MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Cobalt Chromium (CoCr) Safety Profile

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Executive Summary

Key Points

1. Searches identified 2374 citations; 68 articles were selected for inclusion
2. For cardiac stents, moderate quality evidence from 14 studies reported commonly examined local responses include target lesion/vessel revascularization (no difference in rate compared to other drug-eluting stents), myocardial infarction (no difference from other metal stents), and thrombosis (CoCr may have lower rate than other stents).
3. For cardiac valves, moderate quality evidence from 18 studies reported commonly examined local responses include bleeding (rates range from 2 – 26%), paravalvular leak (1 – 12%), myocardial infarction (0.1 – 2.6%), and endocarditis (1.6%). These responses were typically reported at 30 days to 1 year.
4. For intracranial stents, low quality evidence from 8 studies examined successful occlusion of aneurysms and stenosis/thrombosis at 1 – 62 months.
5. For orthopedic bone and joint, moderate quality evidence from 19 studies indicates responses include aseptic loosening/osteolysis (<1% to 34% depending on joint), periprosthetic fracture (0-15%), and adverse local tissue reaction (0 – 39%) at typically 4 – 10 years. Certain metal-on-metal hip arthroplasties may yield elevated serum chromium concentrations
6. For orthopedic spine, low quality evidence consisted of 4 studies. One study examined adjacent segment degeneration (no difference from anterior cervical discectomy and fusion), adverse local tissue reaction (1.5%), local chromium and cobalt levels (0.31 µg/L and 0.21 µg/L, respectively), radiolucency (14.3%), and subsidence (1.4%) at 5 years.
7. Searches of the Patient Safety Organization and Problem Reporting Network databases did not result in reports related to biocompatibility of CoCr.
8. There were dozens of Accident Investigations that involved medical devices composed of CoCr. However, many of these investigations focused on events that were not related to biocompatibility or structural integrity once inside a patient's body. One investigation involving a tissue valve with CoCr valve frames identified leaflets that lost coaptation over time. While unlikely, it may be possible that the CoCr frames contributed to nonuniform calcification that deformed the leaflet margins.
9. There were 249 manufacturer- and regulatory-issued alerts identified in ECRI's Healthcare Technology Alerts database. The majority of the alerts were unrelated to biocompatibility issues. However, there are some notable alerts including migrating metallic pieces (replacement heart valve), serious complications such as embolization and thrombosis (intravascular/cardiovascular filters), compromised biological safety (fixation rods), and elevated biotoxin levels with residue debris (shoulder prosthesis).
10. Evidence gaps:
    a. There was only very low-quality evidence regarding local responses in the following categories: cardiac filters, pacemakers, dental/ENT, gastric
    b. Systemic responses were not investigated in those same categories.

Overview - Cobalt Chromium

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. 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 cobalt chromium (CoCr). If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research. Literature searches identified 2374 articles and 407 of those met inclusion criteria for the systematic review. After prioritization, 68 articles were ultimately included in this review.

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

Local responses/device events varied somewhat across different device categories (see specific responses/events under 1a. below). Most of the evidence for local responses/events related to CoCr came from human studies of CoCr-containing cardiovascular stents, cardiovascular valve replacements, and orthopedic devices (total hip, knee, and shoulder arthroplasties), with a few additional studies providing evidence on local responses/events. The most often examined local responses include myocardial infarction, thrombosis, aseptic loosening, target lesion/vessel revascularization, bleeding, and postoperative pacemaker implantation.

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?

i. For cardiovascular filters: One study reported filter leg protrusion at 6 months.

ii. For pacemaker leads: One study reported vascular occlusion and thrombosis 6 to 11 years after implantation

iii. For cardiovascular stents: Commonly examined local responses include target lesion/vessel revascularization (no difference in rate compared to other drug-eluting stents), myocardial infarction (no difference from other metal stents), and thrombosis (CoCr may have lower rate than other stents). These responses were typically reported at 1 to 5 years.

iv. For cardiovascular valves: Commonly examined local responses include bleeding (rates range from 2 – 26%), paravalvular leak (1 – 12%), myocardial infarction (0.1 – 2.6%), and endocarditis (1.6%). These responses were typically reported at 30 days to 1 year.

v. For Dental/ENT devices: Two studies reported implant failure occurred in 2% to 18% of cases considered as a result of CoCr hypersensitivity, malocclusion/dislocation/loosening, and heterotopic bone formation. These responses were reported at up to 1 or 5 years.

vi. For Gastric devices: One study on gastric bands reported band slippage (6.9%), erosion into the gastrointestinal tract (1.3%), gastric dilation (2.3%), vomiting (1.6%), and hiatal hernia (1.6%) at 5 years post implantation.

vii. For Intracranial stents: Included studies examined successful occlusion of aneurysms and stenosis/thrombosis at 1 – 62 months.

viii. For Orthopedic joint arthroplasties: Commonly examined responses include aseptic loosening/osteolysis (<1% to 34% depending on joint), periprosthetic fracture (0-15%), and adverse local tissue reaction (0 – 39%) at typically 4 – 10 years.

ix. For Spine implants: One study examined adjacent segment degeneration (no difference from anterior cervical discectomy and fusion), adverse local tissue reaction (1.5%), local chromium and cobalt levels (0.31 µg/L and 0.21 µg/L, respectively), radiolucency (14.3%), and subsidence (1.4%) at 5 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. Mortality was the most commonly examined systemic response for cardiovascular stents and valves and intracranial stents.

i. Studies reported no difference in mortality between CoCr devices and other devices or treatments at follow-up times from 30 days to 5 years.

ii. Stroke along with acute kidney injury were also commonly examined. Studies usually did not find a difference in response between CoCr devices and other devices or treatments.

b. For joint arthroplasties and spine implants, the most commonly examined responses were revision rate and serum chromium and cobalt concentrations.

i. Revision rates ranged from 0 – 38% at 2 – 10 years follow-up, depending on the joint.

ii. For knee arthroplasties, studies did not find CoCr knee implants to have a higher chromium or cobalt concentration compared to other knee implants.

iii. For hip arthroplasties, one study found patients with metal-on-metal systems had higher chromium concentrations than patients with ceramic-on-metal at 6 months. Another study did not find a difference at up to 5 years.

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?

a. Cardiac Stents – while a few studies indicated gender or patient comorbidities may have impacted clinical outcomes, the included studies do not suggest these factors impacted systemic responses.

b. Cardiac valves – One study indicated gender, STS score, and systolic pulmonary artery pressure were correlated with mortality after implantation, the correlation could be procedure related and not linked to the material.

c. Orthopedic Bone and Joint – One study reported correlations between gender and complication rate and revision rate but not specific systemic responses.

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

a. No studies investigated 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?

a. There was only very low-quality evidence regarding local responses in the following categories: cardiac filters, pacemakers, dental/ENT, gastric.

b. Systemic responses were not investigated in those same categories.

Project Overview

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

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

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

Key Questions

1. What is the typical/expected local host response to cobalt chromium?
    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 (SR) and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, 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 contained 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. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in clinical literature. Complications are reported directly by clinical staff; thus, reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a 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 the 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 - Cobalt Chromium

Full Name: Cobalt Chromium
CAS Registry Number: 11114-92-4

Safety Brief - Systematic Review Results

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

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

A summary of our primary findings is shown in Table 1. We then turn to a detailed discussion of research on CoCr as a material as well as research on the various device categories.

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

Table 1: Summary of Primary Findings from the Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Cardiac filter (1 human SAS)	Protrusion, removal/failure to remove	Very low	None examined	Very low
Cardiac pacemaker leads (1 human SAS)	Mitral valve insufficiency, mitral valve regurgitation, perforation, removal/failure to remove, thrombosis, traction, vascular occlusion	Very low	None examined	Very low
Cardiovascular stents (14 human studies, 13 SRs, 1 NRCS)	Coronary evagination, myocardial infarction, reinfarction, restenosis, stent deformation, stent thrombosis, target lesion failure, target revascularization	Moderate	Mortality, stroke	Moderate
Cardiac valves (18 human studies, 16 SRs, 2 RCTs)	Aortic regurgitation, bleeding, endocarditis, major vascular complications, mitral	Moderate	Acute kidney injury, atrial fibrillation, cerebrovascular	Moderate

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	regurgitation, paravalvular leak, thrombosis		events, mortality, myocardial infarction, new-onset dialysis, permanent pacemaker implantation, reoperation rate, sepsis, stroke	
Dental/ENT (2 human SASs)	Bleeding, failure, fracture, heterotopic bone formation, hypersensitivity, loosening, malocclusion, marginal bone loss, numbness/neurological issue, removal	Very low	None examined	Very low
Gastric (1 human SAS)	Band slippage, erosion, gastric dilation, vomiting, hiatal hernia	Very low	None examined	Very low
Intracranial stents (8 human SR studies)	Hemorrhage, ischemia, occlusion, re-rupture, stenosis	Low	Morbidity, mortality, stroke	Low
Orthopedic Bone and Joint (19 human studies, 9 SRs, 6 RCTs, 1 NRCS, 3 SASs)	Adverse reaction to metal debris/adverse local tissue reaction, aseptic loosening/osteolysis, periprosthetic fracture, subsidence	Moderate for ARMD/ALTR, loosening, and fracture Low for all other local responses	Bursitis/pain, elevated serum chromium concentration, elevated serum cobalt concentration, pulmonary embolism, revision	Moderate for serum concentrations, and revision Low for all other local responses
Orthopedic Spine (4 human studies, 3 SRs, 1 RCT)	Adjacent segment degeneration, Adverse local tissue reaction, migration, Radiolucency, Subsidence	Low	Reoperation, Revision	Low

ALTR: adverse local tissue reaction; ARMD: adverse local tissue reaction; NRCS: nonrandomized comparative study; RCT: randomized controlled trial; SAS: single arm study; SR: systematic review

Cardiovascular - Filter

The literature search identified 1 human single arm study[1]. For further information see Table 4 in Appendix D.

Local Responses/Device Events (human studies)

This retrospective single arm study evaluated short-term (6-month) outcomes of prophylactic placement of inferior vena cava (IVC) filters to prevent pulmonary embolism in 25 female gynecological cancer patients with a mean age of 56 years.

Eleven patients underwent attempted filter retrieval at the end of their cancer treatment; filters could not be removed from two patients due to excessive tilt. Sixteen patients still had indwelling IVC filters at 6-month follow-up with one patient exhibiting asymptomatic filter leg protrusion less than 3 mm outside the filter wall. No other complications were observed.

Systemic Responses

None examined.

Overall Quality of Evidence

Only one single-arm study with small sample size and short follow-up period investigated local responses. A manufacturer provided technical assistance with the study, introducing a potential bias. No studies investigated systemic responses. The strength of evidence regarding local and systemic responses was rated as very low.

Cardiovascular - Pacemaker Leads

The literature search identified 1 human single arm study[2]. For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

This retrospective single arm study evaluated long-term (14-year) outcomes of transvenous pacemaker implantation with CoCr pacemaker leads in seven pediatric patients. Patients were 42.9% female, with a mean implantation age of 3 days.

Patients experienced lead traction necessitating lead advancement, dysfunction and defects requiring replacement after two to four years, and attempted removal in five (failed removal in two patients) as a result of dysfunction and a need to switch to epicardial leads; one of these patients experienced malposition after 12 years due to progressive mitral valve regurgitation. Vascular occlusion occurred in two patients 6 and 8 years after implantation, and thrombosis occurred in the same two patients 7 and 11 years after implantation.

Systemic Responses

None examined.

Overall Quality of Evidence

Only one retrospective, single-arm study with a very small sample size investigated local responses. No studies investigated systemic responses. The strength of evidence regarding local and systemic responses was rated as very low.

Cardiovascular - Stents

We included 14 human studies (13 SRs[3-15] and 1 nonrandomized comparative study[16]). For further information see Table 6 in Appendix D.

Local Responses/Device Events (human studies)

Myocardial infarction - Ten SRs[3-5,8-14] and one prospective nonrandomized comparative study[16] examined myocardial infarction in patients who received CoCr stents compared to patients who received stents without CoCr or other treatments (e.g. coronary artery bypass graft (CABG) or percutaneous old balloon angioplasty (POBA)). No significant differences were found when CoCr containing stents were compared to other metallic stents or other treatments such as CABG or POBA[3,4,16]. When a CoCr containing stent was compared to a bioresorbable stent[5], patients with the CoCr containing stent showed a lower risk for MI (p=0.008). When a CoCr containing stent was compared to a drug coated balloon[11], there was almost a statistically lower chance of MI with a drug coated balloon (p=0.06). When a CoCr drug eluting stent was compared to optimal medical therapy (OMT)[13], there was a lower risk of MI with CoCr.

Target lesion/vessel revascularization - Ten SRs[3-6,8-12,14] and one prospective nonrandomized comparative study[16] examined target lesion/vessel revascularization or failure in patients who received CoCr stents compared to patients who received stents without CoCr or other treatments (e.g., CABG or POBA). No significant differences were found when CoCr stents were compared to other drug-eluting stents, bare metal stents and other treatments[3,4,8,9,11,12,14,16]. In a study comparing a CoCr stent to a bioresorbable stent[5], patients treated with the bioresorbable stent showed a significantly higher risk for target lesion failure and target lesion revascularization compared to the CoCr stent. In studies comparing drug-eluting stents to bare metal stents[6,10], there was a lower risk for target vessel revascularization for all drug eluting stents (CoCr and non-CoCr) compared to bare metal stents. Furthermore, Poder et al.[10] reports an even further reduction in the risk of target vessel revascularization in CoCr stents compared to platinum-chromium stents.

Thrombosis - Eight SRs[4-6,8,10-12,14] and one prospective nonrandomized comparative study[16] examined definite/probably stent thrombosis in patients who received a CoCr stent compared to stents without CoCr or other treatments. No statistically significant difference was observed in one SR[3] and one prospective study[16]. In 3 SRs[5,6,14], when stents with CoCr were compared to other drug-eluting stents, bare metal stents and other treatment options, CoCr stents were found to statistically reduce thrombosis. One study[11] compared CoCr stents to a drug coated balloon and found significantly less thrombosis for the drug-coated balloon compared to a CoCr stent (p=0.04). Lastly, in one study[10], the CoCr stent resulted in significantly less late thrombosis (>30 days) and very late thrombosis (>1 year) compared to other drug-eluting stents.

Cardiac death - Six SRs [4-6,8,9,12] and one prospective study[16] examined cardiac death in patients who received a CoCr stent compared to patients who received a CoCr stent compared to stents without CoCr or other treatments. Five studies[4,8,9,12,16] found no significant differences in cardiac death when comparing patients who received a CoCr stent, compared to other groups. Another study[6] found no significant difference between CoCr stents and non-CoCr stents.

Reinfarction - One SR[6] examined reinfarction in patients who received various drug eluting stents, as well as bare metal stents. Patients who received drug-eluting stents of any kind had a significantly lower risk of reinfarction compared to patients who received a bare metal stent. The risk was more significant for CoCr stents compared to bare metal stents.

Restenosis - Two SRs[7,11] examined restenosis in patients who received open and closed stents, as well as patients treated with drug coated balloons. In the study looking at open and closed stents[7], no significant difference in restenosis was observed in restenosis or severe restenosis. In the study comparing drug-eluting stents to drug-coated balloons[11], no significant difference was observed.

Evagination - One SR[15] examined coronary evaginations following deployment of various drug eluting stents. Major evaginations occurred frequently at all time points in SES (26%) and were rarely seen in EES (3%) and ZES (2%, p=0.003).

Systemic Responses

Mortality - Six SRs[3,6,8,10,11,13] examined all-cause mortality for procedures involving CoCr stents compared to stents without CoCr or other treatments (e.g., CABG or POBA). None of the SRs showed a statistical difference specific to CoCr stents. While not significant, one study[10] showed a downward trend with all-cause mortality with second generation drug-eluting stents, particularly the CoCr-EES. Another study[6] showed that drug-eluting stents reduced the risk of all-cause mortality compared to bare metal stents.

Stroke - Two SRs[3,7] reported no significant differences in stroke in patients who received a CoCr stent compared to other stents or other treatments.

Overall Quality of Evidence

Fourteen studies (13 SRs, 1 prospective nonrandomized comparative study) examined local host responses for procedures involving coronary stents. Common local host responses included target lesion/vessel revascularization or failure, definite/probable stent thrombosis, myocardial infarction, cardiac death, reinfarction, restenosis, and coronary evaginations. Seven studies, all SRs, examined systemic responses, including stroke and all-cause mortality. All responses included large patient samples with some inconsistencies with significance across studies. The strength of evidence regarding local and systemic responses was rated as moderate.

Cardiovascular - Valve

We included 18 human studies (16 SRs[17-32] and 2 RCTs[33,34]). For further information see Table 7 in Appendix D.

Local Host Responses

Six studies including five SRs[17,22-24,27] and one randomized controlled trial (RCT)[33] examined local complications for procedures involving CoCr valve prostheses compared to valves composed of other metals (e.g., nitinol). Most studies examined a CoCr balloon expanding valve prosthesis (e.g., Sapien, Sapien 3, and Sapien XT) compared against a nitinol self-expanding valve (e.g., CoreValve, Evolut R, ACURATE Neo, Lotus). The other included study compared Carpentier-Edwards pericardial valve prostheses (CoCr frames) to the Hancock II and Mosaic bioprostheses (non-metallic frames). One RCT[33] suggested greater incidence of structural valve deterioration for patients receiving the Edwards Sapien XT over Medtronic CoreValve devices. Another study[27] discussed lower incidence of local adverse events (e.g. paravalvular leak ≥ 3, valve malposition), however, the authors did not provide any tests of statistical significance. A SR[17] saw lower incidence of life-threatening bleeding with the nitinol-based Evolut R as compared to the CoCr based Sapien 3 valve. The remaining two SRs examining a Sapien valve prosthesis were both written by the same author.[22,23] The SR comparing Sapien 3 to nitinol based ACURATE Neo found significantly fewer paravalvular leak events (both mild and moderate to severe). However, results suggested no difference in moderate to severe paravalvular leaks and significantly less mild paravalvular leaks (PVLs) with Lotus as compared to Sapien 3. Finally, the SR comparing Carpentier-Edwards pericardial bioprostheses to Hancock II and Mosaic only reported on freedom from SVD at 10 and 15 years without any description of statistically significance. All remaining outcomes for local adverse events suggested no differences between CoCr and other materials.

The next two included studies were both SRs with a network meta-analysis (NMA) containing both direct and indirect comparisons against CoCr based balloon expanding valves. One SR[18] examined CoCr balloons, nitinol based self-expanding valves, and surgical aortic valve repair (SAVR). When comparing balloon expanding valves to self-expanding valves, paravalvular leak events (30-day) had lower incidence with balloon expanding valves, while the remaining AEs displayed no differences. As for balloon expanding valves versus SAVR, atrial fibrillation (30-day and 1-year) and major bleeding (30-days) outcomes were favored by balloon expanding valves, whereas major vascular complications (30-days) and PVLs (30-days) were favored by SAVR. All other outcomes showed no differences between groups. The other SR[25] compared each individual device rather than bundling by product category (e.g. balloon-expanding device and self-expanding device). The CoCr devices of interest were the Sapien 3 and Sapien XT, and all other devices were non-CoCr. All comparisons for life-threatening bleeding portrayed no differences between groups. For moderate to severe prosthetic valve regurgitation, Sapien 3 was favored over Sapien XT (both CoCr), Evolut R/Evolut Pro was favored over Sapien XT, Sapien 3 was favored over CoreValve, and all remaining comparisons showed no difference.

One included SR[20] included direct comparisons between MitraClip and surgical mitral valve repair (SMVR). The only examined local AE was recurrent 3+ mitral regurgitation, measured at 30-day, 1-year, and >3 year follow-ups with all three timepoints favoring SMVR over MitraClip. Although SMVR was favored in all cases, authors noted how patients undergoing TMVR with MitraClip were more likely to be older (MD: 5.27, 95% CI: 2.20 to 8.34), have a higher Euroscore rating (MD: 8.79, 95% CI: 5.80 to 11.77), were more likely to have a previous PCI before therapy (OR: 2.44, 95% CI: 1.62 to 3.68), and were more likely to have a previous CABG before therapy (OR: 4.77, 95% CI: 2.68 to 8.49).

Two included studies compared surgical implantation of a CoCr device to optimal medical therapy (OMT). One SR[21] compared MitraClip to OMT. The only examined local AE (myocardial infarction) displayed no differences between groups. The other study, an RCT[34], was a small study (28 patients total) and noted that neither patients receiving caval vein implantation with Sapien XT nor patients receiving OMT alone had any major vascular complications at 3-month follow-up.

The remaining five included studies were all SRs that only included patients receiving a CoCr valve prosthesis. One SR[30] directly compared Sapien 3 and Sapien XT up to 30-days. Most outcomes favored Sapien 3, including major/life-threatening bleeding, major vascular complications, and moderate to severe PVL. Only one outcome, myocardial infarction, showed no differences between groups. The other two SRs including Sapien devices included unique comparisons. The SR[26] found no differences for all local AEs (e.g., life-threatening bleeding, major vascular complications, non-fatal myocardial infarction, and valve dysfunction) between patients with versus without a balloon aortic valvuloplasty and a Sapien 3 or Sapien XT device up to 30 days. The SR[31] included patients with implanted Sapien or Sapien XT aortic valves, and results were grouped by transfemoral (TF) versus transapical (TA) approaches. The local AE of life-threatening bleeding showed no difference between approaches. The remaining two SRs examined patients receiving a MitraClip device. One SR[28] found no differences in cumulative primary safety endpoint (device embolism and single leaflet device attachment) or incidence of mitral regurgitation

grade ≤ 2 for patients with functional mitral regurgitation (FMR) versus degenerative mitral regurgitation (DMR) up to 1 year. The other SR[29] compared patients with and without atrial fibrillation. Between 1 and 12 month follow-up, patients without atrial fibrillation had less major adverse cardiac events than patients with atrial fibrillation.

Systemic Responses

Seven studies including six SRs[17,22-24,27,32] and one randomized controlled trial (RCT)[33] examined systemic responses for procedures involving CoCr valve prostheses compared to valves composed of other metals (e.g., nitinol). One RCT[33] saw no differences for all systemic responses. Authors noted how female sex (HR: 0.58, 95% CI: 0.38 to 0.89, p=0.011) was a predictor of lower mortality at 5 years, whereas higher STS score in % (HR 1.11, 95% CI: 1.06 to 1.15, p<0.001) and higher systolic pulmonary artery pressure in mmHg (HR 1.03, 95% CI: 1.01 to 1.04, p=0.001) were predictors of higher mortality at 5 years. The study[27] discussed lower incidence of systemic responses for Sapien 3 compared to first-generation Sapien and CoreValve devices, however, no statistical tests were performed. A SR[17] found favorable postoperative pacemaker implantation (PPI) and all-cause mortality outcomes for Sapien 3 over Evolut R; all remaining systemic responses had no differences between groups. The remaining two SRs examining a Sapien valve prosthesis[22,23]. The SR comparing Sapien 3 to nitinol based ACURATE Neo found significantly lower mortality and PPI for ACURATE Neo. When comparing Sapien 3 and Lotus valves, cerebrovascular events and PPI events had lower incidence with Sapien 3 than Lotus valves. One SR[24] comparing Carpentier-Edwards pericardial bioprostheses to Hancock II and Mosaic reported survival analyses for early mortality with no comparisons of statistical significance. The other SR[32] found no differences for all comparisons (Carpentier-Edwards pericardial vs. Carpentier-Edwards porcine prostheses, Carpentier-Edwards pericardial vs. stentless prostheses, and Carpentier-Edwards pericardial vs. mechanical prostheses) examining operative mortality, overall mortality, and reoperation rate outcomes.

The next two included studies were both SRs with a network meta-analysis (NMA) containing both direct and indirect comparisons against CoCr based balloon expanding valves. One SR[18] examined CoCr balloons, nitinol based self-expanding valves, and surgical aortic valve repair (SAVR). When comparing balloon expanding valves to self-expanding valves, PPI (30-day and 1-year) had lower incidence with balloon expanding valves, while the remaining AEs displayed no differences. As for balloon expanding valves versus SAVR, acute kidney injury (30-day) showed lower incidence with balloon expanding valves, while PPI (30-day, 1-year) had lower incidence with SAVR. All other outcomes showed no differences between groups. The other SR[25], comparing Sapien XT and Sapien 3, had no differences for all mortality and PPI outcomes, except one comparison showing Sapien XT with lower PPI incidence than CoreValve.

Two included SRs had direct comparisons between MitraClip and surgical mitral valve repair (SMVR). One SR[20] examined mortality, measured at 30-day, 1-year, and >3 year follow-ups. At 30-days, there was no differences between groups, however, SMVR was favored over MitraClip at 1 year and >3 years signifying importance in the long-term outcomes. Although SMVR was favored at 1-year and >3 years, authors noted how patients undergoing TMVR with MitraClip were more likely to be older (MD: 5.27, 95% CI: 2.20 to 8.34), have a higher Euroscore rating (MD: 8.79, 95% CI: 5.80 to 11.77), were more likely to have a previous PCI before therapy (OR: 2.44, 95% CI: 1.62 to 3.68), and were more likely to have a previous CABG before therapy (OR: 4.77, 95% CI: 2.68 to 8.49). The other SR[19] favored SAVR over MitraClip at 30-days for PPI outcomes, however, there was no difference at 1 year, 2 year, and 5 year time points.

