MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Titanium (Ti) Safety Profile

Report Details

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Executive Summary

Key Points

1. Searches identified 6009 citations; 86 articles were selected for inclusion

2. Very low-quality evidence from 1 study indicated comparable rates between titanium (Ti) and non-Ti devices for local responses (structural valve deterioration, de novo atrial fibrillation) from cardiovascular valves. Low-quality evidence from 2 studies were inconsistent with reporting of systemic responses (e.g., stroke, worsening kidney function, prolonged mechanical ventilation).

3. Very low-quality evidence from 1 systematic review (SR) examining cardiovascular catheters indicated low event rates for extravasation, occlusion, bleeding, and rupture.

4. For cardiovascular implanted devices (low quality evidence from 5 studies), lead dislodgement and migration occurred with pacemakers and subcutaneous implantable cardiac defibrillators (S-ICD), respectively. Thrombosis and bleeding occurred with Ti ventricular assist devices (VADs) and medical management so the association with Ti is unclear. Very-low quality evidence from 4 studies indicated no significant difference between Ti devices and medication management in systemic response (e.g., hepatic dysfunction, transplantation).

5. Very-low quality evidence from 1 SR indicated limited local (bleeding) and systemic responses (ischemic stroke, transient ischemic attack, mortality) from Ti atrial occlusion devices.

6. Low- to very low-quality evidence from 10 SRs indicated dehiscence, marginal bone loss, malocclusion, and paresthesia as common local responses from dental implants.

7. For gastrointestinal and renal implants, very-low quality evidence from 2 SRs indicated that the risk of esophageal wall erosion after using a Ti reflux management system in 9453 worldwide implants increased from 0.05% at 1 year to 0.3% at 4 years. 24 (83%) patients with erosion were symptom free within 1.9 months of device removal. After using intragastric balloons, rates for nausea and abdominal pain were similar with Ti and non-Ti devices.

8. For hematology, very-low quality evidence from 1 SR indicated low rates of deep vein thrombosis (DVT), removal due to port blockage or port/catheter damage from a Ti implanted venous access device. Systemic responses were limited to sepsis.

9. For hearing implants, low-quality evidence from 2 RCTs indicated extrusion, facial palsy, sensory neural hearing loss and severe vertigo as local responses. These responses occurred similarly with non-Ti devices so the association with Ti is unclear. 5 SRs only reporting on Ti implants indicated moderate rates of pain (28%) and soft tissue reactions (26.4%).

10. Very-low quality evidence from 1 RCT indicated low occurrence of malposition and obstruction with a Ti eye stent. Iritis, optic disc and subconjunctival hemorrhage occurred with both Ti eye stents and cataract surgery alone so the association with Ti is unclear.

11.	Subsidence and non-fusion were common local responses for spinal cages (based on low to very-low quality evidence from 10 high-quality studies).
12.	For spinal fixation, 19 events of breakage and fracture were described as definitely/probably related to Coflex interlaminar stabilization devices. 5 metallosis-associated complications (sinuses, seromas) developing after use of Ti growth rods all resolved after the device was exchanged or shortened. Systemic responses included inflammation, metal ion levels, serum Ti levels, and whole blood Ti levels. Evidence was rated low to very-low quality for local responses (based on 10 studies), and low for systemic responses (based on 4 studies).
13.	5 studies examining fixation with rods, screws, or plates reported cyst formation and hardware irritation as local responses. 1 study reported no systemic inflammatory reactions from Ti screws for hallux valgus fixation. Evidence was rated low to very-low quality.
14.	Low quality evidence from 4 studies indicated local responses of aseptic loosening, aseptic failure, and fracture in both Ti and non-Ti knee implants. End-of-stem pain occurred in 7 (23.3%) patients from a Ti implant; small diameter stems later indicated as a predictive factor for stem pain.
15.	Local responses from hip prosthetics (low to very-low quality evidence from 5 studies) included failure of Ti acetabular components and cone fracture in >4% of patients, and aseptic loosening, cervical hypertrophy and hematoma in <2% of patients.
16.	For shoulder prosthetics, low quality evidence from 2 SRs indicated dislocation, failure, fracture, loosening, nerve injury, scapula notching and scapula spur as local responses, however these responses also occurred with non-Ti prosthetics. Stress shielding only occurred with Ti prosthetics (rates were 7.8% and 19% with 2 Ti prosthetics).
17.	Low to very low-quality evidence for disc, sacroiliac, and interphalangeal prosthetics indicated that most local responses (ossification, subsidence, pain and explantation/failure) occurred with both Ti and non-Ti implants.
18.	Local (exposure, hematoma, and seizure) and systemic responses (death) occurred with both Ti and non-Ti cranioplasty implants. Quality of evidence was rated moderate for local (based on 9 studies), and very low for systemic responses (based on 1 study).
19.	Low to very-low quality evidence from 4 studies indicated high rates of foreign body sensation and seroma after placement of Ti-coated mesh and Ti spiral tacks for laparoscopic inguinal hernia repair.
20.	Slippage occurred in 33% of patients with Ti surgical ligating clips. The remaining local responses (including abdominal abscess, cystic duct leak, migration, and pancreatitis), occurred in <1% of patients. 2 studies reporting were rated very-low quality.
21.	Searches of the three ECRI databases including the Patient Safety Organization, Problem Reporting Network, and Accident Investigations databases did not result in reports related to biocompatibility of Ti.

22. There were 594 manufacturer issued and 3 regulatory body issued alerts identified in ECRI's Healthcare Technology Alerts database. The majority of the alerts were unrelated to biocompatibility issues. However, some reports associated with protheses (shoulder, hip, knee), ventricular assist devices, and implantable clips may be related to biocompatibility issues. Examples include material deterioration, adverse tissue reactions, and corrosion.

23. Evidence gaps:

    a. 18 (94%) device categories were rated low or very-low quality of evidence for local responses representing areas with potential gaps in the literature. Cranioplasty implants were the notable exception rated moderate quality of evidence. This category included 9 studies (7 SRs) with mostly similar reporting of local responses from 22500 devices and duplicate reporting with other Ti device categories.
    b. 72 (84%) studies did not investigate systemic responses from Ti devices. Of the 7 device categories that did investigate systemic responses, 4 (57%) device categories only had 1 study investigating. Additional research on systemic responses, including patient or material factors, for all Ti device categories is needed.

Overview - Titanium

FDA engaged ECRI to perform a comprehensive literature search and systematic review (SR) to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to Titanium. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research. Literature searches identified 6009 articles and 86 of those met inclusion criteria for the systematic review.

1. What is the typical/expected local host response to these materials?

Local responses/device events varied somewhat across different device categories (see specific responses/events under 1a. below). Most of the evidence for local responses/events related to Ti came from human studies of titanium-containing orthopedic devices (spinal fixation (e.g., stabilization systems, cages, plates), prosthetics (knee/hip/shoulder/disc/sacroiliac/interphalangeal), and cranioplasty), with most remaining studies providing evidence on local responses/events related to cardiovascular implants, and dental implants. Overall, Ti-containing implants showed evidence of good mid-to-long term survival and few biological/inflammatory complications.

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. Early postoperative local responses (<30 days) from cardiovascular valves included de novo fibrillation (rate 28%) and severe thrombocytopenia (rate 3%). Late postoperative outcomes (>30 days) included moderate or severe patient-prosthetic mismatch (PPM) (rate 14%), prosthetic endocarditis (rate 1%), and structural valve deterioration (SVD).

ii. After placement of cardiovascular catheters, 1 SR reported mechanical complications (e.g., reservoir dislocation and extravasation) and occlusion in 25 (2.7%) and 9 (1%) patients, respectively. Bleeding and rupture occurred in ≤2 patients.

iii. Rates for bleeding (rate 63%), cardiac arrhythmia (rate 42%), and right-sided or right ventricular heart failure (rate 31%) were higher than rates for device thrombosis (rate 6.8%) from a Ti VAD. Delayed wound healing, discomfort, failure, hematoma, and lead migration occurred in less than 1% of patients with a subcutaneous implantable cardiac defibrillator (S-ICD) while lead dislodgement occurred in 2.1% of patients with a Ti pacemaker.

iv. Revisions due to bleeding occurred in 2.8% of patients with a Ti atrial occlusion device (1 SR of 11 single-arm studies).

v. Dehiscence, marginal bone loss, malocclusion, and paresthesia were the most commonly reported local responses from 10 SRs examining dental implants. Foreign body reaction, abscess, and temporomandibular joint dysfunction (TMD) from Ti plates/screws were only reported in 1 SR.

vi. Severe dysphagia occurred in 9.3% of patients treated with a Ti reflux management system (rate 6.6% with laparoscopic fundoplication). Use of intragastric balloons (IGBs) resulted in nausea (rates 55% Ti, 73% non-Ti), abdominal pain (rates 50% to 76% Ti, 59% overall IGBs), and vomiting (rates 16% Ti, 76% non-Ti).

vii. 1 study reported DVT (rate range 0.75% to 3.2%), removal due to port blockage (rate range 0.25% to 0.53%), and removal due to port/catheter damage (0.75% to 2.5%) from a Ti implanted venous access device.

viii. 2 studies examining Ti and non-Ti hearing implants reported similarly low rates for extrusion, facial palsy, sensory neural hearing loss and severe vertigo. 5 SRs examining only Ti implants reported moderate rates for pain (28%) and soft tissue reactions (26.4%) and low rates for device failure (2.6%) and precepting magnet movement (1.5%).

ix. Malposition and obstruction only occurred with a Ti eye stent in ≤5 patients. Posterior capsule opacification, elevated intraocular pressure (IOP), blurry vision/visual disturbance, iritis, and optic disc and subconjunctival hemorrhage occurred with both Ti eye stents and cataract surgery alone. Rates for iritis were the most disparate between groups (5.1% surgery alone, 0.9% Ti stent).

x. Evidence from 10 studies indicated subsidence and non-fusion as common local responses from spinal cages. Osteolysis (5.9% Ti, 7.7% nonTi), and neuropathic pain (5 each arm) occurred less frequently, while neuropathic pain (5 each arm), grafted bone back out (1 patient), hematoma (2 each arm), screw loosening with Ti coated and uncoated polyetheretherketon cages (TiPEEK and PEEK), and screw malposition (only 1 patient) rarely occurred.

xi. Breakage, spinous process fracture, loosening, and migration were reported in studies examining spinal fixation. 19 adverse events (AEs) (e.g., breakage, fracture) were described as definitely/probably related to Coflex interlaminar stabilization device. 5 patients developed metallosis-associated complications (2 sinuses, 3 seromas) with Ti growth rods; all events resolved after the device was exchanged or shortened.

xii. 5 studies examining fixation with rods, screws, plates reported cyst formation in the ganglion tibia and ganglion femur with Ti interference screws. Hardware irritation was reported in 20% of patients with Ti elastic nails.

xiii. One SR reported fewer events of aseptic loosening (3 vs 7) and fracture (2 vs 4) with a Ti sleeve vs tantalum cone in revision total knee arthroplasty (TKA). End-of-stem pain in 7 (23.3%) patients occurred only with a Ti sleeve; analysis indicated that small diameter stems were a predictive factor of stem pain. One RCT (n=100) reported DVT (3) and fracture (1) with Ti knee implants vs 0 events with no surgery. One study reported lower revision rates with Ti-coated vs periapatite-coated knee implants (0.2% vs. 0.8%).

xiv. After hip prosthetic placement, rates for overall failure of Ti acetabular components were 9.9% (vs Tantalum 4.4%), while rates for cone fracture were 4.4% with a modular Ti implant. Aseptic loosening (<2%), cervical hypertrophy (0.3%) and hematoma (0.3%) occurred less frequently.

xv. Local responses occurring with Ti-containing shoulder prosthesis included dislocation, failure, fracture, loosening, nerve injury, scapula notching, and scapula spur however these responses also occurred with non-Ti prosthesis so the association with Ti is unclear. Stress shielding only occurred with Ti (rates of 7.8% and 19% with 2 prosthetics), while heterotopic ossification occurred in 24.8% with Ti and only 1.6% with non-Ti. Hematoma, and rotator cuff rupture rarely occurred.

xvi. Hematoma and pain (due to malposition, sacral nerve impingement, and fracture) occurred with iFuse sacroiliac implants. Ossification occurred with both cervical disc and interphalangeal implants. Explantation/failure of interphalangeal implants (rate 27%) was due to aseptic loosening and subsidence.

xvii. Commonly reported local responses from Ti mesh for cranioplasty included cerebrospinal fluid (CSF) leak, exposure, hematoma, and seizure in 9 studies. Effusion and fracture were only reported in 1 study, while hydrocephalus was only reported in 1 patient.

xviii. Foreign body sensation had the highest incidence rate (30%) after placement of Ti-coated surgical mesh for laparoscopic inguinal hernia repair. Seroma was reported in 3 (75%) studies; rate of 6% after Ti-coated mesh, rate of 23.5% after Ti spiral tacks for polypropylene mesh fixation.

xix. Clip slippage occurred in 10 (33%) patients in 1 small RCT. Abdominal abscess, cystic duck leak, hepatic gallbladder bleeding necessitating reoperation, ileus, migration, and pancreatitis occurred in less than 1% of patients.

b. Over what time course does this local host response appear?

De novo fibrillation from a cardiovascular valve occurred within 30 days, while moderate/severe PPM, prosthetic endocarditis, and SVD occurred >30 days. Bleeding and rupture occurred from cardiovascular catheters at 4 to 8 weeks follow-up, while reservoir dislocation and extravasation occurred at 4 to 12 weeks. Delayed wound healing, failure, hematoma and lead migration with a S-ICD were measured at 61 to 2117 days. Lead dislodgement with a Ti pacemaker was measured up to 44.3 months. Revisions due to bleeding from a Ti atrial occlusion device were measured from 7.2 to 44.8 months.

After fixation with dental plates/screws, swelling, dehiscence, and plate exposure were reported <4 weeks; mobility and malunion were reported at 6 to 12 weeks; and abscess, malocclusion and palpability were reported at >12 weeks follow-up. Failure of Ti implants for replacing missing teeth was reported before prosthetic loading, at 1 year, 3 years, 5 years, and 10 years in 1 SR conducted by the Cochrane Oral Health Group. Risk of esophageal wall erosion after use of a Ti reflux management system increased from 0.05% at 1 year to 0.3% at 4 years. Removal of these systems occurred in 6.7% of patients between 12 and 24 months. DVT and removal due to blockage and port/catheter damage were detected from 0 to 2,996 days (8.2 years) after Ti implanted venous access devices. Soft tissue reactions and implant loss were measured up to 168 months in 1 study examining hearing implants. Local responses such as extrusion and facial palsy were only measured up to 12 months for Ti and non-Ti hearing implants. Stent obstruction and stent malposition occurred within 30 days after placement of a Ti eye stent. Corneal edema, anterior chamber cells, corneal abrasion, discomfort, subconjunctival hemorrhage, blurry vision, and floaters were reported as "early postoperative events" from a Ti eye stent. Other postoperative ocular complications (e.g., posterior capsule opacification, elevated IOP, iritis, optic disc hemorrhage) are through 24-month follow-up.

Subsidence and screw loosening were measured as early as 1 month and 2 months, respectively with TiPEEK spinal cages. Grafted bone back out occurred with TiPEEK cages at 6 to 12 months. Hematoma was reported >12 months. Osteolysis was reported at 12 months with Ti spinal cages. Inflammation occurred in 1 patient each at 5 years and 10 years after a Ti growth rod placement. Spinous process fracture and adjacent segment degeneration occurred 3 months to 66 months post-Coflex interspinous device placement. Mechanical defects were detected 1 day to 6 months, while pain/discomfort and rib nonunion were detected ≥3 months with Ti plate fixation. Fracture occurred intraoperatively with a Ti sleeve, while aseptic failure due to pain and instability was observed at 1 year with Ti-coated TKA implant. For calcar-loading short stems (modular stem with Ti neck, or monoblock Ti stems), revision rates were reported at 7 years; and 50% of aseptic stem loosening occurred in the first year postoperatively with 5 cases occurring after 1.5 to 5 years. Ti-neck fractures occurred a mean 4 years (2 to 9 years) after the original operation. Aseptic loosening of acetabular reinforcement rings occurred after a mean of 6.0 years (1.5 to 14 years). 3 intraoperative periprosthetic fractures occurred with a Ti stem for partial collum THA. Arthrofibrosis followed by avascular necrosis occurred 2 years after a shoulder prosthetic placement. Hematoma occurred postoperatively, loosening and malposition occurred within 6 months, and recurrent sacroiliac joint pain occurred at 1 year from IFuse sacroiliac implants.

Diplopia occurred immediately postoperatively, while enophthalmos was considered a "delayed complication" with Ti mesh for orbital wall reconstruction. Exposure occurred 2 months to 7 years after Ti mesh implantation. 1 SR (reporting on >2200 cranioplasties) indicated occurrence of seizure only in studies with >3 months follow-up. Foreign body reaction of Ti surgical mesh was detected in 15 (30%) patients up to 1-year follow-up. Cystic duct leak occurred intraoperatively, and slippage and migration occurred within 3 months of Ti clip placement.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

Overall, 14 (16%) human studies investigated systemic responses. 13 studies addressing cardiovascular implants (7 studies), hematology (1 study), spinal fixation (4), and cranioplasty (1) identified systemic responses. 1 study investigating fixation with Ti screws for hallux valgus fixation did not identify any systemic manifestations.

b. What are the likely systemic manifestations?

For cardiovascular implants:

- 2 studies reported systemic host responses from a Ti or non-Ti aortic bioprosthetic valve. 1 SR (n=11,135) examining Ti valves (Trifecta) vs cobalt-chromium valves (Perimount) indicated similar mortality rates but significantly higher re-interventions with Ti. 1 nonrandomized comparative study reported more patients with the Ti Trifecta valve received prolonged mechanical ventilation than individuals with a stentless valve while all other systemic response (mortality, postoperative pacemaker implantation, stroke, worsening kidney function) showed no differences between groups.
- Of 4 SRs reporting on VADs, 2 SRs compared Ti VADs with medical management (MM). The 1st SR indicated Ti implants were mostly favored over MM for neurological dysfunction, renal dysfunction, sepsis, and stroke. The 2nd SR reported lower recurrence of thrombosis. Results for mortality were mixed. The remaining 2 SRs reported hepatic dysfunction, renal failure, respiratory failure, sepsis, stroke, and mortality as systemic manifestations of Ti VADs (no non-Ti arms).
- 1 SR of 11 single-arm studies reported ischemic stroke in ≤0.6% of patients, and late mortality in 6.3% of patients. Mortality was not attributable to the AtriClip Ti device.

For Ti ports: 1 SR reported sepsis in 0.75% to 1.9% of patients after Ti port placement.

For spinal fixation:

- 1 SR reported serum Ti levels were significantly greater (by 2.98 ng/mL (95% CI, 1.41 to 4.55 ng/mL) in magnetically controlled growing rods (MCGRs) with Ti vs traditional growing rods (TGRs).
- 1 RCT reported inflammatory responses measured by blood IL-1, IL-6, and TNF-a were low with Ti mesh.
- 2 nonrandomized comparative studies reported on whole blood Ti levels. 1 study reported that median whole blood Ti levels were 2.8 times higher with Ti growth rods vs controls (85 ppb Ti growth rods, 30 ppb controls; statistically significant difference), while another study reported no statistically significant difference in whole blood Ti levels from Ti-instrumented spinal fusion patients vs controls with no implant.

For cranioplasty: 1 SR reported death in 1 patient after Ti mesh placement.

c. What is the observed timeline(s) for the systemic manifestations?

For cardiovascular implants:

- 1 SR measured mortality and re-interventions from Ti valves at median follow-up of 2.5 to 4.5 years. 1 nonrandomized comparative study reported systemic responses all occurred within 30 days.
- 2 SRs comparing Ti VADs with MM measured systemic responses at mean 12.6 months (SD 10.4 months) and mean 24 months. 2 SRs investigating Ti VADs alone reported mortality from 61 days to 2117 days and remaining responses (hepatic dysfunction, renal failure, respiratory failure, sepsis, stroke) at 2-year follow-up.

- Ischemic stroke occurred postoperatively and at long-term follow-up (mean 7.2 to 44.8 months). Transient ischemic stroke was only detected at long-term follow-up.

For Ti ports: 1 SR reported sepsis after catheter indwell up to 8.2 years.

For spinal fixation:

- No follow-up data were provided for 1 SR reporting on serum Ti levels in MCGRs with Ti vs TGRs.
- 1 RCT measured inflammatory response on the second day after surgery.
- 2 studies measuring whole blood Ti levels from Ti growth rods at 6±2 years follow-up, and Ti-instrumented spinal fusion at 12 months postoperatively.

For cranioplasty: Up to 9 years follow-up, 1 SR reported death in 1 patient after Ti mesh placement.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

No studies investigated cellular/molecular mechanisms for systemic responses.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

No studies investigated patient-related factors that may predict, increase, or decrease the likelihood and/or severity of systemic responses.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

1 RCT examining inflammatory responses from Ti mesh vs nanohydroxyapatite (nHA) prosthetics in patients with spinal fractures reported the following: "The degree of inflammatory reaction was closely related to the prosthesis biocompatibility. Concerning IL-1, IL-6, and TNF-a, the inflammatory response of the nHA group was slightly lower than that of the Ti mesh group. Still, there was no significant difference, suggesting that the two prostheses had good biocompatibility in vivo, and nHA was relative better" … "Due to the difference between the hardness of Ti alloy and cortical bone, it is easy to cause the subsidence of Ti mesh because of the stress action after surgery, resulting in the loss of the height between the upper and lower vertebral bodies. The loss of vertebral height will compress the nerve root in the intervertebral foramen and affect the stability of the reconstructed vertebral body."

1 nonrandomized comparative study on patients with scoliosis treated with a sliding rod device made of Ti alloy indicated the following: "Since the biocompatibility of Ti is much higher compared to Co and Cr, which are present in CoCr and stainless steels, it might be hypothesized that the optimization of Ti instrumentation design and improvements in its wear resistance by the application of biocompatible wear resistant coatings would certainly be beneficial…Our findings indicate the importance of using wear resistance materials for sliding and extending instrumentation which is used for the treatment of scoliosis in immature patients."

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

a. Long-term human RCTs for local responses to Ti for all device categories to better ascertain associations with these responses to Ti.

b. Additional research on systemic responses, including those on patient or material factors, for all Ti device categories. Systemic responses were only investigated in 14 (16%) studies with no studies investigating the following categories: cardiovascular catheters, dental, gastrointestinal and renal, neurology, ophthalmic, spinal cages, orthopedic prosthetics, and surgical mesh and ligating clips.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by the FDA based on current priority. For 2022, the following 3 topics were chosen:

1. Stainless Steel (SS)
2. Cobalt-Chromium (CoCr)
3. Titanium (Ti)

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to titanium?
    a. *Can that response vary by location or type of tissue the device is implanted in or near?*
    b. *Over what time course does this local host response appear?*
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    a. *What evidence exists to suggest or support this?*
    b. *What are the likely systemic manifestations?*
    c. *What is the observed timeline(s) for the systemic manifestations?*
    d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps exist and what research is needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and EMBASE were conducted using the EMBASE.com platform. Scopus was used initially to search nonclinical literature; however, we determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2012 and 2022 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
    - Strength
    - Embrittlement
    - Degradation
    - Migration
    - Delamination
    - Leaching

- **Host Response**
    - Local
        - Inflammation
        - Sensitization
        - Irritation
        - Scarring/fibrosis
            - *Keloid formation*
            - *Contracture*
        - Ingrowth
        - Erosion
    - Systemic
        - Cancer
        - Inflammation
        - Immune Response
        - Fatigue
        - Memory Loss
        - Rash
        - Joint Pain
        - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Resulting literature was screened by title review, then abstract review, and finally full article review. Data were extracted from the articles meeting our inclusion criteria to address the key questions for each material.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information.

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in clinical literature. Complications are reported directly by clinical staff; thus, reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a PSO by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from the year 2004 through May 2022, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by PSOs.

Category A (No Error)
Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)
An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)
An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)
An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, harm)
An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, harm)
An error occurred that required intervention necessary to sustain life.

Category I (Error, death)
An error occurred that may have contributed to or resulted in patient death.

Definitions

Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.
Monitoring: To observe or record relevant physiological or psychological signs.
Intervention: may include change in therapy or active medical/ surgical treatment.
Intervention necessary to sustain life: includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation).

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - Titanium

Full Name: Titanium
CAS Registry Number: 7440-32-6

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Ti used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of Ti. The devices recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data can be found in the first column of Table 2.

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of Ti. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices below. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 1 followed by a detailed discussion of research on Ti in the various device categories.

In the summary of results section following Table 1, please note that a statement of "no difference" or "no significant difference" between devices/materials does not imply equivalence between devices/materials, as studies with low numbers of patients or events often lack sufficient statistical power to detect a difference between comparators. In addition, when we cite odds ratio(s), an odds ratio >1 means that the rate was higher in the Ti group than in the non-Ti group.

Table 1: Summary of Primary Findings from the Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Cardiovascular - valves (2 human studies)	De novo atrial fibrillation, infusion of >2 inotropes ±intra-aortic balloon pump, moderate or severe patient-prosthetic mismatch, prosthetic endocarditis, reoperation, severe thrombocytopenia, structural valve deterioration	Very low	All-cause mortality, re-intervention rate, mortality, postoperative pacemaker implantation, prolonged mechanical ventilation, stroke, worsening kidney function	Low
Cardiovascular - catheters (1 human study)	Bleeding, catheter dysfunction, extravasation, occlusion, reservoir dislocation, rupture	Very low	No study investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Cardiovascular – implanted devices (5 human studies)	Bleeding, cardiac arrhythmia, device thrombosis, discomfort, failure, hematoma, lead dislodgement, lead migration, need for right VAD, pericardial complications, premature battery depletion, pump replacement, right sided or right ventricular heart failure, total complications, urgent device exchange	Low	Hepatic dysfunction, mortality, neurological dysfunction, recurrence of device thrombosis, renal dysfunction, respiratory failure, sepsis, stroke, transplantation	Very low
Cardiovascular - other (1 human study)	Revision for bleeding	Very low	Ischemic stroke (postoperative at 0.4%, late at 0.5%), transient ischemic attack (late at 0.6%), mortality (late, 6.3%)	Very low
Dental (10 human studies)	Abscess, bleeding, breakage, dehiscence, exposure, failed tooth eruption, failure, fistula, fluid collection, foreign body reaction, granuloma, malocclusion, marginal bone loss, material-related complications, mobility, pain, palpability, paresthesia, plaque index, plate removal, pocket probing depth, relapse, revision, symptomatic device removal, swelling, temporomandibular joint dysfunction, trismus, overall complications	Low for paresthesia, bleeding, plaque index, and mobility Very low for other local responses	No studies investigated	Very low
Gastrointestinal and renal (2 human studies)	Abdominal pain, dysphagia, erosion, explantation, gastroesophageal reflux disease, nausea, vomiting	Very low	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Hematology (1 human study)	Blockage, damage, deep vein thrombosis (DVT)	Very low	Sepsis	Very low
Neurology (7 human studies)	Abscess, abutment change, abutment removal, adverse skin reactions, aural fullness, cerebrospinal fluid leak, dizziness/vertigo, dura exposure, explantation, extrusion rate, facial palsy, failure (implant), , graft extrusion with residual perforation, hematoma, implant loss, mechanical problems, osseointegration failure, pain, pain unspecified, perichondritis of pinna, precepting magnet movement, post-aural fistula or wound infection, profound deafness, reimplantation, repositioning of floating mass transducer, revision surgery, scar hypertrophy, sensory neural hearing loss, severe vertigo, soft tissue reactions, soft tissue/skin overgrowth, spontaneous loss, taste disturbances due to chorda tympani damage, trauma, tumor	Low	No studies investigated	Very low
Ophthalmic (1 human study)	Abrasion, anterior chamber cells, blurry vision/visual disturbance, discomfort, edema, elevated intraocular pressure, floaters, hemorrhage, iritis, malposition, obstruction, posterior capsule opacification	Very low	No studies investigated	Very low
Orthopedic – cages, spinal (10 human studies)	Cage subsidence, non-fusion, grafted bone back out, hematoma, neuropathic pain,	Low for loosening and cage	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	osteolysis, screw loosening, screw malpositioning	subsidence (migration) Very low for other local responses		
Orthopedic – fixation, spine (10 human studies)	Adjacent segment degeneration, black discoloration, component breakage, device-related AEs (definitely/probably), dural sac rupture, dural tears, fracture (spinous process), intervertebral disc herniation, local inflammation, loosening, metallosis-associated complications, migration, nerve paresthesia, nerve root injury, non-fusion, pain, reoperations, revisions, tissue Ti levels, vertebral fracture	Low for breakage, fracture, loosening, and migration. Very low for other local responses.	Inflammatory rate, metal ion levels, serum Ti levels, whole blood Ti levels	Low
Orthopedic – fixation, other (rod, screw, plate) (5 human studies)	Cyst formation, effusion, foreign body reaction, hardware failure, hardware irritation, malunion, protrusion/telescoping/migration, superficial wounds, synovitis	Low	1 study investigated but did not detect any inflammatory reactions.	Very low
Orthopedic – knee prosthesis (4 human studies)	Aseptic failure, aseptic loosening, DVT, fracture, instability, pain (end-of-stem), revision, stiffness (knee requiring brisement force)	Low	No studies investigated	Very low
Orthopedic – hip prosthesis (5 human studies)	Failure, fracture, gaps, hematoma, hypertrophy, instability, loosening, ossification, perforation, resorption, revision, subsidence	Low for failure and instability Very low for other local responses	No studies investigated	Very low
Orthopedic – shoulder prosthesis (2 human studies)	Arthrofibrosis followed by avascular necrosis, dislocation, failure, fracture (periprosthetic humeral, scapular, or perioperative glenoid),	Low	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	hematoma, heterotopic ossification, impingement, instability, loosening, loss of reduction, nerve injury, nonunion, resorption, revision, rotator cuff rupture, scapula notching, scapula spur, screw penetration, stress shielding			
Orthopedic – disc, sacroiliac, interphalangeal prosthesis (4 human studies)	Ankylosis, boutonniere deformity, calcification and heterotopic ossifications, DVT, dysphagia, explantation/failure, fracture, hematoma, heterotopic ossification, impingement, loosening, malposition, ossification development, pain, pseudoarthritis, pseudarthrosis, reoperation, subsidence, swan neck deformity, vascular complications	Low for ossification Very low for other local responses	No studies investigated	Very low
Orthopedic - cranioplasty (9 human studies)	Cerebrospinal fluid leak, effusion, enophthalmos, exposure, failure/removal/reoperation/revision, extraocular muscle limitation with diplopia fluid collection, fracture, hematoma, hydrocephalus, migration/displacement, poor fit, seizure, seroma, surgical site occurrence or local complications	Moderate	Death	Very low
Surgical mesh (4 human studies)	Chronic pain, decreased sperm motility, foreign body sensation, hematoma, recurrence, seroma	Low for foreign body sensation, hematoma, and seroma Very low for other local responses	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Surgical ligating clips (3 human studies)	Abdominal abscess, cystic duct leak, hepatic gallbladder bed bleeding necessitating reoperation, ileus, migration, pancreatitis, slippage	Very low	No studies investigated	Very low

Cardiovascular – valves

2 human studies (1 SR[1] and 1 nonrandomized comparative study[2]). For further information see Table 3 in Appendix D.

Local Responses (human studies)

One prospective nonrandomized comparative study by Cerqueira et al. 2018[2] reported on biocompatibility-related local AEs for patients receiving either the Freedom Solo or Trifecta aortic bioprosthetic valves. Both valves contained bovine tissue, however, the Freedom Solo was stent-less while the Trifecta valve contained a Ti stent. This study included 658 patients (329 per group) that had propensity-score matched on 21 baseline covariates to produce comparable samples. Patients receiving Trifecta had significantly fewer severe thrombocytopenia events within 30 days (10 vs 26); all other local AEs (e.g., structural valve deterioration, de novo atrial fibrillation) were comparable across groups for measures reported both within and after 30 days.

Systemic Responses

Two studies including a SR[1] and a nonrandomized comparative study[2] reported systemic host responses comparing a Ti against a non-titanium aortic bioprosthetic valve. The SR by Yokoyama et al. 2021[1] included 11,135 patients from six nonrandomized comparative studies receiving either a Trifecta (Ti-containing) or Perimount (cobalt-chromium) valve for aortic valve replacement surgery. Both patient groups reported similar mortality rates (hazard ratio [HR]: 1.09, 95% confidence interval [CI]: 0.75 to 1.58), however, patients receiving the Ti-based Trifecta valve had significantly higher re-interventions (HR: 3.16, 95% CI: 1.83 to 5.46) than the cobalt-chromium based Perimount valve at median follow-up 2.5 to 4.5 years. The other study by Cerqueira et al. 2018[2] found fewer patients receiving prolonged mechanical ventilation after the Freedom Solo stentless valve vs the titanium Trifecta valve. All other systemic responses (mortality, postoperative pacemaker implantation, stroke, worsening kidney function) showed no differences between groups.

Overall Quality of Evidence

Overall quality of the evidence for local responses was rated very low due to limited evidence from 1 lower quality study. Quality of evidence for systemic response was rated as low with evidence being based on a larger sample size (1 SR (n=11135) and 1 nonrandomized comparative study), but mostly dissimilar responses.

Cardiovascular - catheters

1 human study (1 SR[3]). For further information see Table 4 in Appendix D.

Local Responses/Device Events (human studies)

One SR by Fornaro et al. 2018[3] examined 390 patients from 6 single-arm studies who received a port-a-cath system for venous access. Although the study did not mention the type of device in the evidence tables, the available devices all have Ti portals. Patients were majority female (57%) with a median age of 56 years (range 18 to 80 years). The study reported complications between 4 and 12 weeks, as well as specific flushing outcomes at 4- and 8- week intervals. All local AEs had low incidence with the most frequent complications being mechanical complications (e.g., reservoir dislocation and extravasation, 2.7%), and occlusion (1.0%). Study authors also looked specifically at standard vs longer term flushing outcomes for occlusion and total complications, finding no differences between groups.

Overall Quality of Evidence

Evidence was limited to one SR of 6 single-arm studies, so the strength of evidence was rated as very low. The quality of evidence was also rated very low for systemic responses (no studies reporting).

Cardiovascular – implanted devices

Five human studies (5 SRs[4-8]). For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

Five SRs[4-8] reported on local AEs for implantable cardiac devices.

Two SRs[5,6] directly compared VADs made of Ti against medical management. One SR by Cavarretta et al. 2019[5] included eight studies (4 RCTs and 4 nonrandomized comparative studies, n=2288) that examined four types of individual VADs, including the HeartMate II, HeartMate 3, HeartMate XVE/VE, and HeartWare at mean follow-up of 24 months. Ti VADs were favored over medical management for all responses (bleeding requiring surgical management, device thrombosis resulting in reoperation or removal, and right ventricular failure).

The other SR by Luc et al. 2019[6] included two clinical trials, four registries, and 37 cohort studies, and also compared surgery (including insertion of a VAD) against medical management. The two outcomes, success rate and urgent device exchange, favored surgical management at mean follow-up of 12.6 months. Data for urgent device exchange was derived from comparative data from cohort studies, whereas success rate contained comparative data from trials and cohort studies (with consistent results across study type).

One SR[4] of 3 RCTs (n=1011) compared Ti VADs (HeartMate II vs Heartmate HVAD) up to two years follow-up. Pump replacement rates were higher for patients receiving HeartMate HVAD, but all other local AEs (bleeding, cardiac arrhythmia, pump thrombosis, right heart failure) showed no differences between groups.

The last two SRs by Shurrab et al. 2018[7] and Chue et al. 2017[9] included patients receiving the MedTronic CapSure Fix Pacing System or subcutaneous implantable cardioverter defibrillators (S-ICDs), respectively, without any non-Ti control group. Shurrab et al. 2018[7] did contain a comparison by whether the pacemakers were MRI-conditional or conventional, and the review included over 2,000 patients followed up between one and 44.3 months. The authors noted lead dislodgement and pericardial complications occurred less frequently for patients receiving conventional pacemakers, however, total complications saw no differences between groups. The SR by Chue et al. 2017[9] contained 16 single-arm studies; 1,670 patients were followed up for 61 to 2,117 days. Although the study refers to S-ICD devices without study-level information on device type, one type of S-ICD is manufactured in the United States (EMBLEM, Boston Scientific). Premature battery depletion occurred most frequently (1.16%) while discomfort (0.75%), delayed wound healing (0.61%), hematoma (0.44%), failure of device communication (0.32%), and lead migration (0.28%) occurred less frequently.

Systemic Responses

Four SRs[4-6,8] reported on systemic AEs for implantable cardiac devices.

Both previously mentioned SRs[5,6] comparing Ti VADs with medical management also reported systemic AEs. In the SR by Cavaretta et al. 2019,[5] VAD implantation was mostly favored over medical management for neurological dysfunction, renal dysfunction, sepsis, and stroke. For mortality however, medical management was preferred vs 3 (75%) VAD devices (based on evidence from RCTs). No information was provided on respiratory failure in VADs vs medical management.

The SR by Luc et al. 2019[6] found less frequent incidence of mortality and recurrence of device thrombosis with surgical management vs medical management. These estimates should be interpreted carefully because the conclusion for recurrence only included cohort studies, and the conclusions for mortality differed between subgroups of RCTs and cohort studies. Both groups saw similar rates of requiring transplantation. No comparative evidence was available for the outcome of hemorrhagic stroke.

The final two SRs[4,8] did not contain a non-Ti control group. An SR by Tang et al. 2020[4] examined the HeartMate II and HeartMate HVAD VAD devices. All outcomes (hepatic dysfunction, renal failure, respiratory failure, sepsis, any type of stroke) showed no differences between the two types of Ti VADs. One subgroup of the stroke outcome (other neurological events) had lower incidence in patients receiving the HeartMate HVAD device, however, all other subgroups of stroke (hemorrhagic

stroke, ischemic stroke) found no differences between groups. The SR by Chue et al. 2017[8] only contained mortality as a systemic response, and the total mortality rate was 3.36% with most events occurring after the hospital stay.

Overall Quality of Evidence

Our review examined five SRs reporting local AEs and four SRs reporting systemic responses. Both responses contained two SRs that reported comparative data against medical management, however, the outcomes for systemic responses contained high variability, particularly by type of device limiting the generalizability of the effect of Ti on systemic AEs. Included studies had large sample sizes with varying levels of imprecision around the point estimates. The strength of evidence was judged to be low for local AEs due to imprecision and very low for systemic AEs due to imprecision and inconsistencies by device type.

Cardiovascular – other

1 human study (1 SR[10]). For further information see Table 6 in Appendix D.

Local Responses/Device Events (human studies)

One SR by Toale et al. 2019[10] examined local AEs for patients with atrial fibrillation receiving the AtriClip Ti device followed between 7.2 and 44.8 months. The study examined 922 patients from 11 single-arm studies between the ages of 62.6 and 74 years. Authors examined both short-term and long-term outcomes. They found no leaks in the left atrial appendage, no device-related serious AEs, and a low incidence of revisions due to bleeding events (2.8%).

Systemic Responses

The same SR by Toale et al. 2019[10] also examined systemic AEs for short- and long-term events. 30-day mortality had an incidence of 0%, and postoperative ischemic stroke was rare (4/900, 0.4%). Late mortality was more common (42/667 patients, 6.3%), but no events were attributable to the AtriClip device. Lastly, late ischemic stroke (5/893, 0.5%) and transient ischemic stroke events (6/893, 0.6%) were rare.

Overall Quality of Evidence

Overall quality of evidence for local and systemic responses was rated very low due to evidence limited to 1 SR of single-arm studies reporting minimal events or events not attributed to the clip.

Dental

10 human studies (10 SRs[11-20]). For further information see Table 7 in Appendix D.

Local Host Responses (human studies)

Plate/screw fixation: 4 SRs[11-13,20] addressed this topic.

2 SRs[11,13] of 44 studies (only 4 RCTs) evaluated Ti vs resorbable (non-Ti) fixation. The first SR[11] examined 160 zygomatic fractures treated with Ti (n=77) or non-Ti fixation (n=83) in mostly males aged 14 to 91 years. Contact duration was 6 months to 5 years. Results indicated a significantly lower need for plate removal (Odds ratio (OR): 0.11, 95% CI: 0.02 to 0.81, p=0.03; 4 RCTs, n=72, 0/37 non-Ti, 4/35 Ti) and dehiscence (OR 0.12, 95% CI 0.02 to 0.63) with non-Ti plates versus Ti plates. No significant difference between groups was reported for occurrence of paresthesia (OR 1.56, 95% CI: 0.42 to 5.80).

The second SR[13] examined 1144 mandibular fractures treated with Ti (n=795) or non-Ti fixation (n=349) in children aged up to 17 years. Contact duration was 1.5 to 67 months. At follow-up of 0.3 to 76.5 months, results indicated no significant difference in complication rate (113/795 (14%) Ti vs 36/349 (10%) non-Ti; p=0.07). Overall complications included malocclusion (75%), plate exposure/wound dehiscence (5.5%), failed tooth eruption (3.4%, all 5 events with Ti), paresthesia (2.7%), trismus (2%), and fistula (1.3%). Fluid collection, persistent swelling, granuloma, and severe pain occurred in less than 1% of patients.

1 SR[12] of 14 RCTs examined Ti (n=1391) vs biodegradeable (non-Ti)(n=1160) fixation in 2551 patients aged 16 to 57 years with dentofacial deformities. Follow-up ranged from 8 weeks to 8 years. Materials used for biodegradeable fixation included poly-L-lactic acid, poly-DL-lactic acid and trimethylene carbonate. Ti and non-Ti osteosyntheses resulted in the following:

- lower (non-significant) rates of abscess (short term, 5% vs 12%), breakage (plates, 0% vs. 4%; screws, 3% vs 0% to 12%), dehiscence (24 vs 37/1000), exposure (0% vs 0% to 9%), malocclusion (113 vs 105/1000), mobility of

bone segments (104 vs 143/1000), revisions (20 vs 28/1000), swelling (short term, 133 vs 201/1000; long term, 20 vs 49/1000), and symptomatic device removal [mostly due to discomfort] (83 vs 107/1000) with Ti plates/screws
- similar rates of abscess at 1 year (3%), and malunion (0%)
- higher rates of palpability with Ti (232 vs 89/1000)
- mixed results for relapse (due to location): Ti significantly favored for mandibular angular, biodegradeable significantly favored for mandibular vertical, no significant difference for maxillary vertical

Responses were reported at short-term follow-up (0 to 4 weeks): swelling, dehiscence, plate exposure; intermediate follow-up (6 to 12 weeks): mobility of bone segments, and malunion; long-term follow-up (>12 weeks): abscess, malocclusion, symptomatic device removal, palpability; and overall follow-up: revision (not device removal).

1 SR[20] of 20 studies (7 RCTs, 12 nonrandomized comparative) examined 1673 absorbable (non-Ti) vs non-absorbable Ti plates/screws (n=775) for maxillofacial fixation. Individuals (gender NR) aged 11 to 71 years were followed up to 8 years. In all maxillofacial surgeries, non-Ti fixation was associated with significantly more overall complications (n=5604: relative risk (RR) 1.20, 95% CI: 1.02 to 1.42; p=0.03), foreign body reaction (6 studies, n=436: RR 1.97; 95% CI: 1.05 to 3.68; p=0.03), and mobility (3 studies, n=108: RR 5.64; 95% CI: 1.10 to 28.85; p=0.04) vs non-absorbable Ti fixation. Results also indicated no significant difference between groups for temporomandibular joint dysfunction (4 studies, n=384: RR 1.00; 95% CI: 0.47 to 2.12; p=1.00), paresthesia (3 studies, n=135: RR 1.08; 95% CI: 0.61 to 1.93; p=0.78), fistulation (4 studies, n=413: RR 2.09; 95% CI: 0.87 to 5.01; p=0.10), palpability (5 studies, n=645: RR 0.90; 95% CI: 0.70 to 1.15; p=0.38), dehiscence (6 studies, n=518: RR 1.12; 95% CI: 0.65 to 1.93; p=0.69), malocclusion (4 studies, n=593: RR 1.11; 95% CI: 0.63 to 1.97; p=0.72), material-related complications (5 studies, n=545: RR 1.70; 95% CI: 0.63 to 4.56; p=0.30), exposure (5 studies, n=266: RR 1.83; 95% CI: 0.71 to 4.75; p=0.21) and relapse (5 studies, n=482: RR 1.41; 95% CI: 0.62 to 3.17; p=0.41).

