MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Nitinol Safety Profile

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Executive Summary

Key Points

1. Searches identified 2944 citations; 92 articles were selected for inclusion

2. For Cardiovascular Clip/Closure/Embolization devices, low-quality evidence from 7 studies indicated several local responses including bleeding and hematoma (1%-10%), buttock claudication (9.4%), endoleaks (5.3%), erectile dysfunction (1.0%), and groin hematoma (1.1%)

3. For inferior vena cava filters, low-quality evidence from 1 study indicated deep vein thrombosis (1%-18%), migration (0% to 4.5%), and vena cava thrombosis or stenosis (4%-8%) as local responses.

4. For cardiovascular graft/stents, moderate-quality evidence from 9 studies indicated varying local responses, including bleeding (3.2%), endoleak types I and II (1.6-2.1%), hemodynamic instability (25%), neck hematoma (1.0%), target lesion revascularization (3.3%), retrograde aortic dissection (1.0%), stent migration (4.7%), and limb occlusion/restenosis (1.5-11%). Moderate -quality evidence from 4 studies indicated mortality, myocardial infarction, stroke, and transient ischemic attack as systemic responses.

5. For aortic and mitral valve replacement/repair, moderate-quality evidence from 10 studies indicated several local responses, including bleeding (1–16%), major vascular complications (1-12%), and postoperative pacemaker implantation (0.5-50%). Moderate-quality evidence from 8 studies also indicates several systemic responses, including mortality (0-48%) and stroke (1-17%).

6. For pacemakers, moderate-quality evidence from 1 study reported complication rates of 0.5-24% at 90 days and 2-7% at 1 year. Micra pacemakers had 51% lower odds of complications compared to transvenous pacemakers.

   For peripherally inserted central catheters, moderate-quality evidence from 1 study reported higher pain scores during insertion and removal but no statistical difference during the dressing change or during the dwell time as well as no difference in bleeding/oozing/hematoma (13-24%), signs of exit site infection (6-7%), or medical adhesive-related skin injuries (6-7%).

7. For biliary devices, moderate-quality evidence from 10 studies indicated several local responses, including recurrent biliary obstruction (0-17%), stent migration (3.2-10%), and inflammation/cholangitis/cholecystitis/pancreatitis (1.4-50%).

8. For pancreatic devices, low-quality evidence from 7 studies indicated several local responses, including migration, splenic vein thrombosis, percutaneous drainage prior to endoscopic ultrasound and dislodged stent during necrosectomy, bleeding, occlusion, and infection.

9. For devices used in the stomach, colon, and rectum, moderate-quality evidence from 10 studies indicated bleeding (14%), migration (rates vary), and perforation (3-11%) as local responses. Low-quality evidence indicated other local responses, including aspiration (3%), inappropriate stent expansion (3%), incisional hernia (6.3%), leakage (12%), obstruction (7-18%), pain (7-22%), peritonitis (4%), and stoma (6%). One study reported lower migration with nitinol (7.1%) vs non-nitinol (25.9%). One study reported no statistical difference in obstruction between nitinol and non-nitinol devices, and one study reported no statistical difference in patency.

10. For devices used in the throat, low-quality evidence from 10 studies indicated several local responses, including migration (5%), pain, recurrent obstruction, and tumor overgrowth (11%). One study reported female sex and proximal stricture were significantly associated with higher

rates for obstruction/major adverse events compared to events for male sex and mild or distal location. Low-quality evidence from 3 studies indicated fever, mortality and pneumonia as systemic responses.

11. For bronchial coils, low-quality evidence from 1 study indicated chronic obstructive pulmonary disease exacerbation, and pneumonia as local responses and cardiovascular events and mortality as systemic responses.

12. For neurovascular devices, low- to moderate-quality evidence from 10 studies indicated several local responses, including hemorrhagic and ischemic/thromboembolic events (moderate-quality) and dislodgement/migration, protrusion, neurological deficit/disability, periprocedural morbidity, and restenosis (low-quality). Low-quality evidence indicated mortality as a systemic response.

13. For ophthalmic devices, low-quality evidence from 3 studies indicated several local responses, including conjunctivitis, uveitis/iritis requiring steroids, and worsening of the visual field.

14. For bone fixation devices, low-quality evidence from 3 studies indicated hardware malfunction/breakage as a local device event.

15. For intrauterine devices, low-quality evidence from 1 study indicated dysmenorrhea, menorrhagia, and procedural pain as local responses.

16. For urinary stents, low-quality evidence from 5 studies indicated several local responses, including encrustation/calcification (6-25%), fistulas (28%), hematuria (13-25%), infections (2-31%), migration (6-9%), obstruction (17%), and pain (1-31%). Low-quality evidence indicated sepsis as a systemic response.

17. Across 26 different medical device types, ECRI Patient Safety Organization (PSO) identified 145 reported complications that involved Nitinol materials that occurred between February 2007 and October 2021. Forty-one reports (28%) involved left atrial appendage closure devices, 15 reports (10%) involved leadless pacemakers, 13 reports (9%) involved mitral valve repair devices. Thirty-four reports indicated patient harm with 25 of those reports classified within the mildest harm category (E). There was one death caused by iatrogenic injury involving a leadless pacemaker.

    The top 5 complications included: 1) Device Malfunction – 47 (32.4%), 2) Hemorrhage/Hematoma – 25 (17.2%), 3) Pericardial effusion – 24 (16.6%), 4) Iatrogenic injury – 13 (9%), 5) Device migration 11 (7.6%).

18. ECRI Problem Reporting Network database includes 14 reports mostly including intraoperative events some of which resulted in patient injury. Six reports described the need to reposition hemostatic metal clips for the gastrointestinal tract resulting in bleeding. Two other reports indicated pieces of the device breaking off inside the patient's body and mitgrating resulting in injury (tracheal prosthesis and thrombus retriever).

19. There were 127 manufacturers issued and 6 regulatory body issued alerts identified in the Healthcare Technology Reports database. 24 of these alerts involved endovascular grafts to treat aortic aneurysm, 19 involved stents, drains, and dilators for biliary ducts, and 10 involved aortic valves. The majority of alerts were unrelated to biocompatibility issues. Rather, they involved device malfunction, regulatory issues (e.g., labeling), sterility compromise, and iatrogenic injuries.

20. Evidence gaps:

    a. No included studies investigated whether there are material-related factors that may affect a sustained immunological/systemic response.

b. Additional research on local responses in cosmetic, ear nose throat, orthopedic and reproductive applications is needed.
c. Additional research on systemic responses, including those on patient or material factors, for most applications is needed. Notable exceptions are vascular grafts/stents and heart repair devices.

Overview - Nitinol

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge regarding 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 Nitinol. 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?

Local responses/device events varied somewhat across different device categories between human studies.

a. Clip, closure, and embolization devices
   i. Seven studies examined clip, closure, and embolization devices. Overall complications rates varied (1% - 17%), including bleeding and hematoma (1%-10%), buttock claudication (9.4%), endoleaks (5.3%), erectile dysfunction (1.0%), and groin hematoma (1.1%).
   ii. Responses occurred up to 40 months after initial placement of the device.
b. Inferior vena cava filters
   i. One systematic review on inferior vena cava filters reported deep vein thrombosis (1%-18%), migration (0% to 4.5%), and vena cava thrombosis or stenosis (4%-8%). Filter perforation, device fracture, and complications from filter removal were also reported.
   ii. Mean followup was 10 months. Many responses, including perforations, migration, fracture, thrombosis, can occur within 30 days.
c. Vascular grafts/stents
   i. Nine studies examined vascular grafts/stents. The more common adverse events reported in these studies include bleeding (3.2%), endoleak types I and II (1.6-2.1%), hemodynamic instability (25%), neck hematoma (1.0%), target lesion revascularization (3.3%), retrograde aortic dissection (1.0%), stent migration (4.7%), and limb occlusion/restenosis (1.5-11%).
   ii. Mean follow-up ranged from 1 to 36 months. One systematic review on self-expanding stents reported 8 occlusions in less than 1 month and 2 occlusions between 1 and 30 months.
d. Aortic and mitral valve replacement/repair
   i. Ten studies examined aortic and mitral valve replacement/repair. These studies most often investigated bleeding (1–16%), major vascular complications (1-12%), and postoperative pacemaker implantation (0.5-50%).
   ii. Mean follow-up ranged from 1 month to 5 years.
e. Pacemakers
   i. One systematic review on pacemakers reported complication rates of 0.5-24% at 90 days and 2-7% at 1 year. Micra pacemakers had 51% lower odds of complications compared to transvenous pacemakers.
   ii. Mean follow-up ranged from 3 to 12 months.
f. Peripherally inserted central catheters
   i. One RCT comparing a nitinol and non-nitinol PICC did not find a difference in bleeding/oozing/hematoma (13-24%), signs of exit site infection (6-7%), or medical adhesive-related skin injuries (6-7%). The report states the nitinol PICC had higher pain scores during insertion and removal, but no statistical difference was seen during the dressing change or during the dwell time.
   ii. Follow-up lasted up to 180 days.
g. Biliary

i. Ten studies examined biliary stents and reported recurrent biliary obstruction (0-17%), stent migration (3.2-10%), and inflammation/cholangitis/cholecystitis, pancreatitis (1.4-50%).
ii. Follow-up ranged from 1 day to about 15 months.

h. Pancreatic
i. Commonly reported responses to pancreatic stents include migration, splenic vein thrombosis, percutaneous drainage prior to endoscopic ultrasound and dislodged stent during necrosectomy, bleeding, occlusion, and infection.
ii. Follow-up ranged from 1 to 12 months.

i. Stomach, colon, and rectum
i. Ten studies examined devices used in the stomach, colon, or rectum. Common responses include aspiration (3%), bleeding (14%), inappropriate stent expansion (3%), incisional hernia (6.3%), leakage (12%), migration (rates vary), obstruction (7-18%), pain (7-22%), perforation (3-11%), peritonitis (4%), and stoma (6%).
ii. One study reported lower migration with nitinol (7.1%) vs non-nitinol (25.9%). One study reported no statistical difference in obstruction between nitinol and non-nitinol devices, and one study reported no statistical difference in patency.
iii. Mean follow-up ranged from 1 week to 21 months.

j. Throat
i. Ten studies examined devices used in the throat. Common responses include migration (5%), pain, recurrent obstruction, tumor overgrowth (11%).
ii. Follow-up ranged from 1 months 3 years.
iii. One study reported female sex and proximal stricture were significantly associated with higher rates obstruction/major adverse event compared to events for male sex and mild or distal location.

k. Neurovascular
i. 10 studies examined neurovascular devices. The most reported responses included dislodgement/migration, protrusion, hemorrhagic events, ischemic/thromboembolic events, neurological deficit/disability, periprocedural morbidity, and restenosis.
ii. Mean follow-up ranged from 3 to 39 months.

l. Urinary
i. 5 studies examined urinary stents. Commonly reported responses included encrustation/calcification (6-25%), fistulas (28%), hematuria (13-25%), infections (2-31%), migration (6-9%), obstruction (17%), and pain (1-31%).
ii. Mean follow-up ranged from 12 to 24 months.

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

a. Vascular grafts/stents
i. Nine studies examined grafts/stents. The more common adverse events reported in these studies include mortality (0.3-4.8%) and stroke (0.1-3.1%).
ii. Mean follow-up ranged from 1 to 36 months.

b. Valve replacement/repair
i. Eight studies examined aortic and mitral valve replacement/repair patients regarding mortality (0-48%) and stroke (1-17%).
ii. Mean follow-up ranged from 1 month to 5 years.

c. Throat
i. One study examined devices used in the throat. The study did not observe any differences in mortality, pneumonia, or fever between nitinol and non-nitinol devices.
ii. Follow-up ranged from 1 months to 3 years.

d. Neurovascular
i. Five studies reported mortality rates (1-11%) in neurovascular devices.
ii. Mean follow-up ranged from 3 to 39 months

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

    a. Among patients who received a leadless pacemaker, patients who had been precluded from receiving a conventional transvenous permanent pacemaker had significantly higher acute mortality (2.75% vs 1.32%; P=.022) and total mortality (38.1% vs 20.6%; P<.001) compared to patients who had not been precluded.

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 included studies investigated whether there are material-related factors that may affect a sustained immunological/systemic response.

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

    All gaps listed here could benefit from future research.
    a. Additional research on local responses in orthopedic and reproductive applications
    b. Additional research on systemic responses, including those on patient or material factors, for most applications, vascular grafts/stents and heart repair being notable exceptions.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge regarding medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. For 2021, the following 19 topics were 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/Eye Applications
15. Data Visualization Tool
16. Hyaluronic Acid (HLA) - Adhesion Barriers
17. Polycaprolactone (PCL)
18. Zirconia
19. 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 Nitinol?

    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 2020, unless otherwise noted.

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

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

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

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

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

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

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

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

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

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

Definitions
Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring: To observe or record relevant physiological or psychological signs.

Intervention: may include change in therapy or active medical/ surgical treatment.

Intervention necessary to sustain life: includes cardiovascular and respiratory support (eg 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 - Nitinol

Full Name: Nitinol
CAS Registry Number: 52013-44-2

Safety Brief - Systematic Review Results

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

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

Regulatory Description	Product Code	Class
Prosthesis, Vascular Graft, Of 6mm And Greater Diameter	DSY	2
Filter, Intravascular, Cardiovascular	DTK	2
Patch, Pledget and Intracardiac, Petp, Ptfe, Polypropylene	DXZ	2
Prosthesis, Esophageal	ESW	2
Replacement, Ossicular Prosthesis, Total	ETA	2
Prosthesis, Partial Ossicular Replacement	ETB	2
Stents, Drains and Dilators for The Biliary Ducts	FGE	2
Mesh, Surgical, Polymeric	FTL	2
Clip, Implantable	FZP	2
Suture, Nonabsorbable, Synthetic, Polyethylene	GAT	2
Device, Neurovascular Embolization	HCG	2
Plate, Fixation, Bone	HRS	2
Plate, Fixation, Bone	HRS	2
Rod, Fixation, Intramedullary and Accessories	HSB	2
Washer, Bolt Nut	HTN	2
Pin, Fixation, Smooth	HTY	2
Screw, Fixation, Bone	HWC	2
Prosthesis, Tracheal, Expandable	JCT	2
Cerclage, Fixation	JDQ	2
Staple, Fixation, Bone	JDR	2
Nail, Fixation, Bone	JDS	2
Device, Vascular, for Promoting Embolization	KRD	2
Ring, Annuloplasty	KRH	2

Appliance, Fixation, Spinal Intervertebral Body	KWQ	2
heart-valve, non-allograft tissue	LWR	3
Splint, Intranasal Septal	LYA	1
Occuluder, Patent Ductus, Arteriousus	MAE	3
Stent, Coronary	MAF	3
Intervertebral Fusion Device with Bone Graft, Lumbar	MAX	2
Intervertebral Fusion Device with Bone Graft, Lumbar	MAX	2
Fastener, Fixation, Nondegradable, Soft Tissue	MBI	2
Device, hemostasis, vascular	MGB	3
System, Endovascular Graft, Aortic, Aneurysm Treatment	MIH	3
Shunt, Portosystemic, Endoprosthesis	MIR	3
Transcatheter septal occluder	MLV	3
Orthosis, Spinal Pedicle Fixation	MNI	2
System, hemodynamic, implantable	MOM	3
Spinal Vertebral Body Replacement Device	MQP	2
Stent, Colonic, Metallic, Expandable	MQR	2
Clip, Implantable, for Coronary Artery Bypass Graft (Cabg)	NCA	2
Marker, Radiographic, Implantable	NEU	2
System, appendage closure, left atrial	NGV	3
Abutment, Implant, Dental, Endosseous	NHA	2
Stent, Carotid	NIM	3
Stent, Iliac	NIO	3
Stent, Superficial Femoral Artery	NIP	3
Intracranial Neurovascular Stent	NJE	HDE (humanitarian device exemption)
Suture, Nonabsorbable, Nitinol	NJU	2
Thoracolumbosacral Pedicle Screw System	NKB	2
Thoracolumbosacral Pedicle Screw System	NKB	2
Posterior Cervical Screw System	NKG	2
Mitral valve repair devices	NKM	3
Aortic valve, prosthesis, percutaneously delivered	NPT	3
Sensor, Pressure, Aneurysm, Implantable	NQH	2
One-Way Air-Leak Valve	OAZ	HDE (humanitarian device exemption)
Intervertebral Fusion Device with Bone Graft, Cervical	ODP	2

Intraocular pressure lowering implant	OGO	3
Right Ventricular Bypass (Assist) Device	OJE	HDE (humanitarian device exemption)
Implanted Subcutaneous Securement Catheter	OKC	2
Intrasaccular Flow Disruption Device	OPR	3
Pedicle Screw Spinal System, Adolescent Idiopathic Scoliosis	OSH	2
Intracranial aneurysm flow diverter	OUT	3
Intervertebral Fusion Device with Integrated Fixation, Lumbar	OVD	2
Intervertebral Fusion Device with Integrated Fixation, Cervical	OVE	2
Fixation, Non-Absorbable or Absorbable, For Pelvic Use	PBQ	2
Pancreatic Stent, Covered, Metallic, Removable	PCU	2
System, endovascular graft, arteriovenous (AV) dialysis access circuit stenosis treatment	PFV	3
Hemostatic Metal Clip for The Gi Tract	PKL	2
Leadless pacemaker	PNJ	3
Short-Term Intravascular Filter Catheter	PNS	2
Stent, iliac vein	QAN	3
Intracranial coil-assist stent	QCA	3
Scaffold, dissection repair	QCT	3

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of Nitinol. 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 Nitinol as a material as well as research on the 16 device categories.

