

# The Development of Active Middle Ear Implants: A Historical Perspective and Clinical Outcomes

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**Objective (s):** Energy emitting, active middle ear implants (aMEI) have taken more than two decades of research to reach technological sophistication, medical safety, and regulatory approval to become a powerful tool in treating sensorineural, conductive, and mixed hearing loss. The present review covers this era.

**Data Source:** Literature found from searching Pubmed (MEDLINE); EMBASE, SciSearch, German Medical Science Journals and Meetings, and The Cochrane Library; and published as of February 2017. Study bibliographies were hand-searched to find further materials.

**Methods:** A systematic literature review was conducted to identify studies evaluating the safety, efficacy, effectiveness, and subjective outcomes of partially implantable aMEIs. Data were extracted on systems with regulatory approval and summarized narratively. Meta-analyses were conducted for aMEIs with more than 25 publications. Study selection, data extraction, and quality appraisal for quantitative data synthesis was carried out by two reviewers.

**Results:** Four hundred thirty-one studies included in narrative synthesis describe that albeit good audiological outcomes, clinical safety and (dis)investment are major barriers to continued market access. The synthesised risk of adverse events was three fold with the MET than with the VIBRANT SOUNDBRIDGE. With the latter system, audiological outcomes were stable and similar for all indications and age groups.

**Conclusion:** To date, the majority of the literature covers the clinical application of the VIBRANT SOUNDBRIDGE system as it is applicable to a wide range of otologic and audiological conditions, particularly with the introduction of couplers to extend its clinical reach. The MAXUM and MET still have to find their way into surgical routine.

**Key Words:** Active middle ear implants, vibrant soundbridge, hearing loss.

**Level of Evidence:**

## INTRODUCTION

The history of active middle ear implants (aMEI) dates back to the 1950s when the idea of additional acoustic amplification instead of replacement of lost middle ear transduction was born. Research was motivated to overcome the unpleasant side-effects of hearing aids, eg, poor sound quality, canal occlusion, and feedback.<sup>1-3</sup>

As early as 1935, Wilska<sup>4</sup> performed experiments using iron particles on the tympanic membrane which were stimulated by an electromagnetic coil. More advanced, Rutschmann<sup>5</sup> glued magnets onto the umbo to

amplify the physiological movements of the ossicular chain with a modulated magnetic field. Using a similar set-up, Glorig<sup>2</sup> demonstrated that hearing and speech perception were comparable between electromagnetic and acoustic stimulation. After many years of testing different coil-magnet configurations in normal hearing and hearing impaired individuals, Goode found that using an in-the-ear coil and a 50-mg samarium-cobalt (Sm-Co) magnet on the umbo could effectively compensate for a mild to moderate sensorineural hearing loss (SNHL).<sup>6</sup> The application of piezoelectric stimulation was also explored and shown to be feasible and effective.<sup>3</sup>

In the decades to come, implantable solutions were developed which paved the way for the variety of recent active middle ear implants. The aim of this study was to review the research and development activities around partially implantable active middle ear implants, identify those successfully on the market, and summarize their outcomes.

## METHODS

### Search Strategy

A systematic literature review was carried out, using the comprehensive search strategy presented in Appendix 1, to identify studies evaluating the safety, efficacy, effectiveness, and subjective outcomes of partially implantable aMEI. The search was conducted in PubMed (MEDLINE); EMBASE, SciSearch, German Medical Science Journals

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and Meetings (German Institute for Medical Documentation and Information); and the Cochrane Library on July 18, 2016 and updated in PubMed (MEDLINE) on February 1, 2017. Study bibliographies were searched to locate additional materials.

### Study Selection and Data Collection

After removing duplicates, titles and abstracts then the full texts were screened against the criteria given in Table I by a single reviewer. Information on study design, sample size and description, indications, and outcomes were collected to develop a historical timeline of research activities for each identified aMEI.

For commercially available aMEI with more than 25 publications, studies were screened again (see Table I) by two reviewers for inclusion in quantitative data synthesis. From selected studies, data were compiled on adverse events, unaided air and bone conduction, pure tone average thresholds (PTA), sound-field hearing thresholds, word recognition scores (WRS), speech reception thresholds (SRT), and signal-to-noise ratios (SNR). Adverse events included any minor or major event potentially requiring medical or surgical management. In cases of missing means and/or standard deviations, values were estimated from median and interquartile and/or range values using the methods described by Wan.<sup>7</sup>

### Quality Appraisal

Due to the large number of search results, only the studies included in quantitative data synthesis were appraised. Quality appraisal was carried out using the ROBINS-I (Cochrane) and the Quality Appraisal Checklist for Case Series (Institute of Health Economics, Alberta, Canada) depending on study design. The latter tool was supplemented with appropriate questions for evaluating research on hearing implants (see supplementary material). Quality appraisal was carried out by one reviewer and checked by a second.

### Quantitative Data Syntheses

The risk and rate of adverse events per patient months was calculated, and their 95% confidence intervals were estimated. For the remaining variables, effect sizes and standard errors were calculated using the formula for repeated measures Hedge's *g* assuming a correlation of 0.5 between paired data (except for functional gain).<sup>7,8</sup> Data syntheses were based on mean differences or standardized mean differences depending on heterogeneity in outcome measures and analyzed using a random-effects model, unless otherwise reported. When standardized mean differences were applied, the results were back-transformed using either the standard deviation of the difference score from the most representative study (according to sample characteristics, size and testing interval) or the pooled standard deviations of the difference scores of few individual studies. Meta-regression was carried out with indication, age group, coupling type, and speech testing material as predictors when possible.