Abutments: 3 SRs[15-17] addressed this topic.

1 SR[15] of 10 studies (6 RCTs, 4 nonrandomized comparative studies) examined overdenture and crown implants with Ti (n=154) vs zirconia (n=187) abutments. The study population was 64% female aged 28 to 60 years, and the mean follow-up was 24 months (range 3 to 72 months). Non-Ti abutments were favored for marginal bone loss (MBL, mean difference (MD) -0.09, 95% CI: -0.17 to 0.00; p=0.05) and pocket probing depth (PPD, MD -0.18, 95% CI: -0.32 to -0.05; p=0.008).

1 SR[16] of 10 RCTs examined Ti (n=94) vs non-Ti (zirconia (n=55), aluminum (n=46)) abutments connected to an implant. Mean follow-up was 36.69 months (range 12 months to 86.4 months); patient characteristics were not reported. Results indicated significantly more bleeding with Ti vs zirconia, but no significant difference between materials for other local responses.

Bleeding on probing (BOP) (mucosal inflammation):

- Ti vs aluminum: 3 RCTs, weighted mean difference (WMD) 4.83, -3.98 to 13.65; p=0.23
- Ti vs zirconia: 3 RCTs, WMD -26.96, 95% CI: -45.0 to -8.9, p=0.003

MBL:

- Ti vs aluminum: 3 RCTs, WMD 0.15, 95% CI: -0.02 to 0.33; p=0.09
- Ti vs zirconia: 4 RCTs, WMD -0.07, 95% CI: -0.34 to 0.18; p=0.56

PPD (mm):

- Ti vs zirconia: 3 RCTs, WMD -0.13, 95% CI: -0.61 to 0.34; p=0.57

Plaque index (PI):

- Ti and aluminum: 2 RCTs, WMD -1.30, 95% CI: -12.23 to 9.62; p=0.81
- Ti and zirconia: 1 RCT, MD -20.0, 95% CI: -41.47 to 1.47; p=0.06

1 SR[17] of 29 studies (15 RCTs, 5 nonrandomized comparative studies, 9 single arm) examined Ti vs alumina, gold, and zirconia abutments. The study included 954 patients (1266 implants); characteristics were not reported. Mean contact duration was 30.05 months (range 6 to 67 months). Results indicated significantly more bleeding with Ti vs zirconia abutments, but no significant difference between materials for other local responses.

MBL:

- Ti vs alumina: 2 studies, WMD 0.15, 95% CI: -0.04 to 0.36; p=0.13
- Ti vs gold: 3 studies, WMD 0.04, 95% CI: -0.30 to 0.30; p=0.98
- Ti vs zirconia: 9 studies, WMD 0.018, 95% CI: -0.063 to 0.099; p=0.66

BOP (%):

- Ti vs alumina: 3 studies, WMD 7.1, 95% CI: -0.18 to 14.42; p=0.06
- Ti vs zirconia: 3 studies, WMD -26.9, 95% CI: -45.0 to -8.9; p=0.003

Plaque (%):

- Ti vs alumina: 3 studies, WMD -4.0, 95% CI: -13.61 to 5.48; p=0.40
- Ti vs zirconia: 1 study, MD -20.0, 95% CI: -41.4 to 1.47; p=0.06

Overall complications (abutment fracture, abutment rotation, crown adaption problems, crown fracture, loss of retention, screw loosening, veneer chipping, veneer fracture)

- Ti vs all materials: "In the controlled studies, the incidence of complications was slightly higher in the test groups than in the Ti group (8.7% vs 5.9%; RR 1.27, 95% CI: 0.64 to 2.53; p=0.49)."

Overdentures: 1 SR[14] of 2 RCTs examined Ti vs ceramic (zirconia) implants for overdentures in 38 patients with mean age 62 years. Implants were placed in the maxilla (125), mandible (95), and palatal regions (38). At >1-year follow-up, results indicated a significant difference favoring Ti for failure rates (20/126 Ti vs 42/153 for ceramic; RR 0.58, 95% CI: 0.36 to 0.94; p=0.03) and mean MBL (0.15 mm Ti, 0.33 mm ceramic; MD -0.15, 95% CI: -0.23 to -0.07; p=0.0002). Failures were all due to osseointegration except for 3 ceramic implants which failed due to fracture.

Barrier materials: 1 SR[18] of 67 studies (23 RCTs and 44 nonrandomized comparative studies) examined barrier materials used in lateral and vertical ridge augmentation including Ti mesh (n=478), collagen-based membrane applications (n=2234), non-resorbable synthetic barriers (extended/dense polytetrafluoroethylene (n=717), and polymer membranes (n=186)). Mean follow-up was 27.4 months (range 3 to 168 months); patient characteristics were not reported. Results indicated that collagen-based barriers (10.4±16.7%) and polymer membrane (37.4±26.5%) (p=0.621) were associated with the lowest and highest complication rates, respectively. Complication rates for Ti mesh (data not specified) were higher than collagen-based barriers (p=0.104).

Ti implants for replacing missing teeth: 1 SR [19] of 27 RCTs, authored by the Cochrane Oral Health Group, addressed this topic. Over 35 Ti devices were examined for early implant failure (before prosthetic loading), failure at 1 year, 3 years, 5 years, and 10 years. No significant differences were reported when comparing different implant systems (4 RCTs), turned versus roughened implants (7 RCTs), different implant surfaces (5 RCTs); implants with different shapes but similar surface preparation and material (7 RCTs), implants with different materials but similar surface preparation and shape (1 RCT); or implants with different surface preparation, shape, material or a combination (13 RCTs). See Table 7 for failure rates by category.

Overall Quality of Evidence

Evidence for paresthesia, bleeding, plaque index, and mobility was in agreement across studies (total N of 1000 to 3000 implants) so we rated the quality as low. Evidence for all other local responses was either inconsistently reported across studies or limited to 1 study reporting so we rated the quality as very low. Evidence for systemic responses was rated very low (no studies reporting).

Gastrointestinal and renal

2 human studies (2 SRs[21,22]). For further information see Table 8 in Appendix D.

Local Responses/Device Events (human studies)

One SR[21] of 35 studies involved a review of a Ti reflux management system's safety in resolving gastroesophageal reflux disease (GERD) alone (n=1452) and compared with laparoscopic fundoplication (LF)(n=485). Another SR[22] of 10 studies examined complications from different subtypes of intragastric balloons (IGB) including one design with Ti components

(n=363). Neither SR included RCTs. Follow-up ranged from 1 to 80 months. Patient gender was only reported in one SR[22] at 71% female, and Ti group size was 363[22] and 1,539 patients,[21] with age ranging from 39 to 54 years.

Dysphagia: Per SR[21], two meta-analyses found a nonsignificant difference comparing the Ti reflux management device to LF, found severe dysphagia in 9.3% of device patients and 6.6% of LF patients.

Erosion: Per SR[21], a study collecting data on 9,453 implantations worldwide until 2017, found that the risk of esophageal wall erosion increased from 0.05% at 1 year to 0.3% at 4 years. 29 patients with erosion had successful device removal; 24 were symptom free within 1.9 months follow-up.

Explantation/removal: Per SR[21], a single-center cohort found that 6.7% of patients had explanted reflux management devices between 12 and 24 months, with the main cause being a recurrence of heartburn or regurgitation.

GERD: Per SR[22], 17% to 24% of Ti balloon patients reported GERD symptoms, compared with 21% in overall IGBs (Ti and non-Ti).

Nausea: Per SR[22], 55% of Ti balloon patients reported nausea, compared with 73% in non-Ti fluid filled IGBs.

Abdominal pain: Per SR[22], 50% to 76% of Ti balloon patients reported abdominal pain, compared with 59% in overall IGBs.

Vomiting: Per SR[22], 16% of Ti balloon patients reported vomiting, compared with 76% in non-Ti fluid filled IGBs.

Overall Quality of Evidence

The quality of evidence for local responses was rated very low due to reporting from SRs consisting of low-quality studies, reporting of 1 SR per category, and inconsistent reporting with other device categories. Systemic responses were also rated very low due to no studies reporting.

Hematology

1 human study (1 SR[23]). For further information see Table 9 in Appendix D.

Local Host Responses (human studies)

Five of 11 studies in SR[23] involved a Ti implanted venous access device. Catheter indwell time ranged to 8.2 years. Relevant group size was 2,396 patients, ranging from 16 to 91 years (patient gender not reported).

Deep Vein Thrombosis /Thrombosis: Thrombosis rates ranged from 0.75% to 3.2% of Ti-port patients, compared to 2.5% for non-Ti ports. Removal due to DVT ranged from 0.25% to 0.59% for Ti port patients, compared to 2.5% for non-Ti ports.

Blockage: Removal due to port blockage ranged from 0.25% to 0.53% of Ti port patients, compared to 1.9% to 3.5% for non-Ti ports.

Damage: Removal due to port/catheter damage ranged from 0.75% to 2.5% of Ti port patients, compared with 2.4% for non-Ti ports.

Systemic Responses

3 studies from SR[23] reported systemic sepsis in 0.75% to 1.9% with Ti ports vs rates of 2.8% to 4.0% with non-Ti ports. Catheter indwell ranged to 8.2 years.

Overall Quality of Evidence

The quality of evidence for local responses was rated very low due to limited reporting of events from 1 study consisting of lower quality studies. Systemic responses were also rated very low.

Neurology

7 human studies (5 SRs[24-28] and 2 RCTs[29,30]). For further information see Table 10 in Appendix D.

Local Responses/Device Events (human studies)

Our review included seven studies[24-30] that examined local AEs for patients undergoing surgical placement of hearing implants. These studies are categorized as neurology since hearing implants are focused on optimizing vibrations received and transduced by the vestibulocochlear nerve.

Two included RCTs[29,30] compared Ti and non-Ti implants. One RCT by Amith et al. 2017[29] enrolled 40 patients with Austin type A ossicular defects and up to 12 months follow-up; 20 patients received an autologous incus implant while the other 20 patients received a Ti partial ossicular replacement prosthesis. All reported AEs (graft extrusion with residual perforation (3 (15%) Ti, 0 non-Ti), perichondritis of pinna (1 (5%) Ti, 0 non-Ti), facial palsy (1 (5%) each arm) were infrequent with no acknowledgment of statistical differences between groups. The other RCT by Faramarzi et al. 2016[30] enrolled 105 patients, 45 receiving the Ti Kurz with omega connector and 60 receiving a Polycel implant. All patients required a two-stage operation and were followed between 6 and 12 months. Both reported local AEs, extrusion rate (2 (4.4%) Ti, 4 (6.7%) non-Ti) and sensory hearing loss (2 (4.4%) Ti, 3 (5%) non-Ti), were uncommon with no differences between patient arms.

The remaining five studies[24-28] were all SRs that only enrolled patients receiving a Ti-based implant. A recent SR by Johansson et al. 2021[24] examined 47 total patients; 35 patients received a bone-anchored hearing system (BAHS) implant while 19 implants were bone anchored implants for auricular epithesis (BAEEs). The authors combined all types of devices for the purposes of their analyses. The most common AEs were adverse skin reactions (23%), and pain (28%), and the less common reported AEs were mechanical problems (3%), trauma (5%), and tumors (5%) between 2 week and 8-year follow-up. No information was provided on patients' baseline characteristics.

Another SR by Kruyt et al. 2020[25] including 20 single-arm studies consisting of 831 patients receiving 952 Ti bone-anchored hearing implants (BAHIs). The type of implant varied in specifications with the majority (72.3%) receiving a small diameter device. Most patients (70.1%) required two stage surgery. Patients were relatively similar in gender characteristics, and only younger (≤21 years of age) patients underwent surgery (mean 8.6 years, range 2 to 21 years). At 168 months follow-up, soft tissue reactions occurred most frequently (26.4%), while revision surgery (16.8%), implant loss (13.3%), and osseointegration failure (6.4%) occurred less frequently. Authors also conducted subgroup analyses based on two types of surgery specifications: one-stage vs two-stage surgery and soft-tissue reduction vs soft tissue preservation techniques. All local AEs had higher incidence rates for two-stage surgery than one-stage surgery. Patients undergoing soft tissue preservation had more frequent revisions and soft-tissue reactions than patients undergoing soft-tissue reduction, however, rates were equivalent for osseointegration failure and implant loss.

The SR by Lagerkvist et al. 2020[26] included 43 single-arm studies consisting of 1,352 patients receiving one of nine versions of a Ponto Ti hearing implant. All reported AEs occurring between 0.5 and 60 months (mean 16.49 months) were infrequent with dura exposure being the most commonly reported at a rate of 6%.

One SR[27] included 234 single-arm studies, however, patient counts were difficult to retrieve from the authors' report of study characteristics. All implants were made of Ti, and the authors reported AEs by type of device. The review also contained a chart (figure 4) of incidence according to follow-up time (<3, 4-6, 7-12, 13-24, 25-48, and >48 months), but the design of the boxplots proved difficult to ascertain the true point estimates. Authors' reports on total complications showed that most patients were likely to have at least one adverse event, but the specific types of AEs had high variability. The most common local responses with active middle ear implants (aMEIs) were taste disturbances due to chorda tympani damage (3%), explantation (2.7%) and implant failure (2.6%). The most common local responses with bone-conducting hearing implants (BCHIs) were skin reactions (Holgers Grade 1 at 6.9%, Holgers Grade 2 at 4.9%) and skin revision surgery due to skin overgrowth or cellulitis (3.8%).

The last SR[28] included both Baha and Ponto implants made of Ti. Authors noted no differences between 2 surgical techniques for adverse skin reactions (rate 11.% open surgery, 8.1% punch technique) at 12 weeks to 24 months.

Overall Quality of Evidence

Our review included seven total studies; two RCTs directly compared Ti and non-Ti hearing implants while five SRs reported events only for patients receiving Ti implants. Most SRs were large with a comprehensive list of local AEs, however, the lack of information on comparative studies limits the ability to determine how many AEs were directly caused by Ti. Also, the two comparative studies were different types of materials (autologous incus and Polycel), creating difficulty in rating consistency in AE reporting. These limitations resulted in a low quality of evidence rating. Systemic responses were rated very low (no studies reporting).

Ophthalmic

1 human study (1 RCT[31]). For further information see Table 11 in Appendix D.

Local Host Responses (human studies)

One RCT compared 98 Ti trabecular micro-bypass stent patients with concomitant cataract surgery with 101 cataract surgery patients alone after 24-month follow-up.

No differences between groups regarding complications were observed. Patients reported experiencing anticipated early postoperative events, as well as posterior capsule opacification, elevated intraocular pressure, visual disturbance, iritis, and optic disc hemorrhage. Complications unique to stent patients were malposition (2.6%) and obstruction (4.3%), which occurred within 30 days postoperatively.

Overall Quality of Evidence

Overall quality of evidence for local responses of a Ti eye stent was rated very low due to limited reporting by 1 small RCT. Systemic responses were also rated very low (no studies investigated).

Orthopedic – cages, spinal

10 human studies (5 SRs,[32-36] and 5 RCTs[37-41]). For further information see Table 12 in Appendix D.

Local Responses (human studies)

Spinal cages for lumbar interbody fusion: 3 SRs[32,34,35] and 4 RCTs in 5 publications.[37-41]

One SR of 3 studies compared cage subsidence in Ti and PEEK cages in 308 patients undergoing lateral lumbar interbody fusion.[32] Two studies reported more subsidence in PEEK cages than Ti cages one year after surgery (100% [21 of 21] of segments vs 81.1% [107 of 132] of segments, p = 0.03; 20.8% [10 of 48] of patients vs 4.5% [2 of 44] of patients, p = 0.012). The third study reported PEEK cages created more endplate injury during surgery than Ti cages (12.4% [21 of 169] of PEEK segments vs 0% [0 of 32] of Ti segments; p=0.04). PEEK was stated to have worse osteoconductivity and bioactivity than Ti.

One SR included 9 retrospective cohort studies, 1 prospective cohort study, and 1 RCT with 743 patients undergoing lumbar interbody fusion and compared Ti cages with PEEK cages.[34] Post-operative hematoma formation was similar between groups (RR 1.30, 95% CI 0.23−7.35, p=0.77). Cage subsidence was slightly higher with Ti cages but not statistically significant (RR 1.82, 95% CI 0.98–3.37, P=0.06). Fusion rate at final follow-up (12 months to 102 months) were similar between groups (OR 1.50, 95% CI 0.57–3.94, P=0.41). In patients who underwent lumbar spine fusion for non-infective conditions (studies examining patients with spinal infections were removed), patients with Ti cages had a higher rate of cage subsidence when compared against PEEK cages (RR 2.17, 95% CI 1.13–4.16, p=0.02). While a Ti cage confers a higher risk of subsidence, there was no difference in postoperative clinical outcomes as compared to patients who had PEEK cages. The authors noted "Due to the difference in modulus of elasticity between Ti and cortical bone, cage subsidence led to postoperative complications such as screw loosening, cage migration, non-union, rod breakage, and may necessitate revision surgery."

One SR included 11 studies and 1,094 patients (8 retrospective observational, 2 prospective comparison studies, and 1 RCT) compared PEEK with Ti and Ti-coated cages used in posterior lumbar interbody fusion (PLIF).[35] PEEK interbody devices were associated with a significantly lower fusion rate compared with Ti interbody devices (OR, 0.62; 95% CI, 0.41–0.93; p = 0.02). Subsidence rates were similar (OR, 0.91; 95% CI, 0.54–1.52; p=0.71). Study follow-up was 6 months to 84 months. The authors believe that Ti-coated PEEK cages reduce subsidence while increasing osseointegration.

One RCT (n=55) compared uncoated PEEK cages and Ti-coated PEEK cages in PLIF.[37] Twelve months after surgery both groups had 100% fusion. No post-operative complications, no revision surgery, and no pseudoarthrosis occurred in either group. The rate of bridging bone outside the cages was 48% in the Ti-coated group and 61% in the uncoated group (not statistically significant).

One RCT (n = 149) compared PEEK cages and Ti-coated PEEK cages in PLIF.[38] By 6 months after surgery, Ti-coated PEEK cages had better fusion rates (odds ratio, 2.27; 95% confidence interval: 1.09– 4.74; P = 0.03). However, at 12 months the fusion rates were Ti-coated PEEK cages 42.0% and PEEK 41.3%, less than that reported in other studies because of a very strict bone fusion definition in this study. Rates of cage subsidence, pedicle screw loosening, and clinical symptoms were not different between the Ti-coated PEEK cages and PEEK groups. At 12 months, 15.6% of Ti-coated PEEK cages and 14.9% of PEEK had subsidence. Two adverse events occurred in the Ti-coated PEEK cages group (one patient experienced screw malpositioning and one experienced a grafted bone back out).

One RCT (n = 75) compared Ti cages with bioactive glass ceramic spacers in 1-level PLIF and reported 12 month and 4-year follow-up data.[39,41] 6-month fusion rates for the bioactive glass ceramics group and the Ti group were 89.7% and 91.4%, respectively. At 12 months, fusion rates based on CT scan were 89.7% and 91.2%, respectively, no significant difference. At 6 months, osteolysis was 7.7% in the bioactive glass group and 5.9% in the Ti group with no significant difference. End plate subsidence in the bioactive glass and Ti groups was 1.10 mm (±0.99) and 0.94 mm (±0.73), respectively, with no significant difference. Sixty-four patients were evaluated at 4 years. Fusion rates were 90.6% in the bioactive glass group and 93.3% in the Ti group, with no significant differences between groups. Osteolysis around the cage and spacer was not observed in either group at 48 months or longer follow-up.

One RCT (n = 127) compared PEEK, Ti-coated, and calcium phosphate-coated PEEK cages in patients undergoing PLIF.[40] At one-year, fusion rates were PEEK 65.6%, Ti-coated 93.9%, and calcium phosphate-coated PEEK 88.0%. Subsidence was not observed in any patients.

Spinal cages for anterior cervical discectomy and fusion:

One SR included 37 studies (design not reported) with 2,363 patients undergoing anterior cervical discectomy and fusion and compared fusion and subsidence rates in patients treated with Ti and PEEK cages.[33] Fusion rates (Ti 84%, PEEK 91%, 26-month median follow-up) and subsidence (Ti 20%, PEEK 26%) were similar.

One SR included 26 studies (12 retrospective cohort studies, 14 retrospective case series, and 4 prospective case series) and 1,133 patients with single or multiple level cervical myelopathy and compared surgical constructs for anterior cervical corpectomy and fusion (Ti mesh cages, nano-hydroxyapatite struts, bone graft alone, corpectomy cages, and PEEK cages).[36] Fusion rates for Ti mesh cages had a range of 93.6% to 100% with 8 studies reporting 100% fusion. Transient dysphagia was reported in 58% of patients in 1 study but was related more to surgical approach than to material used.

Overall Quality of Evidence

Overall quality of evidence for loosening and cage subsidence (migration) was rated low due to being consistently reported across high-quality studies and in agreement with other Ti devices (spinal fixation, cardiovascular implants). The quality of evidence for other local responses and systemic responses (no studies reporting) was rated very low.

Orthopedic – fixation, spinal

10 human studies (6 SRs,[42-47] 2 RCTs,[48,49] and 2 nonrandomized comparative studies[50,51]). For further information see Table 13 in Appendix D.

Local Responses/Device Events (human studies)

Scoliosis:

One SR included 75 studies (2 RCTs, 52 cohort studies, 20 case series, and 1 meta-analysis) of patients undergoing surgical treatment for adolescent idiopathic scoliosis using Ti alloy rods, cobalt-chromium rods, and stainless-steel rods.[42] Revisions did not differ significantly (p>0.05) among rods of different materials or diameters. 3 studies using Ti rods indicated an overall pooled proportion for revision of 6% (95% CI 0.0–12.0%). Two studies using CoCr rods reported revision surgery with an overall pooled proportion of 4% (95% CI 0.0–8.0%).

One SR evaluated complications in early-onset scoliosis patients treated with Ti containing magnetically controlled growing rods or traditional growing rods.[43] A meta-analysis of 7 studies found a lower complication rate among magnetically controlled growing rod patients than traditional growing rod patients (odds ratio 0.42; 95% CI, 0.25 to 0.71). The effect was significant (p = 0.001) but with moderate heterogeneity (I2 = 63%, p = 0.01). Complications included device failure, infections, and unplanned surgical procedures.

One nonrandomized comparative study (25 scoliosis patients and 13 no implanted device patients) compared Ti growth rods (LSZ-4D, Conmet, Moscow, Russia) with no device and reported metallosis and tissue Ti levels.[50] Ti soft tissue content adjacent to implanted sliding device was more than 1,500-fold higher compared with the control group (median concentrations up to 1,300 ug/g). Soft tissues next to implant had a black discoloration indicating significant wear debris. High Ti concentrations were found in tissue 3 cm away from implant capsule (median concentration 6.5 ug/g). Two patients developed local inflammation at 5 and 10 years after surgery; 3 patients developed local seromas or sinus without inflammation between 6 months and 2 years. Clinical symptoms resolved after the device was exchanged or shortened.

Spinal fractures:

One RCT (n = 26) comparing Ti mesh and nanohydroxyapatite prosthesis[48] reported no obvious foreign body reactions after surgery. Prosthesis fusion rate at 1 year was greater than 94% in both treatment groups. Surgical complications (nerve root injuries and nerve paresthesia) were not statistically different, and recurrence remained low at 2 years.

Interspinous devices:

One SR and network meta-analysis included 10 RCTs with 946 patients and compared a Coflex interlaminar stabilization Ti implant with fusion or decompression alone.[45] Four patients with Coflex had complications, including 2 dural sac rupture, 1 Coflex intervention loosening, and 1 vertebral fracture; complication rate was significantly lower in Coflex patients. Dural sac rupture (2), intervention loosening (2), and vertebral fracture (1) also occurred with decompression alone.

One SR and network meta-analysis included 27 studies (5 RCTs and 22 cohort studies) with 2,241 patients and compared interspinous devices (Coflex, Wallis, and X-stop) with PLIF.[44] Coflex and X-stop contain Ti. Five studies reported spinous process fracture occurred in 35 patients with Coflex. Two studies reported intervertebral disc herniation occurred in 12 cases, including 6 in Coflex group and 6 in surgery group. Adjacent segment degeneration was reported in two studies including 7 patients in Coflex group and 17 in PLIF group.

One RCT (n=290) compared Coflex with instrumented fusion in patients with lumbar stenosis and reported need for revisions/reoperations, major-device related complications, and new sensory or motor deficits.[49] Follow-up was 36 months. Important device-related AEs occurred in 8.8% of Coflex patients and 15% of fusion patients; the difference was not statistically significant. Device-related AEs included component loosening (1.9%), component migration (1.4%), component breakage (1.4%), and fracture (3.7%); similar incidence with fusion except fracture which did not occur with fusion. Lastly, reoperations occurred in 30 Coflex patients (15.3%) and 13 fusion patients (13.8%).

Thoracolumbar tuberculosis:

One SR included 8 retrospective studies with 401 patients and compared Ti cages with bone graft alone for treating patients with thoracolumbar tuberculosis.[46] Meta-analysis indicated no differences between the two methods for non-fusion, complications, and recurrence.

Lumbar disc herniation:

One SR included 2 RCTs and 2 retrospective nonrandomized comparative studies with 801 patients and compared the Ti containing Barricaid device with no intervention in the prevention of lumbar disc reherniation after lumbar discectomy.[47] Follow-up was 2 years in 3 studies and 4 years in one study. Reoperation risk was 48% lower in Barricaid-treated patients.

Systemic Responses

One SR evaluated metal ion levels in early-onset scoliosis patients treated with Ti containing magnetically controlled growing rods or traditional growing rods.[43] Meta-analysis found that serum Ti levels were 2.98 ng/mL (95% CI, 1.41 to 4.55 ng/mL) greater in the magnetically controlled growing rod group (n = 30) than the traditional growing rod group (n = 17); the difference was significant (p = 0.0002) and heterogeneity was negligible (I2 = 0%, p = 0.96). The risk of bias was high due to cross-sectional design and baseline differences in comparator groups.

One RCT (n = 26) compared Ti mesh and nanohydroxyapatite prosthesis and reported on inflammatory response on the second day after surgery.[48] Inflammatory responses measured by blood IL-1, IL-6, and TNF-a were low and indicated good biocompatibility.

One nonrandomized comparative study (25 scoliosis patients and 13 no implanted device patients) compared Ti growth rods (LSZ-4D, Conmet, Moscow, Russia) with no device control patients and reported whole blood Ti levels.[50] Median whole blood Ti levels were 30 ppb in control patients and 85 ppb in implant patients, 2.8 times higher than controls and statistically significant.

One prospective nonrandomized comparison study (n = 31) compared Ti instrumented spinal fusion patients with no implant control patients and reported whole blood Ti levels.[51] No statistically significant increase in Ti levels was seen 12 months after surgery (mean difference: -7.2 µg/l, 95% CI: -26.9 to 12.5 µg/l, p = 0.446). Only 4 patients had increased whole blood Ti levels.

Overall Quality of Evidence

The quality of evidence for breakage, fracture, loosening, and migration was rated low due to reporting in ≤2 high quality studies and consistent reporting with other device categories (dental implants, hip prosthetics, spinal cages, and cardiovascular implants). Other local responses were rated very low. Systemic responses were rated low due to limited evidence for responses (e.g., limited number of studies, studies with small enrollment) and inconsistent reporting with other device categories.

Orthopedic – fixation, other

5 human studies (2 SRs,[52,53] and 3 RCTs,[54-56]). For further information see Table 14 in Appendix D.

Local Host Responses (human studies)

One SR including 24 observational studies examined hardware failures in patients with surgically stabilized rib fractures.[52] Ti plates were the most commonly used stabilization hardware (85%), but metal plates were not a factor in predicting hardware failure. Low quality studies prevented accurate hardware failure analysis.

One SR including 67 studies examined intramedullary fixation devices for displaced midshaft clavicle fractures (43 studies of the Ti elastic nail, 10 studies of stainless-steel Rockwood and Hagie clavicle pins, 6 studies of the Sonoma CRx, and 8 studies of other devices).[53] At 12 months, Ti nail patients had hardware irritation in 20%, protrusion/telescoping/migration in 12%, malunion in 7%, and hardware failure in 3%. The stainless-steel clavicle pins had hardware irritation in 22%, malunion in 3%, and hardware failure in 6%.

One RCT (n = 133) compared PEEK with Ti interference screws for anterior cruciate ligament reconstruction.[54] At 2 years, complications included synovitis (PEEK 10%, Ti 22%), cyst formation in the ganglion tibia (PEEK 13%, Ti 18%), and ganglion femur (PEEK 0%, Ti 15%). 4 graft ruptures occurred in the Ti group, but all were due to accidents.

One RCT (n = 168) compared absorbable screws with Ti screws for distal tibiofibular syndesmosis and reported that complications were much higher with non-Ti screws due to foreign body reactions.[55] 4.9% of Ti screw patients reported a complication, all of which were mild foreign body reactions. 33.7% of absorbable screw patients reported a complication, 69% mild and 31% moderate foreign body reactions.

One RCT (n = 26) compared biodegradable magnesium-based screws with Ti screws for hallux valgus fixation and reported no foreign body reactions or osteolysis.[56]

Systemic Responses

One RCT (n = 26) compared biodegradable magnesium-based screws with Ti screws for hallux valgus fixation and reported no systemic inflammatory reactions in either group after 6 months.[56]

Overall Quality of Evidence

The quality of evidence for local responses was rated low either due to high incidence rates from ≤2 high quality studies or consistent reporting with other device categories (dental, and cardiovascular implants). Systemic responses were rated very low due to 1 study investigating and not detecting any inflammatory reactions.

Orthopedic – knee prosthesis

4 human studies (1 SR,[57] 2 RCTs,[58,59] and 1 nonrandomized comparative study[60]). For further information see Table 15 in Appendix D.

Local Responses/Device Events (human studies)

One SR and meta-analysis compared tantalum cone (n=449) with titanium sleeve (n=326) in revision TKA and reported fewer events of aseptic loosening (3 Ti vs 7 tantalum) and fracture with Ti (2 Ti vs 4 tantalum), but end-of-stem pain (7 (23.3%)) only with Ti.[57] Small diameter stems were a predictive factor of stem pain in Ti-sleeve revision TKA. Intraoperative fracture occurred immediately, and pain and loosening were seen during follow-up (24 to 62 months with Ti).

One RCT (n = 89) compared Ti knee implants with cobalt chromium knee implants by randomly assigning a different implant to each knee (bilateral knee replacement) and reported indicators of loosening, osteolysis and metal hypersensitivity (mean follow-up 5.3 years).[58] Two cobalt chromium knees developed instability at 4 weeks and 5 months; 2 cobalt chromium

implants needed revision surgery. The authors reported no metal hypersensitivity, loosening, or osteolysis were observed in either group.

One multicenter RCT (n = 100) compared Ti knee implants with no surgical implants. At 1-year follow-up, DVT (3) and fracture (1) were only reported with Ti implants.[59] Knee stiffness requiring brisement force occurred in both arms (3 Ti, 1 no implant).

One retrospective comparison study (n = 1,024) compared highly porous Ti-coated TKA implants with periapatite (PA)-coated TKA implants and reported revision rates and aseptic failure with 1-year follow-up.[60] Revision rates were very low: 0.2% for Ti-coated and 0.8% for PA-coated. There were 2 aseptic failures (0.9%) in the Ti-coated group (pain and instability at one year) and 3 aseptic failures (0.3%) in the PA-coated group (pain and instability at six weeks, arthrofibrosis at four months, and patellar dislodgement at six weeks).

Overall Quality of Evidence

Overall quality of evidence for local responses was rated low due to agreement with other devices and reporting from mostly high-quality studies. Quality of evidence for systemic responses was rated very low (no studies reporting).

Orthopedic – hip prosthesis

5 human studies (1 SR[61] and 4 nonrandomized comparative studies[62-65]). For further information see Table 16 in Appendix D.

Local Host Responses (human studies)

Stems: 2 nonrandomized comparative studies[62,63] evaluated Ti vs non-Ti stems for total hip arthroplasty (THA).

The first study[62] reported no significant differences between a Ti femoral stem (MiniHip stem)(n=101) vs non-Ti femoral stem (Collum Femoris Preserving C.F.P.)(n=89) for all local responses up to median 6 years follow-up. The study enrolled individuals undergoing "partial collum" THA, 79% were male, with mean age of 47 years.

Rates for proximal femoral osteolysis (0% Ti, 2.2% non-Ti), cervical hypertrophy (0.3% Ti, 0.4% non-Ti), intraoperative periprosthetic fractures (2.9% Ti, 4.4% non-Ti), and septic loosening (0% Ti, 1.1% non-Ti) were lower with Ti implants. Rates for initial subsidence <2 mm (3.9% Ti, 0% non-Ti), and aseptic loosening of the acetabular component treated with revision (1.9% Ti, 0% non-Ti) were higher with Ti.

The second study[63] reported no significant differences between 3 types of Metha (Aesculap) calcar-loading short stems (314 modular stem with Ti neck, 230 modular stem with cobalt chrome (CoCr) neck, and 1090 monoblock Ti stems) for all local responses up to 11 years. Gender was not reported; mean age was 59 years.

Cone fractures (n=15, 4.4%) and femoral perforation (n=1, 0.3%) only occurred with modular Ti implants, while femoral fractures only occurred with monoblock Ti (n=5, 0.4%) and modular CoCr (n=1, 0.4%). Rates for 7-year revisions (5.3% modular Ti, 1.8% CoCr, 1.5% monoblock Ti) and instability (0.6% modular Ti, 0.4% modular CoCr, 0.2% monoblock Ti) were highest with modular Ti implants, and lowest with monoblock Ti implants. Rates for aseptic loosening (0.8% modular CoCr, 0.6% modular Ti patients, 0.5% monoblock Ti) and ossification (0.8% CoCr, 0.3% modular Ti, 0% monoblock Ti) were higher with modular CoCr. Hematoma occurred in ≤3 patients in each arm (similar rate of 0.3%).

Acetabular components: 1 SR of 5 studies (1 RCT, 4 nonrandomized[61] and 1 nonrandomized comparative study[65] evaluated Ti vs non-Ti acetabular components.

The SR[61] evaluated 5 Ti devices vs 5 tantalum devices. The study evaluated 1479 implants (841 Ti, 638 tantalum) up to 10 years follow-up; range of 43% to 63% males per study, aged 54.6 to 72 years. Results indicated significantly higher instability (3 studies: OR 0.45, 95% CI: 0.31 to 0.64; p<0.001) and failure rate (3 studies: OR 0.44, 95% CI: 0.28 to 0.71; p=0.001) with Ti vs tantalum acetabular implants.

The nonrandomized comparative study[65] evaluated THA acetabular revisions using either a Ti (n=536) or tantalum (n=454) component. Mean age was 62.3 for males and 65.1 years for females; 56% were female. Results indicated a significantly higher overall failure with Ti implants (9.9% Ti, 4.4% tantalum; p<0.001) at mean follow-up of 40.2 months (3 months to 13.1 years). Failure of the acetabular components (mostly due to aseptic loosening) was higher with Ti implants (26 vs 7).

Rings: One nonrandomized comparative study[64] evaluated a smooth (n=101) or rough-blasted Ti Muller acetabular reinforcement ring (ARR)(n=140; 26 1st generation, 114 2nd generation) vs a stainless-steel Muller ARR (n=18) for revision

THA. The study enrolled 59% males aged 31 to 91 years (mean 72). Results indicated re-revisions due to aseptic loosening were highest with smooth-blasted Ti ARR (5 smooth-blasted Ti, 2 rough-blasted Ti, 1 SS) after mean 6 (1.5 to 14) years.

Overall Quality of Evidence

Evidence for instability and failure was in agreement in 1 SR and 1 nonrandomized comparative study so we rated the quality of evidence as low. Evidence for all remaining local responses and systemic responses (no studies investigating) was rated very low.

Orthopedic – shoulder prosthesis

2 human studies (2 SRs[66,67]). For further information see Table 17 in Appendix D.

Local Responses/Device Events (human studies)

Both SRs involve analysis of various reverse total shoulder arthroplasty (RTSA) systems or open reduction and internal fixation (ORIF) systems containing Ti components. Follow-up was only reported in one SR[66] at 34.2 to 41 months. Patient characteristics were only reported in the other SR[67] at 86% to 90% female, age 44 to 91 years. Group size ranged from 159 to 1,590 patients.

Scapula Notching: In SR[66] 17% and 47% of patients with two different Ti-containing systems experienced scapula notching, compared to 17% of non-Ti patients.

Scapula Spur: In SR[67] 0.6% and 27.7% of patients with Ti-containing systems experienced scapula spur, compared to 18% of non-Ti patients.

Dislocation: 1 SR reported 0.72% and 5.2% of patients with Ti-containing systems experienced dislocation, compared to 2.5% of non-Ti patients.[66] 1 SR reported 5 patients (3.0%) in the RTSA group experienced dislocation compared to 7 patients (4.4%) in the ORIF group.[67]

Nerve Injury: 0.5% and 1.7% of patients with Ti-containing systems experienced dislocation, compared to 2.3% of non-Ti patients.

Loosening of glenoid component: 1.2% and 7% of patients with Ti-containing systems experienced loosening of the glenoid component compared to 2.5% of non-Ti patients.

Loosening of humeral component: 1.2% and 10% of patients with Ti-containing systems experienced loosening of the humeral component compared to 1.6% of non-Ti patients.

Stress Shielding: 7.8% and 19% of patients with Ti-containing systems experienced stress shielding, compared to 0 non-Ti patients.

Fracture: rates for fracture (periprosthetic humeral, scapular, or perioperative glenoid) ranged from 1.5% to 4.8% with Ti-containing systems compared to 1.7% to 2.7% of non-Ti patients.

Implant Failure: 0.89% and 3.9% of patients with Ti-containing systems experienced implant failure, compared to 5.2% of non-Ti patients.

Heterotopic Ossification: 24.8% of patients with Ti-containing systems experienced heterotopic ossification, compared to 1.6% of non-Ti patients.

Revision: In SR[66], revision was observed in 2.5% and 5.5% of patients with Ti-containing systems, compared to 6.5% of non-Ti patients. In SR[67], revision surgery rates were significantly lower in RTSA compared to ORIF (5.45% vs 14.47%, p=0.02).

Resorption: In SR[67] 7.8% of RTSA patients and 1.9% of ORIF patients experienced resorption of tuberosities.

Other minor complications occurred in ≤4 patients (impingement (2.5%), nonunion (1.9%), loss of reduction (1.9%), instability (1.8%), screw penetration (1.3%), rotator cuff rupture (0.6%), hematoma (0.6%), and arthrofibrosis followed by avascular necrosis in 2 years (0.6%).

Overall Quality of Evidence

The overall quality of evidence for local responses was rated low either due to high incidence rates from ≤2 high quality studies or consistent reporting with other device categories (spinal fixation, and cardiovascular implants). Systemic responses were rated very low (no studies investigating).

Orthopedic – disc, sacroiliac, interphalangeal prosthesis

4 human studies (1 SR,[68] and 3 RCTs,[69-71]). For further information see Table 18 in Appendix D.

Local Host Responses (human studies)

Two RCTs[69,70] compared the iFuse triangular Ti implants for sacroiliac joint fusion vs conservative management; two to four implants were placed per patient. One SR[68] compared AEs of a polyurethane on Ti unconstrained cervical disc (PTUCD) arthroplasty with those of anterior cervical discectomy and fusion (ACDF). A final RCT[71] compared a Ti-polyethylene implant to a pyrocarbon implant and a silicone spacer for surface replacement arthroplasty in proximal interphalangeal joint osteoarthritis. Follow-up ranged from 21.5 to 35 months, with a Ti sample size of 26 to 562 patients (36% to 81% female), aged 43 to 65 years.

Ankylosis, Contracture, Deformity, Ossification, Subsidence: RCT[71] reported implant subsidence in 31% of Ti finger joint replacement patients (n=26) compared to 33% of pyrocarbon implant patients (n=19) and 0 silicone spacer patients (n=18). The authors also reported ossification development in 39% of Ti patients, compared to 28% of pyrocarbon patients and 33% of silicone spacer patients. Ankylosis was found in 8% of Ti patients and 6% of patients in the pyrocarbon and silicone spacer groups. Swan neck deformity was reported in 19% of Ti patients, 11% of patients in the pyrocarbon and silicone spacer groups. Boutonniere deformity was found in 4% of Ti patients compared to 0 pyrocarbon and silicone spacer patients.

Loosening: RCT[71] recorded 27% of patients in the Ti finger joint replacement group requiring explantation due to aseptic loosening or subsidence, compared to 39% in the pyrocarbon group due to loosening or dislocation, and 11% in the silicone spacer group due to implant fracture (p=0.16). The average time until explantation was 23 months.

Pain and hematoma: In SR[68] 1.5% of patients reported neck and arm pain with Ti (n=562) compared to 2.3% of ACDF patients (n=530)(p=0.05). One RCT[69] (n=103) reported 4 severe device or procedure-related AEs with iFuse Ti implants. 2 patients experienced joint pain at 1 year attributed to iFuse device loosening after a fall. New onset leg pain related to malposition, and postoperative hematoma occurred in 1 patient each. Joint pain after device loosening and hematoma also occurred in 1 patient each with the conservative management group after cross-over implant surgery.

The second RCT[70] recorded 3 patients in the iFuse group (n=102) reporting pain related to sacral nerve impingement, fracture of the ilium (later causing buttock pain 3 to 4 months postoperative), and sacroiliac joint pain. Three patients in the conservative management group (n=46) also reported increased sacroiliac joint pain after rehabilitative efforts.

Reoperation/Revision: In SR[68], the recorded reoperation in seven studies with 5.3% of PTUCD patients requiring reoperation and 8.4% patients in the ACDF group (p=0.06). In RCT[70] one patient was considered a study failure at 6-months due to revision for symptomatic implant malposition.

Calcification, DVT, Dysphagia, Explantation/Failure, Heterotopic Ossification, Pseudarthrosis, Vascular Complications: SR[68] recorded ligament calcification and heterotopic ossification in seven studies, occurring in 14.5% of PTUCD patients and 26.3% of ACDF patients (p=0.47) at mean follow-up of 30.9 months. The seven studies also reported information on pseudarthrosis (PTUCD 4.8%, ACDF 6.1%), vascular complications (PTUCD 1.0%, ACDF 0%), DVT (PTUCD 2.8%, ACDF 0%), explantation/failure (PTUCD 1.2%, ACDF 3.6%), and dysphagia (PTUCD 3.2%, ACDF 9.0%) without significant different between the study groups (p=0.05).

Overall Quality of Evidence

For ossification, we rated the quality of evidence as low due to consistent reporting across studies (including high incidence rates from a moderate sized SR) and agreement with other device categories (e.g., shoulder prosthesis). For all other local responses and systemic responses (no studies reporting), we rated the quality of evidence as very low.

Orthopedic – cranioplasty

9 human studies (7 SRs,[72-78] and 2 nonrandomized comparative studies[79,80]). For further information see Table 19 in Appendix D.

Local Responses/Device Events (human studies)

Eight studies[72-78,80] analyzed Ti mesh vs bone (autologous or banked) and various other non-Ti alloplasts (bone cement, calcium phosphate [CP], hydroxyapatite [HA], PEEK, polymethylmethacrylate [PMMA], and porous polypropylene [PP]) used for cranioplasty following decompressive craniectomy. Follow-up ranged from 6 to 185 months, with a Ti sample size of 60 to 1,829 patients (43.2% to 96.6% male), aged up to 90 years. Over 22,500 devices were examined (6419 Ti, 16114 non-Ti).