Two included studies compared surgical implantation of a CoCr device to optimal medical therapy (OMT). One SR[21] compared MitraClip to OMT. MitraClip was favored over OMT for all-cause mortality, hospitalization due to heart failure, need for heart transplantation/left ventricular assist device, and unplanned mitral valve surgery. The authors' subgroup analyses showed that significant results for all-cause mortality was driven by observational trials (HR 0.39, 95% CI: 0.26 to 0.59) since RCTs displayed a non-significant difference (HR 0.80, 95% CI: 0.45 to 1.42). Stroke outcomes displayed no differences between groups. The other study, an RCT[34], noted no differences between caval vein implantation with Edwards Sapien XT and OMT for hospitalization due to heart failure and mortality outcomes.

The remaining five included studies were all SRs that only included patients receiving a CoCr valve prosthesis. One SR[30] directly compared Sapien 3 and Sapien XT up to 30-days. All outcomes favored Sapien 3, including acute kidney injury, mortality, and stroke. The other two SRs including Sapien devices included unique comparisons. The SR[26] compared found no differences for all local AEs (e.g., mortality, hospitalization, new-onset dialysis, PPI, and stroke) between patients with versus without a balloon aortic valvuloplasty and a Sapien 3 or Sapien XT device. The SR[31] included patients with implanted Sapien or Sapien XT aortic valves, and results were grouped by transfemoral (TF) versus transapical (TA) approaches. Mortality (30-day and 1-year) and AKI favored the TF approach, while PPI and stroke outcomes saw no differences between groups. One SR[28] found no differences in incidence of mortality for patients with FMR versus DMR up to 1 year. The study did find less mitral valve re-interventions for patients with FMR. The other SR[29] compared patients with and without atrial fibrillation. Between 1-

and 12-month follow-up, patients without atrial fibrillation had less mortality events, however, stroke events were similar between groups.

Overall Quality of Evidence

Sixteen studies (14 SRs, 2 RCTs) examined local host responses for procedures involving coronary stents, whereas eighteen studies (16 SRs, 2 RCTs) examined systemic responses. Common local host responses included various types of vascular complications, while common systemic responses included mortality rates, PPI, stroke, and other types of events with an indirect relationship to device implantation. Both local and systemic responses included large patient samples with some inconsistencies by type of event across studies, usually driven by comparison type, follow-up, or presence of factors that may influence the outcome responses. The strength of evidence regarding local and systemic responses was rated as moderate.

Dental/ENT

The literature search identified 2 human studies (2 single arm,[35,36]). For further information see Table 8 in Appendix D.

Local Responses/Device Events (human studies)

Both studies are comparative by design but are considered single arm by virtue of having an implant containing CoCr components in both arms of each study. Both studies examined outcomes after CoCr dental implant (fixed partial denture[36] and stock (i.e., not custom) temporomandibular joint reconstruction[35]). Follow-up ranged from 1 to five years, with a sample size of 50 to 70 patients (58% to 66% female), aged 51 to 59 years.

Implant failure occurred in 2% to 18% of cases considered. Failures occurred as a result of CoCr hypersensitivity, malocclusion/dislocation/loosening, and heterotopic bone formation.

Localized neurological issue was reported in one study[35], with all cases resolving spontaneously.

Marginal bone loss of 0.005 mm to 0.086 mm as well as bleeding on probing as indicative of soft tissue inflammation were reported in one study[36], indicating that abutment-level CoCr screw-retained fixed partial dentures may have higher stability within 1 year of implantation.

Systemic Responses

None examined.

Overall Quality of Evidence

Two studies (1 prospective, 1 retrospective), both relatively small, examined local host responses. No studies examined systemic responses. Both studies reported failure and loosening. The strength of evidence regarding local and systemic responses was rated as very low.

Gastric

The literature search identified 1 human, single-arm study.[37] For further information see Table 9 in Appendix D.

Local Responses/Device Events (human studies)

Phillips et al.[37] examined outcomes 5 years after placement of a gastric band. The study enrolled 303 patients, 231 of which completed the 5-year follow-up. Band slippage occurred in 21 (6.9%) of patients. Four (1.3%) patients experienced erosion into the gastrointestinal tract. Seven (2.3%) patients experienced gastric dilation. Five (1.6%) patients experienced vomiting, and 5 (1.6%) suffered a hiatal hernia.

Systemic Responses

None examined.

Overall Quality of Evidence

One moderately sized, single-arm study examined local responses. The product manufacturer sponsored the study and was involved in the study design and execution, putting the study at a high risk of bias. No studies examined systemic responses. The strength of evidence regarding local and systemic responses was rated as very low.

Intracranial stents

We included 8 human study SRs[38-45]). For further information see Table 10 in Appendix D.

Local Responses/Device Events (human studies)

In our review, we included eight total SRs that examined local biocompatibility-related adverse events (AEs) occurring after the surgical implant of at least one intracranial stent made of CoCr. Unfortunately, no randomized controlled trials or nonrandomized comparative studies met inclusion criteria, however, the included SRs captured comprehensive samples of single-arm studies. Four included SRs[39,42,44,45] reported rates by device type, including intracranial stents made of either CoCr or nitinol. One SR[39] examined 911 patients from 8 single-arm studies receiving a CoCr-based flow diverter stent, the Pipeline Embolization Device (PED) with shield technology, or a nitinol-based stent, the Derivo Embolization Device (DED). Enrolled patients were majority female with a wide age range (17 to 82 years) and followed over a median time of 8.24 months. All examined local AEs showed no differences between pooled rates from single-arm studies, however, PED with shield technology consistently showed lower incidence for both morbidity and ischemia rates. Occlusion rates were also similar between groups, however, DED greatly improved between 6- and 12-month follow-up (78.9% to 87.8%) while PED had similar rates (82.7% and 83.2%).

Another SR (Cagnazzo et al. 2019[42]) included 27 single-arm studies that included five different types of flow diverter stents. Two of the stents (PED and Surpass) were made of CoCr while the other three (Flow-Redirection Endoluminal Device [FRED], Silk, and p64) were made of nitinol. Similarly, the patients were majority female and included a wide age range (18 to 82 years). No total patient counts were given in the review, however, the authors noted that the majority of stents (64%) were CoCr-based PED. The only reported AE was treatment-related complications, and rates were similar among all types of devices. Occlusion rates were similar among groups; FRED had the lowest rate (73.8%) while PED was highest (87.3%).

The largest SR (Zhou et al. 2017[44]) enrolled patients receiving one of the eight types of stents: PED (CoCr-based), PED Flex (CoCr-based), Silk (nitinol-based), Surpass (CoCr-based), p64 (nitinol-based), FRED (nitinol-based), Woven Endobridge (WEB) (nitinol-based), or Tubridge (nitinol-based). The authors divided complications into the categories of minor, intermediate, and severe based on the authors' judgments. Both minor and severe complications had low frequency for each type of device, but intermediate complications had very high frequency (34.7%) in the Surpass group, moderate frequency for PED and Silk (13.7% and 15%, respectively), and none observed for FRED. All remaining examined devices were all combined in a column labeled Other and displayed moderate frequency (12%). Lastly, a SR[45] only reported occlusion rates for 2,263 patients receiving PED, Silk, FRED, Surpass, or Tubridge stents. Occlusion, a favorable outcome showing satisfactory dissolution of an intracranial aneurysm, was highest for PED (relative risk [RR] 0.79, 95% confidence interval [CI] 0.74 to 0.85) and lowest for FRED (RR 0.58, 95% CI: 0.41 to 0.74). All other devices had point estimates between 0.70 and 0.75.

One SR[40] contained 15 single-arm studies examining 213 unique intracranial aneurysms. The samples were extremely different; PED was used for 185 aneurysms while other flow diverter stents were used for 28 stents. This major difference between groups limits the comparability of the rates for occlusion and treatment-related complications. Also, the lack of information on types of stents in the 'other' group limits the ability to ascertain whether events were related to a specific material or not. Both outcomes were similar between groups; the occlusion rate was 82% for PED and 90% for other devices, while treatment-related complications had an incidence of 15% for PED and 12% for all other devices.

The three remaining SRs [38,41,43] only examined patients receiving a PED or PED Flex device for intracranial aneurysms. One SR[38] examining 145 patients over 3 to 18 months had a low rate (2.16%) of re-rupture causing an intracranial hemorrhage, moderate rate (16.5%) of any complication, and high success (87.5%) with occlusion. A univariate logistic regression analysis showed a significant association of aneurysm size and re-rupture rate, favoring smaller aneurysms over larger aneurysms. Aneurysm morphology, treatment time, and treatment method had no effect on re-rupture rate. A SR[41] with 879 patients (935 intracranial aneurysms) saw low rates of major complications, major stroke, minor transient ischemic attack (TIA), and symptomatic intracranial hemorrhage. Total complication rates after 30-day follow-up had moderate incidence (9.8%). Lastly, a SR[43] with 1,556 patients receiving a PED had low incidences for all examined local AEs.

Systemic Responses

In our review, five SRs[38,39,41,43,44] examined only one systemic host response: mortality. Two SRs[39,44] provided some insight into mortality rates by type of device. In Li et al. (2021)[39] both nitinol-based DED and CoCr-based PED with shielding technology had low rates of 1.3% and 0.8% respectively, with no significant differences between groups (p=0.410). The other SR[44] had low rates for all types of devices as well. Nitinol-based Silk had the highest rate with 2.8% and FRED had the lowest with 0%.

The other three SRs[38,41,43] only examined CoCr-based PED devices. The highest mortality rate was reported in the SR by Foreman et al. (2021)[38] at 7.91%, likely due to the long follow-up range (3 to 18 months). The SR by Bhatia et al. (2019)[41] reported mortality within 30 days at 1.8%. Similarly, Texakalidis et al. (2017)[43] had a low mortality rate with 2.1%.

Overall Quality of Evidence

Eight studies (8 SRs) examined local host responses for aneurysm occluding procedures involving intracranial stents, whereas five studies (5 SRs) examined systemic responses. Common local host responses included ischemic attacks and general complications, while the only reported systemic response was mortality. Both local and systemic host responses were limited by study design since only reviews of single-arm studies were available as evidence. Sample sizes were robust for both local and systemic host responses and reported point estimates were consistent across studies when examining the same type of AE. The strength of evidence regarding local and systemic responses was rated as low.

Orthopedic – Bone and Joint

The literature search identified 19 human studies (9 SRs[46-54], 6 RCTs[55-60], 1 nonrandomized comparative study [61], 3 single arm studies[62-64]). For further information see Table 11 in Appendix D.

Local Responses/Device Events (human studies)

Sixteen studies, including 6 SRs,[47-50,52,54] 6 RCTs,[55-60] 1 nonrandomized comparative study,[61] and 3 single arm studies[62-64] examined local responses for procedures involving CoCr joint or fixation implants.

Adverse reaction to metal debris (ARMD)/Adverse local tissue reaction (ALTR) - One SR[50] and 2 RCTs[55,58] investigated ARMD/ALTR, in hip arthroplasty patients. In a study including over 18,000 patients, Laaksonen et al.[50] reported median (range) rates of revision due to ALTR of 16.4% (5.3-27.0) in resurfacing patients and 39% (range not reported) in total arthroplasty patients at 6-7 years follow-up. Higgins et al.[55] reported 10/34 (29.4%) of metal-on-metal (MoM) and 7/36 (19.4%) of ceramic-on-metal (CoM) hips were revised due to ARMD. Engh et al.[58] reported 1/196 (0.5%) MoM and 0/194 CoM hips experienced adverse reactions.

Aseptic loosening/osteolysis - Thirteen studies, including 5 SRs,[47-49,52,54] 4 RCTs,[56,57,59,60] 1 NRCSs,[61] and 3 [62-64] examined aseptic loosening and/or osteolysis. These studies included ankle, elbow, hip, knee, shoulder, and wrist arthroplasties as well as fixation. Reported rates were 0-1% in hip,[49,57,59,60] knee,[48,56] and wrist[64] patients, 2 – 4% in ankle[54] and elbow[52] patients, and 0.7 – 34.2% in shoulder[47,62,63] and fixation[61] patients.

Periprosthetic fracture - Seven studies, including 2 SRs,[47,49] 3 RCTs,[55,57,60] and 2 single arm studies[62,63] investigated periprosthetic fracture in hip and shoulder arthroplasty patients. Reported rates were 0 – 2% in hip[49,55,57,60] patients and 0.1 – 15% in shoulder[47,62,63] patients.

Subsidence - One SR[54] including over 2,500 total ankle replacements reported a subsidence rate of 2.2%. One RCT[55] comparing 34 MoM and 36 CoM hip arthroplasties reported 0 incidents of subsidence in the MoM group and 1 (2.8%) case in the CoM group.

Systemic Responses

Fourteen studies, including 7 SRs,[46,47,50-54] 4 RCTs,[55-58] 1 nonrandomized comparative study,[61] and 2 single arm studies[62,63] examined systemic responses.

Pain/bursitis - One RCT[56] and 1 nonrandomized comparative study [61] investigated pain/bursitis. Kim et al.[56] reported that 26/99 (26%) of CoCr knee arthroplasty patients and 27/99 (27%) of oxidized zirconium knee arthroplasty patients experienced some pain, but no patients experienced severe pain. Collado et al.[61] reported that 12/28 (43%) of patients whose osteotomies were fixed with a plate-cable grip system experienced pain or bursitis.

Elevated serum chromium and cobalt concentration – Three studies, including 1 SR[46] and 2 RCTs[57,58] investigated serum chromium and cobalt concentration. Banci et al.[46] compared serum concentrations in patients with CoCr knee implants that were either uncoated or coated with ceramic. At one year, serum chromium concentration was 0.81 for uncoated implants and 0.52 for coated implants. The difference was not significant (p=0.26) . Serum cobalt concentration was 0.38 for uncoated implants and 0.35 for coated implants (p=0.64).

Two RCTs, Borgwardt et al.[57] and Engh et al.[58] compared hip replacements with CoCr femoral heads (MoM) to replacements with ceramic heads (CoM). Borgwardt et al. reported chromium concentration in MoM patients (means 3.21 - 7.01) was much

higher than that in CoM patients by 6 months (0.19 - 3.61) (p<.001). Engh et al. did not find a difference in chromium concentration between MoM (mean 0.95) and CoM (1.13) at up to 5 years follow-up.

Pulmonary embolism – Aibinder et al.[62] reported a rate of pulmonary embolism of 0.03 – 0.05% in a study of over 8,500 total shoulder arthroplasty patients.

Revisions/Removal - 10 studies, including 6 SRs,[47,50-54] 2 RCTs,[55,58] 1 nonrandomized comparative study,[61] and 1 single arm study[63] investigated revision rates. Prissel and Roukis[54] reported a revision rate of 10.7% at 5 years in a SR of approximately 2,500 ankle arthroplasties. In a SR of over 700 elbow arthroplasties, Heijink et al.[52] reported revisions rates ranging from 0% - 29% at a mean follow-up of 45 months. In a small study of hip osteotomy fixation devices, Collado et al.[61] reported a removal rate of 14% at approximately 5 years follow-up. Three studies of hip arthroplasties[50,55,58], including a SR of over 18,000 patients, reported revision rates from 3% - 38% at 4 to 7 years follow-up. Two studies of knee arthroplasties[51,53] reported revision rates of 3.4% and 5.2% at 2 – 10 years follow-up. Two studies of shoulder arthroplasties[47,63] reported revision rates of 1.7% - 5.4% at 3.75 – 5 years follow-up.

Overall Quality of Evidence

16 studies (6 SRs, 6 RCTs, 1 nonrandomized comparative study, 3 single arm studies) examined local host responses to joint arthroplasties or joint fixation. 14 studies (7 SRs, 4 RCTs, 1 nonrandomized comparative study, 2 single arm studies) examined systemic responses. Commonly reported local responses include adverse reactions to metal debris, aseptic loosening, periprosthetic fracture, and subsidence. Investigated systemic responses include serum chromium and cobalt concentrations and revision. Responses included large patient samples with variation in reported rates. The strength of evidence regarding ARMD, aseptic loosening, periprosthetic fracture, serum concentrations, and revision rate were rated as moderate. The strength of evidence regarding subsidence, pain, and pulmonary embolism was rated as low.

Orthopedic - Spine

4 human studies (3 SRs,[65-67] and 1 RCT,[68]). For further information see Table 12 in Appendix D.

All studies compared one- or two-level total disc replacement (TDR) systems with and without CoCr components to anterior cervical discectomy and fusion (ACDF). Follow-up ranged from 12 to 84 months (1 to 7 years), with a sample size of 136 to 1,408 patients with CoCr TDR, aged 38.7 to 46.3 years. Only one study[67] reported patient sex, which was 44.8% to 49.1% female.

Local Responses/Device Events (human studies)

One RCT[68] investigated local responses.

Adjacent segment degeneration (ASD) – TDR with a CoCr implant yielded less ASD at the level superior to the index surgery than ACDF (p<0.01). No difference was found in the rate of ASD at the inferior level (p>0.25).

Adverse local tissue reaction – Two of 136 (1.5%) patients required implant removal due to ALTR.

Chromium levels – Chromium levels slightly decreased between 3 and 60 months postop. The mean level at 60 months was 0.31 µg/L.

Cobalt levels – Cobalt levels steadily decreased between 3- and 60-months post–op. The mean level at 60 months was 0.21 µg/L.

Migration – Migration occurred in 1.4% of TDR patients, with no cases in the ACDF group.

Radiolucency – Radiolucency was noted in 14.3% of TDR patients and 7.0% of ACDF patients (p>0.20).

Subsidence – Subsidence also occurred in 1.4% of TDR patients, with no cases in the ACDF group.

Systemic Responses

All 4 studies[65-68] reported rates of reoperation or implant removal with rates of secondary procedures associated with CoCr TDRs being comparable or lower than those of ACDF or non-CoCr TDRs. Study authors indicated that depending on design, TDR with CoCr components – which also happen to have semi-constrained designs when compared with non-CoCr non-constrained designs – may reduce secondary surgery rates at index and/or adjacent levels, as well as rates of reoperation, revision, and supplemental fixation when compared with ACDF.

Causes of secondary procedures were not consistently reported but may involve adjacent spine level disease, device failure, or unknown reasons.

Overall Quality of Evidence

One moderately sized study (1 RCT) examined local host responses to spine implants. 4 studies (3 SRs, 1 RCT) examined reoperation/revision rates but no other systemic responses. The strength of evidence regarding local and systemic responses was rated as low.

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 CoCr material that occurred between February 2007 and May 2022. However, these reports did not have enough information to directly associate patient harm with the biocompatibility of CoCr.

Accident Investigations

Search Results:

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

Cobalt: 51 Targets, 0 Applicable

Most of the targets pertained to radioactive cobalt used for radiation therapy. The remainder was in literature searches, MAUDE searches, or inventory spreadsheets.

Chromium: 31 Targets, 0 Applicable

These targets mainly pertained to chrome-plated devices or chemical analysis results during investigations of residues in surgical instrument trays.

Stent: 394 Targets, 0 Applicable

Stents are often made from CoCr alloys. ECRI has investigated many types of stents, including coronary, vascular, biliary, esophageal, and renal, some of which are metal and others plastic. Because "stent" can be used as a verb, many of these targets result from quotations or summaries of operative procedures in which "stent" was used, but the investigation did not specifically involve a stent. For example, most of our PTCA device investigations involve balloon entrapment/rupture or guidewire entrapment/fracture during stent placement.

"*Stent*" and "*metal*": 63 Targets, 0 Applicable

This search attempted to single out metal stents, most of which are blood vessel stents. One CoCr stent was identified: An Abbott Alpine Xience Alpine Stent Delivery System under investigation for failure of the stent delivery catheter. The investigation was unrelated to biocompatibility.

CoCr: 9 Targets, 0 Applicable

These targets involved product literature from the investigation of the broken Xience Alpine Stent Delivery Catheter and an investigation of Zimmer orthopedic implants, some of which had CoCr components, in which the packaging was exposed to water during in a storage room.

Heart valve: 107 Targets, 1 Applicable

Many of these targets pertain to the native "heart valve" and are unrelated to implants. Other targets are used in describing heart valve function as it relates to circulation through the heart. Twelve of these targets were investigations of St. Jude Medical or Carbomedics mechanical pyrolytic carbon heart valves for either leaflet fracture or leaflet impingement. These valves contained no metal components. Three targets were investigations of Edwards-Carpentier tissue valves with CoCr valve frames, in which leaflets lost coaptation over time. Examination of the leaflets/cusps, development of non-uniform calcification leading to deformed leaflet margins resulting in incomplete closure. While it is unlikely, it may be possible that the CoCr frame contributed to the changes in the fixed tissue leaflets.

TAVR: 19 Targets, 0 Applicable

These targets pertain to two investigations of fatalities during attempted placement of an Edwards Sapien 3 TAVR (Transcatheter Aortic Valve Replacement). In one case, the valve deployed in the wrong location and in the other case the valve deployed retrograde during balloon expansion and then would not release from the delivery catheter. The valve stent assembly is made from CoCr. Biocompatibility was not at issue in these cases.

Heart Valve Prosthesis: 1 Target, 0 Applicable

Investigation of an Edwards 6900P Mitral Valve suture coaptation of a leaflet. The valve frame is CoCr. Biocompatibility was not a factor in this investigation.

Zimaloy: 2 Targets, 0 Applicable

Zimaloy is one of the oldest CoCr alloys used in medical/dental applications. The targets related to items in an inventory list associated with water damaged Zimmer products. None of these items were implanted.

CoCr alloys are widely employed in orthopedic implants and fixation components. ECRI has occasionally investigated the failure of these items; however, the requests have been rare. The investigation generally focuses on the failure mechanism which is determined by microscopic morphology of the failure surfaces. Metal analysis is not performed. Therefore, in most cases, the alloy is not known to us. Most of these following targets involve reference materials, documents related to implant tracking guidance, or investigations of medical devices that were used during a joint replacement surgery (e.g., anesthesia machine, electrosurgical unit). None of ECRI's investigation of orthopedic implants related biocompatibility.

"*knee*" and "*implant*": 82 Targets, 0 Applicable

"*knee*" and "*prosthesis*": 45 Targets, 0 Applicable

Three of the targets involved failure analysis of explanted total knee prostheses. One pertained to a fractured UHMPE tibial plateau spacer that was severely damaged by chunks of excess bone cement found embedded in the spacer. The other two involved metal fracture; however, the product literature did not specify the alloy.

"*hip*" and "*implant*": 61 Targets, 0 Applicable

"*hip*" and "*prosthesis*": 48 Targets, 0 Applicable

A Wright Medical bipolar hip implant was examined due its having dislocated during an episode of accidental hyperflexion. It employed a UHMWPE acetabular cup (i.e., not a metal on metal).

"*shoulder*" and "*implant*": 62 Targets, 0 Applicable

ECRI has not examined a shoulder implant or prosthesis.

"*pedicle screw*": 22 Targets, 0 Applicable

ECRI has not examined explanted pedicle screws.

ECRI Problem Reports

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

Healthcare Technology Alerts

Search Results: The search returned 249 manufacturer- and regulatory-issued alerts describing problems with CoCr related devices, summarized in Table 2. There are some notable alerts including migrating metallic pieces (replacement heart valve), serious complications such as embolization and thrombosis (intravascular/cardiovascular filters), compromised biological safety (fixation rods), and elevated biotoxin levels with residue debris (shoulder prosthesis). Full text alerts can be found in Appendix G.

