomes, cost-effectiveness and failure and complications or harm of treatments. The clinical questions in chapter 3 and 4 are two examples, which resulted from this meeting. Chapter 3 is illustrative because we did not find evidence against surgery under local anesthesia, but this conclusion resulted in an overheated discussion in Siena between the experts. We hypothesized that patients undergoing stapes surgery under general anesthesia potentially would be exposed to overtreatment because of additional general anesthesia. Furthermore, general anesthesia could generate additional treatment costs and increased procedural time needed. Still, the evidence supporting surgery under local anesthesia is weak and not every surgeon will be able or willing to change from general to local surgery due to local and personal habits and experience. It turned out that local routine, organization and tradition could function as a barrier for implementing a new treatment strategy based on available evidence. Due to the fact that the supporting evidence is weak, a (randomized) trial should be initiated. When such a trial confirms the advantage of local anesthesia, the guideline should advise to change from general into local anesthesia during stapes surgery.

GENETICS AND OTOSCLEROSIS

When looking at the causation of otosclerosis it remains difficult to pinpoint the exact mechanism of disease. Hearing loss can be treated with surgery. As indicated before, surgery restores the conductive qualities of the middle ear resulting in improved hearing. Stapes surgery is not always a solution for the rest of the patient's life due to disease progression or complications, such as a dislocated prosthesis or erosion of the incus (2,8). Different patients will need revision surgery or will be fitted with an additional hearing aid. It is common knowledge that different risk factors influence the disease mechanism (1). Identification of risk factors is necessary when aiming at influencing the disease mechanism in order to prevent the disease from developing. In an attempt to find out the actual cause of otosclerosis, a lot of researchers tried to discover environmental and genetic factors influencing the disease. Measles virus infection, hormonal and endocrine factors in pregnant women and fluoridation of drinking water are suggested as environmental factors influencing the incidence of otosclerosis (9). When looking at the postulated genetic causes, a wide variety of different genes have been reported that are of potential influence (9). But the main problem is a lack of coherence and reproducibility of the genetic evidence. In chapter 5 we assessed the quality and outcomes of the available genetic etiologic research publications. After rating the available genetic literature we were not able to find consistent evidence supporting a uniform genetic effect. This is interesting due to the extensive amount of literature suggesting a genetic etiology (9). In order to improve the quality of genetic otosclerosis research, future publications are advised to follow strict guidelines such as the STREGA (Strenghtening the Reporting of Genetic Association Studies) guidelines (10). It is interesting to note that Strega means 'witch' in Italian. The STREGA method facilitates uniformity among the genetic literature improving the possibility to compare and pool genetic evidence and to find out if results are reproducible.

In chapter 6 we showed that it is possible to generate a predictive model within the otosclerosis field. Perhaps a genetic factor may add to the accuracy of the prediction. Based on our systematic evaluation of the available evidence, we were not able to do so due to the lack of consistent evidence. In our opinion, genetic otosclerosis research is unlikely to have a clinical relevance in the near future.

PROGNOSIS AND CHANGING THE SURGICAL TECHNIQUE

One of the crucial challenges for the otologist is patient selection. He needs to discriminate which patient will benefit most from a surgical intervention and which patient would more likely not benefit from surgery. Predicting postoperative outcome is a difficult area for study. In chapter 6 we were the first to present a prognostic model from which individual absolute risks can be derived for future patients. Based on these results, the otologist in our clinic has the possibility to select future patients during preoperative counseling more accurately and is able to estimate the amount of postoperative return in hearing for the individual patient. 'Age at surgery', 'preoperative mean air-conduction thresholds' and 'preoperative mean air-bone gap' were identified as independent prognostic predictors. Future work should focus on combining the results of different surgeons in order to create a general model useful within different clinics.

Personalized care starts with the derivation of a prognostic model. It is important to note that surgical performance and outcomes do not always correspond with patient satisfaction. Surgeons mainly look at the postoperative mean air-bone gap and name the surgery a success when the air-bone gap is closed to 10 dB or less. But the postoperative air-bone gap may not be relevant at all for a patient. According to Tan et al., audiometric improvement after stapes surgery is not always related to the quality of perceived sound and patients could experience problems with sound quality despite a good postoperative audiogram (11). We therefore advise to look at different outcome measurements, such as the postoperative air-conduction, which we also included in our prognostic model (chapter 6). Unfortunately, we were not able to include quality of life outcomes due to the fact that the prospectively collected data did not include such measurements. Ultimately, we feel that patient satisfaction is a very important outcome measurement for stapes surgery and we are confident that its importance will increase in the near future.