Implant Exposure: In general, Ti mesh saw greater complication rates of exposure than other graft types, which might occur 2 months to 7 years after implantation. Three SRs[73,74,78] and one nonrandomized study[80] reported on Ti mesh exposure. The first SR[73] showed Ti implant was more prone to exposure than non-Ti implants (occurring in 51/569, OR 4.11, 2.27 to 7.44; p<0.00001). The second SR[74] recorded exposure in four studies comparing Ti to PEEK implants with an incidence of 13.4% in the Ti groups vs 2.3% in the PEEK groups. The third SR[78] reported exposure in 1.5% of both Ti and HA patients, 0.6% of PEEK patients, 0.7% of PMMA patients, and 0.2% of autologous bone patients. The nonrandomized study[80] recorded a rate of exposure of 5.96% in Ti patients compared to 0 incidences in autologous bone and PEEK groups.

Hematoma: Five SRs[72-74,76,78] reported on hematoma. The first SR[72] recorded hematoma in 13 studies, with an incidence of 1.6% for Ti and 4.1% overall for all alloplasts. The second SR[73] recorded hematoma in 8 studies, citing that Ti had a statistically significant reduction in the incidence of hematoma compared with non-Ti materials (p=0.0003). The third SR recorded hematoma in 4 studies comparing Ti vs PEEK implants with an incidence of 3.8% in the Ti groups compared to 3.9% in the PEEK groups. The fourth SR[76] recorded an overall postoperative epidural hematoma rate of 3.38% with 4.62% of Ti patients reporting the condition, and 2.77% of Ti patients requiring revision due to postoperative hematoma evacuation. The fifth SR[78] recorded hematoma in 2.8% of Ti patients compared to 4.0% of PEEK patients, 2.3% of autologous bone patients, and 1.7% of HA patients.

Migration/Displacement: Two SRs[76,78] reported on mesh movement. SR[76] recorded displacement in 2.02% of cases overall with 16 of those cases requiring revision; 0.31% of Ti patients had mesh displacement with 0.15% of Ti patients requiring revision. The second SR[78] recorded implant migration in 0.1% of Ti patients compared to 0 PEEK and HA patients, 0.5% of PMMA patients, and 0.3% of autologous bone patients.

Failure/Removal/Reoperation/Revision: All seven SRs reported implant failure or complication potentially resulting in removal/reoperation/revision. The first SR[72] recorded reoperation in nine studies, with an incidence of 24.1% for Ti and 12.6% overall for all alloplasts. The second SR[73] recorded reoperation in eight studies, with no difference in odds of reoperation rate in the Ti group compared to the autologous bone group (p=0.43). The third SR[74] recorded reoperation in four studies comparing Ti to PEEK implants with an incidence of 18.5% in the Ti groups compared to 3.9% in the PEEK groups. The fourth SR[75] recorded a graft failure rate of 3.3% in the Ti mesh group, 16.4% in the PMMA group, 19.3% in the PEEK group, and 19.4% in the autologous bone group. The fifth SR[76] recorded implant fracture in 0.31% of Ti patients with 0.15% of patients requiring revision, 0.34% of patients in the PMMA group also requiring revision due to fracture, 3.5% of patients in the HA group with 0.98% requiring revision, and 0 patients in the PEEK group. The sixth SR[77] reported 6.02% of Ti patients with graft failure, compared to 4.73% in the PMMA group, 8.60% in the PEEK group, and 6.43% in the Norian group. The seventh SR[78] recorded implant removal in 6.7% of Ti patients compared to 7.4% of PEEK patients, 7.9% of PMMA patients, 10.4% of autologous bone patients, and 2.5% of HA patients.

Seizure: Four SRs[72-74,78] reported on seizure. The first SR[72] recorded seizure in six studies, with an incidence of 7.2% for Ti and 7.6% overall for all alloplasts. The second SR[73] recorded seizure in four studies with a rate of 0.067 in the Ti groups and 0.119 in the non-Ti groups (p=0.42). The third SR[74] recorded seizure in four studies comparing Ti to PEEK implants with an incidence of 9.2% in the Ti groups vs 4.7% in the PEEK groups. The fourth SR[78] reported seizures in 1.4% of Ti patients, 2.6% of PEEK patients, 0.7% of PMMA patients, 1.1% of autologous bone patients and 0 HA patients.

Cerebrospinal Fluid (CSF) leak: Three SRs[73,74,78] reported on CSF leak. The first SR[73] recorded CSF leak in four studies with no difference in odds of CSF leak in the Ti group compared to the non-Ti group. However the reported OR from the meta-analysis was significant (n = 278; OR, 2.22; CI, 1.01–4.88; p=0.05). The second SR[74] recorded CSF leak in four studies comparing Ti to PEEK implants with an incidence of 0.4% in the Ti groups vs 0% in the PEEK groups. The third SR[78] reported CSF leak in

0.8% of Ti patients, 1.3% of PEEK patients, 0.7% of PMMA patients, 2.7% of autologous bone patients, and 0.1% of HA patients.

Fluid Collection: One SR[76] recorded 3.62% of patients overall requiring postoperative fluid collection with 19.67% of those patients requiring revision. 5.86% of Ti patients required fluid collection, with 1.08% requiring revision surgery.

Poor Fit: One SR[73] recorded imprecise fit in 3 studies with a pooled rate of 0.041 in Ti groups vs 0.121 in non-Ti groups. The pooled results show Ti linked with a significant decrease in imprecise fit (p=0.04).

Effusion: One SR[74] recorded 4 studies comparing Ti vs PEEK implants. The incidence of subgaleal effusion was 5.0% in the Ti group compared to 4.7% in the PEEK groups.

"Surgical Site Occurrence" or "Local Complication" (e.g., seroma): Three SRs[75,77,78] reported on nonspecific complications related to mesh placement. The first SR[75] reported a 6.7% occurrence rate in the Ti mesh group compared to 18.2% of patients in the PMMA group, 22.6% of patients in the PEEK group, and 20.3% in the autologous bone group. The second SR[77] reported a 13.09% occurrence rate in the Ti group compared to 11.31% in the PMMA group, 17.19% in the PEEK group, and 12.45% in the Norian group. The third SR[78] reported seroma at a rate of 1.5% in Ti patients, 0.7% in PEEK patients, 0.5% in PMMA patients, 0.4% in autologous bone patients, and 0.6% in HA patients.

Fracture: One SR[76] recorded 1.35% of patients overall with fractured prostheses with 0.45% requiring revision. 0.31% of Ti patients had a fractured prosthesis with 0.15% requiring revision.

Hydrocephalus: One SR[76] recorded 1.42% of patients overall with postoperative hydrocephalus with 1.13% requiring surgical treatment. 1 case was found in the Ti group (0.15%) which also required surgical revision.

Ophthalmic outcomes: One nonrandomized study[79] analyzed Ti mesh vs absorbable mesh or silastic sheeting for orbital wall reconstruction. Follow-up ranged from three to 12 months, with a Ti sample size of 238 patients (78.2% male), and a mean age of 31 years. Most complications occurred immediately postoperatively. 1.3% of Ti mesh patients had extraocular muscle limitation with diplopia compared to 3.1% and 1.6% of patients in the silastic sheet and absorbable mesh groups, respectively. 0.4% of Ti mesh patients had enophthalmos compared to 0 patients in either the silastic sheet or absorbable mesh groups.

Systemic Responses

Death: One SR[78] reported 1 patient death in the Ti group (0.1%), compared to 0 PEEK and HA patients, 0.3% of PMMA patients, and 1.4% of autologous bone patients.

Overall Quality of Evidence

Overall quality of evidence was rated moderate for all local responses due to mostly similar reporting across 7 SRs and 2 nonrandomized comparative studies (examining over 22500 devices) and duplicate reporting with other Ti device categories. Systemic responses were rated very low based on 1 event.

Surgical mesh

4 human studies (1 SR,[81] 2 RCTs,[82,83] and 1 nonrandomized comparative study[84]). For further information see Table 20 in Appendix D.

Local Host Responses (human studies)

Studies analyzed Ti-coated mesh vs polypropylene mesh[81,82] and Ti spiral tacks vs glue for polypropylene mesh fixation[83,84] for laparoscopic inguinal hernia repair. Follow-up ranged from 3 months to 3 years, with a Ti sample size of 19 to 50 patients (87.6% to 100% male), with a mean age of 20 to 61 years. Less than 250 Ti devices were examined overall.

Foreign Body Sensation: Fifteen patients (30%) in one RCT[82] Ti-mesh group vs 17 patients (32.7%) in the standard mesh group reported foreign body sensation at 1 year follow-up. The incidence was not significantly different (p>0.05) but was higher in the standard group.

Seroma and/or Hematoma Formation: Two RCTs[82,83] and one nonrandomized study[84] reported on seroma and/or hematoma formation. In the Ti-coated mesh RCT[82], 3 patients in the Ti mesh group developed seroma (6%) compared to 9 patients (17.3%) in the standard polypropylene mesh group. In the mesh fixation RCT[83], 8 patients in the Ti group (23.5%) developed seroma compared to 7 patients (21.9%) in the glue fixation group. Neither RCT found a significant difference among groups.

In the nonrandomized study[84], glue fixation of mesh seemed to decrease the risk of seroma and hematoma formation, but did not eliminate the risk, as they formed in 48 patients (9.6%) in the glue-only group and 4 patients (8.5%) in the glue plus Ti tacks group, compared to 54 patients (15.2%) and 20 patients (22.5%) in the nonfixation and Ti tack-only groups, respectively.

Chronic Pain: One SR[81] and one nonrandomized study[84] reported on chronic pain. In the SR[81], lightweight polypropylene and Ti meshes had no chronic pain at 1- and 3-year follow-ups, compared to reported pain in the heavyweight polypropylene mesh group. In the nonrandomized study[84], no occurrence of chronic pain was noted in the nonfixation and glue-only groups at 19-month follow-up, compared to 2 cases (2.2%) in the Ti tacks-only group, and 1 case (2.1%) in the Ti tacks plus glue fixation group.

Decreased Sperm Motility: One SR[81] reported on decreased sperm motility. The Ti mesh and lightweight polypropylene mesh groups showed decreased sperm motility when compared to heavyweight polypropylene mesh at 1 year follow-up but showed no significant difference after 3-year follow-up.

Recurrence: In the SR[81], lightweight polypropylene and Ti meshes demonstrated low inguinal hernia recurrence at 1- and 3-year follow-ups, compared to recurrence rates in the heavyweight polypropylene mesh group.

Overall Quality of Evidence

Overall quality of evidence was rated low for foreign body sensation, seroma, and hematoma. All other local responses and systemic responses (no studies reporting) were rated very low.

Surgical ligating clips

3 human studies (2 RCTs[85,86] and 1 nonrandomized comparative study[87]). For further information see Table 21 in Appendix D.

Local Responses (human studies)

Overall, 3 studies analyzed 818 Ti clips vs 725 suture or resorbable clips for cystic duct (carries bile from the gallbladder) ligation. Follow-up ranged from two weeks to three months, with Ti sample size of 30 to 728 patients (50% to 61.7% female), and a mean age of 30 to 49 years. Studies did not feature overlap among their reported complications. One RCT[86] observed patients for fever, hemorrhage, or intraabdominal fluid collection after cystic duct ligation and did not find any complications among study participants.

Migration and Slippage: One RCT[85] reported on 11 intraoperative complications in the Ti clip group compared to 0 complications in the suture group. 7 patients had clip slippage with gallstone spillage into the peritoneal cavity, 3 patients had clip slippage with bile spillage into the peritoneal cavity, and 1 patient had clip migration.

Abscess, Cystic Duct Leakage, Ileus, Lung atelectasis, and Pancreatitis: One nonrandomized study[87] (n=1363) reported 0.96% of patients with intraoperative cystic duct leak in the Ti clip group compared with 0% in the resorbable clip group, 0.41% of patients with post-operative pancreatitis in the Ti clip group compared with 0.32% in the absorbable group, 0.55% of patients with post-operative ileus in the Ti clip group compared with 0.47% in the absorbable group, and 0.28% of patients with post-operative abdominal abscess in the Ti clip group compared with 0.16% in the absorbable group.

Overall Quality of Evidence

Overall quality of evidence for local responses was rated very low due to inconsistent reporting across 3 studies. Systemic responses were also rated very low (no studies reporting).

ECRI Surveillance Data

Refer to Appendix F for a list of devices that guided our searches of ECRI Surveillance Data.

Patient Safety Organization

Search Results: ECRI PSO identified thousands of reports that involved Ti material that occurred between February 2007 and May 2022. However, these reports did not have enough information to directly associate patient harm with the biocompatibility of Ti.

Accident Investigations

Search Results:

The digital ECRI Accident Investigation files were searched using character strings chosen to identify devices known to involve Ti or one of its alloys. The character strings used are in italics. As would be expected, there was a significant overlap in Targets with the different search strings. Targets are considered applicable only if the investigation pertained to biocompatibility of the material.

Titanium: 345 Targets, 0 Applicable

These targets included any documents that included the word "titanium" in them. Approximately two thirds of the targets were reference documents such as specification sheets, instructions for use, research papers, and patents in the investigation folders. Thus, most of the targets were not pertinent to this project. Nevertheless, in reviewing our investigation reports, "titanium" was used mostly in relation to surgical instruments and trays and surgical staplers. The investigations of surgical instruments/trays are not germane.

"Titanium" and "Port": 91 Targets, 0 Applicable

ECRI has investigated numerous Ti body subcutaneous infusion ports. With one exception, these investigations have involved failure of the port catheter, not the port body. As for the exception, a Bard implantable SlimPort was used to deliver concentrated electrolytes for a period of days. Post-treatment chest x-rays showed "glass-like particulate" in the patient's lungs. ECRI examined the port for deterioration of the Ti port body and found no evidence of pitting or corrosion with either the interior or exterior of the port body. No subcutaneous pocket irritation or particulate was reported.

"Titanium" and "Staple": 89 Targets, 0 Applicable

ECRI has investigated hundreds of surgical staplers, most of which employ Ti staples. These investigations are almost exclusively related to alleged stapler malfunction at the time of use. On rare occasions, we have investigated post-procedure failure of staple lines in which the staples pulled loose. However, none of our investigations involve the biocompatibility of the staples. For example, we have not investigated adhesions related to staples.

"Titanium" and "Implant": 67 Targets, 0 Applicable

ECRI has investigated numerous orthopedic implant failures, including femoral nails, joint replacements, and spinal fixation systems. Some of them were made from Ti or an alloy of Ti. Nearly all of these investigations were performed on implants involving a component (e.g., plate, screw, rod) fracture. Except for one instance in which the implant recipient leapt off a 20 ft. ladder as it fell, the failures were caused by cyclic fatigue often precipitated by loosening. None of the investigations were requested due to biocompatibility issues.

"Titanium" and "prosthesis": 17 Targets, 0 Applicable

The 17 documents were reference materials.

"Titanium" and "Phaco": 11 Targets, 0 Applicable

In one case, an Alcon Phacoemulsifier tip shed metal particles into the patient's eye during lens emulsification. The phaco tip's surface had two areas of absent material likely resulting from contact with a metal irrigation cannula also in the anterior chamber of the eye. The manufacturer stated that the tips are made from Ti. The particles were successfully flushed from the chamber. There were no tissue compatibility issues.

"Titanium" and "Synchromed": 7 Targets, 0 Applicable

The case of the Synchromed implantable drug delivery pump is made from Ti. With one exception, ECRI's investigations of Synchromed pumps have involved flow rate issues (i.e., over- or under-delivery). In one instance, the weld seam of the case failed allowing fluorocarbon vapor to escape from the case. The vapor dissected along the spinal catheter track where it embolized into the cerebro-spinal space. There were no tissue compatibility issues.

Searchs for common titanium alloys did not identify any investigation related to biocompatibility when using the following character strings.

"Titanium alloy": 1 Target, 0 Applicable

> The one target was an investigation of a Globus Rise intervertebral spacer, which is made from Ti. The spacer slipped during surgical placement.

Ti6Al4V: 0 Targets

Ti6%Al4%V: 0 Targets

"Titanium 6% Aluminum 4% Vanadium": 0 Targets

ECRI Problem Reports

Search Results: The search did not return any reports submitted by ECRI members that were related to the biocompatibility of Ti.

Healthcare Technology Alerts

Search Results: The search returned 594 manufacturer issued alerts and 3 FDA issued alerts describing problems with Titanium-related devices, summarized in Table 2. There are some notable alerts that may be related to the biocompatibility of Ti. These include:

Ventricular Assist Device

1. Graft facture or tearing
2. Graft leakage
3. Thrombosis

Implantable Clip - Fragment dispersion and damage after pressurization

Synthetic, nonabsorbable suture (polyethylene) - Fragment dispersion and damage after pressurization

Intramedullary fixation rod - Migration

Intragastric Implant (for morbid obesity) - Acute pancreatitis

Heart valve (non-allograft tissue) - Valve deterioration

Semi-constrained Metal Shoulder Prosthesis - Increased wear

Semi-constrained, Uncemented Metal Hip Prosthesis – Adverse tissue reaction to metal debris

Knee Prosthesis – adhesive residue may irritate tissue

Hip Prosthesis

1. Adverse tissue reaction to metal debris
2. Corrosion leads to excessive debris/ions

Full text alerts can be found in Appendix G.

Table 2: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
DSQ (Ventricular [Assist] Bypass)	25 manufacturer issued 1 FDA issued	• Cable damage • Cable disconnection • Communication error • Discontinued sale and distribution • Electrostatic discharge or fault • Exchange difficulty • Failure to restart • Graft fracture or tearing • Graft leakage • Graft relief not properly secured • High frequency of use errors resulting in death • High rate of stroke or bleeding complication • Incorrect insertion • Membrane disruption • Misalignment • Occlusion • Pump failure • Thrombosis • Updated IFU • Wear
DSR (Stimulator, Carotid Sinus Nerve)	1 manufacturer issued	• Connection loss
DZE (Implant, Endosseous, Root-Form)	26 manufacturer issued	• Fracture • Inconsistent topography • Incorrect components • Manufactured with incorrect material • Misalignment • Mislabeling • Missing hex or threads • Not cleared for sale in US • Packaging error • Poor implant engagement • Residue on surface
EZX (Mesh, Surgical, Metal)	1 manufacturer issued	• Mislabeling
FZP (Clip, Implantable)	9 manufacturer issued	• Deployment difficulty • Jaw may break • Missing contraindications • Fragment dispersion and damage after pressurization • Incorrect IFU • Compromised sterility • Jammed applier
GAT (Suture, Nonabsorbable, Synthetic, Polyethylene)	1 manufacturer issued	• Compromised sterility • Deployment difficulty • Fragment dispersion and damage after pressurization • Incorrect IFU • Jammed stapler • Jaw may break

Device Type	# Alerts	Reported Problem
		• Missing contraindications
GDW (Staple, Implantable)	25 manufacturer issued	• Cartridge disengagement • Component separation • Compromised sterility • Deployment difficulty • Firing difficulty • Inability to remove device from tissue (bleeding, leak, trauma) • Incomplete staple formation • Incomplete staple line • May dissect tissue without stapling • Missing components • Safety interlock failure (reload could fire a second time) • Stolen before sterilization • Too many staples in well
GWO (Plate, Cranioplasty, Preformed, Alterable)	2 manufacturer issued	• Mislabeling
GXN (Plate, Cranioplasty, Preformed, Non-Alterable)	4 manufacturer issued	• MDR nonconformance • Misassembly • Not MR safe • Unclear IFU
HBW (Fastener, Plate, Cranioplasty)	2 manufacturer issued	• Intraoperative fracture • Out of specification
HCH (Clip, Aneurysm)	2 manufacturer issued	• Discoloration • Missing IFU
HRS (Plate, Fixation, Bone)	34 manufacturer issued	• Incorrect components • Insufficient thread depth • Intraoperative fracture • Locking screws don't engage • Loosening • Mislabeling • No CE certificates • Nonqualified specification • Out of specification • Screw backout • Screw driven through plate • Weak fixation
HSB (Rod, Fixation, Intramedullary and Accessories)	13 manufacturer issued	• Breakage • Compromised sterility • Exceed acceptable revision rate • Failed clinical analysis for survivorship • Incorrect orientation • Migration • Mislabeling • Out of specification • Screw will not advance/reverse
HSD (Prosthesis, Shoulder, Hemi-,	4 manufacturer issued	• Incorrect IFU • Mislabeling

Device Type	# Alerts	Reported Problem
Humeral, Metallic, Uncemented)		
HSN (Prosthesis, Ankle, Semi-Constrained, Cemented, Metal/Polymer)	8 manufacturer issued	• Compromised sterility • Mislabeling • Missing plasma coating • Residue on device surface • Updated IFU
HSX (Prosthesis, Knee, Femorotibial, Non-Constrained, Cemented, Metal/Polymer)	1 manufacturer issued	• Mislabeling
HTY (Pin, Fixation, Smooth)	1 manufacturer issued	• Missing plasma coating
HWC (Screw, Fixation, Bone)	20 manufacturer issued	• Compromised sterility • Deployment difficulty • Inadequate sterilization • Loosening • Malformation • Mislabeling • Missing threads • Out of specification
JDB (Prosthesis, Elbow, Semi-Constrained, Cemented)	2 manufacturer issued	• Compromised sterility • Unacceptable performance levels in terms of: loosening, instability, fracture, cyst formation, stiffness, pain, impingement, heterotopic ossification
JDI (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Cemented)	5 manufacturer issued	• Dislodged components • Mislabeling • Stem missing laser etchings
JDN (Implant, Fixation Device, Spinal)	1 manufacturer issued	• Included in a previous recall
JDO (Device, Fixation, Proximal, Femoral, Implant)	1 manufacturer issued	• Intraoperative fracture
JDP (Condylar Plate Fixation Implant)	1 manufacturer issued	• Mislabeling
JDQ (Cerclage, Fixation)	1 manufacturer issued	• Fracture
JDS (Nail, Fixation, Bone)	10 manufacturer issued	• Incorrect assembly • Incorrect gauge line depth • Incorrect hole position • Incorrect set screw position • Mislabeling • Packaging error • Upside down component
JDW (Pin, Fixation, threaded)	1 manufacturer issued	• Manufacturing defect

Device Type	# Alerts	Reported Problem
JWH (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained, Cemented, Polymer/Metal/Polymer)	40 manufacturer issued	• Compromised sterility • Dimensional mismatch allows interference • Dissociation • Incompatible components • Incorrect product • Loosening • Material defects • Mislabeling • Neck length discrepancy • Out of specification, under-, over-sized components • Screw backout • Tibial inserts improperly mate with baseplate
JXG (Shunt, Central Nervous System and Components)	6 manufacturer issued	• May not withstand anticipated pressure • Mislabeling • Missing components • Missing IFU • Needleless access port is not for injection of fluids
KRO (Prosthesis, Knee, Femorotibial, Constrained, Cemented, Metal/Polymer)	15 manufacturer issued	• Component mismatch • Compromised sterility • Difficult component exchange • Improper adhesion • Incorrect components • Label missing CE mark • Misassembly • Mislabeling • Missing components • Pins dislodged • Protrusion • Screw misalignment • Screws won't loosen intraoperatively • Tolerance changes
KTT (Appliance, Fixation, Nail/Blade/Plate Combination, Multiple Component)	1 manufacturer issued	• Oversized components
KWA (Prosthesis, Hip, Semi-Constrained [Metal Uncemented Acetabular Component])	13 manufacturer issued	• Chatter • Compromised sterility • Incorrect components • Loosening • Marker lines present • Mislabeling • Missing CE mark • Missing plasma coating
KWI (Prosthesis, Elbow, Hemi-Radial, Polymer)	5 manufacturer issued	• Component separation • Implant dissociation • Loosening • Missing orientation marks • Updated IFU

Device Type	# Alerts	Reported Problem
KWP (Appliance, Fixation, Spinal Interlaminal)	1 manufacturer issued	• Out of specification
KWQ (Appliance, Fixation, Spinal Intervertebral Body)	1 manufacturer issued	• Out of specification
KWS (Prosthesis, Shoulder, Semi-Constrained, Metal/Polymer Cemented)	9 manufacturer issued	• Inverted screw • Nonconformance report open • Non-validated manufacturing method • Osseointegration issues • Out of specification • Residue on device surface • Updated IFU
KWY (Prosthesis, Hip, Hemi-, Femoral, Metal/Polymer, Cemented or Uncemented)	1 manufacturer issued	• Metal heads should not replace ceramic during revision
KWZ (Prosthesis, Hip, Constrained, Cemented or Uncemented, Metal/Polymer)	7 manufacturer issued	• High revision rate • Loosening • Mislabeling • Out of specification
KXK (Source, Brachytherapy, Radionuclide)	1 manufacturer issued	• Incorrect seed type
LEI (Implant, Anti-Gastroesophageal Reflux)	1 manufacturer issued	• Out of specification
LGW (Stimulator, Spinal-Cord, Totally Implanted for Pain Relief)	3 manufacturer issued	• Component mismatch • Difficulty establishing stimulation connection • May not recharge
LJT (Port & Catheter, Implanted, Subcutaneous, Intravascular)	15 manufacturer issued	• Component mismatch • Endotoxin test results out of specification • Fracture • Incorrect IFU • Increased incidence of hemolyzed blood samples • Mislabeling • Not visible during implantation • Port abandonment
LKK (Pump, Infusion, Implanted, Programmable)	2 manufacturer issued	• Manufacturer changes MRI status • Potential for overdose during MR imaging
LOZ (Artificial Heart)	1 manufacturer issued	• Valve wear
LPH (Prosthesis, Hip, Semi-Constrained,	15 manufacturer issued	• Bone screw protrusion • Compromised sterility • Debris due to packaging issue • Dome hole plug missing

Device Type	# Alerts	Reported Problem
Metal/Polymer, Porous Uncemented)		• Incorrect IFU • Mislabeling • Missing components • Missing porous coating • Out of specification • Updated IFU
LTI (Implant, Intragastric for Morbid Obesity)	5 manufacturer issued 1 FDA issued	• Acute pancreatitis • Distributed past expiration date • Failure to inflate • Hyperinflation • Missing components • Overinflation • Updated IFU
LWP (Implantable Pulse Generator, Pacemaker [non-CRT])	3 manufacturer issued	• Accelerated battery depletion • Configuration not approved by FDA • Intermittent oversensing may cause syncope
LWQ (Heart-Valve, Mechanical)	3 manufacturer issued	• Inverted implantation • Mislabeling
LWR (Heart-Valve, Non-Allograft Tissue)	1 manufacturer issued	• Valve deterioration
LWS (Implantable Cardioverter Defibrillator [Non-Crt])	4 manufacturer issued	• Accelerated battery depletion • Atypical energy delivery • Electrical shorting • Subject to radiofrequency interference
LZD (Joint, Temporomandibular, Implant)	1 manufacturer issued	• Mislabeling
LZO (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented or Non-Porous, Uncemented)	29 manufacturer issued	• Compromised sterility • Fracture • Incorrect product • Loosening • Mislabeling • Missing components • Missing plasma coating • Updated IFU
MAI (Fastener, Fixation, Biodegradable, Soft Tissue)	2 manufacturer issued	• Compromised sterility
MAX (Intervertebral Fusion Device with Bone Graft, Lumbar)	2 manufacturer issued	• Mislabeling • Reduction in implant height
MBF (Prosthesis, Shoulder, Semi-Constrained, Metal/Polymer, Uncemented)	7 manufacturer issued	• Increased wear • Insufficient adhesion strength • Loosening • Mislabeling • Updated IFU

Device Type	# Alerts	Reported Problem
MBH (Prosthesis, Knee, Patello/Femorotibial, Semi-Constrained, Uncemented, Porous, Coated, Polymer/Metal/Polymer)	8 manufacturer issued	• Fracture • Loosening • Mislabeling • Missing textured surface • Out of tolerance • Protrusion
MBI (Fastener, Fixation, Nondegradable, Soft Tissue)	10 manufacturer issued	• Compromised sterility • Fracture • Incorrectly drilled hole
MDI (Prosthesis, Rib Replacement)	1 manufacturer issued	• Out of specification
MEH (Prosthesis, Hip, Semi-Constrained, Uncemented, Metal/Polymer, Non-Porous, Calcium Phosphate)	12 manufacturer issued	• Adverse tissue reaction to metal debris • Implant failure • Loosening • Malpositioning • Mislabeling • Missing coating • Out of specification • Unable to fasten tibial plateau to stem
MHY (Stimulator, Electrical, Implanted, For Parkinsonian Tremor)	4 manufacturer issued	• Excessive heating • Implant site heating during charge • Loss of function
MJO (Prosthesis, Intervertebral Disc)	3 manufacturer issued	• Incorrect GTIN • Mislabeling
MNH (Orthosis, Spondylolisthesis Spinal Fixation)	5 manufacturer issued	• Component misassembly • Mislabeling
MNI (Orthosis, Spinal Pedicle Fixation)	6 manufacturer issued	• Manufactured with stainless steel instead of Titanium • Mislabeling • Missing components • Out of specification • Pin breakage
MQN (External Mandibular Fixator and/or Distractor)	3 manufacturer issued	• Mislabeling • Updated IFU
MXC (Recorder, Event, Implantable Cardiac [without Arrhythmia Detection])	3 manufacturer issued	• Cybersecurity vulnerability • Incorrectly displaying low battery • Pairing difficulty
MXD (Recorder, Event, Implantable Cardiac [with Arrhythmia Detection])	4 manufacturer issued	• Detections disabled after electrical reset • Disabled after partial electrical reset • Premature alerting • Susceptible to moisture ingress
NEU (Marker, Radiographic, Implantable)	6 manufacturer issued	• Deployment difficulty • Incorrect IFU • Mislabeling

Device Type	# Alerts	Reported Problem
NHA (Abutment, Implant, Dental, Endosseous)	9 manufacturer issued	• Component disconnection • Compromised sterility • Misalignment • Mislabeling • Not cleared for sale in US • Out of specification
NIK (Defibrillator, Automatic Implantable Cardioverter, with Cardiac Resynchronization [Crt-D])	5 manufacturer issued	• Asynchronous pacing behavior • Loss of function • Out of specification • Reduced shock energy • Requires manual programming
NKB (Thoracolumbosacral Pedicle Screw System)	15 manufacturer issued	• Component mismatch • Does not meet traceability requirements • Incorrect color coding • Loosening • Manufactured with stainless steel instead of titanium • Mislabeling • Screw disassembly • Screw head separation • Set screw disengages • Updated IFU
NKG (Posterior Cervical Screw System)	6 manufacturer issued	• Contamination • Incorrect IFU • Insufficient fixation • Mislabeling
NPJ (Prosthesis, Knee Patellofemorotibial, Partial, Semi-Constrained, Cemented, Polymer/Metal/Polymer)	3 manufacturer issued	• Compromised sterility • Mislabeling
NPK (Barrier, Synthetic, Intraoral)	1 manufacturer issued	• Mislabeling
NQP (Posterior Metal/Polymer Spinal System, Fusion)	1 manufacturer issued	• Mislabeling
NRA (Prosthesis, Knee, Femorotibial, Unicompartmental, Semi-Constrained, Metal/Polymer, Mobile Bearing)	2 manufacturer issued	• Component fracture • Incomplete coating compromises attachment
NTG (Prosthesis, Ankle, Uncemented, Non-Constrained)	3 manufacturer issued	• Fracture • Mislabeling
NVZ (Pulse Generator, Permanent, Implantable)	1 manufacturer issued	• Software lockup

Device Type	# Alerts	Reported Problem
OAF (Implant, Hearing, Active, Middle Ear, Totally Implanted)	3 manufacturer issued	• Compromised sterility • Distributed not to standard • Susceptible to noise interference
OQG (Hip Prosthesis, Semi-Constrained, Cemented, Metal/Polymer, + Additive, Porous, Uncemented)	1 manufacturer issued	• Loosening
OVD (Intervertebral Fusion Device With Integrated Fixation, Lumbar)	7 manufacturer issued	• Distributed without CE mark • Incorrect IFU • Mislabeling • Screw not seated properly within cage
OWI (Bone Fixation Cerclage, Sublaminar)	2 manufacturer issued	• Intraoperative fracture • Updated IFU
PHX (Shoulder Prosthesis, Reverse Configuration)	8 manufacturer issued	• Component dislocation • Dissociation • Fracture • Mislabeling • Missing components • Out of specification
PKC (Prosthesis, Total Anatomic Shoulder, Uncemented Metaphyseal Humeral Stem With No Diaphyseal Incursion, Semi-Constrained)	4 manufacturer issued	• Did not meet expected performance rate • Loosening • Mislabeling
PMP (Dorsal Root Ganglion Stimulator for Pain Relief)	1 manufacturer issued	• Fragmentation
PNJ (Leadless Pacemaker)	1 FDA issued	• Cardiac perforation
QES (Reherniation Reduction Device)	2 manufacturer issued	• Mislabeling
QON (Implanted Electrical Device Intended For Treatment Of Fecal Incontinence)	1 manufacturer issued	• Increased stimulation
HSN; HRS	1 manufacturer issued	• Missing sterilization documentation
HRS; LWJ (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Uncemented); LZO	1 manufacturer issued	• Compromised sterility
HRS; HWC	1 manufacturer issued	• Mislabeling

Device Type	# Alerts	Reported Problem
HRY (Prosthesis, Knee, Femorotibial, Semi-Constrained, Cemented, Metal/Polymer); NRA	2 manufacturer issued	• Impingement • Mislabeling
JDI; LZO	1 manufacturer issued	• Debris from packaging
JDI; NRA; PHX	1 manufacturer issued	• Compromised sterility
JWH; KWA	1 manufacturer issued	• Residue on device surface
JWH; MBH	5 manufacturer issued	• Adhesive residue may irritate tissue • Compromised sterility • Mislabeling • Residue on device surface
JWH; MBH; OIY (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained, Cemented, Polymer + Additive/Metal/Polymer + Additive)	1 manufacturer issued	• Compromised sterility
KWA; MBL (Prosthesis, Hip, Semi-Constrained, Uncemented, Metal/Polymer, Porous)	1 manufacturer issued	• Debris from packaging
KWP; NKG	3 manufacturer issued	• Loosening • Out of specification • Reduced strength due to implant cracks
KWS; PHX	5 manufacturer issued	• Incorrect IFU • Mislabeling • Out of specification
KWT (Prosthesis, Shoulder, Non-Constrained, Metal/Polymer Cemented); MBF	2 manufacturer issued	• Incorrect IFU • Metal back dissociation
LPH; LZO	2 manufacturer issued	• Compromised sterility • Staining
LPH; LZO; KWA	4 manufacturer issued	• High cytotoxicity levels • Mislabeling • Residue from packaging
LPH; OQG	1 manufacturer issued	• Tissue reaction to metal debris
LWJ; LZO; MEH	3 manufacturer issued	• Compromised sterility • Incorrect product
LZO; KWA; LPH; KWY; JWH; NJL (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained,	1 manufacturer issued	• Residue on device surface

Device Type	# Alerts	Reported Problem
Metal/Polymer, Mobile Bearing)		
LZO; KWZ; MEH	1 manufacturer issued	• Mislabeling
LZO; LPH	1 manufacturer issued	• Mislabeling
LZO; MEH	3 manufacturer issued	• Adverse tissue reaction to metal debris • Compromised sterility • Mislabeling
LZO; MRA (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Ceramic/ Metal, Cemented Or Uncemented)	1 manufacturer issued	• Distributed before PMA site change approval
MBF; JDI; KWA	1 manufacturer issued	• Elevated bacterial endotoxin and residual debris
MEH; LPF (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Porous Uncemented)	1 manufacturer issued	• Mislabeling
MEH; LPH	1 manufacturer issued	• Mislabeling
MEH; MAY (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous Cemented, Osteophilic Finishs, Calcium Phosphate)	1 manufacturer issued	• Corrosion leads to excessive debris/ions
MNH; MNI; NKB; OSH (Pedicle Screw Spinal System, Adolescent Idiopathic Scoliosis)	1 manufacturer issued	• Mislabeling
MNI; NKB; NQP	2 manufacturer issued	• Mislabeling
NKB; OSH	3 manufacturer issued	• Low fatigue strength • Screw head dissociation • Updated IFU
NKB; PGM (Growing Rod System)	1 manufacturer issued	• Fixation devices may not mate
NVN (Drug Eluting Permanent RV or RA Pacemaker Electrodes); LWP	3 manufacturer issued	• Cybersecurity firmware update • Moisture ingress • Transmitters may initiate a software reset
PBI (Prosthesis, Hip, Constrained, Cemented Or Uncemented, Metal/Polymer, + Additive); LPH	2 manufacturer issued	• Mislabeling

Device Type	# Alerts	Reported Problem
PHX; LPH; KRO; NRA	1 manufacturer issued	• Compromised sterility

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of Nitinol. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

Eighteen (94%) device categories were rated low or very-low quality of evidence for local responses representing areas with potential gaps in the literature. Cranioplasty implants were the notable exception rated moderate quality of evidence. This category included 9 studies (7 SRs) with mostly similar reporting of local responses from 22500 devices and duplicate reporting with other Ti device categories.

Seventy two (84%) studies did not investigate systemic responses from Ti devices. Of the 7 device categories that did investigate systemic responses, 4 (57%) device categories only had 1 study investigating. Additional research on systemic responses, including patient or material factors, for all Ti device categories is needed.

When searching ECRI's PSO and PRN databases, it was difficult to determine if accounts related to Ti were directly associated with biocompatibility issues. Therefore, they were not included in this report.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1. English language publication
2. Published between January 2012 and May 2022
3. Human studies (animal studies that provide unique information will also be considered for inclusion)
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of Titanium or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2012
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies (human and animal) providing relevant data.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – in human and animal studies, what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e., can the adverse effects be attributed to the device)? Animal studies are indirect but may provide the best evidence for the material itself.
6. Is there evidence of a **dose response or time response** (e.g., adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Titanium (Ti)

Set Number	Concept	Search Statement
1.	**Titanium (Ti) and derivatives**	
2.		
3.	Device #1	
4.	Other devices	
5.	General device terms: I	
6.	General device terms: Other	
7.	**Combine sets**	**#1 OR #2 OR #3 OR #4 OR #5 OR #6**
8.	Limit by language and publication date	#7 AND [english]/lim AND [2011–2021]/py
9.	Limit by publication type	#8 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

10.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
11.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
12.		Leachable* OR extractable*
13.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail* OR fragment* OR debond*) NEAR/3 ('restoration?' OR 'abutment?' OR 'crown?' OR 'bridge?' OR 'inlay?' OR 'onlay?' OR 'facing?' OR 'coping?' OR 'implant?' OR 'prosthes*' OR 'tooth' OR 'teeth' OR 'superstructure' OR 'base' OR 'core' OR 'disc')
14.		'mechanics'/exp [see Emtree explosions section at the end of the strategy]
15.		'device material'/exp/mj
16.		'Biomedical and dental materials'/exp/mj
17.	**Combine sets**	**#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16**

Host Response

18.		Host NEAR/2 (reaction* OR response*)
19.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
20.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
21.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti

22.		'inflammation'/exp OR (inflamm* OR 'periimplantitis' OR 'pulpitis' OR 'mucositis'):ti,ab
23.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
24.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab OR 'osteolysis'/exp OR 'osteolysis':ti,ab OR 'osseointegrat*':ti,ab
25.		protrude* OR protrus* OR perforat*
26.		'fibrosis'/exp OR 'fibrosis':ti,ab OR 'fibrotic':ti,ab OR 'fibrous':ti,ab OR OR 'loosen*':ti,ab OR 'migrat*':ti,ab
27.	**Combine sets**	**#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26**

Other Combinations

28.	**Titanium + Material Response + Host Response**	#9 AND #17 AND #27
29.	**Titanium general devices + Host response**	(#3 OR #4 OR #5 OR #6) AND #9 AND #27
30.	**Combine sets**	#28 OR #29
31.	**Titanium systematic reviews**	#9 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
32.	**Combine all**	**#30 OR #31**

Embase term Explosions

Mechanics/exp

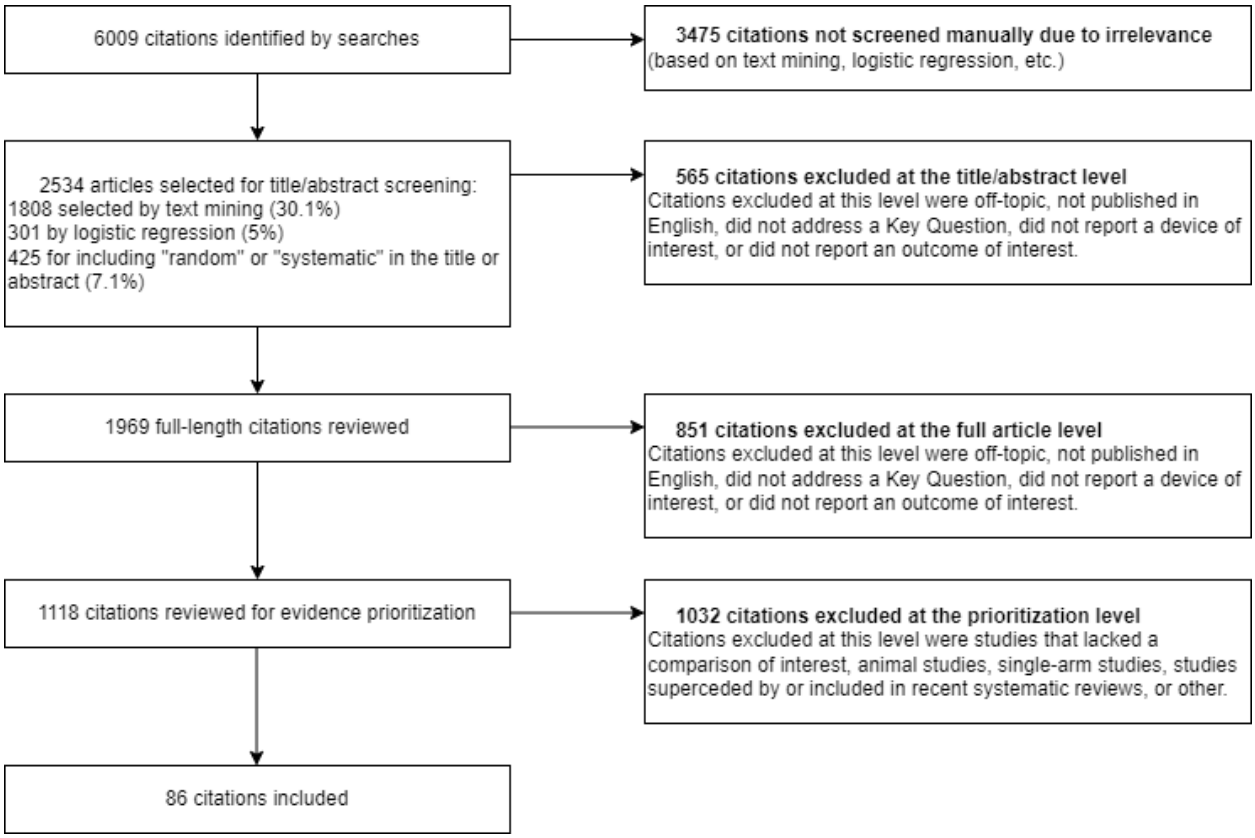
- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight
                            - Extremely low birth weight
            - Body weight change
                - Body weight fluctuation
                - Body weight gain
                    - Gestational weight gain
                - Body weight loss
                    - Emaciation
                - Body weight control
                - Fetus weight
                - Ideal body weight
                - Lean body weight
                - Live weight gain
            - Dry weight
            - Fresh weight
            - Molecular weight
            - Organ weight
                - Brain weight
                - Ear weight
                - Heart weight
                - Liver weight
                - Lung weight
                - Placenta weight
                - Spleen weight
                - Testis weight
                - Thyroid weight
                - Uterus weight

                        - Seed weight
                        - Tablet weight
                        - Thrombus weight
                - Weightlessness
            - Hydrodynamics
                - Hypertonic solution
                - Hypotonic solution
                - Isotonic solution
                - Osmolality
                    - Hyperosmolality
                    - Hypoosmolality
                    - Plasma osmolality
                    - Serum osmolality
                    - Urine osmolality
                - Osmolarity
                    - Blood osmolarity
                    - Hyperosmolarity
                    - Hypoosmolarity
                    - Plasma osmolarity
                    - Serum osmolarity
                    - Tear osmolarity
                    - Urine osmolarity
                - Osmosis
                    - Electroosmotic
                    - Osmotic stress
                        - Hyperosmotic stress
                        - Hypoosmotic stress
            - Photodynamics
                - Photoactivation
                    - Photoreactivation
                - Photodegradation
                - Photoreactivity
                    - Photocytotoxicity
                    - Photosensitivity
                    - Photosensitization
                    - Phototaxis
                    - Phototoxicity
                - Photostimulation
            - Proton motive force
            - Shock wave
                - High-energy shock wave
            - Stress strain relationship
            - Thermodynamics
                - Adiabaticity
                - Enthalpy
                - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow

        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity

        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity
    - Viscoelasticity

Appendix C. Study Flow Diagram



6009 citations were identified by searches, of which:

1. 3475 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.).