TABLE I.  
Study Inclusion Criteria.

| Inclusion criteria                                     |   |
|--|---|
| <i>Systematic review of partially implantable aMEI</i> |   |
| Population   | Animals, temporal bones, or humans with any type of hearing loss  |
| Intervention (s)                                       | Active partially implantable middle ear implants; namely the Vibrant Soundbridge, SOUNDTEC, MAXUM, Middle Ear Transducer, RION, and any other earlier devices                       |
| Comparator (s)   | Unaided hearing, air conduction, or bone conduction hearing aids, other hearing implants  |
| Outcome(s)   | Adverse events, subjective and objective hearing tests, speech audiometry in quiet and noise, patient-reported outcomes, localization, cost-effectiveness                           |
| Study design(s)  | Case reports, case series, before-after studies, cohort studies, case-control studies, systematic and non-systematic literature reviews, quasi or full randomized controlled trials |
| <i>Quantitative data synthesis</i>                     |   |
| Population   | Adults and children with any type of hearing loss   |
| Intervention (s)                                       | Commercially available aMEI   |
| Comparator (s)   | Unaided hearing   |
| Outcome(s)   | Sufficient reporting of at least one of the following: adverse events, pure tone and free-field audiometry, speech perception in quiet and noise                                    |
| Study design(s)  | Case series, before-after studies, cohort studies, case-control studies, quasi or full randomized controlled trials; all with $n > 5$   |

aMEI = active Middle Ear Implants.

All analyses were conducted in STATA 14 (StataCorp LP, Texas, USA).

## RESULTS

The search yielded 1352 results. After removing duplicates, 691 titles/abstracts were screened and the full texts of 391 were obtained. Of these, 34 were excluded due to irrelevant interventions, irrelevant, or pooled outcomes, duplicate or translated publications or publication type. Another 83 papers were identified from study bibliographies, from which six were excluded. Overall, 434 studies were included in a narrative synthesis.

Identified aMEIs with regulatory approval and their current status are presented in Table II. Sixty studies on currently available systems, three on the Middle Ear Transducer (MET), and 57 on the VIBRANT SOUND-BRIDGE (VSB), were selected for quantitative data synthesis. Eight of these studies included concurrent controls. Quality appraisal summarized in Table III conveys uncertainty in the characteristics of study samples, delivery of interventions, and reporting of outcomes. A description of these studies and a flow diagram of study selection are provided in supplementary material.

### Implantable Systems Without Regulatory Approval

Starting in the 1980s, several research groups developed aMEI systems; however, not all were continued and

TABLE II.  
Active Middle Ear Implants With Regulatory Approval.

|          | Indication  | Age group                 | Number of primary research studies | Number of subjects* | Regulatory approval  | Market access            |
|----------|-------------|---------------------------|------------------------------------|---------------------|--|--------------------------|
| Rion     | MHL         | Adults                    | 25 in 44                           | approx. 100         | National approval in 1993  | Discontinued             |
| SOUNDTEC | SNHL        | Adults                    | 10 in 37                           | 167                 | FDA approval in 2002   | Discontinued             |
| MAXUM    | SNHL        | Adults                    | 2 in 7                             | 4                   | FDA approval in 2002 (SOUNDTEC)  | Accessible               |
| MET      | SNHL, MHL   | Adults                    | 32 in 54                           | 344                 | FDA trial not completed, CE approval   | Limited access           |
| VSB      | SNHL, C/MHL | Adults, children >5 years | 223 in 301                         | approx. 2400        | FDA approval for SNHL in 2001, CE approval<br>FDA trial for C/MHL ongoing, CE approval | Accessible<br>Accessible |

\*Estimated from the beginning of phase III clinical trials

C/MHL = conductive and mixed hearing loss; CE = Conformité Européene; FDA = United States Food and Drug Administration; MET = middle ear transducer; MHL = mixed hearing loss; SNHL = sensorineural hearing loss; VSB = Vibrant Soundbridge.

brought to market. Those that were promising and sought regulatory approval include the electromagnetic ossicular replacement device developed by Heide<sup>9</sup> which comprised an in-the-ear external unit and a Sm-Co magnet implanted beneath the umbo; and the electromagnetic aMEI system developed by Maniglia,<sup>10</sup> which comprised a behind-the-ear external unit, an implantable electronics package fixed to the temporal bone, and a neodymium-iron-boron magnet attached to the incus. The clinical trials of these systems were not completed. For a review of early aMEI systems please refer to Carlson.<sup>11</sup>

### Implantable Systems With Regulatory Approval

**RION.** Research and development of the Rion system was launched in 1978 with the support of the Ministry of International Trade and Industry of Japan. After a five-year timeframe prototypes for a partially and fully implantable aMEI were developed; however, only the former underwent human trials.<sup>12</sup> The internal components of the partially implantable system consisted of a fixing plate screwed on to the squamous portion of the temporal bone and extending into the middle ear, and a piezoelectric ceramic biomorph attached to the stapes.<sup>13</sup> Experiments in cats and acute trials in humans showed the procedure to be feasible and that good hearing could be achieved and maintained.<sup>13–16</sup> The device was intended for adults with mixed hearing loss (MHL) who had BC thresholds between 20 to 40 dB SPL. The first patient implanted in 1984 reported good hearing, satisfaction, and sound quality.<sup>17</sup> In the following years, 37 adults were implanted in the same clinic and demonstrated good hearing and speech perception in noise compared to optimally fit hearing aids.<sup>18–20</sup> However, adverse events were reported in as many as 17 (45.9%). In response, a second generation “e-type” aMEI was developed consisting of a thinner internal coil, a stronger lead wire, and a more powerful external unit providing 10 dB more gain. The surgical procedure was also modified to reduce the risk of complications, and a tighter fixation of the fixing plate to the temporal bone was possible.<sup>19</sup> The system obtained regulatory approval in 1993.<sup>21</sup>

The Rion e-type has shown to be effective: Hearing thresholds remain relatively stable over time<sup>19,21–24</sup> and

the complication rate is lower.<sup>19,25</sup> The aMEI was discontinued in 2005 due to financial difficulties. Recent reports indicate 15 individuals continuing to use their device 11 to 22 years after implantation.<sup>25,26</sup>

