

MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Stainless Steel (SS) Safety Profile

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Executive Summary

Key Points

1. Searches identified 2798 citations; 70 articles were selected for inclusion
2. For Stainless Steel (SS) as a material, very low-quality evidence from 6 studies indicated inflammation as local responses to SS implants in animals, and a higher risk of reaction to SS in individuals with metal allergies (vs. no metal allergies) in 1 human study.
3. For neurology, very low-quality evidence from 1 study indicated in-stent restenosis/in-stent occlusion occurred significantly less often with SS and cobalt chromium (CoCr) stents versus platinum chromium (Cr) stents up to 6 months.
4. For obstetrics, very low-quality evidence from 2 studies indicated low rates of seroma, hematoma, and pain with SS staples. These responses also occurred with non-SS sutures and staples so the association with SS is unclear.
5. Very low-quality evidence from 1 systematic review (SR) examining a SS glaucoma filtration device indicated various local responses including hyphema (bleeding inside the eye), shallow/flat anterior chamber, and bleb leak. Most local responses also occurred with standard trabeculectomy.
6. For general plastic surgery, very low-quality evidence from 1 study indicated hemorrhage, myocardial infarction (MI), and pericardial effusion were local responses from a SS distal anastomotic device. Systemic responses included phrenic nerve palsy and cerebrovascular accident (very low-quality evidence). All responses occurred in fewer than 2% of patients.
7. Low- to very low-quality evidence from 1 study indicated migration, pain, and burning as local responses to SS stent placement in esophageal achalasia patients.
8. For dental devices, low-quality evidence from 16 studies indicated failure, inflammation and pain as local responses which occurred similarly with non-SS devices. 1 study reported elevated urinary nickel (Ni) concentrations after 12 months usage of SS arch wires, brackets, and bands.
9. For miscellaneous cardiovascular devices (e.g., ventricular assist devices (VADs), threads for sternal closure, and inferior vena cava (IVC) filters), very low-quality evidence from 7 studies indicated bleeding, thromboembolism, and pain as local responses in both SS and non-SS devices.
10. For cardiovascular grafts, very low-quality evidence from 1 study indicated abdominal compartment syndrome as a local response. Systemic responses included pneumonia, pulmonary tuberculosis, chronic renal failure, and limb ischemia. Authors noted that all responses may be due to underlying conditions (e.g., renal function impairment).
11. Fourteen studies indicated local responses (stent thrombosis and restenosis) and systemic responses (mortality, stroke, and amputation) occurring with coronary and peripheral stent placement. Responses occurred with both SS and non-SS stents so the association with SS is unclear. Evidence was moderate quality for coronary stents, and low quality for peripheral stents.
12. For spinal fixation, very low-quality evidence from 2 studies indicated rod fractures, proximal junctional kyphosis, pseudoarthrosis, and deep/superficial infections as local responses. Elevated Cr levels after SS implant placement were reported in 1 study (low- quality evidence).

13. For orthopedic fixation (non-spinal), low-quality evidence from 9 studies indicated local responses to sternal closure (wound infection and wound instability), distal femoral and distal radial fractures (non-union, malunion), osteotomy (non-union, malunion, infection) and Nuss procedure (allergic reaction). 1 study examining Lisfranc injuries indicated no inflammatory reactions from SS screws (very low-quality evidence).
14. Very low-quality evidence from 4 studies indicated malunions, delayed unions/healing, nail migration, and radial nerve palsy as local responses from orthopedic fixation with intramedullary rods/nails. Malunion and delayed union also occurred with non-SS devices.
15. For orthopedic prosthesis, 7 studies reported failure and pain (low-quality evidence), and dislocation and cortical hypertrophy (very-low quality evidence) as local responses.
16. Local responses for radiology, anesthesiology, and gastroenterology were rated very low-quality due to no evidence for these categories.
17. Evidence for systemic responses was reported for SS as a Material, general plastic surgery, dental, cardiovascular grafts/coronary stents/peripheral stents, and spinal fixation although the direct association with SS is uncertain in all cases.
18. There were no ECRI Patient Safety Organization (PSO) or Accident Investigations that could be directly associated with the biocompatibility of SS.
19. ECRI Problem Reporting Network (PRN) database includes 3 reports and all of them involved intraoperative complications. Two reports summarized broken SS components (lap-band and K-wire) at the time of implantation. The third report involved difficulty removing a screw during a femoral blade removal procedure. No patient injuries occurred during these procedures.
20. There were 164 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. Rather, they involved device malfunction, regulatory issues (e.g., labeling), sterility compromise, and iatrogenic injuries.
21. Evidence gaps:
 - a. 17 (94%) device categories were rated low or very-low quality of evidence for local responses representing areas with potential gaps in the literature. Coronary stents were the notable exception rated moderate quality of evidence. This category included 10 studies; 2 SRs alone meta-analyzed over 50,000 patients with agreement across studies on local responses.
 - b. 52 (74%) studies did not investigate systemic responses from SS 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 SS device categories is needed.

Overview - Stainless Steel

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 stainless steel. If data did not exist to sufficiently address these questions, an evidence gap was noted in this report. These gaps could represent areas of further research. Literature searches identified 2798 articles and 70 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).

- a. *Can that response vary by location or type of tissue the device is implanted in or near?*
 - i. Six studies examined SS as a material. One human study reported patch test reactivity from 5 individuals with metal allergies to SS disks affixed to their backs for 48 hours. Two animal studies reported significant inflammatory response when SS implants were placed in mice peritoneal cavities and in pig skin. Three animal studies reported little to no inflammatory response when SS was placed in rabbit spines, sheep chest, and used for gastric plication in dogs.
 - ii. In-stent restenosis/in-stent occlusion was a local response reported in 1 neurology-related study.
 - iii. Hematoma (rate 1.1% at 10 days), and seroma (rates $\leq 2\%$ at 3 days) were local responses from subcuticular SS staples reported in 2 obstetric-related studies. A reduction in pain was reported by day 3.
 - iv. Various local responses were reported in 1 SR of 18 studies examining a SS glaucoma filtration device. Hyphema (rates up to 15%), shallow/flat anterior chamber (rates up to 20%), and bleb leak (rates up to 29%) were the most commonly reported responses by studies. Only 1 study reported shunt migration and lens opacity.
 - v. Local responses from a SS distal anastomotic device included myocardial infarction (rate 0.8%), post-operative hemorrhage (rate 1.6%), and pericardial effusion (rate 0.8%). Low rates of systemic responses (e.g., cerebrovascular accident, and phrenic nerve palsy) were also reported.
 - vi. Burning, stent migration, and pain occurred from a SS stent in esophageal achalasia patients.
 - vii. Failure, fracture, inflammation and pain were local responses from dental arch wires/wires, screws, paraposts, retainers, and crowns. Failure rate was 7% for screws and ranged from 10% to 36.4% for retainers. Pain at rest ranged from 2% to 16% with SS wires.
 - viii. Bleeding, fibrin embolism, failure, and hemorrhage were local responses from cardiovascular devices such as VADs, threads for sternal closure, and IVC filters. Perforation occurred significantly less with SS IVC filters, and none perforated an adjacent organ.
 - ix. Abdominal compartment syndrome occurred in 1 (17%) patient after cardiovascular graft placement, however the complication may be due to underlying conditions.
 - x. Stent thrombosis and restenosis occurred after coronary and peripheral stent placements. Target lesion and vessel failure only occurred with coronary stents, while hematoma and paresthesia only occurred with peripheral stents.
 - xi. Rod fractures, proximal junctional kyphosis, pseudoarthrosis, and deep/superficial infections were reported in 2 studies after spinal fixation.
 - xii. For orthopedic fixation (non-spinal), local responses for sternal closure (wound infection and wound instability), distal femoral and distal radial fractures (non-union, malunion), osteotomy (non-union,

malunion, infection) and Nuss procedure (allergic reaction) were reported. One study examining Lisfranc injuries indicated no inflammatory reactions from SS screws.

- xiii. Malunions, delayed unions, nail migration, and nerve palsy were local responses from orthopedic fixation with intramedullary rods/nails. Nerve palsy and nail migration occurred in 2 (11%) patients each.
- xiv. Dislocation (rate 6%), hypertrophy (rate 17.1%) and irritation (rate 16.7%) were local responses from orthopedic prosthetics.

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

- i. The local response to SS appeared within 48 hours in humans with metal allergies to SS disks. Significant inflammation occurred within 7 days with uncoated SS implants in mice. In-stent restenosis/in-stent occlusion from a SS stent was measured at 6 months. Seroma, hematoma, and pain were reported within 10 days postoperative in obstetric patients. Ophthalmic-related responses from a SS glaucoma filtration device were reported up to 40 months follow-up; hypotony was reported as early as day 1. At 29 weeks, responses from a SS distal anastomotic device included myocardial infarction, post-operative hemorrhage, and pericardial effusion. Stent migration occurred within 1 month of insertion in esophageal achalasia patients. Pain from dental arch wires/wires was reported within 24 hours, while gingival bleeding from dental crowns was reported as late as 12 months. Hemorrhage and tamponade occurred at day 3 and day 28, respectively after use of a VAD. Abdominal compartment syndrome was identified at a mean follow-up of 22 months in a patient receiving an endovascular graft containing SS. Thrombosis from coronary stent placement was reported at 30 days. No time course was reported for peripheral stent placement. Complications (rod fractures, proximal junctional kyphosis, pseudoarthrosis) with spinal fixation occurred at median follow-up of 37 to 42 months. Responses to SS devices used for orthopedic fixation (non-spinal) were identified at 30 days (deep wound infection and wound instability from sternal closure), 12 weeks (non-union, malunion from distal radial fractures), and mean 22 weeks (allergic reaction from SS bars used in a Nuss procedure). Radial nerve palsy and nail migration were reported at a mean 9.3 to 16.5 weeks. Hip dislocation was noticed in the early post-operative period, while hip hypertrophy was reported at 2- and 6-year follow-up, with progressive enlargement noted up to 12 years.

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, 18 (26%) studies investigated systemic responses. 17 human studies addressing general plastic surgery (1 study), dental devices (1 study), cardiovascular grafts (1 study), cardiovascular - coronary stents (10 studies), cardiovascular - peripheral stents (3 studies), and spinal fixation (1 study) identified systemic responses. One animal study investigating SS as a material did not identify any systemic responses.

b. What are the likely systemic manifestations?

For general plastic surgery: systemic manifestations were limited to 1 (0.8%) report each of patient death, cerebrovascular accident, brachial artery embolization, and phrenic nerve palsy; and 2 (1.6%) reports of pleural effusion requiring intervention. This evidence was reported in only 1 single arm study included in a SR; 120 patients undergoing minimally invasive direct coronary artery bypass or totally endoscopic coronary artery bypass using a SS distal anastomotic device.

For dental devices: One non-randomized comparative study examining fixed appliances (consisting of SS arch wires, brackets and bands) (n=30) vs no fixed appliances in age and gender matched siblings (n=30) reported significantly higher urinary Ni concentrations up to 21 months with fixed appliances vs controls (difference 1.98 $\mu\text{g/L}$, 95% CI: 0.523 to 3.319), and males receiving fixed appliances vs controls (difference 3.02 $\mu\text{g/L}$, 95% CI: 0.479 to 5.513). Authors noted only slight elevation in urinary Ni concentrations from fixed appliances used for at least 12 months.

For cardiovascular grafts: One single arm study reported pneumonia, pulmonary tuberculosis, and urinary bladder incontinence in 1 patient. Another patient experienced chronic renal failure and limb ischemia requiring femorofemoral bypass after stent graft insertion. Authors indicated that the complications may be due to underlying conditions (e.g., renal function impairment).

For cardiovascular – coronary stents: results from 10 studies indicated all-cause mortality, stroke, cardiac deaths, and non-cardiac deaths as systemic manifestations.

For cardiovascular – peripheral stents: Three studies reported amputation, mortality, MI, and stroke as systemic responses. Results were mixed for amputation and mortality (1 SR and 1 RCT reported low rates, 1 SR reported moderate to high rates). One RCT reported rare occurrences of MI and stroke.

For spinal fixation: One study reported that Cr levels were elevated after SS implant placement.

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

For general plastic surgery: patient death, cerebrovascular accident, brachial artery embolization, phrenic nerve palsy, and pleural effusion requiring intervention occurred by 29 weeks.

For dental devices: authors noted only slight elevation in urinary Ni concentrations from fixed appliances (with SS arch wires, brackets, and bands) used for at least 12 months, but significantly higher urinary Ni concentrations with fixed appliances vs controls up to 21 months.

For cardiovascular grafts: pneumonia, pulmonary tuberculosis, urinary bladder incontinence, chronic renal failure and limb ischemia requiring femoro-femoral bypass were reported at 19 to 29 months follow-up.

For cardiovascular – coronary stents: all-cause mortality, stroke, cardiac deaths, and non-cardiac deaths were reported as systemic manifestations up to 5 years follow-up.

For cardiovascular – peripheral stents: MI was reported at 1 year; amputation, mortality, and stroke were reported up to 3 years.

For spinal fixation: elevated Cr levels were noted from 1 month to 14 years follow-up.

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?

One non-randomized comparative study examined urinary nickel (Ni) concentrations after use of fixed appliances (including SS arch wires, brackets, and bands) in 60 age and gender matched siblings (30 each arm). Authors noted that “gender did not have a statistically significant influence on the increase pattern, albeit this increase was somewhat more vivid in males.”

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?

No studies investigated material-related factors that may predict, increase, or decrease the likelihood of an exaggerated, sustained immunological/systemic response.

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 and animal RCTs for local responses to SS as a material and for all device categories to better ascertain associations with these responses to SS.
- b. Additional research on systemic responses, including those on patient or material factors, for all SS device categories. Systemic responses were only investigated in 18 (26%) studies with no studies investigating SS for neurology, obstetrics, ophthalmic, ENT, miscellaneous cardiovascular devices (e.g., VAD, IVC filters), non-spinal orthopedic fixation, orthopedic intramedullary rods/nails, orthopedic prosthetics, radiology, anesthesiology, and gastroenterology.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and SR to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by 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 SR 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 SS?
 - 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, the 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, it was 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 the 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 (PHI).

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. ECRI rarely find chronic conditions or patient follow-up reports, which are more prevalent in the 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 Patient Safety Organization 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 year 2004 through May 2022, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

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 - Stainless Steel

Full Name: Stainless Steel

CAS Registry Number: 12597-68-1, 65997-19-5

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of SS used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of SS. The devices in Table 1 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data.

Table 1: Medical Devices Containing Stainless Steel Provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Abutment, Implant, Dental, Endosseous	NHA	2
Powder, Porcelain	EIH	2
Implant, Endosseous, Root-Form	DZE	2
Teeth, Porcelain	ELL	2
Agent, Tooth Bonding, Resin	KLE	2
Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented	LZO	2
Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Cemented	JDI	2
Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Porous Uncemented	LPH	2
Prosthesis, Hip, Semi-Constrained, Uncemented, Metal / Polymer, Non-Porous, Calcium Phosphate	MEH	2
Prosthesis, Toe, Hemi-, Phalangeal	KWD	2
Prosthesis, Wrist, Carpal Trapezium	KYI	2
Marker, Radiographic, Implantable	NEU	2
Prosthesis, Intervertebral Disc	MJO	2

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of SS. 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 2. We then turn to a detailed discussion of research on Stainless Steel as a material as well as research on the various device categories.

In the summary of results section following Table 2, 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 SS group than in the non-SS group.

Table 2: 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)
Stainless Steel as a material (1 human study and 5 animal studies)	Human: individuals with known metal allergies have higher risk of reaction to SS. Animal studies: Local inflammatory response to SS implants.	Very low Very low	Human studies did not investigate 1 animal study reported no systemic responses	Very low Very low
Neurology (1 human study)	In-stent restenosis/in-stent occlusion	Very low	No studies investigated	Very low
Obstetrics (2 human studies)	Hematoma, pain, seroma	Very low	No studies investigated	Very low
Ophthalmic (1 human study)	Aqueous misdirection; bleb fibrosis; bleb leak; blocked tube; cataract; choroidal detachment; choroidal effusions; choroidal hemorrhage; clotting; conjunctival leakage; corneal Dellen; device-iris or -cornea contact; dislocated implant; dysesthetic bleb; encysted bleb; endophthalmitis; exposed implant; hyphema; hypotony; intraocular hemorrhage; intraocular pressure (IOP) spikes; lens opacity; macular edema; maculopathy; membrane; posterior capsule opacity; retinal branch vein occlusion; shallow/flat anterior chamber; shunt closure; shunt migration.	Very low	No studies investigated	Very low
General, Plastic Surgery (1 human study)	Hemorrhage, myocardial infarction, pericardial effusion	Very low	Death, cerebrovascular accident, brachial artery	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
			embolization, phrenic nerve palsy, and pleural effusion requiring intervention (1 study)	
Ear, Nose, and Throat (1 human study)	Burning, migration, pain	Low for migration and pain Very low for burning	No studies investigated	Very low
Dental (16 human studies)	Breakage, chipping, detachment, deterioration, gingival bleeding, gingival inflammation, failure, fracture/partial fracture, material leakage in saliva, mobility, Ni hypersensitivity reactions, occlusion, pain, plaque, recurrent caries, restorative loss, retention	Low for failure, fracture, inflammation, and pain Very low for other local responses	Urinary Ni concentrations (1 study)	Very low
Cardiovascular – miscellaneous (7 human studies)	Bleeding, bowel ischemia and fibrin embolism, device failure, displacement, hemorrhage, mortality, neurologic events (cerebral hemorrhage), pain, vessel patency, perforation, pump exchange due to fibrin, thrombus formation and expiration, thromboembolism (stroke, transient ischemic attack, arterial non-central nervous system thromboembolism, device exchange due to thrombosis, and venous thromboembolism)	Very low	No studies investigated	Very low
Cardiovascular – grafts (1 human study)	Abdominal compartment syndrome	Very low	Pneumonia, pulmonary tuberculosis,	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
			urinary bladder incontinence, chronic renal failure, and limb ischemia (1 study)	
Cardiovascular – coronary stents (10 human studies)	Myocardial infarctions, major cardiovascular adverse events, stent thrombosis, target lesion and vessel revascularization, target lesion and vessel failure, in-segment late lumen loss, in-segment and in-stent restenosis	Moderate	All-cause mortality, stroke, cardiac deaths, non-cardiac deaths (10 studies)	Moderate
Cardiovascular – peripheral stents (4 human studies)	Bypass, distal embolization, dissection, patency rate, percutaneous transluminal angioplasty, restenosis or occlusion, revascularization, arteriovenous fistula, delayed wound healing, false aneurysm, hematoma, local infection, lymphorrhea, paresthesia, thrombosis, vascular perforation	Low	Amputation, death, myocardial infarct, stroke (3 studies)	Low
Orthopedic fixation, spinal (3 human studies)	Rod fractures, proximal junctional kyphosis, pseudoarthrosis, deep infections, and superficial infections.	Very low	Cr levels are elevated after SS implant placement (1 study)	Low
Orthopedic fixation, non-spinal (10 human studies)	Sternal wound infections, sternal dehiscence, sternal wound instability, non-unions, malunion, infection, allergic reactions, inflammation	Low	No studies investigated	Very low
Orthopedic intramedullary rod/nail (4 human studies)	Malunions, delayed unions, nail migration, nerve palsy	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)
Orthopedic – prosthesis (7 human studies)	Cancellization (thinning of cortex bone), dislocation, hypertrophy, implant failure, loosening, luxation, non-union, pain/irritation, wear	Low for failure and pain Very low for other local responses	No studies investigated	Very low
Radiology	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Anesthesiology	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Gastroenterology	No studies	Very low (no evidence)	No studies	Very low (no evidence)

RCT = randomized controlled trial; SR = systematic review

Stainless Steel as a Material

One human study¹ and 5 animal studies²⁻⁶ evaluated SS as a material. For further information see Table 4 in Appendix D.

Local Responses (human studies)

One clinical study¹ evaluated patch test reactivity to SS in individuals with known metal allergies and patients with no known metal allergies. SS disks were fixed to patients' backs and removed after 48 hours. Five patients with metal allergies reacted to the uncoated metal disks. No nonallergic individuals reacted to the SS disks.

Overall Quality of Evidence

This prospective cohort study with 61 patients examined only local skin responses. The quality of evidence for local responses is very low because it contains only a single small study that lacks randomization and blinding. Because no studies reported whether systemic responses occurred, the quality of evidence for systemic responses is very low.

Local Responses (animal studies)

Local responses to SS were evaluated in 5 animal studies.²⁻⁶

One study² examined the inflammatory response to SS implants placed in the peritoneal cavity of CF1 mice. Uncoated SS implants produced significant inflammation (96% showed macrophage activation in 7 days) compared to glass slides (5%) and coated SS implants. SS induced proinflammatory cytokine release by macrophages.

One study³ examined the inflammatory response to SS catheters placed in the dermis and subcutaneous tissue in the back of farm swine. Significant inflammation occurred around both SS and Teflon catheters up to day 7 with no significant differences. The authors reported "the overall area of inflammation and fat necrosis did not differ between materials and the only effect observed was attributed to wear-time rather than material."

One study⁴ examined the inflammatory response to SS debris injected into the epidural space at L4-L5 of the spine in New Zealand white rabbits. After 24 weeks little to no inflammatory response or fibrosis was observed in the epidural space that received no, 1.5 mg, or 4.0 mg of SS debris.

One study⁵ examined the inflammatory response to SS screws and other SS components in the Barostim neo electrode assembly and implantable pulse generator implanted in male sheep. Only minimal granulomatous inflammation typical of a foreign body reaction elicited by chronic device implantation was observed. No erosion, thrombosis, or stenosis was seen at the implant site. The study did not have a non-SS control device. Two unconnected electrodes served as unstimulated controls.

One study⁶ examined the inflammatory response to SS fastening devices used for gastric plication in dogs. In this study, significant inflammatory responses were observed with full-thickness braided polyester sutures, but only mild mucosal erosion was observed with SS or Ti wire staples and SS tube T-tag fasteners.

Systemic Responses

One study⁴ examined the inflammatory response to SS debris injected into the epidural space at L4-L5 of the spine in New Zealand white rabbits. After 24 weeks the pathology examinations did not detect any gross abnormalities in any organ or body cavity.

Factors Associated with Systemic Responses

The study authors reported “most of the [SS] particles were found in the epidural space of the spine at the injection site indicating little systemic migration.”

Overall Quality of Evidence

The evidence base for animal studies is small with only five studies examining different SS containing devices, using different animal models, and different methods of SS exposure. Findings were mixed. SS produced significant inflammatory responses in 2 studies: when SS implants were placed in mice peritoneal cavities, and when SS catheters were placed in pig skin. SS produced little to no inflammatory response in three studies: when SS debris was placed in the epidural space in rabbit spines, when SS containing pulse generators were placed in the chest of sheep, and when SS sutures and staples were used for gastric plication in dogs. The quality of evidence for local responses is very low because it contains only five studies providing contradictory evidence. The quality of evidence for systemic responses is very low because only one study reported systemic responses.

Neurology

One human study (1 nonrandomized comparative study⁷). For further information see Table 5 Appendix D.

Local Responses/Device Events (human studies)

The study analyzed bare metal stents (SS, CoCr, or platinum Cr) versus non-SS first- and second-generation drug-eluting stents in patients undergoing extracranial vertebral artery stenting. Follow-up was after at least 6 months, with a sample size of 139 patients that were 72.2% male receiving SS bare metal stent, with a mean age of 67.5±8.6 years.

In the bare metal stent group, in-stent restenosis/in-stent occlusion occurred significantly less often with SS (17.8%) and CoCr (19.0%) as compared to platinum-Cr (38.9%) stents up to 6 months, p=0.034.

Overall Quality of Evidence

Overall quality of evidence for local responses was rated very low due to limited reporting from 1 study. Quality of evidence for systemic responses was also very low (no studies reporting).

Obstetrics

Two human studies (1 randomized controlled trial (RCT),⁸ and 1 nonrandomized comparative study⁹). For further information see Table 6 Appendix D.

Local Host Responses (human studies)

Studies analyzed subcuticular SS staples versus polyglactin suture⁸ and polylactic/polyglycolic acid subcuticular staples⁹. Follow-up ranged from 3 to 10 days, with a sample size of 95 to 376 female patients, with a mean age of 27 to 36 years.

Seroma: Both studies reported on seroma formation. The RCT⁸ reported no significant differences in outcomes among 6 patients (1.6%) and 5 patients (1.4%) in the staple and suture groups respectively, with respect to seroma formation at 4 to 10 days post-operatively, with a 0.084 95% confidence interval. The nonrandomized comparative study⁹ reported 2 patients (2.1%) and 1 patient (1.1%) in the SS and polylactic/polyglycolic acid groups, respectively, with seroma formation at 3 days post-operatively.

Hematoma: The RCT⁸ reported no significant differences in outcomes among 4 patients (1.1%) and 2 patients (0.5%) in the staple and suture groups respectively, with respect to hematoma formation at 4 to 10 days post-operatively, with a 0.51 95% confidence interval.

Pain: The nonrandomized comparative study⁹ assessed pain via anti-inflammatory medication use at 3-day follow-up. There was a 1.5-fold decrease in ketorolac use ($p < 0.0001$) and a trend toward decreased ibuprofen use in the poly(lactic)/poly(glycolic) acid staple cohort ($p = 0.06$). There was no difference in the hydrocodone/acetaminophen use between groups ($p = 0.89$).

Overall Quality of Evidence

Overall quality of evidence for local responses was rated very low due to limited reporting of events from 2 studies. Quality of evidence for systemic responses was also very low (no studies reporting).

Ophthalmic

One human study (1 systematic review (SR)¹⁰). For further information see Table 7 Appendix D.

Local Responses/Device Events (human studies)

The SR consisted of 7 single-arm studies assessing the safety of a SS glaucoma filtration device and 11 comparative studies assessing safety of the same device compared with a standard trabeculectomy. Patient characteristics were not reported. Follow-up ranged from 9.7 to 40.1 months with a sample size of 10 to 231 eyes.

Hyphema was the most commonly reported adverse event, appearing in 8 comparative studies at a rate of 0 to 4% in the device group and 5 to 40% in the trabeculectomy group; it was also reported in 5 single-arm studies at a rate of 2 to 15%. Shallow/flat anterior chamber was reported in 7 comparative studies at a rate of 2 to 20% in the device group and 0 to 20% in the trabeculectomy group. Bleb leak was reported in 4 comparative studies at a rate of 1.7 to 29% in the device group and 1.6 to 18% in the trabeculectomy group; it was also reported in 4 single-arm studies at a rate of 4 to 15%. Choroidal effusion was reported in 3 comparative studies at a rate of 0 to 8% in the device group and 3.2 to 38% in the trabeculectomy group; it was also reported in 2 single-arm studies at a rate of 8 to 8.3%. Choroidal detachment was reported in 2 comparative studies at a rate of 7.5 to 20% in the device group and 2.5 to 36% in the trabeculectomy group; it was also reported in 2 single-arm studies at a rate of 8 to 8.3%. Endophthalmitis was reported in 2 comparative studies at a rate of 0 to 2% in the device group and 0 to 1.6% in the trabeculectomy group. Hypotony from 1 day to 1 week was reported in 6 single-arm studies at a rate of 4 to 32%. Maculopathy was reported in 2 comparative studies at a rate of 5% in the device group and 6% in the trabeculectomy group. Blocked tube and device contact with eye anatomy were each reported in 2 single-arm studies at a rate of 1 to 3% and 4 to 12.5%, respectively. Cataract requiring surgical treatment was reported in 1 comparative study at a rate of 5.1% in the device group and 11.5% in the trabeculectomy group. Membrane over tube, shunt migration, and lens opacity were each reported in 1 comparative study at a rate of 3% in the device group, with no cases of membrane or migration in the trabeculectomy group, but a rate of 13% of lens opacity. Cataract requiring surgical treatment was reported in 1 comparative study at a rate of 5.1% in the device group and 11.5% in the trabeculectomy group. Corneal Dellen was reported in 1 comparative study at a rate of 1.7% in the device group, with no cases in the trabeculectomy group. Encysted bleb and opacity of the posterior capsule were each reported in 1 single-arm study at a rate of 54%. Spikes in intraocular pressure within 1 month postoperatively were reported in 1 single-arm study at a rate of 17%. Bleb fibrosis and conjunctival leakage were each reported in 1 single-arm study at rates of 8% and 6%, respectively. Choroidal and intraocular hemorrhage were each reported in 1 single-arm study at rates of 1% and 4%, respectively. Device clotting, macular edema, retinal branch vein occlusion, and shunt closure were each reported in 1 single-arm study at a rate of 4%. Aqueous misdirection was reported in 1 single-arm study at a rate of 1%. Finally dislocated implant, exposed implant, and dyesthetic bleb were each reported in 1 single-arm study at a rate of 0.4%.

Overall, the comparative studies reported lower post-operative complication rates with the device when compared to trabeculectomy.

Overall Quality of Evidence

Overall quality of evidence for local responses is very low due to limited reporting by 1 SR of low-quality studies and the reporting of mostly low rates for responses. Authors indicated that surgical techniques for both trabeculectomy and the EX-PRESS device implantation varied. In addition, the reporting of postoperative complications of surgery in glaucoma clinical trials, as summarized in the Guidelines on Design and Reporting of Glaucoma Surgical Trials, make it difficult to draw firm

conclusions regarding the relative safety of the EX-PRESS device compared with trabeculectomy. Quality of evidence for systemic responses was also very low (no studies reporting).

General, Plastic Surgery

One human study (1 SR¹¹). For further information see Table 8 Appendix D.

Local Host Responses (human studies)

One single arm study in the SR analyzed 120 patients undergoing minimally invasive direct coronary artery bypass or totally endoscopic coronary artery bypass using a SS distal anastomotic device at 29-week follow-up. Patient characteristics were not reported.

There was 1 report of myocardial infarction (0.8%), 2 post-operative hemorrhages (1.6%), and 1 pericardial effusion (0.8%).

Systemic Responses

One single arm study in the SR analyzed 120 patients undergoing minimally invasive direct coronary artery bypass or totally endoscopic coronary artery bypass using a SS distal anastomotic device at 29-week follow-up. Patient characteristics were not reported.

There was 1 report each (0.8%) of patient death, cerebrovascular accident, brachial artery embolization, and phrenic nerve palsy. There were 2 reports of pleural effusion requiring intervention (1.6%).

Overall Quality of Evidence

Overall quality of evidence was very low due to limited reporting by 1 single arm study with low rates for responses. Quality of evidence for systemic responses was also very low.

ENT

One human study (1 single-arm study¹²). For further information see Table 9 Appendix D.

Local Responses/Device Events (human studies)

The study analyzed 59 esophageal achalasia patients receiving a SS stent at a mean follow-up of 36 months. The patients were 50.8% male with a mean age of 53.7±21.6 years.

Twelve patients (25.5%) complained of substernal pain, with four patients requiring analgesics. 5 patients (10.6%) had substernal burning, alleviated by antacids. 4 patients (8.5%) had stent migration within 1 month after insertion. No patients experienced bleeding or esophageal perforation.

Overall Quality of Evidence

Overall quality of evidence for pain and migration is low due to agreement with other devices (dental, cardiovascular, and orthopedic). Overall quality of evidence was rated very low for other local responses (burning) and systemic responses (no studies reporting).

Dental

Sixteen human studies (7 SRs,¹³⁻¹⁹ 5 RCTs,²⁰⁻²⁴ and 4 nonrandomized comparative studies²⁵⁻²⁸). For further information see Table 10 Appendix D.

Local Responses/Device Events (human studies)

Arch wires: One SR¹³ addressed fixed or removeable appliances and auxiliaries (including arch wires). Multistranded SS arch wires (n=43) were compared with non-SS (nickel-titanium; n=42) in 2 RCTs. Eighty-five patients with a mean age of 14 were included; 51% were female. Contact duration was up to 24 hours.

Results indicated significantly greater pain with non-SS arch wires at 12 hours ($p=0.02$), day 1 in the morning ($p=0.03$), afternoon ($p=0.03$), and at bedtime ($p=0.04$); only p values provided. No statistically significant difference was reported for overall pain.

Screws: One RCT²² evaluated 386 bone screws placed in patients requiring bilateral infrazygomatic crest (IZC) anchorage to retract maxillary teeth. Half of the screws were 316LVM surgical SS, and the other half were non-SS (Ti6Al4V TiA). The study population was 80% female with a mean age of 24.3 years (range 10.3 to 59.4 years). Contact duration was 6 months.

No significant difference in failures (27 (7%) SS screws, 22 (5.7%) TiA; $p=0.07$) was reported. Failure rate by mucosal type (attached gingiva (AG), moveable mucosa (MM), right side and left side) indicated significantly higher failure rates with SS in AG (7.4% SS, 5.1% Ti), and right side (7.8% SS, 5.2% Ti).

Paraposts: One RCT²³ addressed SS parapost (PP) vs glass fiber-reinforced post (FRP) for tooth restoration. All the posts were cemented with dual cure resin composite. The study population was 38 patients (19 each arm), with a mean age of 38.2 ± 16.86 years (range 18 to 74). Contact duration was 1 to 6 months.

Results indicated 1 case of core fracture with SS at 1 month in a tooth also reported as having marginal failure and Grade 2 mobility. Initial core failure was however due to loss of adhesive bond between the core material (SS) and the post.

Retainers: Two studies^{14,20} addressed retainers.

One SR¹⁴ of 7 RCTs investigated the failure rate of fixed orthodontic retainers. Materials were 0.0175" SS wire vs. fiber reinforced composite (FRC) retention. The study analyzed 503 patients (715 SS, 654 FRC teeth/retainers); age NR. Contact duration was 1 to 6 years.