2. The remaining 2534 articles were selected for title/abstract level (1808 were selected by text mining in Distiller (30.1%), 301 by logistic regression (5%), and 425 for including "random" or "systematic" in the title or abstract (7.1%)).

    a. 565 citations were excluded at the title/abstract level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

    b. The remaining 1969 full length citations were reviewed, of which:

        i. 851 citations were excluded at the full article level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

        ii. The remaining 1118 citations were reviewed for evidence prioritization:

            1. 1032 citations were excluded at the prioritization level. Citations that may be excluded at this level were studies that lacked a comparison of interest, animal studies, single-arm studies, studies superseded by or included in recent systematic reviews, or other.

            2. 86 citations were included.

Appendix D. Evidence Tables

Table 3: Cardiovascular valves - Health Effects (In Vivo) Human Studies

Local Response/Toxicity

3.1 Source Citation: Cerqueira et al. 2018[2]

Study Design: Prospective nonrandomized comparative study

Device Material: Freedom Solo (bovine stentless) vs. Trifecta (Ti)

Contact Duration: Median f/u in years (IQR): Freedom Solo: 4.0 (2.2 to 6.0), Trifecta: 2.4 (1.4 to 3.7)

Dose: NR

Frequency/ Duration: Multiple procedures, n (%): Freedom Solo: 180 (55%), Trifecta: 180 (55%)

Response: De novo atrial fibrillation, infusion of >2 inotropes ± IABP, moderate or severe PPM, prosthetic endocarditis, reoperation due to bleeding/tamponade, severe thrombocytopenia, SVD and reoperation due to SVD/endocarditis

Patient characteristics (gender, mean age): Female gender, n (%): Freedom Solo: 161 (49%), Trifecta: 168 (51%), p=1.00; median age in years (IQR): Freedom Solo: 74 (69 to 78), Trifecta: 75 (69 to 79)

Number per Group: Freedom Solo: 329 patients, Trifecta: 329 patients

Note: Authors used propensity-score (PS) matching to account for measured confounding. The sample before matching was 397 patients receiving Freedom Solo and 525 receiving the Trifecta bioprosthesis. For the purposes of this report, we will be using the PS-matched sample.

Observed adverse effects:

Early Postoperative Outcomes (<30 days)

De novo atrial fibrillation, n (%): Freedom Solo: 112 (34%), Trifecta: 91 (28%), p=1.00, no difference

Infusion of >2 inotropes ± IABP, n (%): Freedom Solo: 87 (29%), Trifecta: 119 (38%), p=0.28, no difference

Severe thrombocytopenia, n (%): Freedom Solo: 26 (8%), Trifecta: 10 (3%), p=0.048, favors Trifecta

Reoperation due to bleeding/tamponade, n (%): Freedom Solo: 4 (1%), Trifecta: 11 (3%), p=0.95, no difference

Late Postoperative Outcomes (>30 days)

Moderate or severe PPM, n (%): Freedom Solo: 39 (14%), Trifecta: 40 (14%), p=1.00, no difference

Prosthetic endocarditis, n (%): Freedom Solo: 6 (2%), Trifecta: 5 (1%), p=1.00, no difference

SVD, n (%): Freedom Solo: 17 (5%), Trifecta: 3 (1%), p=0.098, no difference

Late Postoperative Outcomes (>30 days)

Reoperation due to SVD/endocarditis, n (%): Freedom Solo: 10 (3%), Trifecta: 2 (0%), p=0.28, no difference

Timing of adverse effects: Outcomes separated by early postoperative (<30 days) and late postoperative (>30 days) time points.

Factors that predict response: Authors performed a non-parsimonious 1:1 nearest-neighbor PS-matching without replacement (caliper of 0.02) based on logistic regression including 21 clinically relevant preoperative independent covariates, regardless of differences between groups. The 21

characteristics included age, gender, BMI, arterial hypertension, DM, smoking, COPD, neoplasia, CAD, CVD, PAD, CKD, a fib, NYHA ≥ III, ≥moderate LV dysfunction, active endocarditis, previous cardiac surgery, urgent/emergency surgery, multiple procedures, aortic regurgitation, and bicuspid aortic valve.

Systemic Response/Toxicity

3.2 Source Citation: Yokoyama et al. 2021[1]

Study Design: Systematic review of 6 nonrandomized comparative studies

Device or Material: Trifecta (Ti) vs. Perimount (CoCr)

Contact Duration: Median follow-up range 2.5 to 4.5 years

Dose: NR

Frequency/Duration: NR

Response: All-cause mortality, re-intervention rate

Patient characteristics (gender, age): Percent female: 28% to 52%, median age range: 65 to 74 years

Number per Group: Trifecta: 4,932 patients, Perimount: 6,203 patients

Note: One study contained a mixture of valve types (Perimount: 80.4%, Mitroflow: 3.8%, Avalus 2.8%, Intuity: 13.1%) for patients allocated to the Perimount study arm.

Observed adverse effects:

All-cause mortality: HR 1.09 (3 studies, 95% CI: 0.75 to 1.58, p=0.67, I^2=12%, no difference)

Re-intervention rate: HR 3.16 (6 studies, 95% CI: 1.83 to 5.46, p<0.0001, I^2=40%, favors Perimount)

Sensitivity analysis removing studies without adjusted HRs using random effects model

Re-intervention rate: HR 3.87 (4 studies, 95% CI: 1.86 to 8.08, p=0.0003, I^2=60%, favors Perimount)

Timing of adverse effects: Median follow-up range 2.5 to 4.5 years

Factors that predict response: NR

3.3 Source Citation: Cerqueira et al. 2018[2]

Study Design: Prospective nonrandomized comparative study

Device Material: Freedom Solo (bovine stentless) vs. Trifecta (Ti)

Contact Duration: Median f/u in years (IQR): Freedom Solo: 4.0 (2.2 to 6.0), Trifecta: 2.4 (1.4 to 3.7)

Dose: NR

Frequency/ Duration: Multiple procedures, n (%): Freedom Solo: 180 (55%), Trifecta: 180 (55%)

Response: Mortality, PPI, prolonged mechanical ventilation, stroke, worsening kidney function

Patient characteristics (gender, mean age): Female gender, n (%): Freedom Solo: 161 (49%), Trifecta: 168 (51%), p=1.00; median age in years (IQR): Freedom Solo: 74 (69 to 78), Trifecta: 75 (69 to 79)

Number per Group: Freedom Solo: 329 patients, Trifecta: 329 patients

Note: Authors used propensity-score (PS) matching to account for measured confounding. The sample before matching was 397 patients receiving Freedom Solo and 525 receiving the Trifecta bioprosthesis. For the purposes of this report, we will be using the PS-matched sample.

Observed adverse effects:

Early Postoperative Outcomes (<30 days)

Mortality, n (%): Freedom Solo: 5 (2%), Trifecta: 16 (5%), p=0.21, no difference

PPI, n (%): Freedom Solo: 8 (2%), Trifecta: 16 (5%), p=1.00, no difference

Prolonged mechanical ventilation, n (%): Freedom Solo: 17 (5%), Trifecta: 40 (12%), p=0.014, favors Freedom Solo

Stroke, n (%): Freedom Solo: 5 (2%), Trifecta: 14 (4%), p=0.52, no difference

Worsening kidney function, n (%): Freedom Solo: 17 (5%), Trifecta: 12 (4%), p=1.00, no difference

Timing of adverse effects: Outcomes separated by early postoperative (<30 days) and late postoperative (>30 days) time points.

Factors that predict response: Authors performed a non-parsimonious 1:1 nearest-neighbor PS-matching without replacement (caliper of 0.02) based on logistic regression including 21 clinically relevant preoperative independent covariates, regardless of differences between groups. The 21 characteristics include age, gender, BMI, arterial hypertension, DM, smoking, COPD, neoplasia, CAD, CVD, PAD, CKD, a fib, NYHA ≥ III, ≥moderate LV dysfunction, active endocarditis, previous cardiac surgery, urgent/emergency surgery, multiple procedures, aortic regurgitation, and bicuspid aortic valve.

a fib: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CI: confidence interval; CKD: chronic kidney disease; CoCr: cobalt chromium; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; DM: diabetes mellitus; f/u: follow-up; HR: hazard ratio; IABP: intra-aortic balloon pump; IQR: interquartile range; LV: left ventricle; NR: not reported; NYHA: New York Heart Association; PAD: peripheral artery disease; PPI: postoperative pacemaker implantation; PPM: patient–prosthesis mismatch; PS: propensity scoring; SVD: structural valve deterioration; Ti: titanium

Table 4: Cardiovascular catheters - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

4.1 Source Citation: Fornaro et al. 2018[3]

Study Design: Systematic review of 6 single-arm studies

Device or Material: Port-a-cath system (Ti)

Contact Duration: The median follow-up was 30 months (range 1–131).

Dose: NR

Frequency/Duration: NR

Response: Bleeding, catheter dysfunction, extravasation, mechanical complications, occlusion, reservoir dislocation, rupture

Patient characteristics (gender, mean age): Female, n (%): 222 (57%); median age in years (range): 56 (18 to 80)

Number per Group: 390 total patients

Observed adverse effects:

4-Week Flushing Outcomes

Bleeding, n: 1

Catheter dysfunction, n: 0

Extravasation, n: 1

Reservoir dislocation, n: 1

Rupture, n: 1

Other (e.g., edema, arterial puncture, etc.), n: 2

8-Week Flushing Outcomes

Bleeding, n: 1

Catheter dysfunction, n: 3

Extravasation, n: 3

Reservoir dislocation, n: 2

Rupture, n: 0

Other (e.g., edema, arterial puncture, etc.), n: 3

4-12 Week Complications

Mechanical Complications (e.g., reservoir dislocation and extravasation) (4 studies, 925 patients), n (%): 25 (2.7%)

Occlusion (4 studies, 925 patients), n (%): 9 (1.0%)

Comparing Standard versus Longer Term Flushing Intervals

Occlusion (3 studies): Standard: 6/120 (5%), Longer Term: 16/406 (3.9%), p=0.61, no difference

Total Complications (e.g., occlusion, mechanical complications) (3 studies): Standard: 21/260 (8.1%), Longer Term: 45/615 (7.3%), p=0.70, no difference

Timing of adverse effects: Outcomes measured between 4 and greater than 12 weeks depending on the outcome of interest or individual study f/u time.

Factors that predict response: NR

f/u: follow-up; NR: not reported; Ti: titanium

Table 5: Cardiovascular implanted devices - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

5.1 Source Citation: Tang et al. 2020[4] **Study Design:** Systematic review of 3 RCTs

Device or Material: Centrifugal continuous flow circulator pump (CCFCP) vs axial continuous-flow pump (ACFP) (Both Ti)

Note: Discussion shows that the HeartMate II was the axial device whereas the HVAD was the centrifugal device, both of which are composed of Ti

Contact Duration: 2-year follow-up

Dose: NR

Frequency/Duration: NR

Response: Bleeding (any, gastrointestinal), bleeding requiring blood transfusion, bleeding requiring re-operation, cardiac arrhythmia (any), need for right VAD, pump replacement, pump thrombosis, right HF

Patient characteristics (gender, mean age): Percent male range: 76.4% to 92.0%; mean age range: 59.0 to 66.2 years,

Number per Group: CCFCP: 621 patients, ACFP: 390 patients

Observed adverse effects:

Bleeding (Any) (3 studies, n=1011): CCFCP: 407/621 (65.5%), ACFP: 234/390 (60%), OR 0.83 (95% CI: 0.62 to 1.11, p=0.21, I^2=7%, no difference)

Bleeding (Gastrointestinal) (2 studies, n=811): CCFCP: 155/487 (31.8%), ACFP: 98/324 (30.2%), OR 1.02 (95% CI: 0.75 to 1.38, p=0.92, I^2=0%, no difference)

Bleeding requiring blood transfusion (2 studies, n=645): CCFCP: 85/431 (19.7%), ACFP: 42/214 (19.6%), OR 1.25 (95% CI: 0.30 to 5.29, p=0.76, I^2=89%, no difference)

Bleeding requiring re-operation (3 studies, n=1011): CCFCP: 176/621 (28.3%), ACFP: 102/390 (26.1%), OR 0.99 (95% CI: 0.54 to 1.79, p=0.97, I^2=67%, no difference)

Cardiac arrhythmia (Any) (3 studies, n=1011): CCFCP: 258/621 (41.5%), ACFP: 166/390 (42.5%), OR 0.93 (95% CI: 0.71 to 1.20, p=0.56, I^2=0%, no difference)

Need for right VAD (3 studies, n=1011): CCFCP: 19/621 (3%), ACFP: 16/390 (4.1%), OR 0.75 (95% CI: 0.38 to 1.49, p=0.41, I^2=0%, no difference)

Pump replacement (2 studies, n=645): CCFCP: 35/431 (8.1%), ACFP: 40/214 (18.6%), OR 0.36 (95% CI: 0.15 to 0.84, p=0.02, I^2=64%, favors CCFCP)

Pump thrombosis (3 studies, n=1011): CCFCP: 26/621 (4.2%), ACFP: 43/390 (11%), OR 0.43 (95% CI: 0.06 to 3.29, p=0.42, I^2=82%, no difference)

Right HF (3 studies, n=1011): CCFCP: 206/621 (33.1%), ACFP: 107/390 (27.4%), OR 1.30 (95% CI: 0.98 to 1.72, p=0.07, I^2=47%, no difference)

Timing of adverse effects: 2-year follow-up

Factors that predict response: NR

5.2 Source Citation: Cavarretta et al. 2019[5]

Study Design: Systematic review of 8 studies (4 RCTs, 4 nonrandomized comparative studies)

Device or Material: HeartMate 3 (Ti), HeartMate II (Ti), HeartMate XVE/VE (Ti), HeartWare (Ti), versus medical management

Contact Duration: Mean f/u 24 months

Dose: NR

Frequency/Duration: NR

Response: Bleeding requiring surgical management, device thrombosis resulting in reoperation or removal of device, right ventricular failure

Patient characteristics (gender, mean age):

4 RCTs: Percent male range: 78.3% to 84.5%, mean age range in years: 60 to 67.1;

4 nonrandomized comparative studies: percent male range: 49% to 86.1%, mean age range in years: 44.0 to 67.4

Number per Group: 4 RCTs: 1141 patients; 4 nonrandomized comparative studies: 1147 patients

Note: No information on number of patients per device or intervention group, only totals

Observed adverse effects:

Bleeding requiring surgical management:

HeartMate 3 vs. HeartMate II: RR 1.41 (95% CI: 0.88 to 2.25), p=0.152, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 1.77 (95% CI: 0.87 to 3.62), p=0.117, no difference;

HeartMate 3 vs. HeartWare: RR 1.30 (95% CI: 0.69 to 2.45), p=0.425, no difference;

HeartMate 3 vs. Medical Management: RR 0.18 (95% CI: 0.06 to 51), p=0.002, favors HeartMate 3;

HeartMate II vs. HeartMate XVE/VE: RR 1.26 (95% CI: 0.74 to 2.15), p=0.396, no difference;

HeartMate II vs. HeartWare: RR 0.93 (95% CI: 0.61 to 1.41), p=0.734, no difference;

HeartMate II vs. Medical Management: RR 0.13 (95% CI: 0.05 to 0.32), p<0.001, favors HeartMate II;

HeartMate XVE/VE vs. HeartWare: RR 0.74 (95% CI: 0.37 to 1.45), p=0.367, no difference;

HeartMate XVE/VE vs. Medical Management: RR 0.10 (95% CI: 0.05 to 0.21), p<0.001, favors HeartMate XVE/VE;

HeartWare vs. Medical Management: RR 0.38 (95% CI: 0.05 to 0.20), p=0.006, favors HeartWare

Device thrombosis resulting in reoperation or removal of device:

HeartMate 3 vs. HeartMate II: RR 58.45 (95% CI: 3.56 to >100), p<0.001, favors HeartMate II;

HeartMate 3 vs. HeartMate XVE/VE: RR 27.08 (95% CI: 0.49 to >100), p=0.001, favors HeartMate XVE/VE;

HeartMate 3 vs. HeartWare: RR 34.54 (95% CI: 1.96 to >100), p=0.001, favors HeartWare;

HeartMate 3 vs. Medical Management: RR 1.77 (95% CI: 0.01 to >100), p=0.814, no difference;

HeartMate II vs. HeartMate XVE/VE: RR 0.45 (95% CI: 0.03 to 8.22), p=0.577, no difference;

HeartMate II vs. HeartWare: RR 0.59 (95% CI: 0.31 to 1.12), p=0.107, no difference;

HeartMate II vs. Medical Management: RR 0.03 (95% CI: 0.00 to 1.73), p=0=0.007, favors HeartMate II;

HeartMate XVE/VE vs. HeartWare: RR 1.28 (95% CI: 0.07 to 24.29), p=0.869, no difference;

HeartMate XVE/VE vs. Medical Management: RR 0.07 (95% CI: 0.00 to 1.12), p=0.027, favors HeartMate XVE/VE;

HeartWare vs. Medical Management: RR 0.05 (95% CI: 0.00 to 3.08), p=0.040, favors HeartWare

Right ventricular failure:

HeartMate 3 vs. HeartMate II: RR 0.88 (95% CI: 0.65 to 1.20), p=0.422, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 2.34 (95% CI: 1.30 to 4.22), p=0.005, favors HeartMate XVE/VE;

HeartMate 3 vs. HeartWare: RR 1.27 (95% CI: 0.83 to 1.93), p=0.270, no difference;

HeartMate 3 vs. Medical Management: RR 0.04 (95% CI: 0.00 to 0.76), p=0.033, favors HeartMate 3;

HeartMate II vs. HeartMate XVE/VE: RR 2.66 (95% CI: 1.61 to 4.39), p<0.001, favors HeartMate XVE/VE;

HeartMate II vs. HeartWare: RR 1.44 (95% CI: 1.08 to 1.92), p=0.013, favors HeartWare;

HeartMate II vs. Medical Management: RR 0.05 (95% CI: 0.00 to 0.85), p=0.008, favors HeartMate II;

HeartMate XVE/VE vs. HeartWare: RR 0.54 (95% CI: 0.30 to 0.97), p=0.040, favors HeartMate XVE/VE;

HeartMate XVE/VE vs. Medical Management: RR 0.02 (95% CI: 0.00 to 0.31), p<0.001, favors HeartMate XVE/VE;

HeartWare vs. Medical Management: RR 0.03 (95% CI: 0.00 to 0.60), p<0.001, favors HeartWare

Timing of adverse effects: Mean f/u 24 months

Factors that predict response: NR

5.3 Source Citation: Luc et al. 2019[6]

Study Design: Systematic review of 43 studies (2 trials, 4 registries, 37 cohort studies)

Device or Material: Surgical management: HeartWare, HeartMate II, Jarvik2000, DuraHeart, MicroMed DeBakey, HeartAssist5, VentrAssist (All Ti) vs medical management

Contact Duration: Mean f/u 12.6 months (SD 10.4 months)

Dose: NR

Frequency/Duration: NR

Response: success rate, urgent device exchange

Patient characteristics (gender, mean age): Male, n/N: 15,414/19,634; Mean age in years: 54.0 (95% CI: 53.9 to 56.0, I^2=98.47%)

Number per Group: HeartWare: 2,931, HeartMate II: 25,296, Jarvik2000: 74, DuraHeart: 2, MicroMed DeBakey: 1, HeartAssist5: 2, VentrAssist: 6

Note: Denominator is number of VADs implanted. Some patients may receive multiple devices.

Observed adverse effects:

Success rate: Medical management (18 studies, n=216): RR 103/216 (46.0%) (95% CI: 33.2% to 59.3%, I^2=58.81%); surgical management (22 studies, n=622): RR 522/622 (80.8%) (95% CI: 70.4% to 88.2%, I^2=68.08%), p=0.001, favors surgical management

Subgroup: Trials Only

Success rate: Medical management (1 study, n=30): RR 15/30 (50.0%) (95% CI: 32.8% to 67.2%, I^2=NA); surgical management (2 studies, n=29): RR 27/29 (91.6%) (95% CI: 75.0% to 97.6%, I^2=88.30%), p=0.002, favors surgical management

Subgroup: Registries Only

Success rate: Medical management (0 studies): NA; surgical management (2 studies, n=368): RR 303/368 (65.9%) (95% CI: 14.7% to 95.6%, I^2=97.27%), p=NA

Subgroup: Cohorts Only

Success rate: Medical management (17 studies, n=186): RR 88/186 (45.4%) (95% CI: 31.2% to 60.3%, I^2=61.09); surgical management (18 studies, n=225): RR 192/225 (81.3%) (95% CI: 70.9% to 88.6%, I^2=36.86%), p<0.001, favors surgical management

Urgent device exchange: Medical management (17 studies, n=218): RR 42/218 (23.4%) (95% CI: 15.5% to 33.7%, I^2=36.84%); surgical management (15 studies, n=152): RR 5/152 (9.4%) (95% CI: 5.4% to 15.9%, I^2=0%), p=0.006, favors surgical management

Subgroup: Trials Only

Transplantation required: Medical management (1 study, n=30): RR 12/30 (40.0%) (95% CI: 24.3% to 58.1%, I^2=NA); surgical management (0 studies): NA

Subgroup: Registries Only

Transplantation required: Medical management (0 studies): NA; surgical management (0 studies): NA

Subgroup: Cohorts Only

Transplantation required: Medical management (16 studies, n=188): RR 30/188 (21.2%) (95% CI: 13.4% to 31.8%, I^2=32.29%); surgical management (15 studies, n=152): RR 5/152 (9.4%) (95% CI: 5.4% to 15.9%, I^2=0%), p=0.006, favors surgical management

Timing of adverse effects: Mean f/u 12.6 months (SD 10.4 months)

Factors that predict response: NR

5.4 Source Citation: Shurrab et al. 2018[7]

Study Design: Systematic review of 6 single-arm studies (5 retrospective and 1 prospective)

Note: Comparison between two types of pacing systems that are both made of Ti.

Device or Material: MedTronic Pacing System (CapSure Fix) with MRI-conditional pacemakers or conventional pacemakers (both Ti)

Contact Duration: Follow-up range: 1 to 44.3 months

Dose: NR

Frequency/Duration: NR

Response: Lead dislodgement, pericardial complications, total complications

Patient characteristics (gender, mean age): Percent male: MRI conditional: 58%, conventional: 55%; mean age in years (SD): MRI conditional: 68 (2.43), conventional: 72 (4.89)

Number per Group: MRI conditional: 969, conventional: 1,149

Observed adverse effects:

Lead dislodgement (6 studies, n=2,118): MRI: 32/969, conventional: 14/1149, OR 2.47 (95% CI: 1.26 to 4.83), I^2=0%, p=0.008, favors conventional

Pericardial complications (4 studies, n=1,913): MRI: 20/880, conventional: 7/1033, OR 4.23 (95% CI: 1.18 to 15.10), I^2=49%, p=0.03, favors conventional

Total complications (6 studies, n=2,118): MRI: 60/969, conventional: 40/1149, OR 2.02 (95% CI: 0.88 to 4.66), I^2=68%, p=0.10, no difference

Timing of adverse effects: Follow-up range: 1 to 44.3 months

Factors that predict response: NR

5.5 Source Citation: Chue et al. 2017[8]

Study Design: Systematic Review of 16 single-arm studies

Device or Material: S-ICD Device (Ti)

Note: The study refers to S-ICD devices without study-level information on device type, however, one type of S-ICD is manufactured in the United States (EMBLEM, Boston Scientific).

Contact Duration: Follow-up range: 61 to 2,117 days

Dose: NR

Frequency/Duration: NR

Response: Delayed wound healing, discomfort, failure of device communication, hematoma, lead migration, premature battery depletion

Patient characteristics (gender, mean age): Percent male range: 59% to 92%, mean age range: 33 to 64 years

Number per Group: 1,670 patients

Observed adverse effects:

Delayed wound healing rate: 0.61%

Discomfort rate: 0.75%

Failure of device communication rate: 0.32%

Hematoma rate: 0.44%

Lead migration rate: 0.28%

Premature battery depletion rate: 1.16%

Timing of adverse effects: Follow-up range: 61 to 2,117 days

Factors that predict response: NR

Systemic Response/Toxicity

5.6 Source Citation: Tang et al. 2020[4]

Study Design: Systematic review of 3 RCTs

Device or Material: Centrifugal continuous flow circulator pump (CCFCP) vs axial continuous-flow pump (ACFP) (Both Ti)

Note: Discussion shows that the HeartMate II was the axial device whereas the HVAD was the centrifugal device, both of which are composed of Ti

Contact Duration: 2-year follow-up

Dose: NR

Frequency/Duration: NR

Response: Hepatic dysfunction**,** other neurological events, renal failure, respiratory failure, sepsis, stroke (any, ischemic, hemorrhagic)

Patient characteristics (gender, mean age): Percent male range: 76.4% to 92.0%; mean age range: 59.0 to 66.2 years,

Number per Group: CCFCP: 621 patients, ACFP: 390 patients

Observed adverse effects:

Hepatic dysfunction (3 studies, n=1011): CCFCP: 22/621, ACFP: 19/390, OR 0.72 (95% CI: 0.38 to 1.35, p=0.30, I^2=0%, no difference)

Renal failure (3 studies, n=1011): CCFCP: 90/621, ACFP: 50/390, OR 1.11 (95% CI: 0.76 to 1.61, p=0.59, I^2=0%, no difference)

Respiratory failure (3 studies, n=1011): CCFCP: 181/621, ACFP: 16/390, OR 1.12 (95% CI: 0.84 to 1.49, p=0.46, I^2=0%, no difference)

Sepsis (3 studies, n=1011): CCFCP: 144/621, ACFP: 73/390, OR 1.19 (95% CI: 0.86 to 1.65, p=0.29, I^2=35%, no difference)

Stroke (Any) (3 studies, n=1011): CCFCP: 131/621, ACFP: 59/390, OR 1.32 (95% CI: 0.40 to 4.35, p=0.65, I^2=90%, no difference)

Stroke (Hemorrhagic) (3 studies, n=1011): CCFCP: 67/621, ACFP: 27/390, OR 1.40 (95% CI: 0.36 to 5.46, p=0.62, I^2=84%, no difference)

Stroke (Ischemic) (3 studies, n=1011): CCFCP: 75/621, ACFP: 39/390, OR 1.14 (95% CI: 0.37 to 3.54, p=0.82, I^2=82%, no difference)

Other neurological events (3 studies, n=1011): CCFCP: 76/621, ACFP: 32/390, OR 1.57 (95% CI: 1.01 to 2.44, p=0.05, I^2=0%, favors ACFP)

Timing of adverse effects: 2-year follow-up

Factors that predict response: NR

5.7 Source Citation: Cavarretta et al. 2019[5]

Study Design: Systematic review of 8 studies (4 RCTs, 4 nonrandomized comparative studies)

Device or Material: HeartMate 3 (Ti), HeartMate II (Ti), HeartMate XVE/VE (Ti), HeartWare (Ti), medical management

Contact Duration: Mean f/u 24 months

Dose: NR

Frequency/Duration: NR

Response: Hepatic dysfunction, mortality, neurological dysfunction, renal dysfunction, respiratory failure, sepsis, stroke

Patient characteristics (gender, mean age):

4 RCTs: Percent male range: 78.3% to 84.5%, mean age range in years: 60 to 67.1;

4 nonrandomized comparative studies: percent male range: 49% to 86.1%, mean age range in years: 44.0 to 67.4

Number per Group: 4 RCTs: 1141 patients; 4 nonrandomized comparative studies: 1147 patients

Note: No information on number of patients per device or intervention group, only totals

Observed adverse effects:

Hepatic dysfunction:

HeartMate 3 vs. HeartMate II: RR 0.95 (95% CI: 0.37 to 2.45), p=0.922, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 0.69 (95% CI: 0.03 to 15.28), p=0.827, no difference;

HeartMate 3 vs. HeartWare: RR 0.55 (95% CI: 0.16 to 1.85), p=0.343, no difference;

HeartMate 3 vs. Medical Management: RR 0.11 (95% CI: 0.00 to 7.94), p=0.340, no difference;

HeartMate II vs. HeartMate XVE/VE: RR 0.73 (95% CI: 0.04 to 13.83), p=0.832, no difference;

HeartMate II vs. HeartWare: RR 0.58 (95% CI: 0.27 to 1.23), p=0.159, no difference;

HeartMate II vs. Medical Management: RR 0.12 (95% CI: 0.01 to 7.50), p=0.209, no difference;

HeartMate XVE/VE vs. HeartWare: RR 0.80 (95% CI: 0.04 to 16.65), p=0.885, no difference;

HeartMate XVE/VE vs. Medical Management: RR 0.16 (95% CI: 0.01 to 3.05), p=0.209, no difference;

HeartWare vs. Medical Management: RR 0.20 (95% CI: 0.00 to 13.82), p=0.508, no difference

Mortality (Note: Only includes RCT evidence):

HeartMate 3 vs. HeartMate II: RR 1.30 (95% CI: 0.83 to 2.01), p=0.247, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 1.61 (95% CI: 0.90 to 2.88), p=0.108, no difference;

HeartMate 3 vs. HeartWare: RR 1.58 (95% CI: 0.94 to 2.64), p=0.082, no difference;

HeartMate 3 vs. Medical Management: RR 2.37 (95% CI: 1.28 to 4.39), p=0.006, favors Medical Management;

HeartMate II vs. HeartMate XVE/VE: RR 1.25 (95% CI: 0.85 to 1.82), p=0.251, no difference;

HeartMate II vs. HeartWare: RR 1.22 (95% CI: 0.93 to 1.60), p=0.151, no difference;

HeartMate II vs. Medical Management: RR 1.83 (95% CI: 1.19 to 2.82), p=0.006, favors Medical Management;

HeartMate XVE/VE vs. HeartWare: RR 0.98 (95% CI: 0.61 to 1.56), p=0.933, no difference;

HeartMate XVE/VE vs. Medical Management: RR 1.47 (95% CI: 1.19 to 1.82), p<0.001, favors Medical Management;

HeartWare vs. Medical Management: RR 1.50 (95% CI: 0.91 to 2.51), p=0.117, no difference

Neurological dysfunction:

HeartMate 3 vs. HeartMate II: RR 0.76 (95% CI: 0.41 to 1.38), p=0.382, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 1.30 (95% CI: 0.57 to 2.95), p=0.543, no difference;

HeartMate 3 vs. HeartWare: RR 1.50 (95% CI: 0.55 to 4.12), p=0.438, no difference;

HeartMate 3 vs. Medical Management: RR 0.30 (95% CI: 0.11 to 0.83), p=0.02, favors HeartMate 3;

HeartMate II vs. HeartMate XVE/VE: RR 1.71 (95% CI: 0.98 to 3.01), p=0.061, no difference;

HeartMate II vs. HeartWare: RR 1.99 (95% CI: 0.88 to 4.48), p=0.097, no difference;

HeartMate II vs. Medical Management: RR 0.40 (95% CI: 0.17 to 0.90), p=0.031, favors HeartMate II;

HeartMate XVE/VE vs. HeartWare: RR 1.16 (95% CI: 0.43 to 3.11), p=0.765, no difference;

HeartMate XVE/VE vs. Medical Management: RR 0.23 (95% CI: 0.13 to 0.42), p<0.001, favors HeartMate XVE/VE;

HeartWare vs. Medical Management: RR 0.20 (95% CI: 0.06 to 0.63), p=0.007, favors HeartWare

Renal dysfunction:

HeartMate 3 vs. HeartMate II: RR 0.79 (95% CI: 0.46 to 1.36), p=0.401, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 2.71 (95% CI: 1.21 to 6.05), p=0.010, favors HeartMate XVE/VE;

HeartMate 3 vs. HeartWare: RR 1.04 (95% CI: 0.50 to 2.16), p=0.923, no difference;

HeartMate 3 vs. Medical Management: RR 1.95 (95% CI: 0.77 to 4.97), p=0.161, no difference;

HeartMate II vs. HeartMate XVE/VE: RR 3.44 (95% CI: 1.91 to 6.17), p<0.001, favors HeartMate XVE/VE;

HeartMate II vs. HeartWare: RR 1.32 (95% CI: 0.81 to 2.14), p=0.263, no difference;

HeartMate II vs. Medical Management: RR 2.47 (95% CI: 1.16 to 5.28), p=0.019, favors Medical Management;

HeartMate XVE/VE vs. HeartWare: RR 0.38 (95% CI: 0.18 to 0.82), p=0.012, favors HeartMate XVE/VE;

HeartMate XVE/VE vs. Medical Management: RR 0.72 (95% CI: 0.45 to 1.16), p=0.174, no difference;

HeartWare vs. Medical Management: RR 1.88 (95% CI: 0.76 to 4.62), p=0.170, no difference

Respiratory failure:

HeartMate 3 vs. HeartMate II: RR 0.95 (95% CI: 0.66 to 1.36), p=0.793, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 2.44 (95% CI: 1.57 to 3.77), p<0.001, favors HeartMate XVE/VE;

HeartMate 3 vs. HeartWare: RR 1.11 (95% CI: 0.70 to 1.77), p=0.673, no difference;

HeartMate II vs. HeartMate XVE/VE: RR 2.57 (95% CI: 2.00 to 3.31), p<0.001, favors HeartMate XVE/VE;

HeartMate II vs. HeartWare: RR 1.18 (95% CI: 0.88 to 1.57), p=0.262, no difference;

HeartMate XVE/VE vs. HeartWare: RR 0.46 (95% CI: 0.31 to 0.67), p<0.001, favors HeartMate XVE/VE;

Sepsis:

HeartMate 3 vs. HeartMate II: RR 1.02 (95% CI: 0.62 to 1.67), p=0.943, no difference;

HeartMate 3 vs. HeartMate XVE/VE: RR 2.84 (95% CI: 1.56 to 5.17), p<0.001, favors HeartMate XVE/VE;

HeartMate 3 vs. HeartWare: RR 1.52 (95% CI: 0.81 to 2.86), p=0.194, no difference;

HeartMate 3 vs. Medical Management: RR 0.70 (95% CI: 0.33 to 1.47), p=0.355, no difference;

HeartMate II vs. HeartMate XVE/VE: RR 2.79 (95% CI: 1.98 to 3.92), p<0.001, favors HeartMate XVE/VE;

HeartMate II vs. HeartWare: RR 1.49 (95% CI: 1.01 to 2.21), p=0.046, favors HeartWare;

HeartMate II vs. Medical Management: RR 0.68 (95% CI: 0.39 to 1.20), p=0.179, no difference;

HeartMate XVE/VE vs. HeartWare: RR 0.54 (95% CI: 0.32 to 0.90), p=0.019, favors HeartMate XVE/VE;

HeartMate XVE/VE vs. Medical Management: RR 0.24 (95% CI: 0.16 to 0.38), p<0.001, favors HeartMate XVE/VE;

HeartWare vs. Medical Management: RR 0.46 (95% CI: 0.23 to 0.91), p=0.027, favors HeartWare

Stroke:

HeartMate 3 vs. HeartMate II: RR 1.87 (95% CI: 1.15 to 3.05), p=0.01, favors HeartMate II;

HeartMate 3 vs. HeartMate XVE/VE: RR 3.09 (95% CI: 1.35 to 7.10), p=0.008, favors HeartMate XVE/VE;

HeartMate 3 vs. HeartWare: RR 5.73 (95% CI: 2.94 to 11.16), p<0.001, favors HeartWare;

HeartMate 3 vs. Medical Management: RR 0.40 (95% CI: 0.09 to 1.67), p=0.221, no difference;

HeartMate II vs. HeartMate XVE/VE: RR 1.71 (95% CI: 0.87 to 3.37), p=0.120, no difference;

HeartMate II vs. HeartWare: RR 3.12 (95% CI: 1.98 to 4.91), p<0.001, favors HeartWare;

HeartMate II vs. Medical Management: RR 0.22 (95% CI: 0.06 to 0.85), p=0.025, favors HeartMate II;

HeartMate XVE/VE vs. HeartWare: RR 1.82 (95% CI: 0.80 to 4.10), p=0.151, no difference;

HeartMate XVE/VE vs. Medical Management: RR 0.13 (95% CI: 0.04 to 0.41), p<0.001, favors HeartMate XVE/VE;

HeartWare vs. Medical Management: RR 0.07 (95% CI: 0.02 to 0.29), p<0.001, favors HeartWare

Timing of adverse effects: Mean f/u 24 months

Factors that predict response: NR

5.8 Source Citation: Luc et al. 2019[6]

Study Design: Systematic review of 43 studies (2 trials, 4 registries, 37 cohort studies)

Device or Material: Surgical management: HeartWare, HeartMate II, Jarvik2000, DuraHeart, MicroMed DeBakey, HeartAssist5, VentrAssist (All Ti) vs medical management

Contact Duration: Mean f/u 12.6 months (SD 10.4 months)

Dose: NR

Frequency/Duration: NR

Response: Hemorrhagic stroke, mortality, recurrence, transplantation required

Patient characteristics (gender, mean age): Male, n/N: 15,414/19,634; Mean age in years: 54.0 (95% CI: 53.9 to 56.0, I^2=98.47%)

Number per Group: HeartWare: 2,931, HeartMate II: 25,296, Jarvik2000: 74, DuraHeart: 2, MicroMed DeBakey: 1, HeartAssist5: 2, VentrAssist: 6

Note: Denominator is number of VADs implanted. Some patients may receive multiple devices.

Observed adverse effects:

Hemorrhagic stroke: Medical management (11 studies, n=131): RR 25/131 (21.9%) (95% CI: 14.9% to 30.9%, I^2=6.59%); surgical management: NA

Subgroup: Trials Only

Hemorrhagic stroke: Medical management (0 studies): NA; surgical management (0 studies): NA

Subgroup: Registries Only

Hemorrhagic stroke: Medical management (0 studies): NA; surgical management (0 studies): NA

Subgroup: Cohorts Only

Hemorrhagic stroke: Medical management (11 studies, n=131): RR 25/131 (21.9%) (95% CI: 14.9% to 30.9%, I^2=6.59%); surgical management: NA

Mortality: Medical management (19 studies, n=229): RR 69/229 (25.8%) (95% CI: 17.3% to 36.5%, I^2=44.14%); surgical management (21 studies, n=569): RR 62/569 (8.4%) (95% CI: 4.0% to 12.9%, I^2=64.76), p=0.030, favors surgical management

Subgroup: Trials Only

Death: Medical management (1 study, n=30): RR 5/30 (16.7%) (95% CI: 7.1% to 34.3%, I^2=NA); surgical management (2 studies, n=59): RR 2/59 (8.4%) (95% CI: 2.4% to 25.0%, I^2=0%), p=0.340, no difference

Subgroup: Registries Only

Death: Medical management (0 studies): NA; surgical management (2 studies, n=368): RR 45/368 (7.1%) (95% CI: 1.0% to 37.5%, I^2=60.18%), p=NA

Subgroup: Cohorts Only

Death: Medical management (18 studies, n=199): RR 64/199 (34.5%) (95% CI: 25.5% to 44.9%, I^2=35.34%); surgical management (17 studies, n=172): RR 15/172 (16.7%) (95% CI: 9.7% to 27.3%, I^2=19.70%), p=0.013, favors surgical management

Recurrence: Medical management (10 studies, n=124): RR 38/124 (30.8%) (95% CI: 18.6% to 46.4%, I^2=49.28%); surgical management (17 studies, n=172): RR 9/172 (11.7%) (95% CI: 7.3% to 18.3%, I^2=0%), p=0.001, favors surgical management

Subgroup: Trials Only

Recurrence: Medical management (1 study, n=30): RR 3/30 (10.0%) (95% CI: 3.3% to 26.8%, I^2=NA); surgical management (1 study, n=4): RR 0/4 (10.0%) (95% CI: 0.6% to 67.4%, I^2=NA%), p=NA

Subgroup: Registries Only

Recurrence: Medical management (0 studies): NA; surgical management (0 studies): NA

Subgroup: Cohorts Only

Recurrence: Medical management (9 studies, n=94): RR 35/94 (38.3%) (95% CI: 26.6% to 51.5%, I^2=NA); surgical management (16 studies, n=168): RR 9/168 (11.8%) (95% CI: 7.3% to 18.6%, I^2=0%), p<0.001, favors surgical management

Transplantation required: Medical management (15 studies, n=196): RR 12/196 (11.4%) (95% CI: 6.5% to 19.5%, I^2=19.06%); surgical management (20 studies, n=232): RR 24/232 (11.2%) (95% CI: 4.9% to 23.4%, I^2=61.61%), p=0.787, no difference

Subgroup: Trials Only

Transplantation required: Medical management (1 study, n=30): RR 2/30 (6.7%) (95% CI: 1.7% to 23.1%, I^2=NA); surgical management (2 studies, n=29): RR 0/29 (4.3%) (95% CI: 0.6% to 25.3%, I^2=0%), p=0.714, no difference

Subgroup: Registries Only

Transplantation required: Medical management (0 studies): NA; surgical management (1 studies, n=31): RR 20/31 (64.5%) (95% CI: 46.6% to 79.1%, I^2= NA), p=NA

Subgroup: Cohorts Only

Transplantation required: Medical management (15 studies, n=166): RR 10/166 (12.2%) (95% CI: 6.6% to 21.6%, I^2=20.37%); surgical management (17 studies, n=172): RR 4/172 (10.0%) (95% CI: 5.6% to 17.2%, I^2=0%), p=0.507, no difference

Timing of adverse effects: Mean f/u 12.6 months (SD 10.4 months)

Factors that predict response: NR

5.9 Source Citation: Chue et al. 2017[8]

Study Design: Systematic Review of 16 single-arm studies

Device or Material: S-ICD Device (Ti)

Note: Although the study refers to S-ICD devices without study-level information on device type, however, only one type of S-ICD is manufactured in the United States (EMBLEM, Boston Scientific).