**SOUNDTEC DIRECT DRIVE SYSTEM.** Early success with the Xomed Audiant Bone Conductor motivated the development of the SOUNDTEC Direct Drive hearing system at the Hough Ear Institute (Oklahoma City, OK, USA).<sup>27</sup> The implantation procedure required the separation of the incudo-stapedial joint to place a rare earth magnet between the malleus and stapes. Bench tests and acute human trials indicated good sound transmission and a safe surgical procedure.<sup>27–29</sup> Individuals with SNHL who were implanted permanently showed improved hearing; however, performance decreased within three months due to magnet oxidation. Changes were made in the choice of magnet, its size, and weight<sup>30</sup> and in 1998 the aMEI received Investigational Device Exemption (IDE). The feasibility study indicated aided hearing and speech perception in quiet to be better than optimally fit hearing aids; however, residual hearing was affected.<sup>31</sup> Using a smaller, lighter magnet in the phase 2 study, the average shift in unaided hearing thresholds was brought down to below 5 dB.<sup>32</sup> The effectiveness of the SOUNDTEC has been demonstrated in a few studies;<sup>32–35</sup> however, the device was withdrawn from the market to investigate an unexpected adverse event.<sup>36</sup>

**MAXUM.** The MAXUM system (Ototronix, Houston, TX, USA), which is based on the SOUNDTEC technology, is indicated for adults with moderate to moderately severe SNHL. Differences to the SOUNDTEC exist in the surgical procedure, further reducing the impact on residual hearing, and in the use of a miniaturized completely-in-the-canal external unit.<sup>36,37</sup> First results indicated a high-frequency functional gain as large as 50 to 60 dB<sup>36,38</sup> and a significant improvement in hearing and word recognition scores over optimally fit hearing aids.<sup>36</sup>

**MET.** Research in to developing the MET dates back to the 1970s, when experiments were carried out on mechanically stimulating the ear at Washington University (St. Louis, MO, USA).<sup>39</sup> An electromagnetic transducer coupled to the incus was described after early

TABLE III.  
Quality Appraisal of Studies Included in Quantitative Data Synthesis.

| Item   | Yes /low bias |      | Partial or unclear / moderate bias |      | No /serious bias |      | Not relevant / no information |      |
|--|---------------|------|------------------------------------|------|------------------|------|-------------------------------|------|
|  | n             | %    | n                                  | %    | n                | %    | n                             | %    |
| <i>Studies with historical controls</i>                |               |      |                                    |      |                  |      |                               |      |
| Clear study objective                                  | 49            | 74.2 | 15                                 | 22.7 | 2                | 3    | -                             | -    |
| Prospective  | 22            | 33.3 | 13                                 | 19.7 | 31               | 47   | -                             | -    |
| Multi-centric  | 16            | 24.2 | 6                                  | 9.1  | 44               | 66.7 | -                             | -    |
| Consecutive recruitment                                | 14            | 21.2 | 52                                 | 78.8 | 0                | 0    | -                             | -    |
| Informed consent*                                      | 24            | 36.4 | 41                                 | 62.1 | 1                | 1.5  | -                             | -    |
| Patient characteristics fully disclosed                | 39            | 59.1 | 25                                 | 37.9 | 2                | 3    | -                             | -    |
| Clear inclusion/exclusion criteria                     | 30            | 45.5 | 13                                 | 19.7 | 23               | 34.8 | -                             | -    |
| Representative sample*                                 | 24            | 36.4 | 41                                 | 62.1 | 0                | 0    | -                             | -    |
| Patients at similar disease state                      | 41            | 62.1 | 23                                 | 34.8 | 1                | 1.5  | -                             | -    |
| Selection bias*  | 6             | 9.1  | 6                                  | 9.1  | 54               | 81.8 | -                             | -    |
| Intervention clearly described                         | 38            | 57.6 | 27                                 | 40.9 | 1                | 1.5  | -                             | -    |
| Same clinician*  | 12            | 18.2 | 37                                 | 56.1 | 17               | 25.8 | -                             | -    |
| Intra-op complications disclosed*                      | 23            | 34.8 | 40                                 | 60.6 | 3                | 4.5  | -                             | -    |
| Planned data collection                                | 30            | 45.5 | 20                                 | 30.3 | 16               | 24.2 | -                             | -    |
| Appropriate outcome measurement                        | 52            | 78.8 | 14                                 | 21.2 | 0                | 0    | -                             | -    |
| Before vs. after / unaided vs. aided                   | 61            | 92.4 | 2                                  | 3    | 3                | 4.5  | -                             | -    |
| Reliable data collection*                              | 20            | 30.3 | 44                                 | 66.7 | 4                | 6.1  | -                             | -    |
| Appropriate statistical analysis                       | 36            | 54.5 | 7                                  | 10.6 | 2                | 3    | 20                            | 30.3 |
| Sufficient follow-up to avoid influence of AP fitting* | 52            | 78.8 | 10                                 | 15.2 | 4                | 6.1  | -                             | -    |
| Losses to follow-up reported with reasons              | 15            | 22.7 | 7                                  | 10.6 | 7                | 10.6 | 37                            | 56.1 |
| Reporting of random variability in outcomes            | 31            | 47   | 27                                 | 40.9 | 8                | 12.1 | -                             | -    |
| Adverse events appropriately reported                  | 18            | 27.3 | 33                                 | 50   | 17               | 25.8 | -                             | -    |
| Selection bias due to negative outcomes*               | 41            | 62.1 | 25                                 | 37.9 | 0                | 0    | -                             | -    |
| Conclusions in line with outcomes                      | 53            | 80.3 | 12                                 | 18.2 | 0                | 0    | -                             | -    |
| Competing interests and financial support disclosed    | 25            | 37.9 | 24                                 | 36.4 | 17               | 25.8 | -                             | -    |
| Affiliation with manufacturers*                        | 5             | 7.6  | 3                                  | 4.5  | 58               | 87.9 | -                             | -    |
| <i>Studies with concurrent controls</i>                |               |      |                                    |      |                  |      |                               |      |
| No effect of confounding                               | 2             | 25   | 6                                  | 75   | 0                | 0    | -                             | -    |
| No selection bias into the study                       | 2             | 25   | 4                                  | 50   | 0                | 0    | 2                             | 25   |
| Correct/appropriate intervention classification        | 6             | 75   | 0                                  | 0    | 1                | 12.5 | 1                             | 12.5 |
| Interventions delivered as intended                    | 8             | 100  | 0                                  | 0    | 0                | 0    | -                             | -    |
| Complete data (no missing data)                        | 6             | 75   | 2                                  | 25   | 0                | 0    | -                             | -    |
| Appropriate outcome measurement                        | 8             | 100  | 0                                  | 0    | 0                | 0    | -                             | -    |
| Full and appropriate reporting                         | 5             | 62.5 | 2                                  | 25   | 1                | 12.5 | -                             | -    |
| Overall good quality                                   | 1             | 12.5 | 5                                  | 62.5 | 2                | 25   | -                             | -    |

