

## MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

# Silver Safety Profile

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## Table of Contents

Executive Summary.....	4
Project Overview.....	5
Literature Search and Systematic Review Framework.....	6
ECRI Surveillance Search Strategy .....	7
Safety Profile - Silver .....	9
Safety Brief - Systematic Review Results .....	9
ECRI Surveillance Data.....	16
Potential Gaps .....	17
Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria .....	18
Appendix B. Search Summary .....	19
Appendix C. Study Flow Diagram .....	25
Appendix D. Evidence Tables .....	26
Appendix E. References.....	61
Appendix F. Surveillance Event Reports - PSO and Accident Investigation.....	65
Appendix G. Regulatory and Manufacturer Safety Alerts .....	66

## Table of Tables

Table 1: Medical Devices Containing Silver provided by FDA to Guide ECRI Searches .....	9
Table 2: Summary of Primary Findings from our Systematic Review .....	10
Table 3: Summary of Regulatory and Manufacturer Alerts .....	17
Table 4: Silver as a Material - Health Effects (In Vivo) Animal Studies .....	26
Table 5: Orthopedics, Bone and Joint - Health Effect (In Vivo) Human Studies .....	30
Table 6: Orthopedics, Bone and Joint - Health Effects (In Vivo) Animal Studies .....	34
Table 7: Orthopedics, Prosthesis - Health Effects (In Vivo) Animal Studies.....	44
Table 8: Orthopedics, Soft Tissue - Health Effects (In Vivo) Animal Studies .....	45
Table 9: Vascular - Health Effect (In Vivo) Human Studies.....	46
Table 10: Vascular - Health Effect (In Vivo) Animal Studies .....	50
Table 11: Silver – Abdominal Wall - Health Effect (In Vivo) Animal Studies .....	51
Table 12: Endodontic/Maxillofacial - Health Effects (In Vivo) Animal Studies .....	52
Table 13: Esophageal - Health Effects (In Vivo) Animal Studies .....	54
Table 14: Hepatic - Health Effect (In Vivo) Animal Studies.....	56
Table 15: Lung - Health Effect (In Vivo) Human Studies.....	57
Table 16: Middle Ear - Health Effect (In Vivo) Human Studies.....	58
Table 17: Middle Ear - Health Effect (In Vivo) Animal Studies .....	59
Table 18: Sutures - Health Effect (In Vivo) Animal Studies.....	60



# Executive Summary

## Key Points

1. Searches identified 856 citations; 48 articles were selected for inclusion.
2. Moderate quality evidence of bone and joint implants containing silver reported argyria and elevated but non-toxic levels of silver concentration. The evidence also found infection rates similar to or lower than infection rates for implants without silver.
3. Moderate quality evidence of vascular implants containing silver reported low rates of graft occlusion and reinfection compared to implants without silver. Low quality evidence reported several other local and systemic responses.
4. There were no relevant reports found in ECRI's PSO, accident investigation, or PRN databases related to devices composed of or coated with silver. Healthcare Technology Alerts search returned 7 manufacturer issued alerts describing problems with sterility, implant loosening, incorrect components, deviations in dimensions, reduced implant diameter, and implant failure.
5. Evidence gaps:
  - a. Systemic responses for all applications other than bone and joint implants
  - b. Local responses for all applications other than bone and joint implants and vascular
  - c. Maximum tolerated dose of silver associated with medical device implantation
  - d. There were no studies that addressed any particular cellular or molecular mechanisms for systemic manifestations.
  - e. Additionally, no studies addressed patient-related or material-related factors that could predict the likelihood and/or severity of immunological/systemic responses.

## Overview - Silver

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 Silver. 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.

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

The vast majority of studies reported that no adverse local responses/device events were observed. (see specific responses/events under 1a. below). There were no relevant reports found in ECRI's PSO, accident investigation, or PRN databases related to devices composed of or coated with silver.

- a. *Can that response vary by location or type of tissue the device is implanted in or near?*
  - i. One systematic review of 3 different silver coated (SC) megaendoprostheses reported occurrences of argyria and elevated concentration of silver in tissue surrounding the implant and in the blood, but no other complications. There were no toxic effects related to the elevated silver concentration. Three other human studies and 10 animal studies reported no complications associated with silver-containing bone and joint implants other than infections, which occurred at a similar or reduced rate compared to non-silver implants.
  - ii. For silver-containing vascular implants, one large systematic review of human studies reported low rates of graft occlusion and reinfection compared to implants without silver. Three other human studies also reported infections as well as several other adverse responses.

- iii. For other applications, including orthopedic prosthesis and soft tissue, abdominal wall, endodontic/maxillofacial, esophageal, hepatic, lung, middle ear, and suture, there is low or very low quality evidence.
    - b. *Over what time course does this local host response appear?*
      - i. N/A
- 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?*

One animal study reported on 70 mice with varying amounts of silver nanoparticles embedded in electrospun membranes, finding common events of loss of skin luster and weight loss. One human systematic review<sup>1</sup> and 1 animal study<sup>2</sup> found the use of silver coated bone and joint implants resulted in elevated concentrations of silver in the blood. However, neither of these studies reported any toxic effects. One human study<sup>3</sup> found no difference in silver concentrations in the blood or urine. One animal study found no difference in the silver concentrations in blood<sup>4</sup> or serum.<sup>5</sup>
  - b. *What are the likely systemic manifestations?*

It is likely that there will be no systemic manifestations for silver-containing bone and joint implants. There is inadequate evidence for all other applications.
  - c. *What is the observed timeline(s) for the systemic manifestations?*

N/A
  - d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*

N/A
- 3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**
- No study addressed this question.
- 4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**
- No study addressed this question.
- 5. What critical information gaps exist and what research is needed to better understand this issue?**
- All gaps listed here could benefit from future research.
- a. Systemic responses for applications other than bone and joint
  - b. Maximum tolerated dose

## 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 2021, the following 18 topics have been chosen.

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women

3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates (PET)
7. Correlations between complications with polypropylene mesh and surgical procedure/anatomical location and chemical/mechanical device properties
8. Dimethacrylates, Trimethacrylates (EDMA, EGDMA, TEGDMA, PEGDMA), and glycerol methacrylate (bis-GMA)
9. Polyethylene glycol (PEG)
10. Other Fluoropolymers (PFPE, PVDF, PVDF-HFP, PCTFE)
11. Silver
12. Small-Molecule Per- and polyfluoroalkyl substances (SM-PFAS)
13. Hyaluronic Acid (HLA) - Muscle/Skeletal Applications
14. Hyaluronic Acid (HLA) - Dermal, Facial, and Eye Applications
15. Hyaluronic Acid (HLA) – Adhesion Barriers
16. Polycaprolactone (PCL)
17. Zirconia
18. Nitinol

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

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

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

## Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's

public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2011 and 2021 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching
- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

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

## ECRI Surveillance Search Strategy

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

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

## ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2021, 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 the patient's 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 - Silver

CAS Registry Number: 7440-22-4

## Safety Brief - Systematic Review Results

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

*Table 1: Medical Devices Containing Silver provided by FDA to Guide ECRI Searches*

Regulatory Description	Product Code	Class
Circulatory Support, Structural and Vascular Devices	LWQ	3
METS (Modular Endoprosthetic Tumour System) with Agluna coating*	N/A	N/A
LUMiC Pedestal Cup with Intelligent Silver*	N/A	N/A

MUTARS (Modular Universal Tumor and Revision System) segmental and growing prostheses*	N/A	N/A
MEGASYSTEM-C/MegaC with PorAg coating*	N/A	N/A
Femoral/tibial: nails, screws, blades, plates and Proximal Femoral Nailing System with OrthoSyn coating*	N/A	N/A
OrthoFuzIon Orthopedic Bone Screw System with AntiBacterIon coating*	N/A	N/A
Silver-coated Sutures*	N/A	N/A

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

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on Silver as a material as well as research on the various device categories.

*Table 2: Summary of Primary Findings from our Systematic Review*

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Silver as a material (7 animal studies)	Corrosion	Very low	Loss of skin luster Weight loss	Very low
Orthopedic implants – Bone and Joint (4 human studies, 18 animal studies)	Argyria Non-toxic elevated silver concentration Infection	Moderate	Non-toxic elevated silver concentration	Moderate
Orthopedic implants – Prosthesis (1 animal study)	No events occurred	Low	Not investigated	Very low
Orthopedic implants – Soft tissue (1 animal study)	No events occurred	Very low	Not investigated	Very low
Vascular (4 human studies, 1 animal study)	Reduced graft occlusion, Reduced infection, Arrhythmia/Myocardial infarction, Intestinal obstruction, Renal insufficiency,	Moderate (occlusion, infection) Low (all other responses)	Reduced amputation, lower limb ischemia, Persistent	Low

	Retroperitoneal abscess and bleeding, Abdominal wall abscesses, rupture of aneurysms		sepsis, Pneumonia	
Abdominal wall (1 animal study)	Reduced inflammation	Very low	Not investigated	Very low
Endodontic/Maxillofacial (3 animal studies)	Mild inflammatory reaction	Low	Not investigated	Very low
Esophageal (2 animal studies)	Reduced inflammation	Very low	Not investigated	Very low
Hepatic (2 animal studies)	No events occurred	Very low	Not investigated	Very low
Lung (1 human study)	Pneumonia	Low	Not investigated	Very low
Middle Ear (1 human study, 1 animal study)	Deterioration of speech understanding	Very low	Cardiovascular complications	Very low
Sutures (1 animal study)	Reduced inflammation	Very low	Not investigated	Very low

## Silver as a Material

7 animal studies (7 nonrandomized comparative studies<sup>6-12</sup>). For further information see Table 1 in Appendix D.

### Local Responses (human studies)

We did not identify any human studies investigating local responses to silver as a material.

### Local Responses (animal studies)

Six studies were performed on rat or mice models with sample sizes ranging from 8 to 18, comparing different types of materials synthesized with and without silver. Most studies<sup>7-10,12</sup> only reported that no serious adverse events were observed. Lastly, another study<sup>6</sup> in mice with subcutaneous implants found higher corrosion rates with silver alloys than alloys without silver.

### Systemic Responses

One study<sup>11</sup> reported on 70 mice with varying amounts of silver nanoparticles embedded in electrospun membranes, finding common events of loss of skin luster and weight loss.

### Overall Quality of Evidence

Seven animal observational studies with small to moderate sample sizes and inconsistently reported local host responses were found as evidence. 1 study reported higher corrosion rates with silver alloys, while the other 5 studies investigating local responses reported no serious adverse events. Study quality for local and systemic responses was determined as very low.

## Orthopedic implants – Bone and Joint

4 human studies (1 SR,<sup>1</sup> 2 non-randomized controlled studies (NRCS)<sup>s,13,14</sup> 1 SAS<sup>3</sup>), and 18 animal studies (1 SR,<sup>2</sup> 5 RCTs,<sup>4,15-18</sup> 12 NRCS<sup>s,19-29</sup>). For further information see Tables 2 and 3 in Appendix D.

### Local Responses (human studies)

One SR of 3 different silver coated (SC) megaendoprostheses, Fiore et al.,<sup>1</sup> reported occurrences of argyria and elevated concentration of silver in tissue surrounding the implant. A study of silver loaded cement spacers did not observe any cases of argyria, and silver concentrations in the blood and urine were close to or below 1 part per billion<sup>3</sup>. None of the studies included reported any complications other than infections.<sup>1,3,13,14</sup>

Fiore et al. found no difference in the overall infection rate between SC and uncoated (UC) implants in primary procedures, but SC implants had a significantly lower infection rate than uncoated implants in revision procedures (13.7% vs 29.2%, p=0.019). Generally, MUTARS produced an almost constant decrease in the incidence of primary prosthetic joint infection (PJI), but there are few data on the effectiveness in revisions. Agluna results in both primary and revision implants are inconsistent. PorAg was effective both in PJI prevention but, especially, when used in PJI revision settings. A study comparing SC and UC LUMiC pedestal cups did not find a difference in infection rates.<sup>14</sup>

### Local Responses (animal studies)

Ten studies reported that there were no overall complications.<sup>2,4,16,18,20-22,24,25,27</sup> Ten studies reported that no specific local responses occurred (specifically no local argyrosis,<sup>5,15</sup> aseptic loosening,<sup>29</sup> foreign body reaction,<sup>28</sup> heterotopic bone formation,<sup>29</sup> inflammation,<sup>4,19,26-28</sup> osteolysis,<sup>25,29</sup> or phagocytosis<sup>26</sup>).

