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REVIEW

Laryngoscope Investigative Otolaryngology

Outcomes following cochlear implantation with eluting electrodes: A systematic review

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Abstract

Objectives: To establish audiological and other outcomes following cochlear implantation in humans and animals with eluting electrodes.

Methods: Systematic review and narrative synthesis. Databases searched (April 2023): MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov, and Web of Science. Studies reporting outcomes in either humans or animals following cochlear implantation with a drug-eluting electrode were included. No limits were placed on language or year of publication. Risk of bias assessment was performed on all included studies using either the Brazzelli or Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) assessment tools. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Results: Searches identified 146 abstracts and 108 full texts. Of these, 18 studies met the inclusion criteria, reporting outcomes in 523 animals (17 studies) and 24 humans (1 study). Eluting electrodes included dexamethasone (16 studies), aracytine (1 study), nicotinamide adenine dinucleotide (1 study), the growth factors insulin-like growth factor 1 (IGF1) and hepatocyte growth factor (HGF) (1 study), and neurotrophin-3 (1 study). All included studies compare outcomes following implantation with an eluting electrode with a control non-eluting electrode. In the majority of studies, audiological outcomes (e.g., auditory brainstem response threshold) were superior following implantation with an eluting electrode compared with a standard

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electrode. Most studies which investigated post-implantation impedance reported lower impedance following implantation with an eluting electrode. The influence of eluting electrodes on other reported outcomes (including post-implantation cochlear fibrosis and the survival of hair cells and spiral ganglion neurons) was more varied across the included studies.

Conclusions: Eluting electrodes have shown promise in animal studies in preserving residual hearing following cochlear implantation and in reducing impedance, though data from human studies remain lacking. Further in-human studies will be required to determine the clinical usefulness of drug-eluting cochlear implants as a future treatment for sensorineural hearing loss.

KEYWORDS
cochlear implantation, eluting electrodes, hearing, otology

1 | INTRODUCTION

1.1 | Background and epidemiology

It is estimated that over 1.5 billion people worldwide suffer from hearing loss.[1] In individuals with profound sensorineural hearing loss, cochlear implants (CI) are currently the only feasible solution to auditory rehabilitation.[2] CIs work by electrically stimulating spiral ganglion neurons (SGNs) via an electrode array implanted into the cochlea.[3] However, CI surgery can be viewed as a destructive inner ear procedure,[4] associated in some with a variety of complications, including the acute or delayed loss of residual hearing.[5]

Early hearing loss that occurs immediately postimplantation can be attributed to direct surgical trauma to inner structures of the cochlea, such as the basilar membrane and spiral ligament.[5] Hearing loss that occurs later is complex and multifactorial. Current research suggests a foreign body reaction occurs in the cochlea, causing infiltration of inflammatory cells, release of proinflammatory cytokines, formation of reactive oxygen species, oxidative stress and programmed cell death, or necrosis of different cell types, including hair cells.[6–9] This may be primed by the surgical trauma of insertion due to the implant itself or to biological materials such as blood or bone dust that are introduced into the perilymph. These events result in osteogenesis and fibrosis within cochlear tissues, which affect the impedance and electrical functioning of the implant.[10,11] Equally importantly, this process may enhance the loss of residual hearing. Preservation of residual audiological function post-implantation is highly desirable, for both electroacoustic hearing and preservation of neural spiral ganglion cells. Thus, reducing the loss of residual hearing following cochlear implantation could play an important part in improving hearing outcomes.

1.2 | Complications of cochlear implantation surgery

Surgical technique and implant electrode design are continually evolving to better preserve audiological function. Atraumatic electrode insertion techniques and shorter electrode arrays have enabled a marked reduction in loss of residual hearing after surgery,[12–14] but gradual loss after implantation is still common.[15] The systemic and local administration of agents such as dexamethasone can be used to reduce the inflammatory response to electrode insertion trauma, and help improve audiological outcomes for patients with CIs.[16] Novel advanced drug delivery systems, such as eluting electrodes (EE), can elute anti-inflammatory or growth-promoting agents to protect and enhance residual hearing.

1.3 | Implant based drug delivery

The cochlea is a notoriously challenging structure for effective drug delivery due to the multitude of barriers that need to be overcome in the drug delivery process.[17] Broadly, there are three potential routes for administration of protective agents to the cochlea: systemic, intratympanic or intracochlear.[18] Cochlear implants utilizing EE are a relatively new model of drug delivery. They are designed to reduce the loss of residual hearing through interruption of the inflammatory pathway and/or to promote regeneration within the inner ear,[19] using an intracochlear drug delivery approach.

Drugs eluted from an EE would be in close proximity to the effector sites, enabling a sustained release of agents directly to the target area,[20] overcoming the challenges of systemic therapy.[16] Eluted agents may include steroids, growth factors, and neurotrophins.[21]

2 | OBJECTIVES

The application of dexamethasone and other anti-inflammatory and anti-apoptotic drugs have shown significant improvement in preservation of residual hearing following cochlear implantation.[22] In this review, we wished to assess if the use of EE in cochlear implantation is effective for the preservation of residual hearing post-implantation, evaluating both animal and human evidence. We also wished to assess non-audiological outcomes following implantation of EE, such as cell

survival (e.g., hair cells, spiral ganglion cells) and histological outcomes (e.g., intracochlear inflammation and fibrosis).

1. Population: Humans (with profound sensorineural hearing loss) or animal models.
2. Intervention: Cochlear implantation with a drug-eluting electrode.
3. Comparator: Comparators are expected to vary according to the study type. Comparators may include cochlear implantation combined with administration of drugs via systemic or local routes, and/or implantation with a standard, non-eluting electrode.
4. Outcomes: Change in audiometric outcomes following implantation, measures of fibrosis or the inflammatory response (e.g. impedance values, histology), measures of neural responses (e.g. evoked compound action potentials, auditory brainstem evoked potentials), measures of cell survival (e.g. spiral ganglion neuron / hair cell density and/or number).

3 | METHODS

The study protocol was registered in the PROSPERO prospective database of systematic reviews (CRD42020192022 and CRD42020190620), and this article followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[23] The PRISMA checklists for the systematic review and abstract can be found in Data S2 and S3.

3.1 | Study inclusion criteria

Studies (either human or animal) which reported at least one outcome following implantation with an eluting cochlear implant (of any drug) were eligible for inclusion. All study designs were eligible, including case–control studies, case series, cohort studies and randomized controlled trials. There were no restrictions placed on the follow-up length or the duration of the study. In addition, no restrictions were placed on language. Only studies with full texts available were included. Animal studies included were required to report at least one quantitative outcome, and all studies were required to include at least 10 subjects.

3.2 | Search Strategy

The following electronic databases were searched: MEDLINE, Embase, CENTRAL, ClinicalTrials.gov, and Web of Science including Web of Science Core collection, BIOSIS, Data Citation Index, Derwent innovations index, KCI-Korean Journal Database, Russian Citation Index, SciELO Citation index, and Zoological Records. No limit was placed on language or year of publication. The search strategies used for the databases searched are shown in Data S1. Hand-searching reference lists of the included and relevant systematic reviews and a citation search were conducted to identify additional studies missed from the electronic database searches.

3.3 | Selection of studies

Searches were performed by one author and checked by a second. Titles and abstracts of the studies were screened independently by two authors, and then full texts were reviewed independently by two authors against the inclusion and exclusion criteria. Disagreements at the abstract and full-text screening stages were discussed within the author team and where applicable, a third reviewer was consulted and a consensus was reached in determining eligible studies.

3.4 | Data extraction

A standardized form using Microsoft Excel was used for data extraction from the included studies. This was designed and piloted prior to the data extraction phase. Data were extracted by the first reviewer and then checked by a second reviewer. The data of interest comprised of study characteristics (study design, location, duration) and primary and secondary outcome data. Missing data were sought, where possible, by email contact with study authors. Any discrepancies were identified and resolved through discussion within the author team.

3.5 | Risk of bias assessment

Two authors independently assessed the methodological quality of the included studies. Animal studies were assessed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) tool.[24] Human studies were assessed using the Brazzelli risk of bias tool for nonrandomized studies.[25,26] Any disagreements were resolved through discussion between the two authors, and where necessary, consultation with the third review author.