Results indicated no significant difference between treatments for failure rate (log risk ratio 0.01, 95% CI: -0.32 to 0.34). Failure rates ranged from 10% to 36.4% for SS, and 11.2% to 50% for FRC retention. Failure rate consisted of detachment, wire breakage, adhesive failure, and retainer loosening.

One RCT²⁰ examined different lingual retainers: dead-soft retainer, SS retainer, a nitinol retainer, and connected bonding pad in 132 patients (33 per arm). Mean age was 16 years. Contact duration was 1 year. Results indicated "no clinically significant worsening of periodontal health and relapse was seen in any groups after 1 year."

Wires: 4 studies^{17,19,24,27} addressed SS retainer wires.

One SR¹⁷ focused on closed treatment for patients with mandibular condyle fractures. SS wires (5 studies; 2 studies used SS wires and elastics) vs guiding elastics/elastics (5 studies) for maxillomandibular fixation. Mean age was 31 years. Mean contact duration was 3 weeks (range 5 days to 49 days).

One SR¹⁹ focused on multistrand SS, 0.015-inch Twistflex (Unitek corp, Monrovia USA) vs Superelastic NiTi, 0.014 heavy Japanese NiTi (GAC International USA) as first arch wires in 21 patients each. Age range was 113 to 202 months. Contact duration was 24 hours to 15 days.

One RCT²⁴ examined SS wire plus composite resin reinforcement vs Ribbond ribbon plus composite resin reinforcement for splinting overunsplinted mobile teeth following periodontal surgery in 30 chronic periodontitis patients with Grade I to Grade II mobility of upper and/or lower anterior teeth. Mean age was 45 years (range 35 to 55 years). Contact duration was 12 weeks.

One nonrandomized comparative study²⁷ examined the level of Ni and Cr released into saliva from fixed orthodontic appliances (4 bands, SS brackets, and upper and lower nickel-titanium or SS arch wires, $n=40$) vs no fixed orthodontic appliances ($n=50$). Mean age was 16 years to 23 years. Contact duration was 1 month to 32 months.

Results for these 4 studies follow:

Occlusion (1 study): 1 SR¹⁷ reported occlusion in 2% to 18% of SS wires (663 wires, 4 studies reporting) vs 24% of elastics (489 elastics, 1 study reporting) up to 7.8 years.

Pain (2 studies): 1 SR¹⁷ reported pain at rest ranging from 2% to 16% with SS wires (4 studies reporting) vs 9% to 15% with elastics (4 studies reporting) up to 7.8 years. 1 SR¹⁹ reported no significant difference with SS wires vs non-SS wires in pain at day 1 (mean difference (MD) -5.3, 95% CI: -18.34 to 7.74) or day 7 (MD -0.7, 95% CI: -1.97 to 0.57).

Mobility, plaque, partial fractures (1 study): 1 RCT²⁴ reported more partial fracture with SS vs Ribbond ribbon. Higher reduction (28.47%) in tooth mobility with splints (SS or Ribbond ribbon) vs no splints. Slightly higher reduction in tooth mobility with SS vs Ribbond (36.11% vs 35.42%). Similar increases in plaque index between SS and Ribbond after flap surgery and splint removal. Both treatments showed “good compatibility with gingival tissues and oral mucosa, were successful in immobilizing teeth, durable in function, and well-tolerated.”

Material leakage in saliva (1 study): 1 nonrandomized comparative study²⁷ reported mean levels of Ni in the fixed orthodontic appliances (with SS brackets and arch wires) were almost twice as high vs controls, while mean levels of Cr were lower with fixed orthodontic appliances. Overall, the Ni and Cr levels in the saliva of individuals receiving fixed orthodontic appliances were much lower than levels that would be considered toxic.

Crowns: Six studies^{15,16,18,21,25,26} addressed this topic.

One SR¹⁵ of 8 studies (6 nonrandomized comparative) focused on hypersensitivity responses and allergic/toxic reactions associated with pediatric SS crowns (SSCs). One large study examined Ni-containing intra-oral devices including SSC (n=350) vs no Ni-containing intra-oral devices (n=350) however the crowns included the old formulation of 72% Ni. Another study compared SSC placement (n=17) with lingual arch space maintainer (n=17). Contact duration was 7 days to 6 months in 1 study reporting.

Responses included Ni hypersensitivity reactions in 2 patients after SSC placement. Perioral skin eruptions at 1 week, and ulcerative contact gingivitis after 1 month occurred in 1 patient each. One study (n=37) reported genotoxic damage at the cellular level of the oral mucosa and an increase in the urinary excretion of Ni within 45 days of exposure. The remaining 5 studies did not report any additional skin hypersensitivities or harmful toxic metal levels with SSCs.

One SR¹⁶ included 6 studies comparing pre-veneered SSCs with other crowns (resin composite strip crowns, open-face SSCs (OSSC), zircon crowns) while 2 studies compared 2 different pre-veneered SSCs (VSSC). Age range was 3 to 9 years. Contact duration was 1 year to 4 years. Responses included chipping, gingival health, plaque, deterioration, fracture, retention, appearance, and failure.

NuSmile VSSCs (n=11) vs SSCs (n=11) in a split-mouth study: Nusmile VSSCs were all partially chipped at 4 years f/u. Better gingival health with SSCs at 6 months; no difference at 4 years.

Different VSSCs (NuSmile® (n=37), Pedo Pearls™ (n=24) and ex vivo VSSC (n=50) with SSCs (3M ESPE; n=93)) or OSSCs (n=60): NuSmile plaque index (PI) was superior to other crowns. Measurements of GI, pocket probing depth, and simplified oral hygiene index (OHI-S) indicated deterioration in all crown types.

Ex vivo VSSCs (n=15) vs open-faced SSCs (n=18): Failure (loss of one-third or more of the aesthetic material) noted in fewer OSSCs (5% OSSC vs 20% ex vivo VSSC). All failures occurred in lower crowns.

VSSCs (NuSmile (n=36) vs Kinder Krowns (n=36)) (2 studies):

Kinder Krown VSSCs were significantly more likely to fracture during year 1 post-placement ($p<0.02$)(data not shown).

Crown retention was 99.2% due to loss of 1 Kinder Krown.

Buccal façade fractures occurred in 9% of crowns; higher proportion of fractures on mandibular m2 than on maxillary m2 regardless of brand.

Occlusal façade fractures occurred in 15% of crowns; higher proportion of fractures on maxillary m1 vs mandibular m1.

Façade wear was reported in 9%, no difference between groups.

3 aesthetic full-coronal restorations (composite SSCs (3M ESPE) (n=43), NuSmile SCCSx (n=43) and Zirkiz zircon crowns (ZCs) (n=43); 1 to 4 crowns per child:

Crowns appeared normal in 78% SSCs, 95% VSSCs, and 100% ZCs (significant difference favoring VSSCs over SSCs ($p=0.04$) and ZCs over SSCs ($p=0.02$).

No significant difference in tooth wear on opposing teeth (100% SCs, 100% VSSCs, 90% ZCs).

Statistically significant difference in mean gingival index (GI) for SCs and ZCs ($p<0.01$), VSSCs and ZCs ($p<0.01$).

One SR¹⁸ of 5 RCTs compared preformed metal crowns (PMCs), SS with white veneer cover, and crowns made wholly of a white ceramic material in 483 children aged 2 to 10 years. Contact duration was 1 year to 5 years. Results included major failure (composite of pain, pulp infection, discharging sinus, dental abscess, or periradicular pathology on radiographs), pain, gingival bleeding, and bone resorption.

Crown vs filling (4 studies):

Failures (1 study): No failures in either group up to 12 months.

Pain (2 studies, 312 teeth): In the long term (12 to 24 months), crowns were favored vs fillings (Risk Ratio (RR) 0.15, 95% CI: 0.04 to 0.67). Short-term results were not estimable.

Gingival bleeding (3 studies): results were not conclusive however increased risk of bleeding with crowns vs fillings; short term (<12 months): RR 1.69, 95% CI: 0.61 to 4.66, $n=226$, 2 studies; long term (12 months): RR 1.74, 95% CI: 0.99 to 3.06, 195 teeth, 2 studies

Crown vs no crown or filling (one 3-arm study (n=92)): When comparing PMC using the Hall technique ($n=44$) vs non-restorative caries treatment (fluoride varnish) ($n=48$), results at 1-year follow-up indicated:

Failures: Crowns less likely to result in a major failure (RR 0.12, 95% CI: 0.01 to 2.18), though the result was inconclusive.

Gingival bleeding: Crowns seemed more likely to cause gingival bleeding though the result was inconclusive (RR 1.09, 95% CI: 0.42 to 2.86).

Crown (SS) vs aesthetic veneer crown using the conventional technique (1 split-mouth study, $n=11$): Follow-up at 6 months and 4 years indicated:

Gingival bleeding: At 6 months, significantly more bleeding with aesthetic veneer (100% (10/11 bled on probing) vs 0% PMC; RR 23, 95% CI: 1.52 to 347.76). At 4 years ($n=10$), similar gingival bleeding in 1 patient each (RR 1, 95% CI: 0.07 to 13.87).

Bone resorption: At 6 months, 1 case of bone resorption with veneer (RR 3, 95% CI: 0.14 to 66.53).

One RCT²¹ compared SS crowns with zirconia crowns in 60 children with pulpectomised bilateral mandibular primary second molars. Mean age was 8.1 years; 63% were female. Results indicated significantly less gingival inflammation (measured by gingival index (GI) and plaque index (PI)) with zirconia crowns vs SSCs at all follow-ups (3 months, 6 months, 9 months, and 12 months).

One nonrandomized comparative study²⁵ reported local responses with 276 SSCs vs 280 composite resin crowns to repair primary molars in 84 patients with caries, pulpitis, and periapical periodontitis. Mean age ranged from 1 year to 8 years. Contact duration was 6, 12, and 24 months. Results indicated restorative loss was significantly less with SSCs (4 SSC, 28 composite resin), and a significant difference in failure due to marginal integrity at 24 months only (4 (7.7%) SSC, 16 (44.4%) resin). Recurrent caries significantly lower with SSCs at all follow-ups (6 months: 1 (0.9%) SS, 7 (7.8%) resin; 12 months: 3 (3.2%) SSC, 8 (13.1%) resin; 24 months: 4 (7.7%) SSC, 16 (47.1%) resin).

Lastly, 1 nonrandomized comparative study²⁶ reported detecting inflammation (macrophage inflammatory protein-1a and protein-1b) in all 80 samples from children with SSCs ($n=20$), dental caries ($n=20$), dental caries involving pulp ($n=20$), and

healthy children (n=20). Highest mean concentration in gingival crevicular fluid was obtained for dental caries with pulp followed by dental caries, then SSCs.

Systemic Responses

One nonrandomized comparative study²⁸ compared fixed appliances (consisting of SS arch wires, brackets and bands)(n=30) vs no fixed appliances in age and gender matched siblings (n=30). Results indicated significantly higher urinary Ni concentrations up to 21 months with fixed appliances vs controls (difference 1.98 $\mu\text{g/L}$, 95% CI: 0.523 to 3.319), and males receiving fixed appliances vs controls (difference 3.02 $\mu\text{g/L}$, 95% CI: 0.479 to 5.513). Authors noted only slight elevation in urinary Ni concentrations from fixed appliances used for at least 12 months.

Overall Quality of Evidence

Overall quality of evidence for failure, fracture, inflammation, and pain was rated low due to being consistently reported across high-quality studies and in agreement with other SS devices (e.g., orthopedic and cardiovascular). Quality of evidence for other local responses and systemic responses was rated very low (only 1 small nonrandomized comparative study reporting urinary Ni concentrations).

Cardiovascular – miscellaneous

Seven human studies (3 SRs,²⁹⁻³¹ 1 RCT,³² and 3 nonrandomized comparative studies³³⁻³⁵. For further information see Table 11 Appendix D.

Local Host Responses (human studies)

Ventricular assist devices (VADs): Two studies^{29,33} addressed this topic. One SR of 27 observational studies²⁹ reported results for a SS VAD (Berlin Heart EXCOR [BHE], Berlin Heart AG, Berlin, Germany) vs non-SS VADs (e.g., Thoratec, Medos, HeartWare HVAD, HeartMate II, and Novacor) in 558 patients with a mean age of 4.7 years (range 3 days to 18 years). VAD support was up to 842 days.

Use of the SS VAD (BHE) was reported in 486 (87%) patients. Use of non-SS VAD was less than 8% of patients in 1 device (7.5% Thoratec) and less than 5% of patients in 4 devices (3.8% Medos, 1.8% HeartWare HVAD, 1.25% HeartMate II, and 0.36% Novacor).

Bleeding incidence was higher with SS vs all non-SS devices (40% BHE (n=471); non-SS: 25% Medos (n=16), 16% Thoratec (n=19), 11.1% HVAD (n=9)). Bleeding incidence was due to gastrointestinal bleeding, intracranial hemorrhage, and chest re-exploration for bleeding.

Thromboembolism incidence with SS was 25% (n=471). Incidence with non-SS was 37.5% (Medos (n=16), 26% Thoratec (n=19), and 33.3% HVAD (n=9). Thromboembolism incidence was defined as neurological thromboembolic events including stroke, transient ischemic attack; arterial non-central nervous system thromboembolism, device exchange due to thrombosis, and venous thromboembolism.

Less death was reported with SS (26.5% BHE) vs 2 non-stainless devices (50% Medos, 47% Thoratec) but higher vs 1 non-stainless (11.1% with HeartWare HVAD). The most frequent causes of death were multi-system organ failure in 17% of patients (24/143), TE neurological complications in 16% (23/143), ICH in 14% (20/143), circulatory failure in 10% (15/143), sepsis in 7% (10/143), systemic TE in 2% (3/143), and pump thrombosis in 0.7% (1/143).

One nonrandomized comparative study³³ also reported use of BHE vs non-SS VADs (CentriMag, HeartWare, and HeartMate II) in 12 patients (13 episodes of heart failure) as a bridge to transplantation or cardiac recovery. BHE was used as a left VAD (LVAD) and biventricular VAD (BIVAD). Average VAD use was 159.7±234.2 days (range 3 to 823 days). Local responses included:

Bleeding: 1 (14.2%) patient with BHE.

Overall incidence of neurologic events was 23%; occurring in all 3 patients in the first 3 months. Cerebral hemorrhage occurred in 2 (28%) patients with BHE (1 with BHE LVAD who died on support, 1 with BHE BIVAD which was exchanged to non-stainless VAD); hemorrhage occurred at day 3 in 1 patient. One patient with non-SS LVAD (50%) had an acute ischemic stroke. Both surviving patients did not have permanent neurological sequelae.

Pericardial window (surgery done on the sac around the heart in which a small part of the sac is removed to allow extra fluid to drain from the sac) was created for relieving tamponade in 2 patients (15%); 1 each SS (BHE LVAD) which occurred at day 28, and non-SS (both patients experienced late death after transplant due to graft rejection).

Bowel ischemia and fibrin embolism occurred in 1 (14.2%) patient with BHE LVAD at day 16.

Pump exchanges (due to fibrin, thrombus formation, or expiration) was required in 4 patients overall (31%); 43% of BHE, 16.6% all non-stainless. Pump exchange with BHE occurred at day 15 and day 45 in 2 patients.

Threads for sternal closure: One RCT³² addressed use of SS wire threads vs. polydioxanone threads (PDS) for sternum closure of pediatric patients after cardiac surgery in 16 patients (8 each arm). Mean age was 8 years; 69% were male. Follow-up was 6, 9 and 12 weeks. Results indicated a significantly higher degree of pain with SS at 6 weeks and 9 weeks, and no significant difference in stability at any time point. Significantly more displacements were reported with PDS at all time points. At 6 weeks and 9 weeks, displacement occurred in 5 patients (1 SS, 4 PDS; $p=0.02$) and 6 patients (1 SS, 5 PDS; $p<0.01$), respectively. At week 12, displacement occurred only with PDS (0 SS, 5 PDS; $p<0.01$).

Distal anastomotic devices (DADs): One SR³⁰ of 28 mostly single arm studies focused on use of DADs during coronary artery bypass graft (CABG) surgery. Devices included 2 DADs with SS components (St. Jude DAD with a SS connector; and the C-port anastomotic system which utilizes 8 separate SS clips); and 6 DADs without SS components (Magnetic vascular positioner (MVP, Heartflo, U-clip device, Vessel Closure System (VCS), DAD with a nitinol ring, and Coronary anastomosis coupler (CAC) device with nitinol frame). Devices evaluated were 452 SS DADs (112 St Jude, 340 C-port), and 667 non-SS DADs (69 MVP, 459 U-clip, 71 Heartflo, 17 VCS, 14 DAD, 37 CAC).

Local responses included 2 cases of myocardial infarction (MI) due to device failure with SS DAD. Rates of postoperative hemorrhage with SS were 1.6% (1/61 with St. Jude) and 2.2% (4/180 with C-port). Rates of postoperative hemorrhage ranged from 0.8% to 5.9% with non-SS ((U-clip: 0.8% (1/123), Heartflo: 1.4% (1/71), VCS: 5.9% (1/17)). Anastomotic patency was similar at early (<1 month), intermediate (1-3 months), and long-term (>3 months) follow-ups. There was a significant reduction in patency from early to late periods with both SS DADs (St. Jude (100% to 73%) and C-port (99.1% to 93.8%)) and 1 non-SS DAD (MVP (96.8% to 88.5%)).

Inferior vena cava (IVC) filters: One nonrandomized comparative study³⁴ addressed use of IVC filters with SS Greenfield filters vs non-SS IVC filters (Gunther Tulip filters from nonferromagnetic Conichrome; and platinum Celest filters). Mean follow-up was 286 days (SS); and 277 and 437 days (non-SS). Mean age was 60 years (range 28 to 87 years); with 51% males. Devices evaluated were 50 SS, and 415 non-SS (160 Tulip, 255 Celest).

Perforation was the only reported local response with SS. Results indicated significantly lower IVC perforation rate with SS Greenfield filters (1 (2%) Greenfield, 126 (49%) Celest, 69 (43%) Tulip filters). Zero SS filters were rated Grade 3 (perforating strut contacted an adjacent organ), while 120 non-SS filters were rated Grade 3 commonly perforating the duodenum, a vertebral body, and the aorta.

Stents for aortic coarctation: One SR³¹ and 1 non-randomized comparison study³⁵ examined stent implantation for treating coarctation of the aorta. The SR by Yang et al. (2016) examined 43 patients undergoing a procedure using a SS-based stent and saw 100% successful cases with only 14% of patients undergoing complications. The authors noted that Begg's test for small study effects showed no evidence of bias for the analysis of success ($p = 0.502$) and stent-related complications ($p = 0.091$), however there was a slight suggestion of bias for the complication outcomes ($p=0.010$). The non-randomized comparative study found that five patients, implanted with two different types of bare SS stents, experienced aortic wall complications, while the remaining patients with a variety of bare metal and coated stents experienced no complications.

Overall Quality of Evidence

Overall quality of the evidence for local responses was rated very low due to a limited number of studies reporting on each device type, and dissimilar reporting of responses. Systemic responses were also rated very low due to no studies reporting.

Cardiovascular – grafts

One human study (1 single-arm study³⁶). For further information see Table 12 Appendix D.

Local Host Responses (human studies)

One single-arm study³⁶ evaluated 6 patients with ruptured abdominal aortic aneurysms who were treated with Zenith AAA Endovascular Graft containing SS. At mean follow-up of 22 months (range 19 to 29 months), 1 patient required exploratory laparotomy with decompression for abdominal compartment syndrome. The complication may be due to underlying conditions (e.g., renal function impairment).

Systemic Responses

One patient experienced pneumonia, pulmonary tuberculosis, and urinary bladder incontinence. Another patient experienced chronic renal failure and limb ischemia requiring femoro-femoral bypass after stent graft insertion. Complications may be related to underlying conditions.

Overall Quality of Evidence

The quality of evidence for local responses and systemic responses is very low because the evidence base is only a single small study that lacks randomization, a control group, and blinding.

Cardiovascular – coronary stents

We included 10 human studies (5 SRs³⁷⁻⁴¹, 2 RCTs^{42,43}, and 3 non-randomized comparative studies⁴⁴⁻⁴⁶). For further information see Table 13 in Appendix D.

Local Host Responses (human studies)

SS steel compared with CoCr based/platinum Cr stents. Seven studies including three systematic reviews (SRs)³⁹⁻⁴¹, two RCTs^{42,43}, and two non-randomized comparative studies^{44,45} examined patients undergoing coronary procedures with SS or CoCr based/platinum Cr stents. For the included SRs, the comparisons were the following: Paclitaxel-eluting stents (PESs) Taxus Liberté, Taxus Express, or Taxus Express2 (SS) vs. everolimus-eluting stents (EESs) Xience V (CoCr)³⁹; sirolimus eluting stents (SESs) Cypher and Cypher Select/Plus (SS) vs. zotarolimus-eluting stents (ZESs) Endeavor (CoCr)⁴⁰; and Taxus Express, Cypher, Taxus Liberté (SS) vs. CoCr (Xience V, Zomaxx, Endeavor, Costar, NEVO).⁴¹

The SR by Alazzoni et al. (2012)³⁹ favored the CoCr-based EESs over SS-based PESs for all local adverse events, including myocardial infarctions (MIs), stent thrombosis (ST), target lesion revascularization (TLR), and target vessel revascularization (TVR) for 24 to 48 month follow-up. Similarly, the SR by Moreno et al. (2011) favored CoCr over SS stents for MI events (OR[odds ratio] 0.72, 95% CI [confidence interval] 0.58 to 0.91, p=0.006), however, there was no difference found for ST occurrence between SS and CoCr stents up to 30-day follow-up. The last SR by Sethi et al. (2012)⁴⁰ favored SS-based SESs over CoCr-based ZESs for most local adverse events, including in-segment late lumen loss (LLL), in-segment restenosis, in-stent restenosis, TLR, and TVR between 12- and 36-month follow-up.

Two RCTs^{42,43} also comparing drug eluting stents (DESs) found no difference or better outcomes with PtCr/CoCr for the majority of adverse events. Gao et al. (2015)⁴² enrolled 500 patients and only found that LLL (in-segment and in-stent) favored PtCr-based EES over SS-based PES up to 1 year. The other RCT by Wijns et al. (2014)⁴³ contained approximately 4,500 patients and favored CoCr-based ZES for MI events, ST, and TLR, whereas, no difference was seen for major adverse cardiac events, thrombolysis in MI, and TVR.

Lastly, two non-randomized comparative studies^{44,45} also examined different types of DESs made of SS or CoCr. One large prospective cohort⁴⁴ with over 10,000 enrolled patients favored CoCr based SESs over SS-based biolimus-eluting stents (BESs) for MI events, target lesion failure (TLF), TLR, target vessel failure (TVF), and TVR up to one year. The other study⁴⁵, a retrospective review with 481 included patients, favored SS-based early-generation DESs for major adverse cardiac events over new-generation DESs made of CoCr or PtCr. All other adverse events (MI, ST, TLR, TVR) had no differences in event rates between early generation and new generation stents.

Stainless steel compared with other non-SS stents. Two studies (one SR³⁷ and one non-randomized comparative studies⁴⁶) compared SS stents to a variety of non-SS stents. The SR³⁷ contained 40 RCTs with 34,850 patients with our analyses focusing on two subgroup comparisons of interest: biopolymer-coated SS DESs vs other alloys (no coating) and SS-DESs (no coating)

vs biopolymer-coated other alloy DESs. All analyses displayed no difference except for ST (definite and probable) between 30 days and 1 year favoring biopolymer-coated DESs over other alloy DESs. One non-randomized comparative study⁴⁶ saw favorable outcomes for cardiac-event free survival, restenosis rate, and TLR for SS-based stents over a mix of bare metal stents.

Stainless steel compared with other SS stents, or single arm studies. A single SR compared two different SS-based stents.³⁸ The SR by Zhang et al. (2014) divided their results based on study design (RCTs, adjusted observational studies, and non-adjusted observational studies) with most results favoring the SS-SES over the SS-PES. The directionality and magnitude of all evidence was dependent on the study design.

Systemic Responses

Stainless steel compared with CoCr based/platinum Cr stents. Six studies (2 SRs^{39,41}, 2 RCTs^{42,43}, and 2 non-randomized comparative studies^{44,45}) examined systemic responses when comparing SS stents and CoCr stents for coronary procedures. All comparisons were different types of DESs, and the systemic outcomes of interest included hemorrhagic stroke, major adverse cardiac and cerebrovascular events, and mortality. One SR by Allali et al. (2018)⁴⁵ reported that early-generation DESs made of SS may show lower mortality rates than new generation DESs made of CoCr up to 5-year follow-up ($p=0.05$). Also, for only the four-year follow-up time, CoCr-based zotarolimus-eluting stents (ZESs) were favored over SS-based SESs. All other studies' outcomes showed no difference between groups.

Stainless steel compared with other non-SS stents. Two studies (1 SR³⁷ and 1 non-randomized comparative study⁴⁶) compared SS-stents to many different types of comparators. The SR by Yan et al. (2016)³⁷ had two unique comparisons: biopolymer-coated SS DESs versus other alloy DESs and SS DESs versus biopolymer-coated other alloy DESs. The study by Hsieh et al. 2013⁴⁶ compared cypher (SS-based), Taxus (SS-based), and bare-metal stents. All studies showed no differences between groups for either mortality or stroke rates.

Stainless steel compared with other SS stents, or single arm studies. Lastly, 1 SR³⁸ compared mortality rates for two different SS-based stents (Cypher and Taxus) for follow-up times between 6 to 60 months. This SR had subgroups based on the study design of included studies. All RCT subgroups showed no difference for mortality rates, however, subgroups containing adjusted or non-adjusted observational studies may favor Cypher over Paxus stents.

Overall Quality of Evidence

Twelve studies (6 SRs, 2 RCTs, and 4 non-randomized comparative studies) examined local host responses for procedures involving coronary stents, whereas nine studies (4 SRs, 2 RCTs, and 3 non-randomized comparative studies) examined systemic responses. Common local host responses included various types of vascular complications, while common systemic responses included mortality rates. Both local and systemic responses included large patient samples with few inconsistencies by type of event across studies. Both local and systemic responses were determined to be moderate strength of evidence.

Cardiovascular – peripheral stents

We included 4 human studies (3 SRs⁴⁷⁻⁴⁹ and 1 RCT⁵⁰). For further information see Table 14 in Appendix D.

Local Host Responses (human studies)

Stainless steel compared with non-SS stents. Four studies including three SRs⁴⁷⁻⁴⁹ and one RCT⁵⁰ examined local complications for procedures involving peripherally placed stents made of SS. The placement of stents varied by study with each specific procedure narratively reported within our results. Two of the included SRs directly reported comparative effectiveness results for SS stents and non-SS stents. One SR by Giannopoulos et al. (2021)⁴⁷ included 468 patients undergoing procedures for femoropopliteal lesions. All included studies utilized ePTFE covered SS stents and included an evidence base of 10 single arm studies and 3 comparative studies. Most of their results are reported as single-arm studies, however, they report comparative effectiveness for patency for two included comparative studies. The authors stated that lesions treated with a heparin bonded ePTFE covered stent had statistically significant superior patency over BMS and POBA stents at 1-year of follow-up (OR: 2.74; 95%CI: 1.63–4.61; $p<0.001$). Another SR by Mwipatyi et al. (2020)⁴⁸ narratively reported results for a variety of SS-based stents for treating aortoiliac occlusive disease. Both primary patency and freedom from target lesion revascularization (TLR) events were comparable between all groups.

Stainless steel compared with surgery or single arm SS. The remainder of results from the included studies did not report any comparative effectiveness results for SS-based stents to non-SS based stents. One SR by Carudu et al. (2016)⁴⁹ compared SS-

based drug eluting stents (DESs) to percutaneous transluminal angioplasty (PTA) for management of below-the knee arterial critical ischemia. The review found no differences between groups for TLR, however, both primary patency and in-segment binary restenosis favored DESs. The study included meta-analyses comparing DESs to BMSs as well, however, one included study compared CoCr based DESs to bare metal stents (BMSs) so these analyses were excluded from our synthesis. One RCT by Gouëffic et al. (2017)⁵⁰ compared surgery versus SS stents for common femoral artery (CFA) stenosis. All local adverse events were infrequent, except for delayed wound healing which occurred in 16.4% of surgery cases and 0% of stent cases. Lastly, the Giannopoulos et al. (2021) review reported many local AEs for ePTFE-covered SS stents. The most common events were primary and secondary patency with other events (bypass, dissection, distal embolization, restenosis or occlusion, revascularization, and TLR) occurring with moderate to low frequency.

Systemic Responses

Two studies (Gouëffic et al. (2017)⁵⁰ and Giannopoulos et al. (2021)⁴⁷) reported low rates of amputation and mortality. The other systemic responses (only reported in Gouëffic et al.⁵⁰) of myocardial infarction and stroke also rarely occurred. The SR by Carudu et al. (2016)⁴⁹ reported moderate to high rates of amputation and mortality, however, they found no differences between groups for DES and PTA study arms.

Overall Quality of Evidence

Four studies (3 SRs and 1 RCT) examined both local and systemic responses for procedures involving peripheral stents. Common local host responses were vascular events, whereas common systemic responses were mortality and amputations. Both local and systemic responses included moderate to large patient samples with some inconsistencies by type of event across studies. Both local and systemic responses were rated low strength of evidence.

Orthopedic fixation, spine

Three human studies (1 SR⁵¹ and 2 non-randomized comparative studies^{52,53}). For further information see Table 15 in Appendix D.

Local Responses/Device Events (human studies)

Two studies reported on local responses.

One non-randomized comparative study⁵² reported implant-related complications (median 37 to 42 months follow-up) in patients receiving SS rods plus Ti screws or Ti rods and T1 screws to correct spinal deformities. Complications (rod fractures, proximal junctional kyphosis, pseudoarthrosis) did not differ among the groups. The Ti group had 15 complications and the SS group had 12 complications. Combining SS rods with Ti screws did not lead to increased implant-related complications.

One non-randomized comparative study⁵³ reported implant-related complications (minimum follow-up of 24 months) in scoliosis patients receiving SS rods or CoCr rods. No neurologic complications occurred. Four deep infections (1 in SS and 3 in CoCr) and 1 superficial infection (SS group) occurred, but no relevant causative factors were identified for the higher-than-expected infection rate.

Systemic Responses

One study reported on systemic responses.

One SR⁵¹ reported on the concentration of metal ions in blood after spinal fusion. Eighteen studies examined 653 patients (9 studies reported Ti, 8 reported Cr, and 6 reported Ni). Length of follow-up was 1 month to 14 years. Ti levels were elevated compared to controls/reference range/preoperative baseline in 7 studies with the other 2 reporting no difference. Cr levels were elevated compared to controls/reference range in 7 studies with 1 reporting no difference. Ni levels showed no difference from controls/reference range in 4 studies with 1 study reporting above normal and another elevated compared to controls. The authors concluded Cr levels are elevated after SS implant placement and Ti levels are elevated after Ti implant placement. The included studies did not evaluate the systemic effects of elevated metal ions.

Overall Quality of Evidence

The 2 studies examining local responses were both retrospective and had small sample sizes. These studies are at high risk for bias, and their complications differed therefore we rated the quality of evidence as very low.

The majority of studies in the SR had limitations, most were retrospective, that reduced their quality and increased their risk of bias. Only 1 study was an RCT. The majority of studies were considered low quality. Therefore, the quality of evidence regarding systemic responses is low.

Orthopedic fixation (non-spinal)

Ten human studies (1 SRs,⁵⁴ 3 RCTs,⁵⁵⁻⁵⁷ and 6 non-randomized comparative studies⁵⁸⁻⁶³). Five of the studies involved closing sternal incisions after cardiac surgery with a primary interest in sternal wound infections. For further information see Table 16 in Appendix D.

Local Host Responses (human studies)

Sternal closure: An RCT⁵⁵ reported no wound infections occurred among 50 patients treated with using SS wire or Ti plates up to 12 weeks. An RCT⁵⁶ comparing polymer cable ties and SS wires for sternal closure reported no differences in the sternal wound infection rate up to 4 weeks follow-up. A non-randomized comparative study⁶⁰ reported SS cables and Ti plates were not as effective at preventing deep sternal wound infections or sterile sternal dehiscence compared with polyether-ether-ketone banding at 31 ± 70 days post-op. A non-randomized comparative study⁶³ compared SS with polyether-ether-ketone banding and reported no differences in sternal wound infection rate up to 12 months after the initial cardiac operation. A non-randomized comparative study⁶² reported deep wound infection and sternal wound instability were significantly more common in patients treated with SS wire compared with nitilium clips at 30 days postoperatively.

Distal femoral fractures: One SR⁵⁴ examined intra-operative factors that contributed to non-union in locked lateral plating for distal femoral fractures, primarily comparing SS plates and Ti plates. The SR included 8 studies and 1,380 distal femoral fractures; 5 of these studies compared SS and Ti. The SR authors reported that 2 studies showed a strong association between SS plates and non-unions, but the other 3 studies showed no relationship. The authors considered the evidence base low quality since all but one of the studies was retrospective.

Distal radial fractures: A non-randomized comparative study⁵⁹ reported that complications (malunion, local pain, fracture repositioning) from internal fixation with SS plates were similar to those from external fixation up to 12 weeks.

Osteotomy: A non-randomized comparative study⁵⁸ reported that SS and nitinol staples had similar complication rates (non-union, malunion, infection) up to 12 weeks when used during osteotomy of the proximal phalanx of the big toe.