Table 2: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
DTK (Filter, Intravascular, Cardiovascular)	5 manufacturer issued 1 Health Canada issued	• Updated IFU and/or labeling • Mislabeling • Serious complications associated with IVC filters: perforation, thrombosis, fracture, embolization, migration, tamponade, death
DYE (Replacement Heart-Valve)	1 manufacturer issued	• May contain metallic particles that can migrate
DZE (Implant, Endosseous, Root-Form)	3 manufacturer issued	• Mislabeling
HCH (Clip, Aneurysm)	1 manufacturer issued	• Missing IFU
HRS (Plates, Fixation, Bone)	3 manufacturer issued	• Mislabeling • Incorrect components
HRS; **LWJ** (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Uncemented); **LZO** (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented)	1 manufacturer issued	• Compromised sterility
HRY (Prosthesis, Knee, Femorotibial, Semi-Constrained, Cemented, Metal/Polymer)	4 manufacturer issued	• Loosening • Product discontinuation
HRY; **NRA** (Prosthesis, Knee, Femorotibial, Unicompartmental, Semi-Constrained, Metal/Polymer, Mobile Bearing)	2 manufacturer issued	• Mislabeling • Impingement
HSB (Rod, Fixation, Intramedullary and Accessories)	2 manufacturer issued	• Compromised biological safety
HSD (Prosthesis, Shoulder, Hemi-, Humeral, Metallic Uncemented); **KWS**	1 manufacturer issued	• Out of specification

Device Type	# Alerts	Reported Problem
(Prosthesis, Shoulder, Semi-Constrained, Metal/Polymer Cemented)		
HSD; **KWS** (Prosthesis, Shoulder, Semi-Constrained, Metal/Polymer Cemented); **PHX** (Shoulder Prosthesis, Reverse Configuration)	1 manufacturer issued	• Elevated biotoxin levels and residual debris
HSN (Prosthesis, Ankle, Semi-Constrained, Cemented, Metal/Polymer)	3 manufacturer issued	• Mislabeling • Compromised assembly due to malformed component • Manufacturing residue may cause wear or adverse reaction
HSN; **NTG** (Prosthesis, Ankle, Uncemented, Non-Constrained)	1 manufacturer issued	• Mislabeling
HSX (Prosthesis, Knee, Femorotibial, Non-Constrained, Cemented, Metal/Polymer)	1 manufacturer issued	• High breakage rate
HSX; **JWH** (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained, Cemented, Polymer/Metal/Polymer)	1 manufacturer issued	• Mislabeling
JDB (Prosthesis, Elbow, Semi-Constrained, Cemented)	3 manufacturer issued	• Compromised sterility • Risk of rupture • Misuse may lead to disassembly
JDI (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Cemented)	12 manufacturer issued	• Mislabeling • Comingled lots • Dislodged components • Residue on device surface • Bioburden exceeds sterility assurance level • Packaging
JDI; **NRA** (Prosthesis, Knee, Femorotibial, Unicompartmental, Semi-Constrained, Metal/Polymer, Mobile Bearing); **PHX** (Shoulder Prosthesis, Reverse Configuration)	1 manufacturer issued	• Compromised sterility
JWH (Prosthesis, Knee, Patellofemorotibial, Semi-	29 manufacturer issued	• Mislabeling • Residue on device surface • Component misalignment

Device Type	# Alerts	Reported Problem
Constrained, Cemented, Polymer/Metal/Polymer)		• Compromised sterility • Component missing feature • No FDA clearance • Nonhomogeneous material defects • Loosening • Fracture/malfunction • Updated indications and contraindications • Cooling agent contamination leads to adverse response
JWH; **KWA** (Prosthesis, Hip, Semi-Constrained (Metal Uncemented Acetabular Component); **LPH** (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Porous Uncemented); **PKC** (Prosthesis, Total Anatomic Shoulder, Uncemented Metaphyseal Humeral Stem With No Diaphyseal Incursion, Semi-Constrained)	1 manufacturer issued	• Residue on device surface
JWH; **MBH** (Prosthesis, Knee, Patello/Femorotibial, Semi-Constrained, Uncemented, Porous, Coated, Polymer/Metal/Polymer)	13 manufacturer issued	• Mislabeling • Compromised sterility • Expired product • Undersized components require more cement • Incorrect implant surface texture • Adhesive residue may irritate tissue • Tibial tray may dissociate
JWH; **MBH**; **OIY** (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained, Cemented, Polymer + Additive/Metal/Polymer + Additive)	1 manufacturer issued	• Compromised sterility
JWH; **NJL** (Prosthesis, Knee, Patellofemorotibial, Semi-Constrained, Metal/Polymer, Mobile Bearing)	1 manufacturer issued	• Mislabeling
KRO (Prosthesis, Knee, Femorotibial, Constrained, Cemented, Metal/Polymer)	11 manufacturer issued	• Mislabeling • Missing components • Component misalignment • Compromised sterility • Outdated components included • Insufficient clearance • Component wear

Device Type	# Alerts	Reported Problem
		• Misleading component height
KWA (Prosthesis, Hip, Semi-Constrained (Metal Uncemented Acetabular Component)	2 manufacturer issued	• Revising ceramic with metal heads can cause adverse effects (pain, effusion, decreased mobility, foreign body reaction, necrosis, pseudotumor, loosening, wear, systemic cobalt toxicity) • Mislabeling
KWA; **LZO** (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented)	2 manufacturer issued	• Revised package insert • Post-op prosthesis fracture
KWD (Prosthesis, Toe, Hemi-, Phalangeal)	2 manufacturer issued	• Contradicting IFU between geographic locations • No valid CE certification
KWI (Prosthesis, Elbow, Hemi-, Radial, Polymer)	10 manufacturer issued	• Post-op hazards: loosening, instability, fracture, cyst, stiffness, pain, impingement, ossification) • Added contraindications • Mislabeling • Compromised sterility • Packaged with incorrect IFU
KWL (Prosthesis, Hip, Hemi-, Femoral, Metal); **KWY** (Prosthesis, Hip, Hemi-, Femoral, Metal/Polymer, Cemented Or Uncemented)	1 manufacturer issued	• Elevated corrosion and metal debris risk
KWL (Prosthesis, Hip, Hemi-, Femoral, Metal); **NXT** (Prosthesis, Hip, Semi-Constrained, Metal/Metal, Resurfacing)	4 manufacturer issued	• Higher than anticipated revision rate • Elevated corrosion and metal debris risk • Updated IFU • Mislabeling
KWP (Appliance, Fixation, Spinal Interlaminal); **NKG** (Posterior Cervical Screw System)	3 manufacturer issued	• Reduced strength due to implant cracks • Loosening • Out of specification
KWS (Prosthesis, Shoulder, Semi-Constrained, Metal/Polymer Cemented)	4 manufacturer issued	• Increased implant wear • Undersized components • Misassembly during manufacture • Insertion screw limitation
KWS; **KWT** (Prosthesis, Shoulder, Non-Constrained,	1 manufacturer issued	• Incorrect IFU

Device Type	# Alerts	Reported Problem
Metal/Polymer Cemented)		
KWS; **KWT**; **PHX** (Shoulder Prosthesis, Reverse Configuration)	3 manufacturer issued	• Comingled lots • Residue on device surface • Manufactured using non-validated method
KXE (Prosthesis, Wrist, Hemi-, Ulnar)	1 manufacturer issued	• Modifications made without FDA approval
LPH (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Porous Uncemented)	6 manufacturer issued	• Incomplete machining leads to improper seating and loosening, fracture, and pain • Compromised sterility • Impingement • Updated IFU • May not meet CoCrMo material requirements
LPH; **LZO** (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented)	1 manufacture issued	• Staining
LPH; **PBI** (Prosthesis, Hip, Constrained, Cemented Or Uncemented, Metal/Polymer, + Additive)	1 manufacture issued	• Mislabeling
LTI (Implant, Intragastric For Morbid Obesity)	1 manufacture issued	• Product nonconformity
LWJ (Prosthesis, Hip, Semi-Constrained, Metal/Polymer, Uncemented); **LZO** (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented)	3 manufacturer issued	• Mislabeling • Compromised sterility • Does not lock onto stem
LWJ; **LZO**; **MEH** (Prosthesis, Hip, Semi-Constrained, Uncemented, Metal / Polymer, Non-Porous, Calcium Phosphate)	2 manufacturer issued	• Mislabeling • Compromised sterility
LWJ; **LZO**; **MEH**; **OQI** (Hip, Semi-Constrained, Cemented, Metal/Ceramic/Polymer +	1 manufacturer issued	• Damaged packaging compromises sterility and may lead to fracture

Device Type	# Alerts	Reported Problem
Additive, Porous Uncemented)		
LZD (Joint, Temporomandibular, Implant)	1 manufacturer issued	• Mislabeling
LZO (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Polymer, Cemented Or Non-Porous, Uncemented)	13 manufacturer issued	• Elevated revision rate • Mislabeling • Loosening • Compromised sterility • Unexpected debris
LZO; **MEH** (Prosthesis, Hip, Semi-Constrained, Uncemented, Metal / Polymer, Non-Porous, Calcium Phosphate)	1 manufacturer issued	• Mislabeling
LZO; **PHX** (Shoulder Prosthesis, Reverse Configuration)	1 manufacturer issued	• Elevated endotoxin level
MAX (Intervertebral Fusion Device With Bone Graft, Lumbar)	1 manufacturer issued	• Manufactured with stainless steel instead of CoCr
MBH (Prosthesis, Knee, Patello/Femorotibial, Semi-Constrained, Uncemented, Porous, Coated, Polymer/Metal/Polymer)	3 manufacturer issued	• Incorrect components
MBL (Prosthesis, Hip, Semi-Constrained, Uncemented, Metal/Polymer, Porous)	4 manufacturer issued	• Elevated revision rate • Out of specification • Undersized components
MEH (Prosthesis, Hip, Semi-Constrained, Uncemented, Metal / Polymer, Non-Porous, Calcium Phosphate)	3 manufacturer issued	• Fretting and corrosion cause excessive metal debris and ions • Premature wear • Inaccurate IFU
MIH (System, Endovascular Graft, Aortic Aneurysm Treatment)	1 manufacturer issued	• Endoleak
MJO (Prosthesis, Intervertebral Disc)	1 manufacturer issued	• Mislabeling
MNH (Orthosis, Spondylolisthesis Spinal Fixation)	3 manufacturer issued	• Mislabeling • Component misassembly

Device Type	# Alerts	Reported Problem
MNH; **MNI** (Orthosis, Spinal Pedicle Fixation); **NKB** (Thoracolumbosacral Pedicle Screw System); **OSH** (Pedicle Screw Spinal System, Adolescent Idiopathic Scoliosis)	2 manufacturer issued	• Out of specification • Mislabeling
MNH; **NKB**	2 manufacturer issued	• Mislabeling
MQN (External Mandibular Fixator And/Or Distractor)	1 manufacturer issued	• Attachment difficulties
MQN; **PBJ** (Cranial Distraction System)	1 manufacturer issued	• Post-op reversal
MRA (Prosthesis, Hip, Semi-Constrained, Metal/Ceramic/Ceramic/ Metal, Cemented Or Uncemented)	1 manufacturer issued	• Packaged before PMA site-change supplement approval
NHA (Abutment, Implant, Dental, Endosseous)	2 manufacturer issued	• Incorrect machining • Mislabeling
NIQ (Coronary Drug-Eluting Stent)	4 manufacturer issued	• May contain bare metal stent • Mislabeling • Packaging
NKB (Thoracolumbosacral Pedicle Screw System)	12 manufacturer issued	• Does not meet traceability requirements • Disassembly during implantation • Miscoloring • Manufacturing defect • Post-op disengagement and/or loosening • Mislabeling • Screw head separation • Component misalignment
NKB; **NKG** (Posterior Cervical Screw System)	1 manufacturer issued	• Manufacturing defect
NKB; **NQP** (Posterior Metal/Polymer Spinal System, Fusion)	2 manufacturer issued	• Mislabeling
NKB; **OSH** (Pedicle Screw Spinal System, Adolescent Idiopathic Scoliosis); **PGM** (Growing Rod System)	2 manufacturer issued	• Out of specification • Screw head dissociation
NKB; **PGM**	1 manufacturer issued	• Component mismatch

Device Type	# Alerts	Reported Problem
NKG (Posterior Cervical Screw System)	2 manufacturer issued	• Mislabeling • Insufficient fixation
NKM (Mitral Valve Repair Device)	4 manufacturer issued	• Device may unexpectedly open • Deployment damage or difficulties • Fractured component may result in detachment difficulties • Risk of thrombus or infection
NPJ (Prosthesis, Knee Patellofemorotibial, Partial, Semi-Constrained, Cemented, Polymer/Metal/Polymer)	3 manufacturer issued	• Mislabeling • Compromised sterility
NPT (Aortic Valve, Prosthesis, Percutaneously Delivered)	1 manufacturer issued	• Balloon may burst
NRA (Prosthesis, Knee, Femorotibial, Unicompartmental, Semi-Constrained, Metal/Polymer, Mobile Bearing)	2 manufacturer issued	• Component fracture • Incomplete coating compromises attachment
NTG (Prosthesis, Ankle, Uncemented, Non-Constrained)	1 manufacturer issued	• Component fracture
NVN (Drug Eluting Permanent RV or RA Pacemaker Electrodes); **LWP** (Implantable Pulse Generator, Pacemaker (Non-CRT))	3 manufacturer issued	• Cybersecurity firmware update • Moisture ingress • Transmitters may initiate a software reset
NXT (Prosthesis, Hip, Semi-Constrained, Metal/Metal, Resurfacing)	5 manufacturer issued	• Out of specification • Labeling not FDA-approved • Elevated revision rate • Updated IFU • Soft tissue reaction to metal debris
OUT (Intracranial Aneurysm Flow Diverter)	2 manufacturer issued	• Wire fracture leads to injury/death
OVO (Prosthesis, Hip, Semi-Constrained, Ceramic-On-Metal Articulation)	1 manufacturer issued	• Mislabeling
PHX (Shoulder Prosthesis, Reverse Configuration)	8 manufacturer issued	• Mislabeling • Missing components • Component fracture • Out of specification

Device Type	# Alerts	Reported Problem
PKC (Prosthesis, Total Anatomic Shoulder, Uncemented Metaphyseal Humeral Stem With No Diaphyseal Incursion, Semi-Constrained)	1 manufacturer issued	• Mislabeling
PKL (Hemostatic Metal Clip For The Gi Tract)	1 manufacturer issued	• May contain Nickel
PMP (Dorsal Root Ganglion Stimulator For Pain Relief)	1 manufacturer issued	• Overstimulation causes discomfort
JDI; **JWH**; **KWT**; **LPH**; **NJL**; **LZO**; **MEH**; **PKC**	1 manufacturer issued	• Residue on device surface

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of CoCr. 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 SR. Topics with very low or low quality of evidence represent areas of potential gaps in literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

There was only very low-quality evidence regarding local responses in the following categories: cardiac filters, pacemakers, dental/ENT, gastric. Additionally, systemic responses were not investigated in those same categories.

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

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

Inclusion Criteria

1. English language publication
2. Published between January 2012 and May 2022
3. Human studies (animal studies that provide unique information will also be considered for inclusion)
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of 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 the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Cobalt-Chromium (CoCr)

Set Number	Concept	Search Statement
1.	**Cobalt-Chromium (CoCr) and derivatives**	
2.		
3.	Device #1	
4.	Other devices	
5.	General device terms: l	
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 [32iopros]/lim AND [2011–2021]/py
9.	Limit by publication type	#8 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

10.		'biocompatibility'/de OR biocompat* OR 33ioprosth* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
11.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR 33ioprosthes* OR 33iopros* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR 33ioprosth* 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.		(34iopro*:ti OR 34ioprosthe*: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.	**Cobalt-Chromium + Material Response + Host Response**	#9 AND #17 AND #27
29.	**Cobalt-Chromium general devices + Host response**	(#3 OR #4 OR #5 OR #6) AND #9 AND #27
30.	**Combine sets**	#28 OR #29
31.	**Cobalt-Chromium 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

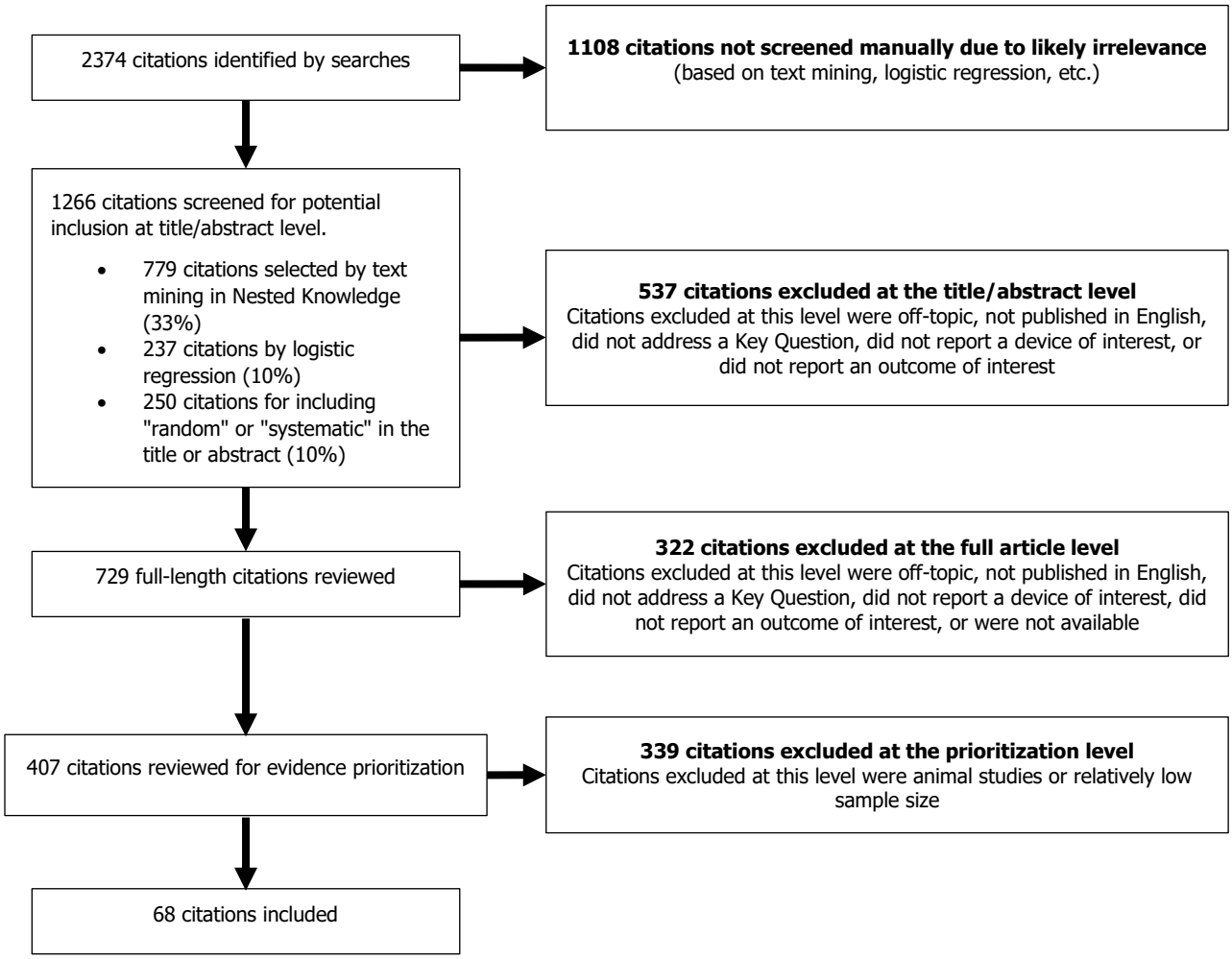
- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- 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



2374 Citations were identified by searches, of which:

1. 1108 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.)

2. The remaining 1266 articles were selected for title/abstract level (779 were selected by text mining in Nested Knowledge (33%), 237 by logistic regression (10%), and 250 for including "random" or "systematic" in the title or abstract (10%))

    a. 537 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 729 full length citations were reviewed, of which:

        i. 322 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 407 citations were reviewed for evidence prioritization:

            1. 339 citations were excluded at the prioritization level. Citations 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. 68 citations were included.

Appendix D. Evidence Tables

Table 4: Cardiac Filter – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

4.1 Source Citation: Babu et al. 2013[1]

Study Design: Single arm study evaluating outcomes of prophylactic placement of inferior vena cava (IVC) filters to prevent pulmonary embolism in women undergoing surgery and chemotherapy for gynecological cancer.

Device Material: Gunther Tulip IVC Filter (CoCr, Cook Medical).

Contact Duration: Follow-up of 6 months.

Dose: NR.

Frequency/Duration: Single administration.

Response: Protrusion, removal/failure to remove.

Patient characteristics (gender, mean age): 100% female, 56±7 years.

Number per Group: 25 women undergoing gynecological cancer treatment participated in the study.

Observed adverse effects: 11 patients (44%) underwent a filter-retrieval attempt after cancer treatment; 9 filters (82%) were uneventfully retrieved, and two filters could not be removed due to excessive filter tilt and an inability to capture.

16 patients still had indwelling IVC filters at 6-month follow-up CT scan; one patient had filter leg protrusion outside the IVC (<3mm outside the wall). The patient was asymptomatic, and no additional events were discerned. No other complications were observed, including IVC occlusions, thrombosis/deep vein thrombosis, filter migration, or pulmonary embolisms.

All patients were alive at 6-month follow-up.

Timing of adverse effects: Follow-up of 6 months.

Factors that predict response: NR.

Abbreviations: CoCr = cobalt chromium; CT = computerized tomography; IVC = inferior vena cava; NR = not reported.

Table 5: Cardiac Pacemaker Leads – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

5.1 Source Citation: Vos et al. 2017[2]

Study Design: Single arm study evaluating long-term outcomes of transvenous pacemaker implantation in pediatric patients.

Device Material: CoCr transvenous pacemaker leads: CapSureFix SP Novus (Medtronic) and Tendril SDX (St. Jude Medical).

Contact Duration: Follow-up of 14 years.

Dose: NR.

Frequency/Duration: Single administration.

Response: Defects/dysfunction, malposition, mitral valve insufficiency, mitral valve regurgitation, perforation, removal/failure to remove, thrombosis, traction, vascular occlusion.

Patient characteristics (gender, mean age): 3 of 7 patients were female (42.9%) with a mean age of 3 days (1 day to 14 months).

Number per Group: 7 pediatric patients participated in the study.

Observed adverse effects:

Lead advancement: 2 patients developed traction without electrical changes on the pacemaker lead with body growth, necessitating lead advancement.

Lead replacement: transvenous lead dysfunction involving high lead impedance and multiple macroscopic isolation defects discovered during lead advancement required lead replacement in 2 patients.

Lead removal: removal of the transvenous lead was attempted in 5 patients. Indications for removal were dysfunction of the transvenous lead and switch to epicardial leads. In 1 patient, malposition of the ventricular lead through a persistent foramen ovale in the left ventricle was discovered at the age of 12 years when a chest x-ray was performed because of progressive mitral valve regurgitation. This lead was surgically removed and a mitral valve plasty for severe mitral valve insufficiency was performed. In two patients, the ventricular lead could be removed with mechanical traction; and in two patients, lead extraction was unsuccessful with leads cut and left *in situ*. One patient received a pacemaker upgrade after 5 years, which was complicated by right atrial perforation by the atrial electrode.

Vascular occlusion: asymptomatic left subclavian vein occlusion occurred in 2 patients after development of an intracardiac lead thrombosis and as a result of Ehlers-Danlos syndrome (unrelated to lead).

Thrombosis: The same two occlusion patients developed a venous thrombosis on the pacemaker lead, one on the atrial lead and one on the ventricular lead. Both were treated successfully with oral and subcutaneous anticoagulants.

All patients were alive at 14-year follow-up.

Timing of adverse effects: Lead replacement required in two patients after 2 and 4 years. Venous thrombosis developed in two patients 7 and 11 years after implantation. Malposition discovered in one patient after 12 years. Vascular occlusion developed in two patients 6 and 8 years after implantation.

Factors that predict response: The study authors note that lead malfunction is not specifically related to transvenous pacing in infants, but to pacing in general or to pacing in small patients. Additionally, most complications related to the transvenous mode of pacing (vascular occlusion, pacemaker lead thrombosis and severe AV valve regurgitation) occurred after the first mid-term follow-up report of this

cohort suggesting that the majority of the long-term complications of transvenous pacing in infants have not yet occurred in the reported cohorts to date.

Abbreviations: AV = atrioventricular; CoCr = cobalt chromium; NR = not reported.

Table 6: Cardiac Stents – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

6.1 Source Citation : Bangalore et al. 2014[3]

Study Design: Systematic Review of 68 studies (4 RCTs CABG vs POBA, 5 RCTs CABG vs BMS, 5 RCTs CABG vs DES, 54 RCTs stent to stent comparison)

Device or Material: Coronary artery bypass graft surgery, balloon angioplasty, Bare metal stent, Paclitaxel, Sirolimus, Zotarolimus-endeavor, Zotarolimus-resolute, PtCr-everolimus, CoCr-everolimus for coronary artery disease

Contact Duration: Up to 10 years

Dose: NR

Frequency/Duration: NR

Response: All-cause mortality, MI, repeat revascularization, stroke

Patient characteristics (gender, mean age): NR

Number per Group: 71,595 total patients (24015 diabetic). Patient counts by group

Observed adverse effects: Note: RRs <1 favor Sapien 3, >1 favor Evolut R

All-cause mortality: Median per 1,000 patient-year of follow-up: CABG=27.08, POBA=33.98, BMS=34.96, Paclitaxel=42.51, Sirolimus=38.86, Zotarolimus-Endeavor=35.65, Zotarolimus-Resolute=39.46, PtCr-Everolimus=NA, CoCr-Everolimus=30.18. **No statistical difference for CoCr-Everolimus compared to CABG**

Myocardial infarction: Median per 1,000 patient-year of followup: CABG=19.88, POBA=22.9, BMS=29.67, Paclitaxel=28.15, Sirolimus=24.16, Zotarolimus-Endeavor=30.57, Zotarolimus-Resolute=22.77, PtCr-Everolimus=NA, CoCr-Everolimus=14.19. **No significant differences.**

Repeat revascularization: Median per 1,000 patient-year of followup: CABG=27.31, POBA=120.3, BMS=87.06, Paclitaxel=49.51, Sirolimus=40.14, Zotarolimus-Endeavor=64.28, Zotarolimus-Resolute=65.25, PtCr-Everolimus=82.23, CoCr-Everolimus=35.71. **Higher for PCI, POBA, BMS, PES and SES. No significant increase for CoCr EES.**

Stroke: Median per 1,000 patient-year of followup: CABG=2.71, POBA=NA, BMS=1.55, Paclitaxel=1.47, Sirolimus=1.7, Zotarolimus-Endeavor= NA, Zotarolimus-Resolute= NA, PrCr-Everolimus= NA, CoCr-Everolimus= NA. **No significant differences.**

Timing of adverse effects: NR

Factors that predict response: Mortality benefit indicates that the presence of diabetes mellitus with multivessel disease should be a compelling indication for CABG rather than PCI.