4 | RESULTS

Searches were initially conducted on May 11, 2020 and updated on April 22, 2023. A flowsheet detailing study selection according to the PRISMA guidelines is shown in Figure 1.

4.1 | Description of Studies

Overall, 18 studies met the inclusion criteria with a total of 547 subjects (24 humans in a single study, and 523 animals across 17 studies). Tables 1–3 provide detailed summaries of each study.

Only one study[20] (published in 2020) assessed the effect of a dexamethasone-EE (eluting electrode) on humans, comparing electrode impedance between two groups of adult cochlear implant recipients up to 24 months following activation: one group receiving a dexamethasone-eluting array and the other group receiving an otherwise identical non-eluting array.

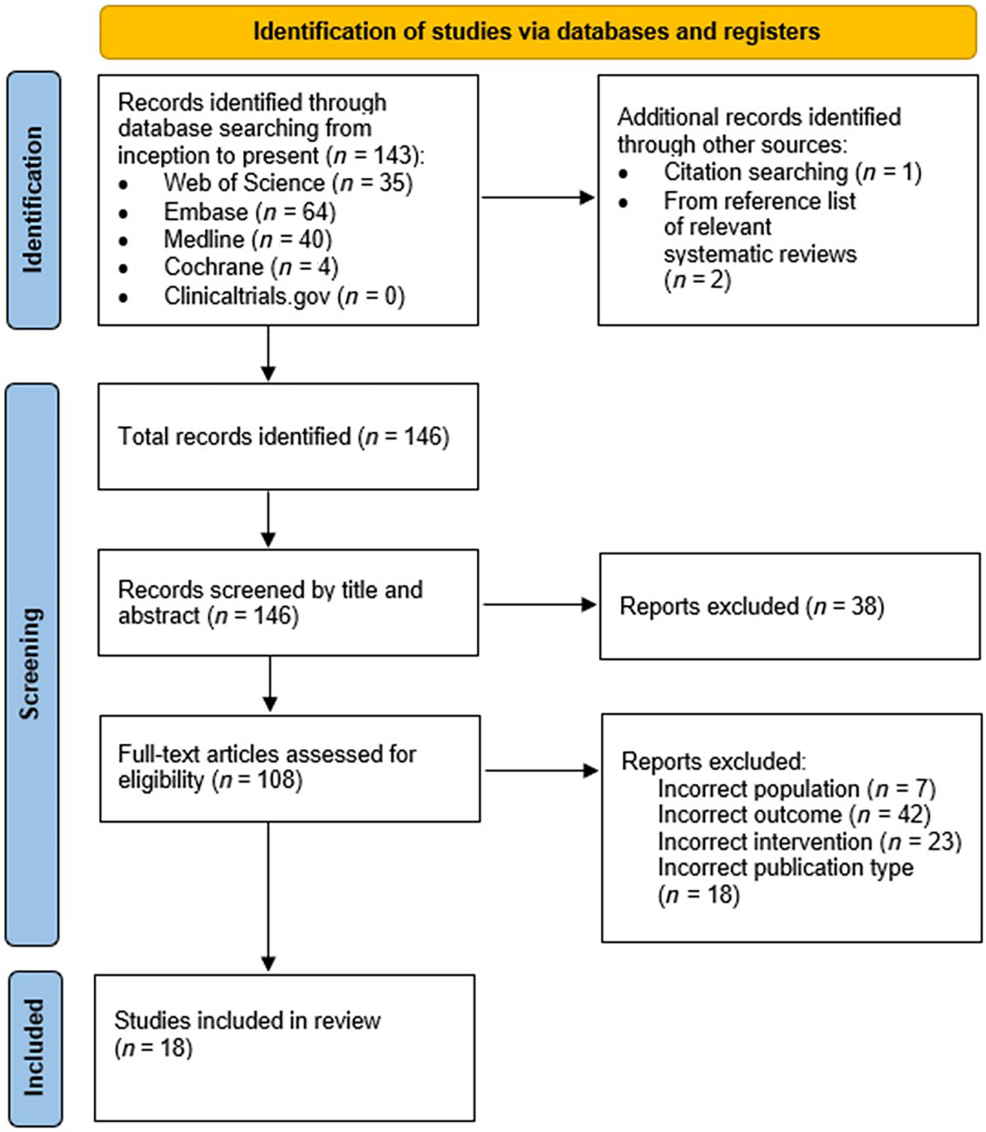

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Seventeen studies[3,5,10,22,27–39] used animal models. These studies were published between 2008 and 2021. Fourteen studies used guinea pigs, two used gerbils, and one used macaques. The substance eluted was described in all 17 studies: 1 assessed growth factors (insulin-like growth factor 1 [IGF-1] and/or hepatocyte growth factor [HGF]), 1 assessed neurotrophin-3, 1 assessed aracytine, 1 assessed nicotinamide adenine dinucleotide, and 15 assessed dexamethasone. The follow-up of animals ranged from 13 to 365 days, with an average follow-up of 123 days. Study characteristics for both human and animal studies included in this review are summarized in Table 1.

4.2 | Quality of studies

The quality of the single human study was assessed using the Brazzelli risk of bias tool, which assesses the quality of studies against 18 domains (Table 4). For the single human study, 13 domains were assessed as having a low risk of bias, 3 were assessed as having a high risk of bias, and in 2 domains the risk of bias was unclear.

The quality of the included animal studies was assessed using the SYRCLE quality assessment tool, which assesses the methodological quality of animal studies against 10 domains (Table 5). Of the 17 animal studies, 2 received a score of 4 (i.e., demonstrated a low risk of bias in 4 domains), 5 received a score of 5, 6 received a score of 6, and 4 received a score of 7 (average quality assessment score of 5.7). The most common domains in which included studies lost points were domains 4 (random housing of animals during the experiment), 5 (blinding of caregivers and/or investigators), 6 (random selection of animals for outcome assessment), and 7 (blinding of the outcome assessor), as the included articles often did not explicitly state whether these features were present in the study.

4.3 | Outcomes—human study

Outcomes reported in the human study are summarized in Table 2. Pre-implantation, all patients had severe-profound hearing loss. The primary outcome measure in this study was post-implantation

TABLE 1 Study characteristics.

	Author, year	Country	Participant type	Study type	Prospective/ retrospective	Number of subjects	Number of study groups	Number of Ears		Drug/agent eluted	Max postimplantation follow-up (days)
								Study	Control(s)		
1	Briggs et al., 2020[20]	Australia	Humans	Cohort study	Prospective	24	2	10	14	Dexamethasone	730
2	Ahmadi et al., 2019[5]	Austria	Animals (Guinea pigs)	Cohort study	Prospective	40	4	10	10	Dexamethasone	120
3	Astolfi et al., 2016[27]	Italy	Animals (Guinea pigs)	Cohort study	Prospective	16	3	10	22	Dexamethasone	14
4	Bas et al., 2016[10]	USA	Animals (Guinea pigs)	Cohort study	Prospective	36[a]	4	27	9	Dexamethasone	90
5	Chambers et al., 2018[28]	Australia	Animals (Guinea pigs)	Cohort study	Prospective	32	4	16	16	Dexamethasone	28
6	Douchement et al., 2014[29]	France	Animals (Gerbils)	Self-controlled study	Prospective	30	1	30	30	Dexamethasone	365
7	Eshraghi et al., 2019[30]	United States	Animals (Guinea pigs)	Cohort study	Prospective	95	5	19	19	Dexamethasone	30
8	Farhadi et al., 2013[31]	Iran	Animals (Guinea pigs)	Cohort study	Prospective	30	3	12	18	Dexamethasone	13
9	Kikkawa et al., 2014[3]	Japan	Animals (Guinea pigs)	Cohort study	Prospective	5	4	Unclear	Unclear	Growth factor (insulin-like growth factor 1 [IGF1] and/or hepatocyte growth factor [HGF])	28
10	Liu et al., 2015[32]	Germany	Animals (Guinea pigs)	Cohort study	Prospective	35	2	18	17	Dexamethasone	168
11	Needham et al., 2020[33]	Australia	Animals (Guinea pigs)	Self-controlled study	Prospective	25	1	25	25	Dexamethasone	28
12	Richardson et al., 2009[34]	Australia	Animals (Guinea pigs)	Cohort study	Prospective	18	4	10	8	Neurotropin NT3	14
13	Stathopoulos et al., 2014[35]	Australia	Animals (Guinea pigs)	Cohort study	Prospective	36	3	24	24	Dexamethasone	90
14	Wilk et al., 2016[36]	Germany	Animals (Guinea pigs)	Cohort study	Prospective	27	3	18	15	Dexamethasone	91
15	Huang et al., 2021[37]	China	Animals (Guinea pigs)	Cohort study	Prospective	65	6	40	25	Dexamethasone aracytine nicotinamide adenine dinucleotide	90
16	Toulemonde et al., 2021[38]	France	Animals (Gerbils)	Cohort study	Prospective	12	2	Unclear	Unclear	Dexamethasone	70
17	Manrique-Huarte et al., 2020[39]	Spain	Animals (Macaques)	Cohort study	Prospective	10	2	5	5	Dexamethasone	183
18	Simoni et al., 2020[22]	Italy	Animals (Guinea pigs)	Cohort study	Prospective	11	2	14	8	Dexamethasone	60

[a]Estimated number of subjects from the article.