Nuss procedure: A non-randomized comparative study⁶¹ reported that 1.8% of patients treated with SS bars had allergic reaction compared with no allergic reactions in patients treated with Ti bars. Mean time for symptoms to be recognized was 22 weeks (range 2 to 52 weeks).

Lisfranc injuries: An RCT⁵⁷ reported that SS screws produced no inflammatory reactions when used for Lisfranc injuries compared with bioabsorbable polylactic acid screws which caused an inflammatory reaction in 1 (5%) patient at 2 years postoperatively.

Overall Quality of Evidence

The evidence base for sternal closure included 2 RCTs and 3 retrospective cohort comparisons and were not consistent across studies in reporting whether SS closure was less or more likely to be associated with sternal wound infections; therefore the quality of evidence is low. Distal femoral fractures were examined in a single SR considered to have low quality evidence. The other four orthopedic fixation categories were examined by only a single study (3 retrospective and 1 RCT), so the quality of evidence is very low. The quality of evidence is very low for systemic responses (no studies investigating).

Orthopedic – intramedullary rod/nail

Four human studies (3 SRs,⁶⁴⁻⁶⁶ and 1 non-randomized comparative study⁶⁷). For further information see Table 17 in Appendix D.

Local Responses/Device Events (human studies)

One SR⁶⁴ examined treating pediatric femoral fractures with intramedullary nails and reported mixed results among SS and Ti nails up to 7 years follow-up. For malunions, 3 studies reported no significant differences and 2 studies reported malunion was significantly higher with Ti nails. Four studies found no significant differences for delayed unions. Although evidence did not

support the superiority of either nail, the authors show an overall trend in support of SS since they were cheaper and provided better clinical and radiological outcomes with fewer complications.

One SR⁶⁵ examined treating extracapsular hip fractures in adults with intramedullary nails and reported no significant differences between SS nails and non-SS nails for serious adverse events and technical complications. The authors concluded the evidence from RCTs was insufficient to determine important differences in outcomes between different intramedullary nail designs.

One SR⁶⁶ examined treating humeral fractures with expandable SS bars (Disc-O-Tech Medical Technologies, Herzeliya, Israel) and reported only 2 instances of radial nerve palsy and 2 instances of nail migration among 176 patients at a mean follow-up of 9.3 weeks to 16.5 weeks.

A non-randomized comparative study⁶⁷ examining limb lengthening reported that among 16 Stryde SS nail patients none had mechanical complications and 4 had delayed healing compared with 18 Precice Ti patients with 3 mechanical complications and one delayed healing up to 14 months follow-up.

Overall Quality of Evidence

The systematic reviews varied in the quality of included studies. Only one SR included only RCTs and considered the evidence low to very low quality. The quality of evidence is very low for local responses/events and systemic responses (no studies investigating).

Orthopedic – prosthesis

Seven human studies (1 RCT,⁶⁸ and 6 nonrandomized comparative studies,⁶⁹⁻⁷⁴). For further information see Table 18 Appendix D.

Local Host Responses (human studies)

Studies analyzed SS implants versus non-SS counterparts in the categories of hip plates and implants^{68-70,73,74}, wrist fusion plates⁷¹, and cerclage tension wires⁷². Mean follow-up ranged from 18.2 months to 10 years with a sample size of 10 to 46 implants in patients with a mean age of 50.2 to 85.6 years; 0% to 87% were female.

One nonrandomized comparative study observed no adverse responses of interest in the SS group⁶⁸, though patients were examined for pseudoarthrosis, dislocation, reduction, and implant breakage.

Cancellization: One nonrandomized comparative study observed cancellization in 16 hips (39.0%) with SS, and 21 hips (48.8%) with non-SS (Ti-alloy) up to 12.4 years.⁷⁰

Hypertrophy: One nonrandomized comparative study observed cortical hypertrophy at 2-to-6-year follow-up, which enlarged progressively from 7 to 12 years before decreasing in 7 hips (17.1%) in the SS group, and 8 hips (18.6%) in the non-SS (Ti-alloy) group⁷⁰.

Dislocation: One nonrandomized comparative study observed early post-operative dislocation in 3 (6%) hips each in the SS and non-SS (Ti-alloy) groups, which were successfully reduced without recurrence up to 12.4 years.⁷⁰

Non-union: One nonrandomized comparative study observed 1 case of non-union (10%) at 3 months with SS with no corresponding cases with non-SS.⁷¹

Pain/Irritation: One nonrandomized comparative study observed 1 case implant removal due to a painful superficial branch of the radial nerve and a protruding screw (10%) at 1 year with SS with no corresponding cases with non-SS.⁷¹ Another nonrandomized comparative study observed 3 cases (16.7%) of implant removal due to irritation at mean 46.9 month follow-up in the SS group, versus 1 patient in the non-SS group.⁷² Another nonrandomized comparative study observed revision as a result of pain in 5 total patients with a SS implant (21.7%) versus 4 patients in all comparative groups (8.3%).⁷³

Wear: One RCT observed femoral head penetration from one year onward as indicative of implant wear. Penetration was lower with non-SS (oxidized zirconium) (0.02-0.03 mm/year) vs SS (0.05-0.11 mm/year).⁶⁸

Loosening: A nonrandomized comparative study observed revision as a result of aseptic loosening in 8 total patients with a SS implant (34.7%) versus 8 patients in all non-SS comparator groups (16.7%).⁷³

Luxation: A nonrandomized comparative study observed revision as a result of repeated luxation in 2 total patients with a SS implant (8.7%) versus 8 patients in all non-SS comparator groups (16.7%).⁷³

Implant failure: In one nonrandomized comparative study,⁷⁴ the 8-year survival of press-fit, grit-blasted SS cups was lower ($p=0.05$) than that of tripod grit-blasted cups made of the same alloy, which in turn had lower survival than grit-blasted cups with flanges secured with additional screws at 91%, 98%, and 100%, respectively. 8-year survival of CoCr cups was greater ($p=0.03$) than that of S cups with no screw fixation: 100% versus 91%. The failure rate was high in the group of SS press-fit grit blasted cups with no additional screw fixation (15 failures, 3.7%), which tilted acutely after symptom-free initial periods (1-9 years). 11 failures (1.3%) occurred in the tripod SS grit-blasted cups, with all but one occurring after 5 years post-operatively.

Overall Quality of Evidence

Overall quality of evidence for failure and pain was rated low due to similar reporting across 3 nonrandomized comparative studies and duplicate reporting with other SS devices (dental and cardiovascular). Quality of evidence was rated very low for other local responses, and for systemic responses (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 SS material that occurred between February 2007 and May 2022. However, these reports did not have enough information to directly associate patient harm to biocompatibility of stainless steel. Of the 1308 devices identified, 297 devices were further investigated resulting in 4050 reports. Of these reports, 42 reports were relevant to this study. The majority (18) of the reports summarized issues related to retained foreign objects followed by device migration (8) and device malfunction/failure (7). Most of these reports resulted in errors without harm (scores of C and D). A summary of the search methodology and high-level summary of the results are below:

Search methodology for Stainless Steel and related products:

- 1) General search on term "stainless steel"
 - a) Queries: 1
 - b) Results: 152 distinct records
- 2) Sampled search on PRODUCT CODE
 - a) Queries: 12
 - b) Results: 1875 distinct records
- 3) Sampled search on manufacturers
 - a) Queries: 42
 - b) Results: 2325 distinct records

55 queries, 4352 records

Devices searched

- 1) Total devices identified – 1308
- 2) Devices reviewed 297 (23%)

Surveillance

- 1) 4050 reports reviewed
- 2) Relevant reports - 42 (1%)

Findings – Complications

- 1) Retained Foreign Object - 18 (43%)
- 2) Device migration – 8 (19%)
- 3) Device malfunction/failure – 7 (17%)

- 4) Burn – 4 (10%)
- 5) Clinical Manifestations – 3 (7%)
- 6) Thrombus – 1 (2%)
- 7) Infection – 1 (2%)

Harm Scores

- 1) B – 3 (7%)
- 2) C – 15 (36%)
- 3) D – 13 (31%)
- 4) F – 1 (2%)
- 5) Not reported – 10 (24%)

Accident Investigations

Search Results:

A Boolean search engine was used to search the digital accident and forensic case files. Searching ["stainless steel"] resulted in 924 targets. The majority of these targets were in reference documents included in the investigation files and were not associated with the circumstances, findings, or conclusions of our investigation. In most of the investigations involving failure of metals, ECRI does not perform metal composition testing because our clients are more interested in its failure mechanism than its composition. Furthermore, manufacturers do not often state the metal composition. For these reasons, occurrences of "stainless steel" in our reports is usually preceded by words like "possibly", "probably", "most likely", and "not".

To limit the search to targets were potentially related to biocompatibility, ECRI searched using ["stainless steel" and "implant"], which returned 120 targets. These were individually reviewed, and 4 investigation reports were identified, none of which were applicable. In three of the cases, the metal was not actually identified, but ECRI surmised that it was probably a stainless steel. The fourth case was a retained foreign body alleged to be a hypodermic needle. ECRI determined was not a stainless-steel hypodermic needle, but a badly corroded chrome-plated iron sewing needle (it had a remnant of its thread eye.)

Searching ["stainless steel" and "tissue"] identified 273 targets of which 8 were investigation reports. Three cases were marginally applicable.

- 1) A few days post-colonoscopy, a patient was diagnosed with a colon perforation caused by a wire alleged to have been introduced during the colonoscopy. By comparison of the retained wire with wires removed from the patient's grill brush, ECRI determined by morphology, metrology, and SEM-EDX spectra (stainless steel formulation) that wires were an exact match.
- 2) At the end of a 12 hour long spinal surgery, dark, circular lesions were noted at many of the SS EMG needle electrode sites. The electrodes were all discarded at the end of the procedure. The injuries were assumed to have been caused by stray electrosurgical current. After months, the patient's lesions would not heal and remained painful. At this point, ECRI became involved and reviewed the medical records which included lesion photos. The appearance of the lesions was inconsistent with electrosurgical injuries, but more likely electrolytic injury by DC current. Biopsies of the tissue done by a wound care specialist identified off-the-chart iron concentration. ECRI recommended that the patient's wounds be x-rayed looking for needle fragments. Many were found. In this case, the source of the DC current was not identified.
- 3) The third case was nearly identical to the previous case; however, it involved a different neural monitor. In addition to injuries at the needle sites, the patient had an abdominal skin "burn" where the skin was seen to be in contact with the turning frame of the operating table. ECRI identified a 12 V, 50 mA DC circuit through the monitor's needle electrodes and operating table that would cease if the table was unplugged, or the ground pin of the monitor's power plug defeated using a "cheater" adapter. The electrodes were saved, and all have various degrees of metal loss indicating that they were anodes and the table frame the cathode.

The other 5 targets involved instrument breakage or corrosion of reusable surgical instruments (e.g., forceps, clamps, etc.)

Searching ["stainless steel" and "prosthesis"] identified 17 targets none of which were investigation reports.

Searching ["stainless steel" and "spinal"] identified 77 targets, which included 5 investigation reports that had already been identified in earlier searches.

Searching ["stainless steel" and "wire"] identified 285 targets of which 6 were investigation reports. One case involved a retained j-wire fragment and the other a retained spring-reinforced, epidural catheter fragment. In the remaining four cases, the stainless steel was part of capital equipment (e.g., housing, chassis, or frame not in contact with the patient).

ECRI Problem Reports

Search Results: The search returned 3 reports submitted by ECRI members. However, they are not directly related to biocompatibility of SS.

- 1) Two reports detailed complications upon insertion of SS implants. The first involved a K-wire that broke, and a small piece was left in the patient that was later removed. The second report involved a lap-band that separated from the collar, which was removed and replaced. No patient injury occurred and pre-use integrity testing within the sterile field was implemented in future cases to avoid future failures.
- 2) The third report summarized difficulties during a femoral blade plate removal surgical procedure. Two of the three screws were removed without complication, but the middle screw was cold-welded into the plate, and it took several attempts to remove the screw. Finally, a burr was used to remove the screw head and trephine to remove the body of the screw. No patient injury was reported, the procedure time was lengthened by about 30 minutes.

Healthcare Technology Alerts

Search Results: The search returned 164 manufacturer-issued, and 3 regulatory agency-issued alerts describing problems with SS-related devices, summarized in Table 3.

Table 3: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
DQY (Cather, Percutaneous)	1 Manufacturer-issued	<ul style="list-style-type: none"> Exposure of wires after insertion
DSQ (Ventricular [Assist] Bypass)	1 Manufacturer-issued	<ul style="list-style-type: none"> Membrane disruption
DSR (Stimulator, Carotid, Sinus Nerve)	1 Manufacturer-issued	<ul style="list-style-type: none"> Connection loss when exposed to MRI
DTK (Filter, Intravascular, Cardiovascular)	5 Manufacturer-issued 1 Health Canada	<ul style="list-style-type: none"> Updated IFU Complications associated with IVC Mislabeling
ELZ (Crown, Preformed)	3 Manufacturer-issued	<ul style="list-style-type: none"> Product out of specification Mislabeling
ETD (Tube, Tympanostomy)	1 Manufacturer-issued	<ul style="list-style-type: none"> Product contamination (ethylene-vinyl acetate copolymer)
FGE (Stents, Drains and Dilators for the Biliary Ducts)	1 Manufacturer-issued	<ul style="list-style-type: none"> Mislabeling
FZP (Clip, Implantable)	2 Manufacturer-issued	<ul style="list-style-type: none"> Device damage and fragmentation Mislabeling
GAQ (Suture, Nonabsorbable, Steel, Monofilament and Multifilament, Sterile)	2 Manufacturer-issued	<ul style="list-style-type: none"> Product diameter out of specification Bioburden out of specification

Device Type	# Alerts	Reported Problem
GDW (Staple, Implantable)	3 Manufacturer-issued	<ul style="list-style-type: none"> Product distributed without sterilization Device separation before use Incomplete staple line firing
HBL (Holder, Head, Neurological [Skull Clamp])	1 Manufacturer-issued	<ul style="list-style-type: none"> Tip breakage during use may lead to loosening
HHS (Transcervical Contraceptive Tubal Occlusion Device)	3 Manufacturer-issued 1 FDA	<ul style="list-style-type: none"> FDA orders manufacturer to conduct post-market surveillance Distribution halted due to CE Mark suspension Manufacturer requests product return after discontinuation
HRS (Plate, Fixation, Bone)	28 Manufacturer-issued	<ul style="list-style-type: none"> Compromised sterility Manufactured from incorrect SS Mislabeling Revised surgical technique Screw may be driven through plates Screw may break Tendon rupture after implantation
HSB (Rod, Fixation, Intramedullary and Accessories)	18 Manufacturer-issued	<ul style="list-style-type: none"> Biocompatibility issues Higher-than-anticipated fracture rate Compromised sterility Implantation difficulty Incorrect screw positioning Minor damage may result in fracture Mislabeling Missing full complement of biological assessments Nail head dissociation Product out of specification
HTY (Pin, Fixation, Smooth)	3 Manufacturer-issued	<ul style="list-style-type: none"> Manufactured from incorrect SS steel Mislabeling Product out of specification
HWC (Screw, Fixation, Bone)	22 Manufacturer-issued	<ul style="list-style-type: none"> Mislabeling Product out of specification Revised surgical technique Updated IFU Weak fixation in bone
JDB (Prosthesis, Elbow, Semi-Constrained, Cemented)	2 Manufacturer-issued	<ul style="list-style-type: none"> Higher-than-anticipated rupture risk Misuse during implantation leads to post-op disassembly
JDI (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Cemented)	4 Manufacturer-issued	<ul style="list-style-type: none"> Bioburden exceeds sterility assurance level Mislabeling Packaging with incorrect product Stem missing laser etchings
JDQ (Cerclage, Fixation)	1 Manufacturer-issued	<ul style="list-style-type: none"> Manufacturing defect
JDW (Pin, Fixation, Threaded)	3 Manufacturer-issued	<ul style="list-style-type: none"> Expiration dating added to product Fracture during insertion Incorrect color

Device Type	# Alerts	Reported Problem
JEC (Component, Traction, Invasive)	1 Manufacturer-issued	<ul style="list-style-type: none"> Expiration dating added to product
JWH (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained, Cemented, Poly/Metal/Polymer)	2 Manufacturer-issued	<ul style="list-style-type: none"> Head may not impact stem Product contamination (low-density polyethylene)
JXG (Shunt, Central Nervous System and Components)	4 Manufacturer-issued	<ul style="list-style-type: none"> Mislabeling Missing CE Mark Updated IFU
KRO (Prosthesis, Knee, Femorotibial, Constrained, Cemented, Metal/Polymer)	1 Manufacturer-issued	<ul style="list-style-type: none"> Missing screw component
KTT (Appliance, Fixation, Nail/Blade/Plate Combination, Multiple Component)	5 Manufacturer-issued	<ul style="list-style-type: none"> Compromised sterility Manufactured from incorrect SS Mislabeling Product out of specification
KWY (Prosthesis, Hip, Hemi-Femoral, Metal/Polymer, Cemented or Uncemented)	2 Manufacturer-issued	<ul style="list-style-type: none"> Insufficient cleaning process leads to adverse reaction Product comingled in packaging
LDF (Electrode, Pacemaker, Temporary)	1 Manufacturer-issued	<ul style="list-style-type: none"> Product contamination (silicone)
LPH (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Porous Uncemented)	1 Manufacturer-issued	<ul style="list-style-type: none"> Updated IFU
LTI (Implant, Intragastric for Morbid Obesity)	3 Manufacturer-issued	<ul style="list-style-type: none"> Distribution after expiration date Missing component Mislabeling Updated IFU
LZO (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented or Noncemented)	6 Manufacturer-issued	<ul style="list-style-type: none"> Mislabeling Missing component Premature wear
MAX (Intervertebral Fusion Device with Bone Graft, Lumbar)	1 Manufacturer-issued	<ul style="list-style-type: none"> Reduction in implant height
MBH (Prosthesis, Knee, Patello-Femorotibial, Semi-Constrained, Uncemented, Porous,	1 Manufacturer-issued	<ul style="list-style-type: none"> Corrosion Discoloration

Device Type	# Alerts	Reported Problem
Coated, Polymer/Metal/Polymer)		
MBI (Fastener, Fixation, Nondegradable, Soft Tissue)	2 Manufacturer-issued	<ul style="list-style-type: none"> Compromised sterility Manufacturing defect
MNH (Orthosis, Spondylolisthesis Spinal Fixation)	1 Manufacturer-issued	<ul style="list-style-type: none"> Mislabeling
MNI (Orthosis, Spinal, Pedicle Fixation)	2 Manufacturer-issued	<ul style="list-style-type: none"> Mislabeling Product out of specification
MVR (Device, Anastomotic, Microvascular)	2 Manufacturer-issued	<ul style="list-style-type: none"> Compromised sterility Mislabeling
NEU (Marker, Radiographic, Implantable)	3 Manufacturer-issued	<ul style="list-style-type: none"> Failure to deploy Mislabeling
NHA (Abutment, Implant, Dental Endosseous)	2 Manufacturer-issued	<ul style="list-style-type: none"> Misalignment Mislabeling
NIN (Stent, Renal)	1 Manufacturer-issued	<ul style="list-style-type: none"> Stent dislodged
NKB (Thoracolumbosacral Pedicle Screw System)	8 Manufacturer-issued	<ul style="list-style-type: none"> Devices may not mate Mislabeling Product out of specification Screw head separation/dissociation Updated IFU
NKE (Pulse Generator, Pacemaker, Implantable, with Cardiac Resynchronization [CRT- P])	2 Manufacturer-issued	<ul style="list-style-type: none"> Implant requires replacement after reverted to permanent safety mode May initiate safety mode with high internal impedance
NVN (Drug Eluting Permanent RV or RA Pacemaker Electrodes); LWP (Implantable Pulse Generator, Pacemaker [Non-CRT])	6 Manufacturer-issued	<ul style="list-style-type: none"> Configuration not FDA-approved Cybersecurity firmware update Intermittent oversensing may cause syncope Moisture ingress Transmitters may initiate a software reset
OUR (Sacroiliac Joint Fixation)	1 Manufacturer-issued	<ul style="list-style-type: none"> Compromised sterility
PKL (Hemostatic Metal Clip for the GI tract)	1 Manufacturer-issued	<ul style="list-style-type: none"> Product contamination (Ni)
PRL (Iliac covered Stent, Arterial)	1 Manufacturer-issued	<ul style="list-style-type: none"> Updated IFU

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 the 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.

The coronary stents category was the only device category rated moderate quality of evidence indicating that most device categories were rated low or very-low quality of evidence and representing areas with gaps in the literature.

These lower quality ratings were mostly due to the number of studies addressing each device category; most categories included <5 studies and several device categories (cardiovascular-grafts, ENT, general plastic surgery, ophthalmic, and neurology) were limited to 1 study each. Additionally, ratings were due to low quality study design (e.g., studies lacking controls), and responses not being replicated within the device category or in agreement with other device categories.

Additionally, there were no studies that met inclusion criteria for SS for radiology, anesthesiology, and gastroenterology indicating an area of future research.

Lastly, only 1 study investigated patient-related factors that may affect a sustained immunological/systemic response, and no studies investigated material-related factors.

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 Stainless Steel 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 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: Stainless Steel (SS)

Set Number	Concept	Search Statement
1.	Stainless Steel (SS) 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 [2012–2022]/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.	SS Steel + Material Response + Host Response	#9 AND #17 AND #27
29.	SS general devices + Host response	(#3 OR #4 OR #5 OR #6) AND #9 AND #27
30.	Combine sets	#28 OR #29
31.	SS 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

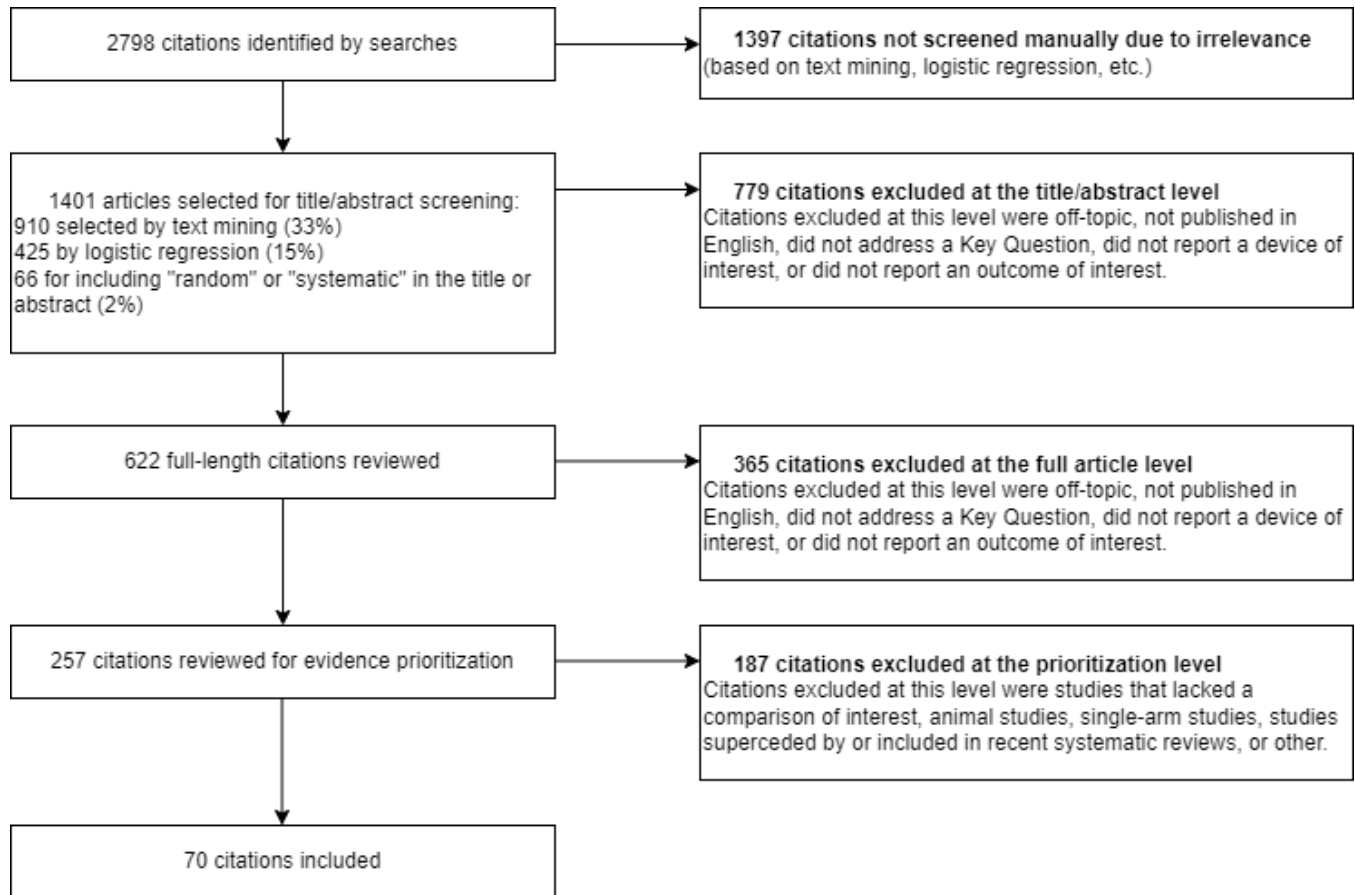
- Artery compliance
 - Vein compliance
 - Heart muscle compliance
 - Heart left ventricle compliance
 - Heart ventricle compliance
 - Lung compliance
- Compressive strength
- Dynamics
 - Compression
 - Computational fluid dynamics
 - Decompression
 - Explosive decompression
 - Rapid decompression
 - 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



2798 citations were identified by searches, of which:

1. 1397 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.).
2. The remaining 1401 articles were selected for title/abstract level (910 were selected by text mining in Distiller (33%), 425 by logistic regression (15%), and 66 for including "random" or "systematic" in the title or abstract (2%)).
 - a. 779 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 622 full length citations were reviewed, of which:
 - i. 365 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 257 citations were reviewed for evidence prioritization:
 1. 187 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. 70 citations were included.

Appendix D. Evidence Tables

Table 4: Stainless Steel as a Material - Health Effects (In Vivo) Human/Animal Studies

Local Response/Toxicity

4.1 Source Citation: Thomas et al. 2016¹

Study Design: Prospective cohort study of patients with known metal allergies and patients with no known metal allergies

Device or Material: patch test reactivity to Ni, Co, or Cr

Route: Skin

Dose: 6 metal disks (CoCrMo and SS uncoated and with 2 different coatings)

Frequency/Duration: disks were fixed on the patients' backs and, identically to routine patch test, removed after 48 hours

Response: contact dermatitis

Patient characteristics (gender, mean age): metal allergy (24 female; 7 male; age 25-74 years, mean 50.35); nonallergic patients (22 female, 8 male; age 20-88 years, mean 49.28)

Number per Group: 31 patients with metal allergy, 30 nonallergic patients

Observed adverse effects: 5 patients with metal allergy reacted to the uncoated metal disks (1/5 to both variants). Two of the 31 patients with metal allergy—of whom 23 were allergic to Ni—showed contact allergic reaction to the SS disk. Four of the patients with metal allergy reacted to the CoCrMo-alloy disk. None of these patients had reacted to the coated disks. The 30 nonallergic individuals had not reacted to any of the disks.

Timing of adverse effects: Within 48 and 72 hours.

Factors that predict response: "Observations point to metal-induced potential toxic or hyperallergic reactions leading to persisting symptoms or even implant failure."

4.2 Source Citation: Wachesk et al. 2021²

Study Design: In vivo animal experiment

Device or Material: Stainless-steel substrate, coated and uncoated, compared with glass slide controls

Route: inserted surgically into the peritoneal cavity.

Dose: NA

Frequency/Duration: 7, 15, and 30 days after the insertion.

Response: peritoneal macrophages, nitric oxide (NO) production

Species: CF1 mice

Gender: NR

Number per Group: 60 total

Observed adverse effects: “Uncoated SS implants presented significant signs of [macrophage] activation (96% in 7 days), which is indicative of the inflammatory process. Macrophage activation decreased at 15 and 30 days, reflecting the body’s response to healing itself.” Control implant showed only a 5% response. Coated implants had reduced counts.

Timing of adverse effects: NR

Factors that predict response: The stainless-steel group suffered considerable inflammation, caused by the release of pro-inflammatory cytokines by macrophages and cytokine production by osteoblasts and fibroblasts.

4.3 Source Citation: Hauzenberger et al. 2018³

Study design: In vivo animal experiment

Device or Material: SS vs Teflon insulin infusion catheters

Route: back

Dose: 6mm

Frequency/Duration: once/7 days

Response: inflammation, kinking, fibrosis

Species (strain): 10 farm swine (*sus scrofa domesticus*)

Gender: female

Number per Group: 4 catheters (2 Sure T™, 6mm steel and 2 Quick-set™, 6mm Teflon) were inserted on day 1, day 4 and day 7 in each animal

Observed adverse effects: Kinking occurred in 2 cannulas in each arm. Inflammation increased significantly around both materials between day 1 and day 4 as well as day 1 and day 7. Area of inflammation around the steel catheter plateaued after 4 days, but further increased around Teflon. After the initial trauma caused by the introducer needle, the distance to the lowest point of observed inflammation was significantly higher for steel vs Teflon on day 4 ($p=0.019$) but was similar on day 7. No significant difference was reported for the qualitative grading of density of inflammatory cells (none, some, mild, moderate, severe) around the insertion channel. Authors concluded that “the area of inflammation increased significantly over time independent of material.”

Timing of adverse effects: Higher fibrin deposition around steel on day 4 of wear time.

Factors that predict response: The authors reported “the overall area of inflammation and fat necrosis did not differ between materials and the only effect observed was attributed to wear-time rather than material.”

4.4 Source Citation: Singh and Rawlinson 2018⁴

Study Design: In vivo animal experiment

Device or Material: SS debris

Route: injected into the epidural space at L4-L5

Dose: negative control, 1.5 mg, and 4.0 mg

Frequency/Duration: 12 and 24 weeks

Response: immunohistochemical and quantitatively analyzed for IL-6 and TNF- α cytokines as indicators of an inflammatory response, tissue pathology

Species: New Zealand white rabbits

Gender: Female

Number per Group: six rabbits per dose/time interval.

Observed adverse effects: "The pathology survey did not detect any gross abnormalities in the other organs or body cavities of any of the rabbits at 12 or 24 weeks. In the epidural space, there was little to no inflammatory response, neovascularization, or fibrosis associated with the particles." Inflammation was not observed in systemic organs with SS particles. "At 12 weeks, the SS challenged groups demonstrated statistically increased amounts of TNF-a and IL-6 levels when compared to control tissues." Amounts of TNF-a and IL-6 decreased by 24 weeks.

Timing of adverse effects: NR

Factors that predict response:

"Histologically, the tissue response to the injected particles, in the low and high dose group, was unremarkable at 12 and 24 weeks; based on standardized scoring, these responses were characterized as non-irritant. Furthermore, at 12 and 24 weeks, in the low and high dose groups most of the SS particles were found in the epidural space of the spine at the injection site indicating little systemic migration."

"These findings indicate that SS wear debris, comparable to the expected usage from a simulated growth guidance system, had no discernible untoward biological effects locally and systemically in an animal model."

4.5 Source Citation: Wilks et al. 2017^s

Study Design: In vivo animal experiment

Device or Material: Barostim neo electrode assembly and implantable pulse generator (IPG). System included SS Set Screws, and port plug (SS shaft and silicone body). Each animal was implanted with a single IPG and four neo electrodes and associated leads, with two electrode-lead assemblies connected to the IPG and two unconnected to serve as unstimulated controls.

Route: stimulation of the internal carotid sinus nerve

Dose: NR

Frequency/Duration: once , 3 months (3 sheep) and 6 months (4 sheep)

Response: Foreign body reaction (FBR)

Species (strain): crossbred sheep between 100 and 150 kg

Gender: male

Number per Group: 7 (3 animals in a 12-week survival group, 4 animals in a 24-week survival group)

Observed adverse effects: No evidence of clinically significant tissue responses; only minimal granulomatous inflammation typical of a FBR elicited by chronic implantation of a device. No signs of erosion, thrombosis, or stenosis at any implant site up to 24 weeks. No microscopic differences in electrically stimulated implant sites vs unstimulated implant sites. No stimulation-induced AEs were observed.

Timing of adverse effects: NR

Factors that predict response: NR

4.6 Source Citation: Menchaca et al. 2011⁶

Study Design: In vivo animal experiment to investigate gastric plication

Device or Material: Fastening devices used were T-tags (12-mm long SS tube), buttressed T-tags, 2 types of suture (monofilament or braided polyester), and 4 types of staple-based fasteners (combinations of SS wire, Ti wire, and braided polyester suture)

Route: Gastric plication

Dose: NA

Frequency/Duration: single administration

Response: inflammation

Species: hound dogs

Gender: 6 male, 32 female

Number per Group: minimum 4 dogs per suture technique

Observed adverse effects: "Significant inflammatory responses were seen in those dogs that had received full-thickness braided polyester sutures, a multifilament, nonabsorbable suture material placed into the nonsterile gastric lumen. Mild mucosal erosion was seen with the metal T-tag ends potentially deployed in direct contact with the tissue walls. Mucosal defects without inflammation were associated with tags that were not yet overgrown with mucosa. Minimal or mild chronic inflammation and fibrosis surrounded the sutures and staples in both the partial-thickness and the full-thickness monofilament treatment groups."