One study reported fewer surgical site infections were observed in animals implanted with silver containing devices compared to animals implanted with devices without silver.<sup>2</sup> Five other studies reported no cases of infection.<sup>5,15,20,25,28</sup>

### Systemic Responses

One human study<sup>1</sup> and 1 animal study<sup>2</sup> found the use of silver coated implants resulted in elevated concentrations of silver in the blood. However, neither of these studies reported any toxic effects. One human study<sup>3</sup> found no difference in silver concentrations in the blood or urine. One animal study found no difference in the silver concentrations in blood<sup>4</sup> or serum<sup>5</sup>.

### Overall Quality of Evidence

The SR of human studies stated some of the 19 studies included were of medium or low quality with different bias risks. The studies we reviewed typically had a relatively low sample size but consistently reported that no adverse responses to silver other than argyria occurred. Therefore, the quality of evidence for local and systemic responses to bone and joint orthopedic devices is moderate.

## Orthopedic implants – Prosthesis

1 animal SAS study.<sup>30</sup> For further information see Table 4 in Appendix D.

### Local Responses (human studies)

No included human studies investigated local responses to silver in prosthetic implants.

### Local Responses (animal studies)

We included 1 single-arm study of silver-coated titanium skin-bone interface pylons (SBIPs) used to anchor a prosthesis.<sup>30</sup> The authors found that there were no infections or inflammation and found tissue responses for the silver-coated SBIPs were similar to those for uncoated SBIPs.

### Systemic Responses

No included studies investigated systemic responses to silver in prosthetic implants.

### Overall Quality of Evidence

Only one single-arm study with a small sample size was included, but the conclusions regarding local responses were consistent with studies for other categories. The study did not investigate systemic responses. Therefore, the quality of evidence for local responses to prosthesis devices is low, and for systemic responses, it is very low.

## Orthopedic implants – Soft Tissue

1 animal RCT.<sup>31</sup> For further information see Table 5 in Appendix D.

### Local Responses (human studies)

No included human studies investigated local responses to silver in soft tissue orthopedic implants.

### Local Responses (animal studies)

We included 1 RCT of a silver-coated nanofibrous membrane meant for use in tendon repair.<sup>31</sup> The authors reported that there were no complications and found the device with increased silver content resulted in decreased adhesion.

### Systemic Responses

No included studies investigated systemic responses to silver in soft tissue orthopedic implants.

### Overall Quality of Evidence

Only one RCT with a small sample size was included, and there were other design variables in addition to silver content. The conclusions regarding local responses were consistent with studies for other categories. The study did not investigate systemic responses. Therefore, the quality of evidence for local and systemic responses to prosthesis devices is very low.

## Vascular

4 human studies (1 SR,<sup>32</sup> 1 nonrandomized comparative study,<sup>33</sup> 2 single-arm studies<sup>34,35</sup>), and 1 animal study (1 single-arm study<sup>36</sup>). For further information see Tables 6 and 7 in Appendix D.

### Local Responses (human studies)

One large SR<sup>32</sup> compared aortic graft reconstructions (AGRs) using silver versus four comparison groups: cryo-all, rifamp, standard polyester, and autogenous veins. Authors reviewed evidence from 25 studies, and meta-analyses displayed statistically significant differences for graft occlusion and reinfection events. Study authors also examined the effect of multiple patient-related factors on local host responses, results of which are displayed in the evidence tables. The paper compared event rates for all five groups, and found statistically significant differences among groups for graft occlusion ( $p=0.002$ ) and reinfection ( $p=0.016$ ). Silver had low event rates for graft occlusion and reinfection at 0.05 and 0.07 respectively. In a meta-regression analysis of the risk of reinfection, no variables had p-values less than 0.05, suggesting age, prosthetic-duodenal fistula (PDF), virulent, and nonvirulent confounders had no effect on local host responses for silver. Age and PDF were patient-specific conditions, whereas, virulence refers to characteristics of organisms present in the initial aortic graft infection.

A single-arm study<sup>34</sup> focusing on patients admitted for secondary aortoenteric fistula following an aortic graft found high rates of cardiac complications, abdominal wall abscesses, and graft infections. That study reported low rates of intestinal obstruction, recurrent fistula, renal insufficiency, and retroperitoneal abscess and bleeding. Another single-arm study<sup>35</sup> examining aortic, peripheral, and/or extra-anatomic reconstructions with silver grafts found high rates of infection and wound revision. Lastly, a small nonrandomized comparative study<sup>33</sup> comparing a silver prosthesis with human allograft found most patients with human allografts reported ruptured aneurysms, as compared to no patients with silver prosthesis.

### Local Responses (animal studies)

One single-arm study<sup>36</sup> examining 15 swine with zinc III silver stents reported no local host responses at 1 month, 3 month, or 6 month time points following stent insertion into the iliofemoral artery.

### Systemic Responses

The same large SR<sup>32</sup> examined amputation event rates for aortic graft reconstructions (AGRs) using silver versus four comparison groups: cryo-all, rifamp, standard polyester, and autogenous veins. Authors reviewed evidence from 25 studies, and meta-analyses displayed statistically significant differences among groups for amputation ( $p<0.0001$ ). Silver had a low event rate for amputation with 0.04.

The same single-arm study<sup>34</sup> on patients admitted for secondary aortoenteric fistula following an aortic graft reported a high rate of lower limb ischemia and low rates of persistent sepsis and pneumonia.

### Overall Quality of Evidence

One large systematic review, as well as several observational studies with large to small sample sizes reported on local host responses. The included systematic review also investigated how specific factors (such as age, PDF, virulent, and nonvirulent confounders) impacted effect sizes of outcomes of interest. The quality of evidence for local host responses is moderate. The same large systematic review and one single arm study reported on systemic responses, although, the confounding effect of specific variables was not examined, resulting in a quality of low.

## Abdominal Wall

1 animal study (1 RCT<sup>37</sup>). For further information see Table 8 in Appendix D.

### Local Responses/Device Events (human studies)

No included human studies investigated local responses to silver in devices implanted into the abdominal wall.

### Local Responses/Device Events (animal studies)

250 male Wistar rats were implanted with one of five types of mesh, two of which contained silver ions (Esfil Ag and Uniflex Ag). When examining the area of cell inflammatory infiltrate, uniflex Ag decreased infiltrate area 2.5 times more than regular uniflex, and esfil Ag decreased the area by 2.4 times more than esfil. All local host responses were examined up to 14 days for the outcomes of interest.

### Systemic Responses

No included studies investigated systemic responses to silver in devices implanted into the abdominal wall.

### Overall Quality of Evidence

One large animal RCT with inconsistent outcomes reporting to other categories. Quality of evidence is very low for local and systemic host responses.

## Endodontic/Maxillofacial

3 animal studies (1 RCT,<sup>38</sup> 2 NRCSs<sup>39,40</sup>). For further information see Table 9 in Appendix D.

### Local Responses/Device Events (human studies)

We did not identify any human studies investigating local responses to silver in endodontic/maxillofacial devices.

### Local Host Responses (animal studies)

Demyashkin et al.<sup>39</sup> observed a mild inflammatory reaction to polylactic acid membranes with silver nanoparticles. Smeets et al.<sup>40</sup> reported no sign of inflammatory cell infiltration, systemic or local rejections, or foreign-body reactions when using a titanium implant with a silver-polysiloxane coating. Similarly, Lee et al.<sup>38</sup> reported that no health complications were detected when using a Titanium-silver alloy.

### Systemic Responses

No included studies investigated systemic responses to silver in endodontic/maxillofacial devices.

### Overall Quality of Evidence

Three studies with small sample size were included. The conclusions regarding local responses were consistent with studies for other categories. None of the included studies investigated systemic responses. Therefore, the quality of evidence for endodontic/maxillofacial devices is low for local responses and very low for systemic responses.

## Esophageal

2 animal studies (1 RCT,<sup>41</sup> 1 NRCS<sup>42</sup>). For further information see Table 10 in Appendix D.

### Local Responses/Device Events (human studies)

No included human studies investigated local responses to silver in esophageal devices.

### Local Host Responses (animal studies)

A study of silver-coated self-expandable metallic stents reported that there were no complications upon gross examination.<sup>41</sup> In a study of rat esophagus segments implanted into dorsal pouches in mice, segments with silver nanoparticles were found to exhibit significantly less inflammatory cells than native tissue.<sup>42</sup>

### Systemic Responses

No included studies investigated systemic responses to silver in esophageal devices.

### Overall Quality of Evidence

Two studies with small sample size and short follow-up were included. Therefore the quality of evidence for local and systemic responses to esophageal devices is very low.

## Hepatic

2 animal studies (2RCTs<sup>43,44</sup>). For further information see Table 11 in Appendix D.

### Local Host Responses (human studies)

No included human studies investigated local responses to silver in hepatic-related devices.

### Local Host Responses (animal studies)

One study<sup>43</sup> examined 24 New Zealand rabbits implanted with self-expandable metal stents (SEMs) in the common bile duct. Six rabbits were assigned to one of four groups: 3 mg/mL silver nitrate (AgNO<sub>3</sub>), 6 mg/mL AgNO<sub>3</sub>, 12 mg/mL AgNO<sub>3</sub>, or control. Authors reported no stent-related adverse events up to 4 weeks. The other study<sup>44</sup> examined 30 male mice implanted with native, non-cross-linked, or cross-linked decellularized liver (DL) slices implanted subcutaneously. Six mice were assigned to silver nanoparticle (AgNP) DL cross-linked slices, native liver slices, non-cross-linked DL slices, glutaraldehyde cross-linked, or ethyl carbodiimide hydrochloride/ N-hydroxysuccinimide cross-linked slices. Authors noted no signs of infection or behavioral changes at 7 day and 21 day follow-up.

### Systemic Responses

No included studies investigated systemic responses to silver in hepatic-related devices.

### Overall Quality of Evidence

Two animal studies with small sample sizes and inconsistent reporting of adverse events examined local host responses. No studies examined systemic responses. Quality of evidence is very low for local and systemic responses.

## Lung

1 human study (1 nonrandomized comparative study<sup>45</sup>). For further information see Table 12 in Appendix D.

### Local Host Responses (human studies)

One nonrandomized comparative study<sup>45</sup> compared silver nitrate (n=15) and n-butyl-2 cyanocrylate histoacryl (n=15) injections in the lungs of patients for up to 3 months.<sup>45</sup> 2 patients with silver nitrate injections reported complications of pneumonia (n=1) and respiratory failure (n=1), whereas, 4 patients with histoacryl injections reported chest pain.

### Local Host Responses (animal studies)

No included animal studies investigated local responses to silver in lung devices.

### Systemic Responses

No included studies investigated systemic responses to silver in lung devices.

### Overall Quality of Evidence

One low quality cohort study with a moderate sample size (n=30) reported on local responses. Systemic responses were not investigated in any study. The quality of evidence for all local host responses is low, and the quality of evidence for systemic responses is very low.

## Middle Ear

1 human study (1 single-arm study<sup>46</sup>), 1 animal study (1 RCT<sup>47</sup>). For further information see Tables 13 and 14 in Appendix D.

### Local Host Responses (human studies)

One single-arm study<sup>46</sup> examined three patients with an otoimplant prosthesis incorporated with silver nanoparticles (0.1% weight) for up to one year. One adverse event of deterioration of speech understanding was found in a patient, which study authors note can be associated with progressive senile hearing loss. No other adverse events were seen, noting no direct germ cell growth, inflammation, or middle ear infection.