Contact Duration: Follow-up range: 61 to 2,117 days

Dose: NR

Frequency/Duration: NR

Response: Mortality (in hospital, total, per-person year)

Patient characteristics (gender, mean age): Percent male range: 59% to 92%, mean age range: 33 to 64 years

Number per Group: 1,670 patients

Observed adverse effects:

Mortality (total) rate: 3.36%

Mortality (in hospital) rate: 0.35%

Mortality (per-person year) rate: 2.1%

Timing of adverse effects: Follow-up range: 61 to 2,117 days

Factors that predict response: NR

ACFP: axial continuous-flow pump; CCFCP: Centrifugal continuous flow circulator pump; CI: confidence interval; f/u: follow-up; HF: heart failure; HVAD: HeartWare Ventricular Assist Device; LVAD: left ventricular assist device; MRI: magnetic resonance imaging; NA: not applicable; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; RR: risk ratio; S-ICD: subcutaneous implantable cardiac defibrillator; SD: standard deviation; Ti: titanium; VAD: ventricular assist device

Table 6: Cardiovascular - Other - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

6.1 Source Citation: Toale et al. 2019[10]

Study Design: Systematic review of 11 single-arm studies

Device or Material: AtriClip Device (Ti) for patients with atrial fibrillation

Contact Duration: Mean follow-up range (long-term outcomes): 7.2 to 44.8 months

Dose: NR

Frequency/Duration: NR

Response: revision for bleeding

Patient characteristics (gender, mean age): Gender: NR; weighted mean age in years (range): 68.2 (62.6 to 74)

Number per Group: 922 patients

Observed adverse effects:

Short-Term

Device-related serious AE, n/N: **0/922**

LAA Leak, n/N**: 0/922**

Revision for bleeding, n/N: 18/631 (2.8%)

Revision for bleeding due to clip, n/N: **0/922**

Timing of adverse effects: Outcomes divided into perioperative/short-term and long-term outcomes. The timing for most of these outcomes is unspecified, however, one short-term outcome (mortality) is specified to 30-days. Long-term outcomes are provided with a mean follow-up range of 7.2 to 44.8 months.

Factors that predict response: NR

Systemic Response/Toxicity

6.2 Source Citation: Toale et al. 2019[10]

Study Design: Systematic review of 11 single-arm studies

Device or Material: AtriClip Device (Ti)

Contact Duration: Mean follow-up range (long-term outcomes): 7.2 to 44.8 months

Dose: NR

Frequency/Duration: NR

Response: Ischemic stroke (postoperative, late), mortality (late), TIA (late)

Patient characteristics (gender, mean age): Gender: NR; weighted mean age in years (range): 68.2 (62.6 to 74)

Number per Group: 922 patients

Observed adverse effects:

Short-Term

Ischemic stroke (postoperative), n/N: 4/900 (0.4%)

Mortality (30-day), n/N: 0/902

TIA (postoperative), n/N: 0/900

Long-Term

Ischemic Stroke (Late), n/N: 5/893 (0.5%)

Mortality (Late), n/N: 42/667 (6.3%)

Mortality (Late and attributable to clip), n/N: 0/667

TIA (Late), n/N: 6/893 (0.6%)

Timing of adverse effects: Outcomes divided into perioperative/short-term and long-term outcomes. The timing for most of these outcomes is unspecified, however, one short-term outcome (mortality) is specified to 30-days. Long-term outcomes are provided with a mean follow-up range of 7.2 to 44.8 months.

Factors that predict response: NR

AE: adverse event; LAA: left atrial appendage; NR: not reported; Ti: titanium; TIA: transient ischemic attack

Table 7: Dental - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

7.1 Source Citation: da Silva et al. 2021[11]

Study Design: SR of 7 studies published from 2007 to 2017; 4 RCTs, 3 nonrandomized comparison studies

Device or Material: Plate fixation (Ti vs resorbable) for zygomatic fractures

Contact Duration: 6 months to 5 years

Dose: NR

Frequency/Duration: once

Response: dehiscence, paresthesia, removal

Patient characteristics (gender, mean age): mostly males, 14 to 91 years

Number per Group: 473 Ti, 322 resorbable; 160 with fractures of the zygomatic maxillary complex (77 treated with Ti, 83 treated with resorbable)

Observed adverse effects: Significantly lower need for plate removal (OR: 0.11, 95% CI: 0.02 to 0.81, p=0.03; 4 RCTs, n=72, 0/37 resorbable, 4/35 Ti) and dehiscence (OR 0.12, 95% CI 0.02 to 0.63) with resorbable plates vs Ti plates. No significant difference between Ti and resorbable plates in occurrence of paresthesia (OR 1.56, 95% CI: 0.42 to 5.80).

Timing of adverse effects: NR

Factors that predict response: NR

7.2 Source Citation: Gareb et al. 2021[12]

Study Design: SR of 33 studies; results based on subgroup of 14 RCTs published from 2003 to 2017

Device or Material: Plates or screw fixation (Ti vs biodegradeable) in patients with dentofacial deformities treated with orthognathic surgery.

Osteosynthesis systems used in 14 RCTs included:

Ti: KLS Martin (4 RCTs), Stryker (4 RCTs), NM (screws only), W. Lorenz, Mathys Compact, Wurzburg, Synthes, and M3 Visidisk.

Biodegradeable: Inion CPS (79/15/6 PLLA/ PDLLA/trimethylene carbonate) in 6 RCTs), Biosorb FX (self-reinforced 70/30 PLLA/PDLLA in 3 studies), Biofix, LactoSorb, Fixorb-MX, Isosorb, and Neofix.

Contact Duration: 1 week to 8 weeks; follow-up ranged from 8 weeks to 8 years

Dose: NR

Frequency/Duration: NR

Response: abscess, breakage, dehiscence, device removal (symptomatic), exposure (plate), malocclusion, malunion, mobility, pain, palpability, relapse, revision, swelling

Patient characteristics (gender, mean age): % female (range 0% to 82%), age range 16 to 57 years in Ti group

Number per Group: 2551 total; 1391 Ti, 1160 biodegradeable; sample size ranged from 10 to 124 in Ti group, 11 to 110 in biodegradeable group

Observed adverse effects in 14 RCTs: Ti and biodegradeable osteosyntheses resulted in lower (non-significant) rates of abscess (short term), breakage, dehiscence, exposure, malocclusion, mobility of bone segments, revisions, swelling, and symptomatic device removal with Ti plates/screws. Similar rates of abscess (1 year), malunion and pain were reported, however higher rates of palpability of plates/screws were reported with Ti. Results for relapse were mixed based on location of fixation (Ti significantly favored for mandibular angular, biodegradeable significantly favored for mandibular vertical, no significant difference for maxillary vertical).

Abscess, short term (1 RCT, n=203): lower with Ti (5% vs 12%)

Abscess, 1 year (1 RCT, n=203): 3% in each arm

Breakage, plate (4 RCTs, n=482): lower with Ti (0% vs. 4%)

Breakage, screws (4 RCTs, n=348): lower with Ti (3% vs range 0% to 12%)

Dehiscence (5 RCTs, n=421; events lower with Ti (24 vs 37/1000)): RR 1.53, 95% CI: 0.52 to 4.50; p=0.44

Exposure, plate (4 RCTs, n=NR): events lower with Ti (0% vs 0-9%)

Malocclusion (3 RCTs, n=217; events lower with Ti (113 vs 105/1000): RR 0.93, 95% CI: 0.39 to 2.26; p=0.88

Malunion (2 RCTs, n=240): 0 events

Mobility of bone segments (2 RCTs, n=115); events lower with Ti (104 vs 143/1000): RR 1.37, 95% CI: 0.47 to 3.99; p=0.57

Pain, intermediate (2 RCTs, n=260): SMD −0.01, 95% CI: −0.26 to 0.24; p=0.93

Pain, long term (3 RCTs, n=220): SMD −0.02, 95% CI: −0.29 to 0.25; p=0.89

Palpability of plates/screws (4 RCTs, n=400; events higher with Ti (232 vs 89/1000): RR 0.38, 95% CI: 0.11 to 12.8; p=0.12

Relapse, maxillary vertical (2 RCTs, n=95): RR 0.07, 95% CI: -0.35 to 0.50; p=0.74

Relapse, mandibular vertical relapse (2 RCTs, n=80): RR -0.63, 95% CI: -1.11 to -0.15; p=0.01 (favors biodegradeable)

Relapse, mandibular angular relapse (2 RCTs, n=80): RR 1.12, 0.08 to 2.16; p=0.03 (favors TiTi)

Revisions (not device removal), overall follow-up (4 RCTs, n=377): lower with Ti (20 vs 28/1000): RR 1.40, 95% CI: 0.37 to 5.34; p=0.62

Swelling, short term (2 RCTs, n=255) events lower with Ti (133 vs 201/1000): RR 1.51, 95% CI: 0.68 to 3.38; p=0.31

Swelling, long term (2 RTs, n=178) events lower with Ti (20 vs 49/1000): RR 2.42, 95% CI: 0.52 to 11.19; p=0.26

Symptomatic device removal [mostly due to discomfort] (7 RCTs, n=777); events lower with Ti (83 vs 107/1000): RR 1.29, 95% CI: 0.68 to 2.44; p=0.44

Timing of adverse effects:

- perioperative

- short-term follow-up (0-4 weeks): swelling, dehiscence, plate exposure
- intermediate follow-up (6-12 weeks): mobility of bone segments, malunion, pain
- long-term follow-up (>12 weeks): abscess (1 year), malocclusion, pain, symptomatic device removal, palpability
- overall follow-up: revision (not device removal)

Factors that predict response: NR

7.3 Source Citation: Pontell et al. 2021[13]

Study Design: SR of 37 studies (5 nonrandomized comparative trials, 19 single arm, 13 case reports)

Device or Material: Open reduction and internal fixation with plates/screws (Ti vs resorbable) for pediatric mandibular fractures

Ti plate manufacturers: 44.2% KLS, 32.8% Synthes, 16.4% SK Surgical, 6.6% Stryker

Resorbable plate manufacturers: 36.3% Inion CPS, 23.1% PolyMax, 15.7% LactoSorb, 13.5% SonicWeld Rx, 4.6% Rapidsorb, 4.1% BioSorb FX, 1.5% Grand Fix, 0.6% MacroSorb, 0.3% Delta, 0.3% OSTEOTRANS MX

Contact Duration: NR, 1.5 to 67 months follow-up

Dose: NR

Frequency/Duration: NR, follow-up from 0.3 months to 76.5 months

Response: dehiscence, granuloma, malocclusion, failed tooth eruption, fistula, fluid collection, paresthesia, persistent swelling, plate exposure, severe pain, and trismus (lock jaw)

Patient characteristics (gender, mean age): NR, range 0.5 to 17 years

Number per Group: overall 1144 (795 Ti hardware, 349 resorbable hardware)

Observed adverse effects: No significant difference in complication rate (113/795 (14%) Ti vs 36/349 (10%) resorbable; p=0.07). Complications included malocclusion (75%), plate exposure/wound dehiscence (5.5%), failed tooth eruption (3.4%, all 5 events with Ti), paresthesia (2.7%), trismus (2%), and fistula (1.3%). Fluid collection, persistent swelling, granuloma, and severe pain occurred in less than 1% of patients.

Analysis by dentition stage indicated similar complication rate for Ti (12.5% primary (6 months to 6 years), 12% mixed (>6 years to 12 years), 11.1% adult (>12 years), but higher complication rate for primary with resorbable systems (13.3% primary, 6.7% mixed, 6.1% adult). Analysis by fracture site (e.g., ramus, condyle/sub-condyle) indicated no significant difference in materials.

Timing of adverse effects: NR

Factors that predict response: NR

7.4 Source Citation: da Silva et al. 2021[14]

Study Design: SR of 2 RCTs (published in 2014 and 2015)

Device or Material: Ti vs ceramic (zirconia) implants for overdentures

Contact Duration: NR

Dose: NR

Frequency/Duration: NR, follow-up> 1 year (n=38)

Response: failure, MBL

Patient characteristics (gender, mean age): NR, 62 years

Number per Group: 38 patients (19 each arm) available at 1 year follow-up; 112 Ti, 146 ceramic (zirconia) implants were evaluated after 1 year. Ti implants were placed in the maxilla (56), mandible (40), and palatal (16). Ceramic implants were placed in the maxilla (69), mandible (55), and palatal (22).

Observed adverse effects: Significant difference favoring Ti was reported for failure rates (20/126 Ti vs 42/153 for ceramic; RR 0.58, 95% CI: 0.36 to 0.94; p=0.03) and mean MBL (0.15 mm Ti, 0.33 mm ceramic; mean difference -0.15, 95% CI: -0.23 to -0.07; p=0.0002).

Failures were all due to osseointegration except for 3 ceramic implants which failed due to fracture.

Timing of adverse effects: NR

Factors that predict response: NR

7.5 Source Citation: Cao et al. 2019[15]

Study Design: SR of 10 studies published from 1996 to 2017; 6 RCTs and 4 nonrandomized comparative studies

Device or Material: Implants (overdenture, single crown) with Ti vs zirconia abutments

Ti abutments included SPIEASY, NobelBiocare, TiDesign, MC-M, Profile Bi-Abutment, Ankylos Regular Abutment, and Procera.

Zirconia abutments included SPIART, Prozyr, ZirDesign, AC-C, Dentsply, ST Zir-Design, Ankylos Cercon Balance, and Nobel Biocare AB.

Contact Duration: mean follow-up 24 months (range 3 to 72 months)

Dose: NR

Frequency/Duration: NR

Response: MBL and PPD

Patient characteristics (gender, mean age): 64% female (range 50 to 85), 45 years (range 28 to 60)

Number per Group: 154 Ti, 187 zirconia

Observed adverse effects: Zirconia was favored for MBL (MD -0.09, 95% CI: -0.17 to 0.00; p=0.05) and PPD (MD -0.18, 95% CI: -0.32 to -0.05; p=0.008).

Timing of adverse effects: >3 months follow-up (an inclusion criteria)

Factors that predict response: NR

7.6 Source Citation: Sanz Martin et al. 2018[16]

Study Design: SR of 10 RCTs

Device or Material: Abutments (Ti vs zirconia, aluminum) connected to an implant; devices NR

Contact Duration: mean folllowup was 36.69 months (range 12 months to 86.4 months)

Dose: NR

Frequency/Duration: NR

Response: inflammation indicated by BOP, MBL, plaque accumulation

Patient characteristics (gender, mean age): NR

Number per Group: 195 total (4 studies not reporting); 94 Ti, 46 aluminum, 55 zirconia

Observed adverse effects:

BOP (mucosal inflammation):

- No significant difference between Ti vs aluminum (3 RCTs, WMD 4.83, -3.98 to 13.65; p=0.23
- Significantly more inflammation with Ti vs zirconia (3 RCTs, WMD -26.96, 95% CI: -45.0 to -8.9, p=0.003

MBL:

- No significant difference between Ti vs aluminum (3 RCTs, WMD 0.15, 95% CI: -0.02 to 0.33; p=0.09)
- No significant difference between Ti vs zirconia (4 RCTs, WMD -0.07, 95% CI: -0.34 to 0.18; p=0.56

PPD (mm):

- No significant difference between Ti and zirconia (3 RCTs, WMD -0.13, 95% CI: -0.61 to 0.34; p=0.57

Plaque index:

- No significant difference between Ti and aluminum (2 RCTs, WMD -1.30, 95% CI: -12.23 to 9.62; p=0.81
- No significant difference between Ti and zirconia (1 RCT, MD -20.0, 95% CI: -41.47 to 1.47; p=0.06

Timing of adverse effects: NR; follow-up up 12 to 86.4 months

Factors that predict response: NR

7.7 Source Citation: Sanz Sanchez 2018[17]

Study Design: SR of 29 studies (15 RCTs, 5 nonrandomized comparative studies, 9 case series)

Device or Material: abutments (Ti vs alumina, gold, zirconia); devices NR

Contact Duration: mean 30.05 months (range 6 to 67 months)

Dose: NR

Frequency/Duration: NR

Response: BOP, incidence of complications (abutment fracture, abutment rotation, crown adaption problems, crown fracture, loss of retention, screw loosening, veneer chipping, veneer fracture), MBL, plaque

Patient characteristics (gender, mean age): NR

Number per Group: 954 patients (1,266 implants); NR by material

Observed adverse effects:

MBL:

- No significant difference between Ti and alumina (2 studies, WMD 0.15, 95% CI: -0.04 to 0.36; p=0.13), Ti and gold (3 studies, WMD 0.04, 95% CI: -0.30 to 0.30; p=0.98), or Ti and zirconia (9 studies, WMD 0.018, 95% CI: -0.063 to 0.099; p=0.66).

BOP (%)

- No significant difference between Ti and alumina (3 studies, WMD 7.1, 95% CI: -0.18 to 14.42; p=0.06), but significantly more bleeding with Ti vs zirconia abutments (3 studies, WMD -26.9, 95% CI: -45.0 to -8.9; p=0.003)

Plaque (%)

- No significant difference between Ti and alumina (3 studies, WMD -4.0, 95% CI: -13.61 to 5.48; p=0.40) and Ti and zirconia (1 study, MD -20.0, 95% CI: -41.4 to 1.47; p=0.06).

Risk of technical complications

- "In the controlled studies, the incidence of complications was slightly higher in the test groups than in the Ti group (8.7% vs 5.9%; RR 1.27, 95% CI: 0.64 to 2.53; p=0.49)"

Timing of adverse effects: NR

Factors that predict response: NR

7.8 Source Citation: Troeltzsch 2016 [18]

Study Design: SR of 184 papers (including 23 RCTs, 44 nonrandomized comparative studies) published from 1999 to 2017

Device or Material: barrier materials used in lateral and vertical ridge augmentation (Ti, collagen based, polytetrafluoroethylene, polymer)

Contact Duration: 27.4 months (range 3 to 168 months)

Dose: NR

Frequency/Duration: NR

Response: complication rate

Patient characteristics (gender, mean age): NR, NR

Number per Group: 478 Ti mesh, 717 non-resorbable synthetic barriers (extended/dense polytetrafluoroethylene), 186 applications of polymer membranes (polyactic acid, polyglycolic acid (PLA/PGA), 2234 collagen-based membrane applications

Observed adverse effects: The complication rate was lowest for collagen-based barriers (10.4±16.7%) and highest for polymer membrane (37.4±26.5%) (p=0.621). Complication rates for Ti mesh (data not specified) were higher than collagen-based barriers (p=0.104).

Timing of adverse effects: NR

Factors that predict response: NR

7.9 Source Citation: Esposito 2014[19]

Study Design: SR of 27 RCTs (Cochrane review)

Device or Material: Ti implants to replace missing teeth

Ti implants included:

- Ankylos Plus® grit-blasted and high temperature etched surface, Tigrade 2 cylindrical screws with internal conical connection (Dentsply-Friadent, Mannheim, Germany)
- Astra® turned Ti grade 3 cylindrical screws with internal connection (Astra Tech AB, Mölndal, Sweden)
- Astra® TiO2 -blast Ti grade 3 cylindrical screws with internal connection (Astra Tech AB)
- Astra® TiO2 -blast Ti grade 3 tapered screws with internal connection (Astra Tech AB)
- Brånemark® Standard turned Ti grade 1 cylindrical screws with external hexagon (Nobel Biocare AB, Göteborg, Sweden)
- Brånemark® Mark II turned Ti grade 1 cylindrical screws with external hexagon (NobelBiocare AB)
- Brånemark® conical transmucosal turned Ti grade 1 cylindrical screws with external hexagon (Nobel Biocare AB)
- Brånemark® Mark III turned Ti grade 4 cylindrical screws with external hexagon (Nobel Biocare AB)
- Brånemark®Mark III TiUnite oxidised Ti grade 4 cylindrical screws with external hexagon (Nobel Biocare AB)
- Brånemark® Mark IV turned Ti grade 4 screws with external hexagon (Nobel Biocare AB)
- Brånemark®Mark IV TiUnite oxidized Ti grade 4 cylindrical screws with external hexagon (Nobel Biocare AB)
- NobelActive® TiUnite oxidised Ti grade 4 tapered screws with internal connection (Nobel Biocare AB)
- NobelActive® TiUnite oxidised Ti grade 4 tapered screws with external hexagon (Nobel Biocare AB)
- NobelReplace® Tapered Groovy TiUnite oxidised Ti grade 4 tapered screws with internal connection (Nobel Biocare AB)

- Replace® Select Tapered TiUnite oxidised Ti grade 4 tapered screws with internal connection (NobelBiocare AB)
- Nobel Speedy Groovy TiUnite oxidised Ti grade 4 tapered screws with external connection (Nobel Biocare AB)
- Implantium® sand-blasted, large grit, acid-etched (SLA) Ti grade 4 cylindrical screws with microthreads 0.5 mm below the top of the implant and internal connection (Dentium, Seoul, Korea)
- Implantium® SLA Ti grade 4 cylindrical screws with microthreads to top of the implant and internal connection (Dentium)
- IMZ® TPS (Ti plasma-sprayed) Ti grade 2 cylindrical screws with internal interlocking connection (Friedrichsfeld AG, Mannheim, Germany)
- ITI® TPS Ti grade 4 cylindrical screws with internal connection (Institut Straumann AG, Waldenburg, Switzerland)
- ITI® TPS Ti grade 4 cylindrical hollow screws with internal connection (Institut Straumann AG)
- ITI® SLA Ti grade 4 cylindrical solid screws with internal connection with a 2.8-mm turned neck (Institut Straumann AG)
- ITI® SLA solid Ti grade 4 tapered screws with internal connection (Institut Straumann AG)
- ITI® SLActive solid Ti grade 4 cylindrical screws with internal connection (Institut Straumann AG)
- ITI® SLActive solid Ti grade 4 tapered screws with internal connection (Institut Straumann AG)
- ITI® Roxolid™ SLActive solid TTi grade 4 tapered screws with internal connection (Institut Straumann AG)
- MegaGen EZ Plus Ti grade 4 tapered screw with internal connection (MegaGen Implant, Gyeongbuk, South Korea)
- MegaGen EZ Plus Xpeed Ti grade 4 tapered screw with internal connection (MegaGen Implant)
- Neoss sand-blasted, acid-etched Ti grade 4 cylindrical screws with internal connection (Neoss Ltd, Harrogate, UK)
- Seven TPS Ti grade 4 screws with external hexagon (Sweden & Martina, Padua, Italy)
- Southern® sand-blasted Ti grade 4 cylindrical screws with external hexagon (Southern Implants)
- Southern® sand-blasted Ti grade 4 8-mm wide tapered screws with external hexagon (Southern Implants)
- SPI® Element implant sand-blasted acid-etched Ti grade 4 cylindrical screw with internal connection (Thommen Medical, Waldeburg, Switzerland)
- SPI® Element implant sand-blasted acid-etched Ti grade 4 cylindrical screw with internal connection (Thommen Medical) treated with a monolayer of permanently bound multi-phosphonic acid molecules (Nano Bridging Molecules, Gland, Switzerland)
- Steri-Oss® HL series, 3.8-mm diameter acid-etched Ti grade 5 cylindrical screws with external hexagon (Steri-Oss, Yorba Linda, CA, USA)
- SwissPlus® sand-blasted acid-etched Ti grade 4 cylindrical screw with internal connection (Zimmer Dental Inc. Carlsbad, USA)
- WINSIX® implant sand-blasted acid-etched Ti grade 4 cylindrical screw with internal connection (Winsix Ltd, London, UK)
- WINSIX® implant sand-blasted acid-etched Ti grade 4 tapered screw with internal connection (Winsix Ltd)

Contact Duration: 1 to 10 years; 12 months (9 studies), 14 months (1 study), 18 months (2 studies), 24 months (2 studies), 36 months (5 studies), 60 months (4 studies), 10 years (4 studies)

Dose: NR

Frequency/Duration: NR

Response: failure

Patient characteristics (gender, mean age): NR, range 20 to 80 years (5 studies reporting)

Number per Group: 1512 patients (3230 implants); 38 implant types with different surface characteristics, shapes, degree of Ti purity and Ti alloys

Observed adverse effects: No significant differences were reported when comparing different implant systems (4 RCTs), turned versus roughened implants (7 RCTs), different implant surfaces (5 RCTs); implants with different shapes but similar surface preparation and material (7 RCTs), implants with different materials but similar surface preparation and shape (1 RCT); or implants with different surface preparation, shape, material or a combination (13 RCTs).

Different implant systems: Branemark turned vs ITI TPS hollow Ti screws (2 RCTs)

Implant failure: 1 year (2 RCTs, n=99): RR 1.64, 95% CI: 0.22 to 12.01; p=0.63

Implant failure: 3 years (2 RCTs, n=96): RR 2.38, 95% CI: 0.37 to 15.38; p=0.36

Implant failure: 5 years (1 RCT, n=54): RR 3.0, 95% CI: 0.13 to 70.53; p=0.5

Implant failure: 10 years (1 RCT, n=54): RR 3.0, 95% CI: 0.13 to 70.53; p=0.5

Different implant systems: Southern blasted/etched Ti screws vs Steri-Oss (2 RCTs)

Implant failure: 1 year (2 RCTs, n=48): RR 0.14, 95% CI: 0.02 to 1.08; p=0.06

Implant failure: 3 years (2 RCTs, n=47): RR 0.14, 95% CI: 0.02 to 1.06; p=0.06

Implant failure: 5 years (2 RCTs, n=46): RR 0.14, 95% CI: 0.02 to 1.08; p=0.06

Implant failure: 10 years (2 RCTs, n=39): RR 0.14, 95% CI: 0.02 to 1.10; p=0.06

Turned vs roughened implants (7 RCTs)

Early implant failure (7 RCTs, n=404): RR 2.79, 95% CI: 0.87 to 8.90; p=0.08

Trials comparing different implant surfaces (5 RCTs)

Brånemark Mark III implants: turned versus oxidised surface (TiUnite) (Fröberg 2006, n=15): no implant failure at 1 year

Brånemark Mark IV implants: turned versus oxidised surface (TiUnite) (Schincaglia 2007, n=10): implant failure: RR 0.33 (p=0.49; 95% CI did not align with RR).

ITI regular neck: SLA standard versus SLActive surface (Heberer 2011, n=20): implant failure at 1 year: RR 5.00, 95% CI: 0.26 to 98.00; p=0.29

MegaGen EZ Plus implants with blasted surface: standard versus calcium-incorporated (Xpeed) surface (Esposito 2012, n=60): no implant failure at 1 year

SPI Element implants with sand-blasted acid-etched: standard versus SurfLink-modified surface (Esposito 2013a, n=22): no implant failure at 1 year

Trials comparing implants with different shapes, but having similar surface preparation and material (7 RCTs)

Astra cylindrical versus Astra conical implants (Lee 2007, n=17): no implant failure

Brånemark Mark II type versus Brånemark conical transmucosal implants (Gatti 2002, n=10): no implant failure

Implantium microthreads at the top versus Implantium microthreads 0.5 mm below the top (Song 2009): no implant failure

ITI cylindrical versus ITI tapered implants (Lang 2007, n=208): no implant failure

NobelActive external connection versus NobelActive internal connection implants (Kielbassa 2009, n=127):

implant failure at 1 year: RR 1.06, 95% CI: 0.25 to 4.51; p=0.94

implant failure at 3 years: RR 0.66, 95% CI: 0.17 to 2.58; p=0.55

NobelActive external connection versus NobelReplace implants (Kielbassa 2009, n=127):

implant failure at 1 year: RR 0.67, 95% CI: 0.17 to 2.67; p=0.57

implant failure at 3 years: RR 1.00, 95% CI: 0.21 to 4.67; p=1.00

NobelActive internal connection versus NobelReplace implants (Kielbassa 2009, n=127)

implant failure at 1 year: RR 0.90, 95% CI: 0.25 to 3.15; p=0.86

implant failure at 3 years: RR 1.00, 95% CI: 0.21 to 4.67; p=1.00

WINSIX cylindrical versus WINSIX tapered implants (Prosper 2009, n=66): implant failure at 1 year: RR 2.00, 95% CI: 0.38 to 10.58; p=0.41

ITA SLActive implants: Ti grade 4 versus Ti-13zirconium (Roxolid) (Al-Nawas 2012, n=89): implant failure at 1 year: RR 2.00, 95% CI: 0.18 to 21.66; p=0.57

Trials comparing implants with different surface preparation, shape, material or a combination (13 RCTs)

Ankylos Plus Dentsply versus Seven Sweden & Martina implants (Crespi 2009, n=45): no implant failures

Astra TiO2 -blast cylindrical versus turned Brånemark Mark II implants (Astrand 1999, n=26):

implant failure at 1 year: RR 0.25, 95% CI: 0.03 to 2.12; p=0.20

implant failure at 3 years: RR 0.40, 95% CI: 0.08 to 1.92; p=0.25

implant failure at 5 years: RR 0.43, 95% CI: 0.09 to 2.04; p=0.28

Astra TiO2 -blast versus ITI SLA Ti implants (Akoglu 2011, n=36): no implant failures

Astra TiO2 -blast versus SwissPlus (Zimmer) cylindrical implants (Akoglu 2011, n=36): no implant failures

Brånemark versus IMZ implants (Batenburg 1998, n=83):

implant failure at 1 and 3 years: RR 1.00, 95% CI: 0.07 to 15.26; p=1.00

implant failure at 5 years: RR 1.11, 95% CI: 0.07 to 16.91; p=0.94

implant failure at 10 years: RR 0.27, 95% CI: 0.03 to 2.25; p=0.23

Brånemark MKII versus ITI TPS hollow screw implants- (Batenburg 1998, n=83; Moberg 2001, n=36): implant failure at 3 years: RR 2.38, 95% CI: 0.13 to 70.53; p=0.5

Brånemark MKII versus ITI TPS hollow screw implants (Batenburg 1998, n=83): implant failure at 5 years: RR 3.00, 95% CI: 0.37 to 15.38; p=0.36

Brånemark MKII versus ITI TPS hollow screw implants (Batenburg 1998, n=83): implant failure at 10 years: RR 3.00, 95% CI: 0.37 to 15.38; p=0.36

Brånemark MKII versus ITI TPS solid screw implants (Astrand 2002, n=26): implant failure at 3 years: RR 0.05, 95% CI: 0.05 to 5.20; p=0.56

Brånemark MKIV TiUnite versus Southern regular implants (Payne 2004, n=38): implant failure at 1 year: RR 0.57, 95% CI: 0.20 to 1.63; p=0.30

IMZ Ti TPS versus ITI TPS hollow implants (Batenburg 1998, n=83):

implant failure at 1 and 3 years: RR 2.90, 95% CI: 0.12 to 68.50; p=0.51

implant failure at 5 years: RR 2.71, 95% CI: 0.12 to 63.84; p=0.54

implant failure at 10 years: RR 8.40, 95% CI: 0.47 to 149.04; p=0.15

IMZ Ti TPS versus ITI TPS solid implants (Heydenrijk 2002, n=37)

implant failure at 1 and 3 years: RR 3.00, 95% CI: 0.13 to 69.52; p=0.49

implant failure at 5 years: RR 2.85, 95% CI: 0.12 to 65.74; p=0.51

ITI SLA versus Southern implants (Payne 2003, n=38): no implant failures at 10 years

ITI SLA Ti implants versus SwissPlus (Zimmer) cylindrical implants (Akoglu 2011, n=36): no implant failure

NobelReplace Select Tapered versus NobelReplace Groovy implants (den Hartog 2011, n=93): implant failure at 1 year: RR 3.00, 95% CI: 0.13 to 70.92; p=0.50

Southern regular versus turned Neoss implants (Alsabeeha 2011, n=35): implant failure at 1 year: RR 3.25, 95% CI: 0.15 to 72.36; p=0.46

Southern wide versus turned Neoss implants (Alsabeeha 2011, n=35): no implant failures

Southern regular versus Southern wide (Alsabeeha 2011, n=35): implant failure at 1 year: RR 3.25, 95% CI: 0.15 to 72.36; p=0.46

Timing of adverse effects: early implant failure (before prosthetic loading), failure at 1 year, 3 years, 5 years, and 10 years

Factors that predict response: NR

7.10 Source Citation: Yang 2013[20]

Study Design: SR of 20 studies (7 RCTs, 13 nonrandomized comparative) published from 2002 to 2012

Device or Material: Absorbable vs non-absorbable (Ti) plates/screws for maxillofacial fixation after bilateral sagittal split ramus osteotomy (BSSRO; 6 studies), Le Fort I osteotomy (2 studies) or maxillofacial fracture fixation (5 studies); 3 studies described multiple operations (SSRO plus Le Fort I), 4 studies weren't classified due to different kinds of maxillofacial surgeries

Contact Duration: up to 8 years for BSSRO, up to 5 years for Le Fort I, not able to ascertain f/u for fracture fixation

Dose: NR

Frequency/Duration: once

Response: dehiscence, exposure, fistulation, foreign body reaction, malocclusion, material-related complications, mobility, palpability, paresthesia, relapse, temporomandibular joint dysfunction

Patient characteristics (gender, mean age): NR, range 11 to 71 years

Number per Group: 1673 (775 Ti, 898 absorbable including poly(L-lactide-co-D/L-lactide (P (L/DL) LA), poly(L-lactic-co-glycolic acid), PGA, PLLA, LactoSorb, Delta and INION)

Observed adverse effects: In all maxillofacial surgeries, absorbable fixation was associated with significantly more overall complications (n=5604: RR 1.20, 95% CI: 1.02 to 1.42; p=0.03), foreign body reaction (6 studies (n=436): RR 1.97; 95% CI: 1.05 to 3.68; p=0.03), and mobility (3 studies (n=108): RR 5.64; 95% CI: 1.10 to 28.85; p=0.04) vs non-absorbable Ti fixation.

No significant difference was reported between Ti and absorbable groups with temporomandibular joint dysfunction (4 studies (n=384): RR 1.00; 95% CI: 0.47 to 2.12; p=1.00), paresthesia (3 studies (n=135): RR 1.08; 95% CI: 0.61 to 1.93; p=0.78), fistulation (4 studies (n=413): RR 2.09; 95% CI: 0.87 to 5.01; p=0.10), palpability (5 studies (n=645): RR 0.90; 95% CI: 0.70 to 1.15; p=0.38), dehiscence (6 studies (n=518): RR 1.12; 95% CI: 0.65 to 1.93; p=0.69), malocclusion (4 studies (n=593): RR 1.11; 95% CI: 0.63 to 1.97; p=0.72), material-related complications (5 studies (n=545): RR 1.70; 95% CI: 0.63 to 4.56; p=0.30), exposure (5 studies (n=266): RR 1.83; 95% CI: 0.71 to 4.75; p=0.21) and relapse (5 studies (n=482): RR 1.41; 95% CI: 0.62 to 3.17; p=0.41).

Analysis by surgery type indicated no significant difference between groups except for fracture fixation which indicated a significantly lower rate of complications with absorbable vs Ti fixation (5 studies (n=1032): RR 0.71, 95% CI: 0.52 to 0.97; p=0.03). For fracture fixation, subgroup analysis by complications indicated significantly more palpability with Ti (RR = 0.38; 95% CI: 0.22–0.68; P = 0.001).

Timing of adverse effects: NR

Factors that predict response: NR

BOP: bleeding on probing; CI: confidence interval; MBL: marginal bone loss; MD: mean difference; NR: not reported; OR: odds ratio; PDLLA: poly-DL-lactic acid; PGA: polyglycolic acid; PLLA: poly-L-lactic acid; PPD: pocket probing depth; RCT: randomized controlled trial; RR: relative risk or risk ratio; SR: systematic review; Ti: titanium; weighted mean difference

Table 8: Gastrointestinal and renal - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

8.1 Source Citation: Schizas et al. 2020[21]

Study Design: SR to investigate the LINX Reflux Management System's safety and efficacy in resolving gastroesophageal reflux disease (GERD) symptoms. Overall, this review included 35 studies (0 RCTs) with 2,511 patients. Twenty of those studies (1,539 patients) investigated the LINX alone, whereas the others compared the system to laparoscopic fundoplication (LF).

Device or Material: LINX Reflux Management System (Ti, Torax Medical) alone or versus LF.

Contact Duration: Follow-up ranged from 1 month to 80 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Belch, bloat, dysphagia, esophageal wall erosion, heartburn, regurgitation, removal.

Patient characteristics (gender, mean age): NR. Mean age in the LINX groups, 39.3 to 54 years; mean age in the LF groups, 43.8 to 54 years.

Number per Group: LINX groups: 1,539 patients with 1,452 making it to follow-up; LF groups: 525 with 485 making it to follow-up.

Observed adverse effects:
Overall, the most common complication was mild dysphagia, occurring in 6% to 83% of patients. In 2% of patients, device removal was required, due to dysphagia or recurrent heartburn/regurgitation or esophageal wall erosion.

In two meta-analyses comparing LINX to LF, severe dysphagia treated with endoscopic dilation occurred in 9.3% of LINX patients and 6.6% of LF patients, a difference though not statistically significant. In addition, results demonstrated a strong association between LINX and less bloating symptoms ($P < 0.001$), a greater ability to vomit ($P < 0.001$) and belch ($P < 0.001$). There was no statistically significant difference between proton pump inhibitor suspension and reoperation rates.

One study analyzed data from 1000 patients undergoing implantation at 82 institutions worldwide. 3.4% of patients were re-operated nonemergently and no device migrations or malfunctions were noted, with erosion occurring in one patient (0.1%). Another study collecting data from FDA's Manufacturer and User Facility Device Experience (MAUDE) database from 2012 to 2016 included a total number of 3,283 patients with an overall incidence of device removal of 2.7% within 2 years of implantation. A single-center cohort estimated device safety examining reoperations for device removal out of 164 LINX patients. In total, 11 patients (6.7%) were explanted between 12 and 24 months after implantation with the main cause of reoperation in 46% of those patients being a recurrence of heartburn or regurgitation.

A study collecting data in 9,453 implantations worldwide until 2017 found that the risk of erosion increased from 0.05% at 1 year to 0.3% at 4 years. 29 patients with erosion had successful device removal with a return to baseline in 24 patients within 1.9 month follow-up.

Timing of adverse effects: Device removal due to dysphagia, erosion, or recurrent heartburn/regurgitation from 12 to 24 months.

Factors that predict response: NR.

8.2 Source Citation: Trang et al. 2018[22]

Study Design: SR and meta-analysis to examine the rates of nausea and vomiting along with other common side effects from different subtypes of intragastric balloons (IGBs) placed in obese adults. Three of 10 total studies in 938 patients (0 RCTs) involved the Obalon device in 363 of those patients.

Device or Material: Obalon (titanium, Obalon Therapeutics Inc), Ellipse (non-Ti, Allurion Technologies), Orbera (non-Ti, Apollo Endosurgery), ReShape Duo (non-Ti, ReShape Medical).

Contact Duration: Follow-up ranged from 3 to 12 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Abdominal pain, nausea, reflux, gastroesophageal reflux disease (GERD), vomiting.

Patient characteristics (gender, mean age): 71%±27.9% female, 40.5±1.4 years.

Number per Group: Obalon groups, n=363; Elipse, Orbera, and ReShape groups, n=575.

Observed adverse effects: Seven studies with fluid-filled IGB placement (Elipse, Orbera, and ReShape) reported nausea in 394 out of 575 patients at a rate of 72.99% (95% CI 69.54%-76.45%) and vomiting in 434 patients with a rate of 76.95% (95% CI 73.86%-80.05%). Three studies with Obalon IGB placement reported nausea in 200 out of 363 patients with a rate of 55.10% (95% CI 50.00%-60.00%) and vomiting in 62 out of 363 patients with rate of 16.20% (95% CI 12.43%-19.96%).

The three Obalon studies reported abdominal pain in 50% to 76.47% of patients and GERD in 16.96% to 23.53% of patients. Overall, 521 patients reported experiencing abdominal pain at a rate of 58.55% (95% CI 56.41%-60.68%) and 183 patients experiencing reflux/GERD at a rate of 20.57% (95% CI 18.47%-22.67%).

Timing of adverse effects: Follow-up ranged from 3 to 12 months.

Factors that predict response: NR.

Table 9: Hematology - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

9.1 Source Citation: Burbridge et al. 2017[23]

Study Design: SR and meta-analysis of publications related to forearm implantation of venous access devices by interventional radiology department personnel. Eleven studies met review criteria (0 RCTs), 10 of which were retrospective. Five of these studies involved a titanium port, accounting for 2,396 ports.

Device or Material: Vital Port Mini Titanium (Cook Medical).

Contact Duration: Catheter indwell ranged from 0 to 2,996 days (8.2 years).

Dose: NR.

Frequency/Duration: Single administration.

Response: Damage, deep vein thrombosis (DVT), removal, thrombosis.

Patient characteristics (gender, mean age): NR. Patient age ranged from 16 to 91 years.

Number per Group: Vital Port Mini Titanium port, n=2,396.

Observed adverse effects: Three studies reporting on the Vital Port Mini Titanium reported venous thrombosis ranging from 0.75% to 3.2% of patients; rates for non-Ti ports were 2.5%.

Two studies reported removal due to port/catheter damage ranging from 0.75% to 2.5% of Ti patients; rates for non-Ti ports were 2.4%.

Two studies reported removal due to DVT ranging from 0.25% to 0.59% of patients; rates for non-Ti ports were 2.5%.

Two studies reported removal due to port blockage in 0.25% to 0.53% of patients; rates for non-TI ports were 1.9% to 3.5%.

Timing of adverse effects: Catheter indwell ranged from 0 to 2,996 days (8.2 years).

Factors that predict response: NR.

Systemic Response/Toxicity

9.2 Source Citation: Burbridge et al. 2017[23]

Study Design: SR and meta-analysis of publications related to forearm implantation of implanted venous access devices by interventional radiology department personnel. Eleven studies met review criteria (0 RCTs), 10 of which were retrospective. Five of these studies involved a titanium port, accounting for 2,396 ports.

Device or Material: Vital Port Mini Titanium (Cook Medical).

Contact Duration: Catheter indwell ranged from 0 to 2,996 days (8.2 years).

Dose: NR.

Frequency/Duration: Single administration.

Response: Sepsis.

Patient characteristics (gender, mean age): Patient sex NR. Patient age ranged from 16 to 91 years.

Number per Group: Vital Port Mini Titanium port, n=2,396.

Observed adverse effects: Three studies reporting on the Vital Port Mini Titanium reported systemic sepsis ranging from 0.75% to 1.9% of patients; rates for non-Ti ports ranged from 2.8% to 4.0%.

Timing of adverse effects: Catheter indwell ranged from 0 to 2,996 days (8.2 years).

Factors that predict response: NR.

Table 10: Neurology - Health Effect (In Vivo) Human Study

Local Response/Toxicity

10.1 Source Citation: Johansson et al. 2021[24]

Study Design: Systematic review of 10 single-arm studies

Device or Material: BAHS and BAAE implants (Cochlear) (both commercially pure Ti)

Contact Duration: Between 2 weeks and 8 years

Dose: Diameter: 3.75 mm, length: 3 or 4 mm

Frequency/Duration: Single excision

Note: The purpose of the study was for histological analysis, and the reported AEs are the common reasons the patients decided to undergo implant excision.