Timing of adverse effects: 56 to 59 days

Factors that predict response: NR

Table 5: Neurology - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

5.1 Source Citation: Maciejewski et al. 2019⁷

Study Design: Nonrandomized comparative of patients undergoing extracranial vertebral artery stenting.

Device or Material: Bare metal stents (SS, CoCr, or platinum Cr) vs. first and second generation drug eluting stents (non SS, DES I [sirolimus and paclitaxel] and DES II [everolimus, biolimus, and zotarolimus], respectively).

Contact Duration: At least 6-month follow-up.

Dose: NA.

Frequency/Duration: Single administration.

Response: In-stent restenosis/occlusion (ISR/ISO)

Patient characteristics (gender, mean age): Bare metal stent group: 72.2% male, 67.5±8.6 years. DES groups: 68.1% male, 66.6±8.5 years.

Number per Group: Bare metal stents: SS, n=139; CoCr, n=123; platinum Cr, n=18. DES I: sirolimus, n=14; paclitaxel, n=7. DES II: everolimus, n=57; biolimus, n=35; zotarolimus, n=36.

Observed adverse effects: There were no ischemic strokes, myocardial infarction, or any death within 30 days in either group. In the bare metal stent group, ISR/ISO occurred significantly less often with SS (17.8%) and CoCr (19%), as compared to platinum Cr (38.9%), $p=0.034$.

Timing of adverse effects: At least 6-month follow-up.

Factors that predict response: None reported.

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

Local Response/Toxicity

6.1 Source Citation: MacKeen et al. 2014⁸

Study Design: RCT.

Device or Material: SS staples vs. 4-0 poliglecaprone (Monocryl or Monocryl Plus) or polyglactin (Vicryl or Vicryl Plus) suture (non-SS, Ethicon).

Contact Duration: 4-10 days postoperatively.

Dose: NA.

Frequency/Duration: Single administration of multiple staples.

Response: Hematoma, seroma.

Patient characteristics (gender, mean age): 100% female. Staple group, 31.0 years (26.5-35.6 years); suture group, 31.0 years (26.9-35.4 years).

Number per Group: Staple group, $n=376$; suture group, $n=370$.

Observed adverse effects: There were no significant differences between the groups with respect to hematoma (staple group, 4 patients [1.1%]; suture group, 2 patients [0.5%]; 95% confidence interval 0.51), or seroma (staple group, 6 patients [1.6%]; suture group, 5 patients [1.4%]; 95% confidence interval 0.084).

Timing of adverse effects: 4-10 days postoperatively.

Factors that predict response: None reported.

6.2 Source Citation: Nitsche et al. 2012⁹

Study Design: Nonrandomized comparative.

Device or Material: Proximate PXW 35 staples (SS, Ethicon Endo-Surgery, Inc.) vs. INSORB staples (polylactic/polyglycolic acid [non-SS], Incisive Surgical).

Contact Duration: 3 days postoperatively.

Dose: NA.

Frequency/Duration: Single administration of multiple staples.

Response: Pain (as determined by analgesic use), seroma.

Patient characteristics (gender, mean age): 100% female. SS group, 29.5 ± 0.6 years; INSORB group, 29.1 ± 0.6 years.

Number per Group: SS staple group, $n=95$; INSORB group, $n=89$.

Observed adverse effects: There were two wound seromas in the surgical steel staple group and one wound seroma in the absorbable staple group. There was a 1.5-fold decrease in ketorolac use ($p<0.0001$) and a trend

toward decreased ibuprofen use in the INSORB cohort ($p=0.06$). There was no difference in the hydrocodone/acetaminophen use between groups ($p=0.89$).

Timing of adverse effects: SS group, 2.8 ± 0.06 hospital days; INSORB group, 3.0 ± 0.06 hospital days.

Factors that predict response: Subcuticular absorbable staples do not pierce the epidermis, which is heavily innervated with pain fibers.

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

Local Response/Toxicity

7.1 Source Citation: Shaarawy et al. 2015¹⁰

Study Design: SR to assess the safety of the EX-PRESS glaucoma filtration device and to compare with that of trabeculectomy. Eighteen publications met quality requirements for analysis including 7 publications of 7 single-cohort studies (or studies with all arms containing EX-PRESS devices) and 11 publications of 9 comparative studies between EX-PRESS device and trabeculectomy (4 publications described different results of the same 2 studies).

Device or Material: EX-PRESS glaucoma filtration device (SS, Alcon Laboratories) alone or vs. trabeculectomy. EX-PRESS models R-50, T-50, X-50, and/or X-200.

Contact Duration: Mean follow-up 9.7 to 40.1 months.

Dose: NA.

Frequency/Duration: Single administration per eye.

Response: aqueous misdirection; bleb fibrosis; bleb leak; blocked tube; cataract; choroidal detachment; choroidal effusions; choroidal hemorrhage; clotting; conjunctival leakage; corneal Dellen; device-iris or -cornea contact; dislocated implant; dysesthetic bleb; encysted bleb; endophthalmitis; exposed implant; hyphema; hypotony; intraocular hemorrhage; intraocular pressure (IOP) spikes; lens opacity; macular edema; maculopathy; membrane; posterior capsule opacity; retinal branch vein occlusion; shallow/flat anterior chamber; shunt closure; shunt migration.

Patient characteristics (gender, mean age): Not reported.

Number per Group: 10-231 eyes.

Observed adverse effects: Aqueous misdirection is reported in 1 single arm study at a rate of 1%.

Bleb fibrosis is reported in 1 single arm study at a rate of 8%.

Bleb leak is reported in 4 single arm studies at a rate of 4%-15%. It is reported in 4 comparative studies at a rate of 1.7%-29% in the device group, and a rate of 1.6%-18% in the trabeculectomy group.

Blocked tube is reported in 2 single arm studies at a rate of 1%-3%.

Cataract requiring surgical treatment is reported in 1 comparative study at a rate of 5.1% in the device group, and a rate of 11.5% in the trabeculectomy group.

Choroidal detachment is reported in 3 single arm studies at a rate of 2%-24%. It is reported in 2 comparative studies at a rate of 7.5%-20% in the device group, with a rate of 2.5%-36% in the trabeculectomy group.

Choroidal effusion is reported in 2 single arm studies at a rate of 8%-8.3%. It is reported in 3 comparative studies at a rate of 0%-8% in the device group, and a rate of 3.2%-38% in the trabeculectomy group.

Hemorrhage, choroidal is reported in 1 single arm study at a rate of 1%.

Hemorrhage, intraocular is reported in 1 single arm study at a rate of 4%.

Device clotting is reported in 1 single arm study at a rate of 4%.

Conjunctival leakage requiring contact lens is reported in 1 single arm study at a rate of 6%.

Corneal Dellen is reported in 1 comparative study at a rate of 1.7% in the device group, with no cases in the trabeculectomy group.

Device contact or touch with the iris or cornea is reported in 2 single arm studies at a rate of 4%-12.5%.

Dislocated implant is reported in 1 single arm study at a rate of 0.4%.

Dysesthetic bleb is reported in 1 single arm study at a rate of 0.4%.

Encysted bleb is reported in 1 single arm study at a rate of 54%.

Endophthalmitis is reported in 1 single arm study at a rate of 4%. It is reported in 2 comparative studies at a rate of

0%-2% in the device group, with a rate of 0%-1.6% in the trabeculectomy group.
 Exposed implant is reported in 1 single arm study at a rate of 0.4%.
 Hyphema is reported in 4 single arm studies at a rate of 2%-15%. It is reported in 8 comparative studies at a rate of 0%-4% in the device group, and a rate of 5%-40% in the trabeculectomy group.
 Hypotony is reported in 6 single arm studies at a rate of 4%-32%. Only non-hypotony complications are tabulated in the comparative studies.
 IOP spikes are reported in 1 single arm study at a rate of 17%.
 Maculopathy is reported in 2 comparative study at a rate of 4% in the device group, with a rate of 6% in the trabeculectomy group.
 Macular edema is reported in 1 single arm study at a rate of 4%.
 Membrane over tube is reported in 1 comparative study at a rate of 3% in the device group, and a rate of 0% in the trabeculectomy group.
 Opacity of the posterior capsule is reported in 1 single arm study at a rate of 54%.
 Opacity of the lens is reported in 1 comparative study at a rate of 3% in the device group, with a rate of 13% in the trabeculectomy group.
 Retinal branch vein occlusion is reported in 1 single arm study at a rate of 4%.
 Shallow or flat anterior chamber is reported in 3 single arm studies at a rate of 4.1%-8%. It is reported in 7 comparative studies at a rate of 2%-20% in the device group, and a rate of 0% to 20% in the trabeculectomy group.
 Shunt closure is reported in 1 single arm study at a rate of 4%.
 Shunt migration to anterior chamber is reported in 1 comparative study at a rate of 3% in the device group, with no cases in the trabeculectomy group.

Two of the randomized trials reported a lower overall postoperative complication rate with EX-PRESS device implantation ($p=0.05$ and 0.013) and another showed no significant differences in any of the individual postoperative complication rates. Two randomized trials also showed significantly better or faster recovery from loss of visual acuity in the EX-PRESS device group as compared to the trabeculectomy group. In a prospective, nonrandomized study, there were no statistical comparisons of complication rates; however, the device group had no postoperative complications, whereas the trabeculectomy group had a high complication rate: hyphema (40%), shallow anterior chamber (30%), and choroidal detachment (15%). Of the remaining four nonrandomized studies, one reported on complication rate that was significantly different between groups (choroidal effusion, favoring the EX-PRESS device). The rest of the complications had no significant differences between groups.

Timing of adverse effects: Hypotony reported from 1 day to 1 week. IOP spikes are reported within the first month postoperatively. Mean follow-up 9.7 to 40.1 months.

Factors that predict response: Study authors felt that their learning curve for device implantation elevated the rate of hypotony.

Table 8: General, Plastic Surgery - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

8.1 Source Citation: Soylyu et al. 2016¹¹

Study Design: SR of 6 studies incorporating 139 subjects undergoing minimally invasive direct coronary artery bypass (MIDCAB) or totally endoscopic coronary artery bypass (TECAB) using a distal anastomotic device. The most widely used anastomotic device was the C-Port (SS, 120 cases), however this was all from one case series (Balkhy et al.)

Device or Material: C-Port (SS), MVP (non-SS, magnetic vascular port device), and U-Clip (non-SS).

Contact Duration: 29-week follow-up.

Dose: NA.

Frequency/Duration: Single administration.

Response: Effusion; hemorrhage; myocardial infarction (MI).

Patient characteristics (gender, mean age): None reported.

Number per Group: n=120 C-Port cases.

Observed adverse effects: No device failure was observed with either the U-Clip or C-Port anastomotic devices. For C-Port, there was 1 MI (0.8%), 2 post-operative hemorrhages (1.6%); and 1 pericardial effusion (0.8%).

Timing of adverse effects: 29-week follow-up.

Factors that predict response: None reported.

Systemic Response

8.2 Source Citation: Soylyu et al. 2016¹¹

Study Design: SR of 6 studies incorporating 139 subjects undergoing minimally invasive direct coronary artery bypass (MIDCAB) or totally endoscopic coronary artery bypass (TECAB) using a distal anastomotic device. The most widely used anastomotic device was the C-Port (SS, 120 cases), however this was all from one case series (Balkhy et al.)

Device or Material: C-Port (SS), MVP (non-SS, magnetic vascular port device), and U-Clip (non-SS).

Contact Duration: 29-week follow-up.

Dose: NA.

Frequency/Duration: Single administration.

Response: Cerebrovascular accident (CVA); death; effusion; embolization; myocardial infarction (MI).

Patient characteristics (gender, mean age): None reported.

Number per Group: n=120 C-Port cases.

Observed adverse effects: No device failure was observed with either the U-Clip or C-Port anastomotic devices. For C-Port, there was 1 death (0.8%), 1 CVA (0.8%), 1 brachial artery embolization (0.8%), 2 pleural effusions requiring intervention (1.6%), and 1 case of phrenic nerve palsy (0.8%).

Timing of adverse effects: 30-day mortality rate reported.

Factors that predict response: None reported.

Table 9: ENT - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

9.1 Source Citation: Zeng et al. 2014¹²

Study Design: Single arm.

Device or Material: Z-stent (SS, Sigma), 2.0-2.5 cm diameter, 5-7 cm length.

Contact Duration: Mean follow-up period was 36 months.

Dose: NA.

Frequency/Duration: Single administration.

Response: Burning sensation; migration; pain.

Patient characteristics (gender, mean age): Male/female ratio was 30/29, 53.7±21.6 years.

Number per Group: N = 59 esophageal achalasia patients.

Observed adverse effects: Twelve patients (25.5%) complained of substernal pain, with four requiring analgesics for severe pain. Five patients (10.6%) had substernal burning, which was relieved by antacids. Stent migration occurred in four patients (8.5%); three stents fell into the stomach and were removed by endoscopy, and one was extruded via the anus. No patients experienced bleeding or esophageal perforation.

Timing of adverse effects: Stent migration occurred within 1 month after stent insertion. Mean follow-up period was 36 months.

Factors that predict response: The addition of a covering membrane may enhance stent migration. Studies found that, as the diameter of the metal stent increased, the potential for stent migration was reduced. Stent migration in patients with benign esophageal strictures has also been associated with low temperature. During the low-temperature phase, the material becomes very pliable, facilitating migration, but reducing complications associated with stent migration.

Table 10: Dental - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

10.1 Source Citation: Turner et al. 2021¹³

Study Design: Systematic review of 24 RCTs (2 relevant RCTs in 3 different comparisons); focus on interventions to prevent or correct dental crowding in children using fixed or removable appliances and auxiliaries (including archwires), and extractions

Device or Material: Nickel-titanium versus multistranded SS archwires (2 RCTs); nickel-titanium versus SS archwires (1 relevant study did not report data in a way that facilitated assessment of harms); multistranded SS versus SS archwires (1 relevant study did not report data in a way that facilitated assessment of harms)

Contact Duration: Up to 24 hours

Dose: NR

Frequency/Duration: once

Response: Pain (1 study reporting)

Patient characteristics (gender, mean age): 43 female, 42 male; mean age 14

Number per Group: 85 overall; 42 nickel-titanium, 43 multistranded SS archwires

Observed adverse effects: Pain with superelastic nickel-titanium archwires was significantly greater at 12 hours ($p=0.02$), day 1 in the morning ($p=0.03$), afternoon ($p=0.03$), and at bedtime ($p=0.04$); only p values provided. No statistically significant difference in overall pain.

Timing of adverse effects: 12 hours, day 1

Factors that predict response: NR

10.2 Source Citation: Jedliski et al. 2021¹⁴

Study Design: Systematic review of 7 RCTs; focused on investigating the failure rate of fixed orthodontic retainers.

Device or Material: 0.0175" SS wire vs. fiber reinforced composite (FRC) retention

Contact Duration (years): 1 (3 studies), 1.5 (1 study), 2 (2 studies), 6 (1 study)

Dose: 0.0175" multistranded SS wire

Frequency/Duration: once

Response: Failure rate (detachment, wire breakage, adhesive failure, retainer loosening)

Patient characteristics (gender, mean age): 284 women, 264 men enrolled; age NR

Number per Group: teeth/retainers analyzed: 715 SS, 654 FRC; 503 patients (516 retainers) analyzed

Observed adverse effects: No significant difference between treatments for failure rate (log risk ratio 0.01, 95% CI: -0.32 to 0.34). Failure rates ranged from 10% to 36.4% for SS, and 11.2% to 50% for FRC retention.

Bolla 2011: Overall failure rate lower with FRC (34% SS, 22.9% FRC). Failure rates for detachment in the mandibular arch (15.6% SS, 11.7% glass fiber), and maxillary arch (22.2% SS, 21% glass fiber); authors indicated detachment occurred equally often. Failure rates for breakage in the mandibular arch (15.6% SS, 8.8% glass fiber), and maxillary arch (16.7% SS, 7.1% glass fiber); authors indicated less often (but not significantly different) with wire.

Nagani 2020: Overall failure rate significantly lower with SS (31.4% SS, 42.9% FRC). Bond failure was most often due to adhesive failure [no retained resin on enamel surface].

Salehi 2013: Overall failure rates lower with SS (36.4% SS, 50% FRC). Complete detachment occurred in 1 multistranded retainer. Retainer loosening was the most frequent failure for SS retainers (22/27, 81.48% maxilla; 27/28, 96.42% mandible). Retainer fracture was the most frequent type of failure for ribbon retainer group (30/34, 88.23% maxilla; 19/29, 65.51% mandible). Authors noted comparable rates of broken or detached retainers.

Scribante 2011: Detachment lower with FRC (22.5% SS, 14.4% FRC).

Rose 2002: Failure rates lower with SS (10% SS, 50% FRC). Most frequent type of failure was loosening.

Sfondrini 2014: Failure rates lower with FRC (17.73% SS, 11.25% FRC). Reason behind failure not described.

Sobouti 2016: Failure rates lower with SS (26.8% SS, 35.7% FRC). Reason behind failure not described.

Timing of adverse effects: NR

Factors that predict response: NR

10.3 Source Citation: Adanur-Atmaca et al. 2021²⁰

Study Design: RCT

Device or Material: 0.0215-in 5-strand SS wire (Pentaflex, GC Orthodontics America Inc, Alsip, Ill, USA) compared with dead-soft wire (Bond-ABraid, Reliance Orthodontic Products, Itasca, Ill, USA), nitinol retainer (Memotain, CA-Digital, Mettman, Germany), and connected bonding pad retainer (Leone SpA, Firenze, Italy).

Contact Duration: 1 year

Dose: N/A

Frequency/Duration: once

Response: Plaque, gingival and calculus indexes were used to evaluate periodontal health.

Patient characteristics (gender, mean age): 30.3% male, 69.7% female; mean age 16 years

Number per Group: 33 per group, 4 groups

Observed adverse effects: "no clinically significant worsening of periodontal health and relapse was seen in any groups after 1 year."

Timing of adverse effects: 1 year

Factors that predict response: Time was the main reason for changes in periodontal health and not material

10.4 Source Citation: Zafar and Siddiqi 2020¹⁵

Study Design: Systematic review of 8 studies (6 nonrandomized comparative). Included studies focused on biological kinetics, hypersensitivity responses, allergic/toxic reactions, and the release of ions (mainly Ni) associated with pediatric SS crowns (SSCs). Chemically, SSCs are manufactured from type 303 austenitic alloy with the chemical composition of iron (Fe: 69%), chromium (Cr: 18.4%), nickel (Ni: 9.1%), magnesium (Mg: 1.5%), silicon (Si: 1%), and other elements, including aluminum (Al: 0.6%) and molybdenum (Mo: 0.4%) [10]. Ni is a trace mineral or micronutrient that plays an important role in overall health in small doses, aiding in Fe absorption as well as glucose metabolism. However, at higher doses, Ni has been found to be harmful.

Device or Material: pediatric SSCs were examined in all studies; 1 large study (Feasby 1988) examined Ni-containing intra-oral devices including SSC (n=350) vs No Ni-containing intra-oral devices (n=350) however the crowns included the old formulation of 72% Ni; another study compared SSC placement (n=17) with lingual arch space maintainer (n=17)

Contact Duration: 7 days to 6 months (1 study NR)

Dose: N/A

Frequency/Duration: once

Response: Ni hypersensitivity reactions (perioral skin eruptions, ulcerative contact gingivitis)

Patient characteristics (gender, mean age): NR

Number per Group: range 1 to 700; 1 patient (2 studies), 30 to 37 patients (5 studies), 700 (1 study)

Observed adverse effects: Perioral skin eruptions were reported in a 13-year old female following SSC placement for restoring a decayed first permanent molar. Ni hypersensitivity was diagnosed by a patch test, and the lesions resolved following the removal and replacement of the SSC with a bis-acryl crown and bridge. The severe occurrence of ulcerative contact gingivitis was reported in a 2-year-old boy following placement of SSCs that resolved following crown removal and replacement with composite resin crowns. After SSC placement, 1 study (n=37) reported genotoxic damage at the cellular level of the oral mucosa and an increase in the urinary excretion of Ni. The remaining 5 studies did not report any additional skin hypersensitivities (from skin allergy patch tests) or harmful toxic metal levels (from saliva or hair analysis) after SSC placement.

Timing of adverse effects: Perioral skin eruptions at 1 week, ulcerative contact gingivitis after 1 month. Genotoxic damage (cellular level) of the oral mucosa and increase in the urinary excretion of Ni within 45 days of exposure.

Factors that predict response: NR

10.5 Source Citation: Mathew et al. 2020²¹

Study Design: RCT

Device or Material: SS crowns (3M ESPE, Minneapolis, MN) vs zirconia crowns (Kinder Krowns, Minneapolis, MN) in children with pulpectomised bilateral mandibular primary second molars

Contact Duration: 12 months

Dose: N/A

Frequency/Duration: once

Response: plaque accumulation, gingival inflammation measured by gingival index (GI) and plaque index (PI)

Patient characteristics (gender, mean age): 63% female, 8.1±1.1

Number per Group: 60 total (30 each arm)

Observed adverse effects: Significantly lower PI and GI scores with zirconia crowns vs SSC at all follow-ups (3 months, 6 months, 9 months, and 12 months).

3 months (mean±standard deviation (SD)): PI: 0.80 (0.1) zirconia, 1.48 (0.2) SSC (p=0.008); GI: 0.80 (0.1) zirconia, 1.38 (0.1) SSC (p<0.0001)

6 months (mean±SD): PI: 0.95 (0.1) zirconia, 1.75 (0.1) SSC (p<0.0001); GI: 1.12 (0.2) zirconia, 1.63 (0.2) SSC (p=0.011)

9 months (mean±SD): PI: 0.99 (0.1) zirconia, 1.92 (0.1) SSC (p<0.0001); GI: 1.47 (0.1) zirconia, 1.89 (0.1) SSC (p<0.0001)

12 months (mean±SD): PI: 1.01 (0.1) zirconia, 2.41 (0.1) SSC (p<0.0001); GI: 1.76 (0.1) zirconia, 2.11 (0.3) SSC (p<0.001)

Timing of adverse effects: NR

Factors that predict response: The surface texture of the SSC is modified for proper adaptation, and thus could be the primary factor contributing towards plaque accumulation between the two crown types.

10.6 Source Citation: Chang et al. 2019²²

Study Design: RCT

Device or Material: 316LVM surgical SS vs. Ti6Al4V Ti alloy (TiA) bone screws (BSs) placed in patients requiring bilateral infrazygomatic crest (IZC) anchorage to retract maxillary teeth

Contact Duration: 6 months

Dose: N/A

Frequency/Duration: once

Response: Failure was due to loose (mobile) screws that exfoliated or were deemed too loose to provide effective anchorage. Temporary anchorage device (TAD) failures may also be due to fracture, mobility, uncontrollable soft tissue inflammation, and/or host factors such as pain or root damage.

Patient characteristics (gender, mean age): 80% female, mean 24.3 years (range 10.3 to 59.4 years)

Number per Group: 386 per metal; 193 per 4 groups divided into left and right-sided screws). 772 consecutive 2 x 12-mm OrthoBone Screw TADs (Newton's A Ltd, Hsinchu City, Taiwan) were placed bilaterally in the IZCs of 386 patients. Using a randomized split-mouth design, half of the IZC BSs (386) were made of 316LVM surgical SS, and the other half were composed of Ti6Al4V TiA.

Observed adverse effects: No significant difference in failures (27 (7%) SS screws, 22 (5.7%) TiA; $p=0.07$). Failure rate by mucosal type (attached gingiva (AG), moveable mucosa (MM), right side and left side) indicated significantly higher failure rates with SS in AG (7.4% SS, 5.1% Ti), and right side (7.8% SS, 5.2% Ti). No fracture or "appreciable pain" was reported.

Timing of adverse effects: NR

Factors that predict response: Authors noted that due to the lack of a significant materials effect, that the predisposition to failure appears to be predominantly genetic.

10.7 Source Citation: Chen et al. 2018²⁵

Study Design: Nonrandomized comparative

Device or Material: SS crowns (SSCs) vs composite resin crowns to repair primary molars with caries, pulpitis, and periapical periodontitis

Contact Duration: 6, 12, and 24 months

Dose: N/A

Frequency/Duration: once

Response: loss of restoration, marginal failures, and recurrent caries

Patient characteristics (gender, mean age): 54% male, mean 3 years and 5 months (range 1 year and 10 months to 8 years and 8 months)

Number per Group: 276 SSCs, 280 composite resin crowns (total 556 primary molars) in 84 patients

Observed adverse effects: Restorative loss was significantly less with SSCs (4 SSC, 28 composite resin). Significant difference in failure due to marginal integrity at 24 months only (4 (7.7%) SSC, 16 (44.4%) resin). Recurrent caries significantly lower with SSCs at all follow-ups (6 months: 1 (0.9%) SS, 7 (7.8%) resin; 12 months: 3 (3.2%) SSC, 8 (13.1%) resin; 24 months: 4 (7.7%) SSC, 16 (47.1%) resin).

Timing of adverse effects: 6 to 24 months

Factors that predict response: NR

10.8 Source Citation: Aiem et al. 2017¹⁶

Study Design: Systematic review of 7 RCTs; 6 studies compared pre-veneered SSCs with other crowns (resin composite strip crowns, open-face SSCs (OSSC), zircon crowns) while 2 studies compared 2 different pre-veneered SSCs (VSSC). 1 study addressed primary incisors, while 6 studies addressed primary molars.

Device or Material:

1. NuSmile® VSSCs vs. SSCs (2 studies).
2. VSSCs (NuSmile®, Pedo Pearls™ and ex vivo by laboratory procedures) vs SSCs (3M ESPE) or OSSCs (1 study).
3. ex vivo VSSC vs open-faced SSCs (1 study).
4. VSSCs (NuSmile vs. Kinder Krowns) (2 studies).
5. Three aesthetic full-coronal restorations (composite SCs (3M ESPE)(n=43), NuSmile SCCSx (n=43) and Zirkiz zircon crowns (ZCs)(n=43)(1 study); 1 to 4 crowns per child

Contact Duration: 1 year (2 studies), 18 months (2 studies), 4 years (2 studies)

Dose: N/A

Frequency/Duration: once

Response: chipping, gingival health, plaque, deterioration, fracture, retention, appearance, failure

Patient characteristics (gender, mean age): gender NR; 1 study each reported 3 to 5 years old, 5 to 8 years, mean age 6.28 years (1 study); 2 studies reported 2 to 9 years or NR

Number per Group:

1. NuSmile VSSCs (n=11) with SSCs (n=11).
2. VSSCs (NuSmile® (n=37), Pedo Pearls™ (n=24) and ex vivo VSSC (n=50) vs SSCs (3M ESPE; n=93)) or OSSCs (n=60).
3. Ex vivo VSSCs (n=15) vs open-faced SSCs (n=18); at least 1 crown per child.
4. VSSCs (NuSmile (n=36, 60 teeth) vs Kinder Krowns (n=36; 60 teeth).
5. 1 study addressed 3 aesthetic full-coronal restorations (composite SSCs (3M ESPE)(n=43), NuSmile SCCSx (n=43) and Zirkiz zircon crowns (ZCs)(n=43); 1 to 4 crowns per child.

Observed adverse effects:

1. NuSmile VSSCs (n=11) vs SSCs (n=11) in a split-mouth study: Nusmile VSSCs were all partially chipped at 4 years follow-up. Better gingival health with SSCs at 6 months; no difference at 4 years.
2. Different VSSCs (NuSmile® (n=37), Pedo Pearls™ (n=24) and ex vivo VSSC (n=50) with SSCs (3M ESPE; n=93)) or OSSCs (n=60): NuSmile plaque index (PI) was superior to other crowns. Measurements of GI, pocket probing depth, and simplified oral hygiene index (OHI-S) indicated deterioration in all crown types.
3. Ex vivo VSSCs (n=15) vs open-faced SSCs (n=18): Failure (loss of one-third or more of the aesthetic material) noted in fewer OSSCs (5% OSSC vs 20% ex vivo VSSC). All failures occurred in lower crowns.
4. VSSCs (NuSmile (n=36) vs Kinder Krowns (n=36))(2 studies):
 - Kinder Krown VSSCs were significantly more likely to fracture during year 1 post-placement ($p<0.02$)(data not shown).
 - Crown retention was 99.2% due to loss of 1 Kinder Krown.
 - Buccal facade fractures occurred in 9% of crowns; higher proportion of fractures on mandibular m2 than on maxillary m2 regardless of brand.
 - Occlusal facade fractures occurred in 15% of crowns; higher proportion of fractures on maxillary m1 vs mandibular m1.
 - Façade wear was reported in 9%; no difference between groups.
5. 3 aesthetic full-coronal restorations (composite SSCs (3M ESPE)(n=43), NuSmile SCCSx (n=43) and Zirkiz zircon crowns (ZCs)(n=43); 1 to 4 crowns per child:
 - Crowns appeared normal in 78% SSCs, 95% VSSCs, and 100% ZCs (significant difference favoring VSSCs over SSCs ($p=0.04$) and ZCs over SSCs ($p=0.02$).
 - No significant difference in tooth wear on opposing teeth (100% SCs, 100% VSSCs, 90% ZCs).
 - Statistically significant difference in mean gingival index (GI) for SCs and ZCs ($p<0.01$), VSSCs and ZCs ($p<0.01$).

Timing of adverse effects: 1 year to 4 years

Factors that predict response: NR

10.9 Source Citation: Rozeboom et al. 2017¹⁷

Study Design: Systematic review of 16 studies (10 studies reported interventions and included) focused on closed treatment for patients with mandibular condyle fractures.

Device or Material: SS wires (5 studies; 2 studies used SS wires and elastics) vs guiding elastics/elastics (5 studies) for maxillomandibular fixation (MMF)

Contact Duration (mean): mean duration 3 weeks; range 5 days to 49 days; follow-up 5.4 months to 7.8 years

Dose: N/A

Frequency/Duration: once

Response: occlusion, pain

Patient characteristics (gender, mean age): 3 to 1 male to female ratio; 31 years

Number per Group: 663 SS wires, 489 guiding elastics/elastics

Observed adverse effects: Occlusion ranged from 2% to 18% with SS wires (4 studies reporting) vs 24% with elastics (1 study reporting). Pain at rest ranged from 2% to 16% with SS wires (4 studies reporting) vs 9% to 15% with elastics (4 studies reporting).

Timing of adverse effects: NR

Factors that predict response: NR

10.10 Source Citation: Kumar et al. 2016²⁶

Study Design: Nonrandomized comparative comparing different groups of children

Device or Material: SS crowns

Contact Duration:

Dose: N/A

Frequency/Duration: once

Response: inflammation

Patient characteristics (gender, mean age): gender NR, children aged 3 to 5 years

Number per Group: 20 each arm (healthy children (Group 1); children with dental caries (Group 2), individuals with dental caries involving the pulp (Group 3), children with SS crowns (Group 4)

Observed adverse effects: Macrophage inflammatory protein-1 α (MIP-1 α) and MIP-1 β were detected in all the samples. Highest mean concentration in gingival crevicular fluid (GCF) was obtained for Group 3 followed by Groups 2 and 4, with the lowest concentration in Group 1. Results suggested that MIP-1 α and MIP-1 β levels in GCF increased proportionately with the inflammation.

MIP-1 α (mean \pm SD): 197.60 \pm 40.83 Group 1, 900.40 \pm 209.04 Group 2, 1286.55 \pm 382.7 Group 3, 682.55 \pm 59.97 Group 4

MIP-1 β (mean \pm SD): 287.85 \pm 42.20 Group 1, 1048.85 \pm 212.07 Group 2, 1208.85 \pm 235.69 Group 3, 884.35 \pm 125.46 Group 4

Timing of adverse effects: NR

Factors that predict response: "The variability of MIP-1 α and MIP-1 β concentrations within subjects of each group could be due to their role in different stages of disease process at the time of GCF collection."

10.11 Source Citation: Innes et al. 2015¹⁸

Study Design: Systematic review of 5 RCTs to determine clinical effectiveness and safety of all types of preformed crowns for restoring primary teeth compared with conventional filling materials.

Device or Material: SS crowns (preformed metal crowns (PMCs), SS with white veneer cover, crowns made wholly of a white ceramic material. Teeth were most likely trimmed for the crowns to be fitted conventionally using a local anaesthetic, OR in the case of the Hall Technique, PMCs are pushed over the tooth with no local anaesthetic, carious tissue removal or tooth preparation.

Atieh 2008: PMCs (68 teeth) vs modified open-sandwich technique using resin-modified glass ionomer cement or composite resin restorations (65 teeth)

Hutcheson 2012 (n=37, 74 teeth; split-mouth study): SS crown vs resin composite multi-surface, fitted using open sandwich technique.

Innes 2011 (n=124, 124 teeth): PMC (SSC) placed by the Hall Technique with no caries removal (132 teeth) vs. control (132 teeth) with restorations with glass ionomer (69%), amalgam (8%), compomer (5%), composite (11%), SSC (1% with tooth preparation), fissure sealant (2%) and no restoration provided (3%).

Ram 2003 (n=11, 22 teeth; split mouth trial): SSC vs aesthetic crown

Santamaria 2014 (n=148; 3-arm RCT): SSC with Hall Technique (Group 1, n=52), fillings using resin composite (Group 2, n=65), non-restorative caries treatment (Group 3, n=52)

Contact Duration (year): 1 (2 studies), 2 (1 study), 4 (1 study), 5 (1 study)

Dose: N/A

Frequency/Duration: once

Response: major failure (composite of pain, pulp infection, discharging sinus, dental abscess, or periradicular pathology on radiographs), pain, gingival bleeding, bone resorption

Patient characteristics (gender, mean age): 206 males, 182 females (3 studies reporting); age range 2 to 10 years (4 studies reporting)

Number per Group: 438 children (693 teeth); see N per study listed above

Observed adverse effects:

Crown vs filling (4 studies; Atieh 2008, Hutcheson 2012, Innes 2011, Ram 2003):

- Failures (3 studies, 346 teeth): No failures in either group up to 12 months (based on 1 study, n=38, 76 teeth). From 12 to 48 months, crowns were favored over fillings (Odds Ratio 0.18, 95% Ci: 0.06 to 0.56).