6.2 Source Citation : Cassese et al. 2017[4]

Study Design: Systematic review of 7 clinical trials

Device or Material: PtCr-EES, early-generation DES, BES, Biomatrix Flex, CoCr-EES, ZES

Contact Duration: Median follow up = 12 months

Dose: NR

Frequency/Duration: NR

Response: Target lesion revascularization, definite/probably stent thrombosis, myocardial infarction, target vessel revascularization, death, cardiac death, longitudinal stent deformation

Patient characteristics (gender, mean age): mean 74% male, median 63.5 years (interquartile range, 63.3 to 65.0)

Number per Group: 11,036 patient total (6,613 durable polymer and 4,423 other DES; other DES: 325 biolimus, 1,940 cobalt chromium everolimus and 2,158 zotarolimus)

Observed adverse effects:

Target lesion revascularization: **No significant differences.**

Definite/probable stent thrombosis: **No significant differences.**

Myocardial infarction: **No significant differences.**

Target vessel revascularization: **No significant differences.**

Death: **No significant differences.**

Cardiac death: **No significant differences.**

Timing of adverse effects: Median = 12 months

Factors that predict response: NR

6.3 Source Citation : Cassese et al. 2018[5]

Study Design: Systematic review of midterm outcomes for 7 clinical trials

Device or Material: Bioresorbable vascular scaffold versus everolimus-eluting stent (96% CoCr)

Contact Duration: 12 months

Dose: NR

Frequency/Duration: NR

Response: Target lesion failure, cardiac death, target vessel myocardial infarction, ischemia-driven target lesion revascularization, definite/probable stent (scaffold) thrombosis

Patient characteristics (gender, mean age): 74% male (5,583 total patients); mean age between 57.4 and 67.2 years

Number per Group: 3,187 BVS, 2,265 EES

Observed adverse effects:

Target lesion failure: **Patients treated with BVS showed a higher risk for TLF than EES, (p=0.0028)**

Cardiac death: **No statistical differences**

Target vessel myocardial infarction: **Patients treated with BVS showed a higher risk for MI than EES, (p=0.008)**

Ischemia-driven target lesion revascularization: **Patients treated with BVS showed a higher risk for target lesion revascularization than EES, (p=0.007)**

Definite/probable stent (scaffold) thrombosis: **Patients treated with BVS showed a higher risk for thrombosis than EES, (p=0.0018)**

Timing of adverse effects: 12 months

Factors that predict response: Higher risk for poor outcomes with BVS increased with time.

6.4 Source Citation : Chichareon et al. 2019[6]

Study Design: Systematic review of 15 randomized studies of PCI in patients with ST-segment elevation myocardial infarction (STEMI)

Device or Material: Bare metal stent, durable polymer paclitaxel-eluting stent, durable polymer everolimus-eluting stent, biodegradable polymer biolimus-eluting stent, durable polymer sirolimus-eluting stent, durable polymer zotarolimus-eluting stent

Contact Duration: at least 12 months

Dose: NR

Frequency/Duration: NR

Response: All cause death, cardiac death, reinfarction, target lesion revascularization, definite/probable stent thrombosis

Patient characteristics (gender, mean age): 2,491 female patients (22.7%), 8,486 male patients (77.3%); mean age = 61 years

Number per Group: Bare metal stent = 3,406; Paclitaxel-eluting stent = 3,173; Sirolimus-eluting stent = 2,044; Zotarolimus-eluting stent = 373; Everolimus-eluting stent = 1,405; Biolumis-eluting stent = 575.

Observed adverse effects: No significant differences in ischemic and safety outcomes were observed between the various types of DES. Second-generation DES (Everolimus, Biolumis) were associated with a significant reduction in the risk of stent thrombosis compared with first-generation DES (Paclitaxil, Sirolimus, Zotarolimus) and BMS.

All cause death: Risk was significantly lower in patients treated with DP-PES, -SES, and -EES and BP-BES compared with BMS. Treatment with DP-EES was associated with a significantly lower risk of all-cause mortality compared with BMS (not significant when adjusted, where risk was similar for all groups).

Cardiac death: Patients treated with DP-PES, DP-SES, and DP-EES and BP-BES had significantly lower risk compared to BMS.

Reinfarction: Risk was significantly lower in patients treated with DP-PES, -SES, and -EES and BP-BES compared with BMS.

Target lesion revascularization: Patients treated with DP-PES, DP-SES, and DP-EES and BP-BES had significantly lower risk compared to BMS.

Definite/probably stent thrombosis: Treatment with DP-EES was associated with a significantly lower risk compared to BMS and DP-SES. No significant difference in the risk among patients with BMS, DP-PEP, DP-ZES, BP-BES.

Timing of adverse effects: NR

Factors that predict response: Lower risk of TVR led to lower risk of other outcomes.

6.5 Source Citation : Clavel et al. 2019[7]

Study Design: Systematic review of 40 studies reporting on restenosis and stroke following angioplasty and stenting of the cervical carotid artery

Device or Material: Open- and closed-cell stents

Contact Duration: 30 days, 6 months and 12 months

Dose: NR

Frequency/Duration: NR

Response: Restenosis (stenosis >50%) at 1-year, severe restenosis (stenosis >70%) at 1 year, restenosis (stenosis >50%) at 6 months, new ipsilateral ischemic stroke within 30 days

Patient characteristics (gender, mean age): 68.9% men; mean age = 70.1 years

Number per Group: 16,337 arteries in 15,943 patients

Observed adverse effects:

Restenosis (stenosis >50%) at 1 year: 5.7% restenosis (5.2% in closed cell stent only stents, no significant difference)

Severe restenosis (stenosis >70%) at 1 year: 4.8% for 70-year-olds, 1.1% for 80-year-olds

Restenosis (stenosis >50%) at 6 months: 3.9% restenosis

New ipsilateral ischemic stroke within 30 days: 1.6% ipsilateral stroke (0.5% in closed cell stent only stents, no significant difference; 0.9% in procedures using an embolic protection device, no significant difference)

Timing of adverse effects: 30 days, 6 months and 12 months

Factors that predict response: Severe restenosis decreased with age.

6.6 Source Citation : Jang et al. 2021[16]

Study Design: Prospective study of 4 types of second-generation drug-eluting stents (BP-BES, PtCr-EES, CoNi-ZES and CoCr-EES) for PCI for coronary bifurcation lesion

Device or Material: BP-BES, PtCr-EES, CoNi-ZES and CoCr-EES

Contact Duration: 5 years

Dose: NR

Frequency/Duration: NR

Response: Target lesion failure, cardiac death, target vessel MI, target lesion revascularization, stent thrombosis

Patient characteristics (gender, mean age): BP-BES: mean age=63.1 years, male=394 (76.7%); PtCr-EES: mean age=63.3 years, male=356 (75.3%); CoNi-ZES: mean age=64.1 years, male=569 (77.3%); CoCr-EES: mean age=63.9 years, male=602 (75.0%)

Number per Group: BP-BES: n=514; PtCr-EES: n=473; CoNi-ZES: n=736; CoCr-EES: n=803

Observed adverse effects:

Target lesion failure: not significantly different among the four DES groups (p=0.434)

Cardiac death: not significantly different among the four DES groups (p=0.800)

Target vessel MI: not significantly different among the four DES groups (p=0.606)

Target lesion revascularization: not significantly different among the four DES groups (p=0.576)

Stent thrombosis: not significantly different among the four DES groups (p=0.875)

Timing of adverse effects: median follow up = 1,574 days [1,080-2,040]

Factors that predict response: NR

6.7 Source Citation : Liao et al. 2021[8]

Study Design: Systematic review of 19 articles containing 13 randomized controlled trials comparing BP-SES to DP-DES

Device or Material: Ultrathin BP-SES and ultrathin DP-DES for PCI

Contact Duration: 9-60 months

Dose: NR

Frequency/Duration: NR

Response: Target lesion failure, all cause death, cardiac death, myocardial infarction, target lesion revascularization, definite/probable stent thrombosis

Patient characteristics (gender, mean age): 74.6% men. Mean age between 58 and 66 years.

Number per Group: 14,841 patients total. BP-SES : n=7,921. DP-DES : n=6,920

Observed adverse effects:

Target lesion failure: Risk ratio lower in BP-SES compared to DP-SES (p=0.04)

All cause death: No statistical difference in all cause death (p=0.08)

Cardiac death: No statistical difference in cardiac death (p=0.63)

Myocardial infarction: Trend towards lower risk for BP-SES compared to DP-DES, but no statistical difference (p=0.17)

Target lesion revascularization: No statistical difference

Definite/probably stent thrombosis: No statistical difference

Timing of adverse effects: 9-60 months

Factors that predict response: Outcomes better for female patients, patients with STEMI and ACS and patients without diabetes.

6.8 Source Citation : Monjur et al. 2020[9]

Study Design: Prospective systematic review and meta-analysis of randomized clinical trials comparing Orsiro BP-SES against DP-DES

Device or Material: Orsiro BP-SES against DP-DES

Contact Duration: mean weighted follow up = 2.8 years (1-5 years)

Dose: NR

Frequency/Duration: NR

Response: Target lesion failure, cardiac death, target vessel myocardial infarction, clinically indicated target lesion revascularization

Patient characteristics (gender, mean age): Mean age for all 10 studies: 59.1-66 years, % male: 68-78%

Number per Group: BP-SES: 6,328; DP-DES: 5,424

Observed adverse effects:

Target lesion failure: There was a statistically significant reduction in the primary outcome (TLF) among patients randomized to Orsiro BP-SES (501/6089 (8.2%)) compared with DP-DES (495/5213 (9.5%); OR 0.82; 95% CI 0.69 to 0.98; p=0.037)

Cardiac death: No statistical difference between groups (p=0.92)

Target vessel myocardial infarction: There was a statistically significant reduction in TVMI with BP-SES over DP-DES (OR 0.80; 95% CI 0.65 to 0.98; p=0.03).

Clinically indicated target lesion revascularization: No statistical difference between groups (p=0.28)

Timing of adverse effects: 1-5 years

Factors that predict response: NR

6.9 Source Citation : Poder et al. 2017[10]

Study Design: Systematic review of meta-analyses comparing second generation drug eluting stents (DES-2) to bare metal stents (BMS)

Device or Material: Cobalt-chromium everolimus-eluting stent (Co-Cr-EES), platinum-chromium everolimus-eluting stent (Pt-Cr-EES), Resolute Integrity zotarolimus-eluting stent (Re-ZES), and the polymer-coated zotarolimus-eluting stent (PC-ZES or phophorylcholine-polymer-ZES). Some studies did not specify the DES type; only the eluant (i.e., everolimus or zotarolimus).

Contact Duration: 2 years

Dose: NR

Frequency/Duration: NR

Response: Target vessel revascularization (TVR), mortality, in-stent thrombosis, myocardial infarction

Patient characteristics (gender, mean age): NR

Number per Group: Total patients in all 10 studies: 300,418 (potential overlap).

Observed adverse effects:

Target vessel revascularization (TVR): The meta-analyses overall revealed a significant reduction in TVR in patients who received a DES-2 instead of a BMS, with the exception of zotarolimus stents (PC-ZES was less effective). Moreover, the reduction in TVR rate was higher with the platinum-chromium alloy than with the chromium-cobalt alloy.

Mortality: No statistical difference was observed with respect to total mortality. Most of the DES-2 stents were associated with a downward trend in mortality, particularly with Co-Cr-EES.

In-stent thrombosis: Except in the case of PC-ZES, the reduction in the rate of subacute thromboses (<30 days) was statistically significant, regardless of the type of DES-2. Only the Co-Cr-EES evidenced a reduction in the rate of late (>30 days) and/or very late (>1 year) thromboses. The other DES-2 stents indicated a downward trend in this rate compared to BMS.

Myocardial infarction: Nearly all of the studies with infarction occurring at one year or less indicated a significant drop in the myocardial infarction rate, with the exception of PC-ZES in one study.

Timing of adverse effects: Up to 2 years

Factors that predict response: NR

6.10 Source Citation : Radu et al. 2014[15]

Study Design: Assessment of evaginations following implantation of drug-eluting stents

Device or Material: sirolimus(SES)-, paclitaxel-,biolimus-, everolimus (EES)-, or zotarolimus (ZES)-eluting stents

Contact Duration: Up to 5 years

Dose: NR

Frequency/Duration: NR

Response: Coronary evaginations

Patient characteristics (gender, mean age): 228 patients, mean age = 60 years, 179 (78.5%) male patients

Number per Group: EES: 27, PES: 55, BES: 18, ZES: 37, SES: 91, Multivessel disease: 23

Observed adverse effects:

Coronary evaginations: Major evaginations (ME) occurred frequently at all time points in SES (26%) and were rarely seen in EES (3%) and ZES (2%, P=0.003). Sirolimus-eluting stent implantation was the strongest independent predictor of ME [adjusted OR (95% CI) 9.1 (1.1–77.4), P=0.008]

Timing of adverse effects: Up to 5 years

Factors that predict response: Evaginations appear to be related to vessel injury at baseline; are associated with positive vessel remodeling; and correlate with uncoverage, malapposition, and thrombus at follow-up.

6.11 Source Citation : Sanz Sanchez et al. 2020[11]

Study Design: Meta-analysis of studies comparing drug coated balloons to drug-eluting stents for patients with native small vessel coronary artery disease

Device or Material: Drug coated balloons (SeQuent please, IN.PACT falcon, Dior, Restore, Elutax SV), drug-eluting stents (Taxus element, Xience, Taxus Liberte, Resolute Integrity)

Contact Duration: Up to 12 months

Dose: NR

Frequency/Duration: NR

Response: Target vessel revascularization, myocardial infarction, target lesion revascularization, all-cause death, angiographic restenosis and vessel thrombosis.

Patient characteristics (gender, mean age): Drug coated balloon: 75% men. Drug-eluting stent: 73% men. Mean age: 60-68 years.

Number per Group: Five trials enrolling 1,459 patients were included. Drug coated balloon: 734. Drug-eluting stent: 725.

Observed adverse effects:

Target vessel revascularization: No significant difference observed (DCB: 5.86%. DES: 6.34%. p=0.92)

Myocardial infarction: ALMOST significantly less for drug coated balloon (DCB: 1.5%. DES: 3.17%. p=0.06)

Target lesion revascularization: No significant difference observed (DCB: 7.1%. DES: 5.16%. p=0.33)

All-cause death: No significant difference observed (DCB: 0.57%. DES: 0.57%. p=0.98)

Angiographic restenosis: No significant difference observed (DCB: 12.43%. DES: 11.6%. p=0.64)

Vessel thrombosis: Significantly less for drug coated balloon (DCB: 0%. DES: 1.26%. p=0.04)

Timing of adverse effects: Up to 12 months

Factors that predict response: NR

6.12 Source Citation : Sethi et al. 2021[12]

Study Design: Meta-analysis comparing BP-SES (Orsio) to DP-EES (Xience)

Device or Material: Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent

Contact Duration: 1-5 years

Dose: NR

Frequency/Duration: NR

Response: Target lesion failure, target lesion revascularization, TVMI, cardiac death, target vessel failure, definitive or probable stent thrombosis

Patient characteristics (gender, mean age): Mean age: 58.4 – 64.8 years; % male: 64.5 – 80

Number per Group: 6,550 overall, NR amount per group

Observed adverse effects:

Target lesion failure: TLF rates for BP-SES and DP-EES were 3.19 and 3.71% per person-year follow-up, respectively, and was not significantly different between the stent types (trend toward lower TLF with BP-SES (P value=0.08))

Target lesion revascularization: No significant difference

TVMI: Cumulative TVMI rate for BP-SES and DP-EES were 1.29 and 1.52% per person-year follow-up, respectively. While there was no statistical difference between the stents, there was trend toward a lower TVMI with BP-SES

Cardiac death: No significant difference

Target vessel failure: Cumulative TVF rates for BP-SES and DP-EES were 3.9 and 4.4% per person-year follow-up, respectively. There was no significant difference between BP-SES and DP-EES: NR

Definitive or probable stent thrombosis: No significant difference

Timing of adverse effects: NR

Factors that predict response: In studies which defined small vessel as ≤2.75mm, there was a significant reduction of TLF with BP-SES

6.13 Source Citation : Taglieri et al 2020[13]

Study Design: Systematic review of coronary artery bypass grafting, stenting or optimal medical therapy in stable coronary artery disease (outcomes = myocardial infarction, death)

Device or Material: Optimal medical therapy, coronary artery bypass graft, stent (PF-SES [Yukon Choice], Bp-CoCr-SES [Osiro, Mistent, Biomime, Firehawk, Tivoli], BP-BES [Nobori, Biomatrix], DP-PtCr-EES [Promus Element], DP-CoCr-EES [Promus, Xience], DP-R-ZES [Resolute], DP-E-ZES [Endevor], DP-SES [Cypher], DP-PES [Taxus], BMS)

Contact Duration: Mean follow-up = 42.5 months

Dose: NR

Frequency/Duration: NR

Response: All cause death, myocardial infarction

Patient characteristics (gender, mean age): NR (maybe in supplemental data, meta-analysis of 75,754 total patients)

Number per Group: NR

Observed adverse effects:

All cause death: Only CABG was associated with all cause death; CABG was associated with a lower risk of death than OMT (exclusion of trials focusing on left main/multivessel disease)

Myocardial infarction: CABG and BP-CoCr-SES were associated with a lower risk of MI, compared to OMT; excluding all-comer and post-MI trials, or trials focusing on left main/multivessel disease, DP-CoCr-EES compared to OMT was associated with lower risk of MI

Timing of adverse effects: NR

Factors that predict response: Patients with left main/multivessel disease had an increased risk of MI with stenting

6.14 Source Citation : Taglieri et al 2020[14]

Study Design: Meta analysis comparing different types of DES

Device or Material: Focus on Orsiro (BP cobalt chromium SES), XIENCE (DP-CoCr-EES), Resolute (DP-ZES, Nobori/BioMatrix (BP BES); Other stents: Promus (DP-CoCr-EES), Promus Element (DP platinum chromium EES), Synergy, Biofreedom, Cre8 (polymer free amphilimus eluting stent), Yukon-PF (polymer free SES), Yukon-BP (BP SES)

Contact Duration: 1 year (up to 5 years)

Dose: NR

Frequency/Duration: NR

Response: Target lesion failure (TLF), definite stent thrombosis, long term TLF, target vessel related myocardial infarction

Patient characteristics (gender, mean age): 77 studies. Mean age: 56-81; Percent male: 28-83, with one study exclusively women

Number per Group: NR, 99,039 patients overall

Observed adverse effects:

Target lesion failure: Orsiro was associated with a significantly lower 1-year rate of TLF compared with XIENCE (p=0.03). Orsiro was also associated with lower rates of TLF than Biofreedom (p=0.04). Orsiro and XIENCE had significantly lower rates of ischemia-driven target lesion revascularization compared with Resolute (p=0.04).

Definite stent thrombosis: Orsiro and XIENCE were associated with a lower rate of definite ST compared with Nobori/Biomatrix (p=0.04).

Long term TLF (>1 year): No statistically significant differences were observed among Orsiro, XIENCE, Resolute and Nobori/BioMatrix.

Target vessel related MI: Orsiro showed a trend towards a long-term lower rate of target vessel-related MI (p=0.06).

Timing of adverse effects: 1-5 years

Factors that predict response: No evidence to support an association between either SEMI or diabetes with the size of treatment effect for the primary endpoint (TLF).

ACS: Acute coronary syndrome; BES: Biolimus eluting stent; BMS: bare metal stent; BP: Biodegradable polymer; BVS: Bioresorbable vascular scaffold; CABG: Coronary Artery Bypass Graft; CI: Confidence interval; CoCr: Cobalt Chromium; CoNi: Cobalt nickel; DEB: drug eluting balloon; DES: drug eluting stent; DP: Durable polymer; EES: Everolimus eluting stent; MI: Myocardial infarction; NR: not reported; PC: Polymer coated; PCI: Percutaneous coronary intervention; PES: Paclitaxel eluting stent; PF: Polymer free; POBA: percutaneous old balloon angioplasty; PtCr: Platinum Chromium; RCT: randomized controlled trial; RR: rate ratio; SES: Sirolimus eluting stent; ST: Stent thrombosis; STEMI: ST-segment elevation myocardial infarction; TLR: target lesion revascularization; TVMI: Target vessel myocardial infarction; TVR: Target vessel revascularization; ZES: Zotarolimus eluting stent

Table 7: Cardiac Valves – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

7.1 Source Citation: Alperi et al. 2021[17]

Study Design: Systematic Review of 9 studies (8 observational studies, 1 RCT)

Device or Material: Sapien 3 (CoCr) vs. Evolut R (Nitinol) Cardiac Aortic Valve Prostheses

Contact Duration: Up to 30 days

Dose: NR

Frequency/Duration: NR

Response: AKI, all-cause mortality, device success, life-threatening bleeding, major vascular complications, moderate to severe AR, post TAVR mean gradient difference, PPI, stroke

Patient characteristics (gender, age): Percent female: Sapien 3: 5.5% to 68.8%, Evolut: 8.1% to 60.8%; Mean age range: Sapien 3: 80.9 to 83 years, Evolut: 81.3 to 84 years

Number per Group: 24,628 patients (12,411 Sapien 3, 12,217 Evolut R).

Observed adverse effects:

AKI (30-day), FE model: Sapien 3: 55.6/752.2, Evolut R: 39.4/607.8, RR 1.17 (95% CI: 0.78 to 1.77), I^2=14.2%, p=0.44, **no difference**

All-cause mortality (30-day), FE model: Sapien 3: 360.6/12339.3, Evolut R: 454.4/12162.7, RR 0.79 (95% CI: 0.69 to 0.90), I^2=0%, p<0.001, **favors Sapien 3**

Device success, FE model: Sapien 3: 761.5/818, Evolut R: 611.5/660, RR 1.00 (95% CI: 0.97 to 1.04), I^2=31.8%, p= 0.84, **no difference**

Life-threatening bleeding (30-day), FE model: Sapien 3: 64.6/1960.2, Evolut R: 32.4/1768.8, RR 1.82 (95% CI: 1.18 to 2.80), I^2=0%, p= 0.006, **favors Evolut R**

Major vascular complications (in-hospital), FE model: Sapien 3: 41.1/837.2, Evolut R: 30.9/676.8, RR 1.03 (95% CI: 0.63 to 1.68), I^2=19.1%, p= 0.91, **no difference**

Moderate to severe AR (in-hospital), FE model: Sapien 3: 11.35/701.69, Evolut R: 16.65/541.31, RR 0.49 (95% CI: 0.20 to 1.17), I^2=0%, p= 0.11, **no difference**

Post TAVR mean gradient difference in mmHg, FE model: MD 3.92 (95% CI: 3.31 to 4.54), I^2=0%, p=0.11, **no difference**

Post-TAVR PPI, RE model: RR 0.66 (95% CI: 0.55 to 0.80), I^2=0%, p<0.001, **favors Sapien 3**

Stroke, RE model: Sapien 3: 30.65/1955.3, Evolut R: 40.35/1760.7, RR 0.95 (95% CI: 0.34 to 2.66), I^2=0%, p= 0.92, **no difference**

Note: RRs <1 favor Sapien 3, >1 favor Evolut R

Timing of adverse effects: All adverse effects were early (in-hospital or 30-day) outcomes.

Factors that predict response: Examination of publication bias found no statistically significant effect. Life-threatening bleeding, PPI, moderate to severe AR, and all-cause mortality outcomes were driven by case-matched studies, propensity-matched studies, and RCTs which all had statistically significant results. These results were deemed insignificant when the same outcome was limited to observational studies without imbalance adjustment for baseline characteristics.

7.2 Source Citation : D'Ascenzo et al. 2021[18]

Study Design: Systematic review with NMA

Device or Material: Balloon expandable aortic valves (all CoCr: Sapien, Sapien 3, Sapien XT), self-expandable aortic valves (all non-CoCr: Corevalve, Evolut R, ACURATE Neo), or SAVR

Note: Study also contained information comparing self-expandable valves vs. SAVR, however, neither group contained devices with CoCr.