### Local Host Responses (animal studies)

One RCT<sup>47</sup> examined 40 rabbits undergoing implantation surgery for the Biovert II middle ear prosthesis with five comparison groups (n=8 per group), split by type of coating, for up to 21 days. Three groups contained silver (silver silica film, dense silver silica film, and blank coating with 1% silver sulfadiazine cream), whereas, two groups only contained silica (silica film, dense silica film). One rabbit given 1% silver sulfadiazine cream experienced severe head tilt. All other animals showed good general health.

### Systemic Responses

The same RCT<sup>47</sup> examining rabbits undergoing implantation surgery for the Biovert II middle ear prosthesis with five comparison groups investigated systemic responses. Two rabbits were observed with cardiovascular complications (one with silica film, another with silver silica coating).

### Overall Quality of Evidence

One human study with a very small sample size (n=3) and an animal study with a moderate sample size examined local responses in middle ear silver prostheses. Systemic responses were investigated in one animal study. The quality of evidence for all local and systemic host responses is very low.

## Sutures

1 animal study (1 RCT<sup>48</sup>). For further information see Table 15 in Appendix D.

### Local Host Responses (human studies)

No included human studies investigated local responses to silver in sutures.

### Local Host Responses (animal studies)

One study<sup>48</sup> allocating 21 mice to silver nanoparticle (n=7), antibiotic-coated (n=7), or normal sutures (n=7) found that mice with silver nanoparticles had the least inflammation up to 28 days.

### Systemic Responses

No included studies investigated systemic responses to silver in sutures.

### Overall Quality of Evidence

One small animal RCT with inconsistent outcome reporting found evidence on local host responses. The quality of evidence for local and systemic host responses is very low.

## ECRI Surveillance Data

There were no relevant reports found in ECRI's PSO, accident investigation, or PRN databases related to devices composed of or coated with silver. Healthcare Technology Alerts search returned 7 manufacturer issued alerts describing problems with sterility, implant loosening, incorrect components, deviations in dimensions, reduced implant diameter, and implant failure.

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 370 reports that occurred between May 2015 and May 2021 and contained the keyword search utilized for Silver; however, none of these involved complications with devices made from Silver.

## Accident Investigations

Search Results: Zero investigations were recovered from the accident investigations database.

## ECRI Problem Reports

Search Results: The search returned zero reports submitted by ECRI members.

## Healthcare Technology Alerts

Search Results: The search returned 7 manufacturer issued alerts describing problems with sterility, implant loosening, incorrect components, deviations in dimensions, reduced implant diameter, and implant failure, summarized in Table 3.

Table 3: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
Orthopedic Implant	7 manufacturer issued	<ul style="list-style-type: none"><li>• Sterility – device stem punctured packaging</li><li>• Implant loosening due to screw connection</li><li>• Incorrect components included</li><li>• Incorrect dimensions of included components</li><li>• Set screw misuse reduces implant diameter</li><li>• Implant failure</li></ul>

## Potential Gaps

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

ECRI identified few implant devices with FDA 510(k) clearance or premarket approval (PMA) and the majority of devices within this report had CE Mark.

Overall, there is a lack of evidence related to both host and material responses at the local and systemic level for device composed of or coated with silver.

We did not identify any human studies investigating local responses to silver as a material and only a few small sample size animal studies reported a lack of adverse events.

There were no studies that addressed any particular cellular or molecular mechanisms for systemic manifestations.

Additionally, no studies addressed patient-related or material-related factors that could predict the likelihood and/or severity of immunological/systemic responses.

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

### Inclusion Criteria

1	English language publication
2	Published between January 2011 and May 2021
3	Human and animal studies
4	Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5	Studies that evaluate toxicity/biocompatibility of Silver or priority devices that include this material

### Exclusion Criteria

1.	Foreign language publication
2.	Published before January 2011
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.	<b>Quality of comparison</b> – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2.	<b>Quantity of data</b> – number of systematic reviews and individual studies providing relevant data.
3.	<b>Consistency of data</b> – are the findings consistent across studies that report relevant data?
4.	<b>Magnitude of effect</b> – 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.	<b>Directness of evidence</b> – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6.	Is there evidence of a <b>dose response or time response</b> (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.

### Literature Search for Silver

Set Number	Concept	Search Statement
<b>Material</b>		
1.	Silver and silver derivatives	'silver'/exp OR 'silver derivative'/exp OR 'silver nanoparticle'/exp OR 'silver nitrate'/exp OR 'silver oxide'/exp OR nanosilver* OR nano silver* OR microsilver* OR 'micro silver*' OR 'silver coated' OR 'silver containing' OR ('silver' NEAR/2 (coat* OR substituted OR ion* OR particle*)) OR (silver*:ti,ab AND (platinum OR 'ag-pt?':ti,ab OR ag:ti,ab OR 'agnp?':ti,ab OR 'ag-np?':ti,ab OR 'agp?':ti,ab))
2.	Silver devices	#1 AND ('prostheses and orthoses'/exp OR 'artificial heart pacemaker'/de OR 'bone implant'/de OR 'bone nail'/de OR 'cement spacer'/de OR 'contact lens'/de OR 'compression screw'/de OR 'humeral stem'/de OR 'implant'/de OR 'mesh sling'/de OR 'orthopedic implant'/de OR 'orthopedic surgery'/exp OR 'prosthesis'/de OR 'spine implant'/de OR 'medical device'/de OR 'stent'/de OR 'tissue scaffold'/de OR 'bone regeneration'/exp OR 'tissue regeneration'/exp OR 'bone graft'/exp OR 'osseointegration'/exp OR valve* OR prosth* OR pacemaker* OR implant* OR nail* OR screw* OR 'intramedullary nail*' OR 'bone cement' OR suture* OR spacer? OR 'humeral stem' OR 'endo-prosth*' OR endoprosth* OR 'mega-prosth*' OR megaprosth* OR neuroprosth* OR mesh* OR stent* OR scaffold* OR sling* OR arthroplasty OR orthop?edic*)
3.	Silver product names	'agluna' OR 'antibacterion' OR 'hyprotect' OR 'implantcast' OR 'loqteq' OR 'megac' OR 'mega c' OR 'megasystem c' OR 'mutars' OR 'ossis' OR 'orthofuzion' OR 'orthosyn' OR 'porag' OR 'porous argentum' OR 'silzone' OR

		'stanmore mets' OR ('silver' NEAR/4 (prosth* OR megaprosth* OR endoprosth* OR 'mega prosth*' OR 'endo prosth*'))
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### Material Response

6.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
7.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
8.		Leachable* OR extractable*
9.		(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 (implant* OR prosthes* OR prosthetic* OR endoprosth* OR 'endo prosth*' OR megaprosth* OR 'mega prosth*' OR orthotic* OR device? OR valve? OR mesh* OR stent? OR graft?)
10.		'mechanics'/exp
11.		'device material'/exp/mj
12.		'Biomedical and dental materials'/exp/mj
13.	Combine sets	#6 OR #7 OR #8 OR #9 OR #10 #11 OR #12
14.	<b>Silver + Material Response</b>	<b>#5 AND #13</b>

### Host Response

15.		<b>Host NEAR/2 (reaction* OR response*)</b>
16.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* OR 'carcinogenicity'/exp OR carcinogen*:ti
17.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
18.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
19.		'inflammation'/exp OR inflamm*:ti,ab
20.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
21.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab
22.		protrude* OR protrus* OR perforat*
23.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'seroma*' OR 'hematoma*' OR 'thrombus'/de OR 'thrombosis'/de OR 'thrombosis':ti,ab OR 'thrombus':ti,ab
24.	Combine sets	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25.	<b>Combine sets</b>	<b>#14 AND #24</b>

	<b>Silver + Material Response+ Host Response</b>	
26.	<b>Silver products + Host response</b>	#3 AND #6 AND #24
27.	<b>Combine sets</b>	#25 OR #26
28.	<b>Silver systematic reviews</b>	#5 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
29.	<b>Final set</b>	<b>#27 OR #28</b>

### Example Embase Explosion

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

- I. 856 citations identified by searches, of which
  - a. **496 citations not screened manually due to likely irrelevance** (based on text mining, logistic regression, etc.)
  - b. 360 citations screened for potential inclusion at title/abstract level, of which:
    - i. 257 citations selected by text mining in Distiller (30%)
    - ii. 103 additional citations: 43 citations by logistic regression (5%), 60 citations for including "random" or "systematic" in the title or abstract
      1. **225 citations excluded at the title/abstract level** Citations excluded at this level were off-topic, not published in English, did not address a Key Question, did not report a device of interest, or did not report an outcome of interest
      2. 135 full-length citations reviewed
        - a. **73 citations excluded at the full article level** Citations excluded at this level were off-topic, not published in English, did not address a Key Question, did not report a device of interest, did not report an outcome of interest, or were not available
        - b. 62 citations reviewed for evidence prioritization
          - i. **14 citations excluded at the prioritization level** Citations excluded at this level were animal studies, of relatively low sample size, or did not address a Key Question
          - ii. 48 citations included

## Appendix D. Evidence Tables

Table 4: Silver as a Material - Health Effects (In Vivo) Animal Studies

### Local Response/Toxicity

Source Citation: Dargusch et al. 2021<sup>6</sup>

Study Design: Nonrandomized comparative study

Make and Model: Fe-35Mn-1Ag vs. WE43 vs. Fe-35Mn

Implant Duration: 4 weeks, 12 weeks

Material Composition/Chemical Properties: Fe-35Mn: density: 6.08 g cm<sup>-3</sup>, general porosity: 21.3%, open porosity: 53% Fe-35Mn-1Ag: density: 6.32 g cm<sup>-3</sup>, general porosity: 17.7%, open porosity: 38%

Mechanics/Morphology: Single subcutaneous implant

Host Response: Corrosion rate

Patient characteristics (gender, mean age): 12 Sprague-Dawley rats, 50% female, mean age NR

Number per group: WE43 magnesium alloy (n=4), Fe-35Mn (n=4), Fe-35Mn-1Ag (n=4)

Observed on adverse effects: Fe-35Mn-1Ag had a higher corrosion rate than Fe-35Mn at both 4 week and 12 week timepoints. Also, both Fe-35Mn and Fe-35Mn-1Ag had significantly higher corrosion rate at 4 weeks than 12 weeks.

Timing of adverse effects: 4 weeks, 12 weeks

Factors that predict response: NR

Source Citation: Bonete et al. 2020<sup>7</sup>

Study Design: Nonrandomized comparative study

Make and Model: Natural latex vs. 0.05% AgNP vs. 0.4% AgNP

Implant Duration: 3 days, 7 days, 25 days

Material Composition/Chemical Properties: NR

Mechanics/Morphology: Single subcutaneous implant

Host Response: No serious AEs

Patient characteristics (gender, mean age): 18 male Wistar rats

Number per group: Natural latex (n=6), latex with 0.05% AgNP (n=6), and latex with 0.4% AgNP

Observed on adverse effects: No statistically significant difference in the tissue response of the different biomaterials was observed, indicating that AgNP did not interfere with the inflammatory reaction,  $p > 0.05$ , or with the angiogenic activity of latex.

Timing of adverse effects: 3 days, 7 days, 25 days

Factors that predict response: NR

Source Citation: Bozinovski et al. 2018<sup>8</sup>

Study Design: Nonrandomized comparative study

Make and Model: Custom material comparisons: Ag/PVA vs. Ag/PVA/Gr vs. Ag/PVA/CHI vs. Ag/PVA/CHI/Gr

Implant Duration: Up to 60 days

Material Composition/Chemical Properties: NR

Mechanics/Morphology: Single subcutaneous implant

Host Response: No serious AEs

Patient characteristics (gender, mean age): 16 adult female rats (species NR)

Number per group: Sterilized nanocomposite hydrogel discs with the following combinations of nanoparticles: Ag/PVA (n=4 rats), Ag/PVA/Gr (n=4 rats), Ag/PVA/CHI (n=4 rats) and Ag/PVA/CHI/Gr (n=4 rats)

Observed on adverse effects: No wound healing complications were observed after the surgery and during the whole experiment.