TABLE 2 Primary outcomes in human studies.

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
Briggs et al., 2020[20]	**Groups:** Group 1: drug-eluting electrode ($n = 10$) Group 2: control, non-eluting electrode ($n = 14$) **Investigational device:** dexamethasone-eluting electrode on liquid silicone rubber on a standard commercially available CI24RE(CA) cochlear implants (CI) **Drug dose:** ≤15 μg (most ≤10 μg) **Drug concentration:** 40% w/w **Mean release rate:** ~40 ng/mL over 42 days **Mean age of subjects:** 65 years (range 39–81 years) **Hearing loss:** severe/profound	**Surgical details:** In group 1: cochleostomy ($n = 6$), extended round window approach ($n = 4$). In group 2: cochleostomy ($n = 12$), extended round window approach ($n = 2$) **Audiological data:** Not stated	**Impedance data:** **MP1 + 2 mean values:** Eluting electrode group had a lower MP1 + 2 impedance than control postoperatively in all cochlear regions at all time points. Mean across all electrodes and time points: group 1: 5.6 kΩ, group 2: 8.9 kΩ 1 week postoperatively there was a mean decrease of 4.8 kΩ for group 1 and 0.4 kΩ for group 2. **four-point:** Eluting electrode group had a significantly lower four-point impedance than the control group in both the basal and middle cochlear regions by 24 months postoperatively. Basal region: 0.4 kΩ lower in eluting group Middle region: 0.21 kΩ lower in eluting group	Impedance was reduced in the dexamethasone-eluting group compared with the control group over the 2 years of follow-up.	**Brazzelli risk of bias checklist:** low = 13, high = 3, unclear = 2

impedance (considered a proxy marker of fibrosis), which was reported using both MP1 + 2 mean values and four-point values. Briefly, using both MP1 + 2 and four-point measurements, impedance was found to be significantly lower in the dexamethasone-eluting electrode group compared with the control group, up to 24 months post-activation. Adverse events related to implantation with EE were not reported in this study.

4.4 | Summary of outcomes—animal studies

Outcomes (audiological and other) reported in the animal studies are detailed in Table 3. A range of different audiological outcome measures were used, leading to inconsistencies in the reporting of audiological data across studies, ultimately precluding meta-analysis in this systematic review; instead, a narrative synthesis is provided of all included studies. Impedance data were reported in 6 studies, auditory brainstem responses (ABR) were recorded in 13 studies, distortion product otoacoustic emissions (DPOAE) were recorded in 1 study, and compound action potential (CAP) scores were measured in three studies. Histological analysis was also used to assess the following outcomes postoperatively: signs of inflammation, fibrosis, neo-osteogenesis, and survival of hair cells and spiral ganglion cells. Lastly, expression of proinflammatory cytokines (i.e., TNFα, IL-6) was reported in three studies. These outcomes are briefly summarized below and are summarized in detail in Table 3.

4.5 | Audiological outcomes

Out of the 17 included animal studies, 15 reported audiological outcomes following cochlear implantation. ABR was reported in 13 studies, the CAP was reported in 4 studies, and 1 study reported DPOAEs. Overall, audiological data suggested a positive impact of the use of EE: 12 of the 15 studies reported an improved audiological outcome (determined using at least one of the above metrics) following implantation with an eluting electrode compared with implantation with a non-eluting electrode. However, there are some important nuances; for example, Stathopoulos et al.[35] reported an improvement in ABR with an eluting electrode in only one out of the three trials used in this study. In addition, although Douchement et al.[29] found an improvement in ABR threshold with EE at all four frequencies tested at 4–

TABLE 3 Primary outcomes in animal studies.

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
Ahmadi et al., 2019[5]	**Groups:** 4 Group 1: control hydrogel and control electrode ($n = 10$); Group 2: dexamethasone hydrogel and control electrode ($n = 10$); Group 3: control hydrogel and dexamethasone-eluting electrode (EE) ($n = 10$); Group 4: dexamethasone hydrogel and dexamethasone EE ($n = 10$) **Investigational device:** Med-El electrode, preceded by intratympanic injection of hydrogel 24 h prior to implantation **Drug dose:** Not stated **Drug concentration:** Not stated **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing loss:** Normal hearing	**Surgical details:** Guinea pigs anesthetized, retroauricular incision made, cochlear implants (CI) inserted to depth of 4 mm. **Audiological data:** **Auditory brainstem responses (ABR):** performed in both ears approximately one week prior to surgery. Animals with hearing thresholds >45 dB at frequencies between 8 and 32 kHz were excluded.	**ABR:** There was no significant difference in postoperative ABR between the groups. Group 1: Day 120 frequencies 1-8 kHz: range from 26 to 32 dB; 16 kHz: 21 dB; 32 kHz: 23 dB Group 3: Day 120 frequencies 1–8 kHz: ranging from 21 to 29 dB; 16 kHz: 32 dB; 32 kHz: 32 dB **Impedance:** No significant differences in post-implantation impedance between study groups. **Tissue response and signs of inflammation:** No significant difference in mean percentage of the scala tympani occupied by tissue response in mid-modiolar sections: Group 1: 11.75% Group 3: 10.45% **Hair cells:** Preserved across all study groups **Spiral ganglion cells (SGCs):** (Mean density ± SEM [/mm^2]) No significant loss of SGCs in any group. Group 1 ($n = 5$): Basal turn = 1362 ± 71; Middle turn = 1307 ± 93; Apical turn = 1118 ± 72 Group 3 ($n = 6$): Basal turn = 1494 ± 82; Middle turn = 1364 ± 64; Apical turn = 1242 ± 65 **Auditory nerve fiber survival:** Use of a dexamethasone-EE (alone and along with prior administration of a dexamethasone-containing hydrogel) significantly protected auditory nerve fibers compared with the non-EE groups.	Dexamethasone-EE had no significant impact on protection of residual hearing, and had no significant effect on fibrosis, hair cell survival, or spiral ganglion survival postoperatively, although the EE did protect auditory nerve fibers.	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
Astolfi et al., 2016[27]	**Groups:** 3 Group 1: 10% dexamethasone EE ($n = 10$); Group 2: non-EE ($n = 10$); Group 3: control received a cochleostomy ($n = 12$) **Investigational device:** Medical-grade silicone (without a contact or wire inside) **Drug dose:** 86.7 µg (whole rod), 39 µg (first 3 mm of the tip) **Drug concentration:** 10% **Mean release rate:** 3.2 µg/90 days **Mean age of subjects:** Not stated **Hearing loss:** Not Stated	**Surgical details:** guinea pigs anesthetized, posterior auricular incision made, insertion depth 3 mm. **Audiological data:** Compound action potentials (CAPs) were recorded presurgery	**CAP:** Two weeks following implantation, the dexamethasone-eluting group showed a lower mean click threshold shift compared with the non-EE group. Group 1: 1 dB +/− 10 dB Group 2: 10 dB +/− 10 dB Group 3: −4 dB +/− 10 dB **Histology:** Amount of tissue growth in the dexamethasone-eluting group was significantly lower than that observed in the noneluting group. Percentage tissue growth in scala tympani: Group 1 = 3.2% Group 2 = 5.3%	Use of dexamethasone-EE reduced mean click threshold shift post-implantation, and reduced the extent of tissue growth within the scala tympani.	**SYRCLE's risk of bias tool:** Low = 5; high = 1; unclear = 4
Bas et al., 2016[10]	**Groups:** 4 Group 1: 0% micronized dexamethasone base (DXMb) EE ($n = 9$); Group 2: 0.1% micronized DXMb EE ($n = 9$);	**Surgical details:** Guinea pigs anesthetized, posterior auricular incision made, insertion depth of 4.5 mm. **Audiological data:** ABR were recorded presurgery	**ABR thresholds (dB Sound Pressure Level [SPL]):** Use of dexamethasone-EE reduced ABR thresholds at 90 days post-implantation compared with the non-eluting group, with greater reductions seen with higher concentrations of dexamethasone used	The use of dexamethasone-EE reduced ABR and CAP thresholds, led to a reduced impedance, protected against hair cell loss and reduced tissue	**SYRCLE's risk of bias tool:** Low = 4; high = 1; unclear = 5