- Pain (2 studies, 312 teeth): In the long term (12 to 24 months), crowns were favored vs fillings (Risk Ratio (RR) 0.15, 95% CI: 0.04 to 0.67). Short-term results were not estimable.
- Gingival bleeding (3 studies): results were not conclusive however increased risk of bleeding with crowns vs fillings; short term (< 12 months): RR 1.69, 95% CI: 0.61 to 4.66, n=226, 2 studies), long term (12 months): RR 1.74, 95% CI: 0.99 to 3.06, 195 teeth, 2 studies)

Crown vs no crown or filling (one 3-arm study (n=92); Santamaria 2014): When comparing PMC using the Hall technique (n=44) vs non-restorative caries treatment (fluoride varnish)(n=48), results at 1 year follow-up indicated:

- Failures: Crowns less likely to result in a major failure (RR 0.12, 95% CI: 0.01 to 2.18), though the result was inconclusive.
- Gingival bleeding: Crowns seemed more likely to cause gingival bleeding though the result was inconclusive (RR 1.09, 95% CI: 0.42 to 2.86).

Crown (SS) vs aesthetic veneer crown using the conventional technique (1 split-mouth study, n=11; Ram 2003): Follow-up at 6 months and 4 years indicated:

- Gingival bleeding: At 6 months, significantly more bleeding with aesthetic veneer (100% (10/11 bled on probing) vs 0% PMC; RR 23, 95% CI: 1.52 to 347.76). At 4 years (n=10), similar gingival bleeding in 1 patient each (RR 1, 95% CI: 0.07 to 13.87).
- Bone resorption: At 6 months, 1 case of bone resorption with veneer (RR 3, 95% CI: 0.14 to 66.53).

Timing of adverse effects: NR

Factors that predict response: NR

10.12 Source Citation: Gbadebo et al. 2014²³

Study Design: RCT

Device or Material: SS parapost (PP) vs glass fiber-reinforced post (FRP) for tooth restoration (23 (57.5% central incisors, 6 (15%) lateral incisors, 7 (17.5%) premolars and 4 (10%) molars). All the posts were cemented with dual cure resin composite.

Contact Duration: 1 and 6 months after post cementation of porcelain fused to metal (PFM) crown.

Dose: N/A

Frequency/Duration: once

Response: core failure, crown mobility, marginal integrity, crown retention

Patient characteristics (gender, mean age): gender NR, mean 38.2±16.86 years (range 18 to 74)

Number per Group: 19 each arm at 1 month; 16 PP and 18 FRP at 6 months

Observed adverse effects: No fractured PFM restoration, fractured root or post, or loss of post retention was reported up to 6 months. 1 case of core fracture in the PP arm at 1 month was in a tooth also reported as having marginal failure and Grade 2 mobility; initial core failure was however due to loss of adhesive bond between the core material (SS) and the post. Authors concluded similar clinical results for SS posts and prefabricated glass fiber posts.

Marginal integrity:

at 1 month (19 each arm): 1 tooth in PP group slight opening of crevice on probing the margin, 0 FRP; at 6 months (16 PP, 18 FRP: 1 tooth in each group had minimal crevice at the margin

Crown mobility:

at 1 month (19 each arm): 1 tooth in PP group had Grade 2 mobility due to core fracture leading to loss of crown retention, 0 FRP; at 6 months (16 PP, 18 FRP: 1 tooth in each arm displayed Grade 1 mobility

Crown retention:

at 1 month (19 each arm): 1 PP, 0 FRP; 0 each arm at 6 months

Failure of core:

at 1 month (19 each arm): 1 tooth in the PP arm due to loss of adhesive bond between the core material and the post (this same tooth was noted for marginal failure and Grade 2 mobility), 0 FRP; 0 each arm at 6 months

Timing of adverse effects: NR

Factors that predict response: NR

10.13 Source Citation: Jian et al. 2013¹⁹

Study Design: 1 SR with 9 RCTs; Of 4 RCTs reporting on SS, 1 RCT reported AEs

Device or Material: Multistrand SS, 0.015 inch Twistflex (Unitek corp, Monrovia USA) vs Superelastic NiTi, 0.014 heavy Japanese NiTi (GAC International USA) as first arch wires

Contact Duration: 24 hours to 15 days

Dose: N/A

Frequency/Duration: 23/43 patients had a second arch wire fitted to the other arch as a second procedure

Response: pain

Patient characteristics (gender, mean age): 23 males, 20 females; range 113 to 202 months; patients required extraction of at least 1 premolar tooth and placement of full arch edgewise fixed appliance.

Number per Group: Multistrand steel, 0.015 inch Twistflex (Unitek corp, Monrovia USA) - first arch wire (n=21), Superelastic NiTi, 0.014 heavy Japanese NiTi (GAC International USA) - first arch wire (n=21). All patients had full arch edgewise fixed appliance, with 0.018 x 0.030 inch standard (triple control) preadjusted bioprogressive brackets (Rocky Mountain Orthodontics, USA)

Observed adverse effects: No significant difference in pain at day 1 (mean difference (MD) -5.3, 95% CI: -18.34 to 7.74) or day 7 (MD -0.7, 95% CI: -1.97 to 0.57).

Timing of adverse effects: NR

Factors that predict response: NR

10.14 Source Citation: Talic et al. 2013²⁷

Study Design: Nonrandomized comparative

Device or Material: SS brackets and arch wires

Contact Duration: 1 month to 32 months

Dose: N/A

Frequency/Duration: once

Response: levels of Ni and Cr released into saliva

Patient characteristics (gender, mean age): 41 males, 49 females; males: 20.1±5.6 appliance, 23.1±4.2 no appliance; female: 16.8±3.4 appliance, 21±8.2 no appliance.

Number per Group: 90 salivary samples were collected; fixed orthodontic appliances (consisting of 4 bands, 20 SS brackets, and upper and lower nickel titanium or SS arch wires, n=40) and no fixed orthodontic appliances (n=50)

Observed adverse effects: Mean levels of Ni in the saliva of the fixed orthodontic appliance group were almost twice as high vs controls, while mean levels of Cr in the saliva were lower in the fixed orthodontic appliance group. Overall, the Ni and Cr levels in the saliva of individuals receiving fixed orthodontic appliances (with SS brackets and arch wires) were much lower than the levels that would be considered toxic.

Ni levels (mean±SD; µg/L [micrograms per litre])

Experimental/Ni (n=39) 4.19 ± 3.05, Control/Ni (n=50) 2.29 ± 2.51; *p*=0.002

Male Experimental/Ni (n=16) 4.31 ± 3.14, Male Control/Ni (n=24) 2.69 ± 2.75; 0.093

Female Experimental/Ni (n=23) 4.11 ± 3.06, Female Control/Ni 26 1.93 ± 2.26; *p*=0.008

Cr levels:

Experimental Cr (n=39) 2.83 ± 1.11, Control Cr (n=50) 3.23 ± 1.33; *p*=0.126; *p*=0.126

Male Exp/Cr (n=17) 3.14 ± 1.08, Male Control/Cr (n=24) 3.10 ± 1.43; *p*=0.921

Female Experimental/Cr (n=23) 2.62 ± 1.10, Female Control/Cr (n=26) 3.36 ± 1.26; *p*=0.034

Timing of adverse effects: Highest level of Ni occurred after 20 months of treatment, while the highest level of Cr occurred after 4 months of treatment.

Factors that predict response: NR

10.15 Source Citation: Chandra Sekhar et al. 2011²⁴

Study Design: RCT

Device or Material: SS wire plus composite resin reinforcement vs Ribbond ribbon plus composite resin reinforcement for splinting over unsplinted mobile teeth following periodontal surgery in 30 chronic periodontitis patients with Grade I to Grade II mobility of upper and/or lower anterior teeth.

Contact Duration: 12 weeks

Dose: NR

Frequency/Duration: once

Response: mobility, plaque, partial fractures

Patient characteristics (gender, mean age): 56% males; 45 years (range 35 to 55)

Number per Group: 20 experimental, 10 controls: Experimental group (20 splints): composite splint plus SS wire (10 splints) or Ribbond ribbon (10 splints) vs controls without splinting. A total of 180 anterior teeth were treated, 120 (80 mobile, 40 firm) in the experimental group and 60 (40 mobile, 20 firm) in the control group.

Observed adverse effects: More partial fracture with SS vs Ribbond ribbon. Higher reduction (28.47%) in tooth mobility with splints (SS or Ribbond ribbon) vs no splints. Slightly higher reduction in tooth mobility with SS vs Ribbond (36.11% vs 35.42%). Similar increases in plaque index between SS and Ribbond after flap surgery and splint removal. Both treatments showed "good compatibility with gingival tissues and oral mucosa, were successful in immobilizing teeth, durable in function, and well-tolerated."

Partial fractures: 9 partial fractures of the splint occurred on the lingual aspect in the SS group at phase 3, 6 and 8. 2 fractures of the splint occurred in the Ribbond group at phase 3.

Tooth mobility (mean value at 12 weeks): 0.6690 controls without splinting, 0.4660 SS wire and composite splint, 0.5090 FRC

Plaque index (mean value at 12 weeks): 0.7000 controls, 0.8100 SS, 0.6300 Ribbond ribbon

Timing of adverse effects: partial fracture occurred with SS during week 9 to 12, and week 9 with Ribbond ribbon.

Factors that predict response: NR

Systemic Response/Toxicity

10.16 Source Citation: Amini et al. 2012²⁸

Study Design: Nonrandomized comparative

Device or Material: fixed appliances consisting of 0.016- and 0.016 × 0.022-in SS archwires, bonded 0.018 inch slot preadjusted Roth prescription SS brackets on all teeth except the molars (Discovery, Dentaaurum, Pforzheim, Germany), and an average of six SS orthodontic bands (Unitek/3M, Monrovia, California, USA).

Contact Duration: 17.1 ± 6.4 months after the initiation of fixed orthodontic treatment (range 12 to 21 months).

Dose: NR

Frequency/Duration: once

Response: urinary Ni concentration

Patient characteristics (gender, mean age (years)): 20 females, 10 males each arm; 20.95±5.3 fixed appliances, 21.8 ± 6.6 no fixed appliances (age and gender matched siblings)

Number per Group: 30 each arm (controls were siblings of individuals with fixed appliances)

Observed adverse effects: Significantly higher urinary Ni concentrations with fixed appliances vs controls (difference 1.98 µg/L, 95% CI: 0.523 to 3.319), and males receiving fixed appliances vs their age and gender matched siblings with no appliances (difference 3.02 µg/L, 95% CI: 0.479 to 5.513). Authors noted only slight elevation in urinary Ni concentrations from fixed appliances used for at least 12 months.

Urinary Ni levels (µg/L):

Overall (30 each arm): 9.81±3.53 appliance, 7.83±2.87 controls; difference 1.98, 95% CI: 0.523 to 3.319 (repeated-measures two-way ANOVA indicated statistically significant difference: $F=6.723$, $p=0.009$)

Females (20 each arm): 9.90±3.83 appliance, 8.43±2.94 controls; difference 1.47, 95% CI: -0.431 to 3.384

Males (10 each arm): 9.67±3.25 appliance, 6.65±2.57 controls; difference 3.02, 95% CI: 0.479 to 5.513

Female patients (n=20) vs male patients (n=10): difference -2.682, 95% CI : -2.682 to 3.133

Female controls (n=20) vs male controls (n=10): difference 1.78, 95% CI: -0.496 to 4.055

Timing of adverse effects: at least 12 months wear of fixed appliance

Factors that predict response: "Gender did not have a statistically significant influence on the increase pattern, albeit this increase was somewhat more vivid in males."

Table 11: Cardiovascular - miscellaneous - Health Effect (In Vivo) Human Study

Local Response/Toxicity

11.1 Source Citation: Bhatia et al. 2020³³

Study Design: nonrandomized comparative

Device or Material: SS (Berlin Heart EXCOR (BHE; Berlin Heart AG, Berlin, Germany) left ventricular assist device (LVAD) and biventricular (BIVAD) vs non-SS VAD (CentriMag (Thoratec Switzerland GmbH, Zurich, Switzerland) LVAD, CentriMag BIVAD, HeartWare (Medtronic HeartWare, Miami Lakes, FL), HeartMate II (Thoratec Corporation, Pleasanton, CA)) as a bridge to transplantation or cardiac recovery

Contact Duration: 159.7±234.2 days (median 45 days; range 3 to 823 days)

Dose: NR

Frequency/Duration: once (BIVAD implantation occurred simultaneously)

Response: bleeding, neurologic events (cerebral hemorrhage), tamponade, fibrin embolism, bowel ischemia, pump exchange

Pump exchange was required in 4 patients (31%). The reason for pump change was fibrin, thrombus formation or pump expiry.

Patient characteristics (gender, mean age): 83% males; median 12 years (range 1 to 17 years)

Number per Group: 7 Berlin Heart EXCOR (5 LVAD, 2 BIVAD), 3 CentriMag (1 LVAD, 2 BIVAD), 2 HeartWare, 1 HeartMate II; 13 episodes of VAD support in 12 patients with heart failure unresponsive to medical therapy

Observed adverse effects:

Bleeding requiring mediastinal re-exploration occurred in 1 patient (14.2% of EXCOR) with BHE LVAD.

Overall incidence of neurologic events was 23%; occurring in all 3 patients in first 3 months. Cerebral hemorrhage occurred in 2 (28%) patients with BHE (1 with BHE LVAD who died on support, 1 with BHE BIVAD which was exchanged to non-SS VAD). One patient with non-SS LVAD (50%) had an acute ischemic stroke. Both 2 surviving patients did not have permanent neurological sequelae.

Pericardial window (surgery done on the sac around heart in which a small part of the sac is removed to allow extra fluid drain from the sac) was created for relieving tamponade in 2 patients (15%); 1 each stainless (BHE LVAD) and non-stainless (both patients experienced late death after transplant due to graft rejection).

Bowel ischemia and fibrin embolism occurred in 1 (14.2%) patient with BHE LVAD.

Pump exchanges (due to fibrin, thrombus formation, or expiration) was required in 4 patients overall (31%); 43% of BHE, 16.6% all non-stainless.

Timing of adverse effects: With EXCOR: cerebral hemorrhage at day 3, pump exchange at day 15, pericardial window at day 28, bowel ischemia and fibrin embolism at day 16; mediastinal exploration and LVAD pump exchange in BHE BIVAD patient at day 45

Factors that predict response: NR

11.2 Source Citation: Hayuningrat et al. 2020³²

Study Design: RCT

Device or Material: SS Wire threads vs Polydioxanone threads (PDS) for sternum closure of pediatric patients after cardiac surgery

Contact Duration: weeks 6, 9 and 12

Dose: NR

Frequency/Duration: once

Response: pain, displacement, stability

Patient characteristics (gender, mean age): 69% male, 8.9±1.56 SS, 8.6±1.32 PDS

Number per Group: 8 each arm

Observed adverse effects: Significantly more pain with SS at weeks 6 and 9, but significantly more displacements with PDS at all time points.

Pain: A significantly higher degree of pain was demonstrated with SS at week 6 (mild: 8 PDS, 2 SS, moderate: 5 SS, severe: 1 SS; $p=0.03$) and week 9 (mild pain: 5 SS, 4 PDS; moderate pain: 3 SS; $p=0.01$); with no pain reported at week 12.

Stability: No significant difference in stability at any time point (6, 9, and 12 weeks). At week 6: 14 patients were stable (8 SS, 6 PDS) and 2 patients with PDS had minimal stability. At week 9: 12 patients were stable (7 SS, 5 PDS) and 4 patients had minimal stability (1 SS, 3 PDS). At week 12, 13 patients were stable (8 SS, 5 PDS) and 3 patients with PDS had minimal stability.

Displacement: Significantly more displacements with PDS at all time points (6, 9, and 12 weeks). At week 6 and week 9, displacement occurred in 5 patients (1 SS, 4 PDS; $p=0.02$) and 6 patients (1 SS, 5 PDS), respectively. At week 12, displacement remained with PDS only (0 SS, 5 PDS; $p=0.009$).

Timing of adverse effects: weeks 6 to 12

Factors that predict response: "The strength of fixation on the sternum is influenced by the type of fixation technique, the amount, strength and thickness of the wire used and the strength of the sternum itself."

11.3 Source Citation: Huang et al. 2018²⁹

Study Design: Systematic review of 27 studies (26 cohort studies, 1 case series)

Device or Material: Berlin Heart EXCOR [BHE], Thoratec, Medos, HeartWare HVAD, HeartMate II, and Novacor. Only EXCOR is on the list of SS devices.

Contact Duration: mean support time was 52 days (range 0 to 842 days)

Dose: NA

Frequency/Duration: Once

Response: bleeding, death, thromboembolism

Patient characteristics (gender, mean age): 4.7 years (range 3 days to 18 years)

Number per Group: BHE (486/558, 87% reported in 20 studies), Thoratec (42/558, 7.5% reported in 1 study), Medos (21/558, 3.8% reported in 3 studies), HeartWare HVAD (10/558, 1.8% reported in 1 study), HeartMate II (7/558, 1.25%), and Novacor (2/558, 0.36%).

Observed adverse effects:

Bleeding incidence was higher with SS vs all non-stainless devices (40% BHE (n=471); non-stainless: 25% Medos (n=16), 16% Thoratec (n=19), 11.1% HVAD (n=9)). Bleeding incidence was due to gastrointestinal bleeding, intracranial hemorrhage, and chest re-exploration for bleeding.

Thromboembolism incidence with SS vs non-stainless (25% BHE (n=471); non-stainless: 37.5% Medos (n=16), 26% Thoratec (n=19), and 33.3% HVAD (n=9)). Thromboembolism incidence was defined as neurological thromboembolic events (including stroke, transient ischemic attack), arterial non-central nervous system thromboembolism, device exchange due to thrombosis, and venous thromboembolism.

Less death was reported with BHE (26.5%) vs 2 non-stainless devices (50% Medos, 47% Thoratec) but higher vs 1 non-stainless (11.1%) with HeartWare HVAD). The most frequent causes of death were: multi-system organ failure in 17% of patients (24/143), TE neurological complications in 16% (23/143), ICH in 14% (20/143), circulatory failure in 10% (15/143), sepsis in 7% (10/143), systemic TE in 2% (3/143), and pump thrombosis in 0.7% (1/143)

Timing of adverse effects: Support time range was 0 to 842 days.

Factors that predict response: "VAD is an increasingly important option for pediatric end-stage heart failure, but the use of VAD entails a high risk of bleeding, thrombosis and mortality. VAD implantation can lead to a disturbance in each of Virchow's components: blood flow is affected by the external control of a pump; vessel damage occurs due to surgery, pump pressure and cannula placement; and changes in hemostatic components occur because blood is constantly exposed to a foreign surface."

11.4 Source Citation: Soylu et al. 2016³⁰

Study Design: Systematic review of 28 studies (3 RCTs, 1 nonrandomized comparative study, 21 case series, and 3 case reports) focused on use of distal anastomotic devices (DADs) during coronary artery bypass graft (CABG) surgery

Device or Material: 8 distal anastomotic devices (SS vs non-SS) vs handsewn cases

2 DADs with SS components: St. Jude DAD with a SS connector, and the C-port anastomotic system (Cardica, Inc., Redwood, CA) which utilizes 8 separate SS clips

6 DADs without SS components: Magnetic vascular positioner (MVP, Ventrica, Inc. Freemont, CA), Heartflo (Perclose/Abbott Labs, Redwood City, VA), U-clip device (Coalescent Surgical, Inc. Sunnyvale, CT), Vessel Closure System (VCS; US Surgical Corporation, Norwalk, CT), DAD (Bypass, Inc.) with a nitinol ring, Coronary anastomosis coupler (CAC) device (Converge Medical Inc., Sunnyvale, CA) with nitinol frame

Contact Duration: 1 week to 76 weeks

Dose: NR

Frequency/Duration: once

Response: myocardial infarction due to device failure, postoperative hemorrhage, anastomotic patency

Patient characteristics (gender, mean age): 60% to 100% males (studies reporting); mean 63 years to 70 (studies reporting)

Number per Group: number of devices = SS (112 St Jude, 340 C-port), non-SS (69 MVP, 459 U-clip, 71 Heartflo, 17 VCS, 14 DAD, 37 CAC)

Observed adverse effects:

2 cases of myocardial infarction were attributed to technical device failure with C-Port; 1 case necessitated conversion to hand-sewn anastomoses. No cases of MI were attributed to other DADs.

Rates for postoperative hemorrhage with SS were 2.2% (4/180 with C-port), and 1.6% (1/61 with St Jude) and ranged from 0.8% to 5.9% with non-SS (U-clip: 0.8% (1/123), VCS: 5.9% (1/17), Heartflo: 1.4% (1/71)).

Anastomotic patency:

- Overall pooled early patency (<1 month) for all DADs was 97.2% (350/360) vs 94.8% (145/153) for hand-sewn anastomoses. Short-term (<1 month) angiographic patency for SS DADs were over 99% (99/1% C-Port and 100% St. Jude) and ranged from 92.9% to 100% for non-SS DADs.
- Overall intermediate-term patency (1-3 months) was 94.6% for DADs vs 93.4% for hand-sewn anastomoses. Intermediate-term patency for SS DADs was 91.3% (St. Jude) and 94.5% (C-Port), and was 96.7% (CAC) and 100% (VCS) for non-SS DADs (no reporting for 4 non-SS DADs).
- Overall long-term (>3 months) was 92.3% for DADS vs 95.1% for hand-sewn anastomoses. Long-term patency for SS was 93.8% (C-port) and 73% (St Jude) and for non-SS was 88.5% (MVP) and 96.1% (U-Clip); no reporting for 4 non-SS devices. There was a significant reduction in patency from early to late periods with both SS DADs (St. Jude (100% to 73%) and C-port (99.1% to 93.8%)) and 1 non-SS DAD (MVP (96.8% to 88.5%)).

Timing of adverse effects: NR

Factors that predict response: NR

11.5 Source Citation: McLoney et al. 2013³⁴

Study Design: nonrandomized comparative

Device or Material: SS Greenfield filters (Boston Scientific, Natick, MA) vs Gunther Tulip filters (from nonferromagnetic Conichrome) and platinum Celect filters (both Cook, Bloomington, IN)

Contact Duration: 0 to 1,987 days

Dose: NR

Frequency/Duration: once; mean follow-up for Greenfield, Tulip and Celect filters was 286 days, 437 days, 277 days

Response: perforation

Patient characteristics (gender, mean age): 51% male, 60 years (range 28 to 87) for Greenfield IVC filters

Number per Group: 50 Greenfield, 160 Tulip, and 255 Celect

Observed adverse effects:

- Significantly lower IVC perforation rate with Greenfield (1 (2%) Greenfield, 126 (49%) Celect, 69 (43%) Tulip filters).
- IVC filters rated as Grade 3 (perforating strut contacted an adjacent organ) were 0 Greenfield, 76 Celect and 44 Tulip filters. The organs most commonly perforated were the duodenum (36 Celect, 19 Tulip), a vertebral body (30 Celect, 15 Tulip), and the aorta (10 Celect, 10 Tulip). The pancreas, kidney, liver, and psoas muscle were also affected.
- IVC filter fracture: 0 Greenfield filters, 1 (0.6%) Tulip filter, and 2 (0.8%) Celect filters.

Timing of adverse effects: NR

Factors that predict response: NR

11.6 Source Citation: Yang et al. 2016³¹

Study Design: Systematic review of patients with aortic coarctation

Device or Material: Palmaz SS stents

Contact Duration: Between 1.8 and 2.4 years

Dose: NR

Frequency/Duration: NR

Response: Successful cases, total complications

Patient characteristics (gender, mean age): Gender NR; Mean age range:

Number per Group: 43

Observed adverse effects: Successful cases: 43/43 (100%)

Total complications: 6/43 (14.0%)

Timing of adverse effects: Between 1.8 and 2.4 years

Factors that predict response: Begg's test for small study effects showed no evidence of bias for the analysis of success ($p = 0.502$) and stent-related complications ($p = 0.091$) however there was a slight suggestion of bias for the complication outcomes ($p=0.010$).

11.7 Source Citation: Butera et al. 2014³⁵

Study Design: Non-randomized comparative study of patients with aortic coarctation

Device or Material: Palmaz SS stents and others, G1 (bare stent implantation) or G2 (covered stent implantation)

Contact Duration: Median length of follow-up (range): 65 months (1 to 149)

Dose: Long-sheath (French size), mean (SD): G1: 10.48 (1.77), G2: 12.42 (1.72), $p<0.001$; balloon diameter in mm, mean (SD): G1: 14.70 (3.28), G2: 13.85 (3.22), $p=0.843$

Frequency/Duration: NR

Response: Aortic wall complications. Note: all other reported outcomes (success rate, reintervention at follow-up, and mortality rate) do not report outcomes by specific device.

Patient characteristics (gender, mean age): Male, n (%): G1: 45 (63.4%), G2: 46 (63.9%); Median age in years (range): G1: 17.0 (13.0 to 29.0), G2: 17.5 (12.0 to 32.5)

Number per Group: G1 (n=71): Bare stent implantation with Palmaz (n=41, 57.7%), Palmaz-Genesis (n=15, 21.1%), Cheatham-Platinum (n=13, 18.3%), and Andrastent (n=2, 2.9%); G2 (n=72): Covered stent with 8-zig CP covered stent (n=62, 86.1%) or Advanta V12 LD stent (n=10, 12.5%)

Observed adverse effects: 5 patients in group 1 had aortic wall complications (4 with Palmaz stent, 1 with Genesis stent), whereas, no patients in group 2 had aortic wall complications.

Timing of adverse effects: Median length of follow-up (range): 65 months (1 to 149)

Factors that predict response: NR

Table 12: Cardiovascular – grafts - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

12.1 Source Citation: Hsiao et al. 2011³⁶

Study Design: Single arm.

Device or Material: Zenith AAA Endovascular Graft (SS, Cook Inc.)

Contact Duration: Mean follow-up of 22 months (19-29 months).

Dose: NA.

Frequency/Duration: Single administration.

Response: Abdominal compartment syndrome.

Patient characteristics (gender, mean age): 84% male; 81 years (79-87 years).

Number per Group: 6 ruptured abdominal aortic aneurysm (AAA) patients.

Observed adverse effects: Patient D experienced abdominal compartment syndrome requiring exploratory laparotomy with decompression. The complication may be due to underlying conditions (e.g., renal function impairment).

Timing of adverse effects: Mean follow-up of 22 months (19-29 months).

Factors that predict response: None reported.

Systemic Response/Toxicity

12.2 Source Citation: Hsiao et al. 2011³⁶

Study Design: Single arm.

Device or Material: Zenith AAA Endovascular Graft (SS, Cook Inc.)

Contact Duration: Mean follow-up of 22 months (19-29 months).

Dose: NA.

Frequency/Duration: Single administration.

Response: Limb ischemia; pneumonia; pulmonary tuberculosis (TB); renal failure; urinary bladder incontinence.

Patient characteristics (gender, mean age): 84% male; 81 years (79-87 years).

Number per Group: 6 ruptured abdominal aortic aneurysm (AAA) patients.

Observed adverse effects: Patient A experienced pneumonia, pulmonary tuberculosis, and urinary bladder incontinence. Patient C experienced chronic renal failure and limb ischemia requiring femoro-femoral bypass after stent graft insertion. Complications are not explicitly device-related and may be due to underlying conditions (e.g., renal function impairment).

Timing of adverse effects: Mean follow-up of 22 months (19-29 months).

Factors that predict response: None reported.

Table 13: Cardiovascular – coronary stents - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

13.1 Source Citation: Vlieger et al. 2021⁴⁴

Study Design: Non-randomized comparative study

Device or Material: Sirolimus-eluting stent (SES): Ulitmaster (CoCr), biolimus-eluting stent (BES): Nobori (SS)

Contact Duration: 1 year

Dose: Strut thickness: SES: 80µm, BES: 120µm; Drug load: SES: 3.9 µg/mm; BES: 15.6µg/mm

Frequency/Duration: Study stents implanted, mean (SD): SES: 1.49 (SD 0.9); BES: 1.47 (0.9)

Response: MI, ST, TLR, TLF, TVF, TVR

Patient characteristics (gender, mean age): Male gender, %: SES: 76.7%; BES: 78.0%; Mean age in years (SD): SES: 64.7 (11.0); BES: 64.4 (11.1)

Number per Group: SES: 8,137; BES: 2,738

Observed adverse effects:

MI: SES: 1.13% (100/8,879); BES: 2.09% (64/3,067), $p < 0.0001$, **favors SES**

TV-MI: SES: 0.92% (82/8,879); BES: 1.76% (54/3,067), $p = 0.0002$, **favors SES**

ST: Definite: SES: 0.45% (40/8,879); BES: 0.55% (17/3,067), $p = 0.4721$; Probable: SES: 0.27% (24/8,879); BES: 0.23% (7/3,067), $p = 0.693$; Definite or probable: SES: 0.71% (63/8,879); BES: 0.78% (24/3,067), $p = 0.6819$; Possible: SES: 0.68% (60/8,879); BES: 0.42% (13/3,067), $p = 0.1228$, **no difference**

TLF: SES: 3.27% (290/8,879); BES: 4.27% (131/3,067), $p = 0.0093$, **favors SES**

TLR: SES: 1.43% (127/8,879); BES: 2.35% (72/3,067), $p = 0.0006$, **favors SES**

TLR (PCI): SES: 1.34% (119/8,879); BES: 2.02 % (62/3,067), $p = 0.0078$, **favors SES**

TLR (CABG): SES: 0.09% (8/8,879); BES: 0.46% (14/3,067), $p < 0.0001$, **favors SES**

TVF: SES: 3.78% (336/8,879); BES: 5.12% (157/3,067), $p = 0.0014$, **favors SES**

TVR: SES: 2.08% (185/8,879); BES: 3.42% (105/3,067), $p < 0.0001$, **favors SES**

TVR (PCI): SES: 1.81% (161/8,879); BES: 2.93% (90/3,067), $p = 0.0002$, **favors SES**

TVR (CABG): SES: 0.30% (27/8,879); BES: 0.62% (19/3,067), $p = 0.015$, **favors SES**

Timing of adverse effects: Up to 1 year

Factors that predict response: Between the SES and BES groups, there was no difference in baseline clinical characteristics except for a higher prevalence of family history of coronary artery disease in the SES group (36.1% vs 30.4%, $p < 0.001$). In addition, a significant interaction ($p = 0.02$) between clinical presentation (acute coronary syndrome [ACS] vs no ACS) and treatment group (SES vs BES) was observed, showing a lower risk of 1-year TLF in ACS patients if treated with SES as compared with BES (3.4% for SES vs 5.4% for BES; relative risk 0.64; 95% CI 0.49–0.83, $p = 0.02$).

13.2 Source Citation: Allali et al. 2018⁴⁵

Study Design: Non-randomized comparative study

Device Material: Early generation drug eluting stents (EG-DES): SES Cypher (Cordis, Miami Lakes, FL, USA) and PES Taxus Liberté (Boston Scientific, Boston, MA, USA) (Both SS); New generation drug eluting stents (NG-DES): CoCR-based EES Xience (Abbott Vascular, Santa Clara, CA, USA), platinum Cr based EES Promus (Boston Scientific, Natick, MA, USA), and CoCR-based SES Orsiro (Biotronik, Bülach, Switzerland)

Contact Duration: Follow-up months, median (IQR): EG-DES: 32 (23-60); NG-DES: 17 (12-31)

Dose: Stent diameter, mean (SD): EG-DES: 2.93 (0.37); NG-DES: 2.93 (0.48), $p=0.84$

Frequency/ Duration: Multiple stenting: EG-DES: 140 (48.6%); NG-DES: 142 (63.1%), $p<0.001$; Number of implanted stents: EG-DES: 1.7 (0.8); NG-DES: 2 (0.9), $p<0.001$

Response: Major adverse cardiovascular events (MACE), MI, ST, TVR, TLR

Patient characteristics (gender, mean age): Age in years, mean (SD): EG-DES: 71 (8); NG-DES: 72 (9); male sex, n (%): EG-DES: 353 (73.4%); NG-DES: 195 (72.8%)

Number per Group: EG-DES: 268; NG-DES: 213

Observed adverse effects:

MACE, rate of reduction: EG-DES: 31.1%, NG-DES: 21.1%, log-rank $p=0.04$, **favors EG-DES**

MI: EG-DES: 4.9%, NG-DES: 4.1%, log-rank $p=0.89$, **no difference**

ST (definite and probable): EG-DES: 0.9%, NG-DES: 2.4%, log-rank $p=0.13$, **no difference**

TLR: EG-DES: 12.7%, NG-DES: 7.9%, log-rank $p=0.13$, **no difference**

TVR: EG-DES: 17.6%, NG-DES: 12.9%, log-rank $p=0.19$, **no difference**

Timing of adverse effects: Up to 5 years

Factors that predict response: The superiority of NG-DES for reducing MACE rate was confirmed (adjusted HR 0.65; 95% CI 0.42–0.98; $p = 0.04$). The incidence of definite and probable stent thrombosis was not statistically significant between groups (adjusted HR 3.33; 95% CI 0.64–17.28; $p = 0.15$).