Timing of adverse effects: 7 days, 15 days, 30 days, and 60 days

Factors that predict response: NR

Source Citation: Takamiya et al. 2016<sup>9</sup>

Study Design: Nonrandomized comparative study

Make and Model: SNA vs. SNP

Implant Duration: 7 days, 15 days, 30 days, 90 days

Material Composition/Chemical Properties: Silver nanoparticles of an average size 5 nm

Mechanics/Morphology: 3 polyethylene tubes implanted with either SNA or SNP per rat

Host Response: No serious AEs

Patient characteristics (gender, mean age): Sixteen 4- to 6-month-old male Wistar Albino rats

Number per group: All rats were implanted with three polyethylene tubes containing a fibrin sponge, silver synthesized with ammonia (SNA), or polyvinylpyrrolidone (SNP)

Observed on adverse effects: Mild inflammatory cell infiltration and a reduction in the thickness of the fibrous capsule were evident from day 30 onward, similar to the control group

Timing of adverse effects: 7 days, 15 days, 30 days, 90 days (4 mice per time period)

Factors that predict response: NR

Source Citation: Alarcon et al. 2015<sup>10</sup>

Study Design: Nonrandomized comparative study

Make and Model: Hydrogel vs. 0.2  $\mu$ M AgNP hydrogel vs. 0.4  $\mu$ M AgNP hydrogel vs. sham

Implant Duration: 24 or 72 hours

Material Composition/Chemical Properties: NR

Mechanics/Morphology: Single subcutaneous insertion

Host Response: No serious AEs

Patient characteristics (gender, mean age): Fifteen 8-week old female C57 mice

Number per group: Hydrogel (n=4), 0.2  $\mu$ M AgNP hydrogel (n=4), 0.4  $\mu$ M AgNP hydrogel (n=4), sham (n=3)

Observed on adverse effects: No visual inflammation was observed for the gels containing AgNPs compared to the sham and/or control groups.

Timing of adverse effects: 24 or 72 hours

Factors that predict response: NR

Source Citation: Marsich et al. 2011<sup>12</sup>

Study Design: Nonrandomized comparative study

Make and Model: Ac-nAg vs. Ac-nAu

Implant Duration: Up to 1 month

Material Composition/Chemical Properties: NR

Mechanics/Morphology: Each rat received one nanocomposite sample and one control sample (AC) subcutaneously on the back.

Host Response: No serious AEs

Patient characteristics (gender, mean age): Eight male Wistar rats

Number per group: Alginate-Chitlac hydrogels containing silver nanoparticles (AC-nAg) vs. Alginate-Chitlac hydrogels containing gold nanoparticles (AC-nAu)

Observed on adverse effects: No damage, infiltration of inflammatory cells or morphological alteration of the surrounding tissues were observed.

Timing of adverse effects: Up to 1 month

Factors that predict response: NR

Source Citation: Wang et al. 2013<sup>11</sup>

Study Design: Nonrandomized comparative study

Make and Model: 6 mg/kg AgNP, 7.5 mg/kg AgNP, 9 mg/kg AgNP, 12 mg/kg AgNP, 15 mg/kg AgNP, commercial AgNP, saline

Implant Duration: Up to 14 days

Material Composition/Chemical Properties: AgNPs were embedded in electrospun membranes

Mechanics/Morphology: Single injection

Host Response: Loss of skin luster, Weight loss

Patient characteristics (gender, mean age): 70 Imprinting Control Region mice aged 6–8 weeks, 50% female

Number per group: 6 mg/kg AgNP (n=10), 7.5 mg/kg AgNP (n=10), 9 mg/kg AgNP (n=10), 12 mg/kg AgNP (n=10), 15 mg/kg AgNP (n=10), commercial AgNP (n=10), saline (n=10)

Observed on adverse effects: All 10 mice in 12 mg/kg and 15mg/kg AgNP group died, and 4 mice in 9 mg/kg group died. All other mice survived successfully. 9 mg/g mice lacked skin luster and lost more body weight

compared to saline control group. Low dose groups (6 mg/kg and 7.5 mg/kg AgNP) lost appetite in first 2 days but recovered.

Timing of adverse effects: All 12 mg/kg and 15 mg/kg AgNP mice died within 10-30 minutes. 3 mice in 9 mg/kg AgNP group died within 12 hours.

Factors that predict response: NR

AC = Alginat-Chitlac; AE = adverse event; AgNP = silver nanoparticle; Chi = chitosan; Fe-35Mn: iron, manganese alloy; Fe-35Mn-1Ag = iron, manganese, silver alloy; Gr = graphene; mg/kg = milligram per kilogram;  $\mu\text{M}$  = micromolar; nAg = silver nanoparticle; nAu = gold nanoparticle; nm = nanometer; NR = not reported; PVA = polyvinyl alcohol; SNA = silver synthesized with ammonia; SNP = silver synthesized with polyvinylpyrrolidone; WE43 = common biodegradable magnesium alloy

Table 5: Orthopedics, Bone and Joint - Health Effect (In Vivo) Human Studies

### **Local Response/Toxicity**

Source Citation: Fiore et al. 2021<sup>1</sup>

Study Design: SR

Device or Material: MUTARS (Implantcast), METS + Alguna (Stanmore Implants), Megasystem C + PorAg (Waldemar Link)

Contact Duration: Mean follow-up times ranged from 16 – 123.6 months

Dose: NR

Frequency/Duration: Single administration

Response: Local argyria, Local silver concentration

Patient characteristics (gender, mean age): SC: 50.6% female, mean age ranged from 19 – 74 yrs, UC: 51.8% female, mean age ranged from 16 – 77.1 yrs

Number per group: 19 studies included: SC: 755 total, 480 primary, 219 revision / UC: 726 total, 507 primary, 146 revision

Observed adverse effects: **Local argyria** was reported in 2.2% (8/357) of patient. Seven of the 8 were in a case series of 32 MUTARS patients. Local silver concentration in tissue or synovial fluid varied from 80 – 1626 ppb for MUTARS and 0.48 to 78 ppb for PorAg. Overall **infection rate** = 17.6% (133/755), significantly less than uncoated (p=0.039). For primary EPR, there was no difference in **infection rate** between SC (9.2%) and uncoated (11.2%). For revisions EPR, SC had a lower **infection rate** than uncoated (13.7% vs 29.2%, p=0.019). Generally, MUTARS® EPR produced an almost constant decrease in the incidence of primary PJI, but there are few data on the effectiveness in revisions. Agluna® results in both primary and revision implants are inconsistent. PorAg® was effective both in PJI prevention but, especially, when used in PJI revision settings.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Alt et al. 2019<sup>3</sup>

Study Design: SAS

Device or Material: Palacos R+G (Heraeus Medical) spacer loaded with MicroSilver BG (Bio-Gate AG)

Contact Duration: 14 days

Dose: 0.8 – 1.2 g of silver in 80 – 120 g of PMMA

Frequency/Duration: Single Administration

Response: None

Patient characteristics (gender, mean age): 42% female, 66.7 yrs (31 – 80 yrs)

Number per group: 12

Observed adverse effects: No adverse events attributable to the silver spacer or other serious adverse events were observed. No silver-specific adverse events, such as argyria or impairment of the femoral or sciatic nerve,

were observed. In all but one patient, the detected silver amount was close to or below the detection limit of 1 ppb of blood in all blood samples and thus several times below the reported values of up to 10 ppb in normal subjects. One patient had a silver concentration of 3.0 ppb and 2.8 ppb (3.0 µg and 2.8 µg silver per kilogram of blood) at 12 hours and 48 hours, respectively, after the implantation of the silver spacer. After exchange of the silver spacer to a silver-free spacer, the silver concentration was 4.1 ppb and 5.3 ppb at 12 hours and 48 hours, respectively, after the intervention. The overall urine silver burden in all urine samples was negligible and found to be below the detection limit of 1 ppb. In general, no considerable systematic differences between microsilver-loaded and silver-free PMMA spacers were detected and the histomorphological features were similar compared with regular diagnostic samples tested in the same period.

Timing of adverse effects: 12 to 48 hours

Factors that predict response: NR

Source Citation: Bus et al. 2017<sup>14</sup>

Study Design: NRCS

Device or Material: LUMic (Implantcast)

Contact Duration: Minimum follow-up 24 months

Dose: NR

Frequency/Duration: NR

Response: Infections

Patient characteristics (gender, mean age): 45% female, 50 yrs (12-78)

Number per group: 29 Silver, 18 non-silver

Observed adverse effects: Deep infections (Henderson Type IV) occurred in 13 patients (28%), 10 within 2 months, two after 3 months, and one after 34 months. Blood loss showed a statistically significant correlation with the risk of infection; blood loss was 2.3 L (range, 0.8–8.2 L) for patients with an infection and 1.5 L (range, 0.4–3.8 L) for those without ( $p = 0.039$ ). Other factors we analyzed (attachment tubes, silver-coated cups) were not correlated to the risk of infection. In all, 71 reoperations were performed in 25 patients (53%; range, one to eight), 59 of which (83%) were in the first postoperative year. Predominant reasons for reoperations were infection ( $n = 46$  [65%]), mechanical reasons ( $n = 15$  [21%]), and local recurrences ( $n = 6$  [8%] after a median of 22 months [range, 10 months to 4.5 years]).

Timing of adverse effects: 10 infections occurred within 2 months, two after 3 months, and one after 34 months.

Factors that predict response: Blood loss showed a statistically significant correlation with the risk of infection; blood loss was 2.3 L (range, 0.8–8.2 L) for patients with an infection and 1.5 L (range, 0.4–3.8 L) for those without ( $p = 0.039$ ).

Source Citation: Calori et al. 2014<sup>13</sup>

Study Design: NRCS

Device or Material: PorAg (LINK)

Contact Duration: Mean follow-up 18 months

Dose: NR

Frequency/Duration: Single administration

Response: None

Patient characteristics (gender, mean age): 75% female, 64 yrs (33-89 yrs)

Number per group: 32

Observed adverse effects: There was only one case of dislocation of the femoral endoprosthesis in a young patient with an elusive acetabulum. Another complication in this study was a proximal femur periprosthetic fracture that occurred in the seventh post-operative day when a patient recovering from distal femur megaprosthesis fell accidentally.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Fiore et al. 2021<sup>1</sup>

Study Design: SR

Device or Material: MUTARS (Implantcast), METS + Alguna (Stanmore Implants), Megasystem C + PorAg (Waldemar Link)

Contact Duration: Mean follow-up times ranged from 16 – 123.6 months

Dose: NR

Frequency/Duration: Single administration

Response: Silver blood concentration

Patient characteristics (gender, mean age): SC: 50.6% female, mean age ranged from 19 – 74 yrs / UC: 51.8% female, mean age ranged from 16 – 77.1 yrs

Number per group: SC: 755 total, 480 primary, 219 revision / UC: 726 total, 507 primary, 146 revision

Observed adverse effects: Concentration of silver in the blood increase from 0-0.37 ppb preop to 0.41 – 30 ppb postop. Studies report blood concentrations of 1.93 – 12.98 ppb at 3 to 24 months postop

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Alt et al. 2019<sup>3</sup>

Study Design: SAS

Device or Material: Palacos R+G (Heraeus Medical) spacer loaded with MicroSilver BG (Bio-Gate AG)

Contact Duration: 14 days

Dose: 0.8 – 1.2 g of silver in 80 – 120 g of PMMA

Frequency/Duration: Single Administration

Response: Blood Silver concentration

Patient characteristics (gender, mean age): 42% female, 66.7 yrs (31 – 80 yrs)

Number per group: 12

Observed adverse effects: In all but one patient, the detected silver amount was close to or below the detection limit of 1 ppb of blood in all blood samples and thus several times below the reported values of up to 10 ppb in normal subjects. One patient had a silver concentration of 3.0 ppb and 2.8 ppb (3.0 µg and 2.8 µg silver per kilogram of blood) at 12 hours and 48 hours, respectively, after the implantation of the silver spacer. After exchange of the silver spacer to a silver-free spacer, the silver concentration was 4.1 ppb and 5.3 ppb at 12

hours and 48 hours, respectively, after the intervention. The overall urine silver burden in all urine samples was negligible and found to be below the detection limit of 1 ppb. In general, no considerable systematic differences between microsilver-loaded and silver-free PMMA spacers were detected and the histomorphological features were similar compared with regular diagnostic samples tested in the same period.