After the patient has been selected and both the patient and the surgeon have agreed to undergo/perform the stapes surgery, it is important to use the most favorable surgical technique. As discussed before, postoperative results differ between clinics. Chapter 7 and 8 were designed to improve postoperative results. These publications were the result of our extensive collaboration with the Jean Causse Ear Clinic in Béziers, France. The surgeon at this institution, Robert Vincent, demonstrates that he is able to achieve superior postoperative hearing results after stapes surgery defining the world standard in hearing outcome (3). Compared to our clinic in Utrecht, he performs the surgery with some modifications. First, he uses a CO_2 laser instead of the KTP laser. Second, he uses a vein graft to cover the fenestration before inserting the prosthesis. We have assessed these differences as major and very important for future stapes surgery and therefore initiated two nonrandomized clinical evaluations.

Following chapter 7, it is plausible that the application of the CO2 laser is associated with improved postoperative results, compared to the application of the KTP laser. We believe that combining the CO2 laser with a vein graft during surgery (chapter 8) has the potential to result in better postoperative hearing compared to stapes surgery using the KTP laser without the vein graft.
Although the change of the laser type and the application of a vein graft are minor alterations within a well-established surgical procedure, chapter 7 and 8 clearly show that it is possible to improve postoperative outcome after stapes surgery.

WHAT DO WE EXPECT FOR THE FUTURE

Implementing guidelines in the clinical field will help to reduce unwanted variation. Treatment based on local and personal habits and experience alone will not be accepted anymore in the near future. We need to be aware of information from research about the balance between benefits, harm and costs. Although experience of experts remains highly important, experts should communicate with each other and arrive at consensus on the best treatment approach based on their collective knowledge and available evidence. Then they also should align their local habits and routines to best practice. Guidelines are a way to reach this goal. In addition, policymakers are aware of the need for guidelines due to performance requirements and the incorporation of costs. The present thesis does not include evaluation of cost-effectiveness, however this should not be ignored in future policy. In Utrecht, each medical student has to follow an entire curriculum about evidence-based medicine in which they learn how to incorporate it during daily clinical practice. This will result in a change of mindset among the future generation of physicians toward evidence informed decision-making and personalized care.
Finally, a guideline program will only succeed with a programmed approach and substantial funding.