Table 2: Summary of Primary Findings from ECRI's Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Cardiovascular – Clip/Closure/Embolization (7 human SRs and RCTs)	Aortic valve regurgitation, arrhythmias, atrial fibrillation, bleeding, buttock claudication, endoleaks, erectile dysfunction, groin	Low	No studies investigated	Very Low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	hematoma, ischemic cerebrovascular events, residual shunts, transient ischemic attack			
Cardiovascular - Filter (1 human SR)	Clotting, DVT, embedded filters, fracture, migration, perforation, retrieval failure, tilting, vena cava thrombosis or stenosis	Low for Migration and thromboembolic responses Very low for other local responses	No studies investigated	Very Low
Cardiovascular – Graft/Stent (9 human SRs)	Bleeding, cerebral hemorrhage, cranial nerve injury, endoleak types I and II, hemodynamic instability, neck hematoma, target lesion revascularization, retrograde aortic dissection, stent migration, and limb occlusion/restenosis	Moderate	Mortality, myocardial infarction, stroke, transient ischemic attack	Moderate
Cardiovascular – Heart Repair (9 human SRs and 1 RCT)	Aortic regurgitation, device failure, bleeding, device-related thrombus, major vascular complications, myocardial infarction, paravalvular regurgitation, pericardial effusion, postoperative pacemaker implantation, valve deterioration	Moderate	acute kidney injury, cerebrovascular accident events, mortality, re-hospitalization, reintervention, stroke	Moderate
Cardiovascular - Pacemaker/PICC (1 human SR, 1 RCT, 1 NRCS)	Bleeding/oozing/hematoma, complications, infection, medical adhesive-related skin injuries, pain	Moderate	Mortality	Low
Cosmetic (1 SAS)	Bruising, erosion/extrusion, infection, hypertrophic scarring, pain, sensitivity, swelling	Low for bruising, swelling, and sensitivity Very low for other local responses	No studies investigated	Very low
Ear Nose Throat (1 NRCS)	Minor granulations, stent dislocation	Very low	No studies investigated	Very low
Gastrointestinal – Biliary	Cholangitis, cholecystitis, inflammation, migration,	Moderate	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
(1 human SR and 9 RCTs)	pancreatitis, recurrent biliary obstruction, stent occlusion			
Gastrointestinal – Pancreatic (7 NRCSs)	Bleeding, dislodgement, infection, migration, occlusion, percutaneous drainage, revision, splenic vein thrombosis	Low	Mortality, diabetes mellitus	Very low
Gastrointestinal – Stomach/Colon/Rectum (3 human SRs, 3 RCTs, 4 NRCSs)	Abscess, aspiration, bleeding, device malfunction, foreign body, hematoma, incisional hernia, leakage, migration, obstruction/patency, pain, perforation, peritonitis, stoma	Moderate for bleeding, migration, and perforation Low for other local responses	No studies investigated	Very low
Gastrointestinal – Throat (3 human SRs, 4 RCTs, 3 NRCSs)	Aspiration, migration, pain, recurrent obstruction, tumor overgrowth	Low	Fever, mortality, pneumonia	Low
Lung (1 human RCT)	chronic obstructive pulmonary disease exacerbation, pneumonia	Very low	Cardiovascular events, mortality	Very low
Neurovascular (10 human SRs)	Device dislodgement and migration, hemorrhagic events, intraprocedural complications, ischemic/thromboembolic events, neurological deficit, periprocedural morbidity, protrusion, restenosis	Moderate for hemorrhagic and ischemic/thromboembolic events Low for other local responses	Mortality	Low
Ophthalmic (2 RCTs, 1 NRCS)	Conjunctivitis, focal peripheral anterior synechiae, post-perative intraocular pressure spikes, temporary reduction of visual activity, uveitis/iritis, worsening of the visual field,	Low	No studies investigated	Very low
Orthopedic – Bone fixation (1 human SR, 1 NRCS, 1 SAS)	Adhesions/scar in interphalangeal joint, avascular necrosis, deformities, hardware malfunction, fracture,	Low for hardware malfunction Very low for other local responses	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	malunion/non-union, transient axillary neuritis, wound complications			
Reproductive (1 SAS)	Bacterial vaginosis, dysmenorrhea, dyspareunia, expulsion, menorrhagia, metrorrhagia, pain, postprocedural hemorrhage, urinary tract infection, uterine spasm, vaginal discharge, vulvovaginal mycotic infection	Low for dysmenorrhea, menorrhagia, and procedural pain Very low for other local responses	Headache, nausea, nasopharyngitis, upper respiratory infection	Very low
Urinary (1 human SR, 1 RCT, 3 SASs)	Encrustation, fistulas, hematuria, infection, migration, obstruction, pain, sexual performance, urinary control, urethral hyperplasia	Low	Sepsis	Low

DVT: deep vein thrombosis; NRCS = nonrandomized comparative study; RCT = randomized controlled trial; SAS = single-arm study; SR = systematic review

Cardiovascular-Clip/Closure/Embolization

The literature search identified 7 human studies, all 7 were systematic reviews (SRs).[1-7] One study[2] compared nitinol to non-nitinol devices. For further information see Table 6 in Appendix D.

Local Responses/Device Events (human studies)

All 7 studies evaluated local responses/device events related to surgical procedures utilizing varied implants (closure, embolization coil / plug) with nitinol in human subjects.

Closure

One SR[1] reported on the use of Amplatzer Duct Occluder II for ventricular septal defect closure in 478 patients. The overall estimated device-implantation success rate was 99% (95% CI, 98%–100%). Residual shunts (pooled rate, 4%; 95% CI, 1%–7%) was the most common complication. Very low rates of cardiac dysrhythmias (pooled rate, 0%; 95% CI, 0–1%) and postoperative valve regurgitation (pooled rate, 1%; 95% CI, 0–3%) were also reported. Only 0.6% of patients developed device embolism.

Pineda et al.[7] focused on adverse events (AEs) between a patent foramen ovale (PFO) closure group treated with Amplatzer or STARFlex in comparison to a medical therapy group. Individual incidence of transient ischemic attack (TIA) and ischemic cerebrovascular events (CVA) was similar with both groups. However, 3.7% of the events were composite of TIA and ischemic CVA in the closure group compared with 5.3% ofof events in the medical therapy group, showing a trend in favor of the PFO closure. The incidence of bleeding episodes was similar between the PFO closure and medical therapy group. There were atrial fibrillation events (2.9%) reported in the PFO closure group versus 0.7% in the medical therapy group, a difference that trended towards statistical significance suggesting that closure of the PFO may be associated with higher incidence of atrial fibrillation.

One SR[2] reported on the complications related to implantation of 7 models of vascular closure devices (VCD). Overall complications trended higher for the StarClose, the only nitinol VCD included, in comparison to the overall complications for all

7 devices in both common femoral artery (7.4% vs 4.6%) and superficial femoral artery (10.1% vs 5.8%). The differences were clinically meaningful but not statistically significant. Bleeding complications were also higher for StarClose in comparison to the overall bleeding complications for all devices in both common femoral artery (6.8% vs 3.6%) and superficial femoral artery (6.4% vs 3.6%) with a statistical difference between different VCDs included in the SR.

Embolization / Coil / Plug

One SR[3] focused on complications related to endovascular aneurysm repair with Amplatzer Vascular Plug (AVP). The following complications were reported: buttock claudication (9.4%), groin hematoma (1.1%), endoleaks (5.3%), and erectile dysfunction (1.0%).

One SR[4] reported on AEs with implantation of Amplatzer Septal Occluder. Overall adverse event rate associated with the implantation was 5.1%. Adverse event rate of arrhythmias associated with implantation was 1.8% An adverse event rate of arrhythmias associated with the device embolism of 0.7% was reported.

Two SRs[5,6] reported on complications related to aneurysm treatment with Woven EndoBridge. One SR[5] reported thromboembolic complications of 9% and failure rate of 5%. One SR[6] a pooled event rate for complications (procedural aneurysm rupture, thromboembolic, and device protrusion in the parent artery) across studies was 17% (95% CI 10–30%).

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The evidence regarding local response came from SRs; only some SRs were based on randomized controlled trials (RCTs). These studies reported a range of complication rates. Therefore, the quality of evidence for local responses is low. Because no studies reported systemic responses, the quality of evidence regarding systemic responses is very low.

Cardiovascular-Filter

The literature search identified 1 human study (1 SR[8]). None of its included studies compared nitinol to non-nitinol devices. For further information see Table 7 in Appendix D.

Local Responses/Device Events (human studies)

1 SR[8] reported results from 37 single-arm studies and 842 Manufacturer and User Facility Device Experience (MAUDE) – categorized reports of 5 FDA-approved retrievable inferior vena cava filters. Overall, data from 4 nitinol filters (G2, Optease, Option, Eclipse) and 3 non-nitinol filters (ALN, Celect, Tulip) were included. Non-nitinol filters were composed of 316L stainless steel (ALN), conichrome (Celect), and a cobalt chromium alloy (Tulip).

The literature review captured data on 2279 nitinol filters (1517 G2, 662 Optease, 100 Option), and 2621 non-nitinol filters (738 ALN, 283 Celect, and 1600 Tulip). Indications for usage were either therapeutic use for patients with venous thromboembolism (VTE) before filter placement or prophylactic use for patients with no VTE at time of placement. The MAUDE database reported complications from 680 nitinol filters (500 G2, 163 Optease, 17 Eclipse), and 162 non-nitinol filters (18 Celect, and 144 Tulip). Mean followup reported in the literature review was 9.9 months (range 2 to 25 months). Mean implantation of removed nitinol filters (4 studies) versus non-nitinol devices (6 studies) was 11 days to 138 days, and 11 days to 179 days, respectively. Data on patient characteristics and dose were lacking.

Filter perforation: The MAUDE database captured 174 reports of filter perforation (visualization of a filter element >3 mm beyond the lumen of the IVC or within an adjacent structure); 150 (86%) with nitinol filters. 21 perforations with nitinol devices occurred ≤30 days.

Filter migration: In the literature review, 16 studies (n=2716) reported migration in 35 patients. Rates were higher with nitinol filters (0% to 4.5%) versus non-nitinol (0.5% to 0.8%). In the MAUDE database, 192 migrations were reported; 157 (82%) with nitinol devices. 12 migrations with nitinol devices occurred ≤30 days.

DVT: In the literature review, 13 studies (n=1277) reported DVT in 69 patients. Similar rates were reported for nitinol devices (0.8% to 18%) versus non-nitinol devices (0% to 14%).

Vena cava thrombosis or stenosis: 15 studies (n=4078) reported higher rates of thrombosis or stenosis with nitinol devices (3.7% to 8%) versus non-nitinol devices (0.6% to 2.3%). 3 thrombosis with nitinol devices occurred ≤30 days.

Fracture: Of 188 fractures, the MAUDE database reported 178 (95%) fractures were with nitinol devices. 1 fracture of a nitinol filter occurred ≤30 days.

Complications from filter removal: 1715 filter removals were reported in the literature review. Of 75 filters categorized as having substantial clots, 32 (42%) were nitinol. Retrieval failure occurred in 36 nitinol filters; 3 were embedded, 21 were tilted, and 12 were clotted. 1 filter tilting occurred ≤30 days. The MAUDE database included 111 complications due to filter removal which were mostly due to the inability to retrieve the filter; 86 (77%) were nitinol.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The evidence for migration and thromboembolic responses agreed with other device categories (e.g., neurovascular, orthopedic bone fixation), but the evidence base was limited to 1 SR, so the quality of evidence is low. The quality of evidence is very low for other local responses/events and systemic responses (no studies investigating).

Cardiovascular-Graft/Stent

The literature search identified 9 human studies, all systematic reviews.[9-17] One study[17] compared nitinol to non-nitinol devices. For further information see Table 8 in Appendix D.

Local Responses/Device Events (human studies)

All 9 studies examined local responses to the implantation of Nitinol stents in diverse procedures (transcervical carotid artery repair, aortoiliac aneurysm repair, thoracic endovascular aortic repair, endovascular aneurysm repair, carotid artery stenting). Enrolled patients (>20,000) were generally older than 65 years and predominantly men (65-94%). Studies followed patients for 30 days up to 1 year. The studies reported the following AEs: bleeding (3.2%), cerebral hemorrhage (0.1-0.3%), cranial nerve injury (0.4%), endoleak types I and II (1.6-2.1%), hemodynamic instability (25%), neck hematoma (1.0%), target lesion revascularization (3.3%), retrograde aortic dissection (1.0%), stent migration (4.7%), and limb occlusion/restenosis (1.5-11%).

The largest systematic review[9] with 14,588 patients reported the following local host responses: bleeding 278/8726 (3.2%), cranial nerve injury 33/8994 (0.4%), hemodynamic instability 1306/5183 (25%), and restenosis 4/260 (1.5%).,The period of observation was one month.

Systemic Responses

Four reviews[9-12] reported mortality rates (0.3-4.8%). Two reviews[9,12] reported myocardial infarction rates (0.5-0.6%) and transient ischemic attack rates (0.6-0.8%). Four reviews[9,10,12,14] reported rates of stroke (0.1-3.1%). The largest systematic review[9] with 14,588 patients reported similar systemic responses: mortality 75/14,427 (0.5%), myocardial infraction 65/14,173 (0.6%), Stroke 179/13,744 (1.3%), and transient ischemic attack 65/8673 (0.7%)

Overall Quality of Evidence

Nine systematic reviews, including one very large review, examined the local and systematic response to cardiovascular interventions with nitinol stents. For responses that were examined in multiple reviews, the reported rates were relatively consistent. Mortality and stroke were examined most often, both being examined in 4 systematic reviews with consistently low rates. However, there is a lack of evidence comparing nitinol to non-nitinol devices. Therefore, the quality of evidence for local and systemic responses.

Cardiovascular-Heart repair

The literature search identified 10 human studies (9 SRs[18-26] and 1 RCT[27]). Three studies[21,23,27] compared nitinol to non-nitinol devices. For further information see Table 9 in Appendix D.

Local Responses/Device Events (human studies)

Three systematic reviews (SRs)[19,21,22] and one RCT[27] all examined patients undergoing aortic valve replacement (AVR) involving the CoreValve device. One SR[19] compared patients receiving CoreValve vs. Evolut R, both containing nitinol, for six local host responses. Three of the responses (device failure, myocardial infarction, and moderate/severe paravalvular

regurgitation) significantly favored Evolut R, whereas the remaining responses showed no statistically significant differences. Another SR[21] examined single arm studies reporting major vascular complications (MVCs) for a variety of aortic valve replacement devices. The two nitinol devices had MVC rates of 7.97% and 5.98% for CoreValve and Evolut R, respectively. The non-nitinol devices had rates of 15.18% for the Sapien, 8.48% for the Sapien XT, and 4.48% for the Sapien 3. One individual RCT, a 5 year follow-up of Abdel-Wahab 2014 (included in 1 SR[21]), favored the Sapien XT for postoperative pacemaker implantation (PPI) events and moderate structural valve deterioration. Lastly, one SR[22] compared aortic regurgitation rates, PPIs, and vascular complications for patients receiving the CoreValve via a transfemoral or a transaxillary approach. All local host responses showed no difference between the two approaches.

The other type of device that examined patients with AVRs was the Perceval nitinol device. One SR[25] compared patients receiving Perceval vs. a conventional bioprosthesis. Perceval had a much lower follow-up rate of 18.25 months compared to the conventional bioprosthesis with 38.3 months. Two local host responses were examined. Postoperative pacemaker implantation (PPI) favored the conventional bioprosthesis with an odds ratio of 2.45 (95% CI: 1.44 to 4.17), whereas there was no difference in the rate of paravalvular leak between groups.

Another type of heart repair procedure examined was mitral valve repair with the MitraClip device. One SR[28] following patients between 30 days and 2 years found that successful implantation was reported in 91.1% of patients. Another SR[18] following patients for up to 6 months found successful implantation in 93.7% of cases with low rates for all local responses.

Lastly, two SRs[23,24] examined patients receiving the Watchman device for atrial appendage occlusion and/or atrial fibrillation. One SR[23] included 4,443 patients receiving the Watchman device, 2,744 patients receiving the Amplatzer Cardiac Plug, and 982 patients receiving another device. These studies reported on device-related thrombus (DRT), which was low (under 4% incidence) for all devices. However, people receiving the Watchman device had 22 DRT-associated events, people receiving the Amplatzer had eight events, and people receiving other devices had zero events. Another SR[24] examined Watchman data from patients enrolled in two RCTs. This SR also contained registry data, although, that data was already examined in another included SR by Alkhouli et al. 2018.[23] In order to prevent extra double counting patient event data, only the novel RCT evidence in this review was examined. For people allocated to the treatment arm involving Watchman implantation, the implantation success was 92.5% and local host responses of device embolization, major bleeding, and pericardial effusion were all low.

Systemic Responses

Eight studies reported on systemic responses for devices categorized as heart repair. Two SRs[19,22] and one RCT[27] examined patients implanted with CoreValve for AVR. One SR[19] comparing Evolut R and CoreValve found acute kidney injury (AKI) was significantly lower in patients with Evolut R, whereas, stroke rates and mortality rates showed no difference between groups. The other SR[22] compared rates of systemic AEs by type of approach for AVR. Patients receiving CoreValve with the transaxillary (Tax) approach had lower rates of AKI than patients with the transfemoral (TF) approach. 30-day and one year mortality rates showed no differences between groups. Lastly, an RCT[27] comparing CoreValve to Sapien XT at 5-year follow-up found no differences in mortality, stroke rates, or repeat hospitalizations. Patients in one SR[25] also underwent AVR, and the nitinol-device Perceval was compared to a conventional bioprosthesis. Patients receiving the Perceval device had significantly fewer AKI events (odds ratio 0.45, 95% CI: 0.65 to 1.74). Rates of mortality (postoperative, 30-day, and one-year) as well as stroke rates were not different between groups.

Three SRs[18,20,26] reported events associated with MitraClip implantation. One SR[18] examining 40 studies with 254 total patients found low rates of mitral valve reintervention and cerebrovascular accident events, although, in-hospital mortality rates and 6-month mortality rates were high with 12.6% and 18.1%, respectively. Another SR[20] also examining mortality with a larger sample size (2,383 patients in 28 studies) found 2.95% mortality at 30-days which increased to 18.86% at 12 months. Lastly, an SR[26] comparing MitraClip implantation with optimum medical treatment (OMT) to OMT alone found higher rates of reoperation with MitraClip and OMT. All other systemic responses (composite endpoint, hospital mortality, long-term mortality, and readmission) had no difference between groups.

One SR[24] of 2 RCTs followed Watchman patients with atrial fibrillation between 11.8 months and 18 months. This study found no procedure-related deaths and a low incidence (0.8%) for procedure-related strokes.

Overall Quality of Evidence

Ten studies (9 SRs and 1 RCT) examined local host responses for studies related to heart repair, whereas eight studies (7 SRs and 1 RCT) examined systemic responses. Common local host responses included vascular complications, PPI, and

implantation success rates. Common systemic responses included AKIs, mortality, and stroke rates. Both local and systemic responses included large patient samples with few inconsistencies by type of event across studies. Both local and systemic responses were determined to be moderate strength of evidence.

Cardiovascular-Pacemakers/PICCs

The literature search identified 3 human studies (1 SR,[29] 1 RCT,[30] and 1 nonrandomized comparative study[31]). Two studies[30,31] compared nitinol to non-nitinol devices. For further information see Table 10 in Appendix D.

Local Responses/Device Events (human studies)

Two included studies examined local AEs related to leadless pacemakers. One included systematic review[29] with 36 included studies examined patients implanted with either Nanostim pacemakers or Micra pacemakers, both containing Nitinol, with follow-up times ranging from 1.8 months to 125 months. Both pacemaker devices had high rates of success with 99.85% (95% confidence interval [CI]: 99.59% to 99.99%) for Micra and 97.12% (95% CI: 95.86% to 98.20%) for Nanostim. The pooled incidence of complications was low for Micra with 0.46% (95% CI, 0.08%–1.05%) at 90 days and 1.77% (95% CI, 0.76%–3.07%) at 1 year. The odds of complications for Nanostim were not pooled, however, incidence ranged from 6.06% to 23.54% at 90 days and 5.33% to 6.67% at 1 year. Lastly, studies comparing Micra pacemakers to transvenous pacemakers found 51% lower odds of complications with Micra (odds ratio [OR], 0.49; 95% CI, 0.34–0.70). The other study, a nonrandomized comparative study,[31] was aimed at comparing patients precluded from receiving a transvenous permanent pacemaker (TV-PPM) from those without reasons that would preclude them. A total of 2,817 patients underwent a Micra implantation event with 2,268 patients assigned to the non-precluded group and 546 assigned as precluded (3 had preclusion status not reported). In addition, the authors also used a historical TV-PPM control group, although, this group was only compared for systemic responses. All local host responses showed no difference between precluded TV-PPM and non-precluded TV-PPM groups (total complication rates of 4.30% and 3.81% respectively) up to 36 months.

