European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-019-05727-8

OTOLOGY

Adverse events associated with bone-conduction and middle-ear implants: a systematic review

Burkard Schwab[1] · **Wilhelm Wimmer**[2] · **Johan L. Severens**[3] · **Marco D. Caversaccio**[4]

Received: 25 June 2019 / Accepted: 7 November 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose To review types and frequencies of adverse events (AE) associated with bone-conduction hearing implants (BCHIs) and active middle-ear implants (aMEIs) as reported in the literature.

Methods Cochrane, PubMed, and EMBASE libraries were searched for primary articles in English or German language that reported on adverse events following BCHI or aMEI implantation, included at least five patients and were published between 1996 and 2016. Study characteristics, demographics, and counts of adverse events were tabulated and analyzed within the R statistical programming environment.

Results Following assessment of the reporting quality of adverse events, we present a brief guideline that potentially improves AE reporting in this field of research. For the full dataset, we summarize study-level adverse event frequencies in terms of ratio of events to ears (REE) by AE groups and by device. For a subset of studies, we also report cumulative incidence (risk) for minor- and major adverse-events by device and by device groups.

Conclusions Data analyzed in this review show that: (1) the reporting quality of adverse events associated with BCHI and aMEIs is often very low; (2) adverse events associated with BCHI and aMEIs are qualitatively different and not equally frequent among devices; (3) state-of-the-art implantable BCHIs and aMEIs are a safe treatment option for hearing loss.

Keywords Hearing loss · Bone-conduction implant · Middle-ear implant · Safety · Adverse event · Medical device

Introduction

According to the latest Global Burden of Disease report, hearing loss (HL) affects about 6.8% of the world's population and is the 4th leading cause of years lived with disability [1, 2]. It is also known that even mild HL might have significant psychological effects upon individuals and their families [3]. Early treatment of HL is therefore highly cost-efficient [3], and this is increasingly recognized by health systems around the globe. The most common treatment options for HL include air conduction (traditional) hearing aids, hearing glasses, reconstruction surgery (including partial- and total middle-ear prostheses), and implantable hearing devices. In cases where traditional hearing aids cannot be used or do not provide enough benefit, implantable hearing devices are the most promising treatment option. Besides cochlear implants—which represent the state-of-the-art treatment for patients with profound HL or deafness—implantable bone-conduction hearing aids (BCHA) and active middle-ear implants (aMEI) effectively rehabilitate mild-to-moderate or mild-to-severe hearing

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00405-019-05727-8) contains supplementary material, which is available to authorized users.

✉ Burkard Schwab
Burkard.Schwab@helios-gesundheit.de

1 Klinik für Hals-Nasen-Ohrenheilkunde, Helios Klinikum Hildesheim, Senator-Braun-Allee 33, 31135 Hildesheim, Germany

2 ARTORG Center for Biomedical Engineering Research, University of Bern, Murtenstrasse 50, 3008 Bern, Switzerland

3 Erasmus School for Health Policy and Management and Institute for Medical Technology Assessment, Erasmus University Rotterdam, Burgemeester Oudlaan 50, 3062 Rotterdam, The Netherlands

4 Universitätsklinik für HNO, Kopf- und Halschirurgie, Inselspital Bern, Freiburgstrasse, 3010 Bern, Switzerland

Published online: 20 November 2019

losses, respectively [4–6]. In both cases, a battery-powered transducer either supports or completely drives functional components of a patient's hearing pathway. While all systems are therefore 'active' by definition [6], not all implants include an 'active' component (see Table 1).

BCHAs exploit the excellent sound-transmission properties of the skull bone. Sounds that are picked up by microphones in the externally worn audio-processor (AP) are converted to vibratory stimuli and either applied directly to the bone ('direct-drive') or indirectly to the skin ('skin-drive'; see Table 1). BCHAs are indicated for conductive HL, mixed HL (with a mild-to-moderate sensorineural component), and single-sided deafness (SSD). In the latter case, sound is transmitted to the opposite, still functional cochlea. In patients with conductive or mixed HL, the air-bone-gap (ABG) can be significantly reduced or even closed with BCHAs [7]. However, the sensorineural component in mixed HL cases cannot be overcome with amplification due to the limited vibration intensity that is technically (and safely!) applicable to the skull. Surgery is generally straightforward since the implant is positioned at the skull surface. Typical adverse events of BCHAs are therefore skin-related complications.

aMEIs stimulate either the ossicular chain or the cochlea directly and offer a variety of specific coupling strategies. Therefore, and because the active component is much closer to the cochlea, aMEIs have a broader indication spectrum compared to BCHAs, including patients with conductive-, mixed-, and sensorineural HL. In addition to closing the ABG, aMEIs can overcome a sensorineural HL component by amplification, especially when directly stimulating the cochlea (e.g., as in CODACS or Vibrant Soundbridge via the round window membrane). Due to their general design, more invasive surgeries are needed. Therefore, the spectrum of potential adverse event is higher in aMEIs compared to BCHAs. For the same reason and because several chronic or recurrent pathologies often concur in aMEI-candidate patients, the incidence of adverse events is also expected to be higher compared to BCHAs.

The true public health burden of adverse events associated with medical devices is unknown. Therefore, treatment safety is a crucial piece of evidence, affecting decisions of health authorities, surgeons, and patients alike: on one side, health authorities and surgeons require evidence that supports the benefit of implantable hearing devices, as these are generally more expensive than traditional hearing aids. On the other side, patients have to ponder the perceived

Table 1 List of included devices and basic system properties

	System	Implant type	Coupling	AP-to-implant connection	Available since[a]
BC hearing implants (BCHIs)					
BAHA® attract system (Cochlear)	Part. impl	Passive	Skin	Transcutaneous	2013
BAHA® connect system (Cochlear)	Part. impl	Passive	Bone	Percutaneous	1987
BONEBRIDGE™ (MED-EL)	Part. impl	Active	Bone	Transcutaneous	2012
Ponto System (Oticon Medical)	Part. impl	Passive	Bone	Percutaneous	2009
Sophono™ (Medtronic)	Part. impl	Passive	Skin	Transcutaneous	2010
Active middle-ear implants (aMEIs)					
Carina® (formerly Otologics, now Cochlear; Data exclusively refer to the Otologics device)	Fully impl	Active	Ossicles	–	2006
CODACS (Cochlear; syn. DACS/DACI)	Fully impl	Active	Ossicles or Cochlea (oval or round window)	–	2004
Esteem® (Envoy Medical)	Fully impl	Active	Ossicles	–	2006
MET (formerly Otologics, now Cochlear; Data exclusively refer to the Otologics device)	Part.impl	Active	Ossicles	–	2006
Soundtec Direct Drive Hearing System (formerly SOUNDTEC, now Ototronix's MAXUM)	Part.impl	Active	Ossicles	–	2009
Vibrant Soundbridge® (MED-EL)	Part.impl	Active	Ossicles or Cochlea (oval or round window)	–	1996

AP audio processor, *part. impl* partially implantable, *fully impl* fully implantable

[a]No liability assumed

burden of HL and the risks of surgery, which influences his/her willingness to undergo implantation. Adverse events not only increase the patient's distress, but also overall treatment costs in the long run. Unfortunately, safety outcomes of implantable hearing devices are not consistently reported in publications from clinical trials and if so, often lack rigor that would enable comparison with other studies. As a consequence, a comprehensive overview of types and frequencies of adverse events associated with implantable hearing devices is still lacking (but see, Kiringoda and Lustig [8] for a device-specific review). Here, we review the existing literature reporting on safety outcomes in two groups of highly specialized treatment options for HL: Bone-conduction hearing aids (BCHAs) and active middle-ear implants (aMEIs). Following recommendations of Golder et al. [9], we include evidence from different types of studies, rather than picking studies of ostensibly high quality. The aims of this systematic review are to (1) summarize device-specific and overall types and frequencies of AEs reported in publications on BCHAs and aMEIs, (2) assess the reporting quality of AEs in publications on BCHAs and aMEIs, and (3) derive guidelines for improved reporting of AEs in this field of research.