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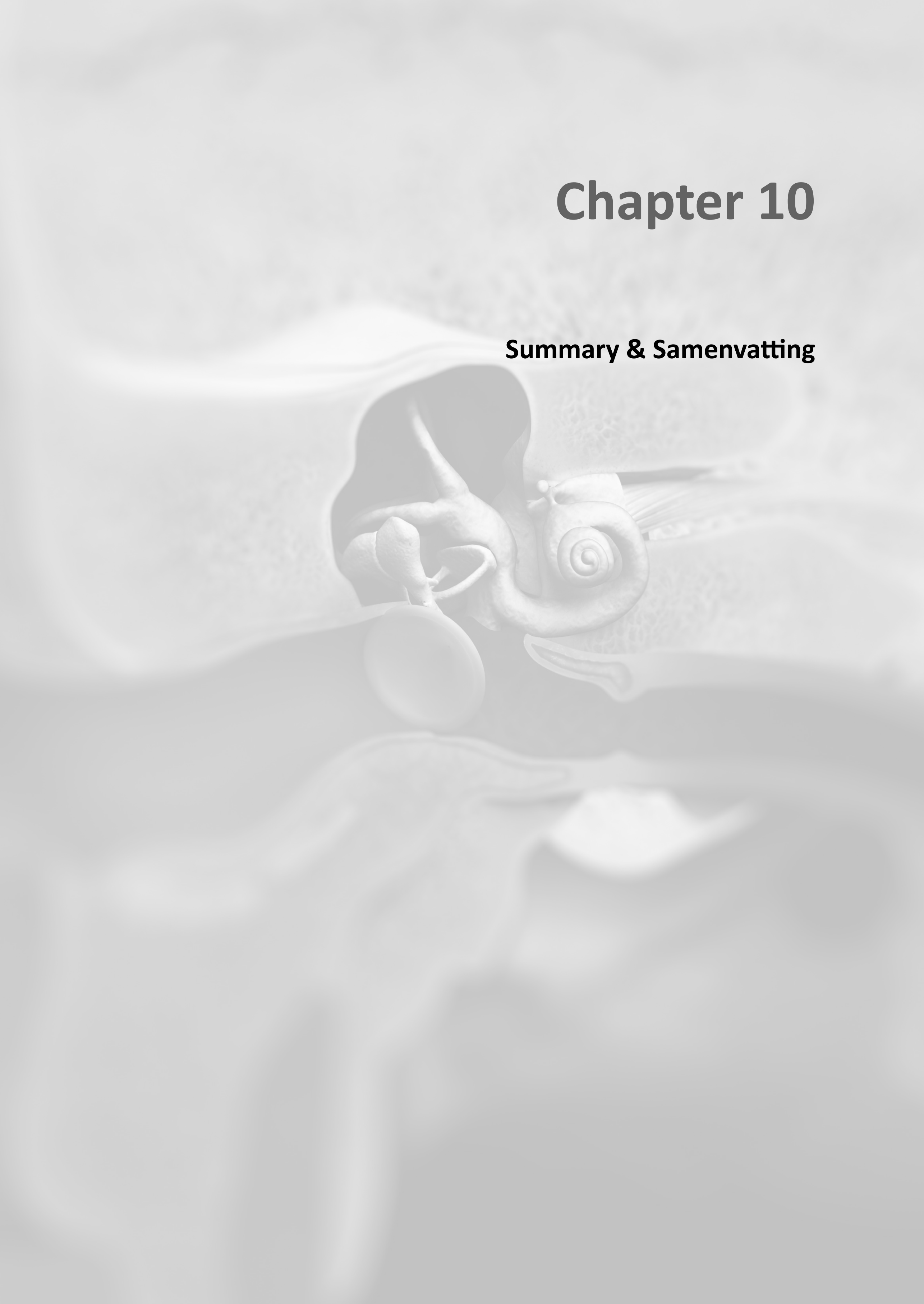
Chapter 10

Summary & Samenvatting



SUMMARY

In **Chapter 1**, a general introduction and the aim and outline of this thesis are presented. In this chapter we introduce the main problem with regard to the surgical treatment of patients with otosclerosis: due to differences in surgical techniques it is questionable if each individual patient will receive the best surgical treatment. We aim to provide an answer on how to reduce this unwanted variety and how to achieve the most optimal balance between harm and benefits.

Chapter 2 is the first step in reducing the unwanted variety. It helps the otologist with an insight in the standardized method used to design clinical practice guidelines. A step-by-step guideline development instruction manual is provided. The first start is to design an entry question including a clinical question regarding the treatment, prognosis or diagnosis of the disease. Following this question a systematic search with selecting and rating the quality of available literature will reveal useful evidence supporting an answer to the question. After this step, the selected evidence must be translated into a recommendation for clinical practice. To translate the evidence-based answer to the entry question into actionable recommendations for patient care, experts need to achieve consensus.

Chapter 3 provides an evidence-based case report answering if patients who undergo stapes surgery should be treated under local or general anesthesia. We did not find evidence against surgery under local anesthesia but the supporting evidence is weak and not every surgeon will be able or willing to change from general to local surgery due to local and personal habits and experience. Due to the fact that the supporting evidence is weak, a (randomized) trial should be initiated.

Chapter 4 provides an evidence-based case report estimating the diagnostic value of an audiogram in patients with otosclerosis. The most striking characteristic on such an audiogram is the so-called 'Carhart notch', which is generally considered a useful finding in diagnosing otosclerosis. We showed that evidence supporting such belief is lacking. Although a 33% increase to 41% in the presence of a Carhart notch on pure-tone audiometry increases diagnostic certainty for ruling in otosclerosis may appear as a considerable additional value, it should be noted that these data come from a population with a low prevalence in a study that carries a high risk of bias.