Timing of adverse effects: 12 to 48 hours

Factors that predict response: NR

EPR = endoprosthesis; NA = not applicable; NR = not reported; ns = not significant; Obs = observational; PJI = prosthetic joint infection; ppb = parts per billion; Retro = retrospective; R = reliable; SC = silver coated; UC = uncoated

Table 6: Orthopedics, Bone and Joint - Health Effects (In Vivo) Animal Studies

### ***Local Response/Toxicity***

Source Citation: Masamoto et al. 2021<sup>15</sup>

Study Design: RCT

Device or Material: Calcium-Strontium-Silver-Titanium (CaSrAg-Ti) alloy

Route: Femoral intramedullary cavity

Dose: 2 rods, 1.5mm diameter x 15 mm length

Frequency/Duration: Single administration / 4 and 8 weeks

Response: None

Species (strain): Wistar/ST rats

Gender: Male

Number per group: **Mechanical testing:** 18 rats, 36 legs. **Histological testing:** 12 rats, 24 legs. **Serum testing:** 45 rats.

Observations on adverse effects (brief): There were no apparent signs of infection or argyrosis in rats. No significant difference in bone-implant failure load or bone-implant contact ratio between CASr-Ti and CaSrAg-Ti at 4 or 8 weeks. The concentration of Ag ions after surgery did not change from the baseline at any time point (measured at 1, 2, 7, and 28).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Ständert et al. 2021<sup>16</sup>

Study Design: RCT

Device or Material: Titanium with silver nanoparticles

Route: Intercondylar fossa

Dose: 1.4mm K-wire

Frequency/Duration: Single administration / 56 days

Response: None

Species (strain): Sprague Dawley rats

Gender: Female

Number per group: 16 per group with 3 groups: Ti K-wire (CTRL), porous SC K-wire (Porous), porous SC and gentamicin coated K-wire (Genta)

Observations on adverse effects (brief): The radiographic follow-up revealed no signs of osteolysis in any of the femora. Weight loss after the operation was minimal ( $0.3 \pm 5$  g) and all animals continued to gain weight until the end of the experiment, without differences between the groups. The maximum push-out shear force was significantly higher ( $p \leq 0.0153$ ) in the Porous and Genta groups compared to the CTRL group. There was no statistical difference between the modified groups. There was significantly ( $p = 0.0012$ ) more fibrous tissue formation in the CTRL group compared to the Porous group. The difference between the CTRL

and Genta groups was not significant. The CTRL group showed significantly less ( $p = 0.0032$ ) bone-implant contact (BIC) compared to the Porous group and the Genta group. Newly formed bone filled the pores of the modified K-wires, resulting in increased direct contact.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Yang et al. 2021<sup>19</sup>

Study Design: NRCS

Device or Material: PLLA-HA-Ag scaffold

Route: Left forearm radius

Dose: 15mm long scaffold

Frequency/Duration: Single administration / 4 and 8 weeks.

Response: None

Species (strain): New Zealand rabbits

Gender: NR

Number per group: 6 per group

Observations on adverse effects (brief): In general, both PLLA-HA-Ag and PLLA scaffolds presented good in vivo biocompatibility without obvious inflammation.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Arens et al. 2020<sup>20</sup>

Study Design: NRCS

Device or Material: Silver coated Ti-6Al-4V locking plates, silver coated screws

Route: Midshaft of humerus

Dose: 60  $\mu\text{g}$  of silver per plate.

Frequency/Duration: Single administration / 10 weeks

Response: None

Species (strain): New Zealand White rabbits

Gender: NR

Number per group: 12 SC, 12 UC

Observations on adverse effects (brief): Surgical wounds healed uneventfully without infection or other disturbances. Animal weight at the end of the study was comparable to the pre-operative weight. No difference between the two groups. Radiographs showed no difference in bone healing, including at 4, 6, and 10 weeks. Micro-CT showed no difference in tissue density. Mechanical testing showed no difference in stiffness. Histology showed no difference in new bone formation. **Blood samples:** 3 animals in the SC group had silver concentrations of 11 – 20 ppb on day 1. 2 of those animals had silver concentrations of 25 and 75 ppb after one week. All other measurements were below the detection limit. All measurements for the UC group were below the detection limit. **Soft tissue:** Silver was detected in 9 of the animals in the SC group with a

median concentration of 60 ppb. No silver was detected in the UC group. **Organs:** Silver could not be detected in liver, kidney, spleen, brain, or axillary lymph nodes. **Feces:** Silver was found in 99 of 120 samples in the SC group, with 24 having concentrations higher than 50 ppb. In the UC group, silver was found in 26 of 51 samples, with 3 having concentrations higher than 50 ppb.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Chen et al. 2020<sup>21</sup>

Study Design: NRCS

Device or Material: Silver-loaded TiO<sub>2</sub> nanotubes (AG@TiO<sub>2</sub>-NTs)

Route: Tibial medullary cavity

Dose: 0.8mm diameter x 12 mm length rod

Frequency/Duration: Single administration / 2 weeks

Response: None

Species (strain): Sprague-Dawley rats

Gender: Male

Number per group: Ti rod: 10; TiO<sub>2</sub>-NT rod: 10; Ag@TiO<sub>2</sub>-NT rod: 10

Observations on adverse effects (brief): NR

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Stein et al. 2020<sup>4</sup>

Study Design: RCT

Device or Material: Titanium-vanadium coated with polysiloxane embedded with silver

Route: Medial femoral condyle, medial tibial diaphysis, proximal tibial metaphysis

Dose: NR

Frequency/Duration: Single administration / 6 months

Response: None

Species (strain): Merino sheep

Gender: Female

Number per group: 8 silver coated, 8 uncoated

Observations on adverse effects (brief): Sheep displayed no abnormalities in movement and there were no macroscopically visible signs of inflammation or disturbed wound healing. After 6 months, there were no visible macroscopic signs of inflammation. All implants were tightly integrated into vital bone with a layer of fibrous or cartilaginous tissue or bone covering the lateral implant surface. Silver content in blood (sampled at 2 and 6 months) and kidney and lymph nodes (sampled at 6 months) was below the detection limit of 3 µg/kg. There was no difference in silver concentration in the liver between SC and UC groups. SC group had a higher silver concentration in the bone and tissue surrounding the implant (9 µg/kg) compared to the UC group (5 µg/kg, p≤0.05). The silver coating did not significantly influence the interface shear strength of the

titanium implants, whether implanted in femur or tibia. No signs of inflammation or particles derived from the implant surface were detectable. Bone apposition to the implants was not significantly influenced by the silver coating.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Lapaj et al. 2019<sup>22</sup>

Study Design: NRCS

Device or Material: TiAl6V4 implants coated with silver doped hydroxyapatite (HA)

Route: Femur

Dose: NR

Frequency/Duration: Single administration / 12 weeks

Response: None

Species (strain): New Zealand White rabbits

Gender: NR

Number per group: 6 silver-doped HA, 6 HA

Observations on adverse effects (brief): No complications

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Deng et al. 2019<sup>2</sup>

Study Design: SR

Device or Material: Silver modified endoprosthesis, pin, or rod

Route: NR

Dose: NR

Frequency/Duration: NR

Response: None

Species (strain): 6 animal studies of silver, 3 rat models, 3 rabbit models

Gender:

Number per group: 10 – 30

Observations on adverse effects (brief): Three studies reported a lower infection rate with RR ranging from 0.13 to 0.71. Moreover, five studies found a lower bacterial load or infection sign. While the elevated mean silver concentrations in the blood or organs were reported in two studies, no side effects were reported.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Liu et al. 2019<sup>23</sup>

Study Design: NRCS

Device or Material: Ti-Ag sintered alloy

Route: Femoral medullary cavity

Dose: 1 implant; 0, 1, 2, and 4 % silver by weight

Frequency/Duration: Single administration / Up to 4 weeks.

Response: Cytotoxicity

Species (strain): Sprague Dawley rats

Gender: Male

Number per group: 90 total, 18 per group, 6 per time point

Observations on adverse effects (brief): From micro-CT, the amount of cancellous bone around the Ti-2% silver nanotube (Ti2%Ag-NT) implants was greater than that of pure Ti at week 2, and not significantly different at weeks 1 and 4. The amounts of cancellous bone around Ti1%Ag-Nt and Ti4%Ag-NT were less than that of pure Ti. The bone volume to total volume ratios for Ti1%Ag-NT and Ti4%Ag-NT was less than that of pure Ti to varying degrees.

Timing of adverse effects: 1 – 4 weeks

Factors that predict response: NR

Source Citation: Vu et al. 2019<sup>17</sup>

Study Design: RCT

Device or Material: ZnSiAg doped plasma sprayed hydroxyapatite coated Ti implant

Route: Distal femur

Dose: NR

Frequency/Duration: Single administration / 5 and 10 weeks

Response: None

Species (strain): Sprague-Dawley rats

Gender: NR

Number per group: 18

Observations on adverse effects (brief): Shear modulus values were highest with ZnSiAg-HA coating and significantly higher than just Ti64 implants but not significantly different from HA coated implants. Pushout strength was not statistically significant between ZnSiAg-HA and HA but both were statistically higher than Ti64 alone.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Zhang et al. 2019<sup>24</sup>

Study Design: NRCS

Device or Material: Nano-hydroxyapatite combined with polyurethan containing silver (Ag/n-HA/PU)

Route: Proximal tibia

Dose: NR

Frequency/Duration: Single administration / 4 days, 3, 6, and 12 weeks

Response: None

Species (strain): New Zealand White rabbits

Gender: Male

Number per group: 16 per group: blank control, n-HA/PU, n-HA/PU with 3% silver (n-HA/PU3), n-HA/PU with 10% silver (n-HA/PU10).

Observations on adverse effects (brief): The white blood cell count was significantly lower in n-HA/PU3 and n-HA/PU10 groups compared to blank control and n-HA/PU groups. Two animals in the n-HA/PU10 had alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values higher than normal, indicating potential impairment of liver function. However, there was no statistical differences between groups in ALT and AST values. A significant control of inflammation was observed in both the n-HA/PU3 group and n-HA/PU10 group, with no bone destruction or soft tissue swelling along with good bone repair after 6 or 12 weeks of treatment. At the same time, the n-HA/PU10 group showed a significant degradation of scaffolds after implantation at postoperative 12 weeks. However, the bone tissue did not closely fix with the smaller scaffolds, and a dead cavity was observed.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Salih et al. 2018<sup>18</sup>

Study Design: RCT

Device or Material: Platelet-rich fibrin matrix (PRFM) with silver nanoparticles (AgNPs)

Route: Tibia

Dose: NR

Frequency/Duration: Single administration / 2 and 4 weeks

Response: None

Species (strain): Local rabbits

Gender: male

Number per group: 5 per group; untreated bone defect (control), PRFM alone, AgNPs alone, PRFM with AgNPs.