One RCT[30] compared peripherally inserted central catheters (PICCs) for a nitinol device (SecurAcath) and a non-nitinol device (StatLock). Patients were randomized 1:1 to SecurAcath (n=52) or StatLock (n=53) and followed up to 180 days. Most local host responses were recorded during the dressing change, which was a median time of 7.3 minutes for StatLock and 4.3 minutes for SecurAcath. Common AEs included bleeding/oozing/hematoma, pain at exit site, signs of exit site infection, and medical adhesive-related skin injuries. Significant differences were only seen for patient pain scores recorded at insertion of PICC and removal of PICC (up to 180 days), however, pain scores recorded at dressing change or during dwell time showed no significant differences.

Systemic Responses

One nonrandomized comparative trial[31] comparing precluded Micra insertion, non-precluded Micra insertion, and a historical control group reported on mortality rates up to 36 months. Both acute mortality (2.75% vs 1.32%; P=.022) and total mortality (38.1% vs 20.6%; P<.001) were significantly higher in the precluded group than in the non-precluded group. When comparing the non-precluded patients and patients implanted with a TV-PPM (historical control groups), mortality rates were similar.

Overall Quality of Evidence

Three studies (one SR, one RCT, and one nonrandomized comparative trial) reported on local responses for nitinol devices associated with pacemakers or PICCs. Adverse events were generally low, although, they increased as patients were followed for longer periods. Given the study designs, sample sizes, and consistency of local host response evidence, the quality of evidence for host responses is moderate. Systemic responses were observed for only one RCT with moderate size. Since only one study reported systemic responses with uneven patient group allocation (2,268 non-precluded patients vs. 546 precluded patients), the quality of evidence is low for systemic responses.

Cosmetic

The literature search identified 1 human single arm study.[32] This study examined use of a nitinol implantable clip system (earFold™, Contract Medical International, GmbH, Dresden, Germany) to treat prominent ears. This study addressed 131 implants (75 ears) in 39 patients aged 7 to 57 years. Followup was 18 months to 47 months. For further information see Table 3 in Appendix D.

Local Responses/Device Events (human studies)

All patients experienced bruising and swelling which increased within a few hours of treatment and subsided within 7 days. "Most patients" reported temporary sensitivity to the implant when lying on their side, which disappeared in all patients by 12 weeks. Erosion/extrusion of the skin over the implant occurred in 5 (13%) patients. Infection and hypertrophic scarring associated with the incisions for implant insertion occurred in 2 (5.1%) patients each. Number of patients experiencing pain was not provided.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The quality of evidence was rated low for bruising, swelling, and sensitivity to the implant due to the occurrence in all or "most patients" in 1 uncontrolled study. The quality of evidence for the remaining local responses and systemic responses (not investigated) was rated very low.

ENT

The literature search identified 1 human studies (1 nonrandomized comparative study[33]), which compared nitinol to non-nitinol devices. For further information see Table 12 in Appendix D.

Local Responses/Device Events (human studies)

One nonrandomized comparative study[33] compared self-expandable nitinol airway stents (n=14 stents) to other stents including the Multilink (n=17 stents), Palmaz (n=20 stents), Jomed (n=69 stents), Poliflex (n=30 stents), and Dumon (n=82 stents). Patients were grouped by general type of stent with 34 receiving only silicone stents, 52 receiving only metallic stents, and 14 receiving a combination of silicone and metallic stents. All 100 patients were children with severe airway obstruction, and the majority of patients received more than one stent. Reported stent duration had a wide range with 1 to 1,489 days for silicone stents and 1.1 to 145.4 days for metallic stents. Six types of local host responses were observed, and most implanted stents had at least one complication. For nitinol-based stents, the most common local host response was minor granulations (n=6, 43%) followed by stent dislocation (n=4, 29%). Common local host responses for other types of stents included major granulation requiring stent replacement and ovalizations requiring dilations. No statistical tests were performed to determine between-group differences.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

One nonrandomized comparative study reported on local host responses for a small number of nitinol-based stents implanted in the airway. All types of airway stents produced high incidence rates of local host responses, although, between-group differences for specific types of local host responses were not reported. The small sample sizes for nitinol stents, study design, crossover between groups (patients receiving different devices), and inability to determine consistency of results all contributed to a very low quality of evidence rating for local host responses. Systemic responses were not reported, resulting in a very low quality of evidence rating for systemic responses.

Gastrointestinal-Biliary

The literature search identified 10 human studies: 1 systematic review[34] and 9 RCTs.[35-43] Two studies[38,41] compared nitinol to non-nitinol devices. The other RCTs compared covered and uncovered nitinol stents. For further information see Table 13 in Appendix D.

Local Responses/Device Events (human studies)

Recurrent biliary obstruction (RBO) and stent occlusion: One SR[34] examined stent occlusion in lumen-opposing metal stents (made of nitinol wire covered with silicon). The SR included 8 cohort studies and 393 patients. The SR reported stent occlusion in 5.2% of patients which was not significantly different from control patients.

An RCT[36] reported silicon-covered stents were less susceptible to tumor ingrowth than uncovered stents (0% versus 16.7%, p <0.01).

An RCT[37] reported occlusion in covered stents was 16.7% and in uncovered stents was 13.2%.

An RCT[39] reported occlusion in covered stents was 72.7% and in uncovered stents was 66.7% in patients with malignant distal biliary obstruction after primary stent failure.

Stent migration:

An SR[34] reported stent migration in 3.2% of patients treated with lumen-opposing metal stents.

An RCT[36] reported covered stents were more susceptible to stent migration than uncovered stents (6.8% versus 0%, p = 0.03).

An RCT[37] reported stent migration in covered stents was 6.9% and in uncovered stents was 0%.

An RCT[38] reported stent migration in covered stents was 10% and in plastic stents was 2.8%.

Stent-related inflammation, including cholangitis (inflammation of the bile ducts), cholecystitis (inflammation of the gallbladder), and pancreatitis:

An SR[34] reported recurrent cholecystitis and/or cholangitis (6 studies, 301 patients, 11 events) was 4.6% (95% CI 2.6-8.0).

An RCT[35] reported one cholecystitis among 73 patients (1.4%) treated with a covered stent and none among 78 patients treated with an uncovered stent.

An RCT[36] reported 9.3% acute cholecystitis, 1.7% acute pancreatitis, and 15.3% cholangitis among patients treated with a covered stent and 4.8% acute cholecystitis, 0% acute pancreatitis, and 13.3% cholangitis among patients treated with an uncovered stent. The stent groups were not significantly different.

An RCT[37] reported 8.3% cholangitis and 2.8% cholecystitis among patients treated with a covered stent and 7.9% cholangitis and 0% cholecystitis among patients treated with an uncovered stent.

An RCT[38] reported acute pancreatitis was 13.3% in patients treated with an uncovered stent and 2.1% in patients treated with plastic stents.

An RCT[39] reported cholangitis in covered stents was 50% and in uncovered stents was 47.6% in patients with malignant distal biliary obstruction after primary stent failure.

An RCT[40] reported pancreatitis was 5.9% and cholecystitis was 11.1% in patients treated with a covered stent and pancreatitis was 0% and cholecystitis was 6.0% in patients treated with an uncovered stent.

An RCT[41] reported 1.5% pancreatitis, 1.5% cholecystitis, and 2% cholangitis in patients treated with partly-covered steel stents and 1.0% pancreatitis, 1.5% cholecystitis, and 2.5% cholangitis in patients treated with a partly-covered nitinol stents.

An RCT[42] reported 5% cholecystitis in patients treated with a covered stent and 0% in patients treated with an uncovered stents. Pancreatitis was not observed in either group.

An RCT[43] reported 1.7% cholecystitis and 1.7% pancreatitis in patients treated with a covered stent and 3.3% cholecystitis and 0% pancreatitis in patients treated with an uncovered stents.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

All publications reported on findings from RCTs except for one SR[34] which included 8 cohort studies. Sample sizes were large in most studies. When considering stent-related inflammation, studies were consistent in reporting no difference between covered and uncovered nitinol stents. Other findings were also consistent, such as stent migration being more prevalent in covered SEMS. Therefore, the quality of evidence was rated moderate.

For systemic responses, the quality of evidence was rated very low (no studies investigating).

Gastrointestinal-Pancreatic

The literature search identified 7 human studies (7 nonrandomized comparative studies[44-50]). Five studies[44,45,47,49,50] compared nitinol to non-nitinol devices. For further information see Table 14 in Appendix D.

Local Responses/Device Events (human studies)

Four nonrandomized comparative studies[46-49] examined patients with pancreatic necrosis. One study[47] compared patients receiving Axios or Niti-S self-expandable metal stents (SEMS) to patients with double-pigtail plastic stents (DPPS) for a follow-up median of eight weeks (interquartile range [IQR] 6 to 12 weeks). Thirteen unique local host responses were examined, with the most common events being migration and splenic vein thrombosis. One AE, bleeding requiring endoscopic intervention, showed significantly greater incidence for DPPS than SEMS (p=0.02). All other Aes showed no significant difference between groups. Another study[48] compared two types of metal stents: the NAGI bi-flagged metal stent (BFMS) versus the Hot AXIOS lumen-apposing metal stent (LAMS) up to 30 days follow-up. The addition of a plastic stent was at the discretion of the endoscopist. Common events included percutaneous drainage prior to endoscopic ultrasound and dislodged stent during necrosectomy; no significant differences were seen for any adverse event (AE). One study[49] had three unique comparisons: patients receiving two DPPSs, a fully covered self-expandable metal stent (FCSEMS) (WallFlex or Viabil) with a DPPS, or a LAMS (Hot Axios). ANOVA analysis found significant differences between groups for bleeding events occurring within one week of the procedure and stent occlusion leading to infection occurring after one week. For those comparisons, LAMS had the highest bleeding rates and DP and FCSEMS had higher occlusion rates than LAMS. No differences found between groups for other Aes. Lastly, a study[46] enrolling 68 patients compared FCSEMS (Hanarostent or WallFlex) and LAMS (Cold Axios and Hot Axios) for management of walled-off necrosis. Common events included stent revision, migration, and bleeding. LAMS generally reported Aes more frequently than FCSEMS.

Three nonrandomized comparative studies[44,45,50] examined patients with a variety of diagnoses undergoing drainage of pancreatic fluid collections and pancreatic pseudocysts. One study including patients with pancreatic pseudocysts and walled-off necrosis included patients treated with LAMS (Hot Axios), SEMS (WallFlex or Niti-S), or DPPS. All patients were followed for up to three months, but authors noted that LAMS was removed within two to four weeks. All reported Aes were infrequent with no reported differences between groups. Another study[45] examined stents in the same three categories, although, the SEMS only included WallFlex stents and the LAMS stents were an un-named stent produced by Micro-Tech. Similarly, this study also reported no differences between groups, although, migration events (after two weeks) and infections (within two weeks) were frequent events. Lastly, a large nonrandomized comparative study[50] compared FCSEMS (WallFlex or Viabil) to DPPS for pseudocyst drainage. Individuals in the FCSEMS received one nitinol stent and one DPPS, whereas, patients in the DPPS had two implanted DPPS. Analysis on early Aes (within 30 days) favored FCSEMS over DPPS, although late Aes were infrequent and similar between groups.

Systemic Responses

Three nonrandomized comparative studies[45,47,48] reported on mortality differences for patients with based on type of stent. Comparisons of interest included SEMS (Axios or Niti-S) versus DPPS, DPPS versus SEMS (Wallflex) versus LAMS, and BFMS versus LAMS. Similarly low rates for mortality were reported. In addition, one study[47] found no differences between DPPS and SEMS for newly onset diabetes mellitus.

Overall Quality of Evidence

Seven studies reported on local host responses for nitinol-based pancreatic stents, whereas, three studies reported on systemic responses. For local host responses, one study[47] reported greater incidence of bleeding for DPPS versus SEMS (p=0.02), and another study[49] found differences between groups for bleeding and occlusion events. One study[46] without comparisons of statistical significance generally reported Aes related to LAMS more frequently than FCSEMS. Lastly, one study[50] favored FCSEMS over DPPS when looking at early AE incidence. All other Aes had no differences between groups. The study design and mixed consistency of results reporting generated a low quality of evidence for local host responses. For systemic responses, mortality and newly-onset diabetes mellitus were both infrequently occurring for all studies. Quality of evidence for systemic responses was very low due to study design and infrequency in utilizing statistical tests for significance.

Gastrointestinal-Stomach/Colon/Rectum

The literature search identified 10 human studies (3 SRs,[51-53] 3 RCTs,[54-56] and 4 nonrandomized comparative studies,[57-60]). Three studies[51,53,60] compared nitinol to non-nitinol devices. For further information see Table 15 in Appendix D.

Nitinol self-expandable metal stents (SEMS) were examined in 2 SRs,[51,52] 1 RCT,[54] and 4 nonrandomized comparative studies;[57-60] most patients with colorectal obstructions. 1 SR focused on perforation from SEMS,[51] while another SR focused on migration from conventional esophageal stents including SEMS.[52] The RCT addressed Niti S colorectal stent versus transanal drainage tube (TDT).[54] The 4 nonrandomized comparative studies compared SEMS with surgery,[57-59] or various uncovered/covered SEMS.[60] The following SEMS were examined:

Uncovered nitinol stents included Alimaxx-ES, Alveolus, Bonastent, Choo, Comvi, Endoflex, Evolution, Hanaro colorectal, Hanaro ECBB, Hanaro GastroSeal, Hanaro, Hanarostent, Niti-S, Ultraflex, and Wallflex.

Covered nitinol stents included Niti-S covered with polyurethane, and Bonastent covered with silicone.

Non-nitinol stents included Dual stent and Wallstent.

Nitinol devices as a compression anastomosis clip (CAC) were examined in 2 studies. 1 SR[53] addressed CAC with Niti memory shape vs. stapler for gastrointestinal and colorectal anastomosis, while 1 RCT[55] addressed CAC with Niti Hand versus hand suture control for jejunojejunostomy in gastric cancer surgery. Lastly, 1 RCT addressed a nitinol endoluminal mechanical device (Satisphere) versus control for obesity.[56]

Local Responses/Device Events (human studies)

Abscess: Evidence from 1 SR of 8 RCTs[53] indicated abscess in 1 patient each with CAC (subphrenic) and stapler (intraabdominal).

Aspiration: Evidence from 1 nonrandomized comparative study[58] addressing SEMS (n=183) vs. surgery (n=127) reported similar aspiration events (5 SEMS, 6 surgery) up to mean 193 days.

Bleeding: 4 studies reported on this outcome; 3 studies addressed SEMS. 1 nonrandomized comparative study[57] addressed SEMS in 81 patients (49 stenting as a bridge to elective surgery, 34 for definitive palliation). Authors reported colorectal bleeding in 11 (14%) patients with SEMS up to 350 days. Results indicated no significant difference for colorectal bleeding with SEMS as a bridge to surgery (n=49) vs. no stenting (n=51), (8.3% SEMS, 12% no stent) up to median 43 months.

2 nonrandomized comparative studies addressing SEMS vs. surgery reported fewer bleeding events with SEMS (4 vs. 8) up to mean 193 days,[58] and death due to bleeding >30 days in 1 patient with SEMS.[59]

1 RCT[55] addressing CAC (n=20) vs. control (n=24) reported esophagojejunostomy (EJ) bleeding with CAC in 1 patient up to 21 days.

Device malfunction was reported in 2 studies. 1 SR of 8 RCTs[53] examining nitinol as a CAC vs. stapler reported lack of 2 anastomosis clips from expelling with stool. 1 nonrandomized comparative study[59] addressing SEMS (n=73) vs. surgery (n=41) reported inappropriate stent expansion within 30 days in 2 (3%) patients.

Foreign body was reported in 1 patient with CAC (n=20) up to 21 days in 1 RCT.[55]

Hematoma was reported in 1 SR of 8 RCTs.[53] This SR examining nitinol as a CAC vs. stapler reported a left subphrenic-infected hematoma in 1 patient with CAC up to 6 months.

Incisional hernia: 1 nonrandomized comparative study[57] reported significantly lower incisional hernia with SEMS as a bridge to surgery vs. no stent (3 (6.3%) SEMS, 11 (22%) no stent) up to median 43 months.

Leakage was reported in 3 studies; studies examining SEMS, CAC and CAR. 1 nonrandomized comparative study[57] (n=132) reported no significant difference in anastomotic leak with SEMS as a bridge to surgery vs. no stent (6 (12.2%) SEMS, 10 (19.6%) no stent) up to median 43 months.
1 SR of 8 RCTs[53] reported anastomotic leak after low anterior resection in 1 patient each with CAR and stapler up to 3 months followup. Lastly, 1 RCT[55] addressing CAC (n=20) vs. control (n=24) reported similar EJ leakage (1 CAC, 2 control), and "early" jejunojejunostomy leakage in 1 patient with CAC up to 21 days.

Migration was reported in 5 studies. Of the 4 studies examining SEMS, 1 SR of 23 single-arm studies reported migration from nitinol stents in 130 patients with sleeve gastrectomy leak up to mean 8.4 months.[52]

Results from 2 nonrandomized comparative studies included 8 (10%) migrations with SEMS up to 350 days,[57] and migration in 5 (7%) patients (3 events within 30 days).[59] A 3rd nonrandomized comparative study[60] addressing SEMS with uncovered nitinol (n=42), covered nitinol (n=30) or non-nitinol (n=27) reported migration in 15 patients (3 uncovered nitinol, 5 covered

nitinol, 7 non-nitinol). Results indicating significantly lower migration with uncovered nitinol vs. non-nitinol (7.1% nitinol, 25.9% non-nitinol; p=0.037). Mean time to migration was approximately 28 days.

Lastly, 1 RCT[56] comparing a nitinol endoluminal mechanical device (n=21) with control (n=10) reported migration in 10 (48%) patients with a nitinol device placed for 3 months to treat obesity. Emergency surgery was required in 2 patients.

Obstruction was reported in 3 studies; 1 study examining CAC. 1 nonrandomized comparative study[59] addressing SEMS (n=73) vs. surgery (n=41) reported stent obstruction caused by tumor ingrowth or tumor outgrowth in 13 (18%) patients with SEMS; 12 events > 30 days. Stent obstruction only occurred in 2 surgery patients; both occurred >30 days. Another nonrandomized comparative study[60] addressing SEMS reported no significant difference in occlusion (obstruction by tumor ingrowth or overgrowth) with uncovered nitinol (7%) vs. non-nitinol SEMS (11.1%). Time to occlusion with uncovered nitinol stents was 69 days, 150 days, and 169 days.

1 SR of 8 RCTs[53] examining nitinol as a CAC vs. stapler reported similar number of events (2 CAC, 3 stapler). Events included small bowel obstruction in 1 patient each, adherent intestinal obstruction distant from the anastomosis site in 1 patient with CAC, and adhesion obstruction in the small bowel in 2 patients with stapler up to 6 months.

Pain was reported in 2 studies. Short-term complications in 1 nonrandomized comparative study[57] examining SEMS (n=81) included 6 (7.4%) abdominal-rectal pain, 1 (1.2%) tenesmus (cramping rectal pain), and 7 (21.9%) recurrent abdominal pain. Long-term complications included recurrent abdominal pain and tenesmus in 7 (21.9%) patients each. In the subgroup of 49 patients undergoing SEMS as a bridge to surgery, results indicated no significant difference for recurrent abdominal pain (12.5% SEMS, 24% no stent) or tenesmus (8.3% SEMS, 8% no stent) up to median 43 months.