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
	Group 3: 1% micronized DXMb EE ($n = 9$); Group 4: 10% micronized DXMb EE ($n = 10$) **Investigational device:** Silicone-based cochlear implant electrode arrays **Drug dose:** 0.6 μg, 6 μg or 60 μg **Drug concentration:** 0.1%, 1.0% or 10% **Mean release rate:** 0.1% = 2.5 ng/day; 1% = 15 ng/day; 10% = 47 ng/day over 90 days **Mean age of subjects:** not stated **Hearing loss:** Normal.		Group 1: 0.5 kHz = 66.43; 1 kHz = 59.29; 4 kHz = 50; 16 kHz = 44.38 Group 2: 0.5 kHz = 48.33; 1 kHz = 46.67; 4 kHz = 28.33; 16 kHz = 25 Group 3: 0.5 kHz = 25.71; 1 kHz = 20; 4 kHz = 12.86; 16 kHz = 10 Group 4: 0.5 kHz = 28.33; 1 kHz = 18.33; 4 kHz = 8.33; 16 kHz = 1.67 **CAP thresholds:** Use of dexamethasone-EE led to lower CAP thresholds by 90 days post-implantation, with higher concentrations of dexamethasone generally leading to greater reductions in threshold: Group 1: 0.5 kHz = 67.86; 1 kHz = 59.29; 4 kHz = 54.44; 16 kHz = 47.14 Group 2: 0.5 kHz = 43.44; 1 kHz = 40; 4 kHz = 26.67; 16 kHz = 20 Group 3: 0.5 kHz = 22.86; 1 kHz = 12.86; 4 kHz = 14.29; 16 kHz = 10 Group 4: 0.5 kHz = 25; 1 kHz = 20; 4 kHz = 10; 16 kHz = 0 **Impedance (days after electrode-insertion trauma [EIT]):** At 30, 60, and 90 days post-implantation, the impedance of the dexamethasone-EE was significantly lower compared with the non-EE. Group 1: Day 1 = 7.58; day 3 = 5.94; day 7 = 11.32; day 14 = 14.10; day 30 = 17.09; day 60 = 22.70; day 90 = 23.43 Group 2: Day 1 = 6.03; day 3 = 6.20; day 7 = 6.93; day 14 = 7.37; day 30 = 7,93; day 60 = 9.57; day 90 = 10.87 Group 3: Day 1 = 4.73; day 3 = 4.75; day 7 = 6.30; day 14 = 7.93; day 30 = 8.33; day 60 = 9.57; day 90 = 11.12 Group 4: Day 1 = 7.03; day 3 = 8.28; day 7 = 7.42; day 14 = 10.08; day 30 = 6.58; day 60 = 6.16; day 90 = 6.16 **Protection against hair cell loss:** Dexamethasone-EE protected against loss of hair cells following cochlear implantation compared with the non-eluting group. All concentrations of dexamethasone protected against hair cell loss at the apex. The 1% and 10% dexamethasone-eluting electrode protected against hair cell loss in the basal and middle turns. **Tissue fibrosis:** Cochleae implanted with dexamethasone-EE showed reduced tissue growth within the scala tympani compared with the non-eluting control group.	growth within the scala tympani compared with non-EE.	

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
Chambers et al., 2018[28]	**Groups:** 4. Group 1: Low insertion trauma/ control electrode/intravenous (IV) saline ($n = 8$); Group 2: High insertion trauma/ control electrode/IV saline ($n = 8$); Group 3: High insertion trauma/ dexamethasone-eluting electrode/IV saline ($n = 8$); Group 4: High insertion trauma/ dexamethasone-eluting electrode/IV dexamethasone sodium phosphate ($n = 8$) **Investigational device:** Electrode arrays manufactured by Cochlear Limited (Sydney, Australia) **Drug dose:** Not stated **Drug concentration:** 40% w/w **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing status:** Normal hearing	**Surgical details:** guinea pigs anesthetized, posterior auricular incision made. **Audiological data:** Auditory brainstem responses were recorded 3 days prior to surgery: no difference in ABR threshold between 4 groups.	**ABR:** Use of a dexamethasone-eluting electrode did not significantly protect against postoperative hearing loss. Week 1 Group 2 threshold shifts (dB SPL): 2 kHz = −9 dB SPL; 8khz = −27 dB SPL; 16kz = −35 dB SPL; 24khz = −39 dB SPL; 32khz = −32 dB SPL Week 1 Group 3 threshold shifts (dB SPL): 2 kHz = −10 dB SPL; 8 kHz = −30 dB SPL; 16 kHz = −44 dB SPL; 24 kHz = −39 dB SPL; 31 kHz = -24 dB SPL Week 4 Group 2 threshold shifts (dB SPL): 2 kHz = −24 dB SPL; 8 kHz = −35 dB SPL; 16 kHz = −52 dB SPL; 24 kHz = −49 dB SPL; 32 kHz = −36 dB SPL Week 4 Group 3 threshold shifts (dB SPL): 2 kHz = −20 dB SPL; 8 kHz = −43 dB SPL; 16 kHz = −51 dB SPL; 24 kHz = −49 dB SPL; 32 kHz = −35 dB SPL **Osteogenesis:** Osteogenesis was significantly reduced in the presence of a dexamethasone-eluting electrode **Spiral ganglion neuron (SGN) densities:** Dexamethasone-eluting arrays significantly reduced trauma-induced loss of spiral ganglion neurons **Fibrous tissue:** No significant reduction in intracochlear fibrosis with the use of dexamethasone-eluting arrays	Dexamethasone-EE reduced osteogenesis and loss of spiral ganglion neurons postoperatively, but had no significant effect on ABR threshold shift or intracochlear fibrosis.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4
Douchement et al., 2014[29]	**Groups:** 1 ($n = 30$) Dexamethasone-EE implanted on one side, Control non-EE implanted on the other side (experimental and control ears were randomly selected) **Investigational device:** Silicone electrode array designed by the INSERM 1008 Unit, in collaboration with Neurelec **Drug dose:** Not stated **Drug concentration:** 1% or 10% **Mean release rate:** Not stated **Mean age of subjects:** 3 months **Hearing loss:** Normal hearing	**Surgical details:** Animals anesthetized and a retroauricular incision was made **Auditory data:** Auditory brainstem responses were measured prior to implantation	**ABR thresholds:** At 4–6 weeks, there was a significantly greater preservation of residual hearing in the ears implanted with the dexamethasone-eluting electrode compared with the control ears, at all frequencies tested (16,000, 4000, 1000, 500 Hz), regardless of dexamethasone concentration. At 1 year, the ears implanted with dexamethasone-EE showed a greater preservation of hearing at 16,000 Hz, but a reduced preservation of hearing at 1000 Hz and 500 Hz.	Dexamethasone-EE improved preservation of residual hearing in the short-term (4–6 weeks) across a range of frequencies (500–16,000 Hz). Dexamethasone-EE improved the preservation of residual hearing in the long-term (1 year) only at 16,000 Hz, but not for lower frequencies (500-1000 Hz).	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
Eshraghi et al., 2019[30]	**Groups:** 5. Group 1: EIT with dexamethasone EE exposed to noise trauma (NT) ($n = 13$) Group 2: EIT exposed to NT ($n = 13$)	**Surgical details:** Guinea pigs anesthetized, retroauricular incision made. **Audiological data:** Auditory brainstem responses were measured prior to implantation	**ABR to pure-tone stimuli (1, 4, 8, 16 kHz):** Use of dexamethasone-EE led to a significantly lower shift in ABR threshold following electrode-insertion trauma and noise trauma.	Dexamethasone-EE reduced shift in ABR thresholds and reduced expression of proapoptotic and profibrotic genes.	**SYRCLE's risk of bias tool:** Low = 5; high = 2; unclear = 3