Contact Duration: Up to 2 years

Dose: NR

Frequency/Duration: NR

Response: A-fib (30-day, 1 year), AKI (30 day), aortic valve replacement (1 year), cardiovascular mortality (30-day, 1 year, 2 years), endocarditis (1 year), major bleeding (30-day), major vascular complications (30-day), MI (30-day, 1 year), mortality (30-day, 1 year, 2 years), paravalvular leak (30-day), PPI (30-day, 1 year), stroke (30-day, 1 year)

Patient characteristics (gender, age): Mean age range: Balloon expandable: 73.3 to 83.6 years, SAVR: 73.6 to 84.5 years, Self-expandable: 79.2 to 83.2 years

Percent female range: Balloon expandable: 32% to 71%, SAVR: 26% to 47%, Self-expandable: 42% to 59%

Number per Group: 9,752 patients

Observed adverse effects:

Balloon-Expandable Valves vs. SAVR

A-fib (30-days): RR 0.24 (95% CI: 0.14 to 0.42), **favors balloon expandable valves**

A-fib (1 year): RR 0.30 (95% CI: 0.16 to 0.56), **favors balloon expandable valves**

AKI (30 days): RR 0.42 (95% CI: 0.30 to 0.60), **favors balloon expandable valves**

Aortic Valve Replacement (1 year): RR 2.26 (95% CI: 0.93 to 5.47), **no difference**

Cardiovascular mortality (30-days): RR 0.93 (95% CI: 0.63 to 1.37), **no difference**

Cardiovascular mortality (1 year): RR 0.98 (95% CI: 0.77 to 1.27), **no difference**

Cardiovascular mortality (2 years): RR 1.00 (95% CI: 0.83 to 1.21), **no difference**

Endocarditis (1 year): RR 0.96 (95% CI: 0.42 to 2.21), **no difference**

Major bleeding (30-days): RR 0.32 (95% CI: 0.16 to 0.65), **favors balloon expandable valves**

Major vascular complications (30-days): RR 2.29 (95% CI: 1.37 to 3.85), **favors SAVR**

MI (30-days): RR 0.65 (95% CI: 0.36 to 1.17), **no difference**

MI (1 year): RR 0.76 (95% CI: 0.48 to 1.22), **no difference**

Mortality (30-days): RR 0.72 (95% CI: 0.46 to 1.13), **no difference**

Mortality (1 year): RR 0.97 (95% CI: 0.79 to 1.18), **no difference**

Mortality (2 years): RR 1.01 (95% CI: 0.79 to 1.29), **no difference**

Paravalvular leak (30-days): RR 3.18 (95% CI: 1.33 to 7.58), **favors SAVR**

PPI (30-days): RR 1.90 (95% CI: 1.21 to 2.94), **favors SAVR**

PPI (1 year): RR 1.30 (95% CI: 1.03 to 1.63), **favors SAVR**

Stroke (30-days): RR 0.63 (95% CI: 0.37 to 1.09), **no difference**

Stroke (1 year): RR 1.07 (95% CI: 0.81 to 1.41), **no difference**

Balloon-Expandable Valves vs. Self-Expandable Valves

A-fib (30-days): RR 1.17 (95% CI: 0.61 to 2.27), **no difference**

A-fib (1 year): RR 1.18 (95% CI: 0.52 to 2.67), **no difference**

AKI (30 days): RR 0.96 (95% CI: 0.69 to 1.33), **no difference**

Aortic Valve Replacement (1 year): RR 0.72 (95% CI: 0.25 to 2.06), **no difference**

Cardiovascular mortality (30-days): RR 0.94 (95% CI: 0.56 to 1.57) **no difference**

Cardiovascular mortality (1 year): RR 1.20 (95% CI: 0.85 to 1.70), **no difference**

Cardiovascular mortality (2 years): RR 1.05 (95% CI: 0.76 to 1.43), **no difference**

Endocarditis (1 year): RR 1.35 (95% CI: 0.41 to 4.46), **no difference**

Major bleeding (30-days): RR 0.69 (95% CI: 0.31 to 1.41), **no difference**

Major vascular complications (30-days): RR 0.83 (95% CI: 0.49 to 1.40), **no difference**

MI (30-days): RR 0.69 (95% CI: 0.31 to 1.54), **no difference**

MI (1 year): RR 0.72 (95% CI: 0.38 to 1.36), **no difference**

Mortality (30-days): RR 0.73 (95% CI: 0.45 to 1.19), **no difference**

Mortality (1 year): RR 1.12 (95% CI: 0.84 to 1.50), **no difference**

Mortality (2 years): RR 1.07 (95% CI: 0.76 to 1.51), **no difference**

Paravalvular leak (30-days): RR 0.31 (95% CI: 0.17 to 0.55), **favors balloon expandable valves**

PPI (30-days): RR 0.51 (95% CI: 0.33 to 0.79), **favors balloon expandable valves**

PPI (1 year): RR 0.40 (95% CI: 0.30 to 0.55), **favors balloon expandable valves**

Stroke (30-days): RR 0.69 (95% CI: 0.47 to 1.01), **no difference**

Stroke (1 year): RR 1.34 (95% CI: 0.93 to 1.93), **no difference**

Timing of adverse effects: Adverse events reported at 30-day, 1 year, or 2-year follow-ups. Timing of all events is specified in the observed adverse effects heading.

Factors that predict response: NR

7.3 Source Citation : Swift et al. 2021[19]

Study Design: Systematic Review

Device or Material: Balloon-expandable (Sapien, Sapien 3, Sapien XT) (all CoCr) vs SAVR

Note: Study also contained information comparing self-expandable valves vs. SAVR, however, neither group contained devices with CoCr.

Contact Duration: Up to 5 years

Dose: NR

Frequency/Duration: NR

Response: PPI

Patient characteristics (gender, age): Mean age range: 73.3 to 84.5; Gender: NR

Number per Group: 8,818 patients with severe aortic stenosis

Observed adverse effects: Note: only one outcome (PPI) subgrouped an outcome of interest by valve type.

PPI (30-days) (3 studies: n=1,855 patients with balloon expandable valves, n=1,826 patients undergoing SAVR): RR 1.31 (95% CI: 1.01 to 1.69), I^2=0%, **favors SAVR**

PPI (1 year) (3 studies: n=1,855 patients with balloon expandable valves, n=1,826 patients undergoing SAVR): RR 1.21 (95% CI: 0.96 to 1.52), I^2=0%, **no difference**

PPI (2 years) (2 studies: n=1,359 patients with balloon expandable valves, n=1,372 patients undergoing SAVR): RR 1.20 (95% CI: 0.95 to 1.52), I^2=0%, **no difference**

PPI (5 years) (1 study: n=348 patients with balloon expandable valves, n=351 patients undergoing SAVR): RR 1.23 (95% CI: 0.72 to 2.09), I^2=NA, **no difference**

Timing of adverse effects: 30 days, 1 year, 2 years, and 5 years

Factors that predict response: NR

7.4 Source Citation : Yuan et al. 2021[20]

Study Design: Systematic review

Device or Material: TMVR with Mitraclip (CoCr) vs. SMVR

Contact Duration: Up to 5 years

Dose: NR

Frequency/Duration: NR

Response: Mortality, recurrent 3+ MR

Patient characteristics (gender, age): Mean age range: TMVR: 67 to 84.5, SMVR: 63 to 81.9; Gender: NR

Number per Group: 3,355 patients with severe mitral regurgitation (SMR)

Observed adverse effects:

Mortality (30-days): TMVR: 24/913, SMVR: 40/1231, OR: 0.88 (95% CI: 0.53 to 1.47), I^2=17%, p=0.64, **no difference**

Mortality (1 year): TMVR: 163/1122, SMVR: 170/1862, OR: 1.79 (95% CI: 1.40 to 2.28), I^2=45%, p<0.00001, **favors SMVR**

Mortality (>3 years): TMVR: 521/1089, SMVR: 148/660, OR: 2.26 (95% CI: 1.04 to 4.92), I^2=88%, p=0.04, **favors SMVR**

Recurrent 3+ MR (30-days): TMVR: 76/504, SMVR: 13/689, OR: 9.51 (95% CI: 5.38 to 16.83), I^2=0%, p<0.00001, **favors SMVR**

Recurrent 3+ MR (1 year): TMVR: 99/377, SMVR: 47/349, OR: 3.14 (95% CI: 1.20 to 8.25), I^2=67%, p=0.02, **favors SMVR**

Recurrent 3+ MR (>3 years): TMVR: 76/357, SMVR: 17/399, OR: 8.47 (95% CI: 4.76 to 15.10), I^2=49%, p<0.00001, **favors SMVR**

Timing of adverse effects: Adverse effects reported at 30-day, 1 year, and over 3 year follow-up time points.

Factors that predict response: At baseline, patients undergoing TMVR with MitraClip were more likely to be older (MD: 5.27, 95% CI: 2.20 to 8.34), have a higher Euroscore rating (MD: 8.79, 95% CI: 5.80 to 11.77), were more likely to have a previous PCI before therapy (OR: 2.44, 95% CI: 1.62 to 3.68), and were more likely to have a previous CABG before therapy (OR: 4.77, 95% CI: 2.68 to 8.49).

7.5 Source Citation : Abdel-Wahab et al. 2020[33]

Study Design: RCT

Note: This RCT reports the long-term (5 year) results of the CHOICE (Comparison of Transcatheter Heart Valves in High-Risk Patients with Severe Aortic Stenosis: Medtronic CoreValve versus Edwards SAPIEN XT) trial originally published by Abdel-Wahab and colleagues in 2014[69]

Device or Material: Balloon-expandable valves (CoCr: Edwards Sapien XT) vs. Self-expandable valves (Nitinol: Medtronic CoreValve)

Contact Duration: Up to 5 years

Dose: NR

Frequency/Duration: NR

Response: All-cause mortality, aortic valve reintervention, bioprosthetic valve dysfunction, bioprosthetic valve failure, cardiovascular mortality, endocarditis, life-threatening bleeding, major bleeding, major vascular complications, MI, minor vascular complications, moderate to severe mitral regurgitation, moderate to severe tricuspid regurgitation, NSVD, paravalvular aortic regurgitation, PPI, repeat hospitalization for heart failure, stroke, severe hemodynamic SVD, SVD, total aortic regurgitation, transvalvular aortic regurgitation, valve thrombosis, valve-related death

Patient characteristics (gender, age): Mean age (SD): balloon-expandable valve: 81.9 (6.7), self-expanding valve: 79.6 (15.8); female sex, n/N (%): balloon-expandable valve: 69/121 (57.0%), self-expanding valve: 86/120 (71.7%)

Number per Group: Balloon-expandable valve: 121, self-expanding valve: 120

Observed adverse effects: All-cause mortality, n (%): Balloon-expandable valve: 63 (53.4%), self-expanding valve: 54 (47.6%), p=0.38, **no difference**

Aortic valve reintervention, n (%): Balloon-expandable valve: 3 (2.5%), self-expanding valve: 3 (2.6%) p=0.97, **no difference**

Bioprosthetic valve dysfunction, n/N (%): Balloon-expandable valve: 28 (22.5%), self-expanding valve: 26 (20.9%), p=0.91, **no difference**

Bioprosthetic valve failure, n (%): Balloon-expandable valve: 6 (4.1%), self-expanding valve: 3 (3.4%), p=0.63, **no difference**

Cardiovascular mortality, n (%): Balloon-expandable valve: 37 (31.6%), self-expanding valve: 25 (21.5%), p=0.12, **no difference**

Endocarditis, n (%): Balloon-expandable valve: 2 (1.6%), self-expanding valve: 4 (3.4%), p=0.39, **no difference**

Life-threatening bleeding, n (%): Balloon-expandable valve: 21 (17.3%), self-expanding valve: 18 (16.2%), p=0.77, **no difference**

Major bleeding, n (%): Balloon-expandable valve: 28 (26.3%), self-expanding valve: 18 (16.2%), p=0.26, **no difference**

Major vascular complications, n (%): Balloon-expandable valve: 14 (11.6%), self-expanding valve: 14 (12.1%), p=0.89, **no difference**

MI, n (%): Balloon-expandable valve: 2 (1.6%), self-expanding valve: 7 (6.1%), p=0.08, **no difference**

Minor bleeding, n (%): Balloon-expandable valve: 17 (14.3%), self-expanding valve: 12 (10.4%), p=0.37, **no difference**

Minor vascular complications, n (%): Balloon-expandable valve: 5 (4.2%), self-expanding valve: 3 (2.6%), p=0.51, **no difference**

Moderate to severe mitral regurgitation, n/N (%): Balloon-expandable valve: 15/47 (31.9%), self-expanding valve: 9/48 (18.7%), p=0.13, **no difference**

Moderate to severe tricuspid regurgitation, n/N (%): Balloon-expandable valve: 10/45 (22.2%), self-expanding valve: 13/47 (27.6%), p=0.54, **no difference**

NSVD, n (%): Balloon-expandable valve: 17 (17.8%), self-expanding valve: 23 (26.7%), p=0.20, **no difference**

Moderate/severe PPM, n (%): Balloon-expandable valve: 14 (15.9%), self-expanding valve: 13 (16.0%), p=1.0, **no difference**

Moderate/severe PVL, n (%): Balloon-expandable valve: 3 (2.5%), self-expanding valve: 10 (8.5%), p=0.08, **no difference**

Paravalvular aortic regurgitation, n (%): Balloon-expandable valve: none/trace 28 (59.6%), mild 19 (40.4%), moderate 0 (0%), severe 0 (0%); self-expanding valve: none/trace 28 (53.8%), mild 24 (46.2%), moderate 0 (0%), severe 0 (0%); p=0.69, **no difference**

PPI, n (%): Balloon-expandable valve: 28 (25.4%), self-expanding valve: 40 (40.4%), p=0.01, **favors balloon-expandable valves**

Repeat hospitalization for heart failure, n (%): Balloon-expandable valve: 21 (17.5%), self-expanding valve: 19 (16.5%), p=0.73, **no difference**

Stroke, n (%): Balloon-expandable valve: 21 (17.5%), self-expanding valve: 19 (16.5%), p=0.73, **no difference**

Severe hemodynamic SVD, n (%): Balloon-expandable valve: 2 (0.9%), self-expanding valve: 0 (0%) p=0.20, **no difference**

SVD, n/N (%): Balloon-expandable valve: 6 (6.6%), self-expanding valve: 0 (0%), p=0.018, **favors self-expanding valves**

Moderate SVD, n/N (%): Balloon-expandable valve: 4 (5.6%), self-expanding valve: 0 (0%), p=0.047, **favors self-expanding valves**

Severe SVD, n/N (%): Balloon-expandable valve: 2 (0.9%), self-expanding valve: 0 (0%), p=0.20, **no difference**

Total aortic regurgitation, n (%): Balloon-expandable valve: none/trace 27 (57.4%), mild 20 (42.6%), moderate 0 (0%), severe 0 (0%); self-expanding valve: none/trace 25 (48.1%), mild 27 (51.8%), moderate 0 (0%), severe 0 (0%); p=0.42, **no difference**

Transvalvular aortic regurgitation, n (%): Balloon-expandable valve: none/trace 46 (97.9%), mild 1 (2.1%), moderate 0 (0%), severe 0 (0%); self-expanding valve: none/trace 49 (94.2%), mild 3 (5.8%), moderate 0 (0%), severe 0 (0%); p=0.62, **no difference**

Valve-related death, n (%): Balloon-expandable valve: 4 (3.3%), self-expanding valve: 3 (2.6%) p=0.74, **no difference**

Valve thrombosis, n (%): Balloon-expandable valve: 6 (7.3%), self-expanding valve: 1 (0.8%), p=0.06, **no difference**

Timing of adverse effects: Up to 5 years

Factors that predict response: Female sex (HR: 0.58, 95% CI: 0.38 to 0.89, p=0.011) was a predictor of lower mortality at 5 years, whereas higher STS score in % (HR 1.11, 95% CI: 1.06 to 1.15, p<0.001) and higher systolic pulmonary artery pressure in mmHg (HR 1.03, 95% CI: 1.01 to 1.04, p=0.001) were predictors of higher mortality at 5 years.

7.6 Source Citation : Benito-Gonzalez et al. 2019[21]

Study Design: Systematic Review

Device or Material: Percutaneous mitral valve repair (PMVR) with MitraClip (CoCr) vs Stand-Alone Optimal Medical Therapy (OMT)

Contact Duration: Mean follow-up range: 12 months to 33 months

Dose: NR

Frequency/Duration: NR

Response: All-cause mortality (1-year, 2-year), hospitalization due to HF, MI, need for heart transplantation/left VAD, stroke, unplanned mitral valve surgery

Patient characteristics (gender, age): Mean age range: PMVR: 70.1 to 75.4 years, OMT: 68.2 to 76 years

Number per Group: 1,513 patients with functional mitral regurgitation (FMR)

Observed adverse effects:

All-cause mortality: HR 0.56 (95% CI: 0.38 to 0.84), I^2=64%, p=0.005, **favors MitraClip**

> All- cause mortality (1 year), n/N: MitraClip: 120/796, OMT: 157/717, OR 0.57 (95% CI: 0.32 to 1.00), I^2=72%, p=0.05, **favors MitraClip**
>
> All- cause mortality (2 year), n/N: MitraClip: 102/412, OMT: 162/414, OR 0.52 (95% CI: 0.38 to 0.69), I^2=0%, p<0.001, **favors MitraClip**

Hospitalization due to HF: HR 0.65 (95% CI: 0.46 to 0.92), I^2=81%, p=0.01, **favors MitraClip**

MI, n/N: MitraClip: 12/454, OMT: 16/464, OR 0.77 (95% CI: 0.37 to 1.63), I^2=0%, p=0.50, **no difference**

Need for heart transplantation/left VAD, n/N: MitraClip: 15/454, OMT: 31/464, OR 0.48 (95% CI: 0.25 to 0.90), I^2=0%, p=0.021, **favors MitraClip**

Stroke, n/N: MitraClip: 18/454, OMT: 12/464, OR 1.56 (95% CI: 0.74 to 3.28), I^2=0%, p=0.24, **no difference**

Unplanned mitral valve surgery, n/N: MitraClip: 4/412, OMT: 18/414, OR 0.20 (95% CI: 0.07 to 0.57), I^2=0%, p=0.003, **favors MitraClip**

Timing of adverse effects: Mean follow-up range: 12 months to 33 months

Factors that predict response: Subgroup analysis by type of study design showed that significant results for all-cause mortality was driven by observational trials (HR 0.39, 95% CI: 0.26 to 0.59) since RCTs displayed a non-significant difference (HR 0.80, 95% CI: 0.45 to 1.42).

7.7 Source Citation : Dreger et al. 2020[34]

Study Design: RCT

Device or Material: CAVI with Edwards Sapien XT (CoCr) vs. OMT

Contact Duration: Up to 3 months

Dose: NR

Frequency/Duration: NR

Response: Hospitalization due to HF, mortality (all-cause, hemorrhage, right HF, sepsis)

Patient characteristics (gender, age): Median age: CAVI: 77 (IQR 68.2 to 82.0), OMT: 77 (IQR 72.2 to 79.5); percent female: CAVI: 12 (86%), OMT: 7 (50%)

Number per Group: 28 patients with severe tricuspid regurgitation and high surgical risk, CAVI (n=14) and OMT (n=14)

Observed adverse effects:

Hospitalization due to HF, n (%): CAVI: 4 (29%), OMT: 4 (29%), p=1.000, **no difference**

Mortality (all-cause), n (%): CAVI: 8 (57%), OMT: 4 (29%), p=0.159, **no difference**

Mortality (hemorrhage), n (%): CAVI: 1 (7%), OMT: 0 (0%), p=NR, **no difference**

Mortality (right HF), n (%): CAVI: 4 (29%), OMT: 3 (21%), p=NR, **no difference**

Mortality (sepsis), n (%): CAVI: 3 (21%), OMT: 1 (7%), p=NR, **no difference**

There were no major vascular complications in either group.

Timing of adverse effects: Up to 3 months

Factors that predict response: NR

7.8 Source Citation : Gozdek et al. 2020a[22]

Study Design: Systematic Review (5 propensity-score matched retrospective case series, 1 RCT)

Device or Material: Self-expandable aortic valve (Nitinol: ACURATE Neo) vs. Edwards Sapien 3 (CoCr)

Contact Duration: Mean follow-up between 1 and 12.7 months

Dose: NR

Frequency/Duration: NR

Response: AKI, device success, early safety, mild paravalvular leak, major vascular complications, moderate to severe paravalvular leak, mortality (30-day), periprocedural MI, PPI, serious bleeding events, stroke

Patient characteristics (gender, age): 59.7% female Sapien 3, 64.1% female ACURATE, age NR

Number per Group: 2,818 patients (ACURATE neo n=1256, SAPIEN 3 n=1562)

Observed adverse effects: Early safety: ACURATE Neo: 174/1256, Sapien 3: 197/1562, RR: 1.15 (95% CI: 0.94 to 1.40), I^2=0%, p=0.16, **no difference**

AKI: ACURATE Neo: 30/1164, Sapien 3: 31/1470, RR: 1.28 (95% CI: 0.71 to 2.31), I^2=15%, p=0.42, **no difference**

Device success: ACURATE Neo: 918/1164, Sapien 3: 1169/1470, RR: 1.01 (95% CI: 0.92 to 1.10), I^2=89%, p=0.89, **no difference**

Major vascular complications: ACURATE Neo: 86/1256, Sapien 3: 98/1562, RR: 1.21 (95% CI: 0.89 to 1.65), I^2=6%, p=0.23, **no difference**

Mild paravalvular leak: ACURATE Neo: 430/945, Sapien 3: 263/940, RR: 1.60 (95% CI: 1.40 to 1.84), I^2=14%, p<0.00001, **favors Sapien 3**

Moderate to severe paravalvular leak: ACURATE Neo: 147/1256, Sapien 3: 36/1562, RR: 3.70 (95% CI: 2.04 to 6.70), I^2=53%, p<0.0001, **favors Sapien 3**

Mortality (30-day): ACURATE Neo: 36/1256, Sapien 3: 23/1562, RR: 1.77 (95% CI: 1.03 to 3.04), I^2=0%, p=0.04, **favors Sapien 3**

PPI: ACURATE Neo: 127/1256, Sapien 3: 222/1562, RR: 0.72 (95% CI: 0.58 to 0.89), I^2=4%, p=0.003, **favors ACURATE Neo**

Periprocedural MI: ACURATE Neo: 4/1164, Sapien 3: 2/1470, RR: 1.76 (95% CI: 0.36 to 8.47), I^2=0%, p=0.48, **no difference**

Serious bleeding events: ACURATE Neo: 109/1256, Sapien 3: 101/1562, RR: 1.23 (95% CI: 0.95 to 1.61), I^2=0%, p=0.12, **no difference**

Stroke: ACURATE Neo: 28/1256, Sapien 3: 38/1562, RR: 0.95 (95% CI: 0.57 to 1.57), I^2=0%, p=0.84, **no difference**

Timing of adverse effects: Mean follow-up between 1 and 12.7 months

Factors that predict response: Results for device success were highly imprecise and dependent on study design with a preference for ACURATE Neo via RCT evidence (RR 1.44, 95% CI: 1.24 to 1.66) while PS-matched studies preferred Sapien 3 (RR 0.95, 95% CI: 0.91 to 0.99). PPI was also imprecise with no difference for RCT evidence (RR 1.07, 95% CI: 0.69 to 1.67) and favorability towards ACURATE Neo for PS-matched studies (RR 0.64, 95% CI: 0.50 to 0.81). No other outcomes showed major differences

between RCT and PS-matched study outcomes. When taking into account "0 events", evidence for periprocedural MI, stroke, and 30-day mortality were similar to the main analyses.

7.9 Source Citation : Gozdek et al. 2020b[23]

Study Design: Systematic Review

Device or Material: Sapien 3 (CoCr) vs. Lotus (Nitinol) aortic valve replacements

Contact Duration: Between 1 and 36 months

Dose: NR

Frequency/Duration: NR

Response: AKI, cerebrovascular events, device success, early safety, major vascular complications, mild paravalvular leak, moderate to severe paravalvular leak, mortality (30-day), PPI, PPM, serious bleeding

Patient characteristics (gender, age): Mean age range: Sapien 3: 79.8 to 83 years, Lotus: to 79.5 to 83 years; Percent female: Sapien 3: 45.3%, Lotus: 50.8%

Number per Group: 2,836 patients (Lotus n=862, Sapien 3 n=1,974)

Observed adverse effects:

AKI: Lotus: 7/429, Sapien 3: 32/1281, RR 1.11 (95% CI: 0.43 to 2.86), I^2=6%, p=0.82, **no difference**

Cerebrovascular events: Lotus: 26/645, Sapien 3: 41/1524, RR 1.76 (95% CI: 1.03 to 2.99), I^2=0%, p=0.04, **favors Sapien 3**

Device success: Lotus: 587/645, Sapien 3: 1291/1524, RR 1.00 (95% CI: 0.98 to 1.02), I^2=0%, p=0.76, **no difference**

Early safety: Lotus: 52/461, Sapien 3: 147/1162, RR 1.10 (95% CI: 0.79 to 1.52), I^2=0%, p=0.58, **no difference**

Major vascular complications: Lotus: 27/645, Sapien 3: 114/1524, RR 0.82 (95% CI: 0.54 to 1.25), I^2=0%, p=0.36, **no difference**

Mild paravalvular leak: Lotus: 136/724, Sapien 3: 550/1607, RR 0.65 (95% CI: 0.49 to 0.85), I^2=45%, p=0.002, **favors Lotus**

Moderate to severe paravalvular leak: Lotus: 3/828, Sapien 3: 20/1708, RR 0.56 (95% CI: 0.18 to 1.77), I^2=0%, p=0.32, **no difference**

Mortality (30-day): Lotus: 20/645, Sapien 3: 35/1524, RR 1.48 (95% CI: 0.74 to 2.96), I^2=8%, p=0.27, **no difference**

PPI: Lotus: 247/679, Sapien 3: 273/1790, RR 2.30 (95% CI: 1.95 to 2.71), I^2=0%, p<0.00001, **favors Sapien 3**

PPM: Lotus: 55/549, Sapien 3: 181/1315, RR 1.10 (95% CI: 0.82 to 1.47), I^2=0%, p=0.54, **no difference**

Serious bleeding: Lotus: 45/645, Sapien 3: 149/1524, RR 0.94 (95% CI: 0.66 to 1.33), I^2=0%, p=0.72, **no difference**

Timing of adverse effects: Between 1 and 36 months

Factors that predict response: NR

7.10 Source Citation: Malvindi et al. 2020[24]

Study Design: Systematic review

Device or Material: Carpentier-Edwards Pericardial (CoCr), Carpentier-Edwards Porcine (CoCr), Hancock II (non-CoCr), and Mosaic mitral valve 69ioprosthesis

Note: Hancock II and Mosaic bioprosthesis contain a non-metallic frame

Contact Duration: Mean follow-up: Carpentier-Edwards Pericardial: 6.42 years, Carpentier-Edwards Porcine: 5.97 years, Hancock II: 7.28 years, and Mosaic: 7.52 years

Dose: NR

Frequency/Duration: NR

Response: Early mortality, Freedom from SVD (10 years, 15 years), Implant survival

Patient characteristics (gender, age): Mean age: Carpentier-Edwards Pericardial: 65.2 years, Carpentier-Edwards Porcine: 61.5 years, Hancock II: 63.5 years, and Mosaic: 68.0 years; Gender: NR

Number per Group: Carpentier-Edwards Pericardial (5 studies):1143 patients, Carpentier-Edwards Porcine (3 studies): 1361 patients, Hancock II (2 studies): 424 patients, and Mosaic (4 studies): 940 patients

Observed adverse effects:

Early mortality in %: Carpentier-Edwards Pericardial: 4.7%, Carpentier-Edwards Porcine: 9.9%, Hancock II: 8.7%, and Mosaic: 3.7%

Freedom from SVD (10 years): Carpentier-Edwards Pericardial: 91%, Carpentier-Edwards Porcine: 84%, Hancock II: 84%, and Mosaic: 93%

Freedom from SVD (15 years): Carpentier-Edwards Pericardial: 61%, Carpentier-Edwards Porcine: 67%, Hancock II: 66%, and Mosaic: 80%

Note: Implant survival data was also reported, however, survival for each individual device was not reported in the text other than a Kaplan-Meier curve.