1 RCT[56] comparing a nitinol endoluminal mechanical device (n=21) with control (n=10) reported abdominal pain in 1 (5%) patient after 2 months after placement of a nitinol device for obesity.

Patency was reported in 1 nonrandomized comparative study.[60] Authors indicated no significant difference in stent patency up to death with uncovered nitinol vs. non-nitinol (35/42 (83%) nitinol, 17/27 (63%) non-nitinol; p=0.065).

Perforation was reported in 5 studies. 1 SR of 86 studies reported perforation rates for uncovered nitinol stents (4.7% to 10.9%), a covered nitinol stent (3.1%), and non-nitinol stents (7.7% and 8.7%). Days until perforation were 0 (29%), 1 to 3 (23%), 4 to 7 (14%), 8 to 14 (11%), 15 to 30 (7%), and >30 (16%).[51]

Evidence from 4 nonrandomized comparative studies addressing SEMS reported 2 (2.4%) bowel perforations,[57] similar perforation events (5 SEMS, 4 surgery),[58] 1 procedure-related perforation with a covered nitinol stent,[60] and colonic perforation in 8 (11%) patients.[59] Early colonic perforation in 2 patients developed on days 14 and 15, while late colonic perforation in 6 patients occurred on days 125, 202, 333, 403, 507, and 629.[59]

Peritonitis was reported in 1 nonrandomized comparative study.[57] Authors noted no significant difference in peritonitis with SEMS as a bridge to surgery vs. no stent (2 (4.1%) SEMS, 5 (9.8%) no stent; p=0.436) up to median 43 months.

Stoma was reported in 2 nonrandomized comparative studies addressing SEMS. Results indicated significantly lower definitive stoma formation with SEMS as a bridge to surgery vs. no stent (6.3% vs. 26%)[57] and no significant difference in stoma formation >30 days (17.8% SEMS, 24.4% surgery; p=0.401).[59]

No complications were reported in 1 RCT (n=29) with nitinol stents versus TDT (1 perforation) for decompression of acute left-sided malignant colorectal obstruction.[54]

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The quality of evidence was rated moderate for bleeding, migration, and perforation due to consistent reporting of these outcomes from higher-quality studies; all outcomes in agreement with other nitinol devices (e.g., neurovascular, cardiovascular – IVC filter). For other outcomes reported in fewer studies, the quality of evidence is low. For systemic responses, the quality of evidence was rated very low (no studies investigating).

Gastrointestinal-Throat

The literature search identified 10 human studies (3 systematic reviews (SRs),[61-63] 4 RCTs,[64-67] and 3 nonrandomized comparative studies[68-70]). Three studies[62-64] compared nitinol to non-nitinol devices. For further information see Table 16 in Appendix D.

Local Responses/Device Events (human studies)

Three SRs[61-63] each examined local host responses for esophageal stents between 2 months and 6 months. One SR[61] reviewed six studies (n=250 patients) treated for malignant esophageal obstructions using double-layered covered NiTi-S stents. Meta-analyses revealed low proportions of patients with migration (4.7%, 95% CI: 2.5% to 7.7%) and high technical success rates (97.2%, 95% CI: 94.8% to 98.9%), whereas tumor overgrowth (11.2%, 95% CI: 3.7% to 22.1%) and overall complications (27.6%, 95% CI: 20.7% to 35.2%) had moderate to high incidence. Since no comparisons were made in this SR, authors were unable to state comparative effectiveness. Another SR[62] used evidence from two RCTs for patients implanted with nitinol-based Ultraflex stents (n=65) or Wallstents (n=55). Eight unique local host responses were examined with non-significant differences, ranging from an OR of 0.27 favoring Ultraflex stents for tumor overgrowth to an OR of 1.93 for migration favoring Wallstents. Lastly, an SR[63] examined rates of stent migration in nitinol (n=80 stents, 2 studies) and Polyflex stents (n=119 stents, 2 studies) between 24 and 152 weeks. Nitinol stents had a moderate likelihood (OR 0.28, 95% CI: 0.16 to 0.49) and Polyflex had a moderately high likelihood (OR 0.43, 95% CI: 0.27 to 0.67) of migration incidence. Since rates were calculated from different studies, no comparative effectiveness conclusions could be made.

Four RCTs[64-67] ranging from 18 to 95 enrolled patients were found relating to nitinol-based esophageal stents. One RCT[64] randomized patients to WallFlex stents (n=9) or bougie dilation (BD) (n=9) for 12 months. Patients in the WallFlex study arm had stents removed per-protocol at 8 weeks or sooner if complications occurred. Only eight Aes occurred, all in the WallFlex study arm, with one serious AE (aspiration) and seven non-serious. Two RCTs[65,66] enrolled patients with malignant esophageal strictures to receive covered WallFlex stents. One study's comparison group was partially covered WallFlex stents, whereas the other was partially covered UltraFlex stents. Common local host responses included recurrent obstruction, stent migration, and severe pain. Neither study found between group differences for fully covered vs. partially covered treatment arms. Lastly, one RCT[67] enrolling patients with esophageal cancer compared Dostent (n=20) to Choostent with proton-pump inhibitors and postural advice (n=18) with a follow-up of 18 months. Authors noted that overall AEs (combined total of obstructions and migrations) were significantly more common in Dostent than Choostent (55% vs. 18%, p=0.0196).

Three nonrandomized comparative studies[68-70] also examined local host responses related to esophageal stents. One large study[68] retrospectively examined stent migration rates for benign and malignant strictures for up to 4 weeks. Patients received either WallFlex (n=218), Endomaxx (n=96), or Evolution (n=55) stents. For patients with malignant strictures, migration rates (clinically relevant and total) were significantly highest with Evolution stents, however, there were no significant differences for patients with benign strictures. Another moderate-size study[69] also examined migration rates for four types of stents; event rates ranged from 36.4% of patients with Niti-S and 22.4% of patients with WallFlex. Other serious AEs were noted in the study, although, they were examined for the total sample rather than based on stent-type. Lastly, one nonrandomized comparative study compared event rates based off presence of a 5 cm proximal tumor covering. Both study arms experienced 2 cases of tumor overgrowth.

Systemic Responses

One SR[62] and two RCTs[66,67] all examined mortality rates for esophageal stent placement. The SR[62] compared Ultraflex and Wallstents, one RCT[66] compared fully covered WallFlex to partially covered UltraFlex, and another RCT[67] compared Dostent to Choostent. All reported mortality rates had no significant differences between groups. Also, one RCT[65] comparing partially and fully covered WallFlex stents found similarly low rates of pneumonia and fever up to 6 months followup.

Overall Quality of Evidence

Ten studies reported on local host responses for nitinol-based esophageal stents, whereas three studies reported on systemic responses. Most local host responses found no differences between groups. One RCT[67] noted significantly more common obstructions and migration events with Dostent as compared to Choostent, and one nonrandomized comparative study found migration rates were significantly highest in Evolution stents, as compared to WallFlex and Endomaxx. One non-randomized study found similarly high rates of migration (33.3%) with Evolution stents, but it had a sample size and no reported statistical significance. Available evidence had a large cumulative sample size with many systematic reviews and RCTs, however, the inconsistency in migration rates contributed to a low quality of evidence rating for local responses. As for systemic responses,

findings from one SR and two RCTs consistently showed no differences between groups for mortality rates. Although mortality data was consistent, the small evidence base for the remaining systemic responses for fever and pneumonia contributed to a low quality of evidence rating for systemic responses.

Lung

The literature search identified 1 human study (1 RCT[71]), which compared nitinol bronchial coils to usual care. For further information see Table 17 in Appendix D.

Local Responses/Device Events (human studies)

One RCT[71] compared implanted nitinol bronchial coils (n=50) to usual care (n=50) for patients with severe emphysema. Coils were manufactured by PneumRX/BTG and were available in either 100 mm or 25 mm sizes; each patient randomized to the coil arm received around 10 coils placed in two bilateral lobes via two procedures. Six unique local host responses were examined. The most common event was chronic obstructive pulmonary disease (COPD) exacerbation which occurred in 13 patients allocated to coil treatment and 11 patients allocated to usual care. Rates of pneumonia were significantly higher (p=0.02) in patients allocated to coil treatment versus usual care (9 events versus 2 events). No other local host responses were significantly different between groups.

Systemic Responses

The same RCT[71] also examined two systemic responses including cardiovascular-related events and mortality. Both types of events were infrequent (<10% incidence) and no significant differences were seen between groups.

Overall Quality of Evidence

One moderate-sized RCT reported on both local and systemic responses for nitinol-based bronchial coils versus usual care. Only one local host response (pneumonia) was significantly higher for patients receiving coils as compared to usual care. All other local and systemic host responses did not report statistically significant differences. Due to limited evidence for this category with no comparison to non-nitinol devices, both local and systemic responses were rated very low.

Neurovascular

The literature search identified 10 human studies (10 SRs,[72-81]). None of the included studies compared nitinol to non-nitinol devices. For further information see Table 18 in Appendix D.

Intrasaccular flow-diversion: 2 SRs[72,73] addressed Woven EndoBridge (WEB; MicroVention-Terumo, Aliso Viejo, CA) for wide-neck bifurcation aneurysms.

- 1 SR[72] of 18 single-arm studies (n=487) addressed 496 ruptured aneurysms. Retreatment was required in 27 patients. Mean followup was 3 to 15 months.
- 1 SR[73] of 9 single-arm studies addressed 377 acutely ruptured aneurysms. Followup ranged from 3 to 39 months.

Stent-assisted coiling (SAC):

- 1 SR[74] of 6 single-arm studies (n=157) addressed SAC with PulseRider (Cerenovus, New Brunswick, NJ) to treat wide-necked aneurysms. Followup was 6 to 24 months.
- 1 SR[75] of 14 single-arm studies (n=577) addressed SAC with Neuroform Atlas (Stryker Neurovascular, Fremont, CA). 593 intracranial aneurysms were analyzed. Multiple stents were used in 26% of patients. Mean age was 58.2 years; 36% were male. 489 patients were analyzed at a mean followup of 9.1 months.
- 1 SR[76] of 7 single-arm studies (n=557) addressed SAC with Enterprise (Codman Neurovascular, Raynham, MA) to treat intracranial atherosclerotic stenosis. Mean followup was 6.3 to 25.6 months.

SAC versus coiling:

- 1 SR[79] of 14 nonrandomized comparative studies addressed SAC (n=2698) versus coiling (n=29388). Neuroform (12 studies), Enterprise (8 studies), Solitaire (2 studies), Wingspan (Stryker Neurovascular, Kalamazooo, MI; 2 studies), and LEO (3 studies) were used for SAC. Mean followup was 9.7 to >36 months; mean age was ~56 years. 12 studies examined a combination of ≥2 stents.

Y stent assisted coiling (Y-SAC): 2 SRs[77,78] of 45 single-arm studies (n=1071) examined Y-SAC with 2 stent placement. Both SRs examined Acclino (Acandis, Pforzheim, Germany), Enterprise, and Neuroform Atlas stents. In addition, SRs examined LVIS stents (MicroVention, Tustin, CA), Solitaire stents (Covidien, Irvine, CA), Leo Baby stents (Balt Extrusion, Montmorency, France), and Solitaire stents (Medtronic, Irvine, CA). The most common Y-stent configurations in 1 SR were 116 Neuroform-Neuroform, 52 Neuroform-Enterprise, and 100 Enterprise-Enterprise.[78] Average patient age was 56 years. Studies enrolled mostly males in 1 SR,[77] and mostly females in the other SR.[78] Mean followup was ≤18 months.[77,78]

Self-expandable braided stents: 2 SRs[80,81] addressed self-expandable braided stents with Low-profile Visualized Intraluminal Support (LVIS; Microvention) and LEO (Balt Extrusion, Montmorency, France).

- 1 SR[80] of 35 single-arm studies (n=1426) examined LEO and LVIS stents to treat 1518 intracranial aneurysms. Mean radiologic and clinical followups were 10.4 months, and 12 months, respectively. Mean age was 54.5 years; 0.47 male/female ratio.
- 1 SR[81] of 9 single-arm studies (n=384) examined LVIS and LVIS Junior in 390 mostly wide-necked aneurysms. Mean angiographic followup was 5.6 months; mean age 55 years.

Local Responses/Device Events (human studies)

Device dislodgement and migration: Device dislodgement with distal migration into the parent artery with WEB was reported in 1 patient,[73] while stent dislodgement/migration occurred in 8 (1.4%) patients with Neuroform SAC.[75]

Device protrusion: 1 SR reported device protrusion into the parent vessel in 14 (3.7%) procedures with WEB.[73]

Hemorrhagic events:

WEB: 13 hemorrhagic events (2%, 95% CI: 0.8 to 3.3%) resulted in prolonged clinical deterioration or permanent neurologic deficits.[72]

SAC: 1.0% (95% CI: 0.02 to 1.8%) rate of 30-day hemorrhage with Neuroform,[75] and 3.1% (95% CI: 1.9 to 5.0%) rate of hemorrhagic stroke with Enterprise.[76]

Y-SAC: 2% (95% CI: 0.7 to 3%) rate of hemorrhagic events.[77]

Braided stents:

Hemorrhagic/hematoma events with LEO occurred in 1 patient (0.5%, 95% CI: 0.3 to 1.1%).[80]

The hemorrhagic event rate with LVIS/LVIS Junior was 2.1% (95% CI 0.7 to 3.5%), including 0.9% (95% CI 0 to 1.8%) experiencing neurologic hemorrhagic complications (i.e., intracranial hematomas) and 1.9% (95% CI 0.5 to 3.2%) experiencing non-neurologic hemorrhagic complications (i.e., groin hematomas).[81]

Intraprocedural complications (miscellaneous): Pooled incidence rate for intraprocedural complications (vasospasm, hematoma in the groin, and asymptomatic dissection of the stented segment) was 2.2% (95% CI: 1.2 to 4.0%) with Enterprise SAC.[76]

Ischemic/thromboembolic events

WEB:

1 SR reported 41 device-related thromboembolic events (6.8%, 95% CI: 4.6 to 9%) which resulted in prolonged clinical deterioration or permanent neurologic deficits.[72]

1 SR reported thromboembolic events in 17 procedures; 3 events during the hospital stay.[73]

SAC:

With Neuroform, ischemic complications <30 days in 2.9% (95% CI: 1.5 to 4.2%) and stent thrombosis in 1.1% (9/577; 95% CI: 0.03 to 2%).[75]

With Enterprise, ischemic stroke within 30 days in 4.5% (95% CI: 3.0 to 6.73%), and ischemic stroke or TIA in the territory of the qualifying artery beyond 30 days in 3.2% (95% CI: 1.1 to 9.5%).[76]

With PulseRider, 3 procedure-related posterior cerebral artery strokes, 3 thrombus formations, and 1 delayed device thrombosis.[74]

SAC versus coiling: No significant difference was reported for thrombotic complications (7 studies: 4.5% SAC, 4.1% coiling only; OR 1.18, 95% CI: 0.68 to 2.03).[79]

Y-SAC:

1 SR reported ischemic/thromboembolic events in 6.5% (95% CI: 3 to 7.6%), acute in-stent thrombosis in 2.1% (95% CI: 1.6 to 6%), and chronic in-stent stenosis in 2.3% (95% CI: 0.6 to 4%). Delayed complications (after 30 days) included 3 cases of in-stent occlusion, and 5 ischemic events. The complication rate for Enterprise stents (6.5%) was lower versus Neuroform stents (14%), and LVIS braided stents (11%).[77]

1 SR reported a procedure-related stroke rate of 12% (n=12; 95% CI: 4.3 to 15%). In-stent thrombosis at angiographic follow-up was observed in 8 patients (6%, 95% CI: 1.9 to 10%).[78]

Braided stents:

The most common complications with LVIS and LEO stents in 1 SR were ischemic/thromboembolic events in 48 patients (2.4%; 95% CI: 1.5 to 3.4%) and in-stent thrombosis in 35 patients (1.5%; 95% CI: 0.6% to 1.7%). Rates were higher with LEO vs. LVIS for both event types (3.6% versus 1.6% for ischemic/thromboembolic, and 3.2% versus 0.8% for in-stent thrombosis).[80]

The thromboembolic event rate with LVIS/LVIS Junior was 4.9% (95% CI 1.9 to 7.9%), with 2.4% (95% CI 0.9 to 3.9%) experiencing symptomatic thromboembolic events and 1.4% (95% CI 0.2 to 2.5%) experiencing in-stent thrombosis.[81]

Neurological deficit/disability: 1 SR reported permanent residual neurological deficit or disability in 2.7% (23/489; 95% CI: 0.08 to 4.5%) with Neuroform at mean 9.1 months followup.[75] Another SR reported a permanent neurological deficit rate with Y-SAC of 4% (95% CI: 0.2 to 4.5%).[78] As noted above with WEB treatment,[72] 13 hemorrhagic events and 41 device-related thromboembolic events led to prolonged clinical deterioration or permanent neurologic deficits.

Periprocedural morbidity:

Y-SAC: periprocedural treatment-related morbidity in 2.4% (95% CI: 1.2 to 3.7%).[77]

Braided stents: Higher rates of periprocedural/early events were reported vs. delayed events (5% vs. 1%) with complications occurring more frequently with LEO stents vs. LVIS stents (7% vs. 3.4% early events, 2.5% vs. 0.8% delayed events).[80]

Restenosis: The pooled incidence rate of in-stent restenosis (ISR) and symptomatic ISR beyond 30 days with Enterprise SAC was 10.1% (95% CI: 4.6 to 22.2%) and 4.9% (95% CI: 2.9 to 8.5%), respectively.[76]

All complications (SAC vs. coiling): No significant difference was reported for all-complications (7 studies: 12.2% SAC, 12.0% coiling only; OR 1.08, 95% CI: 0.79 to 1.47).[79]

Permanent complications (SAC vs. coiling): No significant difference was reported for permanent complications (4 studies: 4.1% SAC, 3.5% coiling only; OR 1.50, 95% CI: 0.97 to 2.34).[79]

Systemic Responses

Mortality:

- *WEB:* 12 patients undergoing WEB treatment died during the perioperative period resulting in a procedure-related mortality rate of 2.1% (0.8 to 3.3%).[72]
- *SAC:*
    - Overall mortality at mean 9.1 months followup was 1.8% (12/519; 95% CI: 0.07 to 2.9%) with Neuroform.[75]

Rate for mortality within 30 days of percutaneous transluminal angioplasty and stenting was 1.2% (95% CI: 0.5 to 2.6%) with Enterprise.[76] Death was always due to hemorrhagic stroke.