Observations on adverse effects (brief): All experimental animals appeared healthy, without any complications (infection or rejection) in the site of operation, but the animals were unable to bear weight on the operated limb for about 3 days then the animals stood on their forelimb normally.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Harrasser et al. 2016<sup>25</sup>

Study Design: NRCS

Device or Material: Titanium screw coated with hydroxyapatite and silver

Route: Left hind tibia

Dose: NR

Frequency/Duration: Single administration / 42 days

Response: None

Species (strain): Wistar rats

Gender: Male

Number per group: 12 rats per group, HA, HA-Ag, and calcium dihydroxide

Observations on adverse effects (brief): The animals recovered quickly after surgery and showed no signs of discomfort or local infection. X-rays showed no signs of osteolysis, periosteal elevation or implant loosening at day of sacrifice. Retrieved implants showed no bacterial growth, and no histological specimens showed signs of bone infection.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Jia et al. 2016<sup>26</sup>

Study Design: NRCS

Device or Material: TiO<sub>2</sub>/Ag coating on Ti

Route: Dorsal subcutaneous pocket

Dose: 2 Ti implants and 2 Ti/Ag implants

Frequency/Duration: Single administration / 1 month

Response: None

Species (strain): New Zealand white rabbits

Gender: Male

Number per group: 6

Observations on adverse effects (brief): Neither phagocytosis nor inflammation in the ambient connective tissues was found, an implication that silver should have been released locally without any adverse reactions. No significant discrepancy ( $p > 0.05$ ) was found for the amount of fibroblasts or thickness of the fibrous membrane between the two groups.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Behrendt et al. 2015<sup>27</sup>

Study Design: NRCS

Device or Material: Ti plates with TiAlAg composite coating

Route: Dorsal skinfold chamber

Dose: 3mm diameter x 0.1mm thick disc

Frequency/Duration: Single administration / 7 days

Response: None

Species (strain): C57BL/6J and C57BL/6J-Tyr mice

Gender: NR

Number per group: Ti = 6; TiAg = 7, Negative control = 7

Observations on adverse effects (brief): No macroscopic changes in regard to tissue inflammation, edema formation or disturbed perfusion were observed, nor systemic effects as verified by blood cell counts. The silver composite coating had no harmful effect on capillary perfusion and did not evoke enhanced vascular permeability when compared to commercial titanium. Silver coating had no negative effect on leucocyte activation indicating a good biocompatibility.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Tsukamoto et al. 2014<sup>5</sup>

Study Design: NRCS

Device or Material: Ti wire coated with hydroxyapatite (HA) and silver (Ag)

Route: Hind tibial medullary cavities

Dose: 20mm length x 1mm diameter, bilaterally

Frequency/Duration: Single administration / 2, 3, and 4 days and 2, 4, 6, 8, 10, and 12 weeks

Response: None

Species (strain): Sprague-Dawley rats

Gender: Male

Number per group: 9 per group. Ti-HA; Ti-2%Ag-HA; Ti-50%Ag-HA

Observations on adverse effects (brief): No significant differences in mean body weight were found between the three groups at any time point. No animals in any of the three groups died during the measurement period. No animals showed any signs of surgical site infection. No animals displayed any signs of local or systemic argyrosis. **Serum:** The HA, 2% Ag-HA, and 50% Ag-HA coating groups showed mean serum silver concentrations of  $0.60 \pm 0.17$  ppb,  $1.75 \pm 1.08$  ppb, and  $13.8 \pm 3.95$  ppb at 2 days, respectively, and  $0.37 \pm 0.06$  ppb,  $0.95 \pm 0.63$  ppb, and  $16.2 \pm 5.85$  ppb at 3 days, respectively (Figure 2). The silver concentration of serum decreased gradually over the experimental period. Mean concentration of silver in the 50% Ag-HA coating group was significantly higher than that in the other two groups at all time points ( $P < 0.01$  for all comparisons at all periods, Tukey's HSD test). Mean concentration of silver in the 2% Ag-HA coating group showed no significant difference compared with the HA coating group in any experimental periods. In this study, mean silver concentrations in all analyzed organs of the 2% Ag-HA coating group showed no significant differences compared with those in the HA coating group at all experimental periods. The silver concentration of 50% Ag-HA was significantly elevated in all analyzed organs. The highest silver concentrations were found in the brain, liver, kidneys, and spleen of the 50% Ag-HA coating group at 4 weeks, with mean concentrations of  $0.05 \mu\text{g/g}$ ,  $0.05 \mu\text{g/g}$ ,  $0.04 \mu\text{g/g}$ , and  $0.21 \mu\text{g/g}$ , respectively. The concentration of silver decreased gradually over the experimental period, and no significant differences were found between the three groups at 12 weeks, with neither pathological changes in laboratory parameters nor histological changes in tissues. Although the silver concentration in the blood was the highest in the acute phase and silver concentrations of organs peaked in the subacute phase in this study, no silver toxicity was encountered during either period.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Marsich et al. 2013<sup>28</sup>

Study Design: NRCS

Device or Material: FRC BisGMA/TEGDMA thermoset coated by a nanocomposite layer of Chitlac-nAg

Route: Femur

Dose: Implant with diameter 3.6 – 5.0mm and 8mm height

Frequency/Duration: Single administration / 8 weeks

Response: None

Species (strain): Göttingen minipigs

Gender: Male

Number per group: 3

Observations on adverse effects (brief): All animals underwent an uneventful recovery and were in good health during the follow-up period. On sacrifice, no signs of infection, inflammation or foreign body reactions were observed. The presence of silver does not impair the healing process of bone dramatically overall. The presence of nAg on implant surface induces a slight inhibition of osteointegration, showing less bone formation around the implant compared with the other groups. The histomorphometric analysis indicated differences in bone-implant contact between the control implants and the material studied. The main difference between Chitlac and Chitlac-nAg implants was the presence of a large quantity of lamellar bone at the implant interface in the case of Chitlac.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Yonekura et al. 2011<sup>29</sup>

Study Design: NRCS

Device or Material: Silver containing hydroxyapatite (Ag-HA) on Ti wire

Route: Right hind tibial medullary cavity

Dose: 20 mm length x 1mm diameter

Frequency/Duration: Single administration / 2, 4, and 12 weeks

Response: Inhibition of bone formation

Species (strain): Sprague-Dawley rats

Gender: Male

Number per group: 3 or 4 animals per group. Ti, HA, 3%Ag-HA, 50%Ag-HA

Observations on adverse effects (brief): No differences in body weight between groups. No evidence of aseptic loosening, osteolysis or formation of heterotopic bone. Histology showed inhibition of bone formation in the 50%Ag-HA group. The affinity index of bone formation was significantly lower than in HA and 3%Ag-HA at 2 weeks (29.1 % vs 70.4% and 65.7%, respectively,  $p=0.031$  and  $0.033$ ). The difference was no longer significant at 12 weeks (40.5% vs 84.9% and 81.0%). The highest concentrations of serum Ag resulting from the 3%Ag-HA and 50%Ag-HA coatings were 1.1 ppb and 5.3 ppb at two weeks, respectively. These levels were low enough to avoid harmful effects.

Timing of adverse effects: NR

Factors that predict response: NR

BisGMA = bisphenol A glycidylmethacrylate; Chitlac = polysaccharide 1-deoxylactit-1-yl chitosan; EPR = endoprosthesis; FRC = fiber reinforced composite; NA = not applicable; nAg = silver nanoparticles; NR = not reported; ns = not significant; Obs = observational; PJI = prosthetic joint infection; ppb = parts per billion; Retro = retrospective; R = reliable; SC = silver coated; TEGDMA = triethyleneglycol dimethacrylate; Ti = titanium; UC = uncoated

Table 7: Orthopedics, Prosthesis - Health Effects (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Shevtsov et al. 2021<sup>30</sup>

Study Design: SAS

Device or Material: Silver coated titanium

Route: Transcutaneous implantation in dorsum (pig and rabbit), above knee amputation (rabbit)

Dose: 1 SC implant and 1 UC implant

Frequency/Duration: Single administration / 6 months

Response: None

Species (strain): Pig and New Zealand rabbits

Gender: Male

Number per group: 2 pigs, 10 rabbits. Each animal received a silver-coated implant and uncoated implant.

Observations on adverse effects (brief): The authors did not observe any side effects, such as clinical manifestations of infectious complications of soft tissues. Routine clinical laboratory analyses of the CBC, biochemical blood tests as well as urine tests in minipigs did not demonstrate any change of the evaluated parameters as compared to the normal values. The test (silver-coated) and control (non-coated) SBIPs did not show evidence of device-related inflammation (e.g., exuberant neutrophilic or granulomatous) or other adverse tissue responses (e.g., infection, hemorrhage, necrosis, exuberant fibrosis/scarification). The tissue responses for the test and control SBIPs were overall similar.

Timing of adverse effects: NR

Factors that predict response: NR

CBC = complete blood count; NR = not reported; SBIP = Skin-bone interface pylon; SC = silver coated; UC = uncoated

Table 8: Orthopedics, Soft Tissue - Health Effects (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Shalumon et al. 2018<sup>31</sup>

Study Design: RCT

Device or Material: CSNM with silver imbedded in PCL/PEG shell

Route: Hind paw tendon

Dose: NR

Frequency/Duration: Single administration / 6 weeks

Response: None

Species (strain): New Zealand white rabbits

Gender: NR

Number per group: 8 animals per group. Control, SurgiWrap, Silver-HA (H/PPA), Silver-HA-ibuprofen (HI30/PPA)

Observations on adverse effects (brief): For the tendons wrapped with SurgiWrap and H/PPA, the surrounding tissues are adhered to the surgical site through moderate to mild tissue bridging, with H/PPA showing relatively thinner adhesion bands. Both adhesions could be removed through blunt dissection. The HI30/PPA group, with the CSNM that additionally contained ibuprofen and Ag NPs, displayed a smooth morphology with no adhesion observed between the repaired tendon and the peritendinous tissue.

Timing of adverse effects: NR

Factors that predict response: NR

CSNM = core-shell nanofibrous membrane; HA = hyaluronic acid; NP = nanoparticle; NR = not reported; PCL = polycaprolactone; PEG = Polyethylene glycol

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

### Local Response/Toxicity

Source Citation: Batt et al. 2018<sup>32</sup>

Study Design: Systematic Review

Make or Model: Reconstructions for aortic graft reconstructions: silver vs. cryo-all vs. rifamp vs. standard polyester vs. autogenous veins

Implant Duration: Approximately 1 year

Material Composition / Chemical Properties: NR

Mechanics / Morphology: Single insertion of prosthetic

Host Response: Graft occlusion, Reinfection

Patient characteristics (gender, mean age): Mean age 76 years (range 31 to 91 years)

Number per group: Silver: 4 studies, n=86; Cryo-all: 9 studies, n=683; Rifamp:3 studies, n=79; Standard polyester: 3 studies, n=45; Autogenous veins: 6 studies, n=254

Observed adverse effects: Graft occlusion: Silver: FE: n=4 trials, ER 0.05 (95% CI: 0.02 to 0.13), I<sup>2</sup> = 0%, Cryo-all: RE: n=9 trials, ER 0.12 (95% CI: 0.06 to 0.21), I<sup>2</sup>=84%, Rifamp: FE: n=4 trials, ER 0.09 (95% CI: 0.05 to 0.18), I<sup>2</sup>=0%; Standard polyester: FE: n=2 trials, ER 0.1 (95% CI: 0.03 to 0.26), I<sup>2</sup>=0%; autogenous veins: RE: n=4 trials, ER 0.04 (95% CI: 0.01 to 0.12), I<sup>2</sup>=30.1%, p=0.002, **statistically significant differences**  
Reinfection: Silver: FE: n=4 trials, ER 0.07 (95% CI: 0.03 to 0.15), I<sup>2</sup> = 0%, Cryo-all: RE: n=8 trials, ER 0.09 (95% CI: 0.05 to 0.15), I<sup>2</sup>=66%, Rifamp: FE: n=5 trials, ER 0.1 (95% CI: 0.05 to 0.17), I<sup>2</sup>=0%; Standard polyester: RE: n=3 trials, ER 0.2 (95% CI: 0.08 to 0.42), I<sup>2</sup>=31.5%; autogenous veins: FE: n=6 trials, ER 0.05 (95% CI: 0.03 to 0.09), I<sup>2</sup>=0%, p=0.016, **statistically significant differences**