13.3 Source Citation: Yan et al. 2016³⁷

Study Design: Systematic review

Device or Material: BP-stainless DESs vs. other alloy DESs; BP-alloy DESs vs. other stainless DESs

Contact Duration: Median follow-up in months (Range): 19.6 (6 to 50)

Dose: NR

Frequency/Duration: NR

Response: MI, ST (definite), ST (definite/probable), TLR, TVR

Patient characteristics (gender, mean age): Mean age range: 56.7 to 67.5; Percent male range: 47.4 to 86.7. Note: These ranges are for the entire review population.

Number per Group: Total meta-analyzed population of 34,850 patients (49 RCTs). Note: Only 10 trials are reported that compare BP-stainless DESs to other alloy DESs (patient count NR), and 3 trials compare BP-alloy DESs vs other stainless DESs (patient count NR).

Observed adverse effects: Note: all observed adverse effects are using the maximum length of follow-up.

MI: BP-stainless DESs vs. other alloy DESs: OR: 1.01, 95% CI: 0.85 to 1.20, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 1.21, 95% CI: 0.72 to 2.02, **no difference**

ST (definite): BP-stainless DESs vs. other alloy DESs: OR: 1.08, 95% CI: 0.65 to 1.81, **no difference**

ST (definite/probable): BP-stainless DESs vs. other alloy DESs: OR: 0.79, 95% CI: 0.58 to 1.07, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.20, 95% CI: 0.02 to 1.70, **no difference**

TLR: BP-stainless DESs vs. other alloy DESs: OR: 1.00, 95% CI: 0.81 to 1.22, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.87, 95% CI: 0.22 to 3.50, **no difference**

TVR: BP-stainless DESs vs. other alloy DESs: OR: 1.09, 95% CI: 0.92 to 1.28, **no difference**

Timing of adverse effects:

MI:

Within 30 days (short-term): BP-stainless DESs vs. other alloy DESs: OR: 0.90, 95% CI: 0.59 to 1.39, **no difference**;

> 30 days to 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 0.96, 95% CI: 0.77 to 1.18, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 1.26, 95% CI: 0.74 to 2.16, **no difference**

> 1 year (long-term): BP-stainless DESs vs. other alloy DESs: OR: 1.07, 95% CI: 0.83 to 1.39, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.69, 95% CI: 0.26 to 1.84, **no difference**

ST (definite):

Within 30 days (early): BP-stainless DESs vs. other alloy DESs: OR: 1.32, 95% CI: 0.56 to 3.08, **no difference**;

Within 24 hours (acute): BP-stainless DESs vs. other alloy DESs: OR: 0.70, 95% CI: 0.11 to 4.47, **no difference**;

> 24 hours to 30 days (subacute): BP-stainless DESs vs. other alloy DESs: OR: 1.20, 95% CI: 0.16 to 8.74, **no difference**;

> 30 days to 1 year (late): BP-stainless DESs vs. other alloy DESs: OR: 1.21, 95% CI: 0.48 to 3.04, **no difference**;

Within 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 1.20, 95% CI: 0.65 to 2.19, **no difference**;

>1 year (long): BP-stainless DESs vs. other alloy DESs: OR: 1.09, 95% CI: 0.58 to 2.04, **no difference**;

Very late: BP-stainless DESs vs. other alloy DESs: OR: 1.38, 95% CI: 0.41 to 4.73, **no difference**

ST (definite/probable):

Within 30 days (early): BP-stainless DESs vs. other alloy DESs: OR: 0.82, 95% CI: 0.46 to 1.46, **no difference**;

Within 24 hours (acute): BP-stainless DESs vs. other alloy DESs: OR: 1.37, 95% CI: 0.26 to 7.29, **no difference**;

> 24 hours to 30 days (subacute): BP-stainless DESs vs. other alloy DESs: OR: 1.22, 95% CI: 0.28 to 5.31, **no difference**;

> 30 days to 1 year (late): BP-stainless DESs vs. other alloy DESs: OR: 0.46, 95% CI: 0.22 to 0.98, **favours BP-stainless DESs**; BP-alloy DESs vs. other stainless DESs: OR: 0.33, 95% CI: 0.03 to 3.16, **no difference**

Within 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 0.69, 95% CI: 0.47 to 1.03, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.33, 95% CI: 0.03 to 3.16, **no difference**

>1 year (long): BP-stainless DESs vs. other alloy DESs: OR: 0.79, 95% CI: 0.49 to 1.29, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.20, 95% CI: 0.02 to 1.70, **no difference**

Very late: BP-stainless DESs vs. other alloy DESs: OR: 1.23, 95% CI: 0.44 to 3.42, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.33, 95% CI: 0.03 to 3.21, **no difference**

TLR:

Within 30 days (short-term): BP-stainless DESs vs. other alloy DESs: OR: 1.13, 95% CI: 0.57 to 2.23, **no difference**;

> 30 days to 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 0.93, 95% CI: 0.73 to 1.19, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.90, 95% CI: 0.28 to 2.88, **no difference**;

> 1 year (long-term): BP-stainless DESs vs. other alloy DESs: OR: 1.11, 95% CI: 0.87 to 1.43, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.87, 95% CI: 0.22 to 3.50, **no difference**

TVR:

Within 30 days (short-term): BP-stainless DESs vs. other alloy DESs: OR: 0.82, 95% CI: 0.43 to 1.54, **no difference**;

> 30 days to 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 1.10, 95% CI: 0.91 to 1.31, **no difference**;

> 1 year (long-term): BP-stainless DESs vs. other alloy DESs: OR: 1.15, 95% CI: 0.89 to 1.49, **no difference**

Factors that predict response: The results did not significantly change after the sequential removal of individual studies or after the removal of the article published in Chinese via sensitivity analyses.

13.4 Source Citation: Gao et al. 2015⁴²

Study Design: RCT

Device or Material: PES: Taxus Liberté stent (SS); PtCr-EES: Promus Element stent (Boston Scientific, Marlborough, MA) (PtCr)

Contact Duration: Up to 1 year

Dose: Total nominal stent length implanted in mm: PES: 25.57 (9.62); PtCr-EES: 24.84 (8.40)

Frequency/Duration: Multiple stents implanted, n (%): PES: 4 (3.1%); PtCr-EES: 12 (3.2%)

Stents per patient, mean (SD): PES: 1.03 (0.18); PtCr-EES: 1.03 (0.20)

Response: ARC Stent Thrombosis, LLL (in-stent, in-segment), binary restenosis (in-stent, in-segment), MI (q-wave, non-q-wave, target vessel, non-target vessel), TLF, TVF, TVR (TLR, non-TLR)

Patient characteristics (gender, mean age): Male gender, n (%): PES: 88 (69.3%), PtCr-EES: 268 (71.8%); Mean age in years (SD): PES: 57.55 (9.50), PtCr-EES: 57.12 (9.90)

Number per Group: PES: 127; PtCr-EES: 373

Observed adverse effects: LLL and binary restenosis outcomes reported via 9-month angiographic readings. All other outcomes examined at 1 year. Only LLL results showed significant differences.

ARC Stent Thrombosis, n (%): PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

Binary restenosis (in-segment), n (%): PES: 9 (7.8%), PtCr-EES: 10 (3.0%), p=0.06, **no difference**

Binary restenosis (in-stent), n (%): PES: 6 (5.2%), PtCr-EES: 7 (2.1%), p=0.11, **no difference**

LLL (in-segment), mean in mm (SD): PES: 0.27 (0.45), PtCr-EES: 0.06 (0.36), p<0.001, **favors PtCr-EES**

LLL (in-stent) mean in mm (SD): PES: 0.40 (0.45), PtCr-EES: 0.11 (0.36), p<0.001, **favors PtCr-EES**

MI, n (%): PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

MI (q-wave): PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

MI (non-q-wave): PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

MI (target vessel): PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

MI (non-target vessel): PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

TLF, n (%): PES: 5 (4.0%), PtCr-EES: 8 (2.2%), p=0.33, **no difference**

TVF, n (%): PES: 6 (4.8%), PtCr-EES: 10 (2.7%), p=0.25, **no difference**

TVR, n (%): PES: 6 (4.7%), PtCr-EES: 10 (2.7%), p=0.26, **no difference**

TVR (non-TLR): PES: 5 (3.9%), PtCr-EES: 8 (2.2%), p=0.33, **no difference**

TVR (TLR): PES: 1 (0.8%), PtCr-EES: 3 (0.8%), p=1.00, **no difference**

Timing of adverse effects:

ARC Stent Thrombosis, n (%):

9-month: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

1-year: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

Binary restenosis (in-segment), n (%) (9-month): PES: 9 (7.8%), PtCr-EES: 10 (3.0%), $p=0.06$, **no difference**

Binary restenosis (in-stent), n (%) (9-month): PES: 6 (5.2%), PtCr-EES: 7 (2.1%), $p=0.11$, **no difference**

LLL (in-segment), mean in mm (SD) (9-month): PES: 0.27 (0.45), PtCr-EES: 0.06 (0.36), $p<0.001$, **favours PtCr-EES**

LLL (in-stent), mean in mm (SD) (%) (9-month): PES: 0.40 (0.45), PtCr-EES: 0.11 (0.36), $p<0.001$, **favours PtCr-EES**

MI, n (%) 9-month: PES: 1 (0.8%), PtCr-EES: 0 (0%), $p=0.26$; 1-year: PES: 1 (0.8%), PtCr-EES: 0 (0%), $p=0.26$, **no difference**

MI (q-wave):

9-month: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

1-year: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

MI (non-q-wave):

9-month: PES: 1 (0.8%), PtCr-EES: 0 (0%), $p=0.26$, **no difference**

1-year: PES: 1 (0.8%), PtCr-EES: 0 (0%), $p=0.26$, **no difference**

MI (target vessel):

9-month: PES: 1 (0.8%), PtCr-EES: 0 (0%), $p=0.26$, **no difference**

1-year: PES: 1 (0.8%), PtCr-EES: 0 (0%), $p=0.26$, **no difference**

MI (non-target vessel):

9-month: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

1-year: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

TLF, n (%):

9-month: PES: 5 (4.0%), PtCr-EES: 8 (2.2%), $p=0.33$, **no difference**

1-year: PES: 5 (4.0%), PtCr-EES: 8 (2.2%), $p=0.33$, **no difference**

TVF, n (%):

9-month: PES: 5 (4.0%), PtCr-EES: 10 (2.7%), $p=0.55$, **no difference**

1-year: PES: 6 (4.8%), PtCr-EES: 10 (2.7%), $p=0.25$, **no difference**

TVR, n (%): 9-month: PES: 5 (4.0%), PtCr-EES: 10 (2.7%), $p=0.55$; 1-year: PES: 6 (4.7%), PtCr-EES: 10 (2.7%), $p=0.26$, **no difference**

TVR (non-TLR):

9-month: PES: 0 (0%), PtCr-EES: 3 (0.8%), $p=0.58$, **no difference**

1-year: PES: 1 (0.8%), PtCr-EES: 3 (0.8%), $p=1.00$, **no difference**

TVR (TLR): PES: 1 (0.8%), PtCr-EES: 3 (0.8%), $p=1.00$, **no difference**

9-month: PES: 5 (4.0%), PtCr-EES: 8 (2.2%), $p=0.33$, **no difference**

1-year: PES: 5 (3.9%), PtCr-EES: 8 (2.2%), $p=0.33$, **no difference**

Factors that predict response: NR

13.5 Source Citation: Wijns et al. 2014⁴³

Study Design: RCT

Device or Material: ZES: Endeavor (cobalt alloy) vs. SES: Cypher (SS)

Contact Duration: 4 years

Dose: Total stent length per patient in mm, mean (SD): ZES: 31.28 (20.80); SES: 31.20 (20.75)

Frequency/Duration: Number of stents per patient, mean (SD): ZES: 1.63 (0.99); SES: 1.59 (0.96);
number of stents per lesion, mean (SD): ZES: 1.16 (0.49); SES: 1.13 (0.46)

Response: MACE, MI (any, large MI) ST (any, definite, possible, probable), TIMI (major, major + minor), TLR, VR (TVR, non-target VR).

Note: MI and large MI based on the extended historical definition. Results for stent thrombosis are based off the Academic Research Consortium definition.

Patient characteristics (gender, mean age):

Number per Group: ZES: 4,357 patients with 6,151 lesions; SES: 4,352 patients with 6,139 lesions

Observed adverse effects:

MACE: ZES: 602 (14.0%), SES: 588 (13.8%), HR: 1.03, 95% CI: 0.92 to 1.16, p=0.563, **no difference**;

MI: ZES: 196 (4.6%), SES: 246 (5.8%), HR: 0.79, 95% CI: 0.66 to 0.96, p=0.015, **favors ZES**;

Large MI: ZES: 74 (1.7%), SES: 111 (2.7%), HR: 0.66, 95% CI: 0.49 to 0.89, p=0.006, **favors ZES**;

ST (any): ZES: 144 (3.4%), SES: 192 (4.6%), HR: 0.75, 95% CI: 0.60 to 0.92, p=0.007, **favors ZES**;

Definite ST: ZES: 35 (0.8%), SES: 74 (1.8%), HR: 0.47, 95% CI: 0.31 to 0.70, p<0.001, **favors ZES**;

Possible ST: ZES: 79 (1.9%), SES: 90 (2.2%), HR: 0.87, 95% CI: 0.65 to 1.18, p=0.376, **no difference**;

Probable ST: ZES: 32 (0.8%), SES: 34 (0.8%), HR: 0.94, 95% CI: 0.58 to 1.52, p=0.793, **no difference**;

TIMI: ZES: 232 (5.5%), SES: 220 (5.2%), HR: 1.05, 95% CI: 0.88 to 1.27, p=0.577, **no difference**;

Major TIMI: ZES: 92 (2.2%), SES: 85 (2.0%), HR: 1.05, 95% CI: 0.88 to 1.27, p=0.577, **no difference**;

Major + Minor TIMI: ZES: 129 (3.1%), SES: 127 (3.0%), HR: 1.01, 95% CI: 0.79 to 1.29, p=0.919, **no difference**;

TLR: ZES: 252 (5.9%), SES: 189 (4.5%), HR: 1.35, 95% CI: 1.12 to 1.63, p=0.002, **favors SES**;

TVR: ZES: 382 (9.0%), SES: 361 (8.6%), HR: 1.07, 95% CI: 0.93 to 1.23, p=0.368, **no difference**;

Non-target VR: ZES: 392 (9.3%), SES: 404 (9.6%), HR: 0.97, 95% CI: 0.84 to 1.11, p=0.623, **no difference**

Timing of adverse effects: Authors report 1, 2, 3, and 4 year results for definite or probably ST.

Definite or probable ST, n/N (%):

1-year: ZES: 48/4325 (1.1%), SES: 31/4305 (0.7%), RR: 1.54, 95% CI: 0.98 to 2.42, p=0.070,
no difference;

2-year: ZES: 53/4305 (1.2%), SES: 51/4286 (1.2%), RR: 1.03, 95% CI: 0.71 to 1.52, p=0.921,
no difference;

3-year: ZES: 60/4271 (1.4%), SES: 75/4261 (1.8%), RR: 0.80, 95% CI: 0.57 to 1.12, p=0.194,
no difference;

4-year: ZES: 67/4217 (1.6%), SES: 106/4215 (2.5%), RR: 0.63, 95% CI: 0.47 to 0.86, p=0.03,
favours ZES

Factors that predict response: Definite or probable ST was impacted by the following pre-defined subgroups: age (≥ 75 years or age <75 years) (p=0.046), number of vessels with stents (single vessel or multivessel) (p=0.034), and lesion length (> 18 mm or ≤ 18 mm) (p=0.027).

13.6 Source Citation: Zhang et al. 2014³⁸

Study Design: Systematic Review

Device or Material: SES: Cypher (SS-based) vs. PES: Taxus (SS-based)

Contact Duration: 6 to 60 months

Dose: NR

Frequency/Duration: NR

Response: LLL (In-Segment), LLL (In-Stent), MACE, MI, Restenosis (In-Segment), Restenosis (In-Stent), ST (Any, definite, definite + probable), TLR, TVR

Patient characteristics (gender, mean age): Percent male range: 53% to 91%; Mean age range: 53 to 69 years

Number per Group: This SR included 33 RCTs (SES: 7,590 patients, PES: 7,520 patients), 27 adjusted observational studies (SES: 39,904 patients, PES: 31,694 patients), and 41 non-adjusted observational studies (SES: 44,734 patients, PES: 33,240 studies).

Observed adverse effects:

LLL (In-Segment): RCTs (n=18 studies): WMD -0.19, 95% CI: -0.24 to -0.14, **favours SES**

LLL (In-Stent): RCTs (n=14 studies): WMD -0.23, 95% CI: -0.28 to -0.17, **favours SES**

MACE: RCTs (n=26 studies): RR 0.79, 95% CI: 0.72 to 0.87, **favours SES**; Adj-OS (n=18 studies): RR 0.86, 95% CI: 0.78 to 0.95, **favours SES**; Non-adj-OS (n=32 studies): RR 0.91, 95% CI: 0.84 to 0.98, **favours SES**

MI: RCTs (n=29 studies): RR 0.85, 95% CI: 0.73 to 0.99, **favours SES**; Adj-OS (n=9 studies): RR 0.85, 95% CI: 0.74 to 0.98, **favours SES**; Non-adj-OS (n=30 studies): RR 0.80, 95% CI: 0.69 to 0.93, **favours SES**

Restenosis (In-Segment): RCTs (n=25 studies): RR 0.50, 95% CI: 0.38 to 0.65, **favours SES**; Adj-OS (n=4 studies): RR 0.36, 95% CI: 0.16 to 0.82, **favours SES**; Non-adj-OS (n=12 studies): RR 0.49, 95% CI: 0.33 to 0.74, **favours SES**

Restenosis (In-Stent): RCTs (n=14 studies): RR 0.42, 95% CI: 0.28 to 0.62, **favours SES**

ST (Any): RCTs (n=12 studies): RR 0.96, 95% CI: 0.74 to 1.24, **no difference**; Adj-OS (n=4 studies): RR 0.62, 95% CI: 0.45 to 0.86, **favours SES**; Non-adj-OS (n=22 studies): RR 0.77, 95% CI: 0.65 to 0.92, **favours SES**

Definite ST: RCTs (n=15 studies): RR 0.89, 95% CI: 0.62 to 1.26, **no difference**; Adj-OS (n=5 studies): RR 0.59, 95% CI: 0.45 to 0.77, **favours SES**; Non-adj-OS (n=15 studies): RR 0.74, 95% CI: 0.61 to 0.89, **favours SES**

Definite + Probable ST: RCTs (n=12 studies): RR 0.78, 95% CI: 0.57 to 1.07, **no difference**; Adj-OS (n=6 studies): RR 0.98, 95% CI: 0.69 to 1.37, **no difference**; Non-adj-OS (n=11 studies): RR 0.74, 95% CI: 0.65 to 0.86, **favours SES**

TLR: RCTs (n=26 studies): RR 0.61, 95% CI: 0.49 to 0.76, **favours SES**; Adj-OS (n=12 studies): RR 0.87, 95% CI: 0.76 to 1.01, **no difference**; Non-adj-OS (n=26 studies): RR 0.80, 95% CI: 0.69 to 0.93, **favours SES**

TVR: RCTs (n=19 studies): RR 0.61, 95% CI: 0.49 to 0.76, **favours SES**; Adj-OS (n=14 studies): RR 0.87, 95% CI: 0.76 to 1.01, **no difference**; Non-adj-OS (n=26 studies): RR 0.80, 95% CI: 0.69 to 0.93, **favours SES**

Timing of adverse effects: Results for restenosis and LLL are reported for up to 60-month follow-up. The remaining AEs are divided into 2 timing categories: within 1 year and over 1 year.

Within 1-year:

MACE: RCTs (n=20 studies): RR 0.74, 95% CI: 0.66 to 0.83, **favours SES**; Adj-OS (n=12 studies): RR 0.85, 95% CI: 0.75 to 0.96, **favours SES**; Non-adj-OS (n=24 studies): RR 0.88, 95% CI: 0.80 to 0.96, **favours SES**

MI: RCTs (n=24 studies): RR 0.86, 95% CI: 0.71 to 1.03, **no difference**; Adj-OS (n=5 studies): RR 0.81, 95% CI: 0.66 to 1.00, **trends favoring SES**; Non-adj-OS (n=23 studies): RR 0.74, 95% CI: 0.61 to 0.90, **favours SES**

ST (Any): RCTs (n=12 studies): RR 0.71, 95% CI: 0.45 to 1.11; Adj-OS (n=4 studies): RR 0.62, 95% CI: 0.45 to 0.86, **favours SES**; Non-adj-OS (n=18 studies): RR 0.83, 95% CI: 0.67 to 1.03, **no difference**

Definite ST: RCTs (n=11 studies): RR 0.93, 95% CI: 0.55 to 1.58; Adj-OS (n=5 studies): RR 0.76, 95% CI: 0.47 to 1.24, **no difference**; Non-adj-OS (n=7 studies): RR 0.76, 95% CI: 0.50 to 1.17, **no difference**

Definite + Probable ST: RCTs (n=8 studies): RR 0.69, 95% CI: 0.43 to 1.10, **no difference**; Adj-OS (n=6 studies): RR 0.98, 95% CI: 0.69 to 1.37, **no difference**; Non-adj-OS (n=10 studies): RR 0.67, 95% CI: 0.57 to 0.79, **favours SES**

TLR: RCTs (n=21 studies): RR 0.55, 95% CI: 0.42 to 0.73, **favours SES**; Adj-OS (n=5 studies): RR 0.81, 95% CI: 0.59 to 1.10, **no difference**; Non-adj-OS (n=18 studies): RR 0.78, 95% CI: 0.63 to 0.96, **favours SES**

TVR: RCTs (n=15 studies): RR 0.62, 95% CI: 0.47 to 0.82, **favours SES**; Adj-OS (n=8 studies): RR 0.88, 95% CI: 0.68 to 1.15, **no difference**; Non-adj-OS (n=17 studies): RR 1.00, 95% CI: 0.87 to 1.16, **favours SES**

Over 1 year:

MACE: RCTs (n=13 studies): RR 0.84, 95% CI: 0.74 to 0.95, **favours SES**; Adj-OS (n=10 studies): RR 0.91, 95% CI: 0.82 to 1.02, **no difference**; Non-adj-OS (n=15 studies): RR 0.91, 95% CI: 0.85 to 0.97, **favours SES**

MI: RCTs (n=13 studies): RR 0.82, 95% CI: 0.65 to 1.04, **no difference**; Adj-OS (n=6 studies): RR 0.85, 95% CI: 0.72 to 1.01, **no difference**; Non-adj-OS (n=12 studies): RR 0.86, 95% CI: 0.76 to 0.97, **favours SES**

ST (Any): RCTs (n=7 studies): RR 1.02, 95% CI: 0.78 to 1.33, **no difference**; Non-adj-OS (n=5 studies): RR 0.64, 95% CI: 0.48 to 0.87, **favours SES**

Definite ST: RCTs (n=8 studies): RR 0.93, 95% CI: 0.62 to 1.40, **no difference**; Adj-OS (n=5 studies): RR 0.52, 95% CI: 0.39 to 0.68, **favours SES**; Non-adj-OS (n=14 studies): RR 0.75, 95% CI: 0.62 to 0.90, **favours SES**

Definite + Probable ST: RCTs (n=8 studies): RR 0.91, 95% CI: 0.64 to 1.29, **no difference**; Non-adj-OS (n=5 studies): RR 0.74, 95% CI: 0.64 to 0.87, **favours SES**

TLR: Adj-OS (n=8 studies): RR 0.87, 95% CI: 0.74 to 1.04, **no difference**; Non-adj-OS (n=10 studies): RR 0.83, 95% CI: 0.70 to 0.98, **favors SES**

TVR: Adj-OS (n=8 studies): RR 0.91, 95% CI: 0.75 to 1.11, **no difference**; Non-adj-OS (n=12 studies): RR 0.92, 95% CI: 0.78 to 1.08, **no difference**

Factors that predict response: Meta-analyses were also performed in people with co-occurring diabetes, acute MI, and long coronary lesions. Results were mainly similar in directionality and impact to the total population.

13.7 Source Citation: Hsieh et al. 2013⁴⁶

Study Design: Non-randomized comparative study

Device or Material: Cypher (SS) vs. Taxus (SS) vs. BMS (mixed devices including Palmaz-Schatz [(Johnson & Johnson Inc.), Multi-Link (Guaidant Inc., Santa Clara, California, USA), Driver (Medtronic Inc., Minneapolis, Minnesota, USA), and Express (Boston Scientific Inc.)]

Contact Duration: Follow-up in months (SD): BMS: 63 (55), Cypher: 35 (24), Taxus: 35 (23)

Dose: Maximum balloon diameter in mm, mean (SD): BMS: 3.61 (0.59), Cypher: 3.67 (0.44), Taxus: 3.59 (0.43)

Frequency/Duration: Number of stents: BMS: 247, Cypher: 77, Taxus: 104

Response: CABG, Cardiac event-free survival, New lesion stenting, Recurrent angina, Reinfarction (STEMI or NSTEMI), Restenotic rate, ST (late, very late), TLR

Patient characteristics (gender, mean age): Age in years, mean (SD): BMS: 63 (10), Cypher: 61 (12), Taxus: 63 (11); male, n (%): BMS: 194 (80%), Cypher: 65 (84%), Taxus: 86 (86%)

Number per Group: BMS: 243 patients with 247 lesions, Cypher: 77 patients with 77 lesions, Taxus: 100 patients with 104 lesions

Observed adverse effects:

CABG, n (%): BMS: 13 (5%), Cypher: 2 (3%), Taxus: 4 (4%), p=0.653, **no difference**

Cardiac event-free survival, n (%): BMS: 146 (61%), Cypher: 66 (86%), Taxus: 78 (79%), p<0.0001, **differences between groups favoring Cypher and Taxus**

New lesion stenting, n (%): BMS: 18 (8%), Cypher: 3 (4%), Taxus: 7 (7%), p=0.457, **no difference**

Recurrent angina, n (%): BMS: 50 (21%), Cypher: 7 (9%), Taxus: 15 (15%), p=0.510, **no difference**

Reinfarction (STEMI or NSTEMI), n (%): BMS: 14 (6%), Cypher: 2 (3%), Taxus: 5 (5%), p=0.643, **no difference**

Restenotic rate, n (%): BMS: 58 (33%), Cypher: 3 (6%), Taxus: 6 (8%), p<0.001, **differences between groups favoring Cypher and Taxus**

ST (late), n (%): BMS: 0 (0%), Cypher: 0 (0%), Taxus: 1 (1%), p=0.201, **no difference**

ST (very late), n (%): BMS: 0 (0%), Cypher: 0 (0%), Taxus: 1 (1%), p=0.201, **no difference**

TLR, n (%): BMS: 41 (17%), Cypher: 3 (4%), Taxus: 6 (6%), p=0.002, **differences between groups favoring Cypher and Taxus**

Timing of adverse effects: All events, except for restenotic rate, occurred within the follow-up described in contact duration. Restenotic rate was quantified by angiographic measurement within 6-to-9-month follow-up.

Factors that predict response: NR

13.8 Source Citation: Alazzoni et al. 2012³⁹

Study Design: Systematic Review of 4 RCTs

Device or Material: EES: Xience V (CoCr) vs PES: Taxus Liberté, Taxus Express, or Taxus Express2 (SS)

Contact Duration: Between 24 and 48 months

Dose: NR

Frequency/Duration: NR

Response: MI, ST (definite, definite and probable, early, late, very late), TLR, TVR

Patient characteristics (gender, mean age): Gender NR; Mean age range: EES: 62.0 to 63.3, PES: 62.0 to 63.6

Number per Group: EES: 4,247; PES: 2,541

Observed adverse effects:

MI: EES: 126/4179, PES: 140/2504, OR: 0.56, 95% CI 0.43 to 0.72, $p < 0.0001$, **favours EES**

ST (definite): EES: 21/4179, PES: 40/2499, OR: 0.33, 95% CI 0.19 to 0.57, $p = 0.0001$, **favours EES**

ST (definite and probable): EES: 28/4169, PES: 57/2489, OR: 0.32, 95% CI 0.2 to 0.51, $p < 0.0001$, **favours EES**

TLR: EES: 4.2%, PES: 6.8%, OR: 0.57, 95% CI: 0.46 to 0.71, $p < 0.0001$, **favours EES**

TVR: EES: 294/4194, PES: 243/2517, OR: 0.64, 95% CI: 0.54 to 0.77, $p < 0.0001$, **favours EES**

Timing of adverse effects: All adverse events, except ST, reported clinical outcomes for 24 to 48 month follow-ups. Authors provided outcomes of ST (definite and probable) at early (0-30 days), late (31-365 days), and very late (>365 days), listed below:

ST (Early): EES: 8/4238, PES: 23/2535, OR: 0.24, 95% CI 0.11 to 0.54, $p = 0.0005$, **favours EES**

ST (Late): EES: 7/4157, PES: 15/2476, OR: 0.32, 95% CI 0.13 to 0.78, $p = 0.01$, **favours EES**

ST (Very Late): EES: 10/4175, PES: 19/2498, OR: 0.34, 95% CI 0.15 to 0.77, $p = 0.009$, **favours EES**

Factors that predict response: NR

13.9 Source Citation: Sethi et al 2012⁴⁰

Study Design: Systematic review of 6 RCTs

Device or Material: ZES: Endeavor (CoCr); SES: Cypher and Cypher Select/Plus (SS).

Note: One study (Zomaxx I) compared Zomaxx to Taxus Express 2. For the purposes of this analysis, we exclude any meta-analyses involving this comparison since it is SS vs. SS.

Contact Duration: Between 12 and 36 months

Dose: NR

Frequency/Duration: NR

Response: In-Segment LLL, In-Segment Restenosis, In-Stent Restenosis, ST, TLR, TVR,

Patient characteristics (gender, mean age): Gender NR; Mean age range: 57 to 67 years

Number per Group: ZES: 3588; SES: 2606, PES: 1769

Observed adverse effects:

In-Segment LLL: Mean difference 0.39, 95% CI 0.34 to 0.44, $p < 0.00001$, **favours SES**

In-Segment Restenosis: ZES: 215/1550, SES: 68/1357, OR 3.46, 95% CI 1.59 to 7.50, $p < 0.002$, **favours SES**

In-Stent Restenosis: ZES: 155/2354, SES: 24/2177, OR 6.13, 95% CI 3.96 to 9.50, $p < 0.00001$, **favours SES**

ST: ZES: 29/2815, SES: 21/2606, OR 1.12, 95% CI 0.41 to 3.08, $p = 0.82$, **no difference**

TLR: ZES: 194/2781, SES: 81/2580, OR 2.46, 95% CI 1.36 to 4.46, $p = 0.003$, **favours SES**

TVR: ZES: 196/2368, SES: 69/2161, OR 2.36, 95% CI 1.78 to 3.14, $p = 0.00001$, **favours SES**

Timing of adverse effects: Between 12 and 36 months

Factors that predict response: NR

13.10 Source Citation: Moreno et al. 2011⁴¹

Study Design: Systematic Review of 11 RCTs. Note: 2 RCTs did not have data at the time of this analysis, so 9 RCTs were included in the meta-analysis.

Device or Material: Taxus Express, Cypher, Taxus Liberté (all SS) vs. Xience V, Zomaxx, Endeavor, Costar, NEVO (all CoCr)

Contact Duration: 30 days

Dose: Strut thickness: SS (97 µm to 140 µm), CoCr (81 µm to 99 µm); stent length range: 20.5 mm to 49.6 mm (2 studies N/A)

Frequency/Duration: NR

Response: MI (any, Q-Wave MI, Non-Q-Wave MI), ST

Patient characteristics (gender, mean age): Percent female range: 22.3% to 34.0%; mean age range: 61.5 to 63.7 years

Number per Group: 11,313 total patients

Observed adverse effects:

MI (any): CoCr: 127/5478, SS: 212/5492, OR 0.72, 95% CI 0.58 to 0.91, p=0.006, **favors CoCr**

Non-Q-Wave MI: CoCr: 79/3629, SS: 168/4289, OR 0.67, 95% CI 0.51 to 0.88, p=0.005, **favors CoCr**

Q-Wave MI: CoCr: 9/3629, SS: 19/4289, OR 0.60, 95% CI 0.28 to 1.30, p=0.19, **no difference**

ST: CoCr: 28/5480, SS: 25/5496, OR 1.09, 95% CI 0.63 to 1.89, p=0.76, **no difference**

Timing of adverse effects: Up to 30 days

Factors that predict response: NR

Systemic Response/Toxicity

13.11 Source Citation: Vlieger et al. 2021⁴⁴

Study Design: Non-randomized comparative study

Device or Material: Sirolimus-eluting stent (SES): Ulitmaster (CoCr), biolimus-eluting stent (BES): Nobori (SS)

Contact Duration: 1 year

Dose: Strut thickness: SES: 80µm, BES: 120µm; Drug load: SES: 3.9 µg/mm; BES: 15.6µg/mm

Frequency/Duration: Study stents implanted, mean (SD): SES: 1.49 (SD 0.9); BES: 1.47 (0.9)

Response: Mortality

Patient characteristics (gender, mean age): Male gender, %: SES: 76.7%; BES: 78.0%; Mean age in years (SD): SES: 64.7 (11.0); BES: 64.4 (11.1)

Number per Group: SES: 8,137; BES: 2,738

Observed adverse effects:

All mortality: SES: 2.31% (205/8,879); BES: 1.92% (59/3,067), p=0.211, **no difference**

Cardiac Death: SES: 1.45% (129/8,879); BES: 1.30% (40/3,067), p=0.5478, **no difference**

Non-Cardiac Death: SES: 0.86% (76/8,879); BES: 0.62% (19/3,067), p=0.2037, **no difference**

Timing of adverse effects: Up to 1 year

Factors that predict response: Between the SES and BES groups, there was no difference in baseline clinical characteristics except for a higher prevalence of family history of coronary artery disease in the SES group (36.1% vs 30.4%, p< 0.001).