SAC vs. coiling: Significantly higher mortality with SAC (9 studies: 1.4% SAC, 0.2% coiling only; OR 2.16, 95% CI: 1.33 to 3.52), although this rate was mostly driven by 1 study with significantly larger-sized aneurysms in stented patients. Authors noted that mortality was higher in studies using Leo stents (11.1%) vs. Neuroform (3.0%) or Enterprise (5.3%).[79]

Y-SAC: SRs reported a procedure-related mortality rate of 2% (n=7; 95% CI: 0.6 to 3.8%),[78] and a periprocedural treatment-related mortality rate of 1.1% (95% CI: 0.3 to 1.9%).[77]

Braided stents: 1 SR reported comparable treatment-related mortality between LEO and LVIS stents (0.7% LEO, 0.8% LVIS).[80]

Overall Quality of Evidence

The evidence for hemorrhagic and ischemic/thromboembolic events was consistently reported across high quality studies, and in agreement with reporting with other nitinol categories (e.g., cardiovascular IVC filter), so the quality of evidence is moderate. For other local responses/events, the quality of evidence is low due to limited reporting in high quality studies. The evidence for systemic responses was rated low due to the low rates of mortality and unclear association with the device.

Ophthalmic

The literature search identified 3 human studies (2 RCTs[82,83] and 1 nonrandomized comparative study[84]). None of the included studies compared nitinol to non-nitinol devices. For further information see Table 19 in Appendix D.

Local Responses/Device Events (human studies)

Two RCTs both examined implantation of a single Hydrus Microstent (in combination with cataract surgery or as a stand-alone device) into the Schlemm canal versus cataract surgery alone.[82,83] Enrolled patients were generally older (mean age over 70 years for all study arms), and both studies followed patients for up to 2 years. The larger RCT with over 500 included patients examined 20 unique AEs.[82] The most common events included conjunctivitis, uveitis/iritis requiring steroids, and worsening of the visual field with a mean deviation of 2.5 decibels (dB). No reported AEs were statistically significant between groups, and all had low incidence rates. In addition, there were no reported serious ocular AEs related to the Microstent. The smaller RCT enrolled 50 patients per arm to either Microstent with cataract surgery or cataract surgery alone, reporting AE incidence at both 1 year and 2 years. No significant differences were seen at year 1, however, the Microstent and cataract surgery group displayed significantly higher rates of focal peripheral anterior synechiae (PAS) than cataract surgery alone. All other Aes reported three or less events per study arm at one-year and two-year time points.

The one nonrandomized comparative study also examined 31 patients receiving Hydrus Microstent and 25 patients receiving selective laser trabeculoplasty (SLT). The patients were generally older (mean age of 70.8 (SD 11.83) for Microstent and 69.0 (standard deviation [SD] 11.28) for SLT). No patients receiving SLT reported any Aes, while patients receiving Microstent reported 3 post-operative intraocular pressure (IOP) spikes and 2 cases of temporary reduction of visual activity. All post-operative IOP spikes were resolved within a week.

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

Two RCTs along with one nonrandomized comparative trial with large to moderate sizes of enrollees all examined local responses related to the Hydrus Microstent product against a relevant comparator. Only one AE reported within one RCT (focal PAS) had a significant difference against a comparator. All other Aes did not report statistically significant differences. No studies reported on systemic responses. Given the study designs, sample sizes, and consistency of local host response evidence, the quality of evidence for local responses is low. The quality of evidence for systemic responses is very low.

Orthopedic-Bone fixation

The literature search identified 3 human studies (1 SR,[85] 1 nonrandomized comparative study,[86] and 1 single-arm study[87]). One study[85] compared nitinol to non-nitinol devices. For further information see Table 20 in Appendix D.

The SR[85] included 9 studies (3 nonrandomized comparative, 6 single-arm) examining intramedullary devices for proximal inter-phalangeal (PIP) joint arthrodesis for hammertoe. Smart Toe (Stryker Osteosynthesis, Mahwah, NJ), a nitinol device, was the sole focus of 3 studies (107 toes); and compared with traditional K-wire in 3 studies (101 toes). Studies also examined devices with stainless steel (ProToe VO (63 toes), Ipp On (156 toes)), and titanium (StayFuse (188 toes)). Followup for studies examining Smart Toe was 6 to 40 months. Due to the limited information included in the SR, we sought additional details from the abstracts of the individual studies.

The nonrandomized comparative study[86] (n=96, 186 toes) examined intramedullary hammertoe fixation with Smart Toe in 94 toes, TenFuse bone allograft (Solana Surgical, Memphis, TN) in 27 toes, and K-wire in 65 toes. Patients were mostly females; mean age 62 years (range 20 to 81 years). Followup was 12 months, although K-wire was removed after 6 weeks.

The single-arm study[87] (n=31) examined an intramedullary nitinol cage and plate (Conventus Orthopedics; Maple Grove, MN) to treat proximal humeral fractures. The implant allows screw placement through the cage both from the outside and through the plate. Patients were mostly females; mean age 64 years. Followup was up to 27 months; mean followup was 91 weeks.

Local Responses/Device Events (human studies)

Avascular necrosis (AVN): 1 single-arm study reported symptomatic AVN in 4 (13%) patients implanted with a nitinol cage and plate to treat proximal humeral fractures.[87] AVN was discovered on radiographs obtained ≥1 year postoperatively in 3 patients. Radiographs of 1 patient showed no evidence of AVN at 7 months, development at 1 year and progression from 14 to 27 months before undergoing arthroplasty. Mild AVN was discovered 2 years postoperatively in 1 patient. Authors noted a higher-than-expected rate of AVN versus studies "using a similar fixation construct."

Hardware malfunction (breakage, failure, displaced fixation): 1 single-arm study reported that 1 (3%) patient underwent removal of a broken locking screw which had backed out of a nitinol cage.[87]

1 nonrandomized comparative study, focused on intramedullary hammertoe fixation, reported significantly higher breakage with Smart Toe vs. K-wire (10.6% Smart Toe, 0% K-wire; p=.007), while no significant difference was reported between Smart Toe and bone allograft (10.6% Smart Toe, 0% bone allograft; p=.079) Breakage occurred with Smart Toe prior to 12 months.[86]

1 single-arm study (n=35, 65 toes) in the SR,[85] reported hardware failure not requiring revisions/removal with Smart Toe in 2 (3%) patients up to 40 months. Another single-arm study (n=24, 42 toes) reported hardware failure with Smart Toe in 5% of patients up to 12 months.

2 single-arm studies (n=45, 95 toes) in the same SR,[85] reported that Smart Toe was associated with displaced fixation rates of 1.5% and 13% up to 40 months.

Fracture: 1 nonrandomized comparative study (n=86) in the SR,[85] reported higher (non-significant) rates of fracture with Smart Toe vs. K-wire (12/58 (20.7%) vs. 2/28 (7.1%)) up to ~38 months.

Transient axillary neuritis: 1 single-arm study reported transient axillary neuritis in 2 (6.4%) patients using a nitinol cage. Followup was up to 27 months.[87]

Adhesions/scar tissue in the interphalangeal joint (IPJ): 1 nonrandomized comparative study reported no significant differences for adhesions/scar tissue in the IPJ between nitinol and non-nitinol fixation (2.1% Smart Toe, 9.2% K-wire, 0% bone allograft).[86]

Wound complications: No significant differences were reported for wound complications (e.g., dehiscence, infection) at 12 months followup for nitinol vs. non-nitinol hammertoe fixation (7.4% with Smart Toe and bone allograft, 4.6% with K-wire).[86]

Deformities: 1 single-arm study (n=10, 30 toes) in the SR, reported that Smart Toe was associated with a 23% rate of secondary contracture of the distal IPJ (mallet toe), while another study reported this deformity in 2% of patients after 1 year with a non-nitinol fixation device. In addition, 1 single-arm study (n=24, 42 toes) in this SR, reported minor digital rotational deformity with Smart Toe in 1 toe at 12 months followup.[85]

Malunion and non union: 1 single-arm study (n=10, 30 toes) in the SR, reported that Smart Toe was associated with a malunion rate of 7%, while another single-arm study (63 toes) in the SR reported a malunion rate of 2.4% with a non-nitinol fixation device.[85]

Rates for asymptomatic non union with Smart Toe reported in the SR were 1.5% and 6.7% up to 40 months.[85]

Systemic Responses

No studies reported whether any systemic responses occurred.

Overall Quality of Evidence

The evidence for hardware malfunction (breakage, failure, displaced fixation) was in agreement with other device categories (e.g., neurovascular, cardiovascular IVC filters) but the evidence base was limited to 3 studies, so the quality of evidence is low. The quality of evidence is very low for other local responses/events and systemic responses (no studies investigating).

Reproductive

The literature search identified 1 human study (1 single arm study[88]). The study did not compare nitinol to non-nitinol devices. For further information see Table 21 in Appendix D.

1 single arm study (n=286) examined use of a nitinol and copper intrauterine device (VeraCept, Sebela Pharmaceuticals, Roswell, GA). Safety was examined up to 3 years; data on 283 patients at 12 months. Mean age was 27.1 years (range 18 to 40 years). 19 patients required a second attempt at placement.

Local Responses/Device Events (human studies)

3 serious events occurring in 1 (0.3%) patient each and noted as "unlikely related to treatment" included ectopic pregnancy in year 3, hemorrhagic cyst, and pelvic inflammatory disease at day 119. Expulsion (device moving part way into the vagina or all the way out of the body) occurred in 5 (1.8%) patients. 3 expulsions occurred in year 1, while 2 expulsions occurred year 1 to year 3.

The following local responses occurred in 6% to 10% of patients: vaginal discharge in 18 (6.4%), dyspareunia and postprocedural hemorrhage in 21 (7.4%) each, lower abdominal pain in 23 (8.1%), vulvovaginal mycotic infection in 25 (8.8%), and uterine spasm in 26 (9.2%).

The following local responses occurred in 11% to 25% of patients: urinary tract infection in 31 (11%), bacterial vaginosis in 32 (11.3%), back pain in 33 (11.7%), metrorrhagia and pelvic pain in 39 (13.8%) each, and abdominal pain in 44 (15.5%). Pelvic pain occurred in 5 (1.8%) patients in year 2.

Lastly, dysmenorrhea (142 (50.2%)), menorrhagia (73 (25.8%)) and procedural pain (105 (37.1%)) occurred in more than 25% of patients. Dysmenorrhea occurred in 8 (2.8%) patients in year 2. Authors noted that 48 (17%) patients discontinued the trial due to AEs.

Systemic Responses

Nausea was reported in 15 (5.3%) patients, while headache (37) and upper respiratory infection (38) were reported in 13% of patients. Nasopharyngitis was reported in 61 (21.6%) patients up to 12 months.

Overall Quality of Evidence

The quality of evidence was rated low for dysmenorrhea, menorrhagia, and procedural pain due to the occurrence in more than 25% of patients in 1 uncontrolled study. For other local responses and systemic responses, we rated the quality of evidence as very low due to less frequent occurrence in 1 uncontrolled study.

Urinary

The literature search identified 5 human studies (1 SR,[89] 1 RCT,[90] 3 SASs[91-93]). None of the included studies compared nitinol to non-nitinol devices. For further information see Table 22 in Appendix D.

Local Responses/Device Events (human studies)

Encrustation**:** A systematic review on ureteral stents by Corrales et al.[89] reported an encrustation rate of 6% in 186 patients from 5 studies. One single-arm study on urethral stents by Barbagli et al.[92] found one patient (6%) experienced obliterative encrustation and four patients (25%) showed small calcifications. A second single-arm study[93] on urethral stents reported a 13% encrustation rate.

Fistulas: Corrales et al.[89] reported 28% of patients developed a Clavien-Dindo class IIIb: fistula.

Hematuria: Corrales et al.[89] reported hematuria in 25% of ureteral stent patients. One RCT[90] and one single-arm study[93] reported hematuria rates of 13.6% and 13% in urethral stent patients, while another study[92] reported there were no cases of hematuria.

Infections: The systematic review,[89] one RCT,[90] and one single-arm study[93] reported rates of urinary tract infections ranging from 1.7% to 17%. The systematic review[89] also reported a fungal infection rate of 6%. One single-arm study[92] reported 31% of patients had an infection, but did not describe the type of infection.

Migration: The systematic review[89] reported migration in 9% of ureteral patients, and one single-arm study[92] reported migration in 6% of urethral patients.

Obstruction: The systematic review[89] reported obstruction in 17% of ureteral patients, but state the obstruction was mostly due to tumor progression that led to stent blockage.

Pain: The RCT[90] reported dysuria in 22.9% of urethral stent patients and pain in 0.8%. On single-arm study[93] reported 26% of urethral stent patients had transient pain that resolved in a few weeks. Another single-arm study[92] reported the urethral stent was removed because of pain in 5 patients (31%) 4 to 9 months after implantation. The systematic review[89] stated three of the included studies reported lower abdominal pain but did not reported a rate.

Sexual performance: Two studies[90,91] on a temporary urethral stent found no deterioration in erectile or ejaculatory function.

Urinary control: The RCT[90] reported 5.1% of patients experienced micturition urgency, 6.8% experienced pollakiuria, and 5.9% experienced urinary retention. A single-arm study[92] reported no cases of urinary incontinence occurred.

Urethral hyperplasia: One single-arm study[93] reported urethral hyperplasia in 8% of patients.

Systemic Responses

Sepsis: The RCT[90] reported 0.8% of patients experienced sepsis.

Overall Quality of Evidence

The number of patients included in any study was of low to moderate size, and there was some inconsistency in the reported responses. Therefore, the quality of evidence was rated low for both local and systemic responses.

ECRI Surveillance Data

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

Patient Safety Organization

Search Results: Across 26 different medical device types, ECRI PSO identified 145 reported complications that involved Nitinol materials that occurred between February 2007 and October 2021. Thirty-four of these reports indicated patient harm with 25 of those reports classified within the mildest harm category I.

The top 5 complications included: 1) Device Malfunction – 47 (32.4%), 2) Hemorrhage/Hematoma – 25 (17.2%), 3) Pericardial effusion – 24 (16.6%), 4) Iatrogenic injury – 13 (9%), 5) Device migration 11 (7.6%).

Forty-one reports (28%) involved left atrial appendage closure devices. Seventeen of these reports involved pericardial effusions, 7 of which caused patient harm (3 mild, 3 moderate, and one severe). Fifteen of these reports involved hemorrhage/hematoma, 7 of which caused patient harm (7 mild and one severe).

Fifteen reports (10%) involved leadless pacemakers. The most common event was pericardial effusion (5) leading to two reports of mild harm. Both instances or severe harm and death resulted from iatrogenic injury.

Thirteen reports (9%) involved mitral valve repair devise. Six of these reports involved device malfunction with one event leading to moderate harm. Four reports involved hemorrhage/hematoma of which three caused moderate harm. There was one report of severe harm involving pericardial effusion.

Tables 3 and 4 illustrate the Nitinol-related complications and harm scores, respectively.

All individual PSO event reports are redacted and included in Appendix F.

Table 3: Complications in Nitinol-related PSO Event Reports

Complication	Aortic valve, prosthesis, percutaneously delivered	Appliance, Fixation, Spinal Intervertebral Body	Device, hemostasis, vascular	Device, Vascular, For Promoting Embolization	Filter, Intravascular, Cardiovascular	Heart-Valve, Non-Allograft Tissue	Hemostatic Metal Clip For The Gi Tract	Intracranial Coil-Assist Stent	Intracranial Neurovascular Stent	Leadless Pacemaker	Marker, Radiographic, Implantable	Mitral Valve Repair Devices	Pancreatic Stent, Covered, Metallic, Removable	Pin, Fixation, Smooth	Prosthesis, Esophageal	Prosthesis, Tracheal, Expandable	Right Ventricular Bypass (Assist) Device	Sensor, Pressure, Aneurysm, Implantable	Stent, Colonic, Metallic, Expandable	STENT, ILIAC	Stent, iliac vein	STENT, SUPERFICIAL FEMORAL ARTERY	Stents, Drains And Dilators For The Biliary Ducts	System, appendage closure, left atrial	System, Endovascular Graft, Aortic Aneurysm Treatment	System, Endovascular Graft, Arteriovenous (Av) Dialysis Access Circuit Stenosis Treatment	Transcatheter Septal Occluder	Total
Device Malfuntion	1	1	7	1	5		2	1	1	1	5	6	3			4	1	1	1	1		1	1	2			1	47
Hemorrhage/Hematoma										2		4			1	1							1	15	1			25
Pericardial effusion										5		1												17			1	24
Iatrogenic injury						1	1			2	1		2		2				3					1				13
Device Migration										1			3		1			1	2					2			1	11
Clinical Manifestations										2		2			1								1	2				8
Device expired		1												1	1						1	1				1		6
Device Fracture		1																				2						3
Infection		1									1													1				3
Pseudoaneurysm					1					1																		2
Retained Foreign Object										1																		1
Retroperitoneal bleed																								1				1
Paralysis																	1											1
Total	**1**	**4**	**7**	**1**	**6**	**1**	**3**	**1**	**1**	**15**	**7**	**13**	**8**	**1**	**6**	**5**	**2**	**2**	**6**	**1**	**1**	**4**	**3**	**41**	**1**	**1**	**3**	**145**

Table 4: Harm Scores Associated with Nitinol-related Event Reports

Harm Scores (NCC-MERP)		Aortic valve, prosthesis, percutaneous	Appliance, Fixation, Spinal	Device, hemostasis, vascular	Device, Vascular, Embolization Promotion	Filter, Intravascular, Cardiovascular	Heart-Valve, Non-Allograft Tissue	Hemostatic Metal Clip For The Gi Tract	Intracranial Coil-Assist Stent	Intracranial Neurovascular Stent	Leadless Pacemaker	Marker, Radiographic, Implantable	Mitral Valve Repair Devices	Pancreatic Stent, Covered, Metallic	Pin, Fixation, Smooth	Prosthesis, Esophageal	Prosthesis, Tracheal, Expandable	Right Ventricular Bypass (Assist) Device	Sensor, Pressure, Aneurysm, Implantable	Stent, Colonic, Metallic, Expandable	STENT, ILIAC	Stent, iliac vein	STENT, SUPERFICIAL FEMORAL ARTERY	Stents, Drains. Dilators For Biliary Ducts	System, appendage closure, left atrial	System, Endovascular Graft, AA	System, Endovascular Graft, (Av) Dialysis Access Circuit Stenosis	Transcatheter Septal Occluder	**Total**
A	No Error		1					1			2		3			1				1					7			1	17
B 1	Error, No Harm																												0
B 2											2		1							1									4
C		1	1	4	1	4	1	2		1	1	3										1		1	6			1	28
D				2							3	1	1	2		1		1	1				1	1	11				25
E	Error Harm										2		3	1	1	1	2	1		1			1		10	1	1		25
F													1			2			1		1				2				7
G																													0
H											1		1																2
I	Error Death										1																		1
NULL			2	1		2			1		3	3	3	5		1	3			3			2	1	5			1	36
Total		**1**	**4**	**7**	**1**	**6**	**1**	**3**	**1**	**1**	**15**	**7**	**13**	**8**	**1**	**6**	**5**	**2**	**2**	**6**	**1**	**1**	**4**	**3**	**41**	**1**	**1**	**3**	**145**

Accident Investigations

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

ECRI Problem Reports

Search Results: The search returned 14 reports submitted by ECRI members and are summarized in Table 5.

Key Issues: The reports detail devices that would not deploy, deployed inadvertantly, would not pass through the delivery systems, could not be used, broke off, and migrated.

Safety Concerns: The reports detail procedures that could not be completeled, additional procedures or devices were necessary, bleeding, crushing chest pain, plueral effusion and myocardial perforation or erosion following device placement, device breaking off and getting stuck in the mid-cerebral artery, and migration of a device into the patients lungs.