\*Extra items included for assessing studies on hearing implants  
AP = audio processor.

studies. Through bench testing the surgical approach was optimized<sup>40</sup> and effective sound transmission was demonstrated acutely and over time.<sup>41,42</sup> The aMEI was presented in 1995 as a treatment alternative for moderate to severe SNHL. The system utilizes an electromagnetic transducer connected to a mounting shaft that is secured to the skull; the transducer tip is then placed into a laser-ablated hole in the incus.<sup>42,43</sup> Acute trials in five adults, two with hearing loss, showed good hearing, sound quality, and speech recognition. The phase I trial initiated by Otologics LLC found that implantation did not damage the ear and that there were benefits of wearing the MET

compared to optimally fit hearing aids. Sound quality was rated superior; however, there was no significant improvement in speech understanding. As a response, device output was increased by 15 dB for the phase 2 study.<sup>43</sup> Clinical trials in Europe and the United States covered 282 adults followed up for 12 months. In most patients, differences in pure tone thresholds were not significant and aided thresholds were better than 35 dB at frequencies below 2 kHz. Despite improved output, speech recognition and subjective benefit were not significantly better than optimally fit hearing aids. All outcomes were shown to be better with more severe preoperative

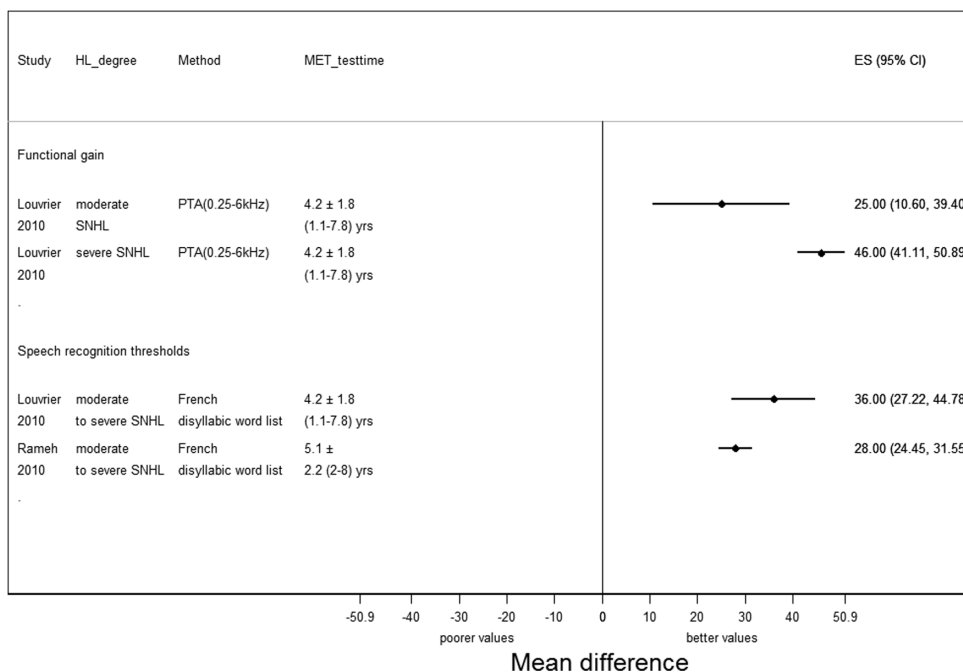


Fig. 1. Audiological outcomes measured before and after Middle Ear Transducer (MET) implantation. HL = hearing loss; PTA = pure tone average thresholds; SNHL = sensorineural hearing loss.

hearing thresholds.<sup>44</sup> The US clinical trials were closed without obtaining FDA approval and the MET has since been marketed in Europe only.<sup>45</sup>

In the literature, up to 100 adults with SNHL have been implanted since the European clinical trials.<sup>46–52</sup> Outcomes indicate the MET to be a powerful device, providing very good hearing outcomes over a long time.<sup>48,50,52,53</sup> Figure 1 illustrates audiological outcomes from studies reporting summary statistics. Speech recognition is also better than optimally fit hearing aids in the long-term.<sup>50,54</sup> The improvement in quality of life after implantation also remains relatively stable over time.<sup>50,55–57</sup> The MET was demonstrated to be a cost-effective solution at a cost of €16085 per QALY compared to no intervention.<sup>55</sup> Nevertheless, few papers evaluating safety outcomes show the rate of complications to be high. In a total of 61 individuals, 53 adverse events were observed, some experiencing multiple complications. Thirteen device failures were observed, which were mostly reported for the first-generation implants.<sup>46,48,51,52</sup> Another drawback of the system is that it is not MRI compatible.<sup>45</sup>

Over the years, the surgical procedure for implanting the MET has been optimized. There is no longer a need to create a hole in the incus for positioning the transducer tip<sup>58</sup> and couplers have been proposed for improving sound transmission.<sup>59</sup> Since 2009, several studies have also evaluated the feasibility of treating MHL, primarily otosclerosis, by stimulating the round window or a third window.<sup>60</sup> In an earlier paper, the MET was implanted in two cases with otosclerosis. The first patient received sufficient amplification while the second did not experience a benefit and discontinued using their device.<sup>61</sup>

In 2012 Otologics LLC ran into financial difficulties and subsequently acquired by Cochlear (NSW, Australia).

Since then the MET has been provided on-demand as efforts are focused on providing a fully-implantable alternative.