Timing of adverse effects: Approximately 1 year

Factors that predict response: Meta Regression analysis of factors predicting AEs: **Reinfection** Age: Silver: n=4 trials, slope 0.05 (95% CI: -0.17 to 0.27), p=0.68; Cryo-all: n=8 trials, slope 0.03 (95% CI: -0.14 to 0.21), p=0.69; Rifamp: n=5 trials, slope 0.23 (95% CI: -0.49 to 0.94), p=0.53; Standard polyester: n=3 trials, slope 0.059 (95% CI: -0.13 to 1.31), p=0.11; autogenous veins: n=6 trials, slope 0.27 (95% CI: 0.066 to 0.48), p=0.009 PDF: Silver: n=4 trials, slope -0.01 (95% CI: -0.08 to 0.06), p=0.78; Cryo-all: n=8 trials, slope 0.02 (95% CI: -0.01 to 0.05), p=0.29; Rifamp: n=4 trials, slope 0.008 (95% CI: -0.024 to 0.04), p=0.61; Standard polyester: NR; autogenous veins: n=5 trials, slope 0.06 (95% CI: 0.02 to 0.11), p=0.004 Virulent: Silver: n=4 trials, slope -0.01 (95% CI: -0.04 to 0.018), p=0.41; Cryo-all: n=6 trials, slope 0.018 (95% CI: -0.0023 to 0.038), p=0.08; Rifamp: n=4 trials, slope -0.12 (95% CI: -0.45 to 0.20), p=0.46; Standard polyester: n=3 trials, slope -0.005 (95% CI: -0.07 to 0.08), p=0.88; autogenous veins: n=5 trials, slope -0.06 (95% CI: -0.12 to -0.0066), p=0.028 Nonvirulent: Silver: n=4 trials, slope 0.04 (95% CI: -0.018 to 0.10), p=0.17; Cryo-all: n=6 trials, slope -0.032 (95% CI: -0.07 to 0.004), p=0.08; Rifamp: n=4 trials, slope 0.001 (95% CI: -0.056 to 0.06), p=0.95; Standard polyester: n=3 trials, slope -0.19 (95% CI: -0.47 to 0.068), p=0.144; autogenous veins: n=5 trials, slope -0.077 (95% CI: -0.13 to -0.02), p=0.005

Source Citation: Gnus et al. 2016<sup>34</sup>

Study Design: Single-arm study

Make and Model: Silver impregnated prosthesis

Implant Duration: Up to 1-year

Material Composition / Chemical Properties: NR

Mechanics / Morphology: Graft removal and replacement in situ

Host Response: In-hospital, Cardiac complications (arrhythmia/MI), Intestinal obstruction, Renal insufficiency, Retroperitoneal abscess, Retroperitoneal bleeding Late, Abdominal wall abscess, Graft infection, Recurrent fistula

Patient characteristics (gender, mean age): 25% female, mean age 58.8 years

Number per group: All patients diagnosed with SAEF following AAG implementation (n=24); 22 patients present during in-hospital f/u, 15 contributed data to 1-year f/u

Observed adverse effects: Abdominal wall abscess: 4 events; cardiac complications (arrhythmia/MI): 4 events; femoral pseudoaneurysm: 1 event; graft infection: 4 events; intestinal obstruction: 2 events; lower limb ischemia: 4 events; persistent sepsis: 3; pneumonia: 1 event; recurrent fistula: 1 event; renal insufficiency: 2 events; retroperitoneal abscess: 1 event; retroperitoneal bleeding: 2 events

Timing of adverse effects: In-hospital complications: cardiac complications (arrhythmia/MI): 4 events; exenteration: 1 event; intestinal obstruction: 2 events; lower limb ischemia: 2 events; persistent sepsis: 3; pneumonia: 1 event; renal insufficiency: 2 events; retroperitoneal abscess: 1 event; retroperitoneal bleeding: 2 events Late complications: abdominal wall abscess: 4 events; graft infection: 4 events; lower limb ischemia: 4 events; recurrent fistula: 1 event

Factors that predict response: NR

Source Citation: Zegelman et al. 2013<sup>35</sup>

Study Design: Single-arm study

Make and Model: SG (B. Braun, Germany)

Implant Duration: Mean f/u 15.6 months (SD 8.3)

Material Composition / Chemical Properties: Full range of SG was available to all investigators and included bifurcations (14 × 7, 16 × 8, 18 × 9, 20 × 10) and straight tubes ranging from 6 to 20 mm in various lengths from 15 to 80 cm.

Mechanics / Morphology: Single administration of SG prosthesis

Host Response: Bypass explantation, Drainage, Infection, Other revision, Thromboectomy, Vacuum therapy, Wound revision

Patient characteristics (gender, mean age): Mean age 66.3 years (SD 10.8); 21.3% female

Number per group: Patients with high-risk factors underwent aortic, peripheral and/or extra-anatomic reconstructions with SG (n=230)

Observed adverse effects: At Discharge Infection: 14 events Long-term f/u: Bypass explantation: 4 events; drainage: 2 events; Other revision: 8 events; thromboectomy: 10 events; vacuum therapy: 2 events; wound revision: 13 events

Timing of adverse effects: Mean f/u 15.6 months (SD 8.3); minimum 12 months

Factors that predict response: NR

Source Citation: Zhang et al. 2011<sup>33</sup>

Study Design: Nonrandomized comparative trial

Make and Model: InterGard silver prosthesis vs. cryopressed human allograft

Implant Duration: Mean 4.4 years

Material Composition / Chemical Properties: NR

Mechanics / Morphology: Single surgery

Host Response: Rupture of aortic aneurysms

Patient characteristics (gender, mean age): 33.3% female, mean age 65.6 years

Number per group: Six patients with concomitant infected abdominal aortic aneurysms underwent repair with interGard silver prosthesis (n=3) or cryopressed human allograft (n=3)

Observed adverse effects: Rupture of aortic aneurysms in 2 patients with cryopressed human allograft. One patient with silver prosthesis died at 7 months, and another patient with a cryopressed human allograft died at 8 months. No evidence of ongoing infection at f/u.

Timing of adverse effects: Mean 4.4 years

Factors that predict response: NR

Source Citation: Batt et al. 2018<sup>32</sup> Study Design:

Study Design: Systematic Review

Make and Model: Reconstructions for aortic graft reconstructions: silver vs. cryo-all vs. rifamp vs. standard polyester vs. autogenous veins

Implant Duration: Approximately 1 year

Material Composition / Chemical Properties: NR

Mechanics / Morphology: Single insertion of prosthetic

Host Response: Amputation

Patient characteristics (gender, mean age): Mean age 76 years (range 31 to 91 years)

Number per group: Silver: 4 studies, n=86; Cryo-all: 9 studies, n=683; Rifamp:3 studies, n=79; Standard polyester: 3 studies, n=45; Autogenous veins: 6 studies, n=254

Observed adverse effects: Amputation: Silver: FE: n=4 trials, ER 0.04 (95% CI: 0.01 to 0.10),  $I^2 = 0\%$ , Cryo-all: RE: n=6 trials, ER 0.03 (95% CI: 0.01 to 0.06),  $I^2=41\%$ , Rifamp: FE: n=4 trials, ER 0.03 (95% CI: 0.007 to 0.1),  $I^2=0\%$ ; Standard polyester: RE: n=3 trials, ER 0.08 (95% CI: 0.02 to 0.27),  $I^2=20.8\%$ ; autogenous veins: RE: n=6 trials, ER 0.11 (95% CI: 0.05 to 0.21),  $I^2=41\%$ ,  $p<0.0001$ , **statistically significant differences**

Timing of adverse effects: Approximately 1 year

Factors that predict response: NR

Source Citation: Gnus et al. 2016<sup>34</sup> Study Design:

Study Design: Single-arm study

Make and Model: Silver impregnated prosthesis

Implant Duration: Up to 1-year

Material Composition / Chemical Properties: NR

Mechanics / Morphology: Graft removal and replacement in situ

Host Response: Persistent sepsis, Pneumonia, Lower limb ischemia

Patient characteristics (gender, mean age): 25% female, mean age 58.8 years

Number per group: All patients diagnosed with SAEF following AAG implementation (n=24); 22 patients present during in-hospital f/u, 15 contributed data to 1-year f/u

Observed adverse effects: Lower limb ischemia: 4 events; persistent sepsis: 3; pneumonia: 1 event;

Timing of adverse effects: In-hospital complications: lower limb ischemia: 2 events; persistent sepsis: 3; pneumonia: 1 event Late complications: lower limb ischemia: 4 events

Factors that predict response: NR

AAG = abdominal aortic graft; CI = confidence interval; ER = event rate; FE = fixed effects; f/u = follow-up; MI = myocardial infarction; NR = not reported; PDF = prostheticduodenal fistula; RE = random effects; SAEF = secondary aortoenteric fistula; SD = standard deviation; SG = Silver Graft

Table 10: Vascular - Health Effect (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Hehrlein et al. 2019<sup>36</sup>

Study Design: Single-arm study

Make and Model: Zn-3 Ag stents

Implant Duration: 1 months, 3 months, and 6 months

Material Composition/Chemical Properties: Alloy casted and prepared to produce 97 wt-% Zn and 3 wt-% Ag

Mechanics/Morphology: Single insertion into iliofemoral artery

Host Response: No serious AEs

Patient characteristics (gender, mean age): 15 juvenile domestic swine

Number per group: All swine received same intervention, sacrificed at 1-month (n=5), 3-month (n=5), and 6-month (n=5)

Observed on adverse effects: The iliofemoral arteries' angiograms revealed no signs of early thrombosis or post-interventional vessel failure, and only minor luminal narrowing at all follow up time points

Timing of adverse effects: 1-month, 3-month, and 6-months

Factors that predict response: NR

AE = adverse event; Ag = silver; NR = not reported; wt = weight; Zn = zinc; Zn-3 Ag = zinc III silver alloy;

Table 11: Silver – Abdominal Wall - Health Effect (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Mishina et al. 2019<sup>37</sup>

Study Design: Nonrandomized comparative study

Make and Model: Esfil, Esfil Ag, plasmofilter, uniflex, Uniflex Ag

Implant Duration: 3 days, 7 days, 14 days, 21 days, 30 days

Material Composition/Chemical Properties: Esfil (Lintex LLC): light polypropylene mesh (with or without silver ions);

Plasmofilter (JSC): mixture of finely dispersed silver found in poviargol and polyvinylpyrrolidone applied on the mesh; Uniflex (Lintex LLC): ultralight polypropylene mesh (with or without silver ions)

Mechanics/Morphology: Single administration

Host Response: Cell inflammatory infiltrate

Patient characteristics (gender, mean age): 250 male Wistar rats

Number per group: Esfil (n=50), Esfil Ag (n=50), plasmofilter (n=50), uniflex (n=50), Uniflex Ag (n=50). 10 rats per group sacrificed at each time point of interest.

Observed on adverse effects: Uniflex Ag decreased infiltrate area by 2.5 times, whereas, Esfil Ag decreased area 2.4 times.

Timing of adverse effects: Reported complications of interest based on up to 14 days.