Chapter 5 reviewed a potential genetic cause, in order to pinpoint the exact disease mechanism of otosclerosis. We found scattered evidence of limited quality and a lack of replication studies supporting a genetic influence. We were not able to point out one or more responsible genes, which play a key role within the genetic pathophysiologic mechanism of otosclerosis. To our opinion genetic otosclerosis research is unlikely to have a clinical relevance in the near future.

In **Chapter 6** we took the initiative with a more personalized approach in patients with otosclerosis. It turned out to be possible to generate a predictive model from which individual absolute risks can be derived for future patients. 'Age at surgery', 'preoperative air-conduction' and 'preoperative air-bone gap' were independent prognostic determinants. For example, a patient over 40 years with a preoperative mean air-bone gap of 30 dB or less has a chance of 78% to achieve a postoperative mean air-bone gap of 10 dB or less. A patient with a mean air-conduction exceeding 50 dB and a mean air-bone gap exceeding 30 dB has a chance of 86% to achieve a postoperative gain in air- conduction exceeding 20 dB. The otologist within our institution could use this information to inform patients more explicitly about the expected postoperative hearing results.

In **Chapter 7** we compared two different lasers, which are frequently used within stapes surgery; the potassium titanyl phosphate (KTP) laser and the CO2 laser. The chance to achieve a postoperative air-bone gap of 10 dB or less for male patients is 95%, when treated with CO2 laser and 85% when treated with KTP laser. For female patients these chances are 97% and 94% respectively. Sensorineural hearing loss was reported by one patient with KTP laser (0.3%) and by none with CO2 laser. The use of the CO2 laser may be associated with better hearing results than the KTP laser, regarding the postoperative air-bone gap closure within 10 dB.

In **Chapter 8** we compared stapes surgery with and without a vein graft. The postoperative air-bone gap was 10 dB or less in 72.1% of the patients without a vein graft and in 93.2% of patients with a vein graft. After adjustments for differences at baseline, the mean gain in air-bone gap was 18.6 dB in the group without a vein graft compared to 24.2 dB in the group with a vein graft (mean difference 5.6 dB). The mean gain in air-conduction was 19.5 dB in the group without vein graft, compared to 24.3 dB in the group with vein graft (mean difference 4.8 dB). Patients with otosclerosis undergoing stapes surgery may benefit more from a vein graft interposition.

Chapter 9 provides a general discussion. We emphasize that implementing guidelines in the otosclerosis field will help to reduce unwarranted variation. It is unlikely that every otosclerosis patient will receive the best treatment available. We expect that treatment based on local and personal habits and experience alone will not be accepted anymore in the near future. Ultimately, a socially acceptable performance level should be determined.

From this perspective we summarize the findings from the thesis chapters and conclude that we were able to add usable new information to the otosclerosis field. We took the initiative to aim for a more standardized treatment approach with a step-by-step guideline instruction manual (**chapter 2**). This will help the clinician to manage and rate large amounts of literature and to answer clinical questions. Following this, we showed that stapes surgery under local anesthesia could be a reasonable option compared to stapes surgery under general anesthesia (**chapter 3).** However, due to weak evidence, this subject (local/general anesthesia) could be considered as an evidence gap and a randomized controlled trial should be initiated. When looking at the diagnostic course of patients with conductive hearing loss, the diagnostic value of an audiogram, with or without a Carhart notch, is limited for ruling in or ruling out otosclerosis (**chapter 4**). The presence of a Carhart notch is not a solid diagnostic tool for ruling in otosclerosis but the diagnostic certainty will improve. In **chapter 5**, we evaluated and rated the available genetic literature concerning otosclerosis and we were not able to find consistent evidence supporting a uniform genetic effect. To our opinion genetic otosclerosis research is unlikely to have a clinical relevance in the near future. Especially chapter 6, 7 and 8 will help to improve future otosclerosis guidelines. In **chapter 6** we showed that it is possible to generate a predictive model within the otosclerosis field. 'Age at surgery', 'preoperative mean air-conduction thresholds' and 'preoperative mean air-bone gap' were identified as independent prognostic predictors. Such a prognostic model will help to aim for personalized care. In **chapter 7** the KTP laser and the CO2 laser were compared. It seemed plausible that the application of the CO2 laser could be associated with improved postoperative results, compared to the application of the KTP laser. In **chapter 8** the effect of a vein graft was evaluated and revealed that patients with otosclerosis undergoing stapes surgery may benefit more from a vein graft interposition.
Although it will take a lot of time to achieve a standardized approach of patients with otosclerosis, this process could not be ignored during the coming years and the aforementioned information will help to achieve standardization.