**VIBRANT SOUNDBRIDGE.** The development of the VSB system began in the early 1990s at Stanford University (Stanford, CA, USA) by Geoffrey Ball who went on to establish Symphonix Devices, Inc. (San Jose, CA, USA). The aMEI system constitutes an electromagnetic floating mass transducer (FMT) designed to be attached at a single point to the long incus process; the FMT is connected via a conductor link to the receiver unit and demodulator placed on the temporal bone. It was initially designed for adults with moderate to severe SNHL and an intact ossicular chain, who cannot use or are dissatisfied with hearing aids due to medical reasons.<sup>62</sup> Bench tests and temporal bone studies using Laser Doppler Vibrometry indicated efficient and reliable sound transmission with the floating mass transducer.<sup>28,63</sup> Acute testing in five adults undergoing routine stapedotomy demonstrated good sound quality and hearing thresholds.<sup>64</sup> This was followed with clinical trials conducted in Europe and the United States covering 47 and 53 adults, respectively. European results showed implantation to be safe with three patients experiencing minor adverse events, and no significant difference in mean BC hearing thresholds at one-month post-activation.<sup>65</sup> Similar results were observed in the US trial. Further, comparisons drawn to preoperatively worn hearing aids demonstrated higher functional gain and subjective benefit with the VSB, however, no significant differences in speech recognition.<sup>66</sup> Subsequently, the VSB received CE marking in 1998 and FDA approval in 2000.<sup>65,66</sup> Effectiveness data in Europe have also been published,

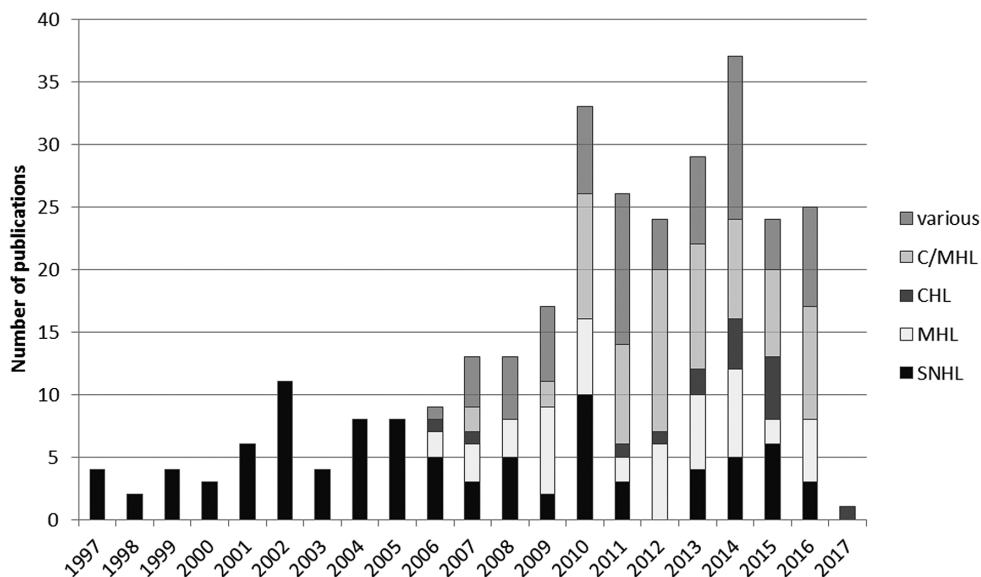


Fig. 2. Number of publications on the Vibrant Soundbridge per year and indication

documenting a hearing benefit translatable to improved speech recognition in majority of patients.<sup>67</sup>

The adoption of the VSB after the clinical trials was relatively slow; therefore, Symphonix was acquired by MED-EL in 2003.<sup>11</sup> Over the years, 301 studies covering approximately 2400 individuals have evaluated the effectiveness of the VSB in treating SNHL and extending indications. Figure 2 illustrates the number of publications per year and indication. In 2006, the feasibility of implanting the VSB on the round window with a bell coupler for managing MHL primarily due to chronic middle ear infections was explored.<sup>68</sup> The first patient was successfully implanted in Italy<sup>69</sup> and another was implanted in Germany for conductive hearing loss (CHL) due to bilateral microtia.<sup>70</sup> CE marking for these indications was granted in 2009.<sup>71</sup> Recently, the VSB has shown to be effective in reducing the perceived levels of tinnitus<sup>72,73</sup> and has started to be explored as an alternative for managing balance problems together with SNHL.<sup>74</sup>

### Quantitative Data Synthesis

**ADVERSE EVENTS.** Table IV presents 34 studies, three on the MET and 31 on the VSB, that provided sufficient reporting for data synthesis. An estimated number of 28 patients with a MET experienced 50 adverse events, and 130 patients with a VSB experienced 148 adverse events. Across studies, the risk of developing at least one adverse event was three-fold with the MET than with the VSB (49.12%, 95% CI 36.1–62.1 vs. 15.63%, 95% CI 12.7–18.6%). A lower risk was reported for the MET in Louvrier 2010; this study accounted for only explantations with/without reimplantations. With the VSB, risk is generally low across the different follow-up times. The rate of developing an adverse event was 1 in 51.3 patient months (95% CI 1 in 38.9–69) with the MET and 1 in 134 patient months (95% CI 1 in 114.1–158.6) with the VSB.

In terms of adverse event management; eight patients with a MET (28.6%) required revision surgery,

seven (25%) required permanent explantation, and six (21.4%) underwent 12 reimplantations. In contrast, 49 patients with a VSB (37.7%) required 55 revision surgeries, five (3.85%) required six permanent explantations, and 13 (10%) required 15 reimplantations.

**BC THRESHOLDS.** Twelve studies covering 17 subgroups of 358 individuals measured BC PTA calculated over 0.5 to 4 kHz, with or without 3 kHz. The meta-analysis based on mean differences indicated no significant difference between pre- and postoperative BC thresholds (ES =  $-.215$ , 95% CI  $-1.712$ – $1.283$ ,  $P = .779$ ). The threshold shift varied substantially between studies but remained within 10 dB, indicating no clinical importance. Meta-regression showed no differences in outcomes when comparing SNHL, MHL, and conductive or mixed hearing loss (C/MHL) ( $P = .515$ ); and studies with adults and those including children (0.904). A significant difference in the degree of BC shift was found between different coupling modalities ( $P = .026$ ), and also when limiting analysis to only C/MHL ( $P = .045$ ).