Response: Adverse skin reactions, mechanical problems, pain, spontaneous loss, trauma, tumor

Patient characteristics (gender, mean age): neither reported

Number per Group: 54 implants from 47 patients; 35 were BAHS implants from 35 patients while 19 BAEE implants were from 12 patients

Observed adverse effects:

Adverse skin reactions, n (%): 9 (23%)

Mechanical problems, n (%): 1 (3%)

Pain, n (%): 11 (28%)

Spontaneous loss, n (%): 2 (5%)

Trauma, n (%): 2 (5%)

Tumor, n (%): 2 (5%)

Timing of adverse effects: Between 2 weeks and 8 years

Factors that predict response: NR

10.2 Source Citation: Kruyt et al. 2020[25]

Study Design: Systematic review of 20 single-arm studies

Device or Material: Bone-Anchored Hearing implant (BAHI) (Ti)

Contact Duration: Mean follow-up range: 0 to 168 months

Dose: Implant type: small diameter: 599 (72.3%), wide diameter: 219 (26.4%)

Frequency/Duration: One-stage surgery: 274 (29.9%), two-stage surgery: 643 (70.1%)

Response: Implant loss, OIF, revision surgery, soft tissue reactions

Patient characteristics (gender, mean age): Gender: 406 male, 371 female, 71 NA; Mean age at implantation in years (range): 8.6 (2 to 21)

Number per Group: 831 patients receiving 952 implants

Observed adverse effects:

Implant loss, n (%): 127 (13.3%)

Subgroup: One-Stage vs. Two-Stage Surgery

One-stage surgery, n/N (%): 10/202 (5%), two-stage surgery: 49/289 (17%)

Subgroup: Soft-Tissue Reduction Technique vs. Soft-Tissue Preservation Technique

Soft-tissue reduction, n/N (%): 3/41 (7%), soft-tissue preservation: 6/87 (7%)

OIF, n (%): 61 (6.4%)

Subgroup: One-Stage vs. Two-Stage Surgery

One-stage surgery, n/N (%): 2/202 (1%), two-stage surgery: 12/178 (7%)

Subgroup: Soft-Tissue Reduction Technique vs. Soft-Tissue Preservation Technique

Soft-tissue reduction, n/N (%): 2/41 (5%), soft-tissue preservation: 5/87 (6%)

Revision surgery, n (%): 142 (16.8%)

Subgroup: One-Stage vs. Two-Stage Surgery

One-stage surgery, n/N (%): 5/157 (3%), two-stage surgery: 52/156 (33%)

Subgroup: Soft-Tissue Reduction Technique vs. Soft-Tissue Preservation Technique

Soft-tissue reduction, n/N (%): 1/41 (2%), soft-tissue preservation: 21/87 (24%)

Soft tissue reactions, n (%): 251 (26.4%)

Subgroup: One-Stage vs. Two-Stage Surgery

One-stage surgery, n/N (%): 23/153 (15%), two-stage surgery: 57/137 (42%)

Subgroup: Soft-Tissue Reduction Technique vs. Soft-Tissue Preservation Technique

Soft-tissue reduction, n/N (%): 9/28 (32%), soft-tissue preservation: 30/63 (48%)

Timing of adverse effects: Mean follow-up range: 0 to 168 months

Factors that predict response: One-stage surgery and soft-tissue preservation do not seem to result in higher implant loss rates or increased adverse skin reactions based upon limited amounts of literature.

10.3 Source Citation: Lagerkvist et al. 2020[26]

Study Design: Systematic review of 43 single-arm studies

Device or Material: Ponto Plus, Ponto Plus Power, Ponto Pro, Ponto Pro Power, Ponto 3, Ponto 3 SuperPower, Wide Ponto, Ponto BHX, Ponto 3.75 (All Ti)

Contact Duration: The accumulated follow-up time for the included publications (reporting surgical and postsurgical events and complications) was 16.49 months with a range of 0.5 to 60 months.

Dose: NR

Frequency/Duration: NR

Response: Abscess, abutment change, abutment removal, cerebrospinal fluid leak, dura exposure, hematoma, Holgers 4 skin reaction, scar hypertrophy, skin revision surgery

Note: Study also reports 'pain and numbness', however, no effect size estimate provided due to various measures being used for this outcome.

Patient characteristics (gender, mean age): Gender: NR, Age: NR

Number per Group: 1,352 patients

Observed adverse effects:

Abscess (1 study, n=130 implants), n (%): 2 observations (2%)

Abutment change (12 studies, n=666 implants), n (%): 27 observations (4%)

Abutment removal (6 studies, n=264 implants), n (%): 5 observations (2%)

Cerebrospinal fluid leak (5 studies, n=294 implants), n (%): 1 observation (0.3%)

Dura exposure (5 studies, n=294 implants), n (%): 19 observations (6%)

Hematoma (1 study, n=63 implants), n (%): 2 observations (3%)

Holgers 4 skin reaction (19 studies, n=769 implants), n (%): 3 observations (0.4%)

Scar hypertrophy (1 study, n=130 implants), n (%): 1 observation (1%)

Skin revision surgery (15 studies, n=773 implants), n (%): 26 observations (3%)

Timing of adverse effects: Mean 16.49 months (range 0.5 to 60 months)

Factors that predict response: NR

15.4 Source Citation: Schwab et al. 2020[27]

Study Design: Systematic review of 234 single-arm studies

Device or Material: Bone-conducting hearing implants (BCHIs), including BAHA Attract (Cochlear), BAHA Connect (Cochlear), Bonebridge (MED-EL), Ponto (Oticon Medical), and Sophono (Medtronic) (All Ti)

Active middle-ear implants (aMEIs), including Carina (Cochlear, formerly Otologics), CODACS (Cochlear), Esteem (Envoy Medical), MET (Cochlear, formerly Otologics), Soundtec (Ototronix, formerly Soundtec), and Soundbridge (MED-EL) (All Ti)

Contact Duration: Between <3 and >48 months follow-up

Dose: NR

Frequency/Duration: NR

Response: AEs (major, minor, and overall), aural fullness, dizziness/vertigo, explantation, failure to osseointegrate, Holgers Grade 1 skin reaction, Holgers Grade 2 skin reaction, Holgers Grade 3 skin reaction, implant/device failure, pain unspecified, percepting magnet movement, reimplantation, repositioning of FMT, revision surgery, skin complications, skin revision surgery due to skin overgrowth or cellulitis, soft tissue/skin overgrowth, taste disturbances due to chorda tympani damage, unspecified AE

Patient characteristics (gender, mean age): neither reported

Number per Group: Patients: NR

Note: For major and minor AEs, review reports number of ears.

Observed adverse effects: All AEs are reported as the ratio of events to ears (REE)

All Devices

Overall AEs: BAHA Attract (7 studies, 114 ears): mean REE 0.67 (SD 0.32), BAHA Connect (117 studies, 6965 ears): mean REE 0.66 (SD 0.58), Bonebridge (13 studies, 175 ears): mean REE 0.15 (SD 0.16), Ponto (7 studies, 234 ears): mean REE 0.55 (SD 0.35), Sophono (12 studies, 143 ears): mean REE 0.57 (SD 0.43), Carina (11 studies, 334 ears): mean REE 0.48 (SD 0.36), CODACS (3 studies, 43 ears): mean REE 0.61 (SD 0.36), Esteem (6 studies, 131 ears): mean REE 1.62 (SD 1.04), MET (4 studies, 71 ears): mean REE 0.98 (SD 1.03), Soundbridge (59 studies, 1546 ears): mean REE 0.28 (SD 0.30), Soundtec (3 studies, 194 ears): mean REE 0.40 (SD 0.13)

Minor AEs: BAHA Attract (7 studies, 114 ears): mean REE 0.66 (SD 0.34), BAHA Connect (117 studies, 6965 ears): mean REE 0.35 (SD 0.39), Bonebridge (13 studies, 175 ears): mean REE 0.09 (SD 0.11), Ponto (7 studies, 234 ears): mean REE 0.41 (SD 0.26), Sophono (12 studies, 143 ears): mean REE 0.52 (SD 0.39), Carina (11 studies, 334 ears): mean REE 0.15 (SD 0.22), CODACS (3 studies, 43 ears): mean REE 0.26 (SD 0.22), Esteem (6 studies, 131 ears): mean REE 0.87 (SD 0.83), MET (4 studies, 71 ears): mean REE 0.33 (SD 0.59), Soundbridge (59 studies, 1546 ears): mean REE 0.15 (SD 0.21), Soundtec (3 studies, 194 ears): mean REE 0.40 (SD 0.13)

Major AEs: BAHA Attract (7 studies, 114 ears): mean REE 0.01 (SD 0.03), BAHA Connect (117 studies, 6965 ears): mean REE 0.31 (SD 0.38), Bonebridge (13 studies, 175 ears): mean REE 0.06 (SD 0.10), Ponto (7 studies, 234 ears): mean REE 0.14 (SD 0.14), Sophono (12 studies, 143 ears): mean REE 0.06 (SD 0.10), Carina (11 studies, 334 ears): mean REE 0.33 (SD 0.26), CODACS (3 studies, 43 ears): mean REE 0.36 (SD 0.16), Esteem (6 studies, 131 ears): mean REE 0.75 (SD 0.83), MET (4 studies, 71 ears): mean REE 0.65 (SD 0.95), Soundbridge (59 studies, 1546 ears): mean REE 0.13 (SD 0.19), Soundtec (3 studies, 194 ears): mean REE 0.00 (SD 0.00)

BCHIs (Note: Review only lists 10 most frequent AEs, some devices NR)

Failure to osseointegrate: BAHA Connect: REE 0.02, All BCHI devices: 0.01

Holgers Grade 1 skin reaction: BAHA Attract: REE 0.01, BAHA Connect: REE 0.07, Ponto: REE 0.15, All BCHI devices: 0.069

Holgers Grade 2 skin reaction: BAHA Connect: REE 0.05, Ponto: REE 0.08, All BCHI devices: 0.049

Holgers Grade 3 skin reaction: BAHA Connect: REE 0.03, Ponto: REE 0.03, All BCHI devices: 0.025

Reimplantation: BAHA Connect: REE 0.02, Sophono: REE 0.01, All BCHI devices: 0.014

Revision surgery: BAHA Connect: REE 0.02, Bonebridge: REE 0.02, Ponto: REE <0.01, All BCHI devices: 0.016

Skin complications: BAHA Connect: REE 0.01, All BCHI devices: 0.011

Skin revision surgery due to skin overgrowth or cellulitis: BAHA Connect: REE 0.04, Ponto: REE 0.01, Sophono: REE 0.01, All BCHI devices: 0.038

Soft tissue/skin overgrowth: BAHA Connect: REE 0.03, All BCHI devices: 0.025

aMEIs (Note: Review only lists 10 most frequent AEs, some devices NR)

Aural fullness: VSB: 0.03, All aMEI devices: 0.019

Dizziness/vertigo: Carina: <0.01, CODACS: 0.02, Esteem: 0.08, Soundtec: 0.01, VSB: 0.01, All aMEI devices: 0.016

Explantation: Carina: 0.1, CODACS: 0.02, Esteem: 0.03, VSB: 0.01, All aMEI devices: 0.027

Implant/device failure: Carina: 0.15, VSB: 0.01, All aMEI devices: 0.026

Pain unspecified: Carina: <0.01, Esteem: 0.09, VSB: 0.01, All aMEI devices: 0.015

Percepting magnet movement: Soundtec: 0.18, All aMEI devices: 0.015

Repositioning of FMT: VSB: 0.03, All aMEI devices: 0.02

Revision surgery: Carina: 0.01, CODACS: 0.02, Esteem: 0.1, MET: 0.01, VSB: 0.01, All aMEI devices: 0.015

Taste disturbances due to chorda tympani damage: Esteem: 0.27, Soundtec: 0.01, VSB: 0.02, All aMEI devices: 0.03

Unspecified AE: Esteem: 0.35, All aMEI devices: 0.02

Timing of adverse effects: Figure 4 notes timing of AEs by follow-up at <3, 4-6, 7-12, 13-24, 25-48, and >48 months, however, data is difficult to extract with accuracy from boxplots, and authors present no tabular reporting of AE data by follow-up time.

Factors that predict response: NR

10.5 Source Citation: Xiao et al. 2020[28]

Study Design: Systematic review of 8 single-arm studies

Note: Authors compare two different surgical techniques (punch technique and open surgery). Since both groups use Ti implants, the studies are labeled as single-arm studies for the purposes of this report.

Device or Material: Baha and Ponto implants (both Ti)

Note: One study notes an NA implant system.

Contact Duration: Follow-up range: 12 weeks to 24 months

Dose: Abutment length: 6 mm to 14 mm

Frequency/Duration: NR

Response: Adverse skin reaction

Patient characteristics (gender, mean age): Gender: NR; mean age range in years: punch technique: 40.43 to 61.9, open surgery: 16 to 70.5

Number per Group: Punch technique: 218 patients, open surgery: 329 patients

Observed adverse effects: Adverse skin reaction: punch technique: 13/159 (8.1%), open surgery: 18/156 (11.5%), ES 0.67 (95% CI: 0.31 to 1.47), I^2=0%, p=0.73, no difference

Timing of adverse effects: Follow-up range: 12 weeks to 24 months

Factors that predict response: Authors performed subgroup analyses for the three types of open surgeries (dermatome with soft tissue reduction, linear incision with soft tissue reduction, and linear incision without soft tissue reduction) and found no significant differences based on subgroups.

10.6 Source Citation: Naragund and Mudhol 2017[29]

Study Design: RCT

Device or Material: Autologous incus vs. Ti partial ossicular replacement prosthesis for reconstructing Austin type A ossicular defects.

Contact Duration: Up to 12 months follow-up

Dose: NR

Frequency/Duration: Single operation

Response: facial palsy, graft extrusion with residual perforation, perichondritis of pinna, post-aural fistula or wound infection, profound deafness, severe vertigo (fistula)

Patient characteristics (gender, mean age): Female, n/N: Autologous incus: 7/20, Ti PORP: 11/20; mean age in years (SD): Autologous incus: 24 (9.2), Ti PORP: 25 (10.7)

Number per Group: Autologous incus: 20, Ti PORP: 20

Observed adverse effects:

Facial palsy, n (%): Autologous incus: 1 (5%), Ti PORP: 1 (5%)

Graft extrusion with residual perforation, n (%): Autologous incus: 0 (0%), Ti PORP: 3 (15%)

Perichondritis of pinna, n (%): Autologous incus: 0 (0%), Ti PORP: 1 (5%)

Post-aural fistula or wound infection, n (%): Autologous incus: 0 (0%), Ti PORP: 1 (5%)

Profound deafness, n (%): Autologous incus: 0 (0%), Ti PORP: 1 (5%)

Severe vertigo (fistula), n (%): Autologous incus: 1 (5%), Ti PORP: 1 (5%)

Timing of adverse effects: Up to 12 months follow-up

Factors that predict response: NR

10.7 Source Citation: Faramarzi et al. 2016[30]

Study Design: RCT

Device or Material: Ti Kurz (TTP-Vario system, Kurz GmbH, Dusslingen, Germany) with omega connector vs. Polycel (Sheehy Plastipore Polycel, Medtronic Xomed Inc)

Contact Duration: Duration of the follow up: 6-12 months.

Dose: NR

Frequency/Duration: Two-stage operation: 100% of ears

Response: Extrusion rate, sensory neural hearing loss

Patient characteristics (gender, mean age): Female gender, n (%): 60 ears (57%), mean age in years (range): 32 (15 to 61)

Number per Group: Ti Kurz: 45 patients, Polycel: 60 patients

Observed adverse effects:

Extrusion rate, n (%): Polycel: 4 (6.7%), Ti: 2 (4.4%), p=0.70, **no difference**

Sensory neural hearing loss, n (%): Polycel: 3 (5%), Ti: 2 (4.4%), p=NR, **no difference**

Timing of adverse effects: Duration of the follow up: 6-12 months.

Factors that predict response: NR

AE: adverse event; aMEI: active middle-ear implant; BAAE: bone anchored implants for auricular epithesis; BAHA: bone-anchored hearing aid; BAHI: bone-anchored hearing implant, BAHS: bone-anchored hearing system; BCHI: bone-conducting hearing implant; ES: effect size; FMT: floating mass transducer, MET: middle ear transducer; NA: not applicable; NR: not reported; OIF: osseointegration failure; PORP: partial ossicular replacement prostheses; RCT: randomized controlled trial; REE: ratio of event to ear; SD: standard deviation; Ti: titanium

Table 11: Ophthalmic - Health Effect (In Vivo) Human Study

Local Response/Toxicity

11.1 Source Citation: Craven et al. 2012[31]

Study Design: RCT.

Device or Material: iStent (Ti, Glaukos Corp.) versus cataract surgery alone.

Contact Duration: 24-month follow-up.

Dose: L-shaped stent, 1.0mm long by 0.33 mm high.

Frequency/Duration: Single administration per eye; in an eye with intraoperative stent malposition, a second stent was implanted during the same surgery.

Response: Abrasion, anterior chamber cells, blurry vision/visual disturbance, discomfort, edema, elevated intraocular pressure (IOP), floaters, hemorrhage, iritis, malposition, obstruction, posterior capsule opacification.

Patient characteristics (gender, mean age): NR.

Number per Group: iStent group, n=98; surgery-alone group, n=101.

Observed adverse effects: There was no difference between groups in complications. No postoperative inflammatory response or pain from implantation of the stent was reported.

20 patients (17.2%) in the stent group compared to 22 surgery-alone patients (18.8%) experienced an anticipated early postoperative event such as corneal edema, anterior chamber cells, corneal abrasion, discomfort, subconjunctival hemorrhage, blurry vision, and floaters.

7 patients (6.0%) in the stent group compared to 12 patients (10.3%) in the surgery group experienced posterior capsule opacification.

5 patients (4.3%) in the stent group compared to 8 patients (6.8%) in the surgery group experienced elevated IOP with 1 (0.9%) and 3 (2.6%) of those patients requiring intervention.

4 patients (3.4%) in the stent group compared to 8 patients (6.8%) in the surgery group reported blurry vision or visual disturbance.

1 patient (0.9%) in the stent group compared to 6 patients (5.1%) in the surgery group experienced iritis.

1 patient (0.9%) in the stent group compared to 3 patients (2.6%) in the surgery group experienced optic disc hemorrhage.

Complications unique to stent patients were: malposition in 3 patients (2.6) and obstruction in 5 patients (4.3%). Stent-related adverse events were not associated with morbidity to the patients.

Timing of adverse effects: Reports of stent obstruction and stent malposition occurred within 30 days postoperatively in all but 1 eye. Other postoperative ocular complications are through 24-month follow-up.

Factors that predict response: NR.

Table 12: Orthopedic – cages, spinal - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

12.1 Source Citation: Wu et al. 2022[32]

Study Design: SR included 34 studies with 3,233 patients undergoing LLIF: 28 retrospective studies, 5 prospective studies, and 1 RCT. Three studies compared the risk of cage subsidence of PEEK cages and Ti cages in LLIF patients.

Device or Material: Spinal cages made of PEEK or Ti

Contact Duration: up to 1 year

Dose: single cage

Frequency/Duration: single administration

Response: Two types of cage subsidence were recorded in this review: late-onset cage subsidence, which occurs gradually postoperatively, and intraoperative endplate injury, which is derived from iatrogenic endplate violation during endplate preparation or cage insertion.

Patient characteristics (gender, mean age): 58% women

Number per Group: three studies comparing PEEK and Ti cages, n = 308.

Observed adverse effects: Satake et al. (2016) reported that using PEEK cages resulted in a higher incidence of endplate injury than Ti (12.4% [21 of 169] of segments versus 0% [0 of 32] of segments; p = 0.04), immediate postoperative. Satake et al. (2017) reported that levels with late-onset settling had a higher percentage of PEEK cages (100% [21 of 21] of segments versus 81.1% [107 of 132] of segments; p = 0.03), 1 year follow-up. Campbell et al. (2020) reported that the use of PEEK resulted in a higher late-onset subsidence risk at 12 months of follow-up compared with Ti cages (20.8% [10 of 48] of patients versus 4.5% [2 of 44] of patients; p=0.012).

Timing of adverse effects: immediate postoperative and one year follow-up.

Factors that predict response: "The poor performance of PEEK is likely because of its inferior osseoconductivity and bioactivity compared with Ti implants. Although these three studies reported that the inferior performance of PEEK cages had a moderate quality of evidence, more biomechanical evidence might be needed before the most favorable cage material is decided for LLIF because of the complex interaction between the cage and endplate."

12.2 Source Citation: Onyedimma et al. 2021[33]

Study Design: SR included 37 studies with 2,363 patients undergoing ACDF, study designs not reported. SR compared PEEK cages with Ti cages.

Device or Material: Spinal cages made of PEEK or Ti

Contact Duration: minimum 12 months, median follow-up 26 months.

Dose: single cage

Frequency/Duration: single administration

Response: fusion rate, subsidence rate

Patient characteristics (gender, mean age): NR, median age 49.5 years

Number per Group: Not reported

Observed adverse effects: Fusion rate following standalone cage placement for 1- and 2-level ACDF using autograft showed no significant differences between Ti (rate = 84%, 95% C: 0.73-0.91) and PEEK (rate = 91%, 95% CI 0.83-0.95) cage systems (combined rate = 88%, 95% CI 0.81-0.92, P = 0.20). No significant differences were found for neurologic deficits (PEEK: rate = 11%, 95% CI 0.05-0.26, Ti: rate = 10%, 95% CI 0.07-0.14, combined: rate = 10%, 95% CI 0.07-0.14, P = 0.73) or subsidence rates (PEEK: rate = 26%, 95% CI 0.17-0.39, Ti: rate = 20%, 95% CI 0.15-0.26, combined rate = 0.21, 95% CI 0.17-0.27, P = 0.30) following similar substratification, respectively.

Timing of adverse effects: median follow-up 26 months

Factors that predict response: NR

12.3 Source Citation: Schnake et al. 2021[37]

Study Design: RCT comparing uncoated PEEK cages and Ti-PEEK cages in posterior lumbar interbody fusion.

Device or Material: uncoated PEEK cages and Ti-PEEK cages

Contact Duration: 24 months

Dose: single device

Frequency/Duration: single administration

Response: fusion rates

Patient characteristics (gender, mean age): 55 patients (92%) (36 female, 19 male) had a complete follow-up. Ti-PEEK cages n = 27, mean 50.6 years; PEEK cages n = 28, mean 52.9 years.

Number per Group: 60 patients enrolled, 55 patients completed follow-up,

Observed adverse effects: Osseous integration of the cage surface improved significantly ($p < 0.001$) in both groups between 6 and 12 months after surgery. At 12-month follow-up, neither radiolucency nor signs of instability or dislocation were noted. Fusion was present in CT scans as follows: (a) bone growth through cage pores (Ti-PEEK: 100%, PEEK: 100%); (b) bone growth outside the cages (Ti-PEEK: 48%, PEEK: 61%; p=0.3).

No post-operative complications occurred. Revision surgery was not performed in any of the cases during the observation period. No pseudoarthrosis was observed. The rate of bridging bone outside the cages was 48% in the Ti-coated group and 61% in the uncoated group but these differences were not statistically significant.

Timing of adverse effects: 6, 12, and 24 months.

Factors that predict response: Not reported.

12.4 Source Citation: Tan et al. 2021[34]

Study Design: SR of 11 studies with 743 patients undergoing lumbar interbody fusion: 9 retrospective cohort studies, 1 prospective cohort study, and 1 RCT.

Device or Material: Spinal cages made of PEEK or Ti

Contact Duration: average follow-up duration ranged from 12 months up to 102 months.

Dose: single cage

Frequency/Duration: single administration

Response: fusion rate, hematoma, neuropathic pain, cage subsidence

Patient characteristics (gender, mean age): no significant differences between the mean age of patients who received PEEK cages (51.95±9.59 years) and patients who received Ti cages (52.17±7.99 years, p=0.477). Similarly, there are no significant differences in gender distribution when comparing patients who received PEEK cages and patients who received Ti cages (p=0.723).

Number per Group: 334 patients (45.0%) received PEEK cages, while 409 patients (55.0%) received Ti cages

Observed adverse effects: A comparison of 158 patients in the Ti group and 121 patients in the PEEK group showed no statistically significant differences in the rate of postoperative hematoma formation (2 each arm, RR 1.30, 95% CI 0.23−7.35, P=0.77).

Data on postoperative neuropathic pain were available in 4 studies. Comparison of 185 patients in the Ti group and 130 patients in the PEEK group at the final follow-up showed no statistically significant differences in the rate of postoperative neuropathic pain (5 each arm, RR 1.55, 95% CI 0.44−5.39, P = 0.49).

Comparison of 252 patients in the PEEK group and 275 patients in the Ti group showed a trend towards more cage subsidence in the Ti group, although there was no statistically significant difference (RR 1.82, 95% CI 0.98–3.37, P=0.06).

In patients who underwent lumbar spine fusion for non-infective conditions, patients who underwent Ti cage insertion had a higher rate of cage subsidence when compared against PEEK cage insertion (RR 2.17, 95% CI 1.13–4.16, P=0.02). Comparison of 280 patients in the PEEK group and 383 patients in the Ti group showed no statistically significant differences in the rate of spinal fusion at 12 months postoperatively (OR 1.22, 95% CI 0.36–4.15, P=0.41). A comparison of 357 patients in the PEEK group and 443 patients in the Ti group showed no statistically significant differences in the rate of spinal fusion at the final follow-up (OR 1.50, 95% CI 0.57–3.94, P=0.41).

Timing of adverse effects: All occurred after 12 months.

Factors that predict response: Due to the difference in modulus of elasticity between Ti and cortical bone, cage subsidence led to postoperative complications such as screw loosening, cage migration, non-union, rod breakage, and may necessitate revision surgery. This study showed that for patients who underwent lumbar spine fusion for non-infective conditions, Ti cage has 2.12 times increased fusion rate and 2.17 times increased risk of subsidence as compared to PEEK cages. While Ti cage confers a higher risk of subsidence, there is no difference in postoperative clinical outcomes as compared to patients who had PEEK cage insertion.

12.5 Source Citation: Hasegawa et al. 2020[38]

Study Design: Multicenter RCT comparing uncoated PEEK cages and TiPEEK cages in posterior lumbar interbody fusion.

Device or Material: uncoated PEEK cages and TiPEEK

Contact Duration: 1 to 12 months

Dose: single device

Frequency/Duration: single administration

Response: fusion rates, subsidence, and adverse events.

Patient characteristics (gender, mean age): 149 patients (84 men, 65 women, mean age 67 years)

Number per Group: TiPEEK cage (n = 69) or PEEK cage (n = 80)

Observed adverse effects: The interbody union rate was TiPEEK 42.0% and PEEK at 41.3% (P=0.92), respectively at 12 months after surgery which was lower in the current study than previous reports (more than 80%–90%) due to the very strict definition of the union outcome.

Fusion rates were significantly higher at 4 and 6 months after surgery in the TiPEEK group than in the PEEK group in the unadjusted modified intention-to-treat analysis and were significantly higher at 6 months in the unadjusted per-protocol analysis. A TiPEEK cage (odds ratio, 2.27; 95% confidence interval: 1.09– 4.74; P=0.03) was independently associated with bone fusion at 6 months after surgery.

There was no difference in the rates of cage subsidence and pedicle screw loosening, or clinical symptoms between the TiPEEK and PEEK groups. At 12 months 15.6% of TiPEEK and 14.9% of PEEK had cage subsidence; 26.6% of TiPEEK and 20.5% of PEEK had screw loosening.

Adverse events: Two adverse events occurred in the TiPEEK group (one patient experienced screw malpositioning and one experienced a grafted bone back out). In the PEEK group, one adverse event unrelated to the procedure occurred (cerebral infarction), and there were three drop-out cases due to social factors unrelated to health problems.

Timing of adverse effects: 1, 2, 4, 6 and 12 months; cage subsidence with TiPEEK in 1 (1.5%) patient at 1 month, screw loosening at 2 months in 3 (4.5%) patients

Factors that predict response: "Ti implants have some advantages, including the osseointegration phenomenon that is associated with their surface, their biocompatibility, and the robust immobilization that is attributable to TiO2 formation. One potential disadvantage of Ti is the mismatch between the elastic modulus (110 GPa) and the cortical bone (10–30 GPa). This mismatch poses a potential risk of cage subsidence, stress shielding around the implant, and bone atrophy." Ti "provided good bone affinity that facilitated early adhesion to the endplates, reducing microinterbody mobility and bone resorption."

"Our results showed no significant difference in the ratio of cage subsidence and pedicle screw loosening in the TiPEEK and PEEK groups; however, the Ti coating on the PEEK facilitated a reduction in hardness and a reduction in subsidence."

12.6 Source Citation: Lee et al. 2020[39]

Study Design: Multicenter RCT comparing Ti cages with bioactive glass ceramic spacers in 1-level posterior lumbar interbody fusion reported 4-year follow-up. 12-month results are presented in Lee et al. 2016.[41]

Device or Material: Ti cages filled with autologous local bone and glass ceramic spacers

Contact Duration: 4 years

Dose: single device

Frequency/Duration: single administration

Response: fusion rate

Patient characteristics (gender, mean age): BGS-7 24 female, 8 male, 61.5 years; Ti 18 female, 12 male, 61.1 years.

Number per Group: bioactive glass ceramic n = 32, Ti n = 30

Observed adverse effects: Computed tomography scan showed a bone fusion rate of 90.6% in the bioactive glass ceramic spacer group and 93.3% in the control group, with no significant differences between groups. Both groups showed no additional adverse events after 1 year.

Osteolysis around the cage and spacer was not observed in either group at 48 months or more.

Timing of adverse effects: up to 4 years

Factors that predict response: Ti is a biocompatible material that promotes bone growth near the cage surface, it is biologically inert and cannot chemically bind to the bone.

12.7 Source Citation: Massaad et al. 2020[35]

Study Design: SR with meta-analysis examining PEEK and Ti cages for posterior lumbar interbody fusion. Search dates to January 2020. Included 11 studies with 1,094 patients. Eight single center studies were retrospective, observational, and 3 single center studies were prospective studies of which, 1 was a RCT pilot study.

Device or Material: Ti and PEEK cages

Contact Duration: The mean follow-up time in the Ti and PEEK groups was 20.5 and 22.3 months respectively (range, 6–84 months).

Dose: single device

Frequency/Duration: single administration

Response: fusion rate, subsidence.

Patient characteristics (gender, mean age): Overall, 49.5% and 48.9% were men in the Ti and PEEK groups, respectively. Mean age of the Ti (59.23 ± 3.89 years) and PEEK groups (58.44 ± 3.43 years) (p= 0.89).

Number per Group: 673 (61.5%) had lumbar interbody fusion using a Ti cage or Ti-PEEK cage and 421 (38.5%) had lumbar interbody fusion using a PEEK cage.

Observed adverse effects: "The final analysis included 421 patients (38.5%) who had lumbar surgery using a Ti and/or a Ti-coated interbody cage and 673 patient (61.5%) who had lumbar surgery using a PEEK cage. Overall, PEEK interbody devices were associated with a significantly lower fusion rate compared with Ti interbody devices (OR, 0.62; 95% CI, 0.41–0.93; p = 0.02). There was no difference in subsidence rates between Ti and PEEK groups (OR, 0.91; 95% CI, 0.54–1.52; p=0.71)."

Timing of adverse effects: The mean follow-up time in the Ti and PEEK groups was 20.5 and 22.3 months respectively (range, 6–84 months).

Factors that predict response: "The application of PEEK has been limited by the formation of a biofilm layer around its surface that potentially affects fusion to cortical bone. This limitation of PEEK could be avoided by the application of Ti which has a microscopic rough surface that increases osteogenic cell differentiation factors."

"This meta-analysis included exclusively 11 lumbar studies that give our results more power, but also included [Ti-PEEK] cages, a composite that overcomes the modulus of elasticity of Ti that leads to subsidence and provides effective osseointegration. [Ti-PEEK] cages may benefit from the properties of both materials to allow early osseointegration and fusion, at the same time, maintaining ideal disc heights and alignments for degenerative lumbar disease."

12.8 Source Citation: Willems et al. 2019[40]

Study Design: Multicenter RCT of 127 patients undergoing posterior lumbar interbody fusion

Device or Material: PEEK, Ti-nanocoated PEEK, and calcium phosphate-coated PEEK cages

Contact Duration: 1 year

Dose: single device

Frequency/Duration: single administration

Response: fusion

Patient characteristics (gender, mean age): Ti-nanocoated (17 male, 27 female, mean 50.0 years), CaP-nanocoated (23 male, 23 female, 50.3 years), and uncoated PEEK cages (21 male, 16 female, 51.5 years).

Number per Group: Ti-nanocoated (n = 44), CaP-nanocoated (n = 46), and uncoated PEEK cages (n = 37).

Observed adverse effects: One year after the surgery, 65.6% of patients with uncoated PEEK cages achieved definite fusion. Significantly more patients with nanocoated PEEK cages achieved definite fusion: 93.9% for Ti-nanocoating (P = .0034) and 88.0% for CaP-nanocoating (P = .032). No significant differences in fusion were found between the nanocoated cage types (P = .4318).

"No cage migration was observed in the complete study population. Blood loss and the hospital stay duration were comparable between groups."

Timing of adverse effects: 1 year

Factors that predict response: "The nanocoated PEEK cages used in this randomized controlled trial kept wear to a minimum because the thickness was significantly smaller than that of the plasma-sprayed coatings."

12.9 Source Citation: Niedzielak et al. 2018[36]

Study Design: SR and meta-analysis of 26 studies and 1,133 patients with single or multiple level cervical myelopathy secondary to cervical spondylosis or ossified posterior longitudinal ligament examining surgical constructs for anterior cervical corpectomy and fusion. Among the 26 studies, 12 were retrospective cohort studies, 14 were retrospective case series, and 4 were prospective case series. 13 studies examined Ti mesh cages (n = 437).

Device or Material: Constructs that were reported in these studies included Ti mesh cages, nano-hydroxyapatite/polyamide 66 composite struts, bone graft alone, expandable corpectomy cages, and PEEK cages

Contact Duration: minimum 12 months

Dose: single device

Frequency/Duration: single administration

Response: fusion

Patient characteristics (gender, mean age): reported mean age was 57.1 years (range, 51.2–73.5 years).

Number per Group: 13 studies examined Ti mesh cages (n = 437).

Observed adverse effects: Fusion rates for Ti mesh cages had a range of 93.6% to 100% with 8 studies reporting 100% fusion.

Transient dysphagia (58%) was reported in 1 study, but was related more to surgical approach than to material used.

Timing of adverse effects: The mean follow-up reported by these studies was 46.4 months.

Factors that predict response: "The [Ti mesh construct] with or without an anterior cervical plate is one of the most commonly used constructs for [anterior cervical corpectomy and fusion]. It has an abundance of established literature supporting its use."

12.10 Source Citation: Lee et al. 2016[41]

Study Design: Multicenter RCT examining bioactive glass ceramics spacer (experimental) and Ti cages (control) in posterior lumbar interbody fusion.

Device or Material: bioactive glass ceramics spacer and Ti cages

Contact Duration: 12 months

Dose: single device

Frequency/Duration: single administration

Response: fusion rate, subsidence, osteolysis, adverse events

Patient characteristics (gender, mean age): Bioactive glass 61.5 years and 27 female (69%); Ti 61.1 years and 21 female (60%)

Number per Group: 75 patients (39 in the bioactive glass group, 36 in the Ti group) completed the clinical study.

Observed adverse effects: 6-month fusion rates for the bioactive glass ceramics group and the Ti group were 89.7% and 91.4%, respectively. In addition, the 12- month fusion rates based on CT scan were 89.7% and 91.2%, respectively, showing no significant difference.

At 12 months, no significant differences between the two groups were observed in the extent of subsidence and osteolysis. Osteolysis was 7.7% in the experimental group and 5.9% in the control group with no significant intergroup difference. End plate subsidence in the experimental and control groups was 1.10 mm (±0.99) and 0.94 mm (±0.73), respectively, with no significant intergroup difference.

"The numbers of subjects who experienced at least one adverse event in the experimental and control groups were 35 (87.5%) and 37 (94.9%), respectively. A total of 155 incidents were recorded in the experimental group and 132 occurred in the control group, resulting in no significant intergroup difference (p=.43)." "In the experimental group, although one subject experienced back pain caused by osteolysis and a non-union…the symptoms improved, and the subject was followed for further observation without surgical intervention. The other subject in the experimental group developed acute pyelonephritis, whereas the subject in the control group developed hematochezia. However, both subjects recovered, and the events were not related to the medical devices."

No reoperations were reported.

Timing of adverse effects: 3, 6, and 12 months

Factors that predict response: NR

ACDF: anterior cervical discectomy and fusion; CI: confidence interval; CT: computed tomography; LLIF: lateral lumbar interbody fusion; OR: odds ratio; PEEK: polyetheretherketone; RR: relative risk; RCT: randomized controlled trial; SR: systematic review; Ti: Titanium; TiPEEK: titanium coated PEEK; VAS: visual analog scale.

Table 13: Orthopedic – fixation, spine (rod, screw, plate) - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

13.1 Source Citation: Bowden et al. 2022[42]

Study Design: SR and meta-analysis on rod materials and sizes in the surgical treatment of AIS. 75 studies included, 46 studies described rod material and diameter. Ti alloy rods were used in most studies (n=32), followed by CoCr (n=16), and SS (n=8). Included 2 RCTs, 52 cohort studies, 20 case series, and 1 meta-analysis.

Device or Material: Ti alloy rods, CoCr rods, stainless steel rods

Contact Duration: NR

Dose: single device

Frequency/Duration: single administration

Response: revisions

Patient characteristics (gender, mean age): patient age 10–18 years

Number per Group: NR

Observed adverse effects: Three studies using Ti rods reported revisions. The overall pooled proportion for revision was 6% (95% CI 0.0–12.0%). Two studies using CoCr rods reported revision surgery with an overall pooled proportion of 4% (95% CI 0.0–8.0%).

Timing of adverse effects: NR

Factors that predict response: "Present day rod constructs are more likely to consist of either Ti or CoCr. Biomechanical properties of spinal rods are typically differentiated by yield strength and stiffness. Generally, Ti is characterized by high yield strength but a lower stiffness, and CoCr is characterized by a very high stiffness and low yield strength. However, the potential impact of rod material properties observed in the laboratory setting are not easily extrapolated to the clinical reality."

13.2 Source Citation: Bednar et al. 2021[43]

Study Design: SR and meta-analysis to compare the surgical outcomes, complications, metal ion levels, quality-of-life outcomes, and cost of MCGRs with other distraction-based surgical technologies for the treatment of early-onset scoliosis. Included 18 studies: 7 retrospective comparison studies, 5 cross-sectional comparisons, and 6 cost analysis studies.

Device or Material: MCGRs made of Ti, TGR

Contact Duration: NR

Dose: single device

Frequency/Duration: single administration for MCGR, multiple insertions for TGR

Response: complications (e.g., infections, device failures, and unplanned surgical procedures)

Patient characteristics (gender, mean age): aged ≤9 years at the time of index surgical intervention

Number per Group: MCGR n = 287, TGR n = 336

Observed adverse effects:

Seven articles reported on complications including device failures, and unplanned surgical procedures. Three studies had a significantly higher proportion of patients with at least 1 complication in the TGR group compared with the MCGR group (92% versus 33%, 76% versus 37%, and 93% versus 33%). The other 4 studies found no significant difference (41% versus 60%, 25% versus 45%, 48% versus 48%, and 78% versus 70%). Meta-analysis found a lower complication rate per patient in the MCGR group (OR 0.42; 95% CI, 0.25 to 0.71). The effect was significant (p = 0.001) but with moderate heterogeneity (I2 = 63%, p = 0.01).

Timing of adverse effects: no follow-up data were reported

Factors that predict response: NR

13.3 Source Citation: Wang et al. 2021[48]

Study Design: RCT of 26 patients with spinal fractures (no information on study design and conduct other than the study was randomized).

Device or Material: Ti mesh and nHA prosthesis

Contact Duration: 2-year follow-up

Dose: single device

Frequency/Duration: single administration

Response: fusion rate, nerve root injuries, nerve paresthesia, dural tears, postoperative pain

Patient characteristics (gender, mean age): age range 20 to 60 years, specific patient characteristics were not reported.

Number per Group: nHA group (n = 13) and Ti mesh group (n = 13)

Observed adverse effects: After surgical treatment, all patients' spinal symptoms (VAS pain score, Japanese Orthopaedic Association score, and Cobb angle) had improved and did not cause obvious inflammatory foreign body reactions. During a two-year follow-up, the fusion time and support settlement in the nHA group was lower, and the vertebral fusion rate and American Spinal Injury Association Impairment score were higher than those in the Ti mesh group.

A year after surgery, the two groups' prosthesis fusion rates were both greater than 94%.

Both groups had nerve root injuries, dural tears, operation area pain, intervertebral space, and nerve paresthesia, but there was no statistical difference. After two years of follow-up, patients in the nHA group and Ti group had relatively low complication recurrence.

Timing of adverse effects: foreign body reaction was tested 2 days after surgery

Factors that predict response: see under systemic response below

13.4 Source Citation: Fan and Zhu, 2020[45]

Study Design: SR and network meta-analysis comparing decompression alone with fusion and Coflex for lumbar degenerative disease. Included 10 RCTs with 946 patients. 2 RCTs compared Coflex with decompression, 4 RCTs compared decompression with fusion, and 4 RCTs compared Coflex with fusion.

Device or Material: Coflex interlaminar stabilization Ti implant

Contact Duration: 6 studies did not report follow-up, 4 RCTs had 24 months or more follow-up

Dose: single device

Frequency/Duration: single administration

Response: dural sac rupture, loosening, vertebral fracture

Patient characteristics (gender, mean age):

2 RCTs compared Coflex (52.5 and 68 years) with decompression (52.5 and 68 years)

4 RCTs compared decompression (71.2, 73.1, 72.3, 30.3 years) with fusion (69.3, 70.0, 62.1, 34.9 years)

4 RCTs compared Coflex (46.5, 62.1, 52.4, 48.6 years) with fusion (49.4, 64.4, 51.8, 50.4 years)

Number per Group:

2 RCTs compared Coflex (n = 55) with decompression (n = 57)

4 RCTs compared decompression (n = 164) with fusion (n = 164)

4 RCTs compared Coflex (n = 305) with fusion (n = 201)

Observed adverse effects:

"There were 13 patients with decompression alone surgery complained adverse events including 8 relapse and 3 dural sac rupture. Four patients with Coflex technique had complications, including 2 dural sac rupture, 1 Coflex loosening, and 1 vertebral fracture." There were 12 patients with PLIF surgery occurred adverse events, including 3 relapse, 2 dural sac rupture, 1 VTE [venous thromboembolism], 2 intervention loosening, and 1 vertebral fracture. "We found the complication incidence rate of Coflex was lower than the others (P<.05)."

Timing of adverse effects: NR

Factors that predict response: NR

13.5 Source Citation: He et al. 2020[46]

Study Design: SR and meta-analysis of studies comparing Ti mesh with bone graft alone for treating thoracolumbar tuberculosis. Included 8 retrospective studies, all conducted in China, with 401 patients. Patients were diagnosed with thoracolumbar tuberculosis and had surgical indications for decompression and bone grafting.

Device or Material: Ti mesh

Contact Duration: Ti follow-up ranged from 9 to 71 months; bone graft follow-up ranged from 39.5 months to 74 months.

Dose: single device

Frequency/Duration: single administration

Response: fusion, complications, and recurrence.

Patient characteristics (gender, mean age): Ti mean age ranged from 31.2 years to 49.9 years, bone graft mean age ranged from 33.6 years to 55.5 years.

Number per Group: 203 Ti mesh and 198 bone graft

Observed adverse effects: The combined results showed no statistically significant differences in postoperative non-fusion (RR=0.98; 95% CI, 0.26–3.67), complications (RR=1.15; 95% CI, 0.61–2.17) and recurrence (RR= 0.65; 95% CI, 0.13–3.11) between the 2 bone graft methods, indicating that both the bone graft alone and the Ti mesh bone graft were safe for the treatment of thoracolumbar spinal tuberculosis.

"Both Ti mesh and bone grafts alone are effective for the treatment of thoracolumbar spinal tuberculosis based on safety."

Timing of adverse effects: up to 71 months with Ti, up to 74 months with bone graft

Factors that predict response: "Recent studies [2 references] have successively reported reliable spinal reconstruction, a high fusion rate and a lower incidence of complications for Ti mesh bone grafts for the treatment of spinal tuberculosis. This approach can not only avoid pain and infection in the bone-harvesting area of the autologous bone graft but can also allow the Ti mesh to fill with bone and achieve extensive biological integration at the bone interface; thus, immediate stability can be obtained without fusion of the bone in the Ti mesh. In addition, the adjustable length of the Ti mesh and its strong supporting properties have found approval by many clinicians."

13.6 Source Citation: Miller et al. 2020[47]

Study Design: SR and meta-analysis of Barricaid annular closure for lumbar disc reherniation. Included 2 RCTs and 2 retrospective nonrandomized controlled studies (n = 801). Control groups had no intervention.

Device or Material: Barricaid device is an intervertebral biomechanical device that consists of a woven polyethylene terephthalate flexible fabric component that attaches to a Ti alloy (Ti-6Al-4 V ELI) intravertebral bone anchor.