Methods

Systematic review

We explicitly excluded non-implantable bone-conduction hearing aids (e.g., hearing glasses or headband), dental hearing implants and passive ossicular implants used in reconstruction surgeries (i.e., PORPs/TORPs) from this systematic review, because these are either non-implantable, are restricted to SSD patients or are not active systems, respectively. A list of included devices is given in Table 1. All types of adverse events were recorded.

Search strategy

The goal of the search strategy was to identify articles reporting on any adverse events that occurred perioperative or during follow-up (F/U) of any device listed in Table 1. Cochrane, PubMed, and EMBASE libraries were searched for articles published in English and German language between January 1996 and December 2016. The search strategy combined device names with different terms for adverse events and hearing loss (see Appendix A for exact search terms). Systematic reviews, case reports, and studies on cochlear implants were explicitly excluded by the search strategy. Bibliographies of systematic reviews were searched for additional relevant literature.

Screening and data extraction

Initial screening of titles and abstracts was performed by two independent reviewers and aimed at excluding articles that were not related to BCHAs or aMEIs. During full-text screening, the following exclusion criteria were applied: (1) NOT hearing-implant related; (2) NOT including (human) patients; (3) NOT reporting on AEs; (4) Inconclusive reporting of AEs (applies to cases where either different numbers are reported for one outcome or counts that were not consistent with reported demographics); (5) Sample size below $N=5$; 6) Patient pool overlapping with other study/-ies. We explicitly refrained from any general quality-assessment of articles for two reasons: first, AEs are mostly reported as secondary outcomes of clinical studies. There is no reason to believe that studies reporting high-quality evidence for their primary endpoint are reporting AEs more accurately than studies with less sophisticated design or statistical analyses. Additionally, we want to look at the broader picture, which can only be achieved by including all available evidence (see Golder et al. [9]). In the absence of a tool for assessing the quality of AE-reporting, we used reporting frequencies of five extracted-parameters to summarize AE-reporting quality, specifically: number of ears with event, mean F/U time, SD of F/U time, resolution of AEs, and complete AE specification.

Data extracted from the final pool of articles comprised study-specific, demographic, and AE-specific parameters (see Online Resource 1 for a complete list of extracted parameters). Outcomes of primary interest were counts of AEs for all types of AEs. To account for subpopulations of bilaterally implanted subjects, we defined ears (instead of *patient*) as the target unit in this investigation. Adverse events were categorized as device-, skin-, surgery-, patient-related or not specified. This classification was decided by expert group discussion. The incidence of non-users was recorded separately, since non-using a device is mostly a sequela of already recorded AEs (and not an AE itself). However, patients that experienced no benefit from a device were also coded as non-users. Adverse events were defined as major whenever revision surgery was performed to resolve the same AE. In case revision surgery was reported without a specific AE leading to it, it was categorized as not specified major AE. All other AEs were deemed minor. Data were extracted and tabulated separately by two independent reviewers and then compared. Cases of incongruence were settled upon re-examination of the relevant article and consensus among reviewers.

Data synthesis

Tabulated raw data were further processed within the R computational environment [10] via RStudio [11]. The ratio of

events to ears (REE) for each study was calculated by dividing the number of reported events by the number of ears. REEs were calculated separately for AE supercategories (minor, major, and overall), AE categories (device-, skin-, surgery-, patient-related or not specified) and single AEs, and were visualized as boxplots showing median, quartiles, min/max, and outliers. Summary statistics (mean, median, standard deviation, min., and max.) were calculated for devices or device groups. For a subset of studies reporting on the number of ears with event, the cumulative incidence (or risk) was calculated by dividing the number of ears with event by the number of ears in each study. This is a simple measure-of-risk giving the proportion of implanted ears in a study for which at least one event was reported. To investigate the re-occurrence of events in the same patient, the number of events were divided by the number of ears with event. This gives the average number of events that were observed in ears for which at least one event was reported.

Results

Our search yielded 11,099 database hits and 96 additional articles from bibliographies (Fig. 1). After screening of titles and abstracts, 823 articles entered the full-text screening pipeline. We further excluded 589 articles for various reasons (see, Fig. 1), resulting in a final pool of 234 included articles. The full list of included articles can be found in Online Resource 2. Several articles reported on safety outcomes for multiple devices. In such cases, information was extracted separately for each device, giving a total number of 242 samples (rows) in our final dataset. The complete dataset is available as Online Resource 3 along with a short description of all extracted parameters (Online Resource 1).

Studies included were either prospective cohort studies ($N=85$), retrospective chart reviews ($N=149$) or surveys reporting on patient-reported outcomes ($N=8$). The majority of studies ($N=121$) included adult patients only, while 41 studies specifically focused on children. In 77 studies, both adults and children were included. Types of hearing loss included conductive, mixed or sensorineural hearing loss, or single-side deafness. Studies were conducted in 32 different countries in Asia ($N=16$), Australia ($N=5$), Europe ($N=171$), North America ($N=46$), and South America ($N=3$). There was one inter-continental multi-centric study.

Quality of adverse event reporting

Both the extent and quality of reported AEs differed among publications and devices. Overall, only 57.9% of the publications reported on the actual number of ears with AE. The mean F/U time was reported in 66%, while only 19% reported a standard deviation for F/U time. Whether AEs were resolved or not was reported in 43.4% of all studies. Finally, 46.3% of publications included at least one AE that was not clearly defined (e.g., "minor skin issue" or "device problem"). Table 2 lists proportions of publications reporting AE-relevant parameters by device, by device type, and for the overall dataset. For single publications, the respective information is given in the raw data table (Online Resource 3).

Types of adverse events

We found 204 different adverse events across all devices. The five most frequent AEs were: (1) Holger's grade I (minor), (2) Holger's grade II (minor), (3) skin revision surgery because of skin overgrowth (major), (4) Holger's grade III (major), and (5) Soft tissue/skin overgrowth (minor). A full list of AEs including absolute counts and REE for each AE is given in Online Resource 4. In general, many AEs were device-specific and therefore, AEs for BCHIs and aMEIs differed considerably. There was no single AE which occurred in all devices. Table 3 gives the ten most frequent AEs for BCHIs and aMEIs.

Incidence of adverse events

We used the Ratio of events to ears (REE) to estimate device-specific incidence of overall, minor, and major adverse events in the full dataset. We did not correct for different F/U times among studies because we found no significant correlation of REE with Mean F/U time in a subset of studies for which the latter parameter was reported ($N=160$; see Online Resource 5). REE varied substantially among studies, both within and among devices (Fig. 2). Summary statistics are given in Table 4. We also calculated REE separately for the five AE categories (device-related, skin-related, surgery-related, patient-related, and not specified; Fig. 3). This gave a more detailed picture on the strengths and weaknesses of the each single device. Summary statistics are given in Appendix B.