SAMENVATTING

Hoofdstuk 1 geeft een algemene inleiding waarin het doel en de inhoud van dit proefschrift worden beschreven. In dit hoofdstuk introduceren we het belangrijkste probleem rondom de chirurgische behandeling van patiënten met otosclerose: door verschillen in chirurgische technieken is het de vraag of elke individuele patiënt de best beschikbare chirurgische behandeling krijgt. Wij streven ernaar om een antwoord te geven op de vraag hoe deze ongewenste variatie te verminderen en uiteindelijk de meest optimale balans te bereiken tussen voor- en nadelen voor de patiënt.

Hoofdstuk 2 is de eerste stap in het verminderen van de ongewenste variatie. Het helpt de otoloog door een inzicht te geven in een gestandaardiseerde methode om klinische richtlijnen te ontwerpen. Dit wordt beschreven door middel van een handleiding. Dit proces start met de ontwikkeling van een vraag omtrent de behandeling, prognose of diagnose van de betreffende ziekte. Naar aanleiding van deze vraag wordt, door middel van een systematische zoekstrategie, de beschikbare literatuur geselecteerd en beoordeeld op kwaliteit zodat uiteindelijk de bruikbare literatuur overblijft. Na deze stap moet de inhoud van de geselecteerde literatuur omgezet worden in een antwoord op de eerder vastgestelde vraag en dient een aanbeveling voor de praktijk gegeven te worden. Deze 'evidence-based' aanbeveling zal uiteindelijk een combinatie zijn van de literatuur en een consensus tussen deskundigen.

Hoofdstuk 3 presenteert een 'evidence-based' case report welke ingaat op de vraag of patiënten die een stapes operatie ondergaan behandeld moeten worden onder lokale of algehele anesthesie. Wij vonden geen bewijs tegen chirurgische behandeling onder lokale anesthesie. Echter, de ondersteunende literatuur is kwalitatief van beperkte waarde en niet elke chirurg zal in staat of bereid zijn te veranderen van algehele naar lokale anesthesie in verband met lokale en persoonlijke gewoonten en ervaring. Vanwege het feit dat de ondersteunde literatuur zwak is, zal een gerandomiseerde studie opgezet moeten worden.

Hoofdstuk 4 presenteert een 'evidence-based' case report welke ingaat op de vraag wat de diagnostische waarde is van een audiogram bij patiënten met otosclerose. Het meest karakteristieke element op een dergelijk audiogram is de zogenaamde 'Carhart notch', welke wordt beschouwd als een bruikbaar kenmerk tijdens het diagnostisch proces van otosclerose. Wij toonden aan dat literatuur die deze aanname ondersteunt beperkt is. Hoewel een stijging van 33% tot 41% in de aanwezigheid van een 'Carhart notch' de kans op de aanwezigheid van otosclerose doet toenemen, is het belangrijk om te realiseren dat deze uitspraak is gebaseerd op een studie met een lage prevalentie binnen de populatie een hoog risico op bias.

Hoofdstuk 5 gaat in op een mogelijke genetische oorzaak met als doel het exacte mechanisme van de ziekte 'otosclerose' duidelijk te krijgen. Wij vonden wisselend bewijs van beperkte kwaliteit en waren niet in staat om één of meerdere verantwoordelijke genen te identificeren welke een sleutelrol spelen binnen het ontstaan van otosclerose. Naar onze mening is het onwaarschijnlijk dat genetisch otosclerose onderzoek klinische relevantie zal hebben in de nabije toekomst.