Contact Duration: follow-up duration was 2 years in three studies and 4 years in one study

Dose: single device

Frequency/Duration: single administration

Response: reoperation

Patient characteristics (gender, mean age): mean patient age in each study ranged from 40 to 44 years. 60% male.

Number per Group: 381 lumbar discectomy and the Barricaid device, 420 lumbar discectomy alone

Observed adverse effects: The risk of reoperation was 48% lower with the Barricaid device (7.7% vs. 14.5%, risk ratio = 0.52, p = 0.003), all risk ratios were less than 1 (favoring the Barricaid device) in individual studies, and no heterogeneity was observed (I 2 = 0%).

Among the four studies, the risk of symptomatic reherniation over 2 years of follow-up was 55% lower with the Barricaid device (9.3% vs. 20.3%, risk ratio = 0.45, p < 0.001). The results were consistent among studies since each study reported a risk ratio of less than 1, and no heterogeneity was observed (I2 = 0%).

Timing of adverse effects: data were extracted for 2-year follow-up

Factors that predict response: NR

13.7 Source Citation: Mo et al. 2019[44]

Study Design: SR and network meta-analysis comparing PLIF and the three commonly used interspinous devices including Coflex, Wallis, and X-stop for lumbar degenerative diseases. Included 27 studies with 2,241 patients: 5 RCTs, 22 cohort studies; 16 studies compared Coflex with PLIF, 4 studies compared Wallis with PLIF, 2 studies compared Wallis with X-stop, and 5 studies compared Coflex with Wallis,

Device or Material: Coflex contains Ti, Wallis second generation is made of PEEK, and X-stop contains Ti

Contact Duration: follow-up ranged from 3 months to 66 months

Dose: single device

Frequency/Duration: single administration

Response: fracture, disc herniation, adjacent segment degeneration

Patient characteristics (gender, mean age): NR

Number per Group: 1,066 patients were included in Coflex groups, 695 in PLIF groups, 420 in Wallis groups, and 60 in X-stop groups.

Observed adverse effects:

Nineteen studies mentioned adverse events. Nine studies reported no adverse events. Five studies reported spinous process fracture occurred in 35 patients in Coflex group. Two studies reported intervertebral disc herniation occurred in 12 cases, including 6 in Coflex group and 6 in PLIF group.

Adjacent segment degeneration was reported in two studies including 7 patients in Coflex group and 17 in PLIF group.

Timing of adverse effects: follow-up ranged from 3 months to 66 months

Factors that predict response: "Compared with posterior lumbar interbody fusion, Coflex, Wallis and X-stop had the same effectiveness in relieving pain, improving quality of life, recovering disc space height and lumbar function, but may lower incidence of adjacent segment degeneration."

13.8 Source Citation: Bae et al. 2016[49]

Study Design: Multicenter RCT of Coflex interlaminar stabilization compared with instrumented fusion in patients with lumbar stenosis

Device or Material: Coflex

Contact Duration: 36-month follow-up

Dose: single device

Frequency/Duration: single administration

Response: reoperations, revisions, device-related complications (component loosening, component migration, component breakage, fracture, pain), new sensory or motor deficits.

Patient characteristics (gender, mean age): mean age at surgery for patients examined at 36 months, Coflex 62.0 years, fusion 62.0 years

Number per Group: 196 Coflex and 94 fusion patients at 36 months

Observed adverse effects:

"Important harms/severe adverse events that were deemed either definitely or probably related to the device occurred in 19 [Coflex] patients (8.8%) and in 16 fusion patients (15%) (Fisher exact test, P = .13). Important harms that were deemed either definitely or probably related to the surgery occurred in 26 [Coflex] patients (12.1%) and 19 fusion patients (17.8%) (P = .18)."

Device-related AEs at the operative site included:

Component loosening: 4 (1.9%) Coflex, 5 (4.7%) fusion

Component migration: 3 (1.4%) Coflex, 1 (0.9%) fusion

Component breakage: 3 (1.4%) Coflex, 2 (1.9%) fusion

Fracture: 8 (3.7%) Coflex, 0 (0%) fusion

Pain; new, worsening: 14 (6.5%) Coflex, 13 (12.1%) fusion

Pseudoarthrosis: 0 (0%) Coflex, 1 (0.9%) fusion

Other: 1 (0.5%) Coflex, 1 (0.9%) fusion

Reoperations in Coflex arm occurred in 30 patients: 16 due to persistent pain, 7 due to wound issues (2 cerebrospinal fluid leaks, 1 wound dehiscence), 3 due to component loosening, and 4 due to fractures (2 spinous process fractures, 2 pars fractures).

Reoperations in fusion arm occurred in 13 patients: 9 due to persistent pain, 2 due to component failure (1 broken screw, 1 screw loosening), 1 due to pars fracture, 1 due to wound hematoma.

Timing of adverse effects: 36-month follow-up

Factors that predict response: NR

13.9 Source Citation: Lukina et al. 2015[50]

Study Design: Single-center retrospective case-control study of patients with scoliosis treated with the sliding growth guidance instrumentation LSZ-4D (Conmet, Moscow, Russia). Control patients had no implanted devices.

Device or Material: sliding rod device made of Ti alloy (Ti6Al4V)

Contact Duration: 6 ± 2 years

Dose: single device

Frequency/Duration: single administration

Response: metallosis associated with device, Ti, Al and V metal ions in tissues around the implanted device, histology

Patient characteristics (gender, mean age): Treated group - 3 males, 22 females, average age at primary surgery for scoliosis treatment was 11.4±1.2 years

Number per Group: 25 patients with high growth potential treated with device, 13 patient control group with no implants.

Observed adverse effects: "5 of 25 patients in the study group developed metallosis associated complications (two sinuses and three seromas in the lumbar part of the spine). Revisions were carried out in two of these patients. 90% of patients in the study group had increased content of Ti and V ions in the blood (2.8 and 4 times, respectively). Median content of Ti ions in soft tissues adjacent to implanted sliding device was more than 1,500-fold higher compared with the control group. These levels are much higher than previously reported for spinal instrumentation."

"Black discoloration of soft tissues adjacent to growth guidance sliding LSZ-4D devices was observed in all patients, indicating significant amounts of wear debris."

"Median concentration of these elements in tissues of patients with implanted growth guidance sliding devices LSZ-4D taken from the capsule around fixture-rod junction increased dramatically up to 1,300 μg/g (range 103 - 5,750) for Ti, 18 μg/g (range 2 – 106) for aluminum and 11 μg/g (range 2 – 109) for vanadium, indicating statistically significant increase of all elements."

"The concentration of metal ions was measured in soft tissues collected 3 cm away from the capsule indicating that elevated ions were not just associated with capsular tissue adjacent to the implant but were found at a deeper level. Median values were 6.5 μg/g (range 1.3 – 34) for Ti, 0.9 μg/g (range 0.4 – 6) for aluminum and 0.1 μg/g (0.02 – 0.8) for vanadium, which are significantly higher compared with control group, but significantly lower compared with tissues collected from the capsule."

Timing of adverse effects: One of these patients developed seroma accompanied with elevated body temperature and increased erythrocyte sedimentation rate in her blood which were regarded as signs of inflammation 10 years after the surgery.

A second patient developed a sinus with local inflammation 5 years after the surgery. Clinical symptoms were resolved once the device had been exchanged or shortened.

Another three patients developed seromas or sinus without inflammation 0.5 – 2 years after the implantation of LSZ-4D devices.

Clinical symptoms resolved after the device was exchanged or shortened.

Factors that predict response: "Since the biocompatibility of Ti is much higher compared to Co and Cr, which are present in CoCr and stainless steels, it might be hypothesized that the optimization of Ti instrumentation design and improvements in its wear resistance by the application of biocompatible wear resistant coatings would certainly be beneficial."

"Our findings indicate the importance of using wear resistance materials for sliding and extending instrumentation which is used for the treatment of scoliosis in immature patients."

Systemic Response/Toxicity

13.10 Source Citation: Bednar et al. 2021[43]

Study Design: SR and meta-analysis to compare the surgical outcomes, complications, metal ion levels, quality-of-life outcomes, and cost of MCGRs with other distraction-based surgical technologies for the treatment of early-onset scoliosis. Included 18 studies: 7 retrospective comparison studies, 5 cross-sectional comparisons, and 6 cost analysis studies.

Device or Material: MCGRs made of Ti, TGR

Contact Duration: NR

Dose: single device

Frequency/Duration: single administration for MCGR, multiple insertions for TGR

Response: serum Ti levels, metal ion levels

Patient characteristics (gender, mean age): aged ≤9 years at the time of index surgical intervention

Number per Group: MCGR n = 287, TGR n = 336

Observed adverse effects: Meta-analysis found that serum Ti levels were 2.98 ng/mL (95% CI, 1.41 to 4.55 ng/mL) greater in the MCGR group (n = 30) than the TGR group (n = 17); the difference was significant (p = 0.0002) and heterogeneity was negligible (I2 = 0%, p = 0.96). Risk of bias in these studies was high due to cross-sectional design and baseline differences in comparator groups.

Two cross-sectional case series reported on metal ion levels in patients with MCGRs compared with other distraction-based implants. One study reported serum Ti levels in patients treated with MCGRs (n = 8), TGRs (n = 2), or vertical expandable prosthetic Ti rib (n = 13); serum Ti levels were 4.5 ±2.1, 1.5 ±0.7, and 7.6 ±3.7 ng/mL, respectively. These differences were significant (p = 0.021). The other cross-sectional case series measured serum levels of Ti, vanadium, aluminum, boron, and iron in patients treated with MCGRs (n = 22) or TGRs (n = 15) in comparison with age-matched nonoperative controls. Serum levels in mg/mL in the MCGR group were 10.2 ±6.8 for Ti, 0.5 ±0.5 for vanadium, 7.8 ±5.1 for aluminum, 85.0 ±6.6 for boron, and 102.4 ±31.4 for iron. Serum levels in mg/mL in the TGR group were 7.3 ±4.3 for Ti, 0.2 ±0 for vanadium, 8.1 ±7.4 for aluminum, 86.9 ±2.5 for boron, and 76.3 ±39.8 for iron. Serum vanadium levels were significantly higher in the MCGR group than the TGR group (p = 0.004).

Timing of adverse effects: no follow-up data were reported

Factors that predict response: NR

13.11 Source Citation: Wang et al. 2021[48]

Study Design: RCT of 26 patients with spinal fractures (no information on study design and conduct other than the study was randomized).

Device or Material: Ti mesh and nHA prosthesis

Contact Duration: 2-year follow-up

Dose: single device

Frequency/Duration: single administration

Response: inflammatory rate

Patient characteristics (gender, mean age): age range 20 to 60 years, specific patient characteristics were not reported.

Number per Group: nHA group (n = 13) and Ti mesh group (n = 13)

Observed adverse effects:

Inflammatory responses measured by blood IL-1, IL-6, and TNF-a were low and indicated good biocompatibility.

Inflammatory response: "On the second day after surgery, 5 mL of venous blood was collected from patients. After high-speed centrifugation, the supernatant was stored in a −80 C medical refrigerator; then, IL-1, IL-6, and TNF-a were detected using an ELISA kit."

Timing of adverse effects: 2 year follow-up

Factors that predict response: The degree of inflammatory reaction was closely related to the prosthesis biocompatibility. Concerning IL-1, IL-6, and TNF-a, the inflammatory response of the nHA group was slightly lower than that of the Ti mesh group. Still, there was no significant difference, suggesting that the two prostheses had good biocompatibility in vivo, and nHA was relative better.

"Due to the difference between the hardness of Ti alloy and cortical bone, it is easy to cause the subsidence of Ti mesh because of the stress action after surgery, resulting in the loss of the height between the upper and lower vertebral bodies. The loss of vertebral height will compress the nerve root in the intervertebral foramen and affect the stability of the reconstructed vertebral body."

13.12 Source Citation: Lukina et al. 2015[50]

Study Design: Single-center retrospective case-control study of patients with scoliosis treated with the sliding growth guidance instrumentation LSZ-4D (Conmet, Moscow, Russia). Control patients had not implanted devices.

Device or Material: sliding rod device made of Ti alloy (Ti6Al4V)

Contact Duration: 6 ± 2 years

Dose: single device

Frequency/Duration: single administration

Response: Ti, Al and V metal ions in the whole blood

Patient characteristics (gender, mean age): Treated group - 3 males, 22 females, average age at primary surgery for scoliosis treatment was 11.4±1.2 years

Number per Group: 25 patients with high growth potential treated with device, 13 patient control group with no implants.

Observed adverse effects:

"The median values of Ti, aluminum and vanadium in the whole blood of patients from the control group without implants was 30 ppb (range 30- 40) for Ti, 30 ppb (range 20-40) for aluminum and 0.08 ppb (range 0.06- 0.1) for vanadium. Patients with implanted LSZ-4D sliding devices had much higher ion levels with 85 ppb (range 28-180) of Ti, 30 ppb (18-150) of aluminum and 0.3 ppb (range 0.2-0.5) of vanadium. Statistical analysis using Mann-Whitney non-parametric test revealed statistically significant ($p=0.0001$) raised levels of Ti and vanadium (2.8 and 4 times respectively) in the whole blood of patients with implanted LSZ-4D devices."

Timing of adverse effects: 6 ± 2 years follow-up

Factors that predict response: "Since the biocompatibility of Ti is much higher compared to Co and Cr, which are present in CoCr and stainless steels, it might be hypothesized that the optimization of Ti instrumentation design and improvements in its wear resistance by the application of biocompatible wear resistant coatings would certainly be beneficial."

"Our findings indicate the importance of using wear resistance materials for sliding and extending instrumentation which is used for the treatment of scoliosis in immature patients."

13.13 Source Citation: Ipach et al. 2012[51]

Study Design: Nonrandomized comparison study of patients with Ti spinal implants and patients with no implants. Implanted patients: degenerative lumbar scoliosis, lumbar spondylolisthesis, lumbar spinal canal stenosis.

Device or Material: instrumented spinal fusion with Muenster-Anterior/Posterior-Doublerod System (Schäfer. Micromed, Schorndorf, Germany) and the Expedium (Depuy-spine Raynham, Massachusetts, USA) systems containing Ti

Contact Duration: up to 12 months

Dose: single device

Frequency/Duration: single administration

Response: whole blood Ti levels

Patient characteristics (gender, mean age): Ti implant 47 ± 22 years (range 16 - 85 years) 3 male and 12 female; control 33.2 years, 6 male and 10 female

Number per Group: Ti implant n = 15, control n = 16

Observed adverse effects: "No statistically significant increase in the Ti level was seen 12 months after surgery (mean difference: -7.2 µg/l, 95% CI: -26.9 to 12.5 µg/l, p = 0.446). By observing the individual Ti levels, 4 out of 15 patients demonstrated an increase in Ti levels 12 months after surgery."

Timing of adverse effects: first, second and 10th day postoperatively, as well as 3 and 12 months after surgery.

Factors that predict response: No explanation for low Ti blood levels or why 4 patients had high Ti blood levels.

AIS: adolescent idiopathic scoliosis; CI: confidence interval; CoCr: cobalt–chromium; CrI: credible interval; ELISA: enzyme-linked immunosorbent assay; IL: interleukin; MCGR: magnetically controlled growing rods; MD: mean difference; nHA: nanohydroxyapatite; NR: not reported; ODI: Oswestry Disability Index; OR: odds ratio; PEEK: polyetheretherketone; PLIF: posterior lumbar interbody fusion; RCT: randomized controlled trial; RR: relative risk; SMD: standardized mean difference; SR: systematic review; SS: stainless steel; TGR: traditional growing rods; Ti: titanium; TNF-a: tumor necrosis factor alpha; VAS: visual analog scale.

ACDF: anterior cervical discectomy and fusion; CT: computed tomography; LLIF: lateral lumbar interbody fusion; TiPEEK: titanium coated PEEK;

Table 14: Orthopedic – fixation, other (rod, screw, plate) - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

14.1 Source Citation: Choi et al. 2021[52]

Study Design: SR and meta-analysis on surgical stabilization of rib fractures (SSRF) after traumatic rib fractures to investigate hardware failure. Included 24 observational studies: 17 Ti studies (n = 2,089) with 86 hardware failures, remaining 7 studies used absorbable or stainless-steel fixation (n = 315) with 15 hardware failures.

Device or Material: Ti, stainless steel, and absorbable fixation

Contact Duration: follow-up range was 3 months to 4 years

Dose: single device

Frequency/Duration: single administration

Response: hardware failure

Patient characteristics (gender, mean age): Most study populations were middle-aged or older adults, with mean or median ages between 43 years and 63 years.

Number per Group: range from 10 to 1224

Observed adverse effects: Among patients who experienced SSRF hardware failure (n = 101), Ti plates were the most commonly used stabilization hardware (n = 86/101 [85%]). A majority of patients with hardware failure had undergone SSRF for acute fractures (n = 77/101 [76%]) at mean or median between 2 days and 5 days after injury.

Pooled prevalence of hardware failure was 4(3-7)%. Meta-regression showed fracture acuity was a significant moderator (P = 0.002) but metal plate was not (P = 0.23). Subgroup hardware failure prevalence ranged from 2(1-4)% [metal plate] and 7(3-12)% [not metal plate] among patients with acute fractures to 25(12-42)% [metal plate] and 12(2-29)% [not metal plate] among patients with chronic fractures. Studies had moderate to large heterogeneity with I^2 = 53(21-86)% and Cochrane's Q statistic = 49 (P = 0.001).

Timing of adverse effects: The timing of failure after surgery was highly variable: mechanical defects 1 day to 6 months; pain/discomfort and rib nonunion: ≥3 months).

Factors that predict response: Low quality observational studies with very high heterogeneity. "Insufficient individual patient data precluded meaningfully characterizing the where and why of hardware failures."

14.2 Source Citation: Hoogervorst et al. 2020[53]

Study Design: SR and meta-analysis of intramedullary fixation devices for displaced midshaft clavicle fractures. Included 67 studies (62 used in meta-analysis):

Device or Material:

Ti Elastic Nail (TEN) (Depuy Synthes, Warsaw, IN, USA or Stryker, Kalamazoo, MI, USA) the 43 studies that were incorporated in the analysis were comprised of seven level I, eight level II, eleven level III, and seventeen level IV studies.

Rockwood and Hagie clavicle pins: 10 studies concerning the Rockwood clavicle pin (DePuy, Warsaw, IN, USA) and Hagie pin (Smith & Nephew, Memphis, TN, USA) were identified and included in the analysis (two level I, two level III, and six level IV studies). These devices were evaluated together since they are essentially the same. They are made of stainless steel.

Sonoma CRx (Arthrex, Naples, FL, USA) for which 6 studies (three level I, one level II, one level III, and one level IV) were identified. Sonoma CRx is made of stainless steel. Less frequently described intramedullary fixation devices were the threaded Ti elastic nails (Kang Li Min Medical Devices Co. Ltd., Tianjin, China), the Knowles pin (Zimmer Biomet, Warshaw, IN, USA), and a study describing a second-generation Ti elastic nail (Puwei Medical Appliances Inc., Shanghai, China).

Contact Duration:

TEN remained in place from 3 months to 8.8 months.

Dose: single device

Frequency/Duration: single administration

Response: hardware failure, hardware irritation**,** malunion, protrusion/telescoping/migration

Patient characteristics (gender, mean age): Not reported

Number per Group: TEN: n = 1,772. Rockwood and Hagie clavicle pins: n = 337. Sonoma CRx: n = 191.

Observed adverse effects:

TEN: Data from 43 studies were pooled in the meta-analysis for evaluating complications rates using the TEN. The two most common complications reported, protrusion/telescoping/migration and hardware irritation, are implant related. The pooled incidence was 12% (95%CI 8–18 in 1105 clavicles) and 20% (95%CI 14–26 in 1273 clavicles), respectively. Malunion after surgical management by means of a TEN was reported in 7% (95%CI 4–11 in 193 clavicles) and hardware failure was 3% (95%CI 2–5 in 800 clavicles). Incidence of a nonunion using a TEN was 3% (95%CI 2–4 in 1436 clavicles). The confidence in these estimates from the meta-analyses according to GRADE ranged from moderate to very low.

Rockwood and Hagie clavicle pins: "The highest pooled incidences were found for complications hardware irritation (22%, 95%CI 13–35 in 253 clavicles), and soft tissue problems (9%, 95%CI 6–13 in 207 clavicles). The pooled incidence of hardware failure and nonunion was 6% (95%CI 3–10 in 216 clavicles) and 3% (95%CI 1–8 in 337 clavicles), respectively. The confidence in the estimates from the meta-analyses according to GRADE ranged between low and very low."

Sonoma CRx: "The pooled incidence for cosmetic dissatisfaction was highest at 6% (95%CI 2–17 in 92 clavicles), followed by of hardware failure (4%; 95%CI 2–8 in 191 clavicles). No reports of non-union using the Sonoma CRx were reported. The confidence in the estimates from the meta-analyses according to GRADE concerning the functional outcomes were considered moderate. Although the results were consistent, the data originate from very limited group of authors. The confidence in the other meta-analyses according to GRADE were low to very low."

Timing of adverse effects: Data were collected at 12 months.

Factors that predict response: "For the TEN, hardware irritation, protrusion, telescoping and migration, are major contributors to the total complication rate. The explanation for this finding may be that the TEN re-aligns but does not fixate in both fracture elements of the DMCF. These TEN-specific complications lead to infection, soft-tissue problems, pain, early reinterventions (removal or additional cutting of the nail) and loss of reduction with subsequent secondary shortening. When using the Rockwood/Hagie Pin, pooled incidence of hardware irritation was 22% (95%CI 13–35). This may be explained by the two bulky nuts at the posterolateral aspect of the clavicle where the pin is inserted and has been reported to be an important disadvantage of the implant."

14.3 Source Citation: Shumborski et al. 2019[54]

Study Design: RCT of anterior cruciate ligament reconstruction

Device or Material: PEEK compared with Ti interference screws

Contact Duration: 2-year follow-up

Dose: Each patient received 2 screws, one at each end of the hamstring autograft.

Frequency/Duration: single administration

Response: cyst formation, effusion, synovitis

Patient characteristics (gender, mean age): PEEK mean 33.3 years, 44.6% female; Ti 35.3 years, 44.1% female

Number per Group: PEEK n = 68, Ti n = 65. At two years, 64 (94%) in the PEEK group and 51 (90%) in the Ti group had complete subjective and objective evaluation.

Observed adverse effects: There were 4 ACL graft ruptures over the two-year period in the Ti group, and none in the PEEK group (p=0.054). The graft ruptures occurred at 3-, 5-, 9-, and 24-months post-surgery, and the respective causes were fall whilst intoxicated, soccer, soccer, and fall from a ladder.

12-month MRI findings – Effusion: PEEK 67%, Ti 76%. Synovitis: PEEK 10%, Ti 22%. Cyst/ganglion tibia: PEEK 13%, Ti 18%. Cyst/ganglion femur: PEEK 0%, Ti 15%.

Timing of adverse effects: up to 2 years from surgery

Factors that predict response: Study results indicate equivalence between PEEK and Ti interference screws when used for ACL reconstruction. PEEK screws did not show any difference in rates of synovitis, edema or cyst formation on MRI compared to Ti screws at 12 months. Compared to bioabsorbable screws, PEEK does not cause cysts or inflammatory change due to degradation, showing comparable results to Ti.

14.4 Source Citation: Sun et al. 2014[55]

Study Design: RCT comparing absorbable and metallic screws for distal tibiofibular syndesmosis.

Device or Material: Poly-L-Lactic acid (PLLA) (Takiron, Tokyo, Japan) and a Ti alloy (Synthes, West Chester, Pennsylvania) screws.

Contact Duration: Ti screw was removed after 8 weeks. PLLA hydrolyzes slowly, losing strength over 9 months.

Dose: single device

Frequency/Duration: single administration

Response: foreign body reaction

Patient characteristics (gender, mean age): PLLA mean 39.7 years, 62% male; Ti screw mean 37.1 years, 55% male.

Number per Group: PLLA n = 86, Ti n = 82

Observed adverse effects:

Complications – total: PLLA 33.7%, Ti 4.9%; mild foreign body reaction: PLLA 69.2% of all complications, Ti 100% of all complications; moderate foreign body reaction: PLLA 30.8%, Ti 0%; heterotopic ossification: PLLA 3.5%, Ti 0%.

Timing of adverse effects: mean follow-up 55.8 months, range 48 to 66 months. Three patients in the PLLA group and none in the metallic group had heterotopic ossification (p = 0.246). This was seen on radiographs at nine months post-operatively in one patient and at one year in two patients.

Factors that predict response: Primarily discussed PLLA increased foreign body reactions.

14.5 Source Citation: Windhagen et al. 2013[56]

Study Design: RCT comparing biodegradable magnesium-based screw with Ti screw for hallux valgus fixation.

Device or Material: MAGNEZIX compression screw (Syntellix AG, Hannover, Germany), aluminum-free magnesium alloy and standard Ti screws (Fracture compressing screw, Königsee Implantate GmbH, Am Sand 4, 07426 Allendorf, Germany).

Contact Duration: patients were followed for 6 months

Dose: single device

Frequency/Duration: single administration

Response: superficial wounds

Patient characteristics (gender, mean age): Magnesium screw: 11 female, 2 male, mean 57.2 years; Ti screw 13 women, 0 male, mean 49.9 years.

Number per Group: Magnesium screw n = 13, Ti screw n = 13.

Observed adverse effects: No foreign body reactions, or osteolysis were detected. The groups were not significantly different in terms of radiographic or laboratory results.

Complications did not occur in any patients during the follow-up period, except for 3 superficial wounds.

Timing of adverse effects: Patients were observed for 6 months.

Factors that predict response: NR

Systemic Response/Toxicity

14.6 Source Citation: Windhagen et al. 2013[56]

Study Design: RCT comparing biodegradable magnesium-based screw with Ti screw for hallux valgus fixation.

Device or Material: MAGNEZIX compression screw (Syntellix AG, Hannover, Germany), aluminum-free magnesium alloy and standard Ti screws (Fracture compressing screw, Königsee Implantate GmbH, Am Sand 4, 07426 Allendorf, Germany).

Contact Duration: patients were followed for 6 months

Dose: single device

Frequency/Duration: single administration

Response: laboratory analyses for kidney and liver function.

Patient characteristics (gender, mean age): Magnesium screw: 11 female, 2 male, mean 57.2 years; Ti screw 13 women, 0 male, mean 49.9 years.

Number per Group: Magnesium screw n = 13, Ti screw n = 13.

Observed adverse effects: No systemic inflammatory reactions were detected. The groups were not significantly different in terms of radiographic or laboratory results.

Timing of adverse effects: Patients were observed for 6 months.

Factors that predict response: NR

Table 15: Orthopedic – knee prosthesis - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

15.1 Source Citation: Kim et al. 2021[58]

Study Design: RCT, bilateral primary total knee arthroplasty (TKA) with titanium (Ti) implant in one knee and cobalt chromium (CoCr) implant in the contralateral knee. Allocation of treatment and outcome assessment were blinded.

Device or Material: Buechel-Pappas Ti Rotating Platform TKA (Endotec), LCS-RP CoCr TKA (non-Ti, DePuy Synthes).

Contact Duration: Mean follow-up of 5.3 years (1 to 7 years).

Dose: Single device.

Frequency/Duration: Single administration per knee.

Response: Radiolucent line (RLL) as an indicator of loosening or osteolysis.

Patient characteristics (gender, mean age): 94.4% female, 69.9±6.0 years.

Number per Group: 89 knees in each group.

Observed adverse effects: 2 knees in the CoCr group showed instability after TKA. Two knees in the CoCr group underwent revision surgery because of medial tibial bone resorption and osteolysis. The rate of observing RLL was 9% in the Ti group and 19% in the CoCr group ($P<0.05$), but no case of RLL progression to loosening was found. There were no significant differences in the degree of medial bone loss.

There was no recording of metal hypersensitivity in either group during the follow-up period.

Timing of adverse effects: CoCr group instability at 4 weeks and 5 months post-operatively.

Factors that predict response: NR.

15.2 Source Citation: Kim et al. 2018[57]

Study Design: SR and meta-analysis comparing the outcomes of revision total knee arthroplasty (TKA) performed using a tantalum cone versus a titanium sleeve. Nineteen articles were included in the final analysis, 6 studies involving 318 patients with 326 knees receiving titanium-sleeve revision TKA. 1 RCT was included in the analysis but did not involve Ti-sleeves. The remaining studies were 17 case series and 1 cohort study.

Device or Material: Ti metaphyseal sleeve revision TKA (Zimmer), tantalum trabecular metal cone revision TKA (non-Ti, DePuy Synthes).

Contact Duration: Follow-up of at least 2 years (24 to 62 months in the Ti-sleeve group, 24 to 106 months in the tantalum-cone group).

Dose: single device.

Frequency/Duration: Single administration per knee.

Response: Aseptic loosening, fracture, end-of-stem pain.

Patient characteristics (gender, mean age): Ti-sleeve group: 37% to 58% male, 48 to 92 years; tantalum-cone group: 29% to 69% male, 32 to 91 years.

Number per Group: Ti-sleeve group, n=326; tantalum-cone group, n=449.

Observed adverse effects: Aseptic loosening was seen in 3 cases in the Ti-sleeve group and 7 cases in the tantalum-sleeve group. Intraoperative fracture was reported in 2 cases in the Ti-sleeve group and 4 cases in the tantalum-cone group. Periprosthetic fracture was seen in 0 cases in the Ti-sleeve group and 10 cases in the tantalum-cone group. One Ti-sleeve study reported end-of-stem pain in 7 patients (23.3%). No complications were reported in 1 Ti-sleeve study and 2 tantalum-cone studies.

Timing of adverse effects: Intraoperative fracture occurred immediately; pain, periprosthetic fracture (tantalum), and loosening were seen during follow-up.

Factors that predict response: Small diameter stems were predictive factor of stem pain in Ti-sleeve revision TKA.

15.3 Source Citation: Harwin et al. 2017[60]

Study Design: Single center retrospective comparison study of patients undergoing a primary cementless posterior stabilized TKA.

Device or Material: Highly porous titanium-coated (Tritanium Triathlon, Stryker) versus periapatite (PA)-coated (non-Ti, cobalt chrome [CoCr] Triathlon, Stryker) cementless total knee arthroplasty (TKA).

Contact Duration: Follow-up of 4.4 years.

Dose: single device.

Frequency/Duration: Single administration per knee.

Response: Aseptic failure (pain, instability).

Patient characteristics (gender, mean age): Ti-coated group: 69% female, 66 years; PA-coated group: 70% female, 57 years.

Number per Group: Ti-coated group, n=219; PA-coated group, n=805.

Observed adverse effects: All-cause implant survivorship was 99.5% (05% CI, 92.7%-99.9%) in the Ti-coated group, and 99.5% (85% CI, 97.9-99.9%) in the PA-coated group. The revision rate PA-coated (6 [0.8%]) and Ti-coated (2 [0.2%]; P=0.936). There were 2 aseptic failures (0.9%) in the Ti-coated group: pain and instability at one year and 3 aseptic failures (0.3%) in the PA-coated group: pain and instability at six weeks, arthrofibrosis at four months, and patellar dislodgement at six weeks. There were 5 nonfailure complications (2.3%) in the TI-coated group and 18 (2.2%) in the PA-coated group. There were no progressive radiolucencies or osteolysis on radiographic evaluation at the final follow-up.

Timing of adverse effects: Pain and instability at 1 year follow-up.

Factors that predict response: NR.

15.4 Source Citation: Skou et al. 2015[59]

Study Design: Multicenter RCT of patients with moderate-to-severe knee osteoarthritis comparing TKA to no surgery. Blinding was not possible.

Device or Material: NexGen (Ti, Zimmer) total knee replacement (TKR) surgical intervention followed by nonsurgical treatment versus nonsurgical treatment alone.

Contact Duration: Follow-up of 12.1 months.

Dose: Single device.

Frequency/Duration: Single administration per knee.

Response: deep vein thrombosis (DVT), fracture, stiffness

Patient characteristics (gender, mean age): Ti-group, 60% female, 67.0±8.7 years; nonsurgical group, 64% female, 65.8±8.7 years.

Number per Group: 50 patients per group.

Observed adverse effects: 3 patients in the Ti-group experienced knee stiffness requiring brisement force (i.e., manipulation of the knee while the patient is under anesthesia to improve range of motion) compared to 1 patient in the nonsurgical group.

3 patients in the Ti-group experienced DVT requiring anticoagulation compared to 0 patients in the nonsurgical group. 1 patient in the Ti-group experienced supracondylar femur fracture compared to 0 patients in the nonsurgical group.

Timing of adverse effects: Before 12-month follow-up.

Factors that predict response: Serious adverse events were more likely to occur after TKR had been performed than before.

Table 6: Orthopedic – hip prosthesis - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

16.1 Source Citation: Buttaro et al. 2021[62]

Study Design: Nonrandomized comparative study.

Device or Material: MiniHip stem (Ti, Corin) versus Collum Femoris Preserving (CFP) short stem (non-Ti, Waldemar Link GmbH) for partial Collum THA .

Contact Duration: Follow-up of 72 months.

Dose: single device.

Frequency/Duration: Single administration per hip.

Response: Fracture, hypertrophy, loosening, resorption, revision, subsidence.

Patient characteristics (gender, mean age): 79.5% male, 47±8.92 years.

Number per Group: MiniHip, n=101; CFP, n=89.

Observed adverse effects: There were 4 patients in the MiniHip group that showed an initial subsidence (<2mm), compared to 0 patients in the CFP group (p=0.643). There were 0 patients in the MiniHip group with cases of proximal femoral osteolysis compared to 2 patients in the CFP group (p=0.834). Median femoral neck resorption was 1mm in the MiniHip group, compared to 0mm in the CFP group (p=0.06). Median lateral cortex hypertrophy was 0mm for both cohorts (p=0.306), whereas cervical hypertrophy was observed in 3 MiniHip cases compared to 4 CFP cases (p=0.708).
No significant differences were observed in terms of loosening and instability. There were 2 aseptic acetabular component loosening treated with revision in the MiniHip group, compared to 0 cases in the CFP group. There were 0 reports of septic loosening in the MiniHip group, compared to 1 case in the CFP group, which was treated with revision THA. There were no cases of instability or residual thigh pain in either cohort. There were 3 IPPFs in the MiniHip group, compared to 4 IPPFs in the CFP group (OR 3.23; 95% CI 0.250-42.034, p=0.368).

Timing of adverse effects: IPPFs were intraoperative; median follow-up of 72 months.

Factors that predict response: Prior acetabular fractures were associated with a greater risk of IPPF than either implant design (OR 66.85, 95% CI 1.142-3911, p=0.043).

16.2 Source Citation: Chu et al. 2018[61]

Study Design: SR of 5 studies (1 RCT, 4 nonrandomized comparative) in the relevant meta-analysis

Device or Material: Ti compared with tantalum acetabular components after THA

Ti devices:

- Ti acetabular components: Zimmer; Warsaw, Indiana
- A titanium fiber metal cup: Trilogy1 Acetabular Hip System; Zimmer
- Porous-coated titanium cups
- Porous-coated titanium-alloy: Elliptical
- Hemispherical HA-coated titanium acetabular cup: Stryker Orthopaedics, Mahwah, NJ

Tantalum devices:

- Ta acetabular components: Zimmer; Warsaw, Indiana
- Porous tantalum cup: Trabecular MetalTM Modular Acetabular System; Zimmer
- Porous tantalum: Trabecular Metal, Zimmer, Inc
- Porous tantalum: Hedrocel
- Elliptical tantalum acetabular cup: TM; Zimmer, Warsaw, IN

Contact Duration: up to 10 years

Dose: NR

Frequency/Duration:

Response: failure, gaps, instability

Patient characteristics (gender, mean age): 43% to 63% male, 54.6 to 72

Number per Group: 1,479 (841 Ti, 638 tantalum)

Observed adverse effects: Significantly higher instability (3 studies: OR = 0.454, 95% CI: 0.31 to 0.64; p<0.001) and failure rate (3 studies: OR = 0.44, 95% CI: 0.28 to 0.71; p=0.001) with Ti compared with tantalum acetabular implants. No significant difference was detected for incidence of gaps (3 studies: OR = 0.40, 95% CI: 0.07 to 2.21; p=0.29).

Timing of adverse effects: NR

Factors that predict response: "In our meta-analysis by incorporating all relevant data together, we detected that patients receiving titanium acetabular implants had significantly higher failure rate and instability rate than those receiving tantalum acetabular components." The authors suggested that Ti may degrade more than tantalum leading to more failures in patients receiving Ti implants.

16.3 Source Citation: Meuller et al. 2017[64]

Study Design: Nonrandomized comparative study.

Device or Material: Smooth or rough-blasted Ti Müller ARR versus stainless steel Müller ARR (both Zimmer) in revision THA.

Contact Duration: Up to 27 years (mean 10 years).

Dose: single device.

Frequency/Duration: Single administration per hip.

Response: Loosening, re-revision.

Patient characteristics (gender, mean age): 59% male, 72 years (31 to 91 years).

Number per Group: Ti ARR, total n=241 (smooth-blasted, n=101; 1st generation rough-blasted, n=26; 2nd generation rough-blasted, n=114); stainless steel ARR, n=18.

Observed adverse effects: 1 stainless steel, 5 smooth-blasted Ti, and 2 rough-blasted Ti ARRs were re-revised for aseptic loosening. No cups had to be revised for recurrent dislocations.

Timing of adverse effects: Aseptic loosening after mean 6.0 years (1.5 to 14 years).

Factors that predict response: NR.

16.4 Source Citation: Schnurr et al. 2017[63]

Study Design: Nonrandomized comparative study.

Device or Material: Metha (Aesculap) calcar-loading short stems: modular stem with Ti neck, modular stem with CoCr, non-Ti neck, monoblock (Ti) stems.

Contact Duration: Follow-up of 6 years (1 to 11 years).

Dose: single device.

Frequency/Duration: Single administration per hip.

Response: Fracture, hematoma, instability, loosening, ossification, perforation, revision.

Patient characteristics (gender, mean age): Patient sex NR, 59 years.

Number per Group: Modular Ti group, n=314; modular CoCr group, n=230; monoblock group, n=1,090.

Observed adverse effects: 15 modular Ti implants (4.4%) were affected by cone fractures while no cone fractures occurred with modular CoCr necks and monoblock Ti implants. The 7-year revision rate was 5.3% for modular Ti stems, 1.5% for monoblock Ti stems, and 1.8% for CoCr stems. The rate of aseptic loosening did not differ between the three stem types occurring in 6 monoblock Ti patients (0.5%), 2 modular Ti patients (0.6%), and modular CoCr patients (0.8%).
Hematoma occurred in 3 monoblock Ti patients (0.3%), and 1 modular Ti and CoCr patient each (0.3% each). Instability occurred in 2 monoblock Ti patients (0.2%), 2 modular Ti patients (0.6%) and 1 modular CoCr patient (0.4%). Ossification occurred in 0 monoblock Ti patients, 1 modular Ti patient (0.3%), and 2 CoCr patients (0.8%). Femoral fracture occurred in 5 monoblock Ti patients (0.4%), 0 modular Ti patients, and 1 modular CoCr patient (0.4%). Femoral perforation occurred in 1 modular Ti patient only (0.3%).

Timing of adverse effects: 7-year revision rates provided; 50% of aseptic stem loosening occurred in the first year after operation, the remaining 5 cases occurring after 1.5 to 5 years; Ti-neck fractures occurred a mean 4 years (2 to 9 years) after the original operation.

Factors that predict response: From 2004 to 2006, only the modular Ti neck adapters were available, but these were replaced by modular CoCr necks in December 2006 after a series of adapter breakages. The manufacturer reported 68 Ti modular cone adapter fractures after approximately 5,000 implantations (1%). Those failures occurred predominantly in heavy male patients after an average period of 2 years.

16.5 Source Citation: Tokarski et al. 2015[65]

Study Design: Nonrandomized comparative study.

Device or Material: Revision THA acetabular revisions using either a Ti (various manufacturers) or tantalum (non-Ti, Zimmer) component.

Contact Duration: Follow-up of 40.2 months (3 months to 13.1 years).

Dose: single device.

Frequency/Duration: Single administration per hip.

Response: Aseptic failure including instability, loosening, and periprosthetic fracture.

Patient characteristics (gender, mean age): 56.4% female, 65.1 years; 43.6% male, 62.3 years.

Number per Group: Ti group, n=536; tantalum group, n=454.

Observed adverse effects: Failure of the acetabular component had occurred in 73 hips (7.1%) with 26 aseptic failures in the Ti group and 7 aseptic failures in the tantalum group. The causes of failure were aseptic loosening (30), instability (5), and periprosthetic fracture (1). The overall incidence of failure was significantly lower in hips with tantalum acetabular components which were revised at 4.4% compared with 9.9% for Ti components ($p<0.001$).

Timing of adverse effects: Failure noted at latest follow-up.

Factors that predict response: Multivariate analysis revealed that young age (OR 1.04; 95% CI 1.09, 1.53; p=0.029), Charlson Comorbidity Index per point increase (OR 1.3; 95% CI 1.09, 1.53; p=0.003), the use of acetabular bone graft or augment (OR 1.9; 95% CI 1.13, 3.30; p=0.016), and Ti acetabular components (OR 2.7; 95% CI 1.56, 4.66; p<0.001) were independent factors for subsequent failure of the acetabular component.

AAR: acetabular reinforcement ring; CI: confidence interval; CoCr: cobalt chromium; IPPF: intraoperative periprosthetic fractures; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; SR: systematic review; THA: total hip arthroplasty; Ti: titanium

Table 17: Orthopedic –shoulder prosthesis - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

17.1 Source Citation: Burden et al. 2021[66]

Study Design: SR and meta-analysis that asks which patterns of complications are associated with the three reverse total shoulder arthroplasty (RTSA) prosthetic designs in patients undergoing RTSA for the management of cuff tear arthropathy, massive cuff tear, osteoarthritis, and rheumatoid arthritis. 42 articles met inclusion criteria, 37 (0 RCTs) of which involve RTSAs designs with titanium shoulder implant components.

Device or Material:
Medial glenoid/medial humerus (MGMH, all contain Ti): Delta III (DePuy International), Delta Xtend (DePuy-Johnson & Johnson International), Systema Multiplana Randelli (SMR, LimaCorporate), Aequalis (Tornier), Global Unite (DePuy International).
Medial glenoid/lateral humerus (MGLH, all contain Ti): Ascend Flex (Wright Medical), Zimmer Comprehensive (Zimmer Biomet), Zimmer TM (Zimmer Biomet), Equinoxe (Exactech).
Lateral glenoid/medial humerus (LGMH, non-Ti): Arrow (FH Orthopedics), DJO (DJO Surgical).

Contact Duration: Follow-up of 34.2 to 41 months.

Dose: NR.

Frequency/Duration: Single administration per shoulder.

Response: Dislocation, failure, fracture, heterotopic ossification, loosening, nerve injury, revision, scapular spur, stress shielding.

Patient characteristics (gender, mean age): NR.

Number per Group: MGMH, n=1,590 patients; MGLH, n=995 patients; LGMH, n=687 patients.