13.12 Source Citation: Allali et al. 2018⁴⁵

Study Design: Non-randomized comparative study

Device Material: Early generation drug eluting stents (EG-DES): SES Cypher (Cordis, Miami Lakes, FL, USA) and PES Taxus Liberté (Boston Scientific, Boston, MA, USA) (Both SS); New generation drug eluting stents (NG-DES): CoCR-based EES Xience (Abbott Vascular, Santa Clara, CA, USA), platinum Cr based EES Promus (Boston Scientific, Natick, MA, USA), and CoCR-based SES Orsiro (Biotronik, Bülach, Switzerland)

Contact Duration: Follow-up months, median (IQR): EG-DES: 32 (23-60); NG-DES: 17 (12-31)

Dose: Stent diameter, mean (SD): EG-DES: 2.93 (0.37); NG-DES: 2.93 (0.48), p=0.84

Frequency/ Duration: Multiple stenting: EG-DES: 140 (48.6%); NG-DES: 142 (63.1%), p<0.001; Number of implanted stents: EG-DES: 1.7 (0.8); NG-DES: 2 (0.9), p<0.001

Response: Mortality (all-cause, cardiovascular, non-cardiovascular)

Patient characteristics (gender, mean age): Age in years, mean (SD): EG-DES: 71 (8); NG-DES: 72 (9); male sex, n (%): EG-DES: 353 (73.4%); NG-DES: 195 (72.8%)

Number per Group: EG-DES: 268; NG-DES: 213

Observed adverse effects:

Mortality, all-cause: EG-DES: 13.5%, NG-DES: 8.2%, log-rank p=0.13, **no difference**

Mortality, cardiovascular: EG-DES: 5.8%, NG-DES: 6.8%, log-rank $p=0.64$, **no difference**

Mortality, non-cardiovascular: EG-DES: 8.2%, NG-DES: 1.5%, log-rank $p=0.05$, **may favor NG-DES**

Timing of adverse effects: Up to 5 years

Factors that predict response: By multivariable analysis, the use of new-generation DES was independently associated with a lower incidence of all-cause mortality (HR 0.49; 95% CI 0.26–0.92; $p = 0.03$). Cardiovascular mortality was not statistically different between the two groups (HR 0.82; 95% CI 0.37–1.85).

13.13 Source Citation: Yan et al. 2016³⁷

Study Design: Systematic review

Device or Material: BP-stainless DESs vs. other alloy DESs; BP-alloy DESs vs. other stainless DESs

Contact Duration: Median follow-up in months (Range): 19.6 (6 to 50)

Dose: NR

Frequency/Duration: NR

Response: Mortality (all-cause, cardiac mortality)

Patient characteristics (gender, mean age): Mean age range: 56.7 to 67.5; Percent male range: 47.4 to 86.7. Note: These ranges are for the entire review population.

Number per Group: Total meta-analyzed population of 34,850 patients (49 RCTs). Note: Only 10 trials are reported that compare BP-stainless DESs to other alloy DESs (patient count NR), and 3 trials compare BP-alloy DESs vs other stainless DESs (patient count NR).

Observed adverse effects: Note: all observed adverse effects are using the maximum length of follow-up)

All-Cause Mortality: BP-stainless DESs vs. other alloy DESs: OR: 0.99, 95% CI: 0.84 to 1.16, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.74, 95% CI: 0.36 to 1.52, **no difference**

Cardiac Mortality: BP-stainless DESs vs. other alloy DESs: OR: 1.08, 95% CI: 0.87 to 1.33, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.35, 95% CI: 0.04 to 2.93, **no difference**

Timing of adverse effects:

All-Cause Mortality:

Within 30 days (short-term): BP-stainless DESs vs. other alloy DESs: OR: 1.01, 95% CI: 0.47 to 2.18, **no difference**;

> 30 days to 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 0.94, 95% CI: 0.74 to 1.18, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.52, 95% CI: 0.21 to 1.31, **no difference**;

> 1 year (long-term): BP-stainless DESs vs. other alloy DESs: OR: 1.05, 95% CI: 0.85 to 1.29, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.76, 95% CI: 0.31 to 1.86, **no difference**

Cardiac mortality:

Within 30 days (short-term): BP-stainless DESs vs. other alloy DESs: OR: 1.11, 95% CI: 0.47 to 2.62, **no difference**;

> 30 days to 1 year (mid-term): BP-stainless DESs vs. other alloy DESs: OR: 1.11, 95% CI: 0.84 to 1.46, **no difference**;

> 1 year (long-term): BP-stainless DESs vs. other alloy DESs: OR: 1.03, 95% CI: 0.76 to 1.39, **no difference**; BP-alloy DESs vs. other stainless DESs: OR: 0.35, 95% CI: 0.04 to 2.93, **no difference**

Factors that predict response: The results did not significantly change after the sequential removal of individual studies or after the removal of the article published in Chinese via sensitivity analyses.

13.14 Source Citation: Gao et al. 2015⁴²

Study Design: RCT

Device or Material: PES: Taxus Liberté stent (SS); PtCr-EES: Promus Element stent (Boston Scientific, Marlborough, MA) (PtCr)

Contact Duration: Up to 1 year

Dose: Total nominal stent length implanted in mm: PES: 25.57 (9.62); PtCr-EES: 24.84 (8.40)

Frequency/Duration: Multiple stents implanted, n (%): PES: 4 (3.1%); PtCr-EES: 12 (3.2%)

Stents per patient, mean (SD): PES: 1.03 (0.18); PtCr-EES: 1.03 (0.20)

Response: Mortality (cardiac, non-cardiac)

Patient characteristics (gender, mean age): Male gender, n (%): PES: 88 (69.3%), PtCr-EES: 268 (71.8%); Mean age in years (SD): PES: 57.55 (9.50), PtCr-EES: 57.12 (9.90)

Number per Group: PES: 127; PtCr-EES: 373

Observed adverse effects: All outcomes examined at 1 year.

Mortality, n (%): PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

Mortality (cardiac), n (%): PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

Mortality (non-cardiac), n (%): PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

Timing of adverse effects:

Mortality, n (%): 9-month: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**; 1-year: PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

Mortality (cardiac):

9-month: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

1-year: PES: 0 (0%), PtCr-EES: 0 (0%), **no difference**

Mortality (non-cardiac):

9-month: PES: 0 (0%), PtCr-EES: 0 (0%), p=0.26, **no difference**

1-year: PES: 1 (0.8%), PtCr-EES: 0 (0%), p=0.26, **no difference**

Factors that predict response: NR

13.15 Source Citation: Wijns et al. 2014⁴³

Study Design: RCT

Device or Material: ZES: Endeavor (cobalt alloy) vs. SES: Cypher (SS)

Contact Duration: 4 years

Dose: Total stent length per patient in mm, mean (SD): ZES: 31.28 (20.80); SES: 31.20 (20.75)

Frequency/Duration: Number of stents per patient, mean (SD): ZES: 1.63 (0.99); SES: 1.59 (0.96); number of stents per lesion, mean (SD): ZES: 1.16 (0.49); SES: 1.13 (0.46)

Response: hemorrhagic stroke, MACCE, mortality (all-cause, cardiac)

Patient characteristics (gender, mean age):

Number per Group: ZES: 4,357 patients with 6,151 lesions; SES: 4,352 patients with 6,139 lesions

Observed adverse effects:

Hemorrhagic stroke: ZES: 95 (2.3%), SES: 95 (2.3%), HR: 1.00, 95% CI: 0.77 to 1.32, p=0.977, **no difference**;

MACCE: ZES: 659 (15.3%), SES: 645 (15.1%), HR: 1.03, 95% CI: 0.93 to 1.15, p=0.564, **no difference**;

Mortality: ZES: 235 (5.5%), SES: 256 (6.0%), HR: 0.91, 95% CI: 0.76 to 1.09, p=0.311, **no difference**;

Cardiac mortality: ZES: 124 (2.9%), SES: 143 (3.4%), HR: 0.86, 95% CI: 0.68 to 1.10, p=0.227, **no difference**

Timing of adverse effects: Authors report 1, 2, 3, and 4 year results for combined death and large MI results.

Death and large MI, n/N (%):

1-year: ZES: 91/4325 (2.1%), SES: 96/4305 (2.2%), RR: 0.94, 95% CI: 0.71 to 1.25, p=0.712, **no difference**;

2-year: ZES: 159/4305 (3.7%), SES: 177/4286 (4.1%), RR: 0.89, 95% CI: 0.72 to 1.10, p=0.317, **no difference**;

3-year: ZES: 226/4271 (5.3%), SES: 257/4261 (6.0%), RR: 0.88, 95% CI: 0.74 to 1.04, p=0.146, **no difference**;

4-year: ZES: 288/4217 (6.8%), SES: 342/4215 (8.1%), RR: 0.84, 95% CI: 0.72 to 0.98, p=0.025, **favours ZES**

Factors that predict response: NR

13.16 Source Citation: Zhang et al. 2014³⁸

Study Design: Systematic Review

Device or Material: SES: Cypher (SS-based) vs. PES: Taxus (SS-based)

Contact Duration: 6 to 60 months

Dose: NR

Frequency/Duration: NR

Response: Mortality (all-cause, cardiac-related mortality)

Patient characteristics (gender, mean age): Percent male range: 53% to 91%; Mean age range: 53 to 69 years

Number per Group: This SR included 33 RCTs (SES: 7,590 patients, PES: 7,520 patients), 27 adjusted observational studies (SES: 39,904 patients, PES: 31,694 patients), and 41 non-adjusted observational studies (SES: 44,734 patients, PES: 33,240 studies).

Observed adverse effects:

All-Cause Mortality: RCTs (n=27 studies): RR 1.02, 95% CI: 0.85 to 1.22, **no difference**; Adj-OS (n=13 studies), **no difference**: RR 0.91, 95% CI: 0.83 to 1.00, **may favor SES**; Non-adj-OS (n=32 studies): RR 0.95, 95% CI: 0.89 to 1.02, **no difference**

Cardiac-related mortality: RCTs (n=16 studies): RR 1.00, 95% CI: 0.75 to 1.32, **no difference**; Adj-OS (n=4 studies): RR 0.93, 95% CI: 0.61 to 1.44, **no difference**; Non-adj-OS (n=16 studies): RR 1.01, 95% CI: 0.90 to 1.14, **no difference**

Timing of adverse effects: AEs are divided into 2 timing categories: within 1 year and over 1 year.

Within 1-year:

All-Cause Mortality: RCTs (n=21 studies): RR 1.01, 95% CI: 0.78 to 1.32, **no difference**; Adj-OS (n=7 studies): RR 0.86, 95% CI: 0.73 to 1.00, **may favor SES**; Non-adj-OS (n=22 studies): RR 0.87, 95% CI: 0.80 to 0.95, **favors SES**

Cardiac-related mortality: RCTs (n=16 studies): RR 1.00, 95% CI: 0.75 to 1.32, **no difference**; Adj-OS (n=4 studies): RR 0.93, 95% CI: 0.61 to 1.44, **no difference**; Non-adj-OS (n=16 studies): RR 1.01, 95% CI: 0.90 to 1.14, **no difference**

Over 1 year:

All-Cause Mortality: RCTs (n=12 studies): RR 0.99, 95% CI: 0.81 to 1.22, **no difference**; Adj-OS (n=10 studies): RR 0.94, 95% CI: 0.86 to 1.02, **no difference**; Non-adj-OS (n=16 studies): RR 0.91, 95% CI: 0.84 to 0.98, **favors SES**

Cardiac-related mortality: RCTs (n=12 studies): RR 0.84, 95% CI: 0.56 to 1.27, **no difference**; Adj-OS (n=3 studies): RR 0.86, 95% CI: 0.66 to 1.12, **no difference**; Non-adj-OS (n=12 studies): RR 0.79, 95% CI: 0.68 to 0.92, **favors SES**

Factors that predict response: Meta-analyses were also performed in people with co-occurring diabetes, acute MI, and long coronary lesions. Results were mainly similar in directionality and impact to the total population.

13.17 Source Citation: Hsieh et al. 2013⁴⁶

Study Design: Non-randomized comparative study

Device or Material: Cypher (SS) vs. Taxus (SS) vs. BMS (mixed devices including Palmaz-Schatz [(Johnson & Johnson Inc.), Multi-Link (Guidant Inc., Santa Clara, California, USA), Driver (Medtronic Inc., Minneapolis, Minnesota, USA), and Express (Boston Scientific Inc.)])

Contact Duration: Follow-up in months (SD): BMS: 63 (55), Cypher: 35 (24), Taxus: 35 (23)

Dose: Maximum balloon diameter in mm, mean (SD): BMS: 3.61 (0.59), Cypher: 3.67 (0.44), Taxus: 3.59 (0.43)

Frequency/Duration: Number of stents: BMS: 247, Cypher: 77, Taxus: 104

Response: Mortality (all-cause, cardiac, non-cardiac), stroke (non-fatal)

Patient characteristics (gender, mean age): Age in years, mean (SD): BMS: 63 (10), Cypher: 61 (12), Taxus: 63 (11); male, n (%): BMS: 194 (80%), Cypher: 65 (84%), Taxus: 86 (86%)

Number per Group: BMS: 243 patients with 247 lesions, Cypher: 77 patients with 77 lesions, Taxus: 100 patients with 104 lesions

Observed adverse effects:

Mortality (all-cause), n (%): BMS: 34 (14%), Cypher: 6 (8%), Taxus: 6 (6%), p=0.600, **no difference**

Cardiac Mortality, n (%): BMS: 22 (9%), Cypher: 5 (7%), Taxus: 4 (4%), p=0.249, **no difference**

Non-Cardiac Mortality, n (%): BMS: 12 (5%), Cypher: 1 (1%), Taxus: 2 (2%), p=0.273, **no difference**

Stroke (non-fatal), n (%): BMS: 11 (5%), Cypher: 0 (0%), Taxus: 1 (1%), p=0.057, **no difference**

Timing of adverse effects: All events occurred within the follow-up described in contact duration.

Factors that predict response: NR

13.18 Source Citation: Alazzoni et al. 2012³⁹

Study Design: Systematic Review of 4 RCTs

Device or Material: EES: Xience V (CoCr) vs PES: Taxus Liberté, Taxus Express, or Taxus Express2 (SS)

Contact Duration: Between 24 and 48 months

Dose: NR

Frequency/Duration: NR

Response: Mortality (all-cause, cardiac)

Patient characteristics (gender, mean age): Gender NR, Mean age range: EES: 62.0 to 63.3, PES: 62.0 to 63.6

Number per Group: EES: 4,247; PES: 2,541

Observed adverse effects:

Mortality (All-Cause): EES: 106/4194, PES: 80/2517, OR: 0.8, 95% CI 0.59 to 1.07, p=0.14, **no difference**

Cardiac Mortality: EES: 52/4186, PES: 40/2511, OR: 0.85, 95% CI 0.56 to 1.28, p=0.43, **no difference**

Timing of adverse effects: All adverse events reported clinical outcomes for 24 to 48 month follow-ups.

Factors that predict response: NR

13.19 Source Citation: Moreno et al. 2011⁴¹

Study Design: Systematic Review

Device or Material: SS (Taxus Express, Cypher, Taxus Liberté), CoCr (Xience V, Zomaxx, Endeavor, Costar, NEVO)

Contact Duration: 30 days

Dose: Strut thickness: SS (97 µm to 140 µm), CoCr (81 µm to 99 µm); stent length range: 20.5 mm to 49.6 mm (2 studies N/A)

Frequency/Duration: NR

Response: cardiac mortality

Patient characteristics (gender, mean age): Percent female range: 22.3% to 34.0% mean age range: 61.5 to 63.7 years

Number per Group: 11,313 total patients

Observed adverse effects:

Cardiac mortality: CoCr: 12/5161, SS: 9/5373, OR 1.62, 95% CI 0.66 to 3.55, p=0.33, **no difference**

Timing of adverse effects: Up to 30 days

Factors that predict response: NR

ACS: acute coronary syndrome; ARC: Academic Research Consortium; BES: biolimus-eluting stent; BMS: bare metal stent; BP: biodegrading polymer; CABG: coronary artery bypass graft; CI: confidence interval; CoCr: cobalt chromium; DES: drug-eluting stent; EES: everolimus-eluting stent; EG-DES: early generation drug eluting stent; HR: hazard ratio; IQR: interquartile range; LLL: late lumen loss; MACCE: major adverse cardiac and cerebrovascular events; MACE: major adverse cardiac events; MI: myocardial infarction; NG-DES: new generation drug eluting stent; NR: not reported; NSTEMI: non-ST-elevation myocardial infarction; OR: odds ratio; OS: observational study; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; POCE: patient-oriented composite endpoint; PtCr: platinum chromium; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SES: sirolimus-eluting stent; SS: stainless steel; ST: stent thrombosis; STEMI: ST-elevation myocardial infarction; Ta: tantalum; TIMI: thrombolysis in myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularization; TVF: target vessel failure; TVR: target vessel revascularization; VR: vessel revascularization; WMD: weighted mean difference; ZES: zotarolimus-eluting stent

Table 14: Cardio Peripheral - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

14.1 Source Citation: Giannopoulos et al. 2021⁴⁷

Study Design: Systematic Review

Device or Material: Viabahn (SS-based) heparin bonded ePTFE-covered stent for femoropopliteal lesions. Note: This qualitative review examined many different types of stents, however, the only outcomes for stents with SS are reported in the sub-heading labeled *Covered stent subgroup*.

Contact Duration: Up to 5 years

Dose: NR

Frequency/Duration: NR

Response: Bypass, distal embolization, dissection (periprocedural – within 30 days), primary patency rate (30-day, 1-year, 5-year), PTA (early), restenosis or occlusion (early), revascularization (early), secondary patency rate (1-year, 5-year), TLR rate (1-year)

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

Number per Group: 468 patients (10 single-arm studies, 3 comparative studies)

Observed adverse effects: Note: All reported AEs are ranges for Viabahn (SS-based) stents.

Bypass (3 studies): 0% (0% to 2%)

Dissection (periprocedural – within 30 days) (1 study): 3% (1% to 10%)

Distal embolization (2 studies): 11% (0% to 32%)

Primary patency rate (30-day) (5 studies): 99% (93% to 100%, $I^2=44.68\%$)

Primary patency rate (1-year) (9 studies): 69% (61% to 77%, $I^2=51.44\%$)

Primary patency rate (5-year) (2 studies): 39% (31% to 47%)

PTA (early) (2 studies): 2% (0% to 8%)

Restenosis or occlusion (early) (5 studies): 2% (0% to 7%, $I^2=44.68\%$)

Revascularization (early) (3 studies): 5% (0% to 22%)

Secondary patency (1-year) (2 studies): 92% (86% to 96%)

Secondary patency (5-year) (2 studies): 62% (55% to 70%)

TLR rate (1-year) (2 studies): 16% (10% to 23%)

Timing of adverse effects: Unless otherwise specified, adverse effects occurred for patients up to 5 years follow-up.

Factors that predict response: 2 studies reported that lesions treated with a heparin bonded ePTFE covered stent had statistically significant superior patency over BMS and POBA stents at 1-year of follow-up (OR: 2.74; 95%CI: 1.63–4.61; $p < 0.001$).

14.2 Source Citation: Mwipatyi et al. 2020⁴⁸

Study Design: Systematic review

Device or Material: SS: iCast, Advanta V12, Viabahn VBX, Lifestream, Jostent; CoCr: BeGraft for treating aortoiliac occlusive disease

Contact Duration: iCast/Advanta V12: 8.3 to 60.0 months, Viabahn VBX: 9 to 12 months, Lifestream: 9 months, BeGraft: 12 months, Jostent: 6 months

Dose: NR

Frequency/Duration: NR

Response: Freedom from TLR, primary patency

Patient characteristics (gender, mean age): Percent male range: 26.6% to 78.5%; mean age: NR

Number per Group: iCast/Advanta V12: 611 (3 clinical trials, 6 real world studies), Viabahn VBX: 164 (2 clinical trials), Lifestream: 155 (1 clinical trial), BeGraft: 70 (1 clinical trial), Jostent: 12 (1 clinical trial)

Observed adverse effects: All outcomes are noted along with their follow-up times below.

Timing of adverse effects:

Primary patency in months (range):

6 months: iCast/Advanta V12: 87.2% to 97.0%, Viabahn VBX: 100%, Lifestream: NR, BeGraft: NR, Jostent: 92%

9 months: iCast/Advanta V12: 96.4%, Viabahn VBX: 96.7%, Lifestream: 89.1%, BeGraft: NR, Jostent: NA

12 months: iCast/Advanta V12: 83.6% to 96.4%, Viabahn VBX: 96.6%, Lifestream: NA, BeGraft: 94.4%, Jostent: NA

18 months: iCast/Advanta V12: 77.0% to 87.3%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

24 months: iCast/Advanta V12: 68.0% to 92.0%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

36 months: iCast/Advanta V12: 72.0%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

48 months: iCast/Advanta V12: 63.4% to 79.9%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

60 months: iCast/Advanta V12: 74.7%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

Freedom from TLR in months (range):

6 months: iCast/Advanta V12: 92.4% to 99.3%, Viabahn VBX: 100%, Lifestream: 98.1%, BeGraft: NA, Jostent: NA

9 months: iCast/Advanta V12: 97.2%, Viabahn VBX: 97.4%, Lifestream: 96.1%, BeGraft: NA, Jostent: NA

12 months: iCast/Advanta V12: 88.2% to 94.3%, Viabahn VBX: 96.6%, Lifestream: NA, BeGraft: 96.7%, Jostent: NA

24 months: iCast/Advanta V12: 85.6% to 88.3%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

36 months: iCast/Advanta V12: 86.6%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

48 months: iCast/Advanta V12: 67.4%, Viabahn VBX: NA, Lifestream: NA, BeGraft: NA, Jostent: NA

Factors that predict response: NR

14.3 Source Citation: Gouëffic et al. 2017⁵⁰

Study Design: RCT

Device or Material: Surgery vs. SS stent for CFA stenosis

Contact Duration: Up to 24 months

Dose (SS Stents): Self-expandable stents: 48 (67.5%) with a mean diameter of 7 mm (SD 1) and mean length of 41 mm (SD 17); balloon-expandable stents: 23 (32.5%) with a mean diameter of 6 mm (SD 1) and mean length of 25 mm (SD 11)

Frequency/Duration: NR

Response: arteriovenous fistula, delayed wound healing, false aneurysm, hematoma, local infection, lymphorrhea, paresthesia, thrombosis, vascular perforation

Patient characteristics (gender, mean age): Male, n (%): Surgery: 51 (84%), Stent: 48 (86%); Mean age in years (SD): Surgery: 68 (8); Stent: 68 (9)

Number per Group: Surgery: 61, Stent: 56

Observed adverse effects

Arteriovenous fistula: Surgery: 0 (0%), Stent: 0 (0%), p=NR

Delayed wound healing: Surgery: 10 (16.4%), Stent: 0 (0%), p=NR

False aneurysm: Surgery: 0 (0%), Stent: 0 (0%), p=NR

Hematoma: Surgery: 3 (5%), Stent: 0 (0%), p=NR

Local infection: Surgery: 3 (5%), Stent: 1 (1.8%), p=NR

Lymphorrhea: Surgery: 2 (3.2%), Stent: 0 (0%), p=NR

Paresthesia: Surgery: 4 (6.5%), Stent: 0 (0%), p=NR

Thrombosis: Surgery: 0 (0%), Stent: 1 (1.8%), p=NR

Vascular perforation: Surgery: 0 (0%), Stent: 1 (1.8%), p=NR

Timing of adverse effects: Up to 24 months

Factors that predict response: NR

14.4 Source Citation: Carudu et al. 2016⁴⁹

Study Design: Systematic review

Device or Material: DES (all-SS based): Cypher, Taxus Liberté, Yukon, Resolute Cypher Promus vs. control (PTA, BMS, or DEB) for management of below-the-knee arterial critical ischemia. Note: one study compared Xience V (a CoCr-based stent) to BMS. Any meta-analyses including this trial (DESTINY trial) were excluded for the purposes of this report.

Contact Duration: 2 to 36 months

Dose: NR

Frequency/Duration: NR

Response: In-segment binary restenosis, primary patency, TLR

Patient characteristics (gender, mean age): Percent male range: 58% to 76%; mean age range: 69.4 to 73.6

Number per Group: Cypher vs. PTA: 200 patients, Taxus Liberté vs. PTA +/- bailout BMS: 137 patients, Cypher + GPIIb/IIIa vs. BMS+GPIIb/IIIa or PTA alone: 60 patients, Cypher vs. BMS: 50 patients, Yukon vs. BMS: 161 patients, Resolute Cypher Promus vs. DEB (paclitaxel) (1 bailout BMS): 50 patients

Observed adverse effects:

In-segment binary restenosis, n/N (3 studies): DES: 33/151, PTA: 58/139, OR 0.38, 95% CI: 0.23 to 0.63, $I^2=0\%$, $p=0.0002$, **favors DES**;

Primary patency, n/N (3 studies): DES: 96/148, PTA: 74/150, OR 0.48, 95% CI: 0.29 to 0.77, $I^2=0\%$, $p=0.003$, **favors DES**;

TLR, n/N (3 studies): DES: 13/156, PTA: 16/158, OR 0.86, 95% CI: 0.40 to 1.85, $I^2=27\%$, $p=0.701$, **no difference**;

Timing of adverse effects: 2 to 36 months

Factors that predict response: NR

Systemic Response/Toxicity

14.5 Source Citation: Giannopoulos et al. 2021⁴⁷

Study Design: Systematic Review

Device or Material: Viabahn heparin bonded ePTFE-covered stent for femoropopliteal lesions

Contact Duration: Up to 5 years

Dose: NR

Frequency/Duration: NR

Response: Amputation (within 30 days), perioperative mortality (perioperative, 1-year), technical success

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

Number per Group: 468 patients (10 single-arm studies, 3 comparative studies)

Observed adverse effects:

Amputation (within 30 days) (6 studies): 0% (0% to 1%, $I^2=0\%$)

Mortality (Perioperative) (6 studies): 0% (0% to 1%, $I^2=0\%$)

Mortality (1-year) (2 studies): 3% (1% to 7%)

Technical success (7 studies): 99% (90% to 100%, $I^2=79.30\%$)

Timing of adverse effects: All timing of adverse events are specified in the observed adverse effects header.

Factors that predict response: NR

14.6 Source Citation: Mwipatyi et al. 2020⁴⁸

Study Design: Systematic review

Device or Material: SS: iCast, Advanta V12, Viabahn VBX, Lifestream, Jostent; CoCr: BeGraft for treating aortoiliac occlusive disease

Contact Duration: iCast/Advanta V12: 8.3 to 60.0 months, Viabahn VBX: 9 to 12 months, Lifestream: 9 months, BeGraft: 12 months, Jostent: 6 months

Dose: NR

Frequency/Duration: NR

Response: Technical success

Patient characteristics (gender, mean age): Percent male range: 26.6% to 78.5%; mean age: NR

Number per Group: iCast/Advanta V12: 611 (3 clinical trials, 6 real world studies), Viabahn VBX: 164 (2 clinical trials), Lifestream: 155 (1 clinical trial), BeGraft: 70 (1 clinical trial), Jostent: 12 (1 clinical trial)

Observed adverse effects: Technical success range: iCast/Advanta V12: 95.0% to 100%, Viabahn VBX: 100%, Lifestream: 98.3%, BeGraft: 100%, Jostent: 100%.

Timing of adverse effects: Between 6 and 60 months

Factors that predict response: NR

14.7 Source Citation: Gouëffic et al. 2017⁵⁰

Study Design: RCT

Device or Material: Surgery vs. SS stent for CFA stenosis

Contact Duration: Up to 24 months

Dose (SS Stents): Self-expandable stents: 48 (67.5%) with a mean diameter of 7 mm (SD 1) and mean length of 41 mm (SD 17); balloon-expandable stents: 23 (32.5%) with a mean diameter of 6 mm (SD 1) and mean length of 25 mm (SD 11)

Frequency/Duration: NR

Response: Major amputation, Mortality, MI, Stroke

Patient characteristics (gender, mean age): Male, n (%): Surgery: 51 (84%), Stent: 48 (86%); Mean age in years (SD): Surgery: 68 (8); Stent: 68 (9)

Number per Group: Surgery: 61, Stent: 56

Observed adverse effects

Major amputation: Surgery: 0 (0%), Stent: 0 (0%), p=NR

MI: Surgery: 0 (0%), Stent: 0 (0%), p=NR

Mortality: Surgery: 0 (0%), Stent: 0 (0%), p=NR

Stroke: Surgery: 0 (0%), Stent: 1 (1.8%), p=NR

Timing of adverse effects: Up to 24 months

Factors that predict response: NR

14.8 Source Citation: Carudu et al. 2016⁴⁹

Study Design: Systematic review

Device or Material: DES (all-SS based): Cypher, Taxus Liberté, Yukon, Resolute Cypher Promus vs. control (PTA, BMS, or DEB) for management of below-the-knee arterial critical ischemia. Note: one study compared Xience V (a CoCr-based stent) to BMS. Any meta-analyses including this trial (DESTINY trial) were excluded for the purposes of this report.

Contact Duration: 2 to 36 months

Dose: NR

Frequency/Duration: NR

Response: Amputation, mortality

Patient characteristics (gender, mean age): Percent male range: 58% to 76%; mean age range: 69.4 to 73.6

Number per Group: Cypher vs. PTA: 200 patients, Taxus Liberté vs. PTA +/- bailout BMS: 137 patients, Cypher + GPIIb/IIIa vs. BMS+GPIIb/IIIa or PTA alone: 60 patients, Cypher vs. BMS: 50 patients, Yukon vs. BMS: 161 patients, Resolute Cypher Promus vs. DEB (paclitaxel) (1 bailout BMS): 50 patients

Observed adverse effects:

Amputation, n/N (3 studies): DES: 20/168, PTA: 31/170, OR 0.59, 95% CI: 0.32 to 1.09, $I^2=0\%$, $p=0.09$, **no difference**;

Mortality, n/N (3 studies): DES: 28/186, PTA: 36/184, OR 0.71, 95% CI: 0.41 to 1.24, $I^2=40\%$, $p=0.23$, **no difference**

Timing of adverse effects: 2 to 36 months

Factors that predict response: NR

AE: adverse event; BMS: bare metal stent; CFA: common femoral artery; CI: confidence interval; CLI: critical limb ischemia; DEB: drug eluting balloon; DES: drug eluting stent; ePTFE: expanded polytetrafluoroethylene; GPIIb/IIIa: glycoprotein IIb/IIIa inhibitor (abciximab); NA: not applicable; NR: not reported; OR: odds ratio; POBA: percutaneous old balloon angioplasty; PTA: percutaneous transluminal angioplasty; RCT: randomized controlled trial; SD: standard deviation; SS: stainless steel; TLR: target lesion revascularization.

Table 15: Orthopedic – fixation, spinal - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

15.1 Source Citation: Denduluri et al. 2021⁵²

Study Design: Non-randomized comparative study. Adults with spinal deformity who underwent at least 5-level thoracic and/or lumbar posterior fusion or 3-column osteotomy

Device or Material: SS and Ti rods

Contact Duration: Median follow-up was 37–42 months for all groups.

Dose: NA

Frequency/Duration: Single administration

Response: Implant-related complications included pseudarthrosis, proximal junctional kyphosis, hardware failure (rod fracture, screw pullout or haloing), symptomatic hardware, and infection.

Patient characteristics (gender, mean age): SS, n = 31, 28 female, 62.4 years mean age; Ti, n = 24, 11 female, 67.7 years mean age

Number per Group: 61 cases met inclusion criteria: 24 patients received Ti rods with Ti screws (Ti-Ti, 39%), 31 SS rods (SS-Ti, 51%).

Observed adverse effects: Implant-related complications did not differ between the Ti-Ti and SS-Ti groups ($p = 0.08$). Among the Ti-Ti group, there were 15 implant related complications (63%). In the SS-Ti group, there were 12 implant-related complications (39%). There was 1 postsurgical infection in the SS-Ti group. Rod fractures: 4 Ti, 1 SS. Proximal junctional kyphosis: 3 Ti, 4 SS. Pseudoarthrosis: 4 Ti, 2 SS.

Timing of adverse effects: NR

Factors that predict response: We found no evidence that combining Ti screws with SS rods increases the risk for implant-related complications.

15.2 Source Citation: Lamerain et al. 2014⁵³

Study Design: Non-randomized comparative study of patients undergoing surgery for adolescent idiopathic scoliosis.

Device or Material: SS and CoCr rods materials

Contact Duration: minimum 24 months

Dose: NA

Frequency/Duration: single administration

Response: Complications

Patient characteristics (gender, mean age): 70 females (78 %) and 20 males (22 %). Mean age at surgery was 15.2 years (12–18 years).

Number per Group: 64 patients (group 1) were operated on using CoCr rods. 26 patients (group 2) were operated on using SS rods.

Observed adverse effects: No neurologic complications occurred in any of the patients. Four patients (one in SS group and three in CoCr group) had deep wound infection and one patient in SS group had a superficial skin infection due to *Staphylococcus aureus* in four cases (unknown in one case).