Timing of adverse effects: Maximum of 20 years

Factors that predict response: NR

7.11 Source Citation: Quintana et al. 2020[25]

Study Design: Systematic Review

Device or Material: Sapien XT (CoCr), CoreValve (Nitinol), Sapien 3 (CoCr), Lotus or DirectFlow (Nitinol), Evolut R/Pro (Nitinol), Venus (Nitinol)

Contact Duration: NR

Dose: Sapien XT: Small: 99/192, Medium: 72/192, Large: 21/192 (5 studies, 3 studies: NR); CoreValve: Small: 57/213, Medium: 108/213, 47/213 (5 studies, 3 studies: NR); Sapien 3: NR (1 study); Lotus or DirectFlow: NR (1 study); Evolut R/Pro: NR (3 studies); Venus: NR (1 study).

Note: Small valves are 23 to 26 mm, medium 27-29 mm, and large ≥ 29 mm

Frequency/Duration: NR

Response: Device success, life-threatening bleeding, moderate to severe prosthetic valve regurgitation, mortality (30 day), PPI

Patient characteristics (gender, age): Mean age range: Sapien XT: 74 to 82 years (4 studies, 4 studies: NR), CoreValve: 77 to 82 years (5 studies, 3 studies: NR), Sapien 3: NR (1 study), Lotus or DirectFlow: NR (1 study), Evolut R/Pro: 72.5 years (1 study, 2 studies: NR), Venus: NR (1 study)

Percent female: Sapien XT: 28% to 50% (4 studies, 4 studies: NR), CoreValve: 38% to 60% (4 studies, 4 studies: NR), Sapien 3: NR (1 study), Lotus or DirectFlow: NR (1 study), Evolut R/Pro: 45% (1 study, 2 studies: NR), Venus: NR (1 study)

Number per Group: 1547 patients; Sapien XT: 381 patients, CoreValve: 401 patients, Sapien 3: 176 patients, Lotus or DirectFlow: 48 patients, Evolut R/Pro: 527 patients, Venus: 14 patients

Observed adverse effects:

Sapien XT vs. CoreValve

Device success: RR 1.01 (95% CI: 0.97 to 1.06), **no difference**

Life-threatening bleeding: RR 0.81 (95% CI: 0.33 to 2.02), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 0.95 (95% CI: 0.52 to 1.72), **no difference**

Mortality (30 day): RR 0.80 (95% CI: 0.36 to 1.80), **no difference**

PPI: RR 0.60 (05% CI: 0.41 to 0.88), **favors Sapien XT**

Sapien XT vs. Sapien 3 (Note: took reciprocal)

Device success: RR 0.99 (95% CI: 0.94 to 1.04), **no difference**

Life-threatening bleeding: RR 2.13 (95% CI: 0.34 to 14.29), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 5.88 (95% CI: 1.52 to 20), **favors Sapien 3**

Mortality (30 day): RR 2.44 (95% CI: 0.51 to 11.11), **no difference**

PPI: RR 0.82 (95% CI: 0.45 to 1.49), **no difference**

Sapien XT vs. Lotus or DirectFlow (Note: took reciprocal)

Device success: RR 1.09 (95% CI: 0.96 to 1.22), **no difference**

Life-threatening bleeding: RR 1.47 (95% CI: 0.13 to 16.67), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 4.76 (95% CI: 0.76 to 33.33), **no difference**

Mortality (30 day): RR 1.19 (95% CI: 0.19 to 7.14), **no difference**

PPI: RR 0.55 (95% CI: 0.26 to 1.15), **no difference**

Sapien XT vs. Evolut R/Evolut Pro (Note: took reciprocal)

Device success: RR 0.99 (95% CI: 0.93 to 1.05), **no difference**

Life-threatening bleeding: RR 1.01 (95% CI: 0.19 to 5.26), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 3.33 (95% CI: 1.01 to 11.11), **favors Evolut R/Evolut Pro**

Mortality (30 day): RR 0.80 (95% CI: 0.22 to 2.94), **no difference**

PPI: RR 0.93 (95% CI: 0.43 to 1.64), **no difference**

Sapien XT vs. Venus (Note: took reciprocal)

Device success: RR 1.08 (95% CI: 0.76 to 1.52), **no difference**

Life-threatening bleeding: RR 0.64 (95% CI: 0.01 to 50), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 2.27 (95% CI: 0.08 to 50), **no difference**

Mortality (30 day): RR 0.63 (95% CI: 0.03 to 14.29), **no difference**

PPI: RR 1.39 (95% CI: 0.29 to 6.67), **no difference**

Sapien 3 vs. CoreValve

Device success: RR 1.02 (95% CI: 0.97 to 1.08), **no difference**

Life-threatening bleeding: RR 0.38 (95% CI: 0.06 to 2.41), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 0.16 (95% CI: 0.04 to 0.63), **favors Sapien 3**

Mortality (30 day): RR 0.33 (95% CI: 0.07 to 1.60), **no difference**

PPI: RR 0.73 (95% CI: 0.41 to 1.32), **no difference**

Sapien 3 vs. Lotus or DirectFlow

Device success: RR 1.10 (95% CI: 0.97 to 1.23), **no difference**

Life-threatening bleeding: RR 0.69 (95% CI: 0.05 to 11.11), **no difference**

Moderate to severe prosthetic valve regurgitation: 0.81 (95% CI: 0.10 to 6.67), **no difference**

Mortality (30 day): RR 0.49 (95% CI: 0.06 to 4), **no difference**

PPI: RR 0.67 (95% CI: 0.31 to 1.45), **no difference**

Sapien 3 vs. Evolut R/Pro

Device success: RR 1.00 (95% CI: 0.93 to 1.08), **no difference**

Life-threatening bleeding: RR 0.47 (95% CI: 0.06 to 4), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 0.57 (95% CI: 0.10 to 3.13), **no difference**

Mortality (30 day): RR 0.33 (95% CI: 0.06 to 1.89), **no difference**

PPI: RR 1.02 (95% CI: 0.47 to 2.22), **no difference**

Sapien 3 vs. Venus

Device success: RR 1.09 (95% CI: 0.77 to 1.54), **no difference**

Life-threatening bleeding: RR 0.30 (95% CI: 0.003 to 25), **no difference**

Moderate to severe prosthetic valve regurgitation: RR 0.39 (95% CI: 0.01 to 12.5), **no difference**

Mortality (30 day): RR 0.26 (95% CI: 0.01 to 7.14), **no difference**

PPI: RR 1.69 (95% CI: 0.33 to 8.33), **no difference**

Note: All outcomes except for the "Sapien 3 vs CoreValve" and Sapien XT vs CoreValve" were acquired by taking the reciprocal of the relative risks, as well as the reciprocals of the upper and lower bounds of the 95% CI for ease of reporting.

Timing of adverse effects: Mortality outcomes were reported at 30 days. All other outcomes had an unspecified follow up time.

Factors that predict response: NR

7.12 Source Citation : Ashauer et al. 2019[26]

Study Design: Systematic review

Device or Material: Edwards Sapien 3 or Sapien XT (both CoCr)

Note: Authors compare outcomes by whether BAV was used during the procedure.

Contact Duration: 30 days

Dose: Valve Size: TAVI with BAV: 20-23 mm: 28.9%, 26 mm: 45.1%, 29 mm: 26.0%; TAVI without BAV: 20-23 mm: 31.0%, 26 mm: 41.1%, 29 mm: 27.9%

Frequency/Duration: Second valve needed: TAV with BAV: 1.2%, TAVI without BAV: 0.8%

Response: Death, hospitalization, life-threatening bleeding, major vascular complications, new-onset dialysis, non-fatal MI, PPI, stroke, valve dysfunction

Patient characteristics (gender, age): Median age (IQR): TAVI with BAV: 82 (79 to 86), TAVI without BAV: 81 (78 to 86); Female (%): TAVI with BAV: 49.9%, TAVI without BAV: 45.4%

Number per Group: 694 patients (n=339 TAVI with BAV, n=355 TAVI without BAV)

Observed adverse effects: Note: Ors were adjusted for age, gender, prior MI, stroke/TIA, creatinine, ejection fraction, and NYHA class

Death: TAVI with BAV (n=327 patients): 1.8%, TAVI without BAV (n=343 patients): 1.5%, non-adjusted OR: 0.79 (95% CI: 0.23 to 2.65), adjusted OR: 0.4 (95% CI: 0.06 to 1.86), **no difference**

Hospitalization: TAVI with BAV (n=333 patients): 2.7%, TAVI without BAV (n=344 patients): 1.2%, non-adjusted OR: 0.42 (95% CI: 0.11 to 1.31), adjusted OR: 0.48 (95% CI: 0.09 to 1.9), **no difference**

Life-threatening bleeding: TAVI with BAV (n=333 patients): 3.0%, TAVI without BAV (n=345 patients): 1.4%, non-adjusted OR: 0.48 (95% CI: 0.15 to 1.35), adjusted OR: 0.42 (95% CI: 0.09 to 1.48), **no difference**

Major vascular complications: TAVI with BAV (n=333 patients): 4.5%, TAVI without BAV (n=345 patients): 3.5%, non-adjusted OR: 0.76 (95% CI: 0.35 to 1.66), adjusted OR: 0.63 (95% CI: 0.21 to 1.65), **no difference**

New-onset dialysis: TAVI with BAV (n=332 patients): 3.9%, TAVI without BAV (n=348 patients): 3.7%, non-adjusted OR: 0.95 (95% CI: 0.43 to 2.1), adjusted OR: 0.97 (95% CI: 0.4 to 2.32), **no difference**

Non-fatal MI: TAVI with BAV (n=336 patients): 0.6%, TAVI without BAV (n=349 patients): 0.9%, non-adjusted OR: 1.45 (95% CI: 0.24 to 11.05), adjusted OR: 1.29 (95% CI: 0.12 to 13.1), **no difference**

PPI: TAVI with BAV (n=337 patients): 10.1%, TAVI without BAV (n=350 patients): 8.6%, non-adjusted OR: 0.84 (95% CI: 0.5 to 1.4), adjusted OR: 1.17 (95% CI: 0.62 to 2.2), **no difference**

Stroke: TAVI with BAV (n=327 patients): 0.9%, TAVI without BAV (n=341 patients): 0.3%, non-adjusted OR: 0.32 (95% CI: 0.02 to 2.5), adjusted OR: 0.79 (95% CI: 0.02 to 27.7), **no difference**

Valve dysfunction: TAVI with BAV (n=322 patients): 0.9%, TAVI without BAV (n=337 patients): 0%, non-adjusted OR: NA

Timing of adverse effects: 30 days

Factors that predict response: Adjusting outcomes by baseline characteristics of interest did not affect the conclusions of any clinical outcomes. Authors analyzed by route of access (transfemoral, transapical, and transaortic), however, there were too few 30-day outcome events to allow a meaningful interpretation.

7.13 Source Citation : Bob-Manuel et al. 2019[27]

Study Design: Systematic Review

Device or Material: Early Generation Sapien Valves (CoCr: Sapien and Sapien XT), Edwards Sapien 3 (CoCr), CoreValve Early Generation (Nitinol)

Contact Duration: 30 days to 9 years

Dose: Valve size, n (%): Edwards valves (n=269 patients): 23 mm: 61 (22.7%), 26 mm: 136 (50.6%), 29 mm: 72 (26.8%); CoreValve (n=272 patients): 26 mm: 66 (24.3%), 29 mm: 151 (55.5%), 31 mm: 55 (20.2%); Venus: NR; Lotus: NR

Frequency/Duration: NR

Response: conversion to open heart surgery, device success, mortality (30-day, 1 year), PPI, PVL ≥ 3, stroke, valve malposition

Patient characteristics (gender, age): Mean age (SD): 77 years (9.1); Gender: 39.6% female

Number per Group: 1,332 patients with BAV; n=129 Edwards Sapien (11.2%), n=249 Edwards Sapien XT (21.6%), n=219 Edwards Sapien 3 (19.1%), n=477 CoreValve (41.6%), n=23 CoreValve Evolut R (2.0%), n=5 Venus (0.4%), n=46 Lotus (4.0%)

Observed adverse effects: Valve malposition: Edwards early generation valves: 5/248 (2.0%), Edwards Sapien 3: 0/51 (0%), CoreValve early generation: 10/174 (5.7%)

Conversion to open heart surgery: Edwards early generation valves: 3/86 (3.5%), Edwards Sapien 3: 0/51 (0%), CoreValve early generation: 4/181 (2.2%)

Device success: Edwards early generation valves: 134/147 (91.2%), Edwards Sapien 3: 50/51 (98.0%), CoreValve early generation: 239/266 (89.8%)

Mortality (30-day): Edwards early generation valves: 10/193 (5.2%), Edwards Sapien 3: 2/51 (3.9%), CoreValve early generation: 15/230 (6.5%)

Mortality (1 year): Edwards early generation valves: 20/133 (15.0%), Edwards Sapien 3: NR, CoreValve early generation: 26/176 (14.8%)

PPI: Edwards early generation valves: 9/55 (16.4%), Edwards Sapien 3: 12/51 (23.5%), CoreValve early generation: 41/141 (29%)

PVL ≥ 3: Edwards early generation valves: 23/184 (12.5%), Edwards Sapien 3: 0/51 (0%), CoreValve early generation: 15/183 (8.2%)

Stroke: Edwards early generation valves: 3/160 (1.9%), Edwards Sapien 3: 1/51 (2.0%), CoreValve early generation: 5/290 (1.7%)

Timing of adverse effects: 30 days to 9 years

Factors that predict response: NR

7.14 Source Citation: Chiarito et al. 2018[28]

Study Design: Systematic Review (8 observational studies, 1 RCT)

Device or Material: MitraClip (CoCr)

Contact Duration: 1 year

Dose: NR

Frequency/Duration: NR

Response: MR Grade ≤ 2, mortality, MV re-intervention, primary safety endpoint

Patient characteristics (gender, age): Mean age (SD): FMR: 73.1 years (10), DMR: 78.1 (10); Female, n (%): FMR: 610 (34%), DMR: 356 (43%)

Number per Group: 2,615 patients; 1,782 patients with FMR, 833 patients with DMR

Observed adverse effects:

MR Grade ≤ 2: FMR: 719/1304, DMR: 295/504, RR 1.12 (95% CI: 0.86 to 1.47), I^2=70%, p=0.40, **no difference**

Mortality: FMR: 298/1693, DMR: 110/805, RR 1.26 (95% CI: 0.90 to 1.77), I^2=55%, p=0.18, **no difference**

MV re-intervention: FMR: 77/1770, DMR: 80/818, RR 0.60 (95% CI: 0.38 to 0.97), I^2=33%, p=0.04, **favors FMR**

Primary safety endpoint (SLDA and device embolism rate): FMR: 25/969, DMR: 20/464, RR 0.76 (95% CI: 0.08 to 7.28), I^2=78%, p=0.81, **no difference**

Timing of adverse effects: 1 year

Factors that predict response: NR

7.15 Source Citation : Megaly et al. 2018[29]

Study Design: Systematic review

Device or Material: MitraClip

Note: Comparison of patients with a-fib versus without a-fib

Contact Duration: 1 to 12 months

Dose: NR

Frequency/Duration: NR

Response: MACE, mortality, stroke

Patient characteristics (gender, age): Mean age (SD): a-fib: 76.6 (5.7), non-a-fib: 73.1 (6.5); female (%): a-fib: 43.7%, without a-fib: 43.1%

Number per Group: 1,510 patients; 718 with a-fib, 792 without a-fib

Observed adverse effects:

MACE: A-fib: 90/371, non-a-fib: 75/484, OR: 1.46 (95% CI: 1.03 to 2.07), I^2=13%, p=0.03, **favors non-a-fib**

Mortality: A-fib: 142/697, non-a-fib: 101/776, OR: 1.54 (95% CI: 1.16 to 2.04), I^2=0%, p=0.003, **favors non-a-fib**

Stroke: A-fib: 12/697, non-a-fib: 13/776, OR: 1.13 (95% CI: 0.36 to 3.56), I^2=37%, p=0.84, **no difference**

Timing of adverse effects: 1 to 12 months

Factors that predict response: Mortality was similar to the main results when excluding early post-operative follow-up (OR 1.53, 95% CI: 1.15 to 2.03).

7.16 Source Citation : Tummala et al. 2018[30]

Study Design: Systematic Review

Device or Material: Edwards Sapien 3 (CoCr) vs. Sapien XT (CoCr)

Contact Duration: Up to 30 days

Dose: NR

Frequency/Duration: NR

Response: AKI, cardiac mortality (30 days), device success, early safety endpoint, MI, mortality (30 days), major/life-threatening bleeding, major vascular complications, moderate to severe PVL, PPI, stroke

Patient characteristics (gender, age): Mean age range: Sapien 3: 79 to 85 years, Sapien XT: 80 to 84 years; female (%): Sapien 3: 26% to 78%, Sapien XT: 40% to 63%

Number per Group: 4,496 patients; n=1,700 Sapien 3, n=2,796 Sapien XT

Observed adverse effects: Sapien 3 vs Sapien XT

AKI: rate NR, OR: 0.40 (95% CI: 0.27 to 0.59), I^2=77.6%, **favors Sapien 3**

Cardiac mortality (30 days): rate NR, OR: 0.76 (95% CI: 0.32 to 1.83), I^2=0%, **no difference**

Device success: 98.18% vs 93.76%, OR: 3.14 (95% CI: 1.65 to 5.99), I^2=0%, **favors Sapien XT**

Early safety endpoint: OR: 0.48 (95% CI: 0.31 to 0.75), I^2=0%, **favors Sapien 3**

MI: rate NR, OR: 1.41 (95% CI: 0.47 to 4.28), I^2=16.4%, **no difference**

Major/life-threatening bleeding: 6.40% vs 12.03%, OR: 0.50 (95% CI: 0.32 to 0.79), I^2=0%, **favors Sapien 3**

Major vascular complications: 4.07% vs 9.13%, OR: 0.41 (95% CI: 0.29 to 0.58), I^2=45.7%, **favors Sapien 3**

Moderate to severe PVL: 5.58% vs 19.35%, OR: 0.27 (95% CI: 0.21 to 0.36), I^2=0%, **favors Sapien 3**

Mortality (30 days): 3.29% vs 5.68%, OR: 0.51 (95% CI: 0.35 to 0.74), I^2=0%, **favors Sapien 3**

PPI: OR: 13.29% vs 9.23%, 1.58 (95% CI: 1.29 to 1.94), I^2=0%, **favors Sapien XT**

Stroke: OR: 1.48% vs 2.86%, 0.49 (95% CI: 0.27 to 0.87), I^2=0%, **favors Sapien 3**

Timing of adverse effects: Up to 30 days

Factors that predict response: NR

7.17 Source Citation: Ghatak et al. 2015[31]

Study Design: Systematic Review

Device or Material: Edwards Sapien (CoCr) and Sapien XT (CoCr) aortic valves

Note: Comparison between transfemoral (TF) and transapical (TA) approaches

Contact Duration: Between 30 days or 1 year

Dose: NR

Frequency/Duration: NR

Response: AKI, major or life-threatening bleeding, mortality (30-day, 1 year), PPI, stroke

Patient characteristics (gender, age): Age: NR; Female (n=12 studies, 1,985 patients): TF: 50.6%, TA: 50.2%

Number per Group: 6,172 patients; 3,656 patients with TF approach, 2,516 patients with TA approach

Observed adverse effects:

AKI: TF: 48/829, TA: 118/708, RR: 0.53 (95% CI: 0.38 to 0.73), I^2=2.6%, **favors TF approach**

Major or life-threatening bleeding: TF: 97/709, TA: 83/599, RR: 1.04 (95% CI: 0.73 to 1.48), I^2=26.2%, **no difference**

Mortality (30 day): TF: 196/3656, TA: 259/2516, RR: 0.61 (95% CI: 0.46 to 0.81), I^2=31.4%, **favors TF approach**

Mortality (1 year): TF: 163/949, TA: 226/926, RR: 0.68 (95% CI: 0.55 to 0.84), I^2=12.5%, **favors TF approach**

PPI: TF: 84/1428, TA: 103/1304, RR: 0.80 (95% CI: 0.60 to 1.07), I^2=0%, **no difference**

Stroke: TF: 53/1438, TA: 59/1334, RR: 0.88 (95% CI: 0.60 to 1.28), I^2=0%, **no difference**

Timing of adverse effects: Mortality was examined at both 30 day and 1-year timepoints. All other outcomes were only examined at 30 days.

Factors that predict response: Authors examined whether publication occurred before or after implementation of the standardized VARC definition and found similar results between subgroups.

7.18 Source Citation : Magliano et al. 2015[32]

Study Design: Systematic Review (24 observational studies, 4 RCTs)

Device or Material: Carpentier-Edwards Pericardial (CoCr), Carpentier-Edwards Porcine (CoCr), stentless (no CoCr), and mechanical prostheses (no CoCr)

Contact Duration: Between 1 and 20 years

Dose: NR

Frequency/Duration: NR

Response: Operative mortality, overall mortality, reoperation rate

Patient characteristics (gender, age): Mean age range: 53 to 78 years; Female (%): 9% to 60%

Number per Group: 19,615 patients; 12,951 Carpentier-Edwards Pericardial, 6,664 other prostheses

Observed adverse effects:

Carpentier-Edwards Pericardial vs. Carpentier-Edwards Porcine Prostheses

Operative mortality (3 studies, n=5064): OR: 0.74 (95% CI: 0.46 to 1.17), **no difference**

Overall mortality (2 studies, n=3405): OR: 0.63 (95% CI: 0.16 to 2.46), **no difference**

Reoperation rate (2 studies, n=3405): OR: 0.48 (95% CI: 0.12 to 1.90), **no difference**

Carpentier-Edwards Pericardial vs. Stentless Prostheses

Operative mortality (3 studies, n=299): OR: 1.59 (95% CI: 0.40 to 6.24), **no difference**

Overall mortality (2 studies, n=139): OR: 0.80 (95% CI: 0.25 to 2.52), **no difference**

Reoperation rate (2 studies, n=139): OR: 0.32 (95% CI: 0.05 to 1.84), **no difference**

Carpentier-Edwards Pericardial vs. Mechanical Prostheses

Operative mortality (5 studies, n=2063): OR: 1.26 (95% CI: 0.49 to 3.25), **no difference**

Overall mortality (3 studies, n=1762): OR: 1.39 (95% CI: 0.72 to 2.68), **no difference**

Reoperation rate (3 studies, n=1762): OR 4.92 (95% CI: 2.43 to 9.96), **favors mechanical prostheses**

Timing of adverse effects: Overall mortality and reoperation rates required a minimum of 5-year follow-up after the results of a meta-regression showed that follow-up was responsible for 84% of heterogeneity.

Factors that predict response: NR

a-fib: atrial fibrillation; AE: adverse event; AKI: acute kidney injury; AR: aortic regurgitation; BAV: balloon aortic valvuloplasty; CABG: coronary artery bypass graft; CAVI: caval vein implantation; CI: confidence interval; CoCr: cobalt chromium; DMR: degenerative mitral regurgitation; FE: fixed effects; FMR: functional mitral regurgitation; HF: heart failure; HR: hazard ratio; IQR: interquartile range; MACE: major adverse cardiac event; MD: mean difference; MI: myocardial infarction; MR: mitral regurgitation; MV: mitral valve; MVC: major vascular complication; NA: not applicable; NMA: network meta-analysis; NR: not reported; NSVD: nonstructural valve deterioration; NYHA: New York Heart Association; OMT: optimal medical therapy; OR: odds ratio; PCI: percutaneous coronary intervention; PVL: paravalvular leak; PMVR: percutaneous mitral valve repair; PPI: postoperative pacemaker implantation; PPM: prosthesis-patient mismatch; PS: propensity score; RCT: randomized controlled trial; RE: random effects; RR: relative risk; SAVR: surgical aortic valve repair; SLDA: single leaflet device attachment; SMR: severe mitral regurgitation; SLDA: single leaflet device attachment; SMVR: surgical mitral-valve repair; SR: systematic review; SVD: structural valve deterioration; TA: transapical; TAVI:

transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement; TF: transfemoral; TMVR: transcatheter mitral valve repair; VAD: ventricular assist device

Table 8: Dental/ENT – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

8.1 Source Citation: Gonzalez-Perez et al. 2020[35]

Study Design: Single arm study (a nonrandomized comparative study evaluating and comparing outcomes and complications associated with temporomandibular joint [TMJ] reconstruction with two CoCr stock prosthetic systems).