A second meta-analysis comparing short and long-term outcomes indicated no significant difference in BC thresholds over time (ES =  $-0.296$ , 95% CI  $-2.244$ – $1.651$ ,  $P = .765$ ).

**AC THRESHOLDS.** Seven studies covering 13 subgroups of 255 individuals measured AC PTA mostly calculated over 0.5 to 4 kHz. Two studies calculated average thresholds over a wider range of frequencies. The meta-analysis based on standardized mean differences indicated a significant decrease in AC thresholds postoperatively (ES =  $-0.293$ , 95% CI  $-0.526$ – $0.060$ ,  $P = .014$ ). Back-transforming the results for the two indications, based on representative studies, estimated an AC shift of  $-2.594$  dB (95% CI  $-4.657$ – $-.531$ ) for SNHL and  $-5.253$  dB (95% CI  $-9.431$ – $-1.076$ ) for C/MHL. These outcomes are within a 10 dB range and are clinically unimportant. Meta-regression indicated no significant difference in AC shift between C/MHL and SNHL



TABLE IV.  
Frequency of Adverse Events.

| Study                           | Patients with AE | Risk   | Follow-up    | Total time in patient months | Rate of 1 AE per patient months |
|---------------------------------|------------------|--------|--------------|------------------------------|---------------------------------|
| <i>Middle Ear Transducer</i>    |                  |        |              |                              |                                 |
| Louvrier 2010                   | 2 of 15          | 13.33% | 50 (13–94)   | 750                          | 1 in 325                        |
| Rameh 2010                      | 10+ of 19        | 52.63% | 22.8 (12–48) | 433.2                        | 1 in 16.7                       |
| Zwartenkot 2016                 | 16 of 23         | 69.57% | 43.2 (1–153) | 1380                         | 1 in 62.7                       |
| Overall                         | 28+ of 57        | 49.12% | –            | 2563.2                       | 1 in 51.3                       |
| <i>Vibrant Soundbridge</i>      |                  |        |              |                              |                                 |
| Atas 2013                       | 3 of 19          | 15.79% | 3            | 52.5                         | 1 in 17.5                       |
| Claros & Pujol 2013             | 0 of 22          | 0%     | 3            | 66                           | 0                               |
| Frenzel 2015                    | 4 of 19          | 21.05% | 6            | 96.1                         | 1 in 16                         |
| Frenzel 2009                    | 1 of 7           | 14.29% | 8            | 48.03                        | 1 in 48                         |
| de Brito 2016                   | 0 of 12          | 0%     | 8            | 96                           | 0                               |
| Bernardeschi 2011               | 5 of 25          | 20%    | 8 (2–28)     | 189.53                       | 1 in 37.9                       |
| Zahnert 2016                    | 4 of 30          | 13.33% | 12           | 294                          | 1 in 73.5                       |
| Cuda 2009                       | 1 of 8           | 12.5%  | 12 (6–24)    | 84.03                        | 1 in 84                         |
| Dillon 2014                     | 6 of 18          | 33.33% | 12           | 180                          | 1 in 30                         |
| Marino 2013                     | 6 of 18          | 33.33% | 12           | 159.5                        | 1 in 26.6                       |
| Zhao 2015                       | 2 of 9           | 22.22% | 18 (3–41)    | 135                          | 1 in 67.5                       |
| Roman 2012                      | 1 of 10          | 10%    | 18 (12–36)   | 164                          | 1 in 164                        |
| Canale 2014                     | 1 of 18          | 5.56%  | 23 (7–40)    | 395                          | 1 in 395                        |
| Edfeldt 2014                    | 1 of 7           | 14.29% | 26 (6–63)    | 164.5                        | 1 in 164.5                      |
| Colletti 2014                   | 0 of 8           | 0%     | 36           | 288                          | 0                               |
| Baumgartner 2010 & Boeheim 2012 | 5 of 12          | 41.67% | 40 (31–46)   | 385.5                        | 1 in 77.1                       |
| de Abajo 2013                   | 4 of 13          | 30.77% | 41.2 (6–64)  | 572.4                        | 1 in 81.7                       |
| Lassaletta 2015                 | 7 of 12          | 58.33% | 42 (12–76)   | 263.58                       | 1 in 33                         |
| Colletti 2013                   | 8 of 50          | 16%    | 49.5 (12–60) | 2208.13                      | 1 in 276                        |
| Hempel 2013                     | 0 of 12          | 0%     | (6–14)       | 120                          | 0                               |
| Fisch 2001                      | 9 of 47          | 19.15% | 3            | 115.76                       | 1 in 12.9                       |
| Fraysse 2001                    | 4 of 25          | 16%    | 11           | 275                          | 1 in 68.75                      |
| Lenarz 2001                     | 5 of 34          | 14.71% | 16.5         | 561                          | 1 in 112.2                      |
| Bruschini 2009                  | 0 of 12          | 0%     | 21           | 252                          | 0                               |
| Schmuziger 2006                 | 10 of 20         | 50%    | 42           | 840                          | 1 in 84                         |
| Maier 2015                      | 12 of 113        | 10.62% | 84           | 8840.83                      | 1 in 465.3                      |
| Busch 2016                      | 6 of 125         | 4.8%   | 4.1          | 512.5                        | 1 in 85.4                       |
| Ihler 2014                      | 10 of 37         | 27.03% | 10.9         | 415.4                        | 1 in 27.7                       |
| Lim 2012                        | 2 of 7           | 28.57% | 24           | 144.03                       | 1 in 72                         |
| Schraven 2016                   | 13 of 83         | 15.66% | 27           | 1919.5                       | 1 in 147.6                      |
| Overall                         | 130 of 832       | 15.63% | –            | 19837.84                     | 1 in 134                        |

AE = adverse event.

( $P = .084$ ); and between adults and samples including children ( $P = .111$ ).