Factors that predict response: NR

Ag = silver; LLC = limited liability corporation; NR = not reported

Table 12: Endodontic/Maxillofacial - Health Effects (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Demyashkin et al. 2020<sup>39</sup>

Study Design: NRCS

Device or Material: PLA membranes with silver NPs

Route: Cranial bone defect

Dose: Single 1 x 1 cm membrane

Frequency/Duration: Single administration / 2 weeks

Response: Inflammatory reaction

Species (strain): Chinchilla rabbits

Gender: Male

Number per group: 10 control (PLA membranes w/o Ag NPs), 28 received PLA membranes w/ Ag NPs

Observations on adverse effects (brief): Authors observed mild inflammatory reaction with few lymphocytes and macrophages. Immunomarkers (CD3, CD30, CD15) revealed a weak positive reaction: CD3 (6,5±3,1%), CD30 (3,1±1,4%), and CD15 (1,2±0,5%), with a significant decrease in the number of cells immunopositive for CD3 (p=0,03) and CD30 (p=0,01).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Smeets et al. 2017<sup>40</sup>

Study Design: NRCS

Device or Material: Silver NPs embedded in polysiloxane coating (HyProtect, Bio-Gate) on titanium (Semados S-Line, BEGO Implant Systems)

Route: Calvaria

Dose: 3 UC implants, 3 SiO<sub>x</sub>C<sub>y</sub>-coated, 3 SiO<sub>x</sub>C<sub>y</sub>-coated implants

Frequency/Duration: Single administration / 3 months

Response: None

Species (strain): Domestic pigs, strain not reported

Gender: 50% female

Number per group: 8 animals. Each animal received 3 implants from each of 3 groups: 24 UC, 24 SiO<sub>x</sub>C<sub>y</sub>-coated, 24 Ag/SiO<sub>x</sub>C<sub>y</sub>-coated

Observations on adverse effects (brief): There was no systemic or local rejections, no sign of inflammatory cell infiltration, and no foreign-body reactions such as neutrophils, eosinophils, macrophages, or mast cells in any of the thread sections of the tested groups. No implant was lost. All implants healed well and exhibited direct contact with mineralized bone.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Lee et al. 2016<sup>38</sup>

Study Design: RCT

Device or Material: Mini bone plates made from Titanium-Silver (Ti-Ag) alloy

Route: Mandible

Dose: 1 Ti plate and 1 Ti-Ag plate

Frequency/Duration: Single administration / 2 months

Response: None

Species (strain): Mongrel dogs

Gender: Female

Number per group: 5 dogs. Each dog received 1 Ti plate and 1 Ti-Ag plate (randomly assigned to left-right or right-left with a shift in assignment for every other dog)

Observations on adverse effects (brief): No health complications were detected. Radiographic images showed no difference in bone radiopacity. There was no significant difference in biological response score.

Timing of adverse effects: NR

Factors that predict response: NR

NP = nanoparticle; NR = not reported; NRCS = nonrandomized comparative study; PLA = polylactic acid; SAS = single-arm study; UC = uncoated

Table 13: Esophageal - Health Effects (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Zhao et al. 2021<sup>41</sup>

Study Design: RCT

Device or Material: Silver NP-coated SEMS

Route: Esophagus

Dose: NR

Frequency/Duration: Single administration / 4 weeks

Response: None

Species (strain): Sprague-Dawley rats

Gender: Male

Number per group: 6 rats per group. Group A = UC, groups B, C, and D = 6, 12, and 24 mg/mL AgNP coating.

Observations on adverse effects (brief): The gross examination showed moderate to severe tissue ingrowth and outgrowth in 5 rats in group A and 2 rats in group B. In contrast, no animals had moderate or severe tissue ingrowth/outgrowth in groups C and D. The gross examination revealed no complications (e.g., gastrointestinal ulceration and perforation). The percentage of granulation tissue area, number of epithelial layers, thickness of submucosal fibrosis, percentage of connective tissue area, inflammatory cell infiltration grade, degree of collagen deposition, and degrees of Ki67, TUNEL, and  $\alpha$ -SMA-positive deposition were significantly lower in groups C ( $p = 0.003$ ,  $p = 0.002$ ,  $p = 0.001$ ,  $p = 0.008$ ,  $p = 0.005$ ,  $p = 0.001$ ,  $p = 0.003$ ,  $p = 0.029$ ,  $p < 0.001$ , respectively) and D than in group A ( $p=0.003$ ,  $p<0.001$ ,  $p = 0.003$ ,  $p = 0.018$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.003$ ,  $p=0.029$ , and  $p<0.001$ , respectively). However, only the percentage of granulation tissue area, number of epithelial layers, thickness of submucosal fibrosis, and percentage of connective tissue area were significantly lower in group B than in group A ( $p = 0.047$ ,  $p = 0.012$ ,  $p = 0.022$ , and  $p=0.035$ , respectively). No histological parameters were significantly different between group D and group C (all  $p>0.05$ ).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Saleh et al. 2019<sup>42</sup>

Study Design: NRCS

Device or Material: Silver NPs in decellularized rat esophagus

Route: Dorsal subcutaneous pouch

Dose: 1 implant

Frequency/Duration: Single administration / 7 and 21 days

Response: Inflammatory reaction

Species (strain): ICR mice

Gender: Male

Number per group: 30 mice total.

Observations on adverse effects (brief): The scaffolds from the AgNP group showed the lowest number of infiltrated inflammatory cells at both 7 and 21 days PI, with significant differences ( $P < 0.05$ ) only at 7 days.

Timing of adverse effects: NR

Factors that predict response: NR

NP = nanoparticle; NR = not reported; SAS = single-arm study; SEMS = self-expandable metallic stent

Table 14: Hepatic - Health Effect (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Park et al. 2020<sup>43</sup>

Study Design: RCT

Make and Model: Control SEM, SEM with 3 mg/mL AgNO<sub>3</sub>, SEM with 6 mg/mL AgNO<sub>3</sub>, SEM with 12 mg/mL AgNO<sub>3</sub>

Implant Duration: 4 weeks

Material Composition/Chemical Properties: Stents were 4 mm in diameter and 10 mm in length and had radiopaque markers

Mechanics/Morphology: Single implantation

Host Response: No serious AEs

Patient characteristics (gender, mean age): 24 New Zealand rabbits

Number per group: 3 mg/mL AgNO<sub>3</sub> SEM (n=6), 6 mg/mL AgNO<sub>3</sub> SEM (n=6), 12 mg/mL AgNO<sub>3</sub> SEM (n=6), control SEM (n=6)

Observed on adverse effects: Two rabbits died during the insertion of the stent delivery system, whereas, the remaining 22 rabbits survived until the end of the study without stent-related adverse events.

Timing of adverse effects: Up to 4 weeks

Factors that predict response: NR

Source Citation: Saleh et al. 2018<sup>44</sup>

Study Design: RCT

Make and Model: AgNP loaded porcine liver slices vs. other porcine liver slices (native, DL, Glut, or EDC/NHS)

Implant Duration: 7 days, 21 days

Material Composition/Chemical Properties: 5 µg/mL silver nanoparticles (AgNPs)

Mechanics/Morphology: Single implantation

Host Response: No serious AEs

Patient characteristics (gender, mean age): 30 male mice

Number per group: AgNP (n=6), DL (n=6), Glut (n=6), EDC/NHS (n=6), native (n=6)

Observed on adverse effects: None of the animals showed signs of infection or behavioural changes.

Timing of adverse effects: 7 days, 21 days

Factors that predict response: NR

AE = adverse event; AgNO<sub>3</sub> = silver nitrate; AgNP = silver nanoparticle; DL = decellularized liver; EDC/NHS = ethyl carbodiimide hydrochloride/ N-hydroxysuccinimide; glut = glutaraldehyde; mg/mL = milligram per milliliter; mm = millimeter; NR = not reported; RCT = randomized controlled trial; SEM = self-expandable metal stent

Table 15: Lung - Health Effect (In Vivo) Human Studies

**Local Response/Toxicity**

Source Citation: Elnady et al. 2019<sup>45</sup>

Study Design: Nonrandomized comparative study

Make and Model: Silver nitrate vs. Histoacryl

Implant Duration: Up to 3 months

Material Composition/Chemical Properties: Silver nitrate: 5 mL silver nitrate solution; Histoacryl (B. Braun): n-butyl-2 cyanocrylate histoacryl and histoacryl blue in 0.6 mL

Mechanics/Morphology: Single injection

Host Response: Chest pain, Pneumonia, Respiratory failure

Patient characteristics (gender, mean age): 0% female, mean age 55.33 (SD 9.22)

Number per group: Silver nitrate: 15; Histoacryl: 15

Observed on adverse effects: Silver nitrate: 1 pneumonia, 1 respiratory failure, Histoacryl: 4 chest pain

Timing of adverse effects: Up to 3 months

Factors that predict response: NR

mL = milliliters; NR = not reported; SD = standard deviation

Table 16: Middle Ear - Health Effect (In Vivo) Human Studies

**Local Response/Toxicity**

Source Citation: Ziabka et al. 2019<sup>46</sup>

Study Design: Single-Arm Study

Make and Model: Otoimplant prosthesis incorporated with AgNPs (0.1% wt)

Implant Duration: Up to 1 year

Material Composition/Chemical Properties: AgNPs measured below 50 nm, and injected into plasticizing chambers of Otoimplants

Mechanics/Morphology: Single administration

Host Response: Deterioration of speech understanding

Patient characteristics (gender, mean age): 66% female; mean age: 64

Number per group: Otoimplant: 3

Observed on adverse effects: Postoperative deterioration of speech understand was observed in one patient, which may be associated with progressive senile hearing loss. No direct germ cell growth was observed, no yeast-like and mold growth fungi were found, no inflammation, and no chronic middle ear infection was found.

Timing of adverse effects: Up to 1 year

Factors that predict response: NR

AgNP = silver nanoparticle; nm = nanometer; NR = not reported; wt = weight

Table 17: Middle Ear - Health Effect (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Duda et al. 2015<sup>47</sup>

Study Design: RCT

Make and Model: Biovert II prosthesis with silver-containing silica film

Implant Duration: Up to 21 days

Material Composition/Chemical Properties: Silica films coated in 0.5 M AgNO<sub>3</sub>

Mechanics/Morphology: Biovert II with aqueous 0.5M AgNO<sub>3</sub>-solution

Host Response: Severe head tilt

Patient characteristics (gender, mean age): 40 New Zealand White male rabbits

Number per group: All 40 rabbits implanted with Biovert II with different coatings: Silver silica film (n=8), Dense silver silica film (n=8), Silica film (n=8), Dense silica film (n=8), blank nanoporous silica coating with 1% silver sulfadiazine cream (n=8)

Observed on adverse effects: 1 rabbit in the silver coating with 1% silver sulfadiazine cream group was excluded due to severe head tilt. All other animals showed good general health.

Timing of adverse effects: Up to 21 days

Factors that predict response: NR

Source Citation: Duda et al. 2015<sup>47</sup>

Study Design: RCT

Make and Model: Biovert II prosthesis with silver-containing silica film

Implant Duration: Up to 21 days

Material Composition/Chemical Properties: Silica films coated in 0.5 M AgNO<sub>3</sub>

Mechanics/Morphology: Biovert II with aqueous 0.5M AgNO<sub>3</sub>-solution

Host Response: Cardiovascular failure

Patient characteristics (gender, mean age): 40 New Zealand White male rabbits

Number per group: All 40 rabbits implanted with Biovert II with different coatings: Silver silica film (n=8), Dense silver silica film (n=8), Silica film (n=8), Dense silica film (n=8), blank nanoporous silica coating with 1% silver sulfadiazine cream (n=8)

Observed on adverse effects: 1 rabbit in the silica film or dense silica film group died due to cardiovascular failure. 1 rabbit in the silver coating with 1% silver sulfadiazine cream group was excluded due to cardiovascular failure.

Timing of adverse effects: Up to 21 days

Factors that predict response: NR

AgNO<sub>3</sub> = silver nitrate; M = molar; NR = not reported; RCT: randomized controlled trial

Table 18: Sutures - Health Effect (In Vivo) Animal Studies

**Local Response/Toxicity**

Source Citation: Liu et al. 2017<sup>48</sup>

Study Design: RCT

Make and Model: AgNP-coated vs. antibiotic-coated vs. normal suture

Implant Duration: 14 days, 21 days, 28 days

Material Composition/Chemical Properties: Normal (Vicryl, Ethicon) and antibiotic (Vicryl Plus, Ethicon). AgNPs were coated on Vicryl sutures.

Mechanics/Morphology: Single administration

Host Response: Degree of inflammation

Patient characteristics (gender, mean age): 21 C57BL/6 N strain mice

Number per group: AgNP-coated suture (n=7), antibiotic-coated suture (n=7) and normal suture groups (n=7)

Observed on adverse effects: The AgNP-coated suture group had the least macrophage infiltration when compared to the control and antibiotics-suture group, and showed the most resemblance to normal ileum tissue. These results suggested that AgNP-coated suture could effectively decrease inflammatory cell infiltration over the long term.

Timing of adverse effects: Up to 28 days

Factors that predict response: NR

AgNP = silver nanoparticles; NR = not reported

## Appendix E. References

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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.*