Cumulative incidence (risk)

Using a subset of studies for which both the Number of ears with event and mean F/U time were reported ($N=86$), we calculated the cumulative incidence for minor- and major AEs. For three devices (Ponto, CODACS, and Soundtec), no information was available at all. For three other devices (Carina, Esteem, and MET), this information was available only from two studies. All other devices had at least five studies in this subset. Even though we found no significant correlation of Cumulative incidence with Mean F/U time (Online Resource 6), we present Cumulative Incidence (Risk) stratified by Mean F/U time categories because risk

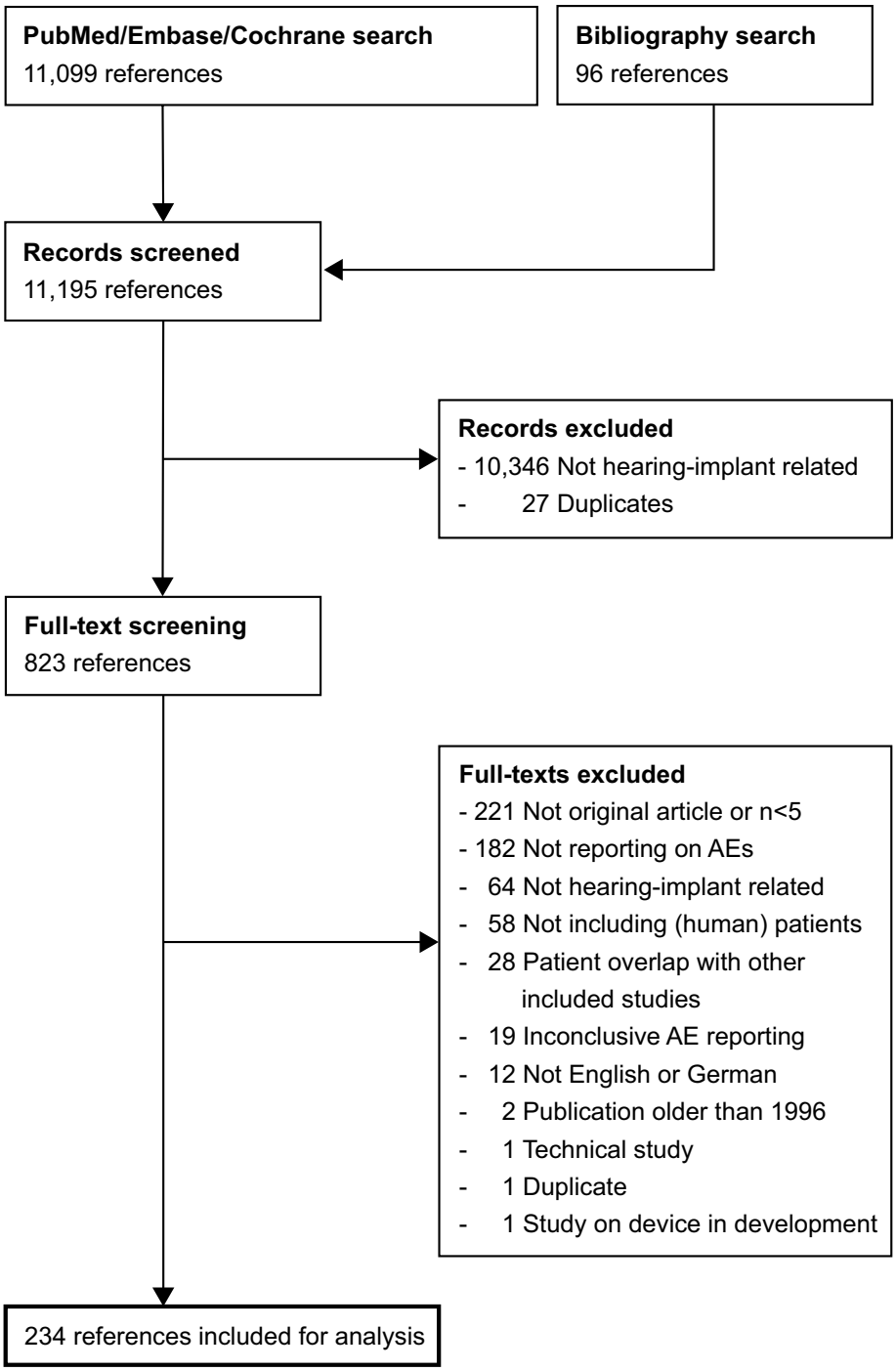

Fig. 1 Flow-chart of the systematic review

inherently relates to a given time period (Fig. 4). Also, we want to visualize the amount of (or the lack of) available long-term evidence.

Average number of events in patients with adverse events

During data extraction it became evident that in many cases, ears that experienced AEs did have multiple AEs during F/U. To investigate the average number of events in ears with at least one AE, we divided the number of events by the number of ears with event for each study (Fig. 5). In the absence of patient-level raw data, we consider this as the best-available approximation to the expected AE load in patients experiencing AEs.

Table 2 Quality assessment of AE reporting based on five AE-relevant parameters

Group name	*N*	Number (percentage) of studies that reported these parameters									
		Number of ears with event		Mean F/U time		SD of mean F/U time		Resolution of AEs		Complete AE specification	
Overall	242	+	140 (57.9%)	+	160 (66.1%)	--	46 (19%)	-	105 (43.4%)	+	130 (53.7%)
BCHIs	156	-	73 (46.8%)	+	100 (64.1%)	--	24 (15.4%)	-	42 (26.9%)	-	78 (50%)
aMEIs	86	+ +	67 (77.9%)	+	60 (69.8%)	-	22 (25.6%)	+	63 (73.3%)	+	52 (60.5%)
BAHA Attract	7	+	5 (71.4%)	+ +	6 (85.7%)	--	1 (14.3%)	+	5 (71.4%)	+ +	6 (85.7%)
BAHA Connect	117	-	44 (37.6%)	+	74 (63.2%)	--	17 (14.5%)	--	16 (13.7%)	-	49 (41.9%)
Bonebridge	13	+ +	13 (100%)	+	8 (61.5%)	--	3 (23.1%)	+ +	13 (100%)	+	8 (61.5%)
Ponto	7	-	2 (28.6%)	+	4 (57.1%)	--	0 (0%)	--	1 (14.3%)	+	5 (71.4%)
Sophono	12	+	9 (75%)	+	8 (66.7%)	-	3 (25%)	+	7 (58.3%)	+ +	10 (83.3%)
Carina	11	+	7 (63.6%)	+	6 (54.5%)	--	1 (9.1%)	+	6 (54.5%)	+	6 (54.5%)
CODACS	3	–	0 (0%)	+ +	3 (100%)	–	0 (0%)	+ +	3 (100%)	–	0 (0%)
Esteem	6	+	4 (66.7%)	-	2 (33.3%)	–	0 (0%)	–	1 (16.7%)	–	1 (16.7%)
MET	4	-	2 (50%)	+ +	4 (100%)	-	2 (50%)	-	2 (50%)	-	2 (50%)
Soundbridge	59	+ +	53 (89.8%)	+	44 (74.6%)	-	19 (32.2%)	+ +	50 (84.7%)	+	40 (67.8%)
Soundtec	3	-	1 (33.3%)	-	1 (33.3%)	–	0 (0%)	-	1 (33.3%)	+ +	3 (100%)

Total number of studies (*N*) as well as numbers and percentages of studies that reported AE-specific parameters are given for overall and device-specific groups. A higher percentage of reporting articles is considered to reflect a higher reporting quality. For ease of comprehension, visual codes denote four categories of reporting proportions: > 75% (+ +), 50–75% (+), 25–50% (-) and < 25%(--)

Discussion

Quality of AE reporting and guideline

Our quality assessment clearly shows that pivotal information regarding adverse events is often missing in publications on BCHIs and aMEIs. More specifically, it should be explicitly stated whether the number of events or the number of patients (or ears) with event is reported in a publication. The latter is more valuable in that it allows estimating the risk of overall or specific AEs by means of cumulative incidence. Apart from AE counts, unambiguous specification of AEs, mean F/U time, standard deviation of F/U time and whether and when AEs were resolved or not should be reported in any publication mentioning adverse events. We compiled a brief guideline for improved AE reporting (Table 5) including benefits and potential pitfalls of most important AE-related outcomes. We want to highlight that—as for other outcomes of medical research—reporting patient-level outcomes is the gold standard.

Indirectly related to AEs but missing in almost every publication was information on the device generation under investigation. Manufacturers generally improve their devices over time and it would have been interesting to see if younger device generations are associated with less AEs. This specifically refers to device generations of the implant and not of any external component. The latter was more often reported but is less relevant in terms of AEs. Our results therefore summarize outcomes from different device generations, a potential source of bias compared to safety outcomes of only the latest device generation. However, this applies equally to all devices included in this review.

Comparative outcomes

Among BCHIs, the majority of reported AEs were skin-related. From a clinical perspective, these can be treated locally most of the time, since the majority of events are minor across devices. Only the two percutaneous devices make an exception here. Both the BAHA Connect and the Ponto system show a relatively high REE for major skin-related AEs compared to transcutaneous devices. Even though the total number of reported cases for the BAHA Connect is at least one order of magnitude higher than for other devices and the longer availability of the system has to be considered when interpreting the data, there is a clear trend towards more (and more serious) skin-related complications in percutaneous devices. As a consequence, all major manufacturers do now have transcutaneous solutions in their portfolio. However, one should be aware that transcutaneous systems differ in terms of audiological output depending on the system's design. From a technological point of view, active transcutaneous bone-conduction implants are certainly the most advanced option, because they combine the benefit of direct stimulation (i.e., same audiological output as percutaneous systems) with the benefit of reduced skin complications of transcutaneous systems.

Table 3 The ten most frequent[a] adverse events for BCHIs and aMEIs

#	AE name	Severity	AE category	All devices	BAHA Attract	BAHA Connect	Bonebridge	Ponto	Sophono
					Ratio of events to ears (REE)				
(A) Most frequent AEs among BCHDs									
1	Holgers grade 1	Minor	Skin	0.069	0.01	0.07	–	**0.15**	–
2	Holgers grade 2	Minor	Skin	0.049	–	0.05	–	**0.08**	–
3	Skin revision surgery due to skin overgrowth or cellulitis	Major	Skin	0.038	–	**0.04**	–	0.01	0.01
4	Holgers grade 3	Major	Skin	0.025	–	**0.03**	–	**0.03**	–
5	Soft tissue/skin overgrowth (minor)	Minor	Skin	0.025	–	**0.03**	–	–	–
6	Infection	Minor	Skin	0.023	**0.03**	0.02	0.01	–	0.01
7	Revision surgery (reason not stated)	Major	Not specified	0.016	–	**0.02**	**0.02**	< 0.01	–
8	Reimplantation	Major	Not specified	0.014	–	**0.02**	–	–	0.01
9	Failure to osseointegrate	Major	Patient	0.014	–	**0.02**	–	–	–
10	Skin complications (minor)	Minor	Skin	0.011	–	**0.01**	–	–	–

#	AE name	Severity	AE category	All devices	Carina	CODACS	Esteem	MET	Soundtec	VSB
					Ratio of events to ears (REE)					
(B) Most frequent AEs among aMEIs										
1	Taste disturbances (chorda tympani damage)	Major	Surgery	0.03	–	–	**0.27**	–	0.01	0.02

Table 3 (continued)

#	AE name	Severity	AE category	All devices	Carina	CODACS	Esteem	MET	Soundtec	VSB
					Ratio of events to ears (REE)					
2	Explantation	Minor	Not specified	0.027	**0.1**	0.02	0.03	–	–	0.01
3	Implant/device failure	Minor	Device	0.026	**0.15**	–	–	–	–	0.01
4	Repositioning of FMT	Major	Surgery	0.02	–	–	–	-	–	**0.03**
5	Not specified (major AE)	Major	Not specified	0.02	–	–	**0.35**	–	–	–
6	Aural fullness	Major	Surgery	0.019	–	–	–	–	–	**0.03**
7	Dizziness/vertigo	mAjor	Surgery	0.016	<0.01	0.02	**0.08**	–	0.01	0.01
8	Percepting magnet movement	Minor	Surgery	0.015	–	–	–	–	**0.18**	–
9	Revision surgery (reason not stated)	Minor	Not specified	0.015	0.01	0.02	**0.1**	0.01	–	0.01
10	Pain n.s	Minor	Patient	0.015	<0.01	–	**0.09**	–	–	0.01

The highest value indicates in bold

[a]Frequency as determined by the highest ratio of events per ears (REE), separately among BCHDs and aMEIs

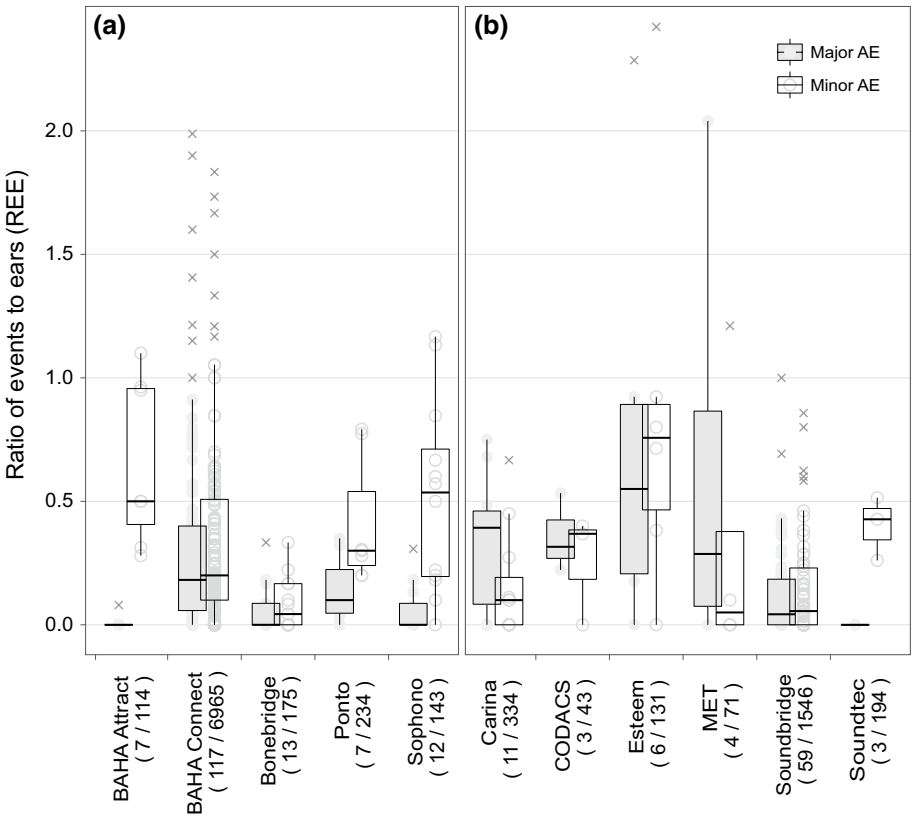

Fig. 2 Ratio of events to ears (REE) for minor- and major adverse events, by device. Each point (crosses are outliers) represents one study. Numbers of included studies and total implanted ears are given in parentheses for each device. A value of 1 indicates that the number of adverse events and the number of implanted ears in a given study were equal. However, this does NOT mean that all ears experienced an adverse event. Instead, some ears might have experienced more than one AE, thus inflating the sum of events in a study

Table 4 Summary statistics of the ratio of events to ears (REE) for overall, minor, and major adverse events

Device	*N*	Overall					Minor					Major				
		Median	Mean	SD	Min.	Max.	Median	Mean	SD	Min.	Max.	Median	Mean	SD	Min.	Max.
BAHA attract	7	0.50	0.67	0.32	0.31	1.10	0.50	0.66	0.34	0.28	1.10	0.00	0.01	0.03	0.00	0.08
BAHA connect	117	0.50	0.66	0.58	0.00	2.83	0.20	0.35	0.39	0.00	1.83	0.18	0.31	0.38	0.00	1.99
Bonebridge	13	0.10	0.15	0.16	0.00	0.50	0.04	0.09	0.11	0.00	0.33	0.00	0.06	0.10	0.00	0.33
Ponto	7	0.34	0.55	0.35	0.20	1.10	0.30	0.41	0.26	0.20	0.79	0.10	0.14	0.14	0.00	0.35
Sophono	12	0.55	0.57	0.43	0.00	1.27	0.54	0.52	0.39	0.00	1.17	0.00	0.06	0.10	0.00	0.31
Carina	11	0.44	0.48	0.36	0.00	1.20	0.10	0.15	0.22	0.00	0.67	0.39	0.33	0.26	0.00	0.75
CODACS	3	0.68	0.61	0.36	0.22	0.93	0.37	0.26	0.22	0.00	0.40	0.32	0.36	0.16	0.22	0.53
Esteem	6	1.47	1.62	1.04	0.38	3.00	0.76	0.87	0.83	0.00	2.42	0.55	0.75	0.83	0.00	2.29
MET	4	0.94	0.98	1.03	0.00	2.04	0.05	0.33	0.59	0.00	1.21	0.29	0.65	0.95	0.00	2.04
Soundbridge	59	0.20	0.28	0.30	0.00	1.46	0.06	0.15	0.21	0.00	0.86	0.04	0.13	0.19	0.00	1.00
Soundtec	3	0.43	0.40	0.13	0.26	0.51	0.43	0.40	0.13	0.26	0.51	0.00	0.00	0.00	0.00	0.00

When compared with BCHIs, aMEIs presented with generally higher REEs. This can be attributed to the higher complexity of both the surgical procedures and the implants itself. The most frequent AE reported in this device group (besides the category 'not specified') was the occurrence of taste disturbances caused by irritation or damage of the chorda tympani. Among aMEIs the Esteem system showed the highest occurrence of AEs, mostly dizziness/vertigo and postoperative pain. As opposed to explantation, re-implantation was not among the most frequent AEs of aMEIs. However, this could be confounding bias since re-implantations might be reported as revision surgeries by some authors.

The surgical perspective

The results of this systematic literature are in line with our own surgical experience. Whenever hearing implants are considered, surgeons find themselves in between the conflicting priorities of optimal hearing rehabilitation and ease

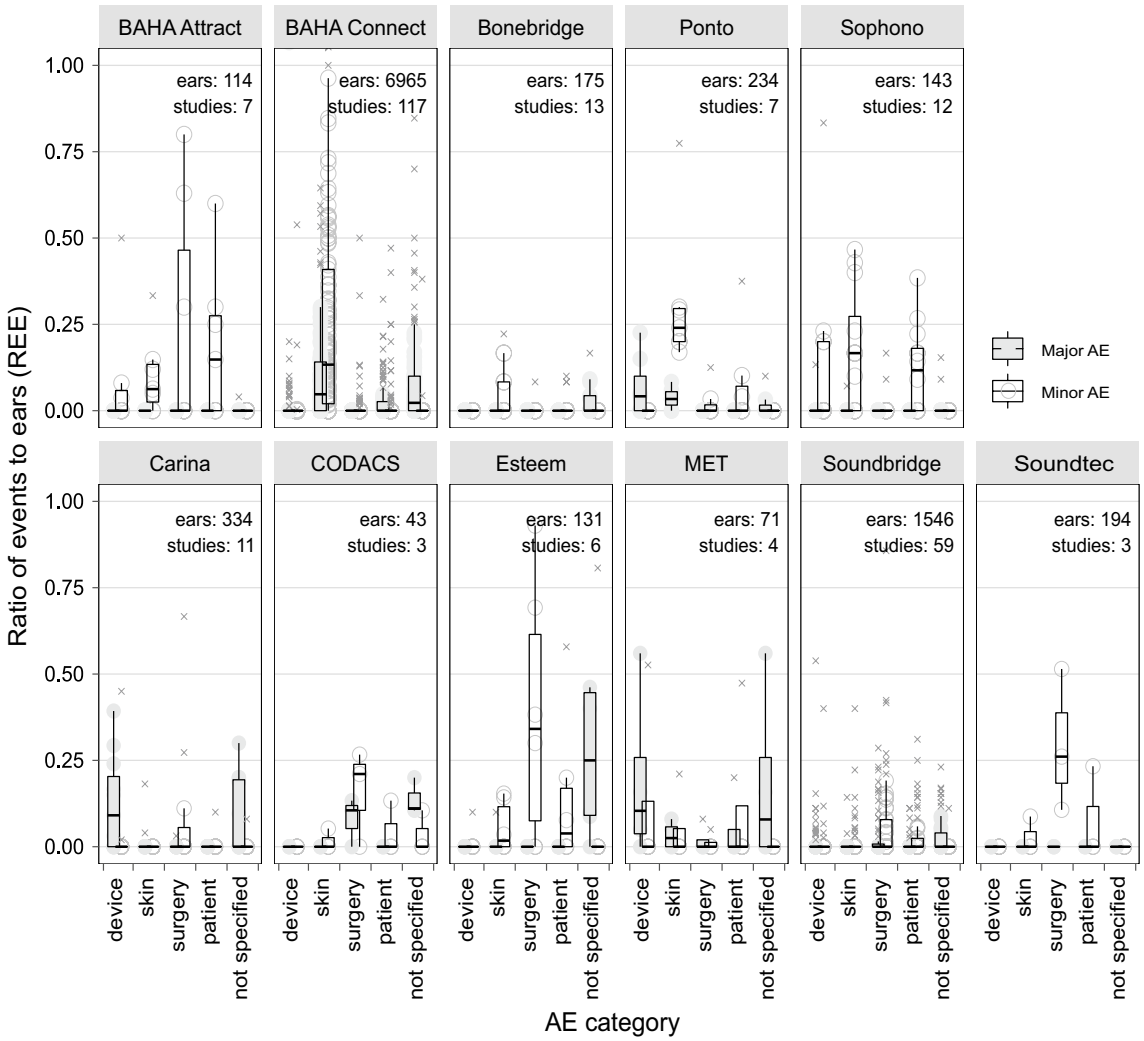

Fig. 3 Ratio of events to ears (REE) by device and AE categories. Each point (crosses are outliers) represents one study. For better visualization, the *y* axis is limited to values between 0 and 1, even though larger values (outliers) were scored by some studies (BAHA Connect and Esteem). Upper row: Bone-conduction implants. Lower row: Middle-ear implants

(or risk) of surgery. In terms of adverse events, there are two implications: first, the more complex surgeries are (as usually the case for aMEIs), the higher the risk of injury to the dura, the chorda tympani, the facial nerve, or even to the cochlea. However, also the ability to stimulate the impaired cochlea increases with surgical complexity, thus promising better outcomes. Second, simpler surgical interventions (basically all BCHIs) lack more serious AEs and are associated with a lower number of AEs in general. However, the amplification power of BCHIs, and thus their overall outcome, is limited because of their distant position to the cochlea. An apparent exception to this rule is the percutaneous BAHA, which combines ease of surgery with an elevated incidence of AEs, specifically skin-related complications.

The reason behind any decision for a more complex surgery is always driven by the pursuit of optimal treatment. Whether one is willing to accept the risk associated with an intervention, always needs to be discussed carefully between surgeon and patient, and ideally includes an evidence-based risk–benefit profile. With this review, we provide such evidence for future patients, surgeons, and decision makers.

Another feature related to implant complexity is an implant's potential to go down-market. A surgically too complex implant may never become available to a broad audience simply because the surgical expertise is a limiting factor. The CODACS is a good example for such a product. Among aMEIs, it was unparalleled in its ability to stimulate the cochlea: touching the indication criteria of cochlear implants, it provided much more natural hearing without the need for a training phase. But due to its highly complex surgery, it flopped commercially.

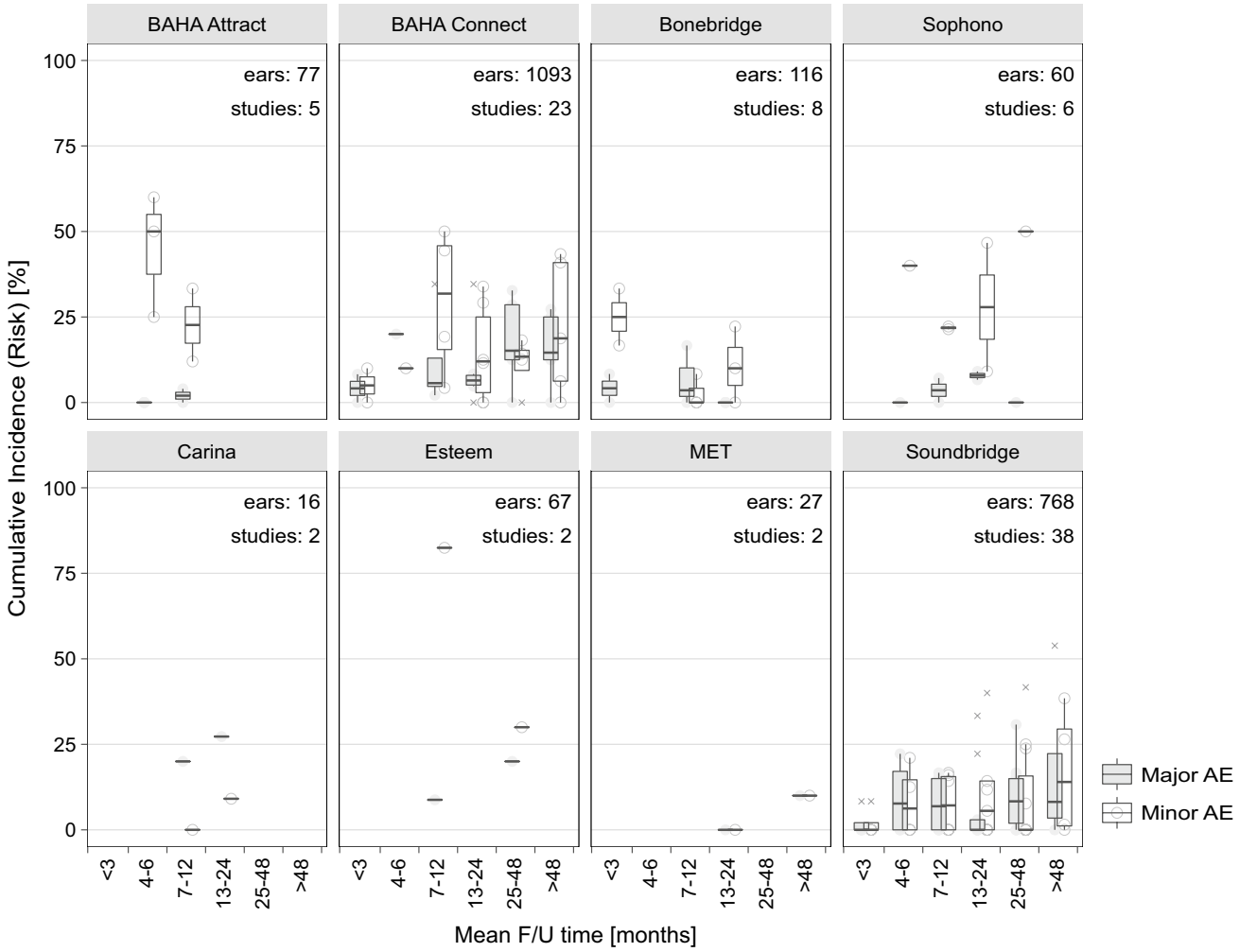

Fig. 4 Cumulative incidence (risk) of minor and major adverse events over mean F/U time strata. Categories were chosen based on typical F/U times seen in clinical trials, e.g., 3, 6, 12, 24, and 48 months

In a nutshell, from a surgeon's perspective, implantable hearing systems need to be as simple as possible to keep the risk for AEs low. At the same time they should provide effective stimulation of the cochlea for broad applicability. This is not an easy task and especially challenging for manufacturers, who have to manage this balancing act.

The HTA perspective

Our work shows the poor quality of evidence regarding adverse events during follow-up of patients using implantable hearing aids. Relatively simple statistics like duration of follow-up were not traceable in original publications making statistical analyses on pooled data invalid or even impossible. Although the evidence provided shows, based on descriptive statistics, trends in adverse events related to specific types of hearing implants, the evidence is definitely insufficient to draw any conclusions, let alone withdraw specific devices from the market.

However, this systematic review shows the potential value of evidence after introduction of a technology in a health care system. Most often, evidence regarding efficacy and adverse events is collected to inform decisions regarding market access and reimbursement decisions. And at this stage of the diffusion of a technology, data requirements are strictly prescribed by for instance Ministry of Health or reimbursement advisory bodies such as NICE in England and Wales, and IQWIG in Germany. Reporting longer term adverse-events does not seem to inform specific decision making moments related to access or reimbursement. This might be explaining the fact that a (min.) standard for registration of adverse events in hearing implants is lacking. So from a health-technology assessment perspective, defining a standard for registering adverse events in this clinical area might be informative

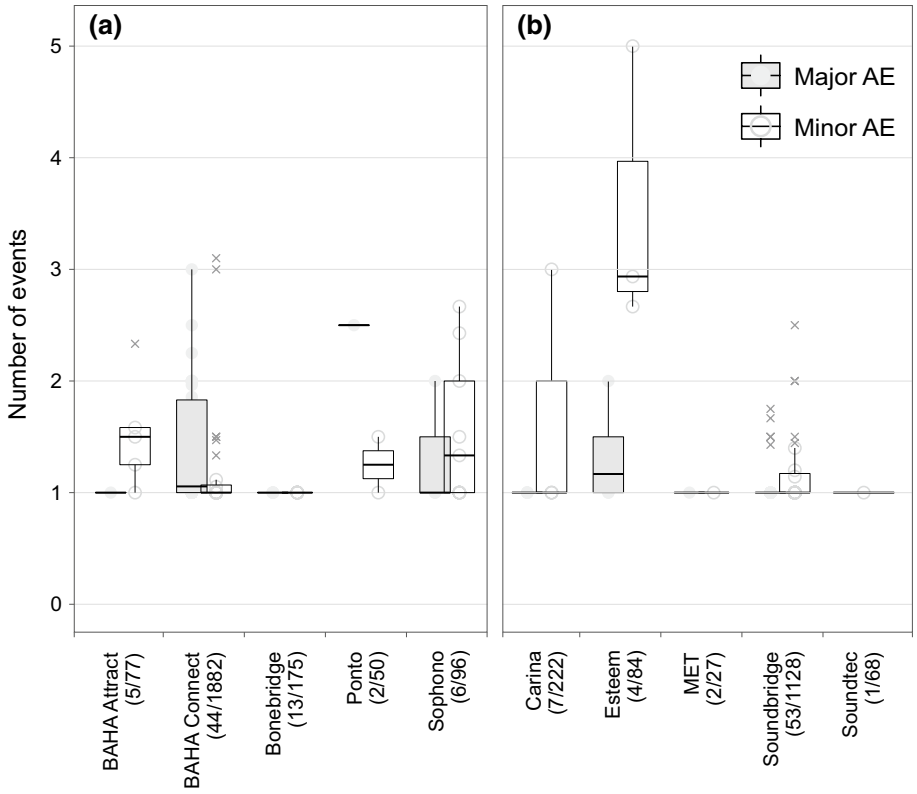

Fig. 5 Average AE load in ears with AEs

to clinical researchers to substantiate clinical guidance for future use of hearing implants. To be as valuable as possible, of course adverse events registration should include the specific type of device, but also patient characteristics. This review shows that an internationally accepted hearing implant-specific post marketing surveillance system can be valuable to increase the health outcome of future patients indicated for this technology.

Conclusion

This is the first comprehensive attempt to systematically review the quality and frequency of adverse events associated with implantable bone-conduction hearing aids and active middle-ear implants. Our results show that many publications lack rigor in reporting adverse events. The resulting gap in data integrity precludes thorough statistical analyses of adverse events associated with these medical devices. This has immediate consequences on decisions made by patients, clinicians, health authorities or advisory bodies around the world. Future publications could thus benefit from minimum standards that are based on international consensus. Based on the results of this review, we derive guidelines that might represent a first step towards common ground.

Acknowledgements The authors would like to thank the Clinical Research Department of MED-EL Medical Electronics (Innsbruck, Austria) for performing the literature search and data extraction.

Compliance with ethical standards

Conflict of interest The authors declare a potential conflict of interest given that literature search, screening, and data extraction were performed by the Clinical Research Department of one manufacturer (MED-EL, Austria). All steps of this literature review followed Cochrane guidelines and are reported in a transparent way. Raw data are provided as Electronic Supplementary Material (Online Resources). The following authors have received funding from manufacturers mentioned in this review: BS was supported by MED-EL and Cochlear. MC and WW, with the Department of ORL, Head and Neck Surgery and the Artorgcenter, University Bern were supported by MED-EL, Cochlear and Oticon Medical. JS has not received any kind of support from any of the manufacturers mentioned in this review.

Appendix A: Search string

Middle ear implant OR aMEI OR Vibroplasty OR middle ear surgery OR implantable hearing aid OR Carina OR Direct acoustic cochlear implant OR DACI OR Direct acoustic cochlear stimulator OR DACS OR Direct acoustic cochlear implant actuator OR CODACS OR Middle ear transducer OR Envoy OR MAXUM OR ear reconstruction surgery OR SOUNDBRIDGE OR Floating mass transducer OR FMT

Table 5 Guidelines for improved reporting of adverse events in clinical studies on BCHIs and aMEIs

Importance	Outcome	Benefit of reporting	Potential pitfalls
Gold standard!	Patient-level data (i.e., list all outcomes for each patient), including time-to-event	Data fully accessible to Readers and to reviews and meta-analyses	Make sure to report ALL outcomes at patient-level, not only some (even if they seem of minor interest)
High	Number of patients (ears) in reported dataset	Common denominator for more elaborate measures and meta-analyses	Specify, whether you are reporting on the number of patients or ears (in case one or more bilateral treatment patients are included). Do not confuse the number of operated patients (ears) with the number of included patients (ears) in study. Both might not correspond to the number of patients (ears) included in any specific analysis
High	Number of patients/ears with any adverse event	Most basic outcome in terms of AE reporting	Not to be confounded with the number of events!
High	Mean follow-up time	Needed to calculate person-time	–
High	Time-to-event	Needed for survival analyses	Define the starting point, e.g., surgery or first fitting
High	Definition of AE categories (e.g., AE/SAE; minor/major; skin-related, etc.)	Only clearly defined categories can be pooled or compared with other studies	Take care to stick to the definition set. Deliberately customized definitions are seldom comparable to results of others
High	Number of patients/ears with any adverse event by category (e.g., AE/SAE; minor/major; skin-related, etc.)	More specific outcome reporting possible	Patients/ears can have events in multiple categories. Therefore, the sum of patient/ear with event across categories may be higher than the total number of patients/ears in reported dataset. Reporting sums across categories potentially introduces bias by double-counting of patients
High	Number of resolved events	More detailed analysis of AEs	–
High	Number of non-resolved events	More detailed analysis of AEs	–
High	Use same patient ID for multiple publications resulting from the same study	Avoid duplicate data in reviews and meta-analyses	Do not include personal information (e.g., initials) in patient ID

OR Soundtec OR bone conduction implant OR bone conduction hearing implant OR bone conduction device OR bone conduction hearing device OR bone conduction hearing aid OR BCHI OR BCHA OR bone anchored hearing implant OR bone anchored hearing device OR bone anchored hearing aid OR Baha OR Ponto OR BONEBRIDGE OR Sophono OR safety OR adverse event OR complications OR revision AND hearing loss NOT Systematic Review NOT case report NOT cochlear implant.

Appendix B: Summary statistics of Ratio of events to ears (REE) for minor and major events, by AE category

Device	AE supercategory	AE category	Median	Mean	SD	Min.	Max.
BAHA Attract	Major	Device	0	0	0	0	0
BAHA Connect	Major	Device	0	0.02	0.1	0	1.07
Bonebridge	Major	Device	0	0	0	0	0
Carina	Major	Device	0.09	0.12	0.14	0	0.39
CODACS	Major	Device	0	0	0	0	0
Esteem	Major	Device	0	0	0	0	0
MET	Major	Device	0.1	0.19	0.25	0	0.56
Ponto	Major	Device	0.04	0.07	0.09	0	0.23
Sophono	Major	Device	0	0.01	0.04	0	0.13
Soundbridge	Major	Device	0	0.02	0.08	0	0.54
Soundtech	Major	Device	0	0	0	0	0
BAHA Attract	Major	Not specified	0	0.01	0.02	0	0.04
BAHA Connect	Major	Not specified	0.02	0.08	0.14	0	0.85
Bonebridge	Major	Not specified	0	0.03	0.05	0	0.17
Carina	Major	Not specified	0	0.09	0.11	0	0.3
CODACS	Major	Not specified	0.11	0.14	0.05	0.11	0.2
Esteem	Major	Not specified	0.25	0.37	0.42	0	1.14
MET	Major	Not specified	0.08	0.18	0.26	0	0.56
Ponto	Major	Not specified	0	0.02	0.04	0	0.1
Sophono	Major	Not specified	0	0.02	0.05	0	0.15
Soundbridge	Major	Not specified	0	0.03	0.06	0	0.23
Soundtech	Major	Not specified	0	0	0	0	0
BAHA Attract	Major	Patient	0	0	0	0	0
BAHA Connect	Major	Patient	0	0.03	0.05	0	0.32
Bonebridge	Major	Patient	0	0	0	0	0
Carina	Major	Patient	0	0	0	0	0
CODACS	Major	Patient	0	0	0	0	0
Esteem	Major	Patient	0	0	0	0	0
MET	Major	Patient	0	0.05	0.1	0	0.2
Ponto	Major	Patient	0	0	0	0	0
Sophono	Major	Patient	0	0	0	0	0
Soundbridge	Major	Patient	0	0.01	0.02	0	0.11
Soundtech	Major	Patient	0	0	0	0	0
BAHA Attract	Major	Skin	0	0	0	0	0
BAHA Connect	Major	Skin	0.05	0.1	0.14	0	0.64
Bonebridge	Major	Skin	0	0	0	0	0
Carina	Major	Skin	0	0.02	0.05	0	0.18
CODACS	Major	Skin	0	0	0	0	0
Esteem	Major	Skin	0	0.02	0.04	0	0.1
MET	Major	Skin	0.03	0.03	0.04	0	0.08
Ponto	Major	Skin	0.03	0.04	0.03	0	0.08
Sophono	Major	Skin	0	0.01	0.02	0	0.07
Soundbridge	Major	Skin	0	0	0.02	0	0.14
Soundtech	Major	Skin	0	0	0	0	0
BAHA Attract	Major	Surgery	0	0	0	0	0
BAHA Connect	Major	Surgery	0	0	0	0	0
Bonebridge	Major	Surgery	0	0	0	0	0
Carina	Major	Surgery	0	0	0.01	0	0.03
CODACS	Major	Surgery	0.11	0.08	0.07	0	0.13
Esteem	Major	Surgery	0	0	0	0	0
MET	Major	Surgery	0	0.02	0.04	0	0.08
Ponto	Major	Surgery	0	0	0	0	0

Device	AE supercategory	AE category	Median	Mean	SD	Min.	Max.
Sophono	Major	Surgery	0	0	0	0	0
Soundbridge	Major	Surgery	0	0.03	0.07	0	0.29
Soundtech	Major	Surgery	0	0	0	0	0
BAHA Attract	Minor	Device	0	0.09	0.18	0	0.5
BAHA Connect	Minor	Device	0	0.02	0.13	0	1.29
Bonebridge	Minor	Device	0	0	0	0	0
Carina	Minor	Device	0	0.04	0.14	0	0.45
CODACS	Minor	Device	0	0	0	0	0
Esteem	Minor	Device	0	0.02	0.04	0	0.1
MET	Minor	Device	0	0.13	0.26	0	0.53
Ponto	Minor	Device	0	0	0	0	0
Sophono	Minor	Device	0	0.12	0.24	0	0.83
Soundbridge	Minor	Device	0	0.01	0.05	0	0.4
Soundtech	Minor	Device	0	0	0	0	0
BAHA Attract	Minor	Not specified	0	0	0	0	0
BAHA Connect	Minor	Not specified	0	0	0.04	0	0.38
Bonebridge	Minor	Not specified	0	0	0	0	0
Carina	Minor	Not specified	0	0.01	0.02	0	0.08
CODACS	Minor	Not specified	0	0.04	0.06	0	0.11
Esteem	Minor	Not specified	0	0.13	0.33	0	0.81
MET	Minor	Not specified	0	0	0	0	0
Ponto	Minor	Not specified	0	0	0	0	0
Sophono	Minor	Not specified	0	0	0	0	0
Soundbridge	Minor	Not specified	0	0	0.01	0	0.11
Soundtech	Minor	Not specified	0	0	0	0	0
BAHA Attract	Minor	Patient	0.15	0.19	0.22	0	0.6
BAHA Connect	Minor	Patient	0	0.02	0.07	0	0.47
Bonebridge	Minor	Patient	0	0.02	0.04	0	0.1
Carina	Minor	Patient	0	0.01	0.03	0	0.1
CODACS	Minor	Patient	0	0.04	0.08	0	0.13
Esteem	Minor	Patient	0.04	0.14	0.23	0	0.58
MET	Minor	Patient	0	0.12	0.24	0	0.47
Ponto	Minor	Patient	0	0.07	0.14	0	0.38
Sophono	Minor	Patient	0.12	0.12	0.13	0	0.38
Soundbridge	Minor	Patient	0	0.03	0.07	0	0.31
Soundtech	Minor	Patient	0	0.08	0.13	0	0.23
BAHA Attract	Minor	Skin	0.06	0.1	0.12	0	0.33
BAHA Connect	Minor	Skin	0.13	0.27	0.34	0	1.73
Bonebridge	Minor	Skin	0	0.06	0.08	0	0.22
Carina	Minor	Skin	0	0	0	0	0
CODACS	Minor	Skin	0	0.02	0.03	0	0.05
Esteem	Minor	Skin	0.02	0.06	0.07	0	0.15
MET	Minor	Skin	0	0.05	0.11	0	0.21
Ponto	Minor	Skin	0.24	0.31	0.21	0.17	0.77
Sophono	Minor	Skin	0.17	0.18	0.17	0	0.47
Soundbridge	Minor	Skin	0	0.02	0.06	0	0.4
Soundtech	Minor	Skin	0	0.03	0.05	0	0.09
BAHA Attract	Minor	Surgery	0	0.25	0.34	0	0.8
BAHA Connect	Minor	Surgery	0	0.01	0.06	0	0.5
Bonebridge	Minor	Surgery	0	0.01	0.02	0	0.08
Carina	Minor	Surgery	0	0.1	0.21	0	0.67
CODACS	Minor	Surgery	0.21	0.16	0.14	0	0.27
Esteem	Minor	Surgery	0.34	0.38	0.37	0	0.93
MET	Minor	Surgery	0	0.01	0.03	0	0.05
Ponto	Minor	Surgery	0	0.02	0.05	0	0.13
Sophono	Minor	Surgery	0	0.02	0.05	0	0.17
Soundbridge	Minor	Surgery	0	0.07	0.15	0	0.86
Soundtech	Minor	Surgery	0.26	0.29	0.21	0.11	0.51

References

1. Wilson BS et al (2017) Global hearing health care: new findings and perspectives. The Lancet 390(10111):2503–2515
2. Vos T et al. (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and

injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 388(10053): 1545–1602
3. Shield B (2006) Evaluation of the social and economic costs of hearing impairment: a report for Hear-it. London South Bank University, London
4. Carlson ML, Pelosi S, Haynes DS (2014) Historical development of active middle ear implants. Otolaryngol Clin North Am 47(6):893–914
5. Tisch M (2017) Implantable hearing devices. GMS Curr Top Otorhinolaryngol Head Neck Surg 16: Doc06
6. Hüttenbrink KB (1999) Current status and critical reflections on implantable hearing aids. Am J Otol 20(4):409–415
7. Bento RF et al (2012) Bone-anchored hearing aid (BAHA): indications, functional results, and comparison with reconstructive surgery of the ear. Int Arch Otorhinolaryngol 16(3):400–405
8. Kiringoda R, Lustig LR (2013) A meta-analysis of the complications associated with osseointegrated hearing aids. Otol Neurotol 34(5):790–794
9. Golder S, Loke YK, Bland M (2011) Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLOS Med 8(5):e1001026
10. R Core Team (2016) R: A language and environment for statistical computing. 2016, R Foundation for Statistical Computing, Vienna
11. R Studio Team (2015) RStudio: Integrated Development for R. RStudio. RStudio, Inc., Boston

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.