All problem reports are redacted and included in Appendix F.

Table 5: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem
Hemostatic Metal Clip For The Gi Tract (PKL)	8	6 reports of the clip not positioned correctly and had to be pulled off tissue causing bleeding. 1 report that the clips would not open, so another model clip had to be used to complete the procedure. 1 report of the clip not deploying, which extended the surgical time and caused bleeding
Prosthesis, Tracheal, Expandable (JCT)	1	1 report that the stent was unable to be opened but the metallic tip travelled to the lung causing patient injury.
Device, Vascular, For Promoting Embolization (KRD)	4	1 report the device would not deploy 1 report that 8 coils were opened but only 4 were usable. They had micro catheter fractures, the headpiece stopped working, or the coil would not deploy 1 report of day 1 after t36utoimmder was placed the patient had chest pain, pleural effusion, and myocardial perforation 1 report of day 1 after th36utoimmder was placed the patient had chest pain, pleural effusion, and myocardial erosion
Catheter, thrombus retriever (NRY)	1	1 report of the solitaire breaking off and getting stuck in the MCA

Healthcare Technology Alerts

Search Results: The search returned 127 manufacturers issued and 6 regulatory body issued alerts describing problems with Nitinol-related devices, summarized in Table 6.

Table 6: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
DSY (Prosthesis, Vascular Graft of 6mm and Greater Diameter)	2 manufacturer issued	• FDA Consent Decree to enhance QMS • Packaging
DTK (Filter, Intravascular, Cardiovascular)	3 manufacturer issued 1 regulatory issued	• Serious complications associated with IVC filters (Health Canada)Incorrect orientation results in serious injury • Upside down implantation as a result of printing error • Mislabeling
ESW (Prosthesis, Esophageal)	2 manufacturer issued	• Migration requiring intervention • Misprinted IFU
FGE (Stents, Drains and Dilators for the Biliary Ducts)	5 manufacturer issued	• Mislabeling • Incorrect IFU • Device malfunction • Partial deployment
FGE (Stents, Drains and Dilators for the Biliary Ducts); NIP (Stents, Drains and Dilators for the Biliary Ducts)	1 manufacturer issued	• Mislabeling
FZP (Clip, Implantable)	1 manufacturer issued	• Deployment difficulty
HCG (Device, Neurovascular Embolization)	1 manufacturer issued	• Premature detachment as a result of component not to specification
HRS (Plate, Fixation, Bone)	2 manufacturer issued	• Mislabeling • Incorrectly sized components
JCT (Prosthesis, Tracheal, Expandable)	1 manufacturer issued	• Mislabeling
JDR (Staple, Fixation, Bone)	2 manufacturer issued	• Nickel amount released above acceptable margin • Missing components
KRD (Device, Vascular, For Promoting Embolization)	3 manufacturer issued	• Thrombus formation after implantation • Mislabeling • Missing implant coil
KWQ (Appliance, Fixation, Spinal Intervertebral Body)	1 manufacturer issued	• Locking mechanism fracture leads to screw migration
LWR (Heart-Valve, Non-Allograft Tissue)	5 manufacturer issued	• Component misalignment • Valve insufficiency due to oversized components • Training on implantation instructions required after leakage • Bacterial contamination may result in infectious endocarditis • Depth marking ring may detach
MAE (Occluder, Patent Ductus, Arteriosus)	2 manufacturer issued	• Tip detachment during prep • Small particles may detach due to mechanical stress
MAF (Stent, Coronary	1 manufacturer issued	• Deployment difficulty

Device Type	# Alerts	Reported Problem
MIH (System, Endovascular Graft, Aortic Aneurysm Treatment)	24 manufacturer issued	• Manufacturing error: incorrect lubricant; incorrect assembly • Packaging issue • Compromised sterility • Susceptible to endoleak • Component separation • Component fracture (may lead to endoleak) • Remaining at intermediate diameter after deployment; did not expand after deployment • Difficulty withdrawing • Mislabeling • Incomplete, partial, or difficult deployment • Difficulty flushing during prep • Manufacturer emphasizes the importance of IFU in preventing thrombus formation or lumen occlusion • Updated IFU • Intraoperative leak
MLV (Transcatheter Septal Occluder)	1 manufacturer issued	• Occluders may rub against heart wall causing tissue erosion
MOM (System, Hemodynamic, Implantable)	1 manufacturer issued	• Coating scratched off
MQR (Stent, Colonic, Metallic, Expandable)	1 manufacturer issued	• Mislabeling
NEU (Marker, Radiographic, Implantable)	1 manufacturer issued	• Compromised sterility
NGV (System, Appendage Closure, Left Atrial)	2 manufacturer issued	• Implant embolization • Cross-threaded valve
NIM (Stent, Carotid)	3 manufacturer issued	• Nose cone separation • Distal tip separation from wire lumen • Partial deployment
NIP (Stents, Drains and Dilators for the Biliary Ducts)	19 manufacturer issued	• Partial or difficulty during deployment • Difficulty releasing • Mislabeling • Cracked luer hub causing leakage • Compromised sterility • Does not conform to specifications • Tip pulled off during use • Distal tip separation due to inadequate adhesive
NJE (Intracranial Neurovascular Stent)	4 manufacturer issued 1 regulatory issued	• Increased risk of stroke or death (FDA) • Incomplete sterility validation • Radial pressure below specification • Coating damage to sheath • Updated IFU

Device Type	# Alerts	Reported Problem
NKM (Mitral Valve Repair Devices)	5 manufacturer issued	• Clip may unexpectedly open • Mandrel fracture causes detachment issues • Incorrectly turned actuator knob during deployment • Unmovable gripper line may result in thrombus formation • Ring detachment may require surgical intervention to retrieve
NPT (Aortic, Valve, Prosthesis, Percutaneously Delivered)	10 manufacturer issued	• Leaflet damage resulting in aortic insufficiency • Nose cone separation • Valve not released during deployment • Removal unused product from field • Pin release before final locking • Valve could not be fully locked • Release mandrel break • Damage during prep • Mislabeling • Updated IFU
OAZ (One-Way Air-Leak Valve)	1 manufacturer issued	• Mislabeling
OJE (Right Ventricular Bypass [Assist] Device)	2 regulatory issued	• FDA EUA for the treatment of acute right heart failure • Implantation associated with higher rate of mortality than premarket studies (FDA)
OZD (Temporary Non-Roller Type Left Heart Support Blood Pump)	2 manufacturer issued 1 regulatory issued	• Incorrect programming may lead to migration (FDA) • Mislabeling • Interaction between motor housing and transcatheter aortic valves may damage impellar blades)
PCU (Pancreatic Stent, Covered, Metallic, Removable)	1 manufacturer issued	• Luer on delivery system may detach
PKL (Hemostatic Metal Clip for the GI Tract)	2 manufacturer issued	• Incorrect assembly causes difficulty in releasing clip • Esophageal laceration
PNK (Leadless Pacemaker)	1 manufacturer issued	• Updated IFU
QAN (Stent, Iliac Vein)	4 manufacturer issued 1 regulatory issued	• Migration • Updated IFU (MHRA) • Inner catheter fracture • Tip separation
QCA (Intracranial Coil-Assist Stent)	1 manufacturer issued	• Mislabeling
QCA (Scaffold, Dissection Repair)	1 manufacturer issued	• Distal catheter tip cracked
Cardiovascular (No FDA Clearance, OUS only)	12 manufacturer issued	• Failure or difficult to deploy • Updated IFU • Release wire fracture after deployment • Tip cracking before or during implantation • Additional procedure may be required to remove delivery system • Undersizing may lead to paravalvular damage

Device Type	# Alerts	Reported Problem
		• Mislabeling • Failure to release • Packaging

Potential Gaps

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

No included studies investigated whether there are material-related factors that may affect a sustained immunological/systemic response.

Regarding local responses, there are a significant evidence gap for a number of applications including cosmetic purposes, ENT, lung, orthopedic and reproductive.

There is also a significant need for further research on systemic responses, including those on patient or material factors, for most applications, vascular grafts/stents and heart repair being notable exceptions.

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

Inclusion Criteria

1. English language publication
2. Published between January 2010 and August 2021
3. Human studies (animal studies that provide unique information will also be considered for inclusion)
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of Nitinol or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2010
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

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

Appendix B. Search Summary

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

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

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

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

Literature Search for Nitinol

Set Number	Concept	Search Statement
1.	**Nitinol**	'nitinol'/exp OR nitinol* OR 'titanium nickelide*' OR (nickel NEAR/2 titanium) OR 'niti':ti,ab OR 'ni-ti':ti,ab
2.		'shape memory' AND 'nickel'/exp AND 'titanium'/exp
3.	Nitinol devices	'absolute pro':ab,dn,ti OR 'absolute 035 peripheral self expanding stent':ab,dn,ti OR 'absolute stent*':ab,dn,ti OR 'acta vos':ab,dn,ti OR 'acta vessel occlusion':ab,dn,ti OR 'active anterior cervical':ab,dn,ti OR 'activortho':ab,dn,ti OR 'aero dv':ab,dn,ti OR 'aero tracheobronchial stent*':ab,dn,ti OR 'aeromini':ab,dn,ti OR 'agile stent*':ab,dn,ti OR 'agile esophageal stent*':ab,dn,ti OR 'alimaxx*':ab,dn,ti OR 'alveolus tb-sts':ab,dn,ti OR 'alveolus tracheobronchial stent*':ab,dn,ti OR 'amplatzer cardiac plug*':ab,dn,ti OR 'amplatzer vascular plug*':ab,dn,ti OR 'amplatzer duct occluder*':ab,dn,ti OR 'amplatzer muscular vsd occluder*':ab,dn,ti OR 'amplatzer occluder*':ab,dn,ti OR 'amplatzer pfo occluder*':ab,dn,ti OR 'amplatzer piccolo occluder*':ab,dn,ti OR 'amplatzer septal occluder*':ab,dn,ti OR 'amsel occluder*':ab,dn,ti OR 'amsel endo occluder*':ab,dn,ti OR 'aneurx*':ab,dn,ti OR 'angel catheter*':ab,dn,ti OR 'anson refix':ab,dn,ti OR 'aorfix*':ab,dn,ti OR 'archsinus':ab,dn,ti OR 'artventive eos':ab,dn,ti OR 'artventive endoluminal occlusion':ab,dn,ti OR 'astron stent*':ab,dn,ti OR 'astron pulsar':ab,dn,ti OR 'aurora stent*':ab,dn,ti OR 'ave bridge':ab,dn,ti OR 'bridge se':ab,dn,ti OR 'axios

Literature Search for Nitinol		
Set Number	**Concept**	**Search Statement**
		stent*':ab,dn,ti OR 'cold axios':ab,dn,ti OR 'hot axios':ab,dn,ti OR 'azur vascular plug*':ab,dn,ti OR 'biomimics 3d':ab,dn,ti OR 'bonastent*':ab,dn,ti OR 'cardioform':ab,dn,ti OR 'cardiomems':ab,dn,ti OR 'endosure':ab,dn,ti OR ('cd horizon':ab,dn,ti AND staple*:ab,dn,ti) OR 'choostent':ab,dn,ti OR 'cinch anchor*':ab,dn,ti OR 'cinch wrc anchor*':ab,dn,ti OR 'cinch bone anchor*':ab,dn,ti OR 'complete se':ab,dn,ti OR 'conformexx':ab,dn,ti OR 'conventus drs':ab,dn,ti OR 'distal radius system':ab,dn,ti OR 'conventus phs':ab,dn,ti OR 'proximal humerus system':ab,dn,ti OR 'conventus prs':ab,dn,ti OR 'proximal radial system':ab,dn,ti OR 'cordis enterprise':ab,dn,ti OR 'enterprise stent':ab,dn,ti OR 'enterprise vascular reconstruction device':ab,dn,ti OR 'cordis smart':ab,dn,ti OR 'smart control':ab,dn,ti OR 'smart control stent*':ab,dn,ti OR 'smart stent*':ab,dn,ti OR ('s.m.a.r.t.':ab,dn,ti AND 'stent*':ab,dn,ti) OR 'corevalve':ab,dn,ti OR 'covera':ab,dn,ti OR 'covera plus':ab,dn,ti OR 'crossclip*':ab,dn,ti OR 'crux vcf':ab,dn,ti OR 'crux vena cava':ab,dn,ti OR ((denali NEAR/3 filter*):ab,dn,ti) OR 'dynabridge':ab,dn,ti OR 'dynalink':ab,dn,ti OR 'dynamx':ab,dn,ti OR 'dynanail*':ab,dn,ti OR 'dynanite':ab,dn,ti OR 'easyclip':ab,dn,ti OR 'easystep':ab,dn,ti OR 'eclipse filter*':ab,dn,ti OR 'e-luminexx':ab,dn,ti OR 'eluminexx':ab,dn,ti OR 'endomaxx':ab,dn,ti OR 'endurant':ab,dn,ti OR (enroute:ab,dn,ti AND stent*:ab,dn,ti) OR 'epic vascular stent*':ab,dn,ti OR 'epic stent*':ab,dn,ti OR 'esophageal tts':ab,dn,ti OR 'everflex':ab,dn,ti OR 'evolution stent*':ab,dn,ti OR 'evolution esophageal':ab,dn,ti OR 'evolution biliary':ab,dn,ti OR 'evolution colonic':ab,dn,ti OR 'evolution duodenal':ab,dn,ti OR 'flexigrip':ab,dn,ti OR 'flexi-grip':ab,dn,ti OR 'flow redirection intraluminal device':ab,dn,ti OR 'fred system':ab,dn,ti OR 'fluency stent*':ab,dn,ti OR 'fluency plus':ab,dn,ti OR 'bard fluency':ab,dn,ti OR 'fuseforce':ab,dn,ti OR 'g2 express filter*':ab,dn,ti OR 'g2 filter*':ab,dn,ti OR 'recovery g2 filter*':ab,dn,ti OR 'bard g2':ab,dn,ti OR 'g-cath':ab,dn,ti OR 'gore excluder':ab,dn,ti OR 'gore hybrid':ab,dn,ti OR 'gore tag':ab,dn,ti OR 'viabahn':ab,dn,ti OR 'viabil':ab,dn,ti OR 'viatorr':ab,dn,ti OR 'hammerlock':ab,dn,ti OR 'hanarostent*':ab,dn,ti OR 'hanaro stent*':ab,dn,ti OR 'hero graft':ab,dn,ti OR ('hydrus':ab,dn,ti AND ('microstent*':ab,dn,ti OR 'micro stent*':ab,dn,ti)) OR 'ibv valve*':ab,dn,ti OR 'superscaffold*':ab,dn,ti OR 'impede embolization plug':ab,dn,ti OR 'impella rp catheter':ab,dn,ti OR 'neospan':ab,dn,ti OR 'incraft':ab,dn,ti OR ('innova':ab,dn,ti AND 'stent*':ab,dn,ti) OR 'instafix':ab,dn,ti OR 'esophacoil':ab,dn,ti OR 'instinct clip':ab,dn,ti OR 'instinct endoscopic':ab,dn,ti OR 'intracoil':ab,dn,ti OR 'lifestent':ab,dn,ti OR 'lifestar':ab,dn,ti OR 'lotus edge':ab,dn,ti OR 'luminexx':ab,dn,ti OR 'luna xd':ab,dn,ti OR 'luna 3d gen2':ab,dn,ti OR 'lvis':ab,dn,ti OR 'lvis jr':ab,dn,ti OR 'low-profile visualized intraluminal support':ab,dn,ti OR 'memo staple*':ab,dn,ti OR 'memory staple*':ab,dn,ti OR 'memotherm':ab,dn,ti OR (('meridian' NEAR/4 'filter*'):ab,dn,ti) OR 'bard meridian':ab,dn,ti OR 'flexfix':ab,dn,ti OR ('micra':ab,dn,ti AND ('pacing':ab,dn,ti OR 'pacemaker*':ab,dn,ti OR 'transcatheter':ab,dn,ti)) OR ('micro-tech':ab,dn,ti AND 'stent*':ab,dn,ti) OR ('misago':ab,dn,ti AND 'stent*':ab,dn,ti) OR 'mitek gii':ab,dn,ti OR 'gii anchor*':ab,dn,ti OR 'mitek g2':ab,dn,ti OR 'g2 anchor*':ab,dn,ti OR 'mitek micro anchor*':ab,dn,ti OR 'mitek knotless anchor*':ab,dn,ti OR 'mitraclip':ab,dn,ti OR 'motoclip':ab,dn,ti
4.		'neotract':ab,dn,ti OR 'neuguide':ab,dn,ti OR 'neuroform':ab,dn,ti OR 'nexstent*':ab,dn,ti OR 'nitiflex':ab,dn,ti OR 'nitibond':ab,dn,ti OR 'niti-s':ab,dn,ti OR 'nit-occlud':ab,dn,ti OR 'novalign':ab,dn,ti OR 'optease':ab,dn,ti OR 'option elite':ab,dn,ti OR 'option filter*':ab,dn,ti OR 'option vena cava filter*':ab,dn,ti OR 'osstaple*':ab,dn,ti OR 'padlock clip':ab,dn,ti OR 'penumbra coil':ab,dn,ti OR 'penumbra smart coil':ab,dn,ti OR 'perceval':ab,dn,ti OR 'physio flex':ab,dn,ti OR 'piton anchor*':ab,dn,ti OR 'pod coil':ab,dn,ti OR 'pod system':ab,dn,ti OR 'precise rx':ab,dn,ti OR 'precise stent*':ab,dn,ti OR 'precise pro':ab,dn,ti OR