Timing of adverse effects: NR

Factors that predict response: We noted four deep and one superficial infection. Despite this elevated rate of infection compared to other data in the literature, we did not identify any relevant causative factor (for example operative time or blood loss which were very low in our series).

Systemic Response/Toxicity

15.3 Source Citation: Siddiqi et al. 2021⁵¹

Study Design: SR to identify and review studies that report the concentration of metal ions following multi-level spinal fusion and to evaluate the impact on clinical outcomes.

Device or Material: SS release of Cr; Ti; Ni

Contact Duration: Length of follow-up was 1 month to 14 years.

Dose: NR

Frequency/Duration: Single administration

Response: Articles were stratified by pre- and post-operative metal ion level measurements according to type of metal ion, and medium in which the ions were measured.

Patient characteristics (gender, mean age): Scoliosis was the most common indication for surgery in 14 studies. The role of patient characteristics (age, gender) on metal ion concentration could not be ascertained.

Number per Group: 18 studies encompassing 653 patients. 9 studies reported Ti ions, eight reported Cr, and six reported Ni.

Observed adverse effects:

Cr concentrations varied between 0.3 and 1.1 µg/L at baseline to 0.3–10.5 µg/L at four or more years after surgery. Seven studies reported that serum Cr levels were higher than the normal reference range, or higher than levels measured in controls more than 4 years after surgery. In contrast, one study found

no significant difference in Cr levels in whole blood among patients with retained implants, patients with removed implants and unmatched controls.

Ti levels were elevated compared to controls/reference range/preoperative baseline in seven studies with the other two reporting no difference. Cr levels were elevated compared to controls/reference range in seven studies with one reporting no difference. Ni levels showed no difference from controls/reference range in four studies with one reporting above normal and another elevated compared to controls. Radiographic evidence of corrosion, implant failure, pseudarthrosis, revision surgery and adverse reaction reporting was highly variable.

Timing of adverse effects:

Factors that predict response:

"Metal ions are elevated after instrumented spinal fusion, notably Cr levels from SS implants and Ti from Ti implants. The association between clinical and radiographic outcomes remain uncertain but is concerning. Further research with standardized reporting over longer follow-up periods is indicated to evaluate the clinical impact and minimizing risk."

"Our results show that the literature to date has focused on SS and Ti-based implants, is mostly retrospective, includes small sample sizes, mostly female participants, and consists of populations of varying ages, duration of follow-up, spinal disorders, and instrumentation. Additionally, different analysis techniques with different lowest detectable levels have been used as well as different sample types (serum, plasma, whole blood) and reference ranges making it difficult to compare absolute values between studies. Despite this our study shows that investigators consistently observed elevated Cr and Ti metal ions levels postoperatively after SS and Ti spinal fusion in the pediatric and adult population particularly in serum and plasma when compared to baseline levels (preoperative or reference), whereas the majority of investigators observed no increase in Ni."

"Soluble metal ions have been shown to bind to proteins, remain in solution, and disseminate into the surrounding tissues, blood stream, lymphatic system, and remote organs. The systemic effects of elevated metal ions are largely unknown but may include negative systemic effects on reproduction including fetal development, poor quality of life, and/or increased risk of cancer. The systemic effects of elevated metal ions were not evaluated in any of the included studies, and as such were not commented on in this review."

Table 16: Orthopedic – fixation, other - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

16.1 Source Citation: Montiel et al. 2020⁵⁸

Study Design: Retrospective comparison study of patient undergoing osteotomy proximal phalanx of the big toe

Device or Material: Staples: Group A made of SS, Group B made of nitinol, Group C unknown.

Contact Duration: 12 weeks

Dose: single staple

Frequency/Duration: single administration

Response: fractures, delayed union, malunion, infection, osteolysis, necrosis, algodystrophy (complex regional pain syndrome)

Patient characteristics (gender, mean age): A – 3 male, 37 female, mean age 60 years, B – 5 male, 60 female, mean age 65, C – 2 male, 38 female, mean age 62 years

Number per Group: A = 40, B = 65, C = 40

Observed adverse effects:

A: 3 fractures, 2 delayed union, 4 malunion, 1 infection, 0 osteolysis, 0 necrosis, 4 algodystrophy

B: 8 fractures, 0 delayed union, 2 malunion, 1 infection, 0 osteolysis, 0 necrosis, 0 algodystrophy

C: 4 fractures, 3 delayed union, 2 malunion, 1 infection, 0 osteolysis, 0 necrosis, 3 algodystrophy

Timing of adverse effects: data were collected at 12 weeks

Factors that predict response: Intra-operative and post-operative complication rates were similar for all groups.

16.2 Source Citation: Royse et al. 2020⁵⁵

Study Design: Open-label RCT examining sternal closure

Device or Material: SS wire cerclage compared with a Ti band and plate system (SternaLock360VR, Zimmer Biomet, Jacksonville, FL, USA).

Contact Duration: 12 weeks

Dose: Single surgery

Frequency/Duration: Data were collected at 12 weeks

Response: Infection

Patient characteristics (gender, mean age): SS 71% male, mean age 64.8 years; Plate 81% male, mean age 64.2 years

Number per Group: SS = 24, Plate = 26

Observed adverse effects: No patient suffered a deep sternal wound infection.

Timing of adverse effects: 12 weeks

Factors that predict response: NR

16.3 Source Citation: Sun et al. 2020⁵⁹

Study Design: Retrospective comparison study of patients undergoing surgery for unstable distal radius fracture.

Device or Material: open reduction & internal fixation (ORIF) with steel plates compared with closed reduction & external fixation (CREF)

Contact Duration: 3 months after surgery

Dose: Single surgery

Frequency/Duration: Once

Response: complex local pain, fracture repositioning, carpal tunnel syndrome, osteoporosis, traumatic arthritis, and malunion

Patient characteristics (gender, mean age): ORIF – male 23, female 30, mean age 49.6 years; CREF – 26 male, 28 female, mean age 50.0 years.

Number per Group: ORIF = 53, CREF = 54

Observed adverse effects: ORIF – 22.64%, 2 complex local pain, 1 fracture repositioning, 3 carpal tunnel syndrome, 3 osteoporosis, 2 traumatic arthritis, and 2 malunion; CREF – 22.22%, 3 complex local pain, 1 fracture repositioning, 2 carpal tunnel syndrome, 3 osteoporosis, 1 traumatic arthritis, and 2 malunion.

Timing of adverse effects: Up to 3 months postsurgery.

Factors that predict response: “The results of this study show that, the two groups demonstrated no significant difference in the excellent and good rate of wrist joint function, incidence of complications and patient satisfaction ($P>0.05$), indicating their similar efficacy.”

16.4 Source Citation: Marzouk et al. 2019⁶⁰

Study Design: Retrospective comparison study of patients undergoing cardiac surgery via median sternotomy.

Device or Material: Rigid sternal fixation using 3 separate techniques (peristernal polyether ether-ketone banding (PEEK), Ti plating, and SS multibraided cables with cannulated screws) was used in 1,111 patients (group A), whereas conventional peristernal/transsternal wiring was used in 13,937 patients (group B).

Contact Duration: Mean time to presentation of primary outcome was 31 ± 70 days after surgery.

Dose: Single surgery

Frequency/Duration: Once

Response: deep sternal wound infection or sterile sternal dehiscence (DSWI/d)

Patient characteristics (gender, mean age): Group A – 20% female, mean age 64.3 years; Group B – 28% female, mean age 65.5 years.

Number per Group: 73 patients in group A were given SS multi-braided cables. 844 patients in group A received PEEK bands.

Observed adverse effects: “We observed a statistically significant benefit associated with PEEK banding with respect to the risk of DSWI/d compared with matched patients in group B (1.5% vs 2.8%, $P = .03$), whereas no benefit was seen with Ti plating (4.8% vs 2.3%, $P = .12$) or multibraided [SS] cables with cannulated screws (2.7% vs 2.6%, $P = .65$; group A vs group B, respectively).”

Timing of adverse effects: 31 ± 70 days after surgery.

Factors that predict response: NR

16.5 Source Citation: Wang et al. 2019⁵⁴

Study Design: SR to identify patient and intra-operative factors that contribute to non-union in locked lateral plating for distal femoral fractures. Low quality evidence, all but one study was retrospective.

Device or Material: SS plates compared with Ti plates

Contact Duration: NR

Dose: Single surgery

Frequency/Duration: NR

Response: Non-union

Patient characteristics (gender, mean age): NR

Number per Group: Eight studies investigating 1,380 distal femoral fractures.

Observed adverse effects:

"Five studies compared the impact of SS and Ti plates. Two papers by Rodriguez et al. with data drawn from the same patient population demonstrated a strong association between SS plate material and non-union ($p < 0.001$). However, three studies demonstrated no statistical difference between the two metals."

Timing of adverse effects: NR

Factors that predict response:

"Plate material selection remains a key surgical decision for distal femoral fracture repair. Although SS is typically cheaper than Ti, it is a much stiffer material with approximately twice the density of Ti. Whilst Rodriguez et al demonstrated a significantly higher rate of nonunion associated with SS plate material ($p < 0.01$), the authors were unable to eliminate the impact of confounding, with the study utilizing primarily Synthes LISS Ti plates accepting only locking screws compared with stainless-steel locking compression plates allowing cortical screws. No significant difference in union rates associated with plate material were found in other studies. Whilst theoretical and in-vivo evidence exists that the stiffness of SS contributes to decreased callus formation, the practical ramifications of plate material on femoral non-union remains uncertain."

16.6 Source Citation: Marasco et al. 2018⁵⁶

Study Design: Single-center, randomized comparison study of sternal wound closure. Patients and assessors were blinded to treatment.

Device or Material: ZIPFIX polymer cable ties (De Puy Synthes, West Chester, Pa) and standard stainless-steel wires.

Contact Duration: Data were collected at 4 weeks.

Dose: 5 ZIPFIX cables and 6 SS wires

Frequency/Duration: Single surgery

Response: postoperative pain, sternal wound infection,

Patient characteristics (gender, mean age): ZIPFIX – 46 male and 11 female, mean age 64.9 years; SS – 46 male, 14 female, mean age 65.6 years.

Number per Group: ZIPFIX = 57, SS = 60.

Observed adverse effects:

“Although there was a significant overall decline in pain with time ($P < .0001$), there was no evidence to suggest that the decline in pain with time differed between groups (interaction $P = .66$).”

Five patients in the entire cohort had sternal wound infection diagnosed during the follow-up period; 3 of 60 patients (5%) in the standard wires group and 2 of 55 patients (3.6%) in the ZIPFIX group ($P = .65$). Of these, 2 infections in the standard wires group and 1 in the ZIPFIX group were deep sternal wound infections requiring sternal debridement and vacuum dressing.”

“We did not see any increases in sternal wound infection, foreign-body reaction, or nonunion in the ZIPFIX group, although our study was not powered to identify differences in these outcomes.”

Timing of adverse effects: up to 4 weeks

Factors that predict response: NR

16.7 Source Citation: Obermeyer 2017⁶¹

Study Design: Single center retrospective comparison study of patients undergoing the Nuss procedure (surgery to correct severe pectus excavatum, sternum of the chest is caved in).

Device or Material: SS bars (SSB) or Ti bars

Contact Duration: Up to 10 years

Dose: single bar

Frequency/Duration: Single surgery

Response: Allergic reaction

Patient characteristics (gender, mean age): Surgery is performed in children, patient characteristics were not reported.

Number per group: SS = 842, Ti = 90

Observed adverse effects:

"Over 10 years, 90 patients had Ti bars placed with no allergic events, while 842 patients had SS bars placed with 15 (1.8%) developing a bar allergy."

"The mean time for symptoms of a SSB allergy to be recognized was 22 weeks (range 2–52 weeks). Pain (73%), peri-incisional erythema (60%), persistent lethargy (33%), and shortness of breath (33%) were the most common symptoms. ... Ni was the most common cause for a SSB allergy in our series (80%) and the most common allergen detected by dermal patch testing (61%), but other elements were also associated with SSB allergies."

Timing of adverse effects: 22 weeks (range 2–52 weeks).

Factors that predict response:

Allergy to Ni 61%, Cr 15%, copper 15%.

"An allergic reaction to a SS bar or a positive patch test was more common in females (OR = 2.3, $p < 0.001$) and patients with a personal (OR = 24.8, $p < 0.001$) or family history (OR = 3.1, $p < 0.001$) of metal sensitivity."

Environmental, food, and drug allergies were not related to metal allergies.

16.8 Source Citation: Ahmad and Jones 2016⁵⁷

Study Design: RCT comparing bioabsorbable and SS fixation of Lisfranc injuries

Device or Material: 4.0 mm partially threaded cannulated cancellous steel screws (Synthes, Paoli, PA) and 4.5 mm partially threaded cannulated cancellous polylactic acid (PLA) screws (Smart Screw, Linvatec, Largo, FL and Bio Trim-It, Arthrex, Naples, FL).

Contact Duration: 1 year

Dose: NR

Frequency/Duration: Single administration

Response: Observed postoperative complications at the foot including recurrence of instability, progression to midfoot degenerative joint disease (DJD), and the need for further revision surgeries.

Patient characteristics (gender, mean age): Screw: 9 male, 11 female, 37.1 years; PLA: 8 male, 12 female, 40.3 years

Number per group: 20 in each group

Observed adverse effects:

"No patients who received steel screws had hardware-related complications, one such problem was seen in a patient who received absorbable Lisfranc fixation. This particular patient (5%) received a single PLA screw for Lisfranc fixation and developed an inflammatory and lytic reaction at an unabsorbed screw head at the proximal second metatarsal at 2 years postoperatively."

Timing of adverse effects: 2 years

Factors that predict response: NR

16.9 Source Citation: Bejko et al. 2015⁶²

Study Design: Retrospective comparison study examining sternal closure

Device or Material: Sternal re-approximation was obtained with the use of nitilium clips in group A, steel wires sternal closure technique in group B.

Contact Duration: 30 days

Dose: 2 to 4 nitilium clips, 5 to 6 steel wires

Frequency/Duration: Single administration

Response: Effect on wound healing

Patient characteristics (gender, mean age): Group A: 73% male, 67.5 years old. Group B: 73% male, 68 years old.

Number per Group: 561 patients (group A), 561 patients (group B)

Observed adverse effects: "The overall incidence of wound complications was 2% (12/561) versus 3.5% (20/561) in group A versus group B, respectively ($P = 0.28$). "In group A, not a single patient experienced a deep wound complication requiring sternal re-wiring, whereas in group B, nine patients presented a deep wound complication with associated SWI [sternal wound instability], requiring re-wiring ($P = 0.003$). "Deep wound and SWI incidence were significantly less frequent in group A in comparison with group B [one patient (0.17%) versus nine patients (1.6%)] ($P = 0.02$)."

Timing of adverse effects: 30 days after surgery

Factors that predict response: "The vast majority of cases of sternal wound infections some degree of sternal instability is always present." SS wires did not provide as much stability as nitinol clips which lead to more complications in the SS group.

16.10 Source Citation: Melly et al. 2013⁶³

Study Design: Retrospective comparison study of sternal closure

Device or Material: Sternal ZipFix (ZF) system made of PEEK compared with SS wires

Contact Duration: Infections were recorded up to 12 months after the initial cardiac operation.

Dose: Single administration

Frequency/Duration: Once

Response: Infection

Patient characteristics (gender, mean age): 76% male, mean 66 years

Number per Group: PEEK = 95, wires = 498

Observed adverse effects: Total infection rate was 6.1%, with a total of 36 diagnosed sternal infections (5 in ZF and 31 in wires). No statistically significant difference related to the device (odds ratio: 0.067, confidence interval: 0.04–9.16, $P = 0.72$). Other postoperative complications had the same occurrence rate in both groups. PEEK versus wire: pneumothorax 2% and 4%, postoperative delirium 13% and 13%, hospital stay 10% and 11%.

Timing of adverse effects: Within one year of surgery

Factors that predict response: "No influence according to our effect model with regard to the 'overall' sternal infection for the biocompatible PEEK sternal closure device."

Table 17: Orthopedic – Intramedullary rod/nail - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

17.1 Source Citation: Galal et al. 2021⁶⁷

Study Design: single-center, retrospective cohort study of internal lengthening nail for femur lengthening

Device or Material: Magnetic internal lengthening nails (MILNs) – Precice Ti, Stryde SS.

Contact Duration: 14 months

Dose: Single nail

Frequency/Duration: Single administration

Response: Complications including infection

Patient characteristics (gender, mean age): Stryde - 2 female, 14 male, mean age 31 years; Precice – 3 female, 15 male, mean age 33 years.

Number per Group: Precice = 18, Stryde = 16

Observed adverse effects:

No patients suffered from nonunion or infection.

“No mechanical nail complications were reported in the Stryde group compared to three events of nail failure in the Precice group. One femur in the Precice group needed bone marrow aspirate concentrate injection for delayed healing compared to four femurs in the Stryde group.”

Healing rate was significantly faster with Precice.

Timing of adverse effects: NR

Factors that predict response: NR

17.2 Source Citation: Mohamed and Rajeev 2017⁶⁴

Study Design: SR of studies for treating pediatric femoral fractures, 1 RCT and 4 non-RCT

Device or Material: SS and Ti elastic intramedullary nail system (TENS)

Contact Duration: Follow-up ranged from 6 months to 7.16 years

Dose: NA

Frequency/Duration: Single administration

Response: Malunion, delayed union, skin irritation, infection rate,

Patient characteristics (gender, mean age): more males than females; age range from 8 years to 11 years.

Number per group: 183 stainless-steel, 198 Ti from 5 studies

Observed adverse effects: “Three studies showed no statistically significant difference in the rates of malunion between the 2 groups. However, the other 2 studies showed that malunion rate was significantly higher in the Ti group than in the stainless-steel group. Four studies found no significant difference in the rates of delayed union. All studies showed no statistically significant difference between

2 nails in rates of skin irritation apart from one study which revealed that they were significantly more frequent in the TENS group. There is no statistically significant difference in the rate on infection between the two groups. One study reported no statistically significant difference in limb length discrepancy between the two nail types.

Timing of adverse effects: See follow-up ranges.

Factors that predict response: "This systematic review reveals that there is no conclusive evidence to indicate superiority of one type of elastic nails over the other in management of paediatric femoral shaft fractures. Nonetheless, and despite the methodological deficiencies, of the included studies, the overall trend is in favour of stainless-steel elastic nails being cheaper and providing better clinical and radiological outcomes with fewer complications."

17.3 Source Citation: Queally et al. 2014⁶⁵

Study Design: SR Cochrane Library: All randomized or quasi-randomized trials comparing different types, or design modifications, of intramedullary nails in the treatment of extracapsular hip fractures in adults. Included 17 trials, testing 12 comparisons of different cephalocondylic nail designs. The quality of evidence was is low or very low, partly because most trials used flawed methods.

Device or Material: Intramedullary nails made of SS – Proximal femoral nail (Synthes), Gamma nail (Stryker-Howmedica), Gliding nail system (Smith-Nephew)

Contact Duration: NR

Dose: Single surgery

Frequency/Duration: NR

Response: "Serious adverse events and technical complications of fixation (e.g. deep infection, avascular necrosis, later fracture of the femur, non-union, cut-out, implant breakage) for which substantive treatment, such as revision surgery, is indicated or performed."

Patient characteristics (gender, mean age): The trials involved a total of 2,130 adults (predominantly female and older people) with mainly unstable trochanteric fractures.

Number per Group: See individual studies

Observed adverse effects

Comparing 2 SS devices: "Four trials (910 participants) compared the proximal femoral nail (PFN) with the Gamma nail. There was no significant difference between the two implants in functional outcome (the very low quality evidence being limited to results from single trials), mortality (low quality evidence: 86/415 versus 80/415; risk ratio (RR) 1.08, 95% confidence interval (CI) 0.82 to 1.41), serious fixation complications (operative fracture of the femur, cut-out, non-union and later fracture of the femur) nor re-operations (low quality evidence: 45/455 versus 36/455; RR 1.25, 95% CI 0.83 to 1.90). ... None of the differences between the two implant groups in specific post-operative complications were statistically significant in [three studies]. [One study] reported no difference between groups in medical complications that had occurred by one year follow up."

Comparing SS to non-SS device: "Seven of the nine trials evaluating different comparisons provided very low quality evidence of a lack of significant between-group differences in all of the reported main outcomes for the following comparisons: ACE trochanteric nail versus Gamma 3 nail (112 participants); gliding nail versus Gamma nail (80 participants); Russell-Taylor Recon nail versus long Gamma nail (34 participants, all under 50 years); proximal femoral nail antirotation (PFNA) nail versus Targon PF nail (80 participants); dynamically versus statically locked intramedullary hip screw (IMHS) nail (81 participants);

sliding versus non-sliding Gamma 3 nail (80 participants, all under 60 years); and long versus standard PFNA nails (40 participants with reverse oblique fractures)."

Timing of adverse effects: NR

Factors that predict response: "The limited evidence from the randomized trials undertaken to date is insufficient to determine whether there are important differences in outcome between different designs of intramedullary nails used in treating extracapsular hip fractures."

"There was insufficient evidence from randomized trials to determine if there are important differences in patient outcomes between the different designs of proximal femoral intramedullary nail produced by different manufacturers when used for the fixation of unstable, or stable, trochanteric fractures."

17.4 Source Citation: Rose et al. 2013⁶⁶

Study Design: SR of humeral fractures, included 13 case series, low quality evidence

Device or Material: Fixation system (Disc-O-Tech Medical Technologies, Herzeliya, Israel), expandable SS nailing system was used in all included studies.

Contact Duration: Total mean time from these studies was 14.9 weeks ranging from a mean 9.3 weeks to 16.5 weeks.

Dose: NA

Frequency/Duration: Single administration

Response: Post-operative complications related to nail: radial nerve palsy, nail migration.

Patient characteristics (gender, mean age):

Number per group: 176 patients with 180 fractured humeri treated with expandable nails

Observed adverse effects: 2 radial nerve palsy, 2 nail migration

Timing of adverse effects: Not reported

Factors that predict response: "The current evidence base consists of the results of several case series. This therefore calls into question the validity of the reported data, since all of the present studies were subject to numerous methodological flaws, thereby introducing bias."

Table 18: Orthopedic – prosthetics - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

18.1 Source Citation: Roche-Albero et al. 2021⁶⁹

Study Design: Nonrandomized comparative.

Device or Material: Cable-Ready plates (SS, Zimmer-Biomet) vs. Dall-Miles plates (SS, Stryker) vs NCB plates (non-SS, Zimmer-Biomet).

Contact Duration: Minimum 2-year follow-up.

Dose: NA.

Frequency/Duration: Single administration.

Response: No adverse responses of interest.

Patient characteristics (gender, mean age): 57% female, 85.6 years (83-95). 8 patients died, average age 85.6 years (83-95), with 4 dying in the first year, average age 87 (83-95).

Number per Group: 37 patients.

Observed adverse effects: No pseudoarthrosis or loss reduction cases requiring osteosynthesis surgery observed. There were no cases of prosthesis dislocation, loss of fracture reduction, or breakage of osteosynthesis plate.

Timing of adverse effects: Time to fracture consolidation ranged 6 to 13 weeks.

Factors that predict response: None reported.

18.2 Source Citation: Fujita et al. 2020⁷⁰

Study Design: Nonrandomized comparative.

Device or Material: Exeter hip stem (SS, Stryker) vs. Ti-alloy stem (non-SS, Kyocera Co. Ltd.).

Contact Duration: Minimum 10-year follow-up. Mean follow-up of 10.8 years for the Exeter group and 12.4 years for the Ti-alloy group.

Dose: NA.

Frequency/Duration: Single administration.

Response: Cancellization; cortical hypertrophy; dislocation.

Patient characteristics (gender, mean age): Exeter group: 13.0% male, 61.8 years (29-84 years). Ti-alloy group: 6.5% male, 62.2 years (42 to 81 years).

Number per Group: 92 primary total hip arthroplasties (THA) belong to 74 patients. N=46 THA in each group.

Observed adverse effects: Cancellization was observed in 16 hips (39.0%) in the Exeter group and 21 hips (48.8%) in the Ti-alloy group. Cortical hypertrophy was observed in 7 hips (17.1%) in the Exeter group and 8 hips (18.6%) in the Ti-alloy group. Three hips in each group dislocated at an early postoperative period and were successfully reduced without recurrence. No patient had symptomatic deep vein thrombosis, nerve palsy, or intra- or postoperative fracture.

Timing of adverse effects: Dislocation observed in an early postoperative period. Cortical hypertrophy was first observed at 2-6 years and enlarged progressively until 7-12 years and then decreased until final follow-up. Mean follow-up of 10.8 years for the Exeter group and 12.4 years for the Ti-alloy group.

Factors that predict response: None reported.

18.3 Source Citation: Hernekamp et al. 2020⁷¹

Study Design: Nonrandomized comparative.

Device or Material: APTUS 2.5 TriLock Wrist Fusion Plate (SS, Medartis Suisse) vs. AO plate (non-SS, Depuy-Synthes).

Contact Duration: Mean follow up at 18.2 months for APTUS group, 37.2 months for AO group.

Dose: NA.

Frequency/Duration: Single administration.

Response: Non-union; Pain.

Patient characteristics (gender, mean age): APTUS group: 100% male; 51.8 years. AO group: 50% female; 53.4 years. Overall: 25% female; 52.6 years (30-78 years).

Number per Group: n=10 patients per group.

Observed adverse effects: Complete osseous healing in all patients in the AO plate group vs. 1 case of non-union in the APTUS group requiring revision surgery using AO-technique. Another plate in the APTUS group had to be removed due to a painful superficial branch of the radial nerve and a protruding screw.

Timing of adverse effects: 3 months; 1 year postoperative, respectively.

Factors that predict response: In one case the superficial branch of the radial nerve was chronically irritated due to extended subcutaneous scarring.

18.4 Source Citation: Atinga et al. 2018⁷²

Study Design: Nonrandomized comparative.

Device or Material: 22G SS cerclage tension wire (group A) versus 1.3 mm Zimmer tension cable (group B).

Contact Duration: Mean follow-up 46.9 months (12-120 months).

Dose: NA.

Frequency/Duration: Single administration.

Response: Required removal of metal work due to irritation.

Patient characteristics (gender, mean age): 22% female; 50.2 years (21-74 years).

Number per Group: Group A, n=18 shoulders; Group B, n=14 shoulders.

Observed adverse effects: 3 patients required hardware removal with SS vs 1 patient in non-SS. Seroma drainage was only required in 1 non-SS patient.

Timing of adverse effects: Mean follow-up 46.9 months (12-120 months).

Factors that predict response: None reported.

18.5 Source Citation: Zaoui et al. 2015⁶⁸

Study Design: RCT

Device or Material: SS femoral head (CMK21, Smith & Nephew) vs. oxidized zirconium femoral head (Oxinium, Smith & Nephew) with either highly crosslinked polyethylene (HXLPE) socket or ultra-high molecular weight polyethylene (UHMWPE) socket.

Contact Duration: Minimum follow-up of 4 years (median 6 years, range 4-8 years).

Dose: NA.

Frequency/Duration: Single administration.

Response: Femoral head penetration as indicative of implant wear.

Patient characteristics (gender, mean age): 64% female; 62 years (21-75 years). Male/female gender ratio in the UHMWPE-SS group was 0.41 with a median age of 64 years (21-72 years). Male/female gender ratio in the UHMWPE-Oxinium group was 0.46 with a median age of 60 years (41-75 years). Male/female gender ratio in the HXLPE-SS group was 0.44 with a median age of 65 years (43-75 years). Male/female gender ratio in the HXLPE-Oxinium group was 0.5 with a median age of 58 years (41-75 years).

Number per Group: 86 total patients were available at follow-up. 22 patients each in the UHMWPE-SS and UHMWPE-Oxinium groups; 21 patients each in the HXLPE-SS and HXLPE-Oxinium groups.

Observed adverse effects: In the UHMWPE series, the steady-state penetration rate from 1 year onward was lower in the oxidized zirconium group (0.03 mm/year [0.003-0.25 mm/year]) than it was in the SS group (0.11 mm/year [0.03-0.29 mm/year]). In the HXLPE series, the steady-state penetration rate from 1 year onward was also lower in the oxidized zirconium group (0.02 mm/year [-0.32-0.07 mm/year]) than it was in the SS group (0.05 mm/year [-0.39-0.11 mm/year]).

No specific complication related to the use of oxidized zirconium femoral heads was recorded and no patient underwent revision surgery.

Timing of adverse effects: From 1 year onward. Minimum follow-up of 4 years (median 6 years, range 4-8 years).

Factors that predict response: The different metal material might explain increased steady-state penetration.

18.6 Source Citation: Jakobsen et al. 2014⁷³

Study Design: Nonrandomized comparative.

Device or Material: Metal-on-metal hip implants. SS, cobalt chromium (CoCrMo) alloy, Ti alloy, Ti, and tantalum-tungsten alloy implants.

Contact Duration: None reported.

Dose: NA.

Frequency/Duration: Single administration.

Response: Revision as a result of aseptic loosening, repeated luxation, pain, or other (not differentiated between infection, polyethylene wear, loosening caused by metastasis, and peri-acetabular ossification).

Patient characteristics (gender, mean age): None reported. Implant components in 15 patients were stored without a personal identification number, and medical history could not be retrieved in all cases of hip arthroplasty removal during revision.

Number per Group: SS groups, n=23. CoCrMo-alloy group, n=23. Ti-alloy group, n=21. Ti group, n=3. Tantalum-tungsten alloy, n=1.

Observed adverse effects: In the SS 316L group, revision came as the result of aseptic loosening (n=1), pain (n=1), and unknown (n=3).

In the SS F1586 group, revision was the result of aseptic loosening (n=7), repeated luxation (n=2), pain (n=4), other (n=2), and unknown (n=4).

In the CoCrMo-alloy group, revision was the result of aseptic loosening (n=3), repeated luxation (n=5), pain (n=3), other (n=4), and unknown (n=8).

In the Ti group, revision was the result of aseptic loosening (n=1) and unknown (n=2).

In the Ti-alloy group, revision was the result of aseptic loosening (n=4), repeated luxation (n=3), pain (n=1), other (n=3), and unknown (n=10).

In the Tantalum-tungsten alloy group, revision was the result of unknown (n=1).

Timing of adverse effects: None reported.

Factors that predict response: In periprosthetic tissue, it is possible, and even likely, that lower metal concentrations may cause sensitization and inflammatory reactions.

18.7 Source Citation: Massin et al. 2012⁷⁴

Study Design: Nonrandomized comparative.

Device or Material: SS press-fit cups (Collegia, Wright Medical; Sunfit, Serf; Polarcup, Smith & Nephew) versus CoCr press-fit cups (Evora, Science et Medecine).

SS press-fit cups with additional extraarticular screws (Gyrus, Depuy; Polarcup, Smith & Nephew).

Tripod fixation cups, material not specified (EOL, Ceramconcept).

Contact Duration: Minimum follow-up of 5 years, mean 7.7 years (5-11 years).

Dose: NA.

Frequency/Duration: Single administration.

Response: Implant survival.

Patient characteristics (gender, mean age): Press-fit SS cups: 1.40 female/male ratio; 72±10 years.

Press-fit CoCr cups: 1.85 female/male ratio; 75±8 years.

Press-fit SS cups with porous coated Ti beads: 0.91 female/male ratio; 71±7 years.

Press-fit CoCr cups: 1.85 female/male ratio; 75±8 years.

Press-fit SS cups with additional screw fixation: 1.68 female/male ratio; 72±10 years.

Press-fit SS cups with plasma-sprayed layer and additional screw fixation: 2.07 female/male ratio; 74±8 years.

Tripod grit-blasted cups: 1.58 female/male ratio; 72±8 years.

Tripod porous-coated cups: 1.45 female/male ratio; 71±10 years.

Number per Group: Press-fit group (n=997 cups for 929 patients): n=91 grit-blasted SS cups with HA layer (Collegia, Wright Medical); n=311 grit-blasted SS cups with bilayer of HA and alumina (Sunfit, Serf); n=404 SS cups with porous coated Ti beads (Polarcup, Smith & Nephew; Amplitude, Valence); n=191 CoCr cups covered with HA layer (Evora, Science et Medecine).

Press-fit with additional extraarticular screws group (n=726 SS cups for 680 patients): n=590 grit-blasted cups (Gyrus, Depuy); n=136 porous-coated cups with a plasma-sprayed layer of Ti beads (Polarcup, Smith & Nephew).

Tripod fixation group (n=878 cups for 799 patients): n=797 grit-blasted cup surfaced with HA bilayer (Novae, Serf); n=81 porous surface cups (EOL, Ceramconcept).

Observed adverse effects: The 8-year survival of press-fit, grit-blasted SS cups was lower ($p=0.05$) than that of tripod grit-blasted cups made of the same alloy: 91% versus 98% respectively. 8-year survival of tripod SS grit-blasted cups was, in turn, lower ($p=0.03$) than that of grit-blasted cups with flanges and secured with additional screws: 98% versus 100%. 8-year survival of CoCr cups was greater ($p=0.03$) than that of SS cups with no screw fixation: 100% versus 91%. The failure rate was high in the group of SS press-fit grit blasted cups with no additional screw fixation (15 failures, 3.7%), which tilted acutely after symptom-free initial periods (1-9 years). 11 failures (1.3%) occurred in the tripod SS grit-blasted cups, with all but one occurring after 5 years post-operatively.

Timing of adverse effects: Most results at 8-year survival; tripod failure noted after 5 years post-operatively.

Factors that predict response: None reported.

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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.