Device Material: Christensen system ([CS] CoCr, TMJ Implants Inc.), Biomet Microfixation TMJ Replacement System ([BS] CoCr, Biomet).

Contact Duration: Follow-up of 5 years.

Dose: NR.

Frequency/Duration: Unilateral and bilateral implantations.

Response: Failure, heterotopic bone formation, hypersensitivity, loosening, malocclusion, numbness/neurological issue, removal.

Patient characteristics (gender, mean age): 65.7% female. CS group has a mean age of 51 years and BS group has a mean age of 53 years.

Number per Group: Total n=70 (CS, n=11; BS, n=59).

Observed adverse effects: Implant failure led to its removal and replacement in 2 CS cases (18.2%) and 3 BS (5.1%) cases, with a significant difference between the groups.

In the CS group, two patients had a numb lip that resolved spontaneously. In the BS group, five patients had a numb lip and two patients had temporary weakness of the temporal branch of the facial nerve that resolved spontaneously.

In the CS group, two patients demonstrated CoCr hypersensitivity two and four years after placement. In the BS group, one patient demonstrated CoCr hypersensitivity requiring removal of the mandibular component.

In the CS group, one patient had an incorrect postoperative occlusal position. In the BS group, three patients had an incorrect occlusal position after one year which indicated instability of the device.

In the BS group, two prostheses were removed because of malocclusion that resulted from screw loosening; one relative to CoCr hypersensitivity, and one that developed heterotopic bone formation requiring reoperation to remove the formations.

Timing of adverse effects: CoCr hypersensitivity two to four years after placement.

Factors that predict response: NR.

8.2 Source Citation : Toia et al. 2019[36]

Study Design: Single arm (an RCT to compare the marginal bone loss [MBL] using an implant restored with a screw-retained CoCr fixed partial denture [FPD] in an implant-level [IL] or abutment-level [AL]).

Device Material: OsseoSpeed EV Astra Tech Implant System (CoCr, Dentsply Sirona Implants).

Contact Duration: Follow-up of 1 year.

Dose: NR.

Frequency/Duration: Two to four implants per patient; implanted then restoration performed after 6 weeks.

Response: Bleeding on Probing (BoP), failure, fracture, loosening, MBL.

Patient characteristics (gender, mean age): 58% female, 58.9 years.

Number per Group: Overall n=50 (25 per group).

Observed adverse effects: At one year, MBL was 0.086±0.313mm and 0.005±0.222mmm in the IL and AL groups, respectively. The presence of BoP was indicative of inflammation increased with time in the IL group, whereas it decreased in the AL group ($p<0.001$).

One abutment loosening occurred at baseline and was secured before final FPD restoration.

One fracture occurred in the IL group and was resolved by polishing.

The overall failure rate of the screw-retained FPD at 1 year was 2%.

Timing of adverse effects: BoP increased between baseline and 6 months in the IL group and decreased between 6 months and 1 year in the AL group.

Factors that predict response: Peri-implant soft tissue shows less inflammation and higher stability in the AL group in the early follow-up phase.

Abbreviations: AL = abutment level; BoP = bleeding on probing; BS = Biomet system; CS = Christensen system; CoCr = cobalt chromium; FPD = fixed partial denture; IL = implant level; MBL = marginal bone loss; NR = not reported; RCT = randomized controlled trial; TMJ = temporomandibular joint.

Table 9: Gastric – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

9.1 Source Citation: Phillips et al. 2021[37]

Study Design: Single-arm study

Device or Material: REALIZE gastric band (CoCr)

Contact Duration: Follow-up was 5 years

Dose: NR

Frequency/Duration: Single administration

Response: Band slippage, erosion into the gastrointestinal tract, gastric dilation, vomiting, hiatal hernia

Patient characteristics (gender, mean age): Majority female, mean age 40.5 years.

Number per group: 303 enrolled, 231 completed 5 year follow-up.

Observed adverse effects: Band slippage occurred in 21 (6.9%) of patients. Four (1.3%) patients experienced erosion into the gastrointestinal tract. Seven (2.3%) patients experienced gastric dilation. Five (1.6%) patients experienced vomiting, and 5 (1.6%) suffered a hiatal hernia.

Timing of adverse effects: NR

Factors that predict response: NR

Table 10: Intracranial stents – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

10.1 Source Citation: Foreman et al. 2021[38]

Study Design: Systematic review of 12 single arm studies

Device or Material: Pipeline Embolization Device (PED) (CoCr)

Contact Duration: 3 to 18 months

Dose: NR

Frequency/Duration: NR

Response: Mortality, occlusion rate, re-rupture causing an intracranial hemorrhage, total complications

Patient characteristics (gender, age): Percent female: 72.3%; mean age: 51 years

Number per Group: 145 patients with 145 treated aneurysms

Observed adverse effects:

Mortality: 11/139 (7.91%)

Occlusion rate: 105/120 (87.5%)

Re-rupture causing an intracranial hemorrhage: 3/139 (2.16%)

Total complications: 23/139 (16.5%)

Timing of adverse effects: All adverse effects occurred between 3 to 18 months.

Factors that predict response: Results from univariate logistic regression analysis showed a significant association with aneurysm size and re-rupture (log OR: 0.16, 95% CI: 0.05 to 0.31, p=0.008), favoring smaller aneurysms. Aneurysm morphology, treatment time, and treatment method had no effect on re-rupture rate. Radiographic occlusion and symptomatic complications had no significant associations when examining the effects of aneurysm size, aneurysm morphology, treatment time, or treatment method.

10.2 Source Citation : Li et al. 2021[39]

Study Design: Systematic review of 8 single arm studies

Device or Material: Pipeline Embolization Device with Shield Technology (SPED) (CoCr) vs Derivo Embolization Device (DED) (Nitinol)

Note: Authors also searched for p64/p48 molecular weight (MW) hydrophilic polymer coating (HPC) but found no studies meeting inclusion criteria.

Contact Duration: Median f/u time: 8.24 months (IQR: 6.67 to 12 months)

Dose: Diameter: SPED: 2.5 to 5 mm, DED: 3.5 to 6 mm; Length: SPED: 10 to 35 mm, DED: 15 to 50 mm

Frequency/Duration: 1086 flow diverters placed (1.02 per aneurysm), 455 were DED (41.9%) and 631 (58.1%) were SPED. Stent-assisted coiling procedure use varied greatly with 6.4% to 88.9% of procedures, depending on the study.

Response: aneurysm occlusion rate (6-month, 12-month), ischemia rate (serious, total), morbidity rate, mortality rate, technical success

Patient characteristics (gender, age): Percent female range: 58.3% to 82%; age range: 17 to 82 years

Number per Group: 911 patients with 1,060 aneurysms

Observed adverse effects:

Aneurysm occlusion rate (6 months): DED: RR: 78.9% (95% CI: 74.3% to 83.1%, I^2=0%), SPED: 82.7% (73.4% to 90.4%, I^2=75.3%), p=0.420, **no difference**

Aneurysm occlusion rate (12 months): DED: RR: 87.8% (95% CI: 80.9% to 93.5%, I^2=NA), SPED: 83.2% (75.8% to 89.5%, I^2=NA), p=0.329, **no difference**

Ischemia rate (Serious): DED: RR: 2.5% (95% CI: 1.0% to 4.6%, I^2=0.00%), SPED: 1.2% (0.1% to 3.2%, I^2=37.0 %), p=0.240, **no difference**

Ischemia rate (Total): DED: RR: 8.3% (95% CI: 2.9% to 15.7%, I^2=75.1%), SPED: 6.3% (3.2% to 10.2%, I^2=50.1 %), p=0.548, **no difference**

Morbidity rate: DED: RR: 6.3% (95% CI: 3.9% to 9.1%, I^2=0.00%), SPED: 5.8% (3.9% to 8.1%, I^2=0.00%), p=0.725, **no difference**

Mortality rate: DED: RR: 1.3% (95% CI: 0.2% to 3.1%, I^2=NA), SPED: 0.8% (0.1% to 1.9%, I^2=NA), p=0.410, **no difference**

Technical success: DED: RR: 100% (95% CI: 99.2% to 100%, I^2=0%), SPED: 99.2% (97.2% to 100%, I^2=54.4%), p=0.165, **no difference**

Timing of adverse effects: Adverse events were examined at 6 or 12 months

Factors that predict response: NR

Note: Study states how aneurysm factors such as rupture status, location, branch vessel coverage, and adverse events were not adequately reported to allow analysis.

10.3 Source Citation : Cagnazzo et al. 2020[40]

Study Design: Systematic review of 15 single-arm studies (14 retrospective, 1 prospective)

Device or Material: Pipeline Embolization Device (PED) (CoCr) or other embolization devices

Contact Duration: Mean clinical follow-up: mean 14 months (range 6 to 28 months). Radiologic outcomes (technical success and occlusion rates) follow-up: mean 13 months (range 4 to 24 months)

Dose: NR

Frequency/Duration: NR

Response: Adequate occlusion rate, treatment-related complications

Note: Study reported other outcomes, however, these were the only two separated by type of embolization device

Patient characteristics (gender, age): Percent male: 42% (95% CI: 35% to 49%); mean age: 52.5 years (range 18 to 82 years)

Number per Group: PED: 185 aneurysms; other embolization device: 28 aneurysms

*Note: Study provided unclear information on number of enrolled patients, all statistics were based on aneurysms

Observed adverse effects: Note: Denominator is number of aneurysms, not patients.

Adequate occlusion rate: PED: 8 studies: 118/149 (82%), 95% CI: 75% to 90%, I^2=25%; other embolization devices: 3 studies: 21/23 (90%), 95% CI: 81% to 98%, I^2=0%

Treatment-related complications: PED: 9 studies: 19/110 (15%), 95% CI: 9% to 21%, I^2=0%; other embolization devices: 3 studies: 3/23 (12%), 95% CI: 6% to 25%, I^2=0%

Timing of adverse effects: Mean clinical follow-up: mean 14 months (range 6 to 28 months). Radiologic outcomes (technical success and occlusion rates) follow-up: mean 13 months (range 4 to 24 months)

Factors that predict response: Authors reported univariate and multivariate regression analyses for the effect of patient age, aneurysm size, type of aneurysm, and aneurysm location on occlusion and complication rates for the full sample, however, they did not perform separate analyses for PED and other flow diverters.

10.4 Source Citation : Bhatia et al. 2019[41]

Study Design: Systematic review of 8 single-arm studies (5 retrospective, 3 prospective)

Device or Material: Pipeline Flex (CoCr)

Contact Duration: Outcomes reported periprocedural (within 30-days) or long-term (>30 days).

Dose: NR

Frequency/Duration: NR

Response: All major complications, major stroke (<30 days), minor stroke/TIA, mortality (<30 days), other complications, procedural success, sICH (<30 days), total complications

Patient characteristics (gender, age): Percent female: 83.4%, mean age: 56.7 years (95% CI: 54.0 to 59.4)

Number per Group: 879 patients receiving 901 treatments for 935 aneurysms

Observed adverse effects: Note: All meta-analyzed outcomes reported per treatment.

All major complications (>30 days): 14 occurrences; RR: 1.8% (95% CI: 1.0% to 2.7%)

Major stroke (<30 days): 4 occurrences; RR: 0.6% (95% CI: 0.2% to 1.2%)

Minor stroke/TIA (>30 days): 17 occurrences; RR: 2.5% (95% CI: 1.0% to 4.8%)

Mortality (<30 days): 5 occurrences; RR: 1.8% (95% CI: 1.0% to 2.7%)

Other complications (>30 days): 67/712; RR: 9.8% (95% CI: 6.3% to 13.9%)

Procedural success (>30 days): 1021/1028; RR: 99.3% (95% CI: 98.5% to 99.8%)

sICH (<30 days): 9 occurrences; RR: 1.2% (95% CI: 0.6% to 2.1%)

Total complications (>30 days): 98/901; RR: 9.8% (95% CI: 5.3% to 16.2%)

Timing of adverse effects: Outcomes reported periprocedural (within 30-days) or long-term (>30 days)

Factors that predict response: Authors performed subgroup analyses on aneurysm size and distal aneurysms and found no significant differences between groups for all major outcomes.

10.5 Source Citation : Cagnazzo et al. 2019[42]

Study Design: Systematic review of 27 single-arm studies (22 retrospective, 5 prospective)

Device or Material: Pipeline Embolization Device (PED) (CoCr), Flow-Redirection Endoluminal Device (FRED) (nitinol), Silk flow diverter (nitinol), p64 (nitinol), Surpass stent (CoCr)

Contact Duration: Mean clinical follow-up: 13 months (range: 6 to 30 months)

Dose: NR

Frequency/Duration: NR

Response: Adequate occlusion rate, treatment-related complications

Note: Study reported other outcomes, however, these were the only two separated by type of embolization device

Patient characteristics (gender, age): Percent male: 36% (95% CI: 31% to 41%), mean age: 54.5 years (range 18 to 82 years)

Number per Group: PED: 62%, FRED: 15.5%, Silk: 10.5%, p64: 7%, Surpass: 5%

Note: Authors only give percentage of aneurysms by device, no numerator or denominator information.

Observed adverse effects: Note: Denominator is number of aneurysms, not patients.

Adequate occlusion rate: 7 studies: FRED: 37/53 (73.8%) (95% CI: 60.1% to 87.5%, I^2=31.7%); 2 studies: p64: 18/22 (82%) (95% CI: 64% to 98%, I^2=41.7%); 13 studies: PED: 143/165 (87.3%) (95% CI: 82.4% to 92.3%, I^2=0%), 2 studies: Silk Surpass: 11/14 (80.9%) (95% CI: 55.5% to 98%, I^2=29.3%)

Treatment-related complications: 28 studies: FRED: 9/66 (11.7%) (95% CI: 3.2% to 20.3%, I^2=29%); 2 studies: p64: 3/23 (12.5%) (95% CI: 1% to 26%, I^2=0%); 12 studies: PED: 20/159 (9.2%) (95% CI: 4.9% to 13.5%, I^2=0%), 3 studies: Silk Surpass: 2/20 (8.2%) (95% CI: 3.2% to 19.5%, I^2=0%)

Timing of adverse effects: Mean clinical follow-up: 13 months (range: 6 to 30 months)

Factors that predict response: Authors reported univariate and multivariate regression analyses for the effect of number of flow diverters, aneurysm size, whether a coil was involved in the procedure, and aneurysm location on occlusion and complication rates for the full sample, however, they did not perform separate analyses for PED and other flow diverters.

10.6 Source Citation: Texakalidis al. 2017[43]

Study Design: Systematic review of 28 single-arm studies (23 retrospective, 5 prospective)

Device or Material: Pipeline Embolization Device (PED) (CoCr)

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: CNS thrombotic/thromboembolic AE (symptomatic, asymptomatic), hemorrhagic AE (symptomatic, asymptomatic), in-pipeline stenosis AE (symptomatic, asymptomatic), morbidity, mortality

Patient characteristics (gender, age): Percent female: 81%; mean age: 55.3 years

Number per Group: 1556 total individuals, 1420 patients with available data (1503 aneurysms)

Observed adverse effects:

CNS thrombotic/thromboembolic AE (asymptomatic): 54 occurrences (3.4%)

CNS thrombotic/thromboembolic AE (symptomatic): 104 occurrences (6.6%)

Hemorrhagic AE (symptomatic): 47 occurrences (3%)

Hemorrhagic AE (asymptomatic): 6 occurrences (0.4%)

In-pipeline stenosis AE (asymptomatic): 18 occurrences (1.1%)

In-pipeline stenosis AE (symptomatic): 5 occurrences (0.3%)

Morbidity: 27/1246 (2.1%)

Mortality: 31/1556 (2.1%)

Timing of adverse effects: NR

Factors that predict response: NR

10.7 Source Citation: Zhou et al. 2017[44]

Study Design: Systematic review of 60 single-arm studies

Device or Material: Pipeline Embolization Device (PED) (CoCr), PED Flex (CoCr), Silk (Nitinol), Surpass (CoCr), p64 (Nitinol), FRED (Nitinol), Woven Endobridge (WEB) (Nitinol), Tubridge (Nitinol)

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Complication rate (minor, intermediate, severe, total), mortality

Note: The complications were divided into 3 categories of minor, intermediate, and severe. Minor complications consisted of minor ischemic events (including distal emboli and transient ischemic attack), transient dysphasia, and access site complications without need for transfusion. The intermediate complications comprised visual impairment, dissections, in-stent stenosis (ISS), branch occlusion, poor stent opening, wire perforation, deployment failure, and device migration or poor position. Severe complications consisted of ipsilateral parenchymal hemorrhage, rebleeding, and major stroke.

Patient characteristics (gender, age): NR

Number per Group: PED: 1570 patients, Silk: 360 patients, FRED: 62 patients, Surpass: 202 patients, multiple devices: 614 patients, other devices: 317 patients

Note: Data on multiple devices are not included for the purposes of this report.

Observed adverse effects:

Complications (Total): PED (33 studies): ES 0.13 (95% CI: 0.10 to 0.16), PED Flex (2 studies): ES 0.07 (95% CI: -0.01 to 0.15), Silk (7 studies): ES 0.15 (95% CI: 0.08 to 0.23), Surpass (2 studies): ES 0.21 (95% CI: 0.01 to 0.41), p64 (1 study): ES 0.07 (95% CI: 0.02 to 0.11), FRED (2 studies): ES 0.07 (95% CI: -0.03 to 0.17), WEB (1 study): ES 0.18 (95% CI: 0.07 to 0.28), Tubridge (1 study, 1 excluded due to inadequate data reporting): ES 0.09 (95% CI: 0.01 to 0.17)

Complications (Minor): PED: 3.7% (n=58), Silk: 0.2% (n=1), FRED: 4.8% (n=3), Surpass: 5.9% (n=12), other devices: 3.2% (n=10)

Complications (Intermediate): PED: 13.7% (n=215), Silk: 15% (n=54), FRED: 0%, Surpass: 34.7% (n=70), other devices: 12% (n=38)

Complications (Severe): PED: 3.1% (n=49), Silk: 2.2% (n=8), FRED: 4.8% (n=3), Surpass: 4% (n=8), other devices: 1.6% (n=5)

Mortality: PED: 1.8% (n=29), Silk: 2.8% (n=10), FRED: 0%, Surpass: 2% (n=4), other devices: 0.3% (n=1)

Note: Data for minor, intermediate, and severe complications, as well as mortality, were retrieved from a summary table. Data for total complications were retrieved from a forest plot.

Timing of adverse effects: NR

Factors that predict response: NR

10.8 Source Citation : Zhou et al. 2016[45]

Study Design: Systematic review of 59 single-arm studies (23 prospective, 32 retrospective, 2 consecutive, 1 matched-pair, 1 unclear)

Device or Material: Pipeline Embolization Device (PED) (CoCr), Silk (nitinol), FRED (nitinol), Surpass (CoCr), Tubridge (nitinol)

Note: Some studies contained combinations of flow diverter devices, however, these data are not included for the purposes of this report.

Contact Duration: Mean follow-up range of 1 month to 62 months

Dose: Pore size (mm^2): PED: 0.020 to 0.052, Silk: 0.014 to 0.063, Surpass: 0.031 to 0.048, FRED: NA, Tubridge: 0.040 to 0.050, p64: NA

Frequency/Duration: NR

Response: Occlusion rate

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

Number per Group: 2263 total patients with 2493 aneurysms

Observed adverse effects:

Occlusion rate: PED (30 studies, 2 excluded studies for inadequate data reporting): RR 0.79 (95% CI: 0.74 to 0.85), Silk (11 studies): RR 0.70 (95% CI: 0.60 to 0.80), FRED (1 study): RR 0.58 (95% CI: 0.41 to 0.74), Surpass (2 studies): RR 0.74 (95% CI: 0.68 to 0.80), Tubridge (1 study): RR 0.72 (95% CI: 0.54 to 0.90)

Timing of adverse effects: Mean follow-up range of 1 month to 62 months

Factors that predict response: Authors performed subgroup analyses on the full sample finding no differences based on follow-up, aneurysm location, aneurysm size, or type of subarachnoid hemorrhage (ruptured vs unruptured)

AE: adverse event; CI: confidence interval; CNS: central nervous system; CoCr: cobalt chromium; DED: Derivo Embolization Device; ES: effect size; FRED: Flow-Redirection Endoluminal Device; HPC: hydrophilic polymer coating; IQR: interquartile range; ISS: in-stent stenosis; MW: molecular weight; NA: not applicable; NR: not reported; OR: odds ratio; PED: Pipeline Embolization Device; RR: risk ratio; sICH: symptomatic intracranial hemorrhage; SPED: Pipeline Embolization Device with Shield Technology; TIA: transient ischemic attack; WEB: Woven Endobridge

Table 11: Orthopedic Bone and Joint – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

11.1 Source Citation: Aibinder et al. 2021[62]

Study Design: Single-arm study

Device or Material: Equinoxe (Exactech) anatomic and reverse total shoulder prosthesis (aTSA and rTSA)

Contact Duration 38±35.8 months for aTSA, 24±24.7 months for rTSA

Dose: Single arthroplasty

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, fracture, infection, pulmonary embolism

Patient characteristics (gender, mean age): aTSA: 50.1% Female, 66±9.1 years. rTSA: 62.6% Female, 72±7.8 years

Number per group: 8513 shoulders. 2947 aTSA and 5566 rTSA

Observed adverse effects: Glenoid or humeral aseptic loosening – 2.8% of aTSA and 0.7% of rTSA. Instability – 0.5% of aTSA, 0.9% of rTSA. Acromial/scapular spine fracture, periprosthetic humeral fracture, or clavicle fracture – as much as 0.3% of aTSA and 2% of rTSA. Infection – 0.8% of aTSA, 0.7% of rTSA. PE – 0.03% of aTSA, 0.05% of rTSA.

Timing of adverse effects: NR

Factors that predict Response: Female aTSA patients had a significantly higher complication rate ($P<0.001$) and a significantly higher revision rate ($P=0.015$) than male aTSA patients. Female rTSA patients had a similar complication rate ($P=0.2$) but a significantly lower revision rate ($P<.0001$) than male rTSA patients.

11.2 Source Citation : Banci et al. 2021[46]

Study Design: Systematic review

Device or Material: Cobalt-chromium-molybdenum (CoCr) with and without ceramic coating of titanium nitride, titanium niobium nitride, or zirconium nitride

Contact Duration Mean (range) 4.6 (2-10) years

Dose: NR

Frequency/Duration: Single administration

Response: serum chromium concentration, serum cobalt concentration

Patient characteristics (gender, mean age): NR

Number per group: 5 studies with 680 knees (321 coated, 359 uncoated)

Observed adverse effects: Serum chromium concentration – 0.81 for uncoated, 0.52 for coated. The difference was not significant (p=0.26) Serum cobalt concentration – 0.38 for uncoated, 0.35 for coated (p=0.64).

Timing of adverse effects: At one year

Factors that predict Response: NR

11.3 Source Citation: Collado et al. 2021[61]

Study Design: Nonrandomized comparative study

Device or Material: Dall-Miles staple (Stryker), Cable-Ready plate (Zimmer), Cerclage wire

Contact Duration Mean (range) : Cable-plate 61.1 (12-175), Cerclage 24.1 (12-69)

Dose: Single implant system

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, bursitis/pain, removal

Patient characteristics (gender, mean age): Percent female and mean (range) age: Cable-plate 35.7%, 71.6 (31-87) years. Cerclage 39.1%, 65.6 (27-89) years

Number per group: 28 in the plate-cable group. 23 in cerclage wire group.

Observed adverse effects: Loosening – 32% in cable-group, 29% in cerclage Pain – Cable-plate: 12/28, Cerclage: 2/23. Removal – Cable-plate 4/28, Cerclage 0/23.

Timing of adverse effects: NR

Factors that predict Response: NR

11.4 Source Citation : Higgins et al. 2020[55]

Study Design: RCT

Device or Material: MoM – CoCr head (Biomet), CoM – Biolox delta ceramic head (CeramTec)

Contact Duration 5 years

Dose: One total hip replacement with 38-mm head

Frequency/Duration: Single administration

Response: ARMD/ATLR, radiolucency, revisions, subsidence

Patient characteristics (gender, mean age): 1.7:1 M:F ratio, mean age 65.2 years

Number per group: 34 MoM, 36 CoM

Observed adverse effects: 10 revisions for ARMD in MoM, 7 in CoM. No patients showed radiolucencies of clinical significance. 13 revisions in MoM, 11 in CoM. 1 revision due to early mild stem subsidence in CoM. No periprosthetic fractures in MoM, 1 in CoM.