Literature Search for Nitinol		
Set Number	**Concept**	**Search Statement**
		'cordis precise':ab,dn,ti OR 'protege everflex':ab,dn,ti OR 'protege rx':ab,dn,ti OR 'protege gps':ab,dn,ti OR 'protege stent*':ab,dn,ti OR 'pro-toe':ab,dn,ti OR 'pulserider':ab,dn,ti OR 'rebound mesh':ab,dn,ti OR 'rebound hrd':ab,dn,ti OR 'bolton relay':ab,dn,ti OR ('stent*':ab,dn,ti AND ('relay':ab,dn,ti OR 'relay plus':ab,dn,ti OR 'relay pro':ab,dn,ti OR 'relaypro':ab,dn,ti)) OR 'micro vascular plug':ab,dn,ti OR 'smileloc':ab,dn,ti OR 'safeflo':ab,dn,ti OR 'savi scout':ab,dn,ti OR 'scout reflector*':ab,dn,ti OR 'scimed radius':ab,dn,ti OR 'radius stent*':ab,dn,ti OR 'securacath':ab,dn,ti OR 'sentinol':ab,dn,ti OR 'sentry filter*':ab,dn,ti OR 'sentry ivc':ab,dn,ti OR 'simon filter*':ab,dn,ti OR 'smart piston':ab,dn,ti OR 'smart stapes':ab,dn,ti OR 'smart toe':ab,dn,ti OR 'x-fuse':ab,dn,ti OR 'memometal':ab,dn,ti OR 'starclose':ab,dn,ti OR 'star close':ab,dn,ti OR ('supera':ab,dn,ti AND stent*:ab,dn,ti) OR 'symmetry aortic connector':ab,dn,ti OR (('symphony' NEAR/3 'stent*'):ab,dn,ti) OR 't2 altitude':ab,dn,ti OR 't2 xvbr':ab,dn,ti OR 'tack endovascular':ab,dn,ti OR 'tack implant*':ab,dn,ti OR (('thermoexpandable' OR 'thermo-expandable') NEAR/3 stent*) OR 'treo':ab,dn,ti OR 'tumark':ab,dn,ti OR 'uclip*':ab,dn,ti OR 'u-clip*':ab,dn,ti OR 'ultracor':ab,dn,ti OR 'ultraflex':ab,dn,ti OR 'valiant navion':ab,dn,ti OR 'valiant captivia':ab,dn,ti OR 'valiant stent*':ab,dn,ti OR 'venovo venous stent*':ab,dn,ti OR 'venovo stent*':ab,dn,ti OR 'vici venous stent*':ab,dn,ti OR 'vici stent*':ab,dn,ti OR 'vici rds':ab,dn,ti OR 'vici sds':ab,dn,ti OR 'wallflex':ab,dn,ti OR (('left atrial appendage closure':ab,dn,ti OR 'laa':ab,dn,ti) AND 'watchman':ab,dn,ti) OR 'web implant*':ab,dn,ti OR 'web device*':ab,dn,ti OR 'woven endobridge':ab,dn,ti OR 'web aneurysm embolization':ab,dn,ti OR 'wingspan stent*':ab,dn,ti OR 'wingspan implant':ab,dn,ti OR 'wingspan device':ab,dn,ti OR 'xact':ab,dn,ti OR 'xceed biliary stent*':ab,dn,ti OR 'zenith alpha':ab,dn,ti OR 'zenith dissection':ab,dn,ti OR 'zenith tx2':ab,dn,ti OR 'zilver':ab,dn,ti
5.	**Combine sets**	**#1 OR #2 OR #3 OR #4**
6.	Limit by language and publication date	#5 AND [english]/lim AND [2011–2021]/py
7.	Limit by publication type	#6 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)
Material Response		
8.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
9.		'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
10.		Leachable* OR extractable*
11.		(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 (fixation OR implant* OR prosth*

Literature Search for Nitinol		
Set Number	**Concept**	**Search Statement**
		OR stent* OR mesh OR patch OR plug? OR splint? OR device? OR mesh OR clip* OR staple? OR spring? OR plate OR plating OR retainer? OR screw? OR pin? OR rod? OR lock? OR ring?)
12.		'mechanics'/exp [see Emtree explosions section at the end of the strategy]
13.		'device material'/exp/mj
14.		'Biomedical and dental materials'/exp/mj
15.	**Combine sets**	**#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14**
Host Response		
16.		Host NEAR/2 (reaction* OR response*)
17.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
18.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj OR 'nickel hypersensitivity'/exp OR 'sensitization'/exp OR 'skin irritation'/exp OR 'pruritus'/exp OR 'edema'/exp OR 'erythema'/exp OR 'ion release' OR 'cerebritis'
19.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
20.		'inflammation'/exp OR inflamm*:ti,ab
21.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
22.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab
23.		protrude* OR protrus* OR perforat*
24.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'thrombus'/de OR 'thrombosis'/de OR 'seroma*':ti OR 'hematoma*':ti OR 'thrombosis':ti OR 'thrombus':ti
25.		'corrosion'/exp OR (corros* OR corrod* OR fretting OR 'metal debris' OR 'metal ions'):ti,ab OR wear:ti
26.	**Combine sets**	**#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**
27.	**Nitinol + Material**	#7 AND #15 AND #26

Literature Search for Nitinol		
Set Number	**Concept**	**Search Statement**
	Response + Host Response	
28.	**Nitinol material + Host response**	(#1 OR #2) AND #7 AND #26
29.	**Combine sets**	#27 OR #28
30.	**Nitinol systematic reviews**	#7 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
31.	**Combine all**	**#29 OR #30**

Example Embase Explosion

Mechanics/exp

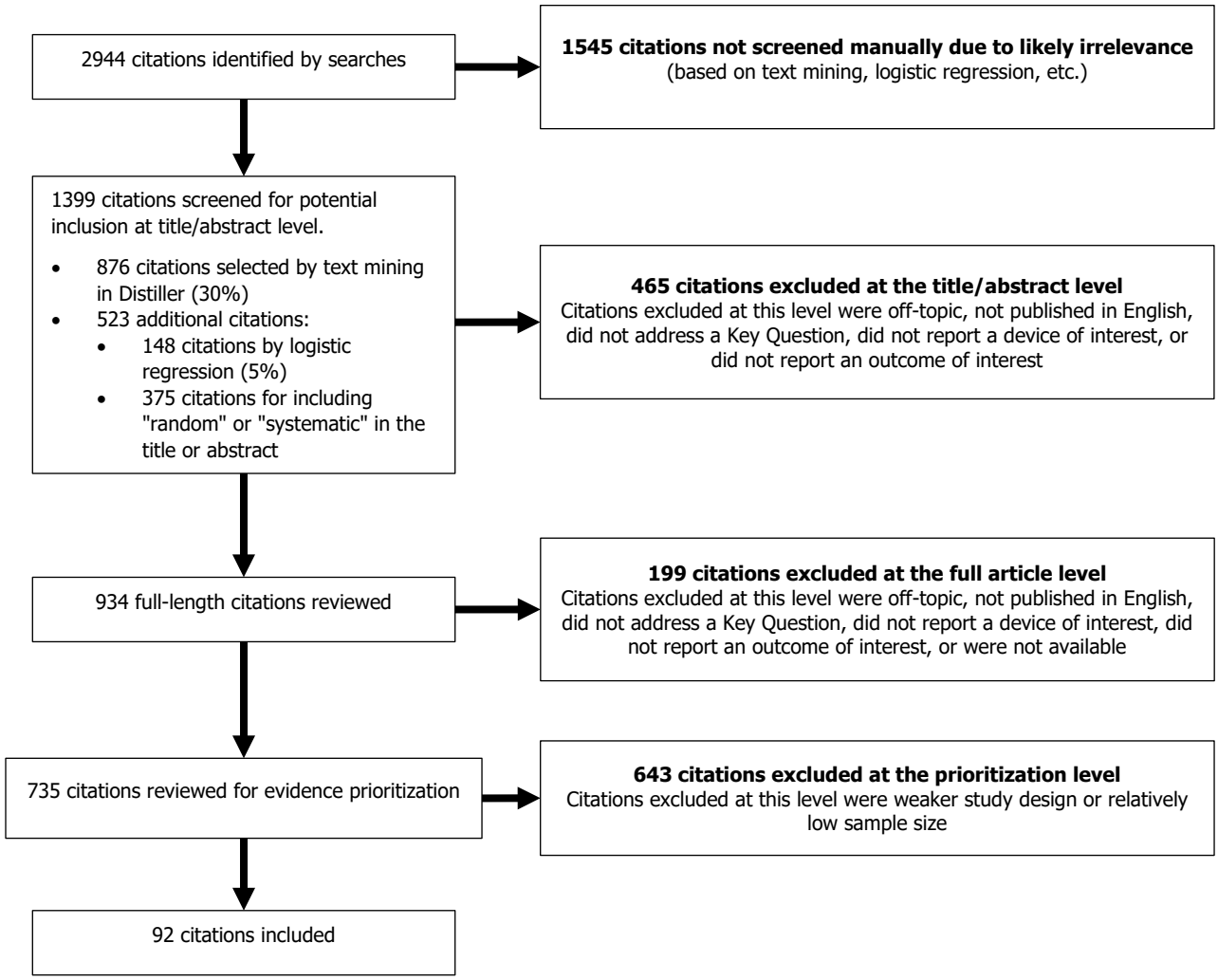
- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength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



2,944 Citations were identified by searches, of which:

1. 1,545 citations were not screened manually due to likely irrelevance (based on text mining or logistic regression or either "random" or "systematic" in the title or abstract)

2. The remaining 1,399 citations were screened for potential inclusion at title/abstract level (876 citations were selected by text mining in Distiller (30%); and 523 additional citations were selected - 148 by logistic regression (5%) and 375 for including "random" or "systematic" in the title or abstract)

    a. 465 citations were excluded at the title/abstract level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

b. The remaining 934 full length citations were reviewed, of which:

i. 199 citations were excluded at 1st pass full article level, Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available.

ii. The remaining 735 citations were reviewed, of which:

1. 643 citations were excluded at the prioritization level. Citations excluded at this level were animal, single-arm or nonrandomized comparative studies; or were individual studies already represented in a systematic review; or were systematic reviews superseded by a more comprehensive systematic review.

2. 92 citations were included.

Appendix D. Evidence Tables

Table 6: Cardiovascular-Clip/Closure/Embolization - Health Effects (In Vivo) Human Studies

6.1 Source Citation: Cen et al. 2021[1]

Study Design: Systematic Review

Device or Material: Amplatzer Duct Occluder (ADO) II (Abbott Laboratories, AbbottPark, Illinois) for ventricular septal defect closure

Contact Duration: Follow up ranged from 6 months to 40 months

Dose: NR

Frequency/Duration: Single Surgery

Response: aortic regurgitations, complete atrioventricular block, device embolisms, residual shunts, success rate, tricuspid regurgitations

Patient characteristics (gender, mean age): Mean age range: 0.7 to 8.9 years; gender: NR

Number per Group: 478 (13 studies)

Observed adverse effects: Aortic regurgitations: ES: 0.00 (95% CI: 0.00 to 001, I^2 = 0.00%); complete atrioventricular block: ES 0.00 (95% CI: 0.00 to 0.01, I^2=0.00%); residual shunts: ES 0.03 (95% CI: 0.01 to 0.05, I^2 = 0.00); success rate: ES 0.99 (95% CI: 0.98 to 1.00, I^2=0.00%), tricuspid regurgitations: ES: 0.01 (95% CI: 0.00 to 0.03, I^2=48.34%). Three patients experienced device embolisms. No patients experienced low ejection fraction, device thrombus, or mitral regurgitations.

Timing of adverse effects: Follow up ranged from 6 months to 40 months

Factors that predict response: NR

6.2 Source Citation: Kennedy et al. 2021[2]

Study Design: Systematic Review

Device or Material:

Nitinol: Starclose (Abbott Vascular Redwood City, California, USA)

Non-Nitinol: Angioseal (St. Jude Medical St. Paul, Minnesota, USA), Exoseal (Cordis Corporation Bridgewater, New Jersey, USA), Femoseal (St Jude Medical Uppsala, Sweden), Glubran 2 (GEM Italy Viareggio, Italy), Mynx (Cardinal Health Dublin, Ohio, USA), Perclose (Abbott Vascular Redwood City, California, USA)

For antegrade use of vascular closure devices

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Pooled Complications, Bleeding complication rate

Patient characteristics (gender, mean age): NR

Number per Group:, Overall number of interventions = 4124. Nitinol: StarClose = 476. Non-nitinol: Angioseal = 2717, Exoseal = 585, Femoseal 111, Glubran 2 = 104, Mynx =108, Perclose 23.

Observed adverse effects:

Starclose

Overall complications common femoral artery (CFA):

Effect Size (95% CI) = 7.4 (4.71, 10.62)

Overall complications superficial femoral artery (SFA):

Effect Size (95% CI) = 10.1 (5.3, 15.9)

Bleeding complications CFA:

Effect Size (95% CI) = 6.78 (4.18, 9.87)

Bleeding complications SFA:

Effect Size (95% CI) = 6.4 (2.6, 11.4)

Observed adverse effects overall

Overall complications common femoral artery (CFA):

Effect Size (95% CI) = 4.55 (2.69, 6.78)

Overall complications superficial femoral artery (SFA):

Effect Size (95% CI) = 5.7 (2.7, 9.7)

Bleeding complications CFA:

Effect Size (95% CI) = 3.55 (1.75, 5.81)

Bleeding complications SFA:

Effect Size (95% CI) = 3.6 (1.0, 7.3)

Timing of adverse effects: NR

Factors that predict response:

Starclose exhibited the highest overall complication rate. Clinically meaningful differences in overall pooled complications were identified between VCDs with a trend toward significance.

Significant differences between VCDs exist with respect to bleeding risk.

No difference was identified between antegrade SFA and CFA VCD use with respect to overall complication and bleeding risks.

6.3 Source Citation: Bracale et al. 2021[3]

Study Design: Systematic Review

Device or Material: Amplatzer Vascular Plug (AVP) (Abbott Vascular, Saint Paul, MN, USA) for prevention of endoleaks during abdominal endovascular aneurysm repair

Contact Duration: range 2-36 months, mean period of follow-up was 12.4 months

Dose: NR

Frequency/Duration: Single administration

Response: buttock claudication, groin hematoma, endoleaks, erectile dysfunction

Patient characteristics (gender, mean age): Gender NR, mean age 72.4 years

Number per Group: Total = 633 patients, AVP was employed in 78.6% of the cases; AVP II, in 2.8% of the cases; and AVP IV, in 18.6% of the cases

Observed adverse effects

buttock claudication (9.4%)

groin hematoma (1.1%)

endoleaks (5.3%)

erectile dysfunction (1.0%)

Timing of adverse effects: NR

Factors that predict response: NR

6.4 Source Citation: Heaton et al. 2021[4]

Study Design: Systematic Review

Device or Material: Amplatzer Septal Occluder (ASO) (Abbott, St. Paul, MN) for closure of secundum type atrial septal defects

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Overall adverse event rate, arrhythmias with implantation, arrhythmias with embolism

Patient characteristics (gender, mean age): 61.7% were female, mean age of patients 21.1 ± 65.8 years.

Number per Group: Total group = 2972, 12 prospectively performed studies

Observed adverse effects:

Pooled technical success rate of implantation was 98% (95% CI: 0.968–0.990, P < 0.01)

Overall adverse event rate associated with implantation was 5.1% (95% CI: 0.035–0.068, P < 0.01, I2 = 67.3%) Any reported event within two years of implantation, which included allergic reactions, new-onset aortic regurgitation, arrhythmia, bleeding, death, effusion, embolism, headache, insertion site hematoma, new-onset mitral regurgitation, pulmonary vein orifice obstruction, retroperitoneal hematoma, thrombus, transient ischemic attack and stroke, and urinary tract disturbance.

Adverse event rate of arrhythmias associated with implantation was 1.8% (95% CI: 0.007–0.032, P < 0.01, I2 = 77.1%)

Adverse event rate of arrhythmias associated with device embolism was 0.7% (95% CI: 0.002–0.013, P < 0.01, I2 = 50.1%)

One death was noted 1.5 years after the implantation, associated with device embolization and sudden cardiac death.

Timing of adverse effects: Any reported event within two years of implantation

Factors that predict response: Typical procedural methods include the use of fluoroscopy with periprocedural TTE, TEE, or ICE. These additional echocardiographic techniques require longer procedure times, additional cost, and may increase complication risks due to additional anesthetic and access requirements.

6.5 Source Citation: Zhang et al.[5]

Study Design: Systematic Review

Device or Material: Woven EndoBridge (WEB) (Sequent Medical, Aliso Viejo, California) for treatment of Wide-Neck Intracranial Aneurysms

Contact Duration: mean follow-up, 9.34 months, (range, 2-18 months)

Dose: NR

Frequency/Duration: Single contact / implant

Response:

Thromboembolic complication, recanalization, mortality, morbidity, treatment failure, and complication rate

Patient characteristics (gender, mean age): Gender NR. The mean age of the included patients was 56.78 years

Number per Group: 35 studies (1737 patients with 1749 aneurysms)

Observed adverse effects

Thromboembolic complication

Pooled Rates (%) (95% Confidence Interval Based on Random-Effect Model)

= 9 (0.08, 0.12), I^2 (P Value of I^2) = 43 (<0.01)

Recanalization

Pooled Rates (%) (95% Confidence Interval Based on Random-Effect Model)

= 9 (0.06, 0.12), I^2 (P Value of I^2) = 30 (0.14)

Mortality

Pooled Rates (%) (95% Confidence Interval Based on Random-Effect Model)

= 7 (0.04, 0.11), I^2 (P Value of I^2) = 67 (<0.01)

Morbidity

Pooled Rates (%) (95% Confidence Interval Based on Random-Effect Model)

= 6 (0.04, 0.08), I^2 (P Value of I^2) = 31 (=0.09)

Failure

Pooled Rates (%) (95% Confidence Interval Based on Random-Effect Model)

= 5 (0.03, 0.07), I^2 (P Value of I^2) = 36 (=0.07)

Intraoperative rupture

Pooled Rates (%) (95% Confidence Interval Based on Random-Effect Model)

= 3 (0.02, 0.05), I^2 (P Value of I^2) = 56 (<0.01)

Timing of adverse effects: Within 18 months

Factors that predict response:

We observed no significant difference in the rate of thromboembolism between the subgroup treated with preoperative antiplatelet medication and the subgroup treated with nonpreoperative antiplatelet medication.

6.6 Source Citation: Harker et al.[6]

Study Design: Systemic Review

Device or Material: Woven EndoBridge (WEB) (Sequent Medical, Aliso Viejo, California) for ruptured intracranial aneurysms

Contact Duration: NR

Dose: NR

Frequency/Duration: Single contact / implant

Response: Rate of rebleeding, overall retreatment rate, early or delayed stent placement, pooled event rate for complications.

Patient characteristics (gender, mean age): NR

Number per Group: Seven articles, all of which were observational case series,

representing 309 ruptured aneurysms were identified and

included in the final analysis

Observed adverse effects:

The likelihood of complete radiographic occlusion following WEB placement for ruptured aneurysms was 62% (95% CI 49–73%) at early 3-to-6-month angiographic follow-up.

The rate of rebleeding was 2.5% (95% CI 1–5%).

The overall retreatment rate was 9% (95% CI 4–17%)

The need for early or delayed stent placement was 5% (95% CI 1–12%).

The pooled event rate for complications (procedural aneurysm rupture, thromboembolic, and device protrusion in the parent artery) across studies was 17% (95% CI 10–30%)

Timing of adverse effects: NR

Factors that predict response: NR

6.7 Source Citation: Pineda et al.[7]

Study Design: Systematic Review

Device or Material: Amplatzer (St. Jude Medical), STARFlex (NMT Medical Inc) for transcatheter Closure of Patent Foramen Ovale

Contact Duration: The mean follow-up in these three trials ranged from 2 to 4 years.

Dose: NR

Frequency/Duration: Single contact / implant

Response: composite of transient ischemic attack (TIA) and ischemic cerebrovascular events (CVA)

Patient characteristics (gender, mean age): Across trials, the weighted mean age was 45.7 +/- 9.8 years and 52.7% were males

Number per Group: Three RCTs met inclusion criteria. The pooled data provided 2,303 patients, of which 1,150 were in the PFO closure group and 1,153 in the medical therapy group.

Observed adverse effects

There were no deaths in this cohort, and the incidence of peripheral embolism was not reported.

The individual incidence of TIA and ischemic CVA was similar in both groups, with 24 (2.1%) transient ischemic attacks in the closure group compared with 29 (2.5%) in the medical therapy (OR = 0.84; 95% CI, 0.48 – 1.45, P = 0.53), and 22 (1.9%) ischemic strokes in the closure group compared with 34 (2.9%) in the medical therapy group (OR = 0.65; 95% CI, 0.36–1.20, P = 0.17).