In **hoofdstuk 6** nemen wij het initiatief met een meer gepersonaliseerde aanpak van patiënten met otosclerose. Het bleek mogelijk om een voorspellend model, met berekening van absolute risico's, te genereren voor toekomstige patiënten met otosclerose. 'Leeftijd op het moment van de operatie', 'preoperatieve luchtgeleiding' en het 'preoperatieve verschil tussen lucht- en beengeleiding' waren onafhankelijke prognostische determinanten. Een patiënt ouder dan 40 jaar met een preoperatief gemiddeld verschil tussen lucht- en beengeleiding gelijk aan of meer dan 30 dB heeft een kans van 78% om postoperatief een verschil tussen lucht- en beengeleiding ≤10 dB te bereiken. Een patiënt met een gemiddelde luchtgeleiding van meer dan 50 dB en een gemiddeld verschil tussen lucht- en beengeleiding van meer dan 30 dB heeft een kans van 86% om postoperatief een verbetering van de luchtgeleiding van meer dan 20 dB te bereiken. De otoloog binnen onze instelling kan deze informatie gebruiken om patiënten preoperatief beter te informeren over de te verwachten postoperatieve uitkomst van het gehoor.

Hoofdstuk 7 vergelijkt twee verschillende lasers die vaak worden gebruikt tijdens stapes chirurgie; de kalium titanyl fosfaat (KTP) laser en de CO2 laser. De kans om bij mannen een postoperatief verschil tussen lucht- en beengeleiding gelijk aan of minder dan 10 dB te bereiken is 95% in geval van de CO2 laser en 85% in geval van de KTP laser. Voor vrouwen zijn deze kansen respectievelijk 97% en 94%. Perceptief gehoorverlies ontstond bij één patiënt die met de KTP laser werd behandeld (0,3%) en niet bij patiënten die met de CO2 laser werden behandeld. Het gebruik van de CO2 laser kan worden geassocieerd met betere gehoorresultaten in vergelijking met de KTP laser, wanneer we kijken naar de het postoperatieve verschil tussen de lucht- en beengeleiding binnen de 10 dB.

Hoofdstuk 8 vergelijkt stapes chirurgie met en zonder een zogenaamde 'vein graft' (stukje van een veneus bloedvat). Het postoperatieve verschil tussen de lucht- en beengeleiding was gelijk aan of minder dan 10 dB in 72,1% van de patiënten behandelde zonder de 'vein graft' en in 93,2% van de patiënten behandeld met een 'vein graft'. Gecorrigeerd voor verschillen bij aanvang van de studie was de gemiddelde winst in reductie van het verschil tussen de lucht- en beengeleiding 18,6 dB in de groep zonder de 'vein graft' en 24,2 dB in de groep met de vein graft (gemiddeld verschil 5,6 dB). De gemiddelde verbetering in luchtgeleiding bedroeg 19,5 dB in de groep zonder de 'vein graft' en 24,3 dB in de groep met de 'vein graft' (gemiddeld verschil 4.8 dB). Patiënten met otosclerose die behandeld worden door middel van een stapes operatie zouden kunnen profiteren van het gebruik van een 'vein graft'.

Hoofdstuk 9 geeft een algemene discussie. Wij benadrukken dat invoering van richtlijnen omtrent otosclerose helpt om onwenselijke variatie te doen afnemen. Het is onwaarschijnlijk dat elke otosclerosepatiënt de best beschikbare behandeling krijgt. We verwachten dat de behandeling op basis van lokale en persoonlijke gewoonten en ervaring in de nabije toekomst niet meer geaccepteerd zal worden. Uiteindelijk dient een sociaal aanvaard prestatieniveau bepaald te worden.