Timing of adverse effects: NR

Factors that predict Response: NR

11.5 Source Citation: Kim et al. 2020[47]

Study Design: Systematic review

Device or Material: CoCr devices in All-polyethylene glenoid (PEG) group: Aequalis (Tornier), Affinis (Mathys), Affiniti Cortiloc (Tornier), BioModular (Biomet), Cofield (Smith & Nephew), Cofield II (Smith & Nephew), Equinoxe (Exactech), Global Advantage (DePuy), ReUnion (Stryker). CoCr devices in metal-backed glenoid (MBG) group: 2nd generation SMR (Lima). Other devices: Sulmesh and Tantalum TM (Zimmer)

Contact Duration PEG 73.1 (12-211) months, MBG 56.1 months

Dose: One total shoulder arthroplasty

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, infection, periprosthetic fracture, revisions

Patient characteristics (gender, mean age): Gender not reported. Mean (range) age: PEG 66.4 (21-93) years, MBG 66.5 (31-88) years

Number per group: A total of 3095 CoCr arthroplasties were included. 3391 PEG (3062 CoCr). 457 MBG (35 CoCr).

Observed adverse effects: Loosening – 12.1% (375). Instability – 0.1% (3). Infection – 0.1% (3). Fracture – 0.1% (2). Revision – 5.4% (167).

Timing of adverse effects: NR

Factors that predict Response: MBG showed lower loosening (P<0.001) and revision (P=0.006) than PEG after 72 months.

11.6 Source Citation : Prasad et al. 2020[48]

Study Design: Systematic review

Device or Material: Press-Fit Condylar cruciate retaining (CR) (DePuy), NextGen* CR, Low Contact Stress (LCS, DePuy), Scorpio (Howmedica/Stryker)

Contact Duration Follow-up ranged from 2 to 16.6 years.

Dose: One total knee arthroplasty

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, infection

Patient characteristics (gender, mean age): 73% female. Mean age range was 54 to 73 years.

Number per group: 6 studies including 755 knees (356 Cemented, 399 Cementless).

Observed adverse effects: 2 knees were revised due to aseptic loosening, both in the cementless group. 2 knees were revised due to instability, both in the cementless group. There were 2 infections, both requiring revision, and both in the cemented group.

Timing of adverse effects: NR

Factors that predict Response: NR

11.7 Source Citation : Kim et al. 2019[56]

Study Design: RCT

Device or Material: CoCr or Oxidized Zirconium (OxZr) Genesis II (Smith & Nephew)

Contact Duration Mean (range) = 13 (10-14) years

Dose: Each patient received one of each type of total knee replacement

Frequency/Duration: Single administration

Response: Dislocation/instability, infection, pain

Patient characteristics (gender, mean age): Gender was not reported. Mean age (range) = 53 (40-55) years

Number per group: 99 knees in each group

Observed adverse effects: 1 OxZr patient was revised for aseptic loosening. Radiographs and CT did not show loosening or osteolysis in either group. 1 CoCr patient was revised for instability. 1 CoCr patient and 1 OxZr patient were revised for infection. 73 CoCr and 72 OxZr patients had no pain. No patient in either group had severe pain.

Timing of adverse effects: NR

Factors that predict Response: NR

11.8 Source Citation : Malahias et al. 2019[49]

Study Design: Systematic review

Device or Material: CoCr on PE THA, Oxidized Zirconium on PE THA

Contact Duration Mean follow up ranged from 2 to 12 years

Dose: Single implant for most patients

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, fracture, infection

Patient characteristics (gender, mean age): Mean age ranged from 42 to 72 years

Number per group: 624 CoCr-PE; 1223 OxZi-PE; 225 Ceramic-PE. 9 studies with 2072 hips

Observed adverse effects: Loosening – 0.6%. Instability – 1%. Fracture – 0.2%. Infection – 0.8%.

Timing of adverse effects: NR

Factors that predict Response: NR

11.9 Source Citation: Borgwardt et al. 2018[57]

Study Design: RCT

Device or Material: ReCap (CoCr), M2a-Magnum (CoCr), C2a-Tabper (Biolox) (Biomet)

Contact Duration 7 years

Dose: One total hip implant

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, elevated serum metal concentration, infection, periprosthetic fracture, serum chromium concentration, serum cobalt concentration

Patient characteristics (gender, mean age): 56% female, Mean age = 60.5 (6.5)

Number per group: 51 Recap, 47 M2a, 54 C2a hips

Observed adverse effects: Loosening – 1 C2a. Instability – 2% in ReCap, 0% in M2a, 3.7% in C2a. 1 ReCap and 1 M2a patient required revision due to elevated concentration. Infection – 1 M2a. Fracture – 1 ReCap. Chromium concentration in ReCap and M2a patients (means 3.21 – 7.01) was much higher than that in C2a patients by 6 months (0.19 – 3.61) ($p<.001$). Cobalt concentration in C2a patients remained around 0.14 throughout the 7-year period, while the cobalt concentration in ReCap and M2a patients increased from 0.14 at baseline to 1.22 ($p<.001$) within 6 weeks, reaching a average maximum of 2.19 (Recap) and 2.63 (M2a) at 2 years.

Timing of adverse effects: See Brief

Factors that predict Response: Acetabular cup inclination (r values 0.305 – 0.423, $p<=0.20$)

11.10 Source Citation : Simovitch et al. 2018[63]

Study Design: Single-arm study

Device or Material: Equinoxe (Exactech) anatomic and reverse total shoulder prosthesis (aTSA and rTSA)

Contact Duration aTSA: 49.7±27.5 months. rTSA: 40.2±18.6 months

Dose: Single arthroplasty

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, fracture, infection, periprosthetic fracture, revisions

Patient characteristics (gender, mean age): aTSA: 53.6% female, 66.5±9.1 years. rTSA: 64.6% female, 72.5±7.5 years.

Number per group: 1856 shoulders. 911 aTSA and 945 rTSA

Observed adverse effects: Loosening – 34.2% (Glenoid-19.4%, humeral-13.4%, combined-1.4%). Instability – 3%. 10.4% had scapula or acromion fractures. Infection – 11.9%. Fracture – 4.5%. Revision – 1.7%.

Timing of adverse effects: NR

Factors that predict Response: NR

11.11 Source Citation: Laaksonen et al. 2017[50]

Study Design: Systematic review

Device or Material: ASR HRA and ASR XL THA (DePuy)

Contact Duration 6 – 7 years

Dose: Single implant

Frequency/Duration: Single administration

Response: ARMD/ALTR, revisions

Patient characteristics (gender, mean age): NR

Number per group: 18384

Observed adverse effects: Median (range) rates of revision in ASR HRA patients for ALTR were 5.3% (3.1 – 13.6) at 2-3 years, 3.4% (28-17.0) at 4-5 years, and 16.4% (5.3-27.0) at 6-7 years. Rates in ASR XL THA patients were 17.4% (6.0-28.7) at 2-3 years, 26.5% (17.0-36.0) at 4-5 years, and 39.0% at 6-7 years. Median (range) rates of revision in ASR HRA patients for ALTR were 3.7% (2.0-18.2) at 2-3 years, 10.3% (5.6-20.4) at 4-5 years, and 17.7% (8.0-31.0) at 6-7 years. Rates in ASR XL THA patients were 17.0% (0-26.0) at 2-3 years, 10.0% (0.0-37.0) at 4-5 years, and 28.0% at 6-7 years.

Timing of adverse effects: See Brief

Factors that predict Response: NR

11.12 Source Citation: Ma et al. 2017[51]

Study Design: Systematic review

Device or Material: CoCr based unicompartmental and total knee systems, including Search (Aesculap), Preservation and Sigma (DePuy), Duece Journey, Genesis II, and UC-Plus Solution (Smith & Nephew), and Gender Solutions PFJ, LPS-Flex, NexGen, ZUK (Zimmer)

Contact Duration Follow-up ranged from 2 – 5 years

Dose: Either 1 total knee arthroplasty or 1 bicompartmental knee arthroplasty

Frequency/Duration: Single administration

Response: Revisions

Patient characteristics (gender, mean age): Gender was not reported in 1 study but was 69% female for the other 4 studies. Mean age ranged from 58.3 – 67.2 years.

Number per group: 5 studies including 261 knees

Observed adverse effects: There were 9 revisions out of 261 knees.

Timing of adverse effects: NR

Factors that predict Response: NR

11.13 Source Citation : Engh et al. 2016[58]

Study Design: RCT

Device or Material: CoCrMo femoral heads or Biolox Delta (CeramTec) femoral heads. Pinnacle titanium acetabular cups with CoCr molybdenum (Mo) liner. Femoral Stems were AML or Prodigy (DePuy, CoCr), Summit or SROM (DePuy, titanium).

Contact Duration Mean follow up was 50 months.

Dose: one total hip

Frequency/Duration: Single administration

Response: ARMD/ALTR, revisions, serum chromium concentration, serum cobalt concentration

Patient characteristics (gender, mean age): Mean age was 59 – 60 years. 54% - 57% male.

Number per group: 196 MoM, 194 CoM

Observed adverse effects: Adverse reaction – 1 in MoM. Revisions – 6 (3%) in MoM including 1 hematoma evacuation at 7 days, 1 recurrent dislocation at 4 months, 1 infection at 19 months, 1 broken femoral component at 44 months, 1 ATLR at 44 months, 1 elevated serum chromium and cobalt with squeaking. SCrC – In CoM, no difference from year 1 (median, range) (1.01, 0.65-1.99) to year 5 (1.13, 0.73-1.35). In MoM, no difference from year 1 (0.84, 0.61-1.24) to year 5 (0.95, 0.60-1.41). No difference between CoM and MoM groups at 5 years. ScoC – In CoM, no difference from year 1 (median, range) (0.88, 0.54-1.49) to year 5 (0.85, 0.73-1.00). In MoM, it increased from year 1 (0.65, 0.42-0.80) to year 5 (1.01, 0.64-2.20). No difference between CoM and MoM groups at 5 years.

Timing of adverse effects: See Brief

Factors that predict Response: NR

11.14 Source Citation: Heijink et al. 2016[52]

Study Design: Systematic review

Device or Material: CoCr: Anatomic Radial Head System (Acumed), Guepar (Depuy), Judet Floating Radial Head (CRF II)/Radial Head System (Tornier), Katalyst Bipolar (Integra), Radial Head (Corin), Radius Head Component (LINK), Monopolar and Bipolar (Avanta), rHead (Small Bone Innovations). Pyrocarbon: MoPyC radial head (Tornier). Titanium: Evolve Modular Radial Head (Wright Medical), Richards radial head (Smith & Nephew). Vitallium: Solar Radial Head (Stryker).

Contact Duration Weighted average follow-up = 45 months

Dose: Generally, one total elbow replacement

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, infection, revisions

Patient characteristics (gender, mean age): Gender was not reported. Mean (range) age = 48.4 (37 – 59.2) years

Number per group: 30 studies including 727 patients. 496 CoCr, 107 pyrocarbon, 77 titanium, 47 Vitallium.

Observed adverse effects: Loosening – 11 CoCr, 0 pyrocarbon, 0 titanium, 2 Vitallium. Infection – 2 CoCr, 0 pyrocarbon, o titanium, 0 Vitallium The range of revision rates for CoCr, pyrocarbon, titanium, and Vitallium were 0 – 29%, 6 – 11%, 0 – 20%, and 0 – 6%, respectively. Mean (95% CI) revision rate per 100 person-years of follow-up ranged from 0.72 (0.06 – 9.14) to 2.82 (1.16 – 6.85) for CoCr, depending on polarity and fixation technique. Rates for pyrocarbon, titanium, and Vitallium were 3.1 (0.73 – 13.2), 4.77 (1.16 – 26.4), and 0.91 (0.11 – 7.82), respectively. The study reported no statistical difference between materials.

Timing of adverse effects: NR

Factors that predict Response: NR

11.15 Source Citation : Axelsson et al. 2015[64]

Study Design: Single-arm study

Device or Material: Herbert UHP (Martin Medizin Technik) ulnar head prosthesis

Contact Duration 7.6 years

Dose: Single arthroplasty

Frequency/Duration: Single administration

Response: Bone resorption

Patient characteristics (gender, mean age): 48% female, 55 years.

Number per group: 21

Observed adverse effects: Loosening – 0. Bone resorption beneath the collar of the implant was observed in all cases, but there was no progression after 12 months. Bone resorption index was 7% (0 – 26%). Infection – 0.

Timing of adverse effects: First 12 months

Factors that predict Response: NR

11.16 Source Citation: Jassim et al. 2015[59]

Study Design: RCT

Device or Material: CoCr head with XLPE liner vs Oxidized Zirconium (OxZi) with XLPE liner vs OxZi head with UHMWPE liner. All patients received Synergy femoral component and Reflection acetabular cup (Smith and Nephew).

Contact Duration 5 years

Dose: one total hip

Frequency/Duration: Single administration

Response: Dislocation/instability, infection

Patient characteristics (gender, mean age): 62% female. Mean age 63 years.

Number per group: 123 CoCr-XL, 121 OxZi-XL, 124 OxZi-UHMW

Observed adverse effects: There were no hips in which osteolysis was observed. One patient in each group was revised due to recurrent instability. One CoCr-XL and one OxZi-UHMW were revised for infection.

Timing of adverse effects: NR

Factors that predict Response: NR

11.17 Source Citation : Chen et al. 2013[53]

Study Design: Systematic review

Device or Material: PCA (Howmedica), Miller-Galante II (ZIMMER), DURACON (HOWMEDICA), KINEMATIC (HOWMEDICA), Press-Fit Condylarprosthesis (Johnson & Johnson), AMK (Depuy), Profix Total Knee System (Smith and Nephew)

Contact Duration Mean follow-up ranged from 2 to 10 years.

Dose: Generally, one total knee arthroplasty

Frequency/Duration: Single administration

Response: Revisions

Patient characteristics (gender, mean age): Gender was not reported. Mean age ranged from 63.6 to 78 years.

Number per group: 14 studies including 1,725 knees

Observed adverse effects: 89 out of 1725 (5.2%) knees were revised. Some of the causes for revision listed were anterior knee pain, infection, sepsis, osteolysis, and aseptic loosening but the rates for specific causes were not reported.

Timing of adverse effects: NR

Factors that predict Response: NR

11.18 Source Citation : Desmarchelier et al. 2013[60]

Study Design: RCT

Device or Material: Cersul (CeramTech) or Metasul (Sulzer) head with Alloclassic stem and Allofit cup (Sulzer).

Contact Duration Mean follow up: Cerasul – 9 years, Metasul – 8.3 years

Dose: Most patients received one total hip replacement. 23 patients received 2 THRs.

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, fracture, infection

Patient characteristics (gender, mean age): Cerasul: 45% female, mean age = 59.6±14.6 years. Metasul: 62% female, mean age = 63.7±12.7 years.

Number per group: 125 Cerasul hips in 116 patients. 125 Metasul in 111 patients.

Observed adverse effects: There was 1 revision in the Metasul group due to aseptic loosening and one revision due to nonosseointegration. One Cerasul insert fractured and was revised. One Metasul implant was revised due to infection.

Timing of adverse effects: NR

Factors that predict Response: NR

11.19 Source Citation: Prissel and Roukis 2013[54]

Study Design: Systematic review

Device or Material: Scandinavian Total Ankle replacement (STAR)

Contact Duration Weighted mean (range) follow-up was 64 (12-156) months

Dose: Not reported

Frequency/Duration: Single administration

Response: Aseptic loosening/osteolysis, dislocation/instability, infection, revisions, subsidence

Patient characteristics (gender, mean age): Gender was not reported. Weighted mean (range) age was 62.3 (22-86) years

Number per group: 20 studies including 2507 ankles

Observed adverse effects: Of the revisions for which a specific cause was identified (183), 89 (48.6%) were due to aseptic loosening, and 2 (1.1%) were due to osteolysis. Instability – 14 (7.7%). Infection – 22 (12%). 269 (10.7%) underwent revision. Subsidence – 4 (2.2%).

Timing of adverse effects: Weighted mean (range) time to revision was 49.7 (1-124) months

Factors that predict Response: NR

ATLR: adverse local tissue reaction; ARMD: adverse reaction to metal debris; aTSA: anatomic total shoulder arthroplasty; CoCr: cobalt chromium; CoM: ceramic on metal; CR: cruciate retaining; MoM: metal on metal; NR: not reported; OxZr: oxidized zirconium; PE: polyethylene; rTSA: reverse total shoulder arthroplasty; ScoC: serum cobalt concentration; SCrC: serum chromium concentration; THA: total hip arthroplasty.

Table 12: Spine implants – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

12.1 Source Citation: Xiang et al. 2018[65]

Study Design: SR and meta-analysis comparing the Mobi-C total disc replacement (TDR) to anterior cervical discectomy and fusion (ACDF) in the treatment of symptomatic degenerative disc disease. The study involved a meta-analysis of six RCTs published from 2008 to 2016 and a total number of 452 Mobi-C patients.

Device Material: Mobi-C (Ti, LDR Medical) versus ACDF.

Contact Duration: Follow-up of 1 to 5 years.

Dose: NR.

Frequency/Duration: One- to two-level TDR.

Response: Non-specified adverse events; reoperation.

Patient characteristics (gender, mean age): Patient sex was NR. Mean age in the CoCr group was 43.3 to 46.3 years; mean age in the ACDF group was 44.0 to 48.5 years.

Number per Group: CoCr group, n=452; ACDF group, n=279.

Observed adverse effects: TDR using Mobi-C resulted in significantly decreased reoperation (RR=0.25; 95% CI=0.16 to 0.39; p<0.00001). Mobi-C treatment led to reduced adverse events than ACDF (RR=0.53; 95% CI=0.38 to 0.73; p=0.0001).

Timing of adverse effects: Follow-up of 1 to 5 years.

Factors that predict response: NR.

12.2 Source Citation : Coric et al. 2018[68]

Study Design: Prospective RCT comparing the five-year results of cervical arthroplasty with those of anterior cervical discectomy and fusion (ACDF).

Device Material: Kineflex-C (CoCr, SpinalMotion) versus ACDF.

Contact Duration: Follow-up of 5 years.

Dose: NR.

Frequency/Duration: One-level total disc replacement (TDR).

Response: Adjacent segment degeneration (ASD), lymphocytic reaction (aka adverse local tissue reaction), migration, radiolucency, reoperation, revision, subsidence.

Patient characteristics (gender, mean age): NR.

Number per Group: CoCr group, n=136; ACDF group, n=133.

Observed adverse effects: 2 (1.5%) patients underwent reoperation for removal of TDR related to a lymphocytic reaction to the implant.

The percentage of patients with device- or surgery-related adverse events was similar in the 2 treatment groups; approximately 8.0% of both groups underwent reoperation or revision surgery. The authors noted that 7.4% of adverse events were "definitely device-related" in the CoCr group, compared to 6.0% in the ACDF group.

5.1% of reoperation in the CoCr group was "definitely device-related", compared to 4.5% in the ACDF group.

Device migration occurred in 1.4% of the CoCr patients, as did subsidence, with no cases in the ACDF group. Radiolucency was noted in 14.3% of CoCr implants and 7.0% of ACDF implants ($p>0.20$). At 60 months after surgery, the CoCr group had statistically significantly less ASD at the level superior to the index surgery than the ACDF group ($p<0.01$). The CoCr group had less ASD at the inferior level, but not significantly less than the ACDF group ($p>0.25$).

From 3 to 60 months post-operatively, mean cobalt levels in the CoCr group steadily decreased whereas mean chromium levels remained stable.

Timing of adverse effects: At 24 and 60 months, the CoCr group had significantly less ASD at the level superior to the operated level than did the ACDF patients.

Factors that predict response: NR.

12.3 Source Citation: Chen et al. 2017[66]

Study Design: SR and meta-analysis comparing cervical disc arthroplasties (CDA) to anterior cervical discectomy and fusion (ACDF) in the treatment of symptomatic degenerative disc disease. The study involved 12 RCTs, 5 of which (published from 2011 to 2015) involved CoCr implants, and a total of 826 patients with CoCr implants.

Device Material: Prodisc-C (CoCr, Synthesis Spine), Mobi-C (CoCr, LDR Medical), Kineflex-C (CoCr, SpinalMotion), Secure-C, (CoCr, Globus Medical), PCM (CoCr, NuVasive), Bryan (non-CoCr, Medtronic), Prestige (non-CoCr, Medtronic), and Discover (non-CoCr, DePuy Spine) versus ACDF.

Contact Duration: Follow-up of 2 to 7 years.

Dose: NR.

Frequency/Duration: One- to two-level CDA.

Response: Breakage, migration, secondary surgical procedure.

Patient characteristics (gender, mean age): Patient sex was NR. Mean age for CoCr CDA groups was 42.1 to 45.3 years; mean age for non-CoCr CDA groups was 40.0 to 47.2 years; and mean age for ACDF groups was 43.0 to 47.7 years.

Number per Group: CoCr CDA groups, n=826; non-CoCr CDA groups, n=748; ACDF groups, n=1,380.

Observed adverse effects: Direct pairwise meta-analysis showed that the rates of secondary surgical procedures were significantly lower in Mobi-C ($P<0.01$), Prestige ($P<0.01$), Prodisc-C ($P<0.05$), Secure-C ($P<0.05$) groups than in ACDF group. No significant difference was detected between Bryan, PCM, Kineflex-C, Discover, and ACDF ($P>0.05$). Causes of secondary procedures in the CDA groups was adjacent level disease, device failure, or unknown.

When compared with ACDF, CDA with Discover, a non-CoCr implant, was associated with significantly higher rates of secondary surgical procedures.

Devices with semi-constrained designs (Prodisc-C, Mobi-C, and Secure-C) were associated with lower rates of secondary surgical procedures, whereas the devices with non-constrained designs (Discover, PCM, and Bryan) were usually associated with higher rates.

The study found that device-related issues, such as breakage or migration, seldom happened or led to secondary surgical procedure. These facts indicated that the devices may already be sturdy enough and the modifications of the designs should focus more on the imitation of biomechanics of normal cervical disc.

Timing of adverse effects: Follow-up of 2 to 7 years.

Factors that predict response: Cause of reoperations was mainly adjacent level diseases. A kinematic analysis of the cervical spine according to device design revealed that devices with a non-constrained design may not be as beneficial to adjacent-level kinematics as semi-constrained prostheses. Arthroplasties were all converted to fusion, instead of revision, after removals.

12.4 Source Citation: Xu et al. 2017[67]

Study Design: SR and meta-analysis comparing the clinical outcomes of anterior cervical discectomy and fusion (ACDF) with total disc replacement (TDR) in the treatment of cervical degenerative disc disease. The study involved 19 RCTs, 10 of which (published from 2008 to 2016) involved TDRs made of CoCr in a total of 1,408 patients.

Device Material: Prodisc-C (Synthesis Spine), Mobi-C (CoCr, LDR Medical), Kineflex-C (CoCr, SpinalMotion), Bryan (non-CoCr, Medtronic), and Prestige (non-CoCr, Medtronic) versus ACDF.

Contact Duration: Follow-up of 24 to 60 months.

Dose: NR.

Frequency/Duration: One- to two-level TDR.

Response: Removal, reoperation, revision, secondary surgery, supplemental fixation.

Patient characteristics (gender, mean age): Patients in the CoCr TDR groups were 44.83% to 59.11% female, with a mean age of 42.8 to 45.59 years. Patients in the non-CoCr TDR groups were 36.16% to 62.5% female, with a mean age of 41.83 to 45.17 years.

Number per Group: CoCr TDR groups, n=1,408; non-CoCr TDR groups, n=1,793; ACDF groups, n=2,681.

Observed adverse effects:

Secondary surgery at an adjacent level: ACDF showed a significantly higher rate of secondary surgery at an adjacent level than TDR with Mobi-C (OR=3.19, 95% CI 1.18-8.90) and Prestige (OR=3.52, 95% CI, 1.39-9.43).

Secondary surgery at the index level: The results showed no significant difference between the pairwise comparisons in the rate for secondary surgery at the index level.

Secondary surgery at both levels: ACDF showed a significantly higher rate of secondary surgery at both levels than TDR with Mobi-C (OR=3.15, 95% CI 1-10.78).

Removal: TDR using Pro-Disc-C showed a significantly higher rate of removal surgery than use of Prestige (OR=16.9, 95% CI 1.027-803.6).

Reoperation: TDR with Mobi-C showed a significantly lower rate of reoperation than ACDF (OR=0.27, 95% CI 0.10-0.74).

Revision: TDR with ProDisc-C was associated with a significantly reduced rate of revision than ACDF (OR=0.03, 95% CI 0.00-0.62).

Supplemental fixation: TDR with Mobi-C was significantly correlated with a reduced rate of supplemental fixation surgery than ACDF (OR=0.11, 95% CI 0.01-0.71).

Timing of adverse effects: Follow-up of 24 to 60 months.

Factors that predict response: Ranking results showed that TDR with Mobi-C disc may be the best choice to reduce secondary surgery rate at both levels, secondary surgery at index level, and reoperation rate. TDR with ProDisc-C may optimally reduce the revision rate.

Abbreviations: ACDF = anterior cervical discectomy and fusion; ASD = adjacent segment degeneration; CDA = cervical disc arthroplasty; CoCr = cobalt chromium; NR = not reported; RCT = randomized controlled trial; SR = systematic review; TDR = total disc replacement.

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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.