However, there were 43 events of the composite of TIA and ischemic CVA in the closure group compared with 61 events in the medical therapy group, showing a trend in favor of the PFO closure (OR = 0.70; 95% CI, 0.47–1.05, P = 0.08)

Key adverse events consistently reported in all trials were the incidence of atrial fibrillation and bleeding episodes.

There were 32 atrial fibrillation events reported in the PFO closure group versus 8 in the medical therapy group, a difference that trended towards statistical significance, with an OR of 3.29 (95% CI, 0.86–12.60, P = 0.08) in favor of medically treated patients.

The incidence of bleeding episodes was similar between the PFO closure (0.02%) and medical therapy group (0.06%) (OR = 1.43; 95% CI, 0.47–4.42, P = 0.53)

Other important adverse events, including pulmonary embolism and intracardiac thrombi were infrequent and not documented in all the trials.

Timing of adverse effects: NR

Factors that predict response:

PFO closure might be associated with a decreased incidence of recurrent neurological events as compared with medical treatment alone

In aggregate, these studies additionally suggest that closure of the PFO may be associated with higher incidence of atrial fibrillation.

Abbreviations: CFA = common femoral artery; CI = confidence interval; CVA = cerebrovascular event; ES = effect size; ICE = intracardiac echocardiography; NR = not reported; OR = odds ratio; PFO = patent foramen ovale; SFA = superficial femoral artery; TEE = transesophageal echocardiography; TIA = transient ischemic attack; TTE = transthoracic echocardiography; VCD = vascular closure device

Table 7: Cardiovascular – IVC filters: Health Effects (In Vivo) Human Studies

7.1 Source Citation: Angel et al. 2011[8]

Study Design: Systematic review of 37 single-arm studies and 842 Manufacturer and User Facility Device Experience (MAUDE) – categorized reports of 5 FDA-approved retrievable inferior vena cava (IVC) filters.

Device or Material: retrievable IVC filters with nitinol (G2, Optease, Option, Eclipse), and non-nitinol (ALN, Celect, Tulip)

G2 filter (Bard Peripheral Vascular; Tempe, AZ) in 5 studies

Optease filter (Cordis; Fremont, CA) in 7 studies

Option filter (Rex Medical; Conshocken, PA) in 1 study

Eclipse filter (C.R. Bard; Tempe, AZ); 17 complications reported in MAUDE

ALN filter (Chirurgicaux; Ghisonaccia, France) with 316L stainless steel in 3 studies

Celect filter (Cook; Bloomington, IN) with conichrome, a **cobalt- chromium-nickel-molybdenum-iron alloy** in 3 studies

Tulip filter (Cook, Bloomington, IN) with a cobalt chromium alloy in 8 studies

Contact Duration: mean followup 9.9 months (range 2 to 25 months). Mean implantation of removed nitinol filters in 4 studies was 138 days (G2), 11 and 19 days (Optease), and 67 days (Option). Mean implantation of removed non-nitinol filters in 6 studies was 51 days (ALN), 179 days (Celect), and 11 days to 58 days (Tulip).

Dose: NR

Frequency/Duration: NR

Response: clotting, DVT, embedded filters, fracture, migration, perforation, retrieval failure, tilting, vena cava thrombosis or stenosis

Patient characteristics (gender, mean age): NR, patient indications were 1) therapeutic use for patients with venous thromboembolism (VTE) before IVC filter placement or 2) prophylactic use for patients with no VTE at the time of placement.

Number per Group: Data from 1517 G2, 662 Optease, 100 Option, 738 ALN, 283 Celect, and 1600 Tulip filters were reported in the literature review. Complications from 500 G2, 163 Optease, 17 Eclipse, 18 Celect, and 144 Tulip filters were reported in the MAUDE database.

Observed adverse effects:

Filter perforation: 174 patients in the MAUDE database; 150 (86%) events with nitinol filters vs. 24 (14%) events with non-nitinol filters.

Filter migration: In the literature review, 16 studies (n=2716) reported migration in 35 patients. Rate range 0% to 4.5% with nitinol vs. 0.5% to 0.8% with non-nitinol. In the MAUDE database, 157 (82%) of 192 migrations were with nitinol, although no conclusions regarding migration rate can be drawn from the MAUDE data, because the number of patients who have received the represented filters is unknown.

DVT: In the literature review, 13 studies (n=1277) reported DVT in 69 patients. Rate range 0.8% to 18% with nitinol devices versus 0% to 14% with non-nitinol devices.

Vena cava thrombosis or stenosis: 15 studies (n=4078) reported rates with nitinol devices from 3.7% to 8%, versus 0.6% to 2.3% with non-nitinol.

Fracture: The MAUDE database reported 188 fractures; 178 (95%) fractures with nitinol devices.

Complications from filter removal: The literature review: 1715 filter removals (41% nitinol). 75 filters had substantial clots; 32 (42%) filters were nitinol. Retrieval failure occurred in 36 nitinol filters; 3 were embedded, 21 were tilted, and 12 were clotted. The MAUDE database: 111 complications due to filter removal which were mostly due to the inability to retrieve the filter; 86 (77%) with nitinol.

Timing of adverse effects: 21 perforations, 12 migrations, 1 fracture, 3 thrombosis, and 1 filter tilting from nitinol devices occurred ≤30 days.

Factors that predict response: NR

Table 8: Cardiovascular – Grafts/Stents: Health Effects (In Vivo) Human Studies

8.1 Source Citation: Khan, et al. 2021[11]

Study Design: Systematic Review

Device or Material: Aorfix Nitinol Bifurcated stent (Lombard Medical)

Contact Duration: 12 months

Dose: Implant

Frequency/Duration: Single contact/implant

Response: Endoleak, Mortality.

Patient characteristics (gender, mean age): Mean age 72.5, males (80.4%)

Number per Group: 442 patients underwent endovascular aneurysm repair

(EVAR) as treatment for abdominal aortic aneurysm (AAA).

Observed adverse effects: Endoleak (at 6 months: 7), Mortality (at 30 days: 2, at 1 year: 21)

Timing of adverse effects: 30 days and 1 year

Factors that predict response: Patients with hostile aortic anatomy are associated with higher rates of complications. Younger open surgical groups, report a lower incidence of adverse events ($p<0.005$) when compared to the sample group.

8.2 Source Citation: Mazzaccaro , et al. 2021[10]

Study Design: Systematic Review

Device or Material: The Roadsaver (Microvention), C-Guard (Inspire MD) and Gore (W.L. Gore & Associates Inc) Nitinol microstents

Contact Duration: 6-12 months

Dose: Implant

Frequency/Duration: Single contact/implant

Response: Stroke, cerebral hemorrhage

Patient characteristics (gender, mean age): Mean age 71.9 (2.9), males (71.6%)

Number per Group: 797 patients underwent TCAR.

Observed adverse effects: Roadsaver (1 stroke, 2 fatal hemorrhage), C-Guard (ipsilateral asymptomatic ischemic lesions 37% of patients within 48 hours, solved after 30 days in all but one patient)

Timing of adverse effects: 30 days

Factors that predict response: In asymptomatic patients the dual-layer stent was preferred over a single-layer one because of the high risk of the carotid plaque.

8.3 Source Citation: Sagris, et al. 2021[9]

Study Design: Systematic Review

Device or Material: Enroute Nitinol arterial stent (Silk Road Medical)

Contact Duration: 30 days

Dose: Implant

Frequency/Duration: Single contact/implant

Response: Mortality, Stroke, transient ischemic attack (TIA), myocardial infarction (MI), In-stent restenosis, cranial nerve (CN) injury, Hemodynamic instability, bleeding.

Patient characteristics (gender, mean age): Mean age 72.6 (3.69); Percent male: 65.6%

Number per Group: 14,588 patients (45 studies) underwent Transcervical artery revascularization (TCAR).

Observed adverse effects: Mortality 75/14,427 (0.5%), Stroke 179/13,744 (1.3%), TIA 65/8673 (0.7%), MI 65/14,173 (0.6%), In-stent restenosis 4/260 (1.5%), Cranial nerve injury 33/8994(0.36%), Hemodynamic instability 1306/5183 (21%), Bleeding 278/8726 (20%).

Timing of adverse effects: 30 days.

Factors that predict response: Patients with symptomatic carotid stenosis at baseline experienced perioperative stroke in 1.6% of cases compared with 0.5% of asymptomatic patients.

8.4 Source Citation: Li, et al. 2020[14]

Study Design: Systematic Review

Device or Material: Zenith (Cook Medical), Valiant (Medtronic), TAG (W.L. Gore & Associates)

Nitinol thoracic aortic stent-graft

Contact Duration: 12 months

Dose: Implant

Frequency/Duration: Single contact/implant

Response: Retrograde type A aortic dissection, type II endoleaks, Stroke.

Patient characteristics (gender, mean age): Mean age 73.6 (4.09), Gender not reported

Number per Group: 99 patients underwent thoracic endovascular aortic repair (TEVAR)

Observed adverse effects: One (1/96, 1%) retrograde type A aortic dissection, two (2/96, 2%) type II endoleaks, and three (3/96 3%) strokes.

Timing of adverse effects: 30 days

Factors that predict response: none reported.

8.5 Source Citation: Mwipatayi, et al. 2020[13]

Study Design: Systematic Review

Device or Material: Viabahn VBX Nitinol balloon-expandable (CBE) stent (W.L. Gore & Associates).

Contact Duration: 12 months

Dose: Implant

Frequency/Duration: Single contact/implant

Response: Target lesion revascularization at 12 months.

Patient characteristics (gender, mean age): Mean age 73.6 (4.09), Gender not reported

Number per Group: 1012 patients underwent treatment for aortoilic occlusive disease.

Observed adverse effects: Target lesion revascularization: 3.3-3.4% at 12 months.

Timing of adverse effects: 12 months

Factors that predict response: none reported.

8.6 Source Citation: Paraskevas, et al. 2020[12]

Study Design: Systematic Review

Device or Material: Enroute Nitinol covered and Uncovered Self expandable stents (Slik Road Medical)

Contact Duration: 30 days

Dose: Implant

Frequency/Duration: Single contact/implant

Response: Mortality, major stroke, minor stroke, transient ischemic attack, intracerebral hemorrhage, myocardial infarction (MI) and neck hematoma.

Patient characteristics (gender, mean age): Mean age 73.6 (4.09), Gender not reported

Number per Group: 2110 patients underwent transcervical CAS.

Observed adverse effects: Mortality 0.48% (10/2096 patients), major stroke 0.71% (15/2110 procedures), minor stroke 0.90% (19/2110 procedures), TIA 0.57% (12/2110), intracerebral hemorrhage 0.14% (3/2110), MI 0.57% (12/2110), and neck hematoma 1.04% (22/2110)

Timing of adverse effects: 30 days

Factors that predict response: The avoidance of the aortic arch and the tortuous supra-aortic vessels are reasons for adverse effects reduction in Transcervical CAS.

8.7 Source Citation: Spanos et al. 2016[15]

Study Design: Systematic Review

Device or Material: Talent (Medtronic) and AneuRX (Medtronic) Nitinol endografts

Contact Duration: 12 to 36 months

Dose: NR

Frequency/Duration: Single implantation

Response: Migration

Patient characteristics (gender, mean age): Mean age (SD): 72.9 (2); Percent male (SD): 88.5% (1.2)

Number per Group: 1666 patients (6 studies meta-analyzed) underwent EVAR. Talent: 199 patients (2 studies), AneuRX: 1467 patients (4 studies)

Observed adverse effects: Migration events n/N (%): 179/1666 (10.7%)

Timing of adverse effects: 12 to 36 months

Factors that predict response: Meta-analyses indicated that AAA diameter is on average 0.719 cm smaller (95% CI: 0.00065 to 1.4384, p=0.00497) for patients with no migration compared to those with migration, and neck length is on average 4.36 mm shorter (95% CI: 1.3277 to 7.394, p=0.0048) for patients with migration compared to those with no migration. There were no statistically significant differences for neck length or neck diameter.

8.8 Source Citation: Vardi et al. 2014[16]

Study Design: Systematic Review

Device or Material: S.M.A.R.T.(Cordis), SUPERA (Abbot), LifeSent/FlexStar/FlexStar XL (C.R. Bard), Protégé Everflex (EV3 Inc.), Complete SE SFA (Medtronic), Luminexx (Bard Peripheral Vascular Inc.), Astron (Biotronik Inc.), Dynalink/Absolute (Guidant Corp.) nitinol stents for superficial femoral artery disease (SFA)

Contact Duration: 30 days to 1 year

Dose: Less than 200 mm in length

Frequency/Duration: Single implantation

Response: PP rate, freedom from PP, freedom from 30-day MAE, re-intervention, mortality, amputation

Patient characteristics (gender, mean age): Mean age range: 66.1 years to 68.7; Percent male range: 59% to 73.5%

Number per Group: NR

Observed adverse effects: PP rate of 1-year: ES 71.6% (5 studies, 95% CI: 66.4% to 76.7%); Freedom from loss of PP: ES 81.0% (95% CI: 76.0% to 85.4%), freedom from 30-day MAE: ES 99.9% (95% CI: 90% to 100%). The rest of the data was qualitatively described as ranges. Re-intervention rates at 1 year ranged from 7.4% to 27.4%, death ranged from 2.1% to 6.0%, amputation of the target limb was rare (ranging from 0% to 3.3%).

Timing of adverse effects: 30 days to 1 year

Factors that predict response: No significant relationship was found between longer lesion length and lower PP rates (p=0.444)

8.9 Source Citation: Donas et al. 2012[17]

Study Design: Systematic Review

Device or Material: Nitinol self-expanding stent-grafts (SeSG) Fluency (Bard Peripheral Vascular Inc.) and Viabahn (W.L. Gore & Associates Inc.)); Balloon-expandable stent-graft (BeSG) – Advanta/iCAST (Atrium Medical Corporation) and Jostent (Abbot Vascular) for repair of iliac artery aneurysms

Contact Duration: Mean follow-up ranged from 2 months to 30.5 months

Dose: NR

Frequency/Duration: Unilateral (n=172)

Response: Occlusions

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

Number per Group: 100 SeSGs implanted, 136 BeSGs implanted in a total of 185 patients.

Observed adverse effects: Occlusions - SeSG: 11/100 (11%), BeSG: 4/136 (2.9%)

Timing of adverse effects: Occlusions - SeSG: 8 occurred in <30 days and 3 occurred in >30 days. BeSG: 2 occurred in <30 days and 2 occurred in >30 days.

Factors that predict response: NR

AEF = aortoenteric fistula; BeSG = balloon-expandable stent-graft; CAS = carotid artery stenting; CBE = Covered balloon-expandable; CN = Cranial Nerve; EVAR = endovascular aortic repair; IBD = iliac branch device; MI = myocardial infarction; NR = none reported; PP = Primary Patency; SeSG = self-expanding stent-grafts; TCAR = transcervical carotid artery repair; TEVAR = thoracic endovascular aortic repair; TIA = transient ischemic attack;

Table 9: Nitinol Heart Repair - Health Effect (In Vivo) Human Studies

9.1 Source Citation: Martinez-Gomez et al. 2021[18]

Study Design: Systematic Review

Device or Material: MitraClip

Contact Duration: Median follow-up 6 months

Dose: NR

Frequency/Duration: Mitraclips per patient, n (SD): 1.8 (0.7)

Response: Cardiac tamponade, major bleeding, major vascular complication, minor vascular complication, PPI, successful implantation, single leaflet detachment, transient afterload mismatch, Mortality (In-Hospital, 6-month), Mitral Valve Reintervention, Cerebrovascular accident

Patient characteristics (gender, mean age): Mean age in years (SD): 70.5 (12.4); Percent Male: 56.6%

Number per Group: 254 patients (40 studies)

Observed adverse effects: Cardiac tamponade, %: 0.4%; major bleeding, %: 1.18%; major vascular complication, %: 0.8%; minor vascular complication, %: 0.4%; PPI, %: 0.4%; successful implantation, %: 93.7%; single leaflet detachment, %: 0.4%; transient afterload mismatch, %: 0.4%; In-Hospital Mortality Rate, %: 12.6%, 6-Month Mortality Rate, %: 18.1%, Mitral Valve Reintervention, n: 1, Cerebrovascular accident, %: 2.4%

Timing of adverse effects: Median follow-up 6 months

Factors that predict response: NR

9.2 Source Citation: Abdel-Wahab et al. 2020[27] (Long-term follow-up of Abdel-Wahab et al. 2014, which is currently included in Rahhab et al. 2019[21]

Study Design: RCT

Device or Material: Nitinol: CoreValve (Medtronic) vs. Non-Nitinol: Sapien XT (Edwards)

Contact Duration: 5 years

Dose: NR

Frequency/Duration: Single implantation

Response: Bleeding (Life threatening, major, minor), BVD, endocarditis, myocardial infarction, NSVD (moderate/severe PPM, moderate/severe PVL), PPI, SVD (moderate, severe), valve thrombosis, Vascular Complications (Major, Minor), Mortality (Any Cause, Cardiovascular Cause, Valve-related), Stroke, Repeat hospitalization

Patient characteristics (gender, mean age): Mean age (SD): CoreValve: 79.6 (15.8); Sapien XT: 81.9 (6.7); Female Sex, n (%): CoreValve: 86 (71.7%); Sapien XT: 69 (57.0%)

Number per Group: CoreValve: 120; Sapien XT: 121

Observed adverse effects: BVD, n (%): CoreValve: 26 (20.9%); Sapien XT: 28 (22.5%), p=0.91;

Endocarditis, n (%): CoreValve: 4 (3.4%); Sapien XT: 2 (1.6%), p=0.39;

Life-Threatening Bleeding, n (%): CoreValve: 18 (16.2%); Sapien XT: 21 (17.3%), p=0.77;

Major Bleeding, n (%): CoreValve: 20 (22.0%); Sapien XT: 28 (26.3%), p=0.26;

Major Vascular Complications, n (%): CoreValve: 14 (12.1%); Sapien XT: 14 (11.6%), p=0.89;

Minor Bleeding, n (%): CoreValve: 12 (10.4%); Sapien XT: 17 (14.3%), p=0.37;

Minor Vascular Complications, n (%): CoreValve: 3 (2.6%); Sapien XT: 5 (4.2%), p=0.51;

Moderate SVD, n (%): CoreValve: 0 (0%); Sapien XT: 4 (5.6%), p=0.047, favors Sapien XT;

Myocardial infarction, n (%): CoreValve: 7 (6.1%); Sapien XT: 2 (1.6%), p=0.08;

Moderate/severe PPM NSVD, n (%): CoreValve: 13 (16.0%); Sapien XT: 14 (15.9%), p=1.0;

Moderate/severe PVL NSVD, n (%): CoreValve: 10 (8.5%); Sapien XT: 3 (2.5%), p=0.08;

PPI, n (%): CoreValve: 40 (40.4%); Sapien XT: 28 (25.4%), p=0.01, favors Sapien XT;

Severe SVD, n (%): CoreValve: 0 (0%); Sapien XT: 2 (0.9%), p=0.20;

Valve thrombosis, n (%): CoreValve: 1 (0.8%); Sapien XT: 6 (7.3%), p=0.06

Any Cause Mortality: CoreValve: 54 (47.6%), Sapien XT: 63 (53.4%), p=0.38;

Cardiovascular-Related Mortality: CoreValve: 25 (21.5%), Sapien XT: 37 (31.6%), p=0.12;

Valve-Related Mortality, n (%): CoreValve: 3 