Vanuit dit perspectief vatten we de bevindingen uit het proefschrift samen en concluderen we dat we in staat zijn geweest om bruikbare nieuwe informatie toe te voegen aan het thema otosclerose. We hebben het initiatief genomen om te streven naar een meer gestandaardiseerde benadering met een richtlijn handleiding (**hoofdstuk 2**). Deze handleiding helpt de arts om grote hoeveelheden literatuur te beheren en te beoordelen en klinische vragen te beantwoorden. Hierop volgend hebben we aangetoond dat stapes chirurgie onder lokale anesthesie een reële optie is (**hoofdstuk 3**). Echter, door het zwakke bewijs is dit onderwerp (lokale/algehele anesthesie) nog niet volledig uitgewerkt en dient een gerandomiseerde studie te volgen. Wanneer we kijken naar het diagnostische traject van patiënten met geleidingsslechthorendheid is de diagnostische waarde van een audiogram, met of zonder een Carhart notch, beperkt voor het aantonen dan wel uitsluiten van otosclerose (**hoofdstuk 4**). De aanwezigheid van een Carhart notch is geen solide diagnostisch middel voor het aantonen van otosclerose maar de waarschijnlijkheid dat er sprake is van otosclerose neemt toe. In **hoofdstuk 5** hebben we de beschikbare genetische literatuur over otosclerose geëvalueerd en beoordeeld. We waren niet in staat om consistent genetisch bewijs aan te tonen welke een uniform genetisch effect op otosclerose ondersteund. Naar onze mening is het onwaarschijnlijk dat genetisch otosclerose onderzoek klinische relevantie zal hebben in de nabije toekomst.
Vooral hoofdstuk 6, 7 en 8 helpt om toekomstige otosclerose richtlijnen te verbeteren. In **hoofdstuk 6** hebben we aangetoond dat het mogelijk is om een voorspellend model voor de patiënt met otosclerose te ontwikkelen. 'Leeftijd op het moment van de operatie', 'preoperatieve luchtgeleiding' en het 'preoperatieve verschil tussen lucht- en beengeleiding'

waren onafhankelijke prognostische determinanten. Een dergelijk prognostisch model helpt om te streven naar een persoonlijke behandeling van de patiënt met otosclerose. In **hoofdstuk 7** werd de KTP laser vergeleken met de CO2 laser. Het lijkt erop dat het gebruik van de CO2 laser geassocieerd kan worden met verbetering van de postoperatieve resultaten, in vergelijking met gebruik van de KTP laser. In **hoofdstuk 8** wordt het effect van een 'vein graft' geëvalueerd en lijkt het erop dat patiënten met otosclerose, die behandeld worden door middel van stapes chirurgie, baat kunnen hebben bij het gebruik van een 'vein graft'.

Hoewel het een tijd zal duren om een gestandaardiseerde benadering van patiënten met otosclerose te bereiken, kan dit proces niet meer genegeerd worden tijdens de komende jaren. De eerder genoemde informatie zal helpen deze standaardisering te bereiken.

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Curriculum Vitae

List of publications

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CURRICULUM VITAE

Arnold Joost Nicolaas Bittermann was born on 27 February 1985 in Giessenburg, the Netherlands. He graduated from the Merewade College in Gorinchem, the Netherlands were he completed the pre-university education program (VWO). From 2003 until 2009 he studied medicine at Maastricht University, the Netherlands. He completed his internship on ear, nose and throat (ENT) surgery at University Hospital Aachen, Germany. During the last year of Medical School he completed an optional scientific and practical internship on ENT surgery at Maastricht University under supervision of Prof. dr. R.J. Stokroos. During his medical school he was a member of the fraternity Circumflex and debating society Mezekouw, both located in Maastricht, the Netherlands.

After graduating from medical school in 2009, he started the Ph.D. research that led to this thesis under the supervision of Prof. dr. W. Grolman, Prof. dr. M.M. Rovers and later on Prof. dr. G.J.M.G. van der Heijden. The Ph.D. research took place at the ENT department at University Medical Center Utrecht, the Netherlands. During this period, apart from the introduction and discussion, all chapters of this thesis have been published in international peer-reviewed journals and several chapters have been presented at national and international conferences. Parallel to his Ph.D. research, he became a resident at the ENT department of the University Medical Center Utrecht in February 2009 (supervisor: Prof. dr. W. Grolman). During his residency he also worked at the St. Antonius Hospital, Nieuwegein (supervisor: dr. M. Copper), Gelre Hospital, Apeldoorn (supervisor: dr. P.P.G. van Benthem) and Gelderse Vallei hospital, Ede (supervisor: M.H.J.M. Majoor).

In his free time he likes to play the clarinet, to sail in the summer and to ski in the winter.

LIST OF PUBLICATIONS

1. *A Nonrandomized Comparison of the Thulium Laser and the CO2 laser in Primary Stapedotomy for Otosclerosis*
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