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
	Group 3: NT only ($n = 13$) Group 4: EIT only ($n = 13$) Group 5: Control ($n = 13$) **Investigational device:** Sterile silicone rod with a recording contact 1 mm from tip **Drug dose:** Not stated **Drug concentration:** 10% **Mean release rate:** Ranges from 166 to 49 ng/day (day 5–day 91) **Mean age of subjects:** Not stated **Hearing status:** Normal hearing		ABR threshold shift (dB SPL) for Group 1 at 30 days post-NT: 1 kHz = 12 dB SPL; 4 kHz = 17 dB SPL; 8 kHz = 20 dB SPL; 16 kHz = 16 dB SPL ABR threshold shift (dB SPL) for Group 2 at 30 days post-NT: 1 kHz = 30 dB SPL; 4 kHz = 32 dB SPL; 8 kHz = 32 dB SPL; 16 kHz = 31 dB SPL **Transcript levels of Tumour Necrosis Factor α (TNF-α), TNFα Receptor 1a (TNFαR1a), and Transforming Growth Factor β (TGFβ):** Dexamethasone-EE significantly reduced expression of proapoptotic (TNF-α and TNFαR1a) and profibrotic (TGFβ) genes		
Farhadi et al., 2013[31]	**Groups:** 3. Group 1: Dexamethasone-eluting electrode ($n = 12$) Group 2: Non-EE ($n = 12$) Group 3: Cochleostomy only ($n = 6$) **Investigational device:** Electrodes made of medical-grade silicone elastomer (Nusil, USA) **Drug dose:** Not stated **Drug concentration:** 2% **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing status:** Normal hearing	**Surgical details:** performed on left ear of all animals, animals anesthetized, retroauricular incision made **Audiological data:** not measured	**Inflammatory response:** Overall, dexamethasone-EE reduced the inflammatory response following electrode insertion. Compared with the control group, the group receiving dexamethasone-EE showed reduced fibroblast, macrophage and giant cell infiltration at day 3 ($p = .04$, .04, and .005, respectively), and a reduction in lymphocyte and macrophage infiltration and capillary formation by day 13 ($p = .001$, .015, and .001, respectively).	Dexamethasone-EE showed promise in reducing inflammation following electrode insertion.	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
Kikkawa et al., 2014[3]	**Groups:** 5 Group 1: Insulin-like growth factor 1 (IGF1)-coated electrode Group 2: Hepatocyte growth factor (HGF)-coated electrode Group 3: IGF1- and HGF-coated electrode Group 4: Control (electrode coated with hydrogel not containing growth factors) Group 5: Control (electrode not coated with hydrogel) **Investigational device:** Silicone electrode analogs coated with gelatine hydrogels **Drug dose:** Not stated **Drug concentration:** HGF: 0.05 mg/mL; IGF1: 0.5 mg/mL **Mean release rate:** Not stated **Mean age of subjects:** 4–9 weeks old **Hearing status:** Normal hearing	**Surgical details:** animals anesthetized, retroauricular incision made **Audiological data:** ABR thresholds were measured preoperatively at 4, 8 and 16 kHz	**ABR:** Electrodes eluting either IGF1 or HGF (groups 1 and 2) led to a significantly lower ABR threshold shift following implantation compared with the control groups (groups 4 and 5) at all 3 frequencies tested. Electrodes eluting both IGF1 and HGF (group 3) led to a significantly lower threshold shift compared with the control groups only at 16 kHz. **Hair cell:** Growth factor-EE had no significant effect on hair cell survival. Total hair cell survival rates (mean ± SD): Group 1: 86.1 ± 15.5% Group 2: 84.6 ± 26.7% Group 3: 90.0 ± 10.9% Group 4: 98.3 ± 5.8% Group 5: 95.1 ± 7.0% **Spiral ganglion cell survival:** Use of growth factor-EE had no significant effect on spiral ganglion cell survival post-implantation. Spiral ganglion cell density (mean ± SD): Group 1: 581 ± 483/μm^2 Group 2: 520 ± 386/μm^2 Group 3: 649 ± 628/μm^2 Group 4: 968 ± 466/μm^2 Group 5: 603 ± 480/μm^2	Use of electrodes eluting either IGF1 or HGF led to a lower ABR threshold shift post-implantation, though these EE had no significant effect on hair cells survival, spiral ganglion cell survival or fibrous tissue growth.	**SYRCLE's risk of bias tool:** Low = 4; high = 0; unclear = 6

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
			Fibrous tissue growth: Growth factor-EE had no significant effect on fibrous tissue growth post-implantation. Fibrous tissue thickness (μm): Group 1: 98 Group 2: 160 Group 3: 210 Group 4: 20 Group 5: 140		
Liu et al., 2015[32]	**Groups:** 2. Group 1: Dexamethasone-EE ($n = 18$) Group 2: non-EE ($n = 17$) **Investigational device:** Silicone rod, with no electrode contacts **Drug dose:** 20.4 μg loaded on rod **Drug concentration:** 2% (w/w), 50 ng/mL **Mean release rate:** 101.21 ± 34.04 ng/mL 1 week postoperatively, and no dexamethasone was detected 6 months postoperatively. **Mean age of subjects:** Not stated **Hearing status:** Normal hearing	**Surgical details:** guinea pigs anesthetized, retroauricular incision made, insertion depth 3 mm **Audiological data:** ABR thresholds (at frequencies 1, 2, 4, 8, 12, 16 and 24 kHz) and Distortion Product Otoacoustic Emissions (DPOAE) thresholds (at frequencies 1, 2, 4, 8, 12 and 16 kHz) were measured preoperatively	**ABR thresholds:** Use of dexamethasone-EE led to a lower ABR threshold shift 24 weeks post-implantation at all frequencies tested, reaching statistical significance for frequencies 8, 12, 16 and 24 kHz. Mean threshold shift at 6 months: postoperatively: Group 1: 29–34 dB Group 2: 38–53 dB **DPOAE thresholds:** Following implantation, DPOAE thresholds recovered significantly more in the dexamethasone-eluting group compared with the non-eluting group at frequencies 4 to 16 kHz over 6 months. **Histology:** Immunohistochemistry revealed that dexamethasone-EE led to reduced TNFα staining within the cochlea compared with non-EE. Intensity of TNF-α staining in the basal turn (arbitrary units): Group 1: 7.14 ± 1.94 Group 2: 9.19 ± 1.65	Dexamethasone-EE improved hearing outcomes (measured using ABR and DPOAE thresholds) following implantation compared with non-EE, and seem to reduce TNFα expression within the cochlea.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4
Needham et al., 2020[33]	**Groups:** 1 ($n = 25$) Dexamethasone-eluting array (left ear) Standard non-eluting array (right ear) **Investigational device:** Bifurcated array, with electrodes embedded within a silicone rubber carrier (Cochlear Limited) **Drug dose:** Not stated **Drug concentration:** 40% w/w in liquefied silicone rubber (60%) **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing status:** Normal hearing	**Surgical details:** guinea pigs anesthetized, dorsolateral incision made **Audiological data:** not measured	**Impedance data:** **MP1 + 2 mean values**: Dexamethasone-eluting arrays did not have any significant effect on MP1 + 2 impedance over the 5 weeks of the study compared with the standard non-eluting arrays. **four-point:** Dexamethasone-EE did lead to a significantly reduced four-point impedance compared with the standard non-eluting array, and the effect of dexamethasone in reducing four-point impedance became greater over the 5 weeks of the study. **SGN densities:** Dexamethasone-eluting arrays had no significant effect on spiral ganglion neuron density **Fibrous tissue:** No significant difference in fibrotic tissue growth between the dexamethasone-eluting and non-EE	Use of dexamethasone-eluting arrays significantly reduced four-point impedance over the course of this study compared with control non-eluting arrays, but had no significant effect on MP1 + 2 impedance, SGN survival or fibrous tissue growth.	**SYRCLE's risk of bias tool:** Low = 5; high = 1; unclear = 4
Richardson et al., 2009[34]	**Groups:** 4 Group 1: Non-EE, no electrical stimulation ($n = 4$)	**Surgical details:** Guinea pigs anesthetized, postauricular incision made	**Electrically evoked ABR thresholds:**	Use of NT3-coated electrodes led to lower electrically evoked ABR thresholds post-implantation, and	**SYRCLE's risk of bias tool:**

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
	Group 2: neurotrophin-3-EE, no electrical stimulation ($n = 6$) Group 3: Non-EE, continuous electrical stimulation ($n = 4$) Group 4: Neurotrophin-3-EE, continuous electrical stimulation ($n = 4$) **Investigational device:** Four-ring platinum electrode arrays, developed using materials from Cochlear Limited **Drug dose:** 2 ng **Drug concentration:** Not stated **Mean release rate:** 0.1 ng/day **Mean age of subjects:** Not stated **Hearing status:** Deafened via aminoglycosides prior to CI	**Audiological data:** ABR measurements taken 1 week prior to deafening.	The increase in EABR threshold 2 weeks post-implantation was smaller in group 4 (NT3-EE) compared with group 3 (non-EE) EABR threshold increase over 2-week period post-implantation: Group 3: 54.4% ± 26.8% Group 4: 28.6% ± 20.5% **Impedances of electrodes over 2-week period:** No significant difference in impedance changes over two weeks between the eluting and non-EE groups. Group 3: 99 ± 30% increase Group 4: 141 ± 56% increase **SGN survival**: Compared with the contralateral non-implanted cochleae, the implanted cochleae of Group 4 showed a significantly greater SGN density, whereas there was no significant difference in SGN density between the implanted and non-implanted cochleae of group 3. Group 4 implanted: 1130 ± 42 SGNs/mm^2 Group 4 non-implanted: 995 ± 33 SGNs/mm^2	appears to promote survival of spiral ganglion cells, but had no effect on electrode impedance.	Low = 6; high = 0; unclear = 4
Stathopoulos et al., 2014[35]	**Groups:** Three separate trials Trial 1: Two groups • Dexamethasone-EE (100 μg) in one ear and unimplanted in the other ($n = 6$) • Control electrode in one ear and unimplanted in the other ($n = 6$) Trial 2: Four groups • Dexamethasone-EE (74 μg) in one ear and unimplanted in the other ($n = 3$) • Dexamethasone-EE (74 μg) in one ear and control electrode in other ($n = 3$) • Control electrode in one ear and other ear "not described" ($n = 3$) • Unimplanted in one ear and other ear "not described" ($n = 3$) Trial 3: One group • Dexamethasone-EE (89 μg) in one ear and control electrode in the other **Investigational device:** Platinum ring electrodes embedded in a silicone rubber elastomer (Cochlear Limited) **Drug dose:** Trial 1: 100 μg Trial 2: 74 μg; Trial 3: 89 μg **Drug concentration:** Not stated	**Surgical details:** guinea pigs anesthetized, postauricular incision made **Audiological data:** Click-evoked ABR thresholds (at 2 and 32 kHz) measured prior to implantation	**ABR Threshold shift (dB SPL)** Cochleae implanted with a dexamethasone-eluting array in trial 2 showed a reduced threshold shift compared with the control arrays, but in trials 1 and 3 there were no significant differences in threshold shift between cochleae implanted with EE and control electrodes. **SGN number:** No statistically significant difference in SGN density between dexamethasone-eluting groups and control groups across all trials. **Fibrosis:** No significant difference in terms of fibrosis between dexamethasone-eluting groups and control groups across all trials. **Osteogenesis:** No significant difference in terms of osteogenesis between dexamethasone-eluting groups and control groups across all trials.	Dexamethasone-EE had no effect on SGN survival, fibrosis or ossification post-implantation. EE did protect against hearing loss in one of the three trials, but had no protective effect on hearing in the other two trials.	**SYRCLE's risk of bias tool:** Low = 5; high = 0; unclear = 5

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
	Mean release rate: Not stated **Mean age of subjects:** Not stated **Hearing status:** Normal hearing				
Wilk et al., 2016[36]	**Groups:** 3 Group 1: 1% dexamethasone EE Group 2: 10% dexamethasone EE Group 3: Control non-EE **Investigational device:** Two platinum contacts embedded within a medical-grade silicone carrier **Drug dose:** 1% or 10% **Drug concentration:** Not stated **Mean release rate:** 1% = 16 ng/day 10% = 49 ng/day **Mean age of subjects:** Not stated **Hearing status:** Normal hearing	**Surgical details:** guinea pigs anesthetized, retroauricular incision made, implant inserted three times (and removed twice) to amplify trauma (EIT). **Audiological data:** ABR thresholds were measured prior to surgery.	**Impedance:** 3 months post-implantation, impedance in both dexamethasone-eluting groups was significantly lower compared with the control non-eluting group, with the 10% group showing a greater effect. **ABR:** After 91 days, no significant differences in ABR threshold were observed across all groups. **Fibrous tissue growth:** The 10% dexamethasone group showed an approximately 80% reduction in fibrous tissue growth compared with the non-EE group. The 1% dexamethasone group showed an approximately 40% reduction in fibrous tissue growth compared with the non-eluting group (although this difference was not statistically significant).	The use of dexamethasone-EE reduced impedance and fibrous tissue growth post-implantation compared with control electrodes (with a higher concentration of dexamethasone generally leading to a greater effect size), though had no effect on ABR threshold.	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
Huang et al., 2021[37]	**Groups:** 6 Group 1: No implant[10] Group 2: Untreated electrode[15] Group 3: Dexamethasone-eluting[10] Group 4: Aracytine-eluting[10] Group 5: Nicotinamide adenine dinucleotide-eluting[10] Group 6: Dexamethasone + aracytine-eluting[10] **Investigational device:** 0.2 mm diameter carbon–fluorine fiber coated with poly-lactic-co-glycolic acid (PLGA) +/− drug **Drug dose:** Dexamethasone: 100 μg Aracytine: 20 μg Nicotinamide adenine dinucleotide (NAD+): 200 μg **Drug concentration:** Not stated **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing loss:** Normal hearing	**Surgical details:** Animals anesthetized, downward arc incision made from midpoint of posterior groove of ear, tympanic bulla opened and cochleostomy performed. Other cochlea exposed in same way, then obliterated. **Audiological data:** ABR thresholds to pure-tone stimuli measured one hour before surgery, then on days 7, 14, 28 and 90 postsurgery	**ABR threshold:** All groups receiving implant showed a significant increase in ABR thresholds postsurgery compared with no implant group. ABR thresholds continued to increase in untreated electrode (0 days: 59.70 dB SPL, 90 days: 64.60 dB SPL) and NAD+ groups (0 days: 59.90 dB SPL, 90 days: 64.70 dB SPL). However, ABR thresholds decreased significantly in the dexamethasone (0 days: 58.10 dB SPL, 90 days: 51.70 dB SPL) and aracytine groups (0 days: 59.00 dB SPL, 90 days: 51.60 dB SPL), beginning from 7 days postsurgery. The use of both dexamethasone and aracytine conferred no further benefit. **Survival of spiral ganglion neurons:** Significantly higher survival of spiral ganglion neurons seen in the dexamethasone, aracytine and dexamethasone + aracytine groups compared with untreated control. **Survival of hair cells and stria vascularis of cochlea:** Drug-EE had no significant effect	Dexamethasone- and aracytine-EE appear to protect residual hearing (as measured by ABR thresholds) following cochlear implantation, as well as enhancing survival of spiral ganglion neurons. NAD+-EE did not have this protective effect, and no drug-EE increased survival of hair cells or stria vascularis of cochlea.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
Toulemonde et al., 2021[38]	**Groups:** 2 Group 1: Non-EE array Group 2: Dexamethasone-EE array **Investigational device:** Prototype implants supplied by Oticon Medical Consisted of an electrode array (either loaded with dexamethasone or not), 2 stimulus-sensing electrodes and the ground electrode **Drug dose:** Not stated **Drug concentration:** Not stated **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing loss:** Normal hearing	**Surgical details:** Animals were anesthetized, right retroauricular incision was made **Audiological data:** Not measured	**Post-implant cochlear fibrosis:** Significantly lower mean volume of endo canal fibrosis observed in the dexamethasone-eluting group compared with the non-eluting group, determined by light-sheet microscopy. Mean volume of fibrosis: Dexamethasone-eluting group: 2.16×10^8 $\mu m^3 \pm 0.15$ Non-eluting group: 3.17×10^8 $\mu m^3 \pm 0.54$	Use of dexamethasone-EE reduced the extent of fibrosis around the electrode array.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4
Manrique-Huarte et al., 2020[39]	**Groups:** 2 Group 1: Non-eluting implant Group 2: Dexamethasone-eluting implant **Investigational device:** CONCERTO cochlear implant **Drug dose:** 16.8 µg per array **Drug concentration:** Not stated **Mean release rate:** 50% released after 871 h, 95% released after 6 months **Mean age of subjects:** Not stated **Hearing loss:** Normal hearing	**Surgical details:** Animals were anesthetized, right retroauricular incision was made **Audiological data:** ABR thresholds were recorded preoperatively	**ABR threshold:** At 6 months, the mean shift in ABR threshold was lower in the dexamethasone-eluting group compared with the control group. Mean ABR click tone thresholds 6 months post-implantation (dB SPL): Dexamethasone-eluting group: 71.5 Non-eluting group: 80.7 **Impedance:** At 6 months, impedance was smaller in dexamethasone-eluting group compared with the control group. Impedance 6 months post-implantation: Dexamethasone-eluting group: 4.61 ± 1.65 kΩ Non-eluting group: 9.13 ± 1.77 kΩ **Evoked compound action potential (eCAP):** At 6 months, eCAP amplitude produced by a stimulating current of 800cu was approximately 2.5-fold higher in the dexamethasone-eluting group compared with the control group Dexamethasone-eluting group: 1338.86 ± 637.87 µV Non-eluting group: 545.00 ± 137.37 µV **Histological findings:** Tissue reaction (fibrosis and ossification) was higher in the control group than in the dexamethasone-eluting group. There was no difference in mean spiral ganglion cell count between the two groups.	Use of dexamethasone-EE led to a reduced ABR threshold, lower impedance and an increased eCAP amplitude. Dexamethasone-EE also reduced fibrosis and ossification following implantation, but had no effect on spiral ganglion cell survival.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4

TABLE 3 (Continued)

Study reference	Study data	Preoperative data	Postoperative data	Summary	Quality assessment
Simoni et al., 2020[22]	**Groups:** 2 Group 1: Dexamethasone-eluting silicone rods Group 2: Non-eluting silicone rods **Investigational device:** Medical-grade silicone rods, without contact or wire **Drug dose:** Not stated **Drug concentration:** 10% (tip of silicone rod composed of silicone mixed with 10% dexamethasone) **Mean release rate:** Not stated **Mean age of subjects:** Not stated **Hearing loss:** Normal hearing	**Surgical details:** Animals were anesthetized, retroauricular incision was made, insertion depth was 3 mm. For subsequent measurement of CAP threshold, a gold wire was placed near the round window. **Audiological data:** Compound action potential was used to assess auditory threshold immediately before cochleostomy	**CAP threshold shift:** At all frequencies tested, the dexamethasone-eluting group showed a lower threshold shift compared with the non-eluting group, although the differences were not statistically significant. **Tissue growth in scala tympani:** Inflammatory reaction (fibrosis and osteogenesis) around rods was markedly reduced in the scala tympani in the dexamethasone-eluting group compared with control. **Cochleostomy healing:** The dexamethasone-eluting group showed a significantly lower amount of new bone formation compared with the control. **Spiral ganglion integrity:** No significant difference observed in neuronal density between the two groups in any region of the cochlea **Immune reaction:** TNFα was not detected within tissue growth in either group. In the non-eluting group, immune cells (lymphocytes and foreign body giant cells) were detected in the inflammatory tissue, and interleukin-6 (IL-6) was detected in inflammatory tissue growth around the cochleostomy and in the scala tympani; this inflammatory reaction was much lower in the dexamethasone-eluting group.	Use of dexamethasone-EE led to a lower CAP threshold shift, reduced tissue growth within the scala tympani and a reduced inflammatory reaction following implantation. There was no effect on spiral ganglion cell density.	**SYRCLE's risk of bias tool:** Low = 5; high = 0; unclear = 5

TABLE 4 Brazzelli risk of bias assessment (human study).

Author(s), year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Briggs et al., 2020[20]																		

Note: Green = yes (low risk of bias); red = no (high risk of bias); yellow = unclear (unclear risk of bias). 1: Were participants a representative sample selected from a relevant patient population?; 2: Were the inclusion/exclusion criteria of participants clearly described?; 3: Were participants entering the study at a similar point in their disease progression?; 4: Was selection of patients consecutive?; 5: Was data collection undertaken prospectively?; 6: Were the groups comparable on demographic characteristics and clinical features?; 7: Was the intervention (and comparison) clearly defined?; 8: Was the intervention undertaken by someone experienced at performing the procedure?; 9: Were the staff, place, and facilities where the patients were treated appropriate for performing the procedure?; 10: Were any of the important outcomes considered?; 11: Were objective (valid and reliable) outcome measures used, including satisfaction scale?; 12: Was the assessment of main outcomes blind?; 13: Was follow-up long enough (≥ 1 year) to detect important effects on outcomes of interest?; 14: Was information provided on nonrespondents, dropouts?; 15: Were the characteristics of withdrawals/dropouts similar to those that completed the study?; 16: Was length of follow-up similar between comparison groups?; 17: Were the important prognostic factors identified?; 18: Were the analyses adjusted for confounding factors?

6 weeks post-implantation, this improvement was only maintained at one frequency by 12 months post-implantation.

4.6 | Impedance

Impedance following implantation with an eluting electrode was reported in six of the included animal studies. Outcomes were generally more positive following implantation with an eluting electrode compared with implantation with a non-eluting electrode: four of the six studies reporting impedance as an outcome found that subjects receiving an eluting electrode had a lower impedance at the end of the study period. Again, there are some nuances to these findings; for example, Needham et al.[33] found that EE gave an advantage only for four-point impedance and had no effect on MP1 + 2 impedance.

4.7 | Histological outcomes

Histological outcomes were reported in 15 animal studies, although the reported impact of EE on these outcomes were somewhat more varied. For example, the extent of intracochlear fibrosis postimplantation was reported in 11 studies, with a positive outcome associated with the use of EE being found in six. Other histological outcomes reported included hair cell survival (just one out of five studies reporting a positive influence of EE), spiral ganglion cell survival (three out of nine studies reporting greater survival following use of EE), and the presence of immune cells (reduced with EE in both studies reporting this outcome).

4.8 | Expression of inflammatory markers

Three animal studies reported the expression of pro-inflammatory cytokines following implantation, which all suggested that EE aid in reducing inflammation following cochlear implantation. All three reported the expression of Tumour Necrosis Factor α (TNFα), with one study also reporting the expression of Interleukin-6 (IL-6). The two studies reporting just TNFα expression reported reduced expression following implantation with an eluting electrode. The study reporting expression of both TNFα and IL-6 failed to detect expression of TNFα with either type of implant but did report a reduced expression of IL-6 with the use of an eluting electrode.

4.9 | Electrodes eluting a drug other than dexamethasone

Of the 17 included animal studies, 3 used drugs other than dexamethasone. One study used electrodes coated with the growth factors IGF1 and/or HGF, which reported improved hearing function following implantation compared with control electrodes (although the growth factors had no effect on intracochlear fibrosis, or the survival of hair cells or spiral ganglion cells). Another study used electrodes coated with neurotrophin-3 and reported that these electrodes led to improved hearing outcomes and a greater density of spiral ganglion neurons post-implantation compared with uncoated control electrodes (although impedance was not affected in this study). Finally, one study tested electrodes eluting the antimitotic drug aracytine and nicotinamide adenine dinucleotide (NAD+, associated with neuroprotective properties). This study reported that aracytine-EE improved audiological outcomes and survival of spiral ganglion neurons post-implantation compared with control electrodes, but NAD+-EE did not have this protective effect.

4.10 | Surgical outcomes

One of the animal studies stated that no "serious adverse events" occurred during the observation period,[3] and three additional animal studies reported that there were no cases of infection associated with implantation of EE[27,28,35]; the remaining animal studies did not comment on surgical adverse events. All 17 animal studies outlined in detail the surgical technique used, with 5 studies stating the insertion depth of the CI. In addition, at least 18 animals died prematurely; however, this was not thought to be related to surgical technique.

TABLE 5 SYRCLE risk of bias assessment (animal studies).

Author(s), year	1 Sequence generation	2 Baseline characteristics	3 Allocation concealment	4 Random housing	5 Blinding	6 Random outcome assessment	7 Blinding	8 Incomplete outcome data	9 Selective outcome reporting	10 Other sources of bias
Needham et al., 2020[33]										
Chambers et al., 2019[28]										
Eshraghi et al., 2019[30]										
Ahmadi et al., 2019[5]										
Bas et al., 2016[10]										
Astolfi et al., 2016[27]										
Wilk et al., 2016[36]										
Douchement et al., 2014										
Kikkawa et al., 2014[3]										
Stathopoulos et al., 2014[35]										
Richardson et al., 2009[34]										
Farhadi et al., 2013[31]										
Liu et al., 2015[32]										
Huang et al., 2021[37]										
Toulemonde et al., 2021[38]										
Manrique-Huarte et al., 2020[39]										
Simoni et al., 2020[22]										

Note: Green = yes (low risk of bias); red = no (high risk of bias); yellow = unclear (unclear risk of bias). 1: Was the allocation sequence adequately generated and applied?; 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?; 3: Was the allocation adequately concealed?; 4: Were the animals randomly housed during the experiment?; 5: Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?; 6: Were animals selected at random for outcome assessment?; 7: Was the outcome assessor blinded?; 8: Were incomplete outcome data adequately addressed?; 9: Are reports of the study free of selective outcome reporting?; 10: Was the study apparently free of other problems that could result in high risk of bias? Items 1, 3, 8, 9, 10 are in agreement with the items in the Cochrane Risk of Bias tool.

5 | DISCUSSION

This systematic review and narrative synthesis reports on a range of outcomes following cochlear implantation with EE compared with control non-EE.

Despite advancements in electrode array design (including reduced diameter, smooth tip, perimodiolar versus lateral wall),[40,41] surgical approach and the use of lubricants, loss of residual hearing post-implantation is a continuing problem. Currently, there is a lack of evidence-based guidance for hearing preservation, but practice in many surgical centers involves administration of systemic dexamethasone at anesthetic induction, and the application of topical, intratympanic dexamethasone to the middle ear cleft before opening the round window or performing cochleostomy.[42] However, it is questionable whether these methods of dexamethasone delivery penetrate the cochlea effectively to produce a protective effect.

5.1 | Eluting electrode versus a non-EE array

The only human study, by Briggs et al.,[20] found implantation of dexamethasone-EE resulted in consistently lower impedance values when compared with non-EE over the 2-year observational period. This was most evident in the monopolar MP1 + 2 impedance values over the first week following implantation, where there were markedly lower impedance values in the dexamethasone-EE group compared with the non-EE group, suggesting reduced inflammation, fibrosis, or other impedance increasing events. The sustained reduction in impedance values over 2 years is an interesting observation, as the dexamethasone-EE was predicted to follow a 42-day delivery of dexamethasone at the above putative level of ~40 ng/mL. To the authors' knowledge, this remains the only reported trial of dexamethasone-EE in humans, although at least one new in-human study of dexamethasone-eluting cochlear implants is currently in progress, which has shown preliminary safety and effectiveness.[43]

Briggs et al.'s[20] findings are further supported by the animal studies included in this systematic review. The majority of animal studies concluded that the short-term effects of dexamethasone-EE had a protective effect on hearing thresholds, primarily measured using ABR thresholds. Furthermore, many studies reported histological outcomes, including intracochlear fibrosis and the survival of hair cells and spiral ganglion neurons post-implantation, although the protective effect of dexamethasone-EE on these outcomes is less clear based on the studies included in this systematic review.

In addition to dexamethasone-EE, one animal study found both IGF1 and HGF EE to improve audiological outcomes following implantation, although they had no effect on spiral ganglion density and hair cell survival. Nevertheless, these findings suggest that growth factor-EE could promote a recovery of hearing post-implantation when compared with the non-EE counterparts, although further studies investigating the effect of growth factor-EE on preservation of residual hearing post-implantation would be desirable before drawing any firm conclusions as to their potential clinical usefulness.

An additional animal study found neurotrophin-3 EE to be superior to non-EE with regards to post-implantation ABR thresholds and spiral ganglion neuron survival. This positive effect is more pronounced if electrical stimulation was added to the neurotrophin-EE, possibly due to the demonstrated enhanced release of neurotophin-3 from the electrode with stimulation, or because electrical stimulation itself has some protective properties, such as upregulating neurotrophin receptors on neurons.[44,45] Again, further studies using neurotrophin-3-EE would be desirable to support the findings from this single study.

5.2 | Impedance and duration of effect

One possible proxy measure of fibrosis and osteogenesis is the electrode impedance. This consists of two components, the access impedance and the polarizing impedance,[46] but most often only the total impedance is measured in clinical systems. The impedance is a measure of the "resistance" to current flow from an electrode to ground for a given voltage (or in CIs, as they are current sources not voltage sources, the voltage needed for a given current to flow). It is thought that reduced fibrosis and secondary tissue growth is likely to lead to lower impedance,[20] possibly with better battery life and less current spread.

Impedance can also be a useful biomarker of pathology, whereby sudden increases in impedance can predict loss of residual hearing after implantation.[47]

Overall, the studies included in this review (both human and animal) suggest that EE can have a positive effect in reducing impedance post-implantation, although an important consideration when interpreting these results is the length of follow-up in these studies. The human study had a follow-up time of around 2 years, and the longest follow-up period among the animal studies was 1 year, with the majority of studies assessing outcomes over a shorter duration. Therefore, it should be considered that the follow-up periods across the studies included in this review may be too short to enable conclusions to be drawn about the long-term efficacy of EE in reducing impedance. Another consideration is what the long-term drug release profile of such electrodes would be, which so far has been studied in vivo in gerbils for up to 2 years.[48] Future studies with longer follow-up periods may allow us to determine how feasible it is for EE to reduce impedance over the longer term, which is essential to understand when evaluating the potential of EE to be used clinically in humans in future.

5.3 | Beyond residual hearing preservation

So far, the focus of research around EE has been on preservation of residual hearing after cochlear implantation. However, we could speculate that if this approach is ultimately used successfully in humans, the principles could potentially be applied more broadly, perhaps to regenerative therapies for the inner ear. Without

intervention, mammalian hair cells cannot regenerate, although hair cell regeneration has been experimentally induced in mice through transient activity of MYC and NOTCH in supporting cells.[49] Prospective CI recipients are likely to be an early trial group for future regenerative therapies for the inner ear, as this group have the greatest need for such therapies and would already be undergoing a procedure involving the opening of the inner ear. Therefore, it is tempting to speculate that if, in future, mammalian hair cell regeneration can be induced by exposure of the damaged inner ear to exogenous factors, implants could be developed which could elute these pro-regenerative factors, with the aim of inducing regeneration in the damaged inner ear. Thus, in future, the principle of drug-eluting cochlear implants could be applied more broadly, beyond residual hearing preservation and perhaps toward inner ear regeneration.

6 | CONCLUSION

Across the human and animal studies included in this systematic review, audiological outcomes following cochlear implantation with EE appear superior compared with the implantation of non-EE. EE also appear to aid in reducing impedance post-implantation and in reducing expression of pro-inflammatory cytokines. The role of EE in enhancing hair cell and spiral ganglion cell survival post-implantation is less clear. With a rise in the UK's aging population and an increasing demand for cochlear implantation, it is more important than ever to adapt and evolve current practice to maximize positive outcomes following cochlear implantation, and the studies described in this review suggest that EE do have the potential to improve outcomes following cochlear implantation in future.

Despite the overall positive audiological outcomes following implantation with EE, the single human study, generally small sample sizes and relatively short follow-up periods within both the human and animal studies are a cause for caution. Further research is required to understand optimal eluting agents, doses and concentrations for cochlear implantation in humans, as well as potential risks of using such devices. With a better understanding of the role of glucocorticoids or other agents in the peri-implant period, and once eluting electrode design has been optimized further, larger multicenter randomized controlled trials will be needed to provide more compelling evidence of the clinical usefulness and safety of EE, and will be key in establishing a better understanding of both short- and long-term outcomes following cochlear implantation with EE.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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