Observed adverse effects:
Scapula notching was observed in 47% of MGMH patients, 17% of MGLH patients, and 17% of LGMH patients.
Dislocation was observed in 5.2% of MGMH patients, 0.72% of MGLH patients, and 2.5% of LGMH patients.
Nerve injury was observed in 1.7% of MGMH patients, 0.5% of MGLH patients, and 2.3% of LGMH patients.
Glenoid component loosening was observed in 7% of MGMH patients, 1.2% of MGLH patients, and 2.5% of LGMH patients.
Humeral component loosening was observed in 10% of MGMH patients, 1.2% of MGLH patients, and 1.6% of LGMH patients.
Humeral stress shielding was observed in 19% of MGMH patients, 7.8% of MGLH patients, and was not reported in any LGMH studies.
Periprosthetic humeral fracture was observed in 2.6% of MGMH patients, 1.5% of MGLH patients, and 1.7% of LGMH patients.
Intraoperative glenoid fracture was observed in 3.4% of MGMH patients, 3.8% of MGLH patients, and 2.5% of LGMH patients.
Scapula fracture was observed in 4.8% of MGMH patients, 1.6% of MGLH patients, and 2.7% of LGMH patients.
Implant failure was observed in 3.9% of MGMH patients, 0.89% of MGLH patients, and 5.2% of LGMH patients.
Heterotopic ossification was observed in 24.8% of MGMH patients, was not reported in any MGLH studies, and 1.6% of LGMH patients.
Scapula spur was observed in 27.7% of MGMH patients, was not reported in any MGLH studies, and 18% of LGMH patients.
Failed graft incorporation was not reported in any MGMH or MGLH studies, and was observed in 6.4% of LGMH patients.
Revision was observed in 5.5% of MGMH patients, 2.5% of MGLH patients, and 6.5% of LGMH patients.

Timing of adverse effects: Follow-up of 34.2 to 41 months.

Factors that predict response: There was no significant difference in revision rates between implant design philosophies.

17.2 Source Citation: Suroto et al. 2021[67]

Study Design: SR and meta-analysis. Six studies (1 RCT) met inclusion criteria, analyzing 324 patients.

Device or Material: Reverse total shoulder arthroplasty (RTSA, all contain titanium components) including SMR Reverse modular shoulder system (Lima Corporate), Delta Xtend Reverse Shoulder System (DePuy Synthes, J&J), Trabecular Metal Reverse (Zimmer), Aequalis Reversed Fracture (Tornier), and Promos Reverse Prosthesis (Smith & Nephew) versus open reduction and internal fixation (ORIF, all containing Ti components) including Anatomical contoured locking proximal humeral plate (DePuy Synthes) and PHILOS plate (DePuy Synthes).

Contact Duration: Follow-up NR.

Dose: NR.

Frequency/Duration: Single administration per shoulder.

Response: Avascular necrosis (AVN), fracture, hematoma, impingement, instability, loss of reduction, nerve injury, nonunion, pain, resorption, revision, rotator cuff rupture, scapular notching, scapular spur, screw penetration, tuberosity lysis.

Patient characteristics (gender, mean age): RTSA group, 89.86% female; ORIF group, 85.71% female. 44 to 91 years.

Number per Group: RTSA group, n=165; ORIF group, n=159.

Observed adverse effects: RTSA resulted in significantly more complication events in comparison to ORIF (32.73% versus 27.04%, risk ratio [RR] 1.42; 95% CI[1.02,1.98, p=0.04, I^2=44%). The most frequent complications were tuberosity lysis/resorption (15/54) and scapular notching (13/54) in the RTSA group, while in the ORIF group, the most common was AVN (17/43). Revision surgery rates were significantly lower in RTSA compared to ORIF (5.45% versus 14.47%, RR 0.37; 95% CI [0.16,0.85], p=0.02, I^2 = 0%). Moreover, the revision surgery in RTSA was mostly component exchange (5/9), while in ORIF it was conversion to RTSA (10/23).
Additional complications: 5 patients (3.0%) in the RTSA group experienced dislocation compared to 7 patients (4.4%) in the ORIF group.
13 patients (7.8%) in the RTSA group experienced resorption of the tuberosities compared to 3 patients (1.9%) in the ORIF group.
2 patients (1.2%) in the RTSA group experienced nerve injury compared to 1 patient (0.6%) in the ORIF group.
1 patient (0.6%) in the RTSA group experienced complex regional pain syndrome.
3 patients (1.8%) in the RTSA group experienced periprosthetic fracture.
1 patient (0.6%) in the RTSA group experienced perioperative glenoid fracture.
3 patients (1.8%) in the RTSA group experienced instability.
1 patient (0.6%) in the RTSA group experienced scapular spur.
1 patient (0.6%) in the RTSA group experienced hematoma.
1 patient (0.6%) in the ORIF group experienced arthrofibrosis followed by AVN in 2 years.
2 patients (1.3%) in the ORIF group experienced screw penetration.
3 patients (1.9%) in the ORIF group experienced nonunion.
1 patient (0.6%) in the ORIF group experienced fracture distal to the plate.
1 patient (0.6%) in the ORIF group experienced rotator cuff rupture.
3 patients (1.9%) in the ORIF group experienced loss of reduction.
4 patients (2.5%) in the ORIF group experienced subacromial impingement.

Timing of adverse effects: In one ORIF case, AVN followed arthrofibrosis by 2 years.

Factors that predict response: The patients' risk of developing complications were significantly higher (42%) following RTSA compared to ORIF. However, the confounding factor here is the follow-up time

and prosthesis design (e.g., scapular notching is related to prosthesis design with a Grammont design (used here) resulting in more notching than modern designs). RTSA significantly reduced the risk of revision surgery by 63% compared to ORIF.

Table 18: Orthopedic – disc, sacroiliac, finger prosthesis - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

18.1 Source Citation: Dengler et al. 2017[69]

Study Design: RCT.

Device or Material: iFuse Implant System (SI-BONE, Inc.) triangular titanium implants for sacroiliac joint fusion versus conservative management (CM).

Contact Duration: Follow-up of 21.5 months.

Dose: NR.

Frequency/Duration: 2 to 4 implants placed per iFuse patient.

Response: Hematoma, loosening, malposition, pain.

Patient characteristics (gender, mean age): 72.8% female, 48.1 years.

Number per Group: iFuse group, n=52; CM group, n=51.

Observed adverse effects: Within 6 months of initial treatment, there were 35 reported adverse events, 17 per group. By month 6, the mean number of events per patient was 0.33 (P=0.9549). At all reported events over mean follow-up of 21.5 months there were 25 events rated severe in the iFuse group and 24 in the CM group, of which most were unrelated to the device or procedure.
Device or procedure-related events: 2 patients in the iFuse group experienced recurrent (~1 year) joint pain attributed to device loosening in the sacrum after a fall; one patient had new onset leg pain postoperatively related to implant malposition; and one patient had a postoperative hematoma. In the CM group, one patient had joint pain attributed to device loosening after a crossover procedure and one patient had hematoma after crossover procedure; note that 21 (43%) CM patients underwent crossover after a 6-month period.

Timing of adverse effects: Adverse events within 6 months of initial treatment; recurrent sacroiliac joint pain at 1 year.

Factors that predict response: Pain may be attributed to device loosening or malposition.

18.2 Source Citation: Aragones et al. 2015[68]

Study Design: SR and meta-analysis to contrast the clinical and radiologic outcomes and adverse events of anterior cervical discectomy and fusion (ACDF) with those of a single cervical disc arthroplasty design, the polyurethane on titanium unconstrained cervical disc (PTUCD). This is a SR of RCTs with evidence level I-II reporting clinical outcomes. 10 RCTs met inclusion criteria for a total of 1,101 patients, 562 of whom received PTUCD.

Device or Material: Bryan Cervical Disc (Ti, Medtronic) versus ACDF.

Contact Duration: Follow-up time of 30.9 months.

Dose: NR.

Frequency/Duration: Single administration per affected cervical disc.

Response: Calcification, deep vein thrombosis (DVT), dysphagia, explantation/failure, heterotopic ossification, pain, pseudarthrosis, reoperation, vascular complications.

Patient characteristics (gender, mean age): 37.5% to 63.8% male. PTUCD group, 43 years; ACDF group, 47 years.

Number per Group: PTUCD group, n=562; ACDF group, n=530.

Observed adverse effects: Anterior longitudinal ligament calcification and heterotopic ossifications were described in 7 trials including a total of 438 patients (221 in PTUCD group and 217 in ACDF group). The pooled results showed that these events had no statistically significant difference between techniques (OR 1.31; 95% CI 0.63, 2.70; p=0.47; I^2=44%), though there was a lower incidence in the PTUCD group (14.5%) compared with the ACDF group (26.3%).

7 trials reported the number of reoperations in a total of 881 patients. In the PTUCD group, there were 24 reoperations (5.3%) and 36 in the ACDF group (8.4%). Although more frequent in the ACDF patients, the difference was not statistically significant (OR 0.61; 95% CI 0.36, 1.03; p=0.06).
7 studies reported information on adverse events in 778 total patients. Pooled results show that there was statistical difference between techniques (OR 0.55; 95% CI 0.29, 1.01; p=0.05). There was a lower incidence in the PTUCD group (3.9%) compared to the ACDF group (7.3%). Adverse events included: device failures or explantations (PTUCD 1.2%, ACDF 3.6%), pseudarthrosis (PTUCD 4.8%, ACDF 6.1%), DVT (PTUCD 2.8%, ACDF 0%), vascular complications (PTUCD 1.0%, ACDF 0%), neck and arm pain (PTUCD 1.5%, ACDF 2.3%), neurologic deficits or complications (PTUCD 0%, ACDF 0.7%), and dysphagia (PTUCD 3.2%, ACDF 9.0%).

Timing of adverse effects: Mean follow-up of 30.9 months.

Factors that predict response: NR.

18.3 Source Citation: Polly et al. 2015[70]

Study Design: RCT.

Device or Material: iFuse Implant System (SI-BONE, Inc.) triangular titanium implants for sacroiliac joint fusion versus conservative management (CM).

Contact Duration: Follow-up of 24 months.

Dose: 99.3% of iFuse implants were 7mm in diameter.

Frequency/Duration: Three implants were placed in 93 iFuse patients (91.2%); 2 implants placed in 5 patients (4.9%), and four implants placed in 4 patients (3.9%).

Response: Fracture, impingement, malposition, pain, revision.

Patient characteristics (gender, mean age): Overall: 69.6% female, 51.3 years; iFuse group: 73.5% female, 50.2 years. CM group: 60.9% female, 53.8 years.

Number per Group: iFuse group, n=102; CM group, n=46.

Observed adverse effects: After 6-months, 79.5% of CM patients elected crossover treatment. In the iFuse group, 1 subject was a failure at the 6-month primary end point due to inadequate pain reduction and revision required for symptomatic implant malposition.
In the first 180 days after start of treatment, 178 adverse events were reported (129 in iFuse group, 49 in CM group). The mean number of events per subject was slightly higher in the iFuse group (1.3 versus 1.1 events; P=0.31). Over the first 12 months of follow-up, adverse event rates were 1.8 and 1.9 per subject in the iFuse and CM groups, respectively.
Two adverse events were rated as definitely related to the iFuse; one subject had implant-related impingement on a sacral nerve root requiring immediate revision; a second subject developed a hairline fracture of the ilium adjacent to the caudal-most implant, causing buttock pain 3 to 4 months after the procedure, possibly related to lifting a heavy object. A third subject developed contralateral sacroiliac joint pain, deemed related to the index-side implants as a result of a change in biomechanics related to the placement of the devices.
Three CM patients experienced increased back or sacroiliac joint pain after physical therapy, steroid injection or radiofrequency ablation, and another subject had flushing and shortness of breath associated with steroid injection. One CM subject had worsening sacroiliac joint pain related to postoperative rehabilitation after surgery.

Timing of adverse effects: Over 12 months of follow-up, leg and pelvic pain were the most common adverse events; one patient developed fracture and buttock pain 3 to 4 months after implantation.

Factors that predict response: NR.

18.4 Source Citation: Daecke et al. 2012[71]

Study Design: RCT.

Device or Material: Titanium-polyethylene implant (Ti, Small Bone Innovations), pyrocarbon implant (non-Ti, Ascension Orthopaedics Inc.), and silicone spacer (non-Ti, Wright Medical Technology Inc.) for surface replacement arthroplasty in proximal interphalangeal joint osteoarthritis.

Contact Duration: Follow-up time of 35±3 months.

Dose: NR.

Frequency/Duration: Ti group: 1 finger in nine patients, 2 fingers in four patients, 3 fingers in three patients.
Pyrocarbon group: 1 finger in seven patients, 2 fingers in four patients, 3 fingers in one patient.
Silicone group: 1 finger in fourteen patients, 2 fingers in two patients.

Response: Ankylosis, contracture, deformity, explantation, granuloma, loosening, ossification, subsidence.

Patient characteristics (gender, mean age): 81% female, 64.9±6.1 years.

Number per Group: Ti group, n=26; pyrocarbon group, n=19; silicone group, n=18.

Observed adverse effects: Sixteen explantations were necessary: 7 of 26 in the Ti group (27%) due to aseptic loosening or subsidence; 7 of 19 in the pyrocarbon group (39%) due to aseptic loosening, restricted range of motion, or dislocation; and 2 of 18 in the silicone group (11%) due to implant fracture. No statistically significant difference was revealed between the three groups concerning explantation frequency (p=0.16). In the Ti group only, 4 secondary surgical procedures without explantation were performed due to extension contracture (2 patients, one later explanted), swan neck deformity (1 patient), and granuloma (1 patient).

Overall complications included: implant subsidence (8 patients in the Ti group [31%], 6 patients in the pyrocarbon group [33%], and 0 patients in the silicone group); dislocation/subluxation (0 patients in the Ti and silicone groups, 3 patients in the pyrocarbon group [17%]); ossification development (10 patients in the Ti group [39%], 5 patients in the pyrocarbon group [28%], and 6 patients in the silicone group [33%]); ankylosis (2 patients in the Ti group [8%], 1 patient in the pyrocarbon group [6%], and 1 patient in the silicone group [6%]); swan neck deformity (5 patients in the Ti group [19%], 2 patients in the pyrocarbon group [11%], and 2 patients in the silicone group [11%]; and boutonniere deformity (1 patient in the Ti group [4%] and 0 patients in the pyrocarbon and silicone groups).

Timing of adverse effects: The average time until explantation was 23 months.

Factors that predict response: Loosening resulting in explantation is common for titanium implants.

Table 19: Orthopedic - cranioplasty - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

19.1 Source Citation: Gerstl et al. 2022[72]

Study Design: SR and meta-analysis to compare cosmetic outcomes and complications of autologous bone grafts and alloplasts used for cranioplasty following decompressive craniectomy. 30 studies were included accounting for 5,314 patients – this includes 10 studies (1 RCT) that involve titanium mesh.

Device or Material: Ti mesh, autologous bone, and non-Ti alloplasts: calcium phosphate (CP), hydroxyapatite (HA), polyetheretherketone (PEEK), polymethylmethacrylate (PMMA), porous polypropylene (PP).

Contact Duration: Follow-up ranged from 9.13 to 62.9 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Hematoma, reoperation, seizure.

Patient characteristics (gender, mean age): 60.2% to 80.7% male, 30 to 51 years.

Number per Group: Ti, n=290; PMMA, n=45; PEEK, n=60; CP, n=6; PP, n=32.

Observed adverse effects: Overall number of complications were reported in 19 studies, with an incidence of 35.5% in autologous bone compared to 27.8% in alloplasts. Incidence of complications for individual alloplasts was 33.8% for Ti (98/290), 27.8% (128/461) for PMMA, 13.3% (6/45) for PEEK, 20.0% (12/60) for HA, and 15.6% for PP (5/32).
Implant migration was reported in five studies. In autologous bone, incidence of migration was 5.6% (43/765) compared to 4.0% for all alloplasts (8/201); the RR was 1.36 (95% CI = 0.63-2.92). Incidence for remaining alloplasts was: 0.0% for Ti (0/31), 5.6% (43/765) for autologous bone, 0.0% for PEEK (0/18), 6.3% for PP (2/32), and 5.5% for PMMA (6/110).
Hematoma was reported in thirteen studies. In autologous bone, incidence of hematoma was 4.2% (56/1340) compared to 4.1% for all alloplasts (33/814); the RR was 0.98 (95% CI = 0.53-1.79). Incidence for remaining alloplasts was: 1.6% for Ti (4/253), 4.7% for PMMA (19/403), 3.8% for PEEK (1/26), 14% for HA (7/50), and 3.1% (1/31) for PP.
Seizure was reported in six studies. In autologous bone, incidence of seizure was 10.4% (71/679) compared to 7.6% for all alloplasts (33/434); the RR was 0.83 (95% CI = 0.29-2.35). Incidence for remaining alloplasts was: 7.2% for Ti (16/222), 8.8% for PMMA (13/148), and 8.3% for PEEK (2/24).
Reoperation was reported in nine studies. In autologous bone, incidence of reoperation was 19.6% (139/709) compared to 12.6% for all alloplasts (36/285); The RR was 1.66 (95% CI = 9.90-3.08). Incidence for remaining alloplasts was 24.1% for Ti (32/133), 16.4% for PMMA (22/134), 11.5% for PEEK (3/26), and 4.0% for HA (2/50).

Timing of adverse effects: Follow-up ranged from 9.13 to 62.9 months.

Factors that predict response: NR.

19.2 Source Citation: Zhu et al. 2021[73]

Study Design: SR and meta-analysis to assess the complications following titanium cranioplasty and to make comparison with nontitanium materials. 15 studies (2 RCTs) were included accounting for 2,258 cranioplasty procedures.

Device or Material: Titanium mesh, autologous bone, bone cement, polyetheretherketone (PEEK), polymethylmethacrylate (PMMA).

Contact Duration: Mean follow-up of 17.8 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Cerebrospinal fluid (CSF) leak, hematoma, implant exposure, imprecise fit, reoperation, seizure.

Patient characteristics (gender, mean age): 75.2% male, 44.1 years.

Number per Group: Ti, n=896; non-Ti materials, n=1,362.

Observed adverse effects: Non-Ti materials showed significant improvement on complications compared to Ti cranioplasty (OR, 0.72; Ci, 0.56-0.91; P = 0.007).
Hematoma was reported in 8 studies. Ti has a statistically significant reduction in the incidence of hematoma compared with non-Ti materials (pooled n=525; OR, 0.31; CI, 0.16-0.58, P=0.0003).
Postoperative seizure was reported in 4 studies. The rate of seizure after Ti cranioplasty was 0.067 (n=24/358) and non-TI was 0.119 (98/817) (OR, 0.81; CI, 0.50-1.34; P=0.42).
CSF leak was reported in 4 studies. The authors reported no difference in odds of CSF leak in the Ti cranioplasty group compared with the non-Ti group but the meta-analysis showed a significant difference favoring non-Ti materials (pooled n=278; OR, 2.22; CI, 1.01-4.88; P=0.05).
Imprecise fit was reported in 3 studies. The pooled rate of poor fit was 0.041 (n=6/148) in Ti cranioplasty and 0.121 (n=13/107) in non-Ti. The pooled results show Ti was linked to a significant decrease in poor fit (n=148; OR, 0.35; 0.13-0.95; P=0.04).
Ti implant is more prone to implant exposure with 51 implant exposures occurring in 569 cranioplasties (n=569; OR, 4.11; CI, 2.27-7.44; P<0.00001).
Reoperation was reported in 8 studies (as a result of CSF leak, hematoma). There was no difference in odds of reoperation rate in the Ti group compared to the autogenous bone group (n=200; OR, 0.66; CI, 0.23-1.86; P=0.43).

Timing of adverse effects: Seizure was reported in studies with follow-up beyond 3 months. Patients presented with mesh exposure from 2 months to 7 years.

Factors that predict response: NR.

19.3 Source Citation: Liu et al. 2020[74]

Study Design: SR and meta-analysis to evaluate complications in cranioplasty in the use of autogenous bone and bone substitutes and to compare bone substitutes, specifically hydroxyapatite (HA), polyetheretherketone (PEEK), and titanium materials. Twenty studies were included, 9 of which (including 2 RCTs) involve Ti mesh.

Device or Material: Ti mesh, autogenous bone, HA, PEEK.

Contact Duration: Follow-up ranged from 6 to 56.6 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Cerebrospinal fluid (CSF) leak, effusion, exposure, implant failure requiring removal/reoperation, seizure.

Patient characteristics (gender, mean age): Patient sex NR, 39.3 to 55.3 years

Number per Group: Ti mesh group, n=810; HA, n=155; PEEK, n=175; autologous bone, n=1,107; PMMA, n=242; "other," n=424.

Observed adverse effects: Four studies compared complications of autologous bone with Ti. There were 50 complications in 92 autologous bone cranioplasties and 25 complications in 69 Ti cranioplasties (OR 2.19, 95% CI, 1.15-4.14, p=0.02).
Two studies compared overall complications of Ti versus HA. There were 22 complications in 57 HA cranioplasties and 14 complications in 33 Ti cranioplasties (OR 1.22, 95% CI, 0.47-3.14, p=0.69).
Four studies compared overall complications of Ti versus PEEK. There were 22 complications in 128 PEEK cranioplasties and 72 complications in 238 Ti cranioplasties (OR 0.51, 95% CI, 0.30-0.87, p=0.01). The incidence of implant exposure was 13.4% in the Ti groups versus 2.3% in PEEK. The incidence of hematoma was 3.8% in Ti groups versus 3.9% in PEEK. The incidence of subgaleal effusion was 5.0% in the Ti groups versus 4.7% in PEEK. The incidence of CSF leak was 0.4% in Ti groups versus 0% in PEEK groups. The incidence of seizure was 9.2% in the Ti groups versus 4.7% in PEEK groups. The incidence of implant failure requiring removal or reoperation was 18.5% in the Ti group versus 3.9% in PEEK.

Timing of adverse effects: NR.

Factors that predict response: High complication rates of Ti mesh related to implant exposure.

19.4 Source Citation: Abu-Ghname et al. 2019[75]

Study Design: SR and meta-analysis to compare different complication rates between cranioplasty materials in the pediatric population following pediatric cranial reconstruction. Twenty studies (0 RCTs) met inclusion criteria, with 5 studies representing 60 patients involving titanium mesh.

Device or Material: Titanium mesh. Non-Ti materials: bone (fresh and banked), polymethylmethacrylate (PMMA), polyetheretherketone (PEEK).

Contact Duration: Mean follow-up ranged from 1 to 8.1 years in the Ti group.

Dose:

Frequency/Duration: Single administration.

Response: Failure, surgical site occurrence (e.g., seroma)

Patient characteristics (gender, mean age): Patient sex NR. Overall age in alloplastic materials was 4 to 17.4 years, and 5 to 12.9 years in the Ti group.

Number per Group: Ti group, n=60; fresh bone, n=245; banked bone, n=194; PMMA, n=110; PEEK, n=31.

Observed adverse effects: The Ti mesh group had 4 patients (6.7%) with total surgical-site occurrence, and 2 patients (3.3%) with graft failure.
The PMMA group had 20 patients (18.2%) with total surgical-site occurrence, and 18 patients (16.4%) with graft failure.
The PEEK group had 7 patients (22.6%) with total surgical-site occurrence, and 6 patients (19.3%) with graft failure.
Total autologous group (i.e., those with fresh and banked bone grafts) had 89 patients (20.3%) with bone flap/graft resorption, 120 patients (27.3%) with total surgical-site occurrence, and 85 patients (19.4%) with graft failure.
In a sub-analysis of patients younger than 6.5 years, fresh bone and titanium mesh demonstrated the lowest complication rates, with no significant difference when compared to each other.

Timing of adverse effects: Follow-up of 1 to 8.1 years.

Factors that predict response: NR.

19.5 Source Citation: Morselli et al. 2019[76]

Study Design: SR and meta-analysis to examine the association between material choice and related complications to suggest the best treatment option for decompressive craniectomy. 27 studies were included in the final analysis accounting for 1,688 custom implants. Among these studies 7 involve titanium mesh 2 RCTs) and 649 implants.

Device or Material: Titanium mesh. Non-Ti materials: polymethylmethacrylate (PMMA), polyetheretherketone (PEEK), hydroxyapatite (HA).

Contact Duration: Mean follow-up of 27 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Displacement, epidural hematoma, fluid collection, fracture, hydrocephalus, revision.

Patient characteristics (gender, mean age): 43.2% to 72.5% male, 43 to 53.1 years.

Number per Group: Ti group, n=649. Non-Ti materials: PMMA, n=298; PEEK, n=223; HA, n=508.

Observed adverse effects: 210 cases of revision were recorded (overall 12.45%) with 78 in the Ti group (12.01%), 52 in the PMMA group (17.57%), 31 in the PEEK group (13.3%), and 49 in the HA group (9.7%).
57 cases of postoperative epidural hematomas were recorded (overall 3.38%) with 30 in the Ti group (4.62%), 2 in the PMMA group (0.68%), 11 in the PEEK group(4.72%), and 14 in the HA group (2.8%).
32 patients overall needed a revision due to postoperative hematoma evacuation: 18 (2.77%) in the Ti group, 2 (0.68%) in the PMMA group, 6 (2.58%) in the PEEK group, and 6 (1.2%) in the HA group.
61 patients reported postoperative fluid collection (3.62%) with 12 of those patients (19.67%) requiring surgical revision. 38 fluid collections (5.86%) were performed in the Ti group with 7 requiring revision surgery (1.08%). 1 fluid collection (0.34%) was observed in the PMMA group and also required surgical revision. 11 fluid collections (4.72%) were recorded in the PEEK group with 4 (1.71%) requiring revision, 1 fluid collections (2.17%) were observed in the HA group with none requiring revision.
21 prostheses fractured (1.35%) with 7 requiring surgical revision (0.45%). 2 fractures occurred in the Ti group (0.31%) with 1 case requiring revision (0.15%), 1 fracture in the PMMA group (0.34%) that also required revision, 0 in the PEEK group, and 18 fractures in the HA group (3.5%) with 5 requiring revision (0.98%).
Displacement occurred in 34 cases (2.02%) with 16 cases requiring surgical revision (0.95%). 2 displacements occurred in the Ti group (0.31%) with 1 requiring revision (0.15%). All 11 patients in the PMMA group (3.72%) had displacements that also required revision. 3 patients in the PEEK group had displacement (1.29%) with none requiring revision, and 18 displacements occurred in the HA group (3.54%) with 4 of them requiring revision (0.8%).
24 patients had postoperative hydrocephalus (1.42%) with 19 of them requiring surgical treatment (1.13%). 1 case was found in the Ti group (0.15%) which also required surgical revision. 11 cases of hydrocephalus were in the PMMA group (3.72%) with 7 cases requiring revision (2.36%). 7 cases of hydrocephalus were in the PEEK group (3.01%) with all requiring revision. 5 cases were recorded in the HA group (0.9%) with 4 of them requiring revision (0.79%).
In this analysis, Ti presented in all studies together with HA a significantly lower rate of postoperative hydrocephalus and a lower rate of postoperative fluid collection.

Timing of adverse effects: Follow-up of greater than 1 month to 42 months in the Ti group.

Factors that predict response: NR.

19.6 Source Citation: Oliver et al. 2019[77]

Study Design: SR and meta-analysis to compare postoperative rates of local complications and allograft failures following cranioplasty reconstruction in adult patients. 53 studies were included, with 16 studies (0 RCTs) involving titanium mesh implants in 1,429 patients.

Device or Material: Titanium mesh. Non-Ti materials: polymethylmethacrylate (PMMA), polyetheretherketone (PEEK), Norian drillable bone void filler (Depuy Synthes).

Contact Duration: Mean follow-up of 26.8 months in the Ti group.

Dose: NR.

Frequency/Duration: Single administration.

Response: Graft failure and "local complication" (e.g., hematoma, screw failure, implant breakage, implant loosening, implant extrusion).

Patient characteristics (gender, mean age): Overall: 96.6% male, 40.1 years. Mean age in the Ti group was 41.4 years. Mean age in the PMMA group was 39.8 years. Mean age in the PEEK group was 39.0 years. Mean age in the Norian group NR.

Number per Group: Ti group, n=1,429. Non-Ti materials: PMMA, n=1,459; PEEK, n=221; Norian, n=482.

Observed adverse effects: Patients in the Ti group showed 187 local complications (13.09%) and 86 graft failures (6.02%). Patients in the PMMA group showed 165 local complications (11.31%) and 69 graft failures (4.73%). Patients in the PEEK group showed 38 local complications (17.19%) and 19 graft failures (8.60%). Patients in the Norian group showed 60 local complications (12.45%) and 31 graft failures (6.43%).

Timing of adverse effects: Mean follow-up of 26.8 months in the Ti group.

Factors that predict response: PEEK implants were associated with a significantly higher local complication rate and the highest ultimate graft failure rate.

19.7 Source Citation: van de Vijfeijken et al. 2018[78]

Study Design: SR and meta-analysis to review available literature about safety of different materials used after decompressive craniectomy for any indication. The search returned 228 studies (2 RCT) comprising a total of 10,346 total cranioplasties reporting an 18.9% complication rate. Note that 17.7% of patients received titanium cranioplasty, however the SR does not indicate the number of studies involving Ti-patients.

Device or Material: Ti mesh, non-Ti materials: autologous bone, hydroxyapatite (HA), polyetheretherketone (PEEK), polymethylmethacrylate (PMMA), and nonspecified other implants.

Contact Duration: Follow-up of 185 months (range 0 to 90 months).

Dose: NR.

Frequency/Duration: Single administration.

Response: Cerebrospinal fluid (CSF) leak, exposure, hematoma, migration, removal, seizure, seroma.

Patient characteristics (gender, mean age): 54.1% male, 0 to 90 years.

Number per Group: Ti group, n=1,829 (17.7%); autologous bone, n=3,336 (32.2%); PMMA, n=1,644 (15.9%); HA, n=905 (8.7%); PEEK, n=250 (2.4%); other, n=2,383 (23.0%).

Observed adverse effects: Hematoma was reported in 50 (2.8%) Ti patients, 9 (4.0%) PEEK patients, 31 (2.1%) PMMA patients, 58 (2.3%) autologous bone patients, 14 (1.7%) HA patients, and 8 (0.3%) other patients.
Seroma was reported in 27 (1.5%) Ti patients, 1 (0.7%) PEEK patient, 8 (0.5%) PMMA patients, 9 (0.4%) autologous bone patients, 5 (0.6%) HA patients, and 5 (0.2%) other patients.
Second trauma was reported in 0 Ti, PEEK, autologous bone, and other patients, and in 1 (0.1%) PMMA patient and 8 (0.9%) HA patients.
Exposure was reported in 27 (1.5%) Ti patients, 2 (0.6%) PEEK patients, 11 (0.7%) PMMA patients, 4 (0.2%) autologous bone patients, 13 (1.5%) HA patients, and 0 other patients.
Implant migration was reported in 1 (0.1%) Ti patient, 0 PEEK patients, 7 (0.5%) PMMA patients, 7 (0.3%) autologous bone patients, 0 HA patients, and 1 (0.0%) other patient.
Bone resorption was reported in 0 Ti and PEEK patients, 1 (0.2%) PMMA patient, 222 (11.3%) autologous bone patients, 1 (0.4%) HA patient, and 2 (0.2%) other patients.
CSF leak was reported in 14 (0.8%) Ti patients, 3 (1.3%) PEEK patients, 10 (0.7%) PMMA patients, 68 (2.7%) autologous bone patients, 1 (0.1%) HA patient, and 22 (1.0%) other patients.
Epilepsy was reported in 0 Ti, PMMA, HA, and other patients, and in 1 (0.4%) PEEK patient, and 13 (0.5%) autologous bone patients.
Seizure was reported in 24 (1.4%) Ti patients, 6 (2.6%) PEEK patients, 11 (0.7%) PMMA patients, 28 (1.1%) autologous bone patients, and 0 HA and other patients.
Implant removal occurred in 100 (6.7%) Ti patients, 18 (7.4%) PEEK patients, 104 (7.9%) PMMA patients, 250 (10.4%) autologous bone patients, 21 (2.5%) HA patients, and 72 (3.2%) other patients.

Timing of adverse effects: Complications were reported immediately to 9 years post-operatively.

Factors that predict response: Bone resorption occurred almost exclusively in autologous bone patients.

19.8 Source Citation: Moon et al. 2014[79]

Study Design: Nonrandomized comparative study.

Device or Material: Titanium mesh, absorbable mesh (non-Ti), silastic sheeting (non-Ti) for orbital wall reconstruction.

Contact Duration: Follow-up was 3 to 12 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Diplopia (double vision), enophthalmos (posterior eye displacement), revision.

Patient characteristics (gender, mean age): 78.2% male, 31 years.

Number per Group: Ti mesh group, n=238; absorbable mesh group, n=64; silastic sheet group, n=129.

Observed adverse effects: 4 patients (1.7%) required revision in the Ti-mesh group compared to 7 patients (5.4%) and 2 patients (3.1%) in the silastic sheet and absorbable mesh groups. The complications that required revision were as follows: 3 patients (1.3%) in the Ti-mesh group had extraocular muscle limitation with diplopia compared to 4 patients (3.1%) and 1 patient (1.6%) in the silastic sheet and absorbable mesh groups. 0 patients in the Ti-mesh group had hematoma, compared to 1 patient each in the silastic sheet (0.8%) and absorbable mesh (1.6%) groups. 1 patient (0.4%) in the Ti-mesh group had enophthalmos compared to 0 patients in either the silastic sheet and absorbable mesh groups. And 0 patients in the Ti-mesh group had implant malposition compared to 2 patients (1.4%) in the silastic sheet group only.

Timing of adverse effects: Diplopia occurred immediately postoperatively. Enophthalmos was considered a "delayed complication".

Factors that predict response: Ti meshes adhere firmly to periorbital tissue, an interaction that can result in extraocular motility restriction, eyelid retraction, and a difficulty in removing the implant during revision.

19.9 Source Citation: Lee et al. 2013[80]

Study Design: Nonrandomized.

Device or Material: Titanium implant, skull bone flap (non-Ti), and polyetheretherketone (PEEK) implants (non-Ti) for repair of skull defects after decompressive craniectomies.

Contact Duration: Follow-up of greater than 1 year.

Dose: NR.

Frequency/Duration: Single administration.

Response: Implant exposure.

Patient characteristics (gender, mean age): 78.4% male, mean age NR.

Number per Group: Ti group, n=218; bone group, n=15; PEEK group, n=10.

Observed adverse effects: 13 patients (5.96%) in the Ti implant group had incidents of implant exposure compared to 0 in the bone flap and PEEK groups.

Timing of adverse effects: Patients presented with mesh exposure between 2 months and 7 years.

Factors that predict response: NR.

Systemic Response/Toxicity

19.10 Source Citation: van de Vijfeijken et al. 2018[78]

Study Design: SR and meta-analysis to review available literature about safety of different materials used after decompressive craniectomy for any indication. The search returned 228 studies (2 RCT) comprising a total of 10,346 total cranioplasties reporting an 18.9% complication rate. Note that 17.7% of patients received titanium cranioplasty, however the SR does not indicate the number of studies involving Ti-patients.

Device or Material: Ti mesh, non-Ti materials: autologous bone, hydroxyapatite (HA), polyetheretherketone (PEEK), polymethylmethacrylate (PMMA), and nonspecified other implants.

Contact Duration: Follow-up of 185 months (range 0 to 90 months).

Dose: NR.

Frequency/Duration: Single administration.

Response: death

Patient characteristics (gender, mean age): 54.1% male, 0 to 90 years.

Number per Group: Ti group, n=1,829 (17.7%); autologous bone, n=3,336 (32.2%); PMMA, n=1,644 (15.9%); HA, n=905 (8.7%); PEEK, n=250 (2.4%); other, n=2,383 (23.0%).

Observed adverse effects: Death was reported in 1 (0.1%) Ti patient, 0 PEEK patients, 4 (0.3%) PMMA patients, 35 (1.4%) autologous bone patients, 0 HA patients, and 1 (0.0%) other patient.

Timing of adverse effects: Complications were reported immediately to 9 years post-operatively.

Factors that predict response: Bone resorption occurred almost exclusively in autologous bone patients.

Table 20: Surgical mesh - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

20.1 Source Citation: Yang et al. 2019[82]

Study Design: RCT.

Device or Material: Titanium-coated mesh (PFM Medical) versus standard polypropylene mesh (Covidien) for laparoscopic inguinal hernia repair.

Contact Duration: 1 year.

Dose: 10 cm by 15 cm mesh applied in both groups.

Frequency/Duration: Single administration.

Response: Foreign body sensation, seroma.

Patient characteristics (gender, mean age): 100% male. Mean age 46.5±10.1 years in the Ti-mesh group and 45.0±10.2 years in the standard mesh group.

Number per Group: Ti mesh group, n=50; standard mesh group, n=52.

Observed adverse effects: In the Ti mesh group, 3 patients (6%) developed seroma, and 15 patients (30%) with foreign body sensation; in the standard mesh group, seroma occurred in 9 patients (17.3%) and foreign body sensation in 17 patients (32.7%). The incidence of seroma and foreign body sensation was not significantly different between these two groups ($p>0.05$). However, the degree of foreign body sensation was higher in the standard mesh group. No recurrence or chronic pain was observed.

Timing of adverse effects: At 1-year follow-up.

Factors that predict response: NR.

20.2 Source Citation: Dong et al. 2018[81]

Study Design: SR to review the available clinical trials examining male infertility after inguinal hernias were repaired using mesh procedures. Twenty-nine related trials with a total of 36,552 patients weren't investigated, included 7 RCTs with 616 patients and 10 clinical trials (1230 patients) with mesh or non-mesh repairs. Of these, 2 RCTs involved the same 19 TiMesh patients.

Device or Material: TiMesh (titanium), Vyproll (non-Ti, lightweight polypropylene), Marlex (non-Ti, heavyweight polypropylene).

Contact Duration: 1 to 3-year follow-up.

Dose: NR.

Frequency/Duration: Single administration.

Response: Chronic pain, decreased sperm motility, recurrence.

Patient characteristics (gender, mean age): 100% male, 20 to 50 years.

Number per Group: TiMesh group, n=19; Vyproll group, n=20; Marlex group, n=20.

Observed adverse effects: Vyproll or TiMesh decreased sperm motility when compared to Marlex mesh after a 1-year follow-up, but there was no significant difference after 3 years. In contrast, the lightweight mesh groups had a lower recurrence rate and no chronic pain.

Timing of adverse effects: 1 year follow-up.

Factors that predict response: Low-weight, large, porous, and elastic samples could have a benefit on the integrity of the vas deferens, when mesh is the required material to be used in younger patients undergoing open hernia repair.

20.3 Source Citation: Liew et al. 2017[83]

Study Design: RCT

Device or Material: ProTack fixation device (Ti, Covidien) versus Enbucrilate glue (non-Ti, B. Braun) in the fixation of polypropylene mesh.

Contact Duration: 3-month follow-up.

Dose: Two 5mm tacks versus 0.5 ml glue.

Frequency/Duration: Single administration.

Response: Seroma.

Patient characteristics (gender, mean age): Patient sex NR. ProTack group median age, 57.0 years; glue group median age, 52.5 years.

Number per Group: ProTack group, n=34; glue group, n=32.

Observed adverse effects: One patient (3.1%) in the glue fixation group developed a large groin hematoma postoperatively and required evacuation of clots via incision and drainage at the inguinal area. There are 8 (23.5%) and 7 (21.9%) cases of seroma in the tacker and glue fixation group respectively, with no significant difference (p=0.873). No patients with early recurrence of inguinal hernia were observed during the 3-month follow-up. The incidence of chronic groin pain was 6.3% in the glue fixation group and none in the tacker group, but no significant difference (p.0.231).

Timing of adverse effects: NR.

Factors that predict response: NR.

20.4 Source Citation: Wang et al. 2013[84]

Study Design: Nonrandomized.

Device or Material: Titanium spiral tacks versus, *n*-butyl-2-cyanoacrylate (NBCA) adhesive, and Ti-tacks plus NCBA for fixation in laparoscopic inguinal hernia repair, compared with no fixation.

Contact Duration: 19-month follow-up.

Dose: Mesh size ranged from 11 cm by 13 cm to 13 cm by 15 cm. 1.5 mL/tube of NBCA was used. Number of tacks not reported.

Frequency/Duration: Single administration.

Response: Chronic pain, hematoma, seroma.

Patient characteristics (gender, mean age): Ti-tacks-only group: 87.6% male, 61.2±11.8 years; NBCA-only group: 84.6% male, 63.1±16.5 years; Ti-tacks plus NBCA group: 87.2% male, 60.9±13.8 years; nonfixation group: 82.3% male, 60.6±13.4 years.

Number per Group: Ti-tacks-only group, n=89; NBCA-only group, n=552; Ti-tacks plus NBCA group, n=47; nonfixation group, n=339.

Observed adverse effects: At final follow-up, no hernia recurrences had occurred in any of the groups. No occurrence of chronic pain was noted in the nonfixation and NBCA-only groups, whereas two cases (2.2%) where noted in the Ti-tacks-only group, and 1 case (2.1%) was noted in the Ti-Tacks plus NBCA group. Glue fixation of the mesh seemed to decrease the risk of hematoma and seroma formation but did not eliminate the risk as they occurred in 48 patients (9.6%) in the NBCA-only group and 4 patients (8.5%) in the Ti-tacks plus NBCA group, versus 54 patients (15.2%) and 20 patients (22.5%) in the nonfixation and Ti-tacks-only groups, respectively.

Timing of adverse effects: 19-month follow-up.

Factors that predict response: Glue fixation seemed to decrease the risk of hematoma and seroma formation but did not eliminate the risk.

Table 21: Surgical ligating clips - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

21.1 Source Citation: Teja et al. 2022[85]

Study Design: RCT.

Device or Material: Titanium clip versus knotted Vicryl suture for cystic duct ligation.

Contact Duration: 3-month follow-up.

Dose: NA.

Frequency/Duration: Single administration of multiple clips.

Response: Migration; slippage.

Patient characteristics (gender, mean age): 1:1 male-to-female ratio, 30 to 49 years.

Number per Group: 30 patients per group.

Observed adverse effects: There were no intraoperative complications in the suture group, compared to 11 patients with intraoperative complications in the Ti clip group. Seven patients had clip slippage with gallstone spillage into the peritoneal cavity, 3 patients had clip slippage with bile spillage into the peritoneal cavity, and 1 patient had clip migration.

Timing of adverse effects: Complications were intraoperative; no significant complications were noted at follow-up.

Factors that predict response: NR.

21.2 Source Citation: Bali and Singal 2018[86]

Study Design: RCT.

Device or Material: Titanium ligaclip versus knotted silk suture for cystic duct ligation.

Contact Duration: 2-week follow-up.

Dose: NR.

Frequency/Duration: Single administration of multiple clips.

Response: No complications reported.

Patient characteristics (gender, mean age): Ti clip group 61.7% female; Suture group 60% female. Mean age NR in either group.

Number per Group: 60 patients per group.

Observed adverse effects: All patients were observed post-operatively for any fever, hemorrhage, or intrabdominal fluid collection. There were no major complications seen in either group.

Timing of adverse effects: No complications noted postoperatively or at 2-week follow-up.

Factors that predict response: NR.

21.3 Source Citation: Yang et al. 2014[87]

Study Design: Nonrandomized.

Device or Material: Titanium versus absorbable polyglyconate-polyglycolic acid ligating clip for cystic duct ligation.

Contact Duration: Follow-up NR.

Dose: NR.

Frequency/Duration: Single administration.

Response: Abscess, bleeding, duct leakage, ileus, lung atelectasis, pancreatitis.

Patient characteristics (gender, mean age): 59.6% female. Ti clip group, 43.1±12.5 years; absorbable clip group, 42.2±13.6 years.

Number per Group: Ti clip group, n=728; absorbable clip group, n=635.

Observed adverse effects:

7 patients (0.96%) in the Ti clip group had cystic duct leak compared with 0% in the absorbable clip group.
3 patients (0.41%) of patients in the Ti clip group had pancreatitis compared to 2 patients (0.32%) in the absorbable clip group.
4 patients (0.55%) in the Ti clip group had ileus compared to 3 patients (0.47%) in the absorbable clip group.struc
2 patients (0.28%) in the Ti clip group had abdominal abscess compared with 1 patient (0.16%) in the absorbable clip group.
2 patients (0.28%) in the Ti clip group had significant postoperative hepatic gallbladder bed bleeding necessitating reoperation compared with 0% in the absorbable clip group, but this was not determined be a consequence of clip failure.

Timing of adverse effects: Intraoperative duct leak. Postoperative complications.

Factors that predict response: NR.

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Specific search terms are provided here. The associated alerts are provided with this report as a separate PDF.