**SOUND-FIELD THRESHOLDS.** Functional gain (FG) was reported in 10 studies covering 13 subgroups of 137 individuals, calculated over 0.5 to 4 kHz with or without 3 kHz. The meta-analysis based on mean differences is presented in Figure 3 and indicated an overall FG of 28.7 dB (95% CI 25.5–31.9,  $P < .001$ ). Meta-regression showed differences between C/MHL and SNHL approached significance ( $P = .066$ ). The FG in C/MHL is slightly higher (FG = 33.585, 95% CI 29.142–38.029) than that for SNHL (FG = 26.235, 95% CI 22.329–30.141).

Four studies covering seven subgroups of 230 individuals compared short- and longer-term sound field thresholds. Meta-analysis based on standardized mean differences showed no significant difference in outcomes over time (ES =  $-0.183$ , 95% CI  $-0.410$ – $0.043$ ,  $P = .112$ ); and meta-regression did not indicate differences between C/MHL and SNHL ( $P = .396$ ).

### Speech recognition

**WRS.** Twenty-two studies covering 42 subgroups of 785 individuals measured WRSs using different test at various presentation levels. Meta-analysis was based on

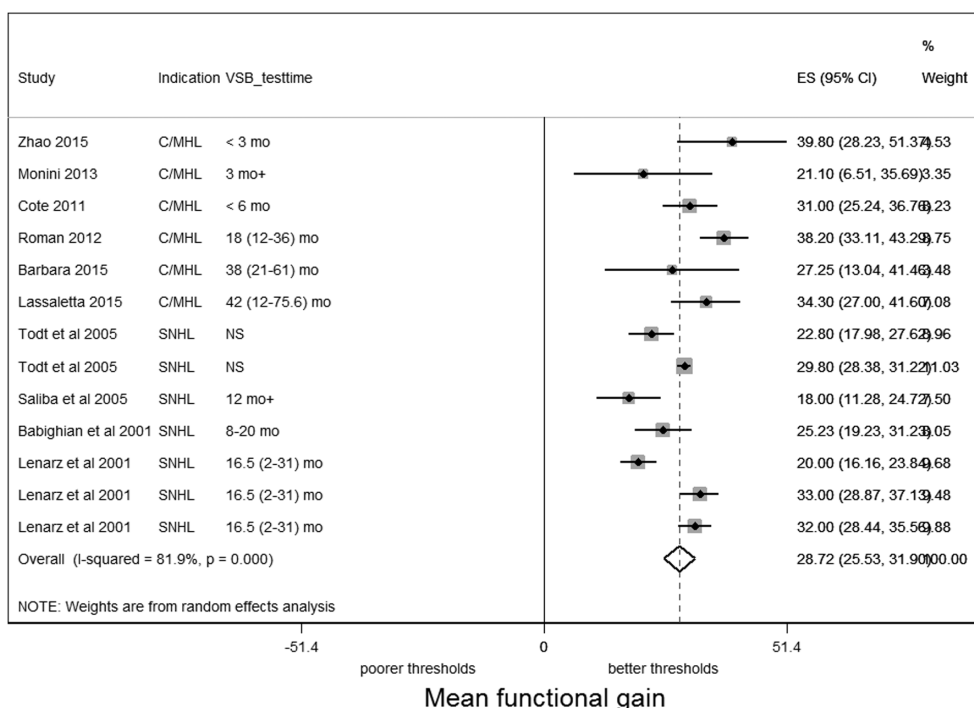


Fig. 3. Functional gain with the Vibrant Soundbridge (VSB) per indication. C/MHL = conductive or mixed hearing loss; CHL = conductive hearing loss; MHL = mixed hearing loss; SNHL = sensorineural hearing loss.

standardized mean differences on tests presented at 65 dB SPL. Results illustrated in Figure 4 showed WRS to significantly improve after implantation (ES = 1.983, 95% CI 1.565–2.402,  $P < .001$ ). Back-transforming the results using the most representative studies for Freiburg monosyllabic word lists presented at 65 dB SPL, the estimated WRS gain was 47.57% (95% CI 37.54–57.62) for SNHL and 43.4% (95% CI 34.25–52.57) for C/MHL. Meta-regression showed difference in outcomes between SNHL, MHL, and C/MHL to be not significant ( $P = .274$ ); as well as between adults and samples including children ( $P = .767$ ) and different speech tests ( $P = .973$ ).

Seven studies covering 11 subgroups of 216 individuals compared short- and longer-term WRS. Meta-analysis based on standardized mean differences on tests presented at 65 dB SPL showed no significant difference in speech recognition over time (ES = -0.216, 95% CI -0.613–0.180,  $P = .285$ ). Comparing C/MHL against SNHL also indicated no differences in outcomes ( $P = .1$ ).

**SRT.** Twelve studies covering 14 subgroups of 217 individuals used different methods for obtaining the SRT. Meta-analysis based on standardized mean differences demonstrated improved speech recognition after implantation (ES = 1.557, 95% CI 1.102–2.011,  $P < .001$ ). Study results depicted in Figure 4 show some variance. Meta-regression indicated a significant difference between SNHL and C/MHL ( $P = .03$ ); but not when comparing adults with samples including children ( $P = .656$ ), or sentence tests with word tests ( $P = .71$ ). Back-transforming the results lead to a SRT gain of 23.2 dB (95% CI 16.5–30) for C/MHL based on the most representative study, and to a gain of 27.7 dB (95% CI 19.6–35.8) for SNHL based on the pooled standard deviation.

**SNR.** Of nine studies measuring speech recognition in noise, four studies covering five subgroups of 51 individuals measured the SNR with speech and noise presented from 0° azimuth. The meta-analysis of these studies was based on mean differences and analyzed using a fixed-effects model as the heterogeneity statistic indicated no difference in between-study variance ( $P = .598$ ). Results indicated an improvement of 6.17 dB in the SNR (95% CI 4.78–7.55).

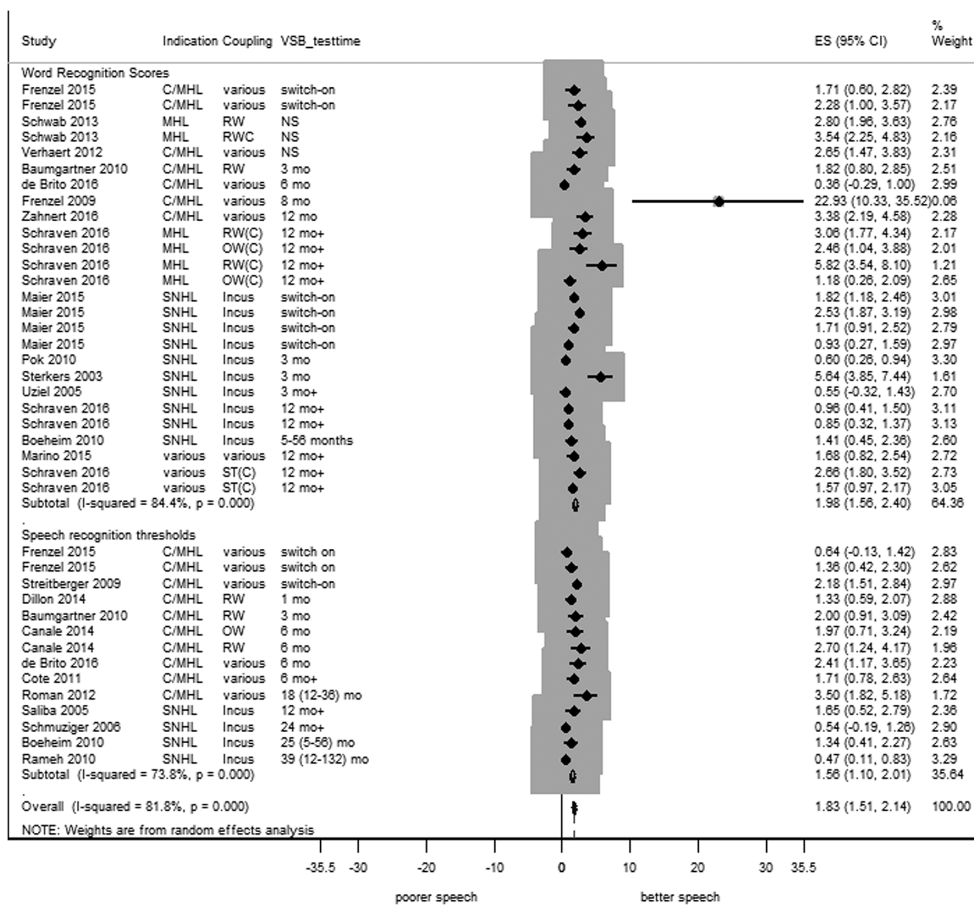
## DISCUSSION

Active middle ear implants have taken a long way from the initial, preliminary experiments to the present level of sophistication. The last two decades have shown a widening range of otological and audiological indications applicable to aMEIs to bridge the gap between conventional hearing aids, tympanoplasty techniques, and cochlear implants. The process of gaining regulatory approval and market access is, however, costly and time-consuming and continues to be a barrier to aMEI utilization.

Few piezoelectric systems have been developed and subsequently entered in to the market.<sup>11</sup> This could be due to their design, which requires modification/disarticulation of the ossicular chain to gain access to the stapes. A high rate of adverse events was observed with the RION, and may have contributed to its discontinuation. Nevertheless, some implantees continued using their systems.<sup>25,26</sup>

Early research into electromagnetic systems encountered problems with magnet adherence/displacement as the magnet was directly attached to a middle ear structure. Successful aMEIs incorporate clips for facilitating





### Standardised mean difference

Fig. 4. Speech recognition in quiet measured before and after Vibrant Soundbridge (VSB) implantation.. C/MHL = conductive or mixed hearing loss; CHL = conductive hearing loss; MHL = mixed hearing loss; OWC = oval window coupler; RW = round window; RWC = round window coupler; RW(C) = round window with or without a coupler; SNHL = sensorineural hearing loss; ST(C) = stapes with or without a coupler.

attachment or a mounting shaft to keep the transducer in position.<sup>59,75</sup> These developments simplify surgery, reduce complications, and provide easier adaption to varying pathologies. The first generation VSB and MET did have relatively high complication rates but provided good amplification. After a business takeover and further development, the risk of adverse events was lower. Additionally, pure tone thresholds are mostly unaffected, remaining stable over time. Compared to the MET, the VSB has a lower risk of adverse events which are mostly overcome by revision surgery. Furthermore, it is MRI conditional for 1.5 Tesla while the MET is not compatible.<sup>45,75</sup> In terms of output, the MET can provide higher amplification than the VSB.<sup>52,53</sup> The MAXUM has a functional gain of 50 to 60 dB in the high frequencies and seems particularly well-suited for ski-slope SNHL.<sup>36,38</sup>

The system with the widest range of applications and the highest number of active users is the VSB. From ear malformations to chronic middle ear infections, and from SNHL to comorbid vestibular disorders, the system has a well-documented record for 20 years. The VSB was first implanted with the FMT coupled to the long incus process in patients with SNHL. This worked remarkably well; functional gain reached 20 to 40 dB (“overclosure”).<sup>66</sup> Over

time, MHL primarily due to chronic otitis media became a very attractive indication, particularly with the introduction of couplers enabling attachment to a variety of middle ear structures. In parallel, the VSB started to be utilized in cases with ear malformations and was granted approval for children in 2009.<sup>71</sup> Meta-analyses showed that the VSB is just as effective in restoring hearing in all indications, with potentially more functional gain and SRT in cases of C/MHL. The audiological outcome in children is as excellent as in adults. Further, the risk of adverse events and pure tone threshold shift is similar between indications and between children and adults.

### CONCLUSION

This systematic review, primarily the meta-analyses, is limited by the number and quality of the included studies and the assumptions made in effect size calculations. Many studies had to be excluded from data synthesis due to overlapping samples and/or insufficient outcome reporting. In particular, the reporting of adverse events was poor. Fifteen studies were excluded due to no information on follow-up and/or number of patients experiencing specific adverse events. Further, the reporting of

time-to-event data was not common. This implies a need for awareness and consensus on adverse events' reporting. Heterogeneity in audiological outcomes also limited the number of included studies, especially for speech in noise, precluding the assessment of publication bias. The evidence base for aMEIs mostly constitutes observational research of low to moderate quality which has been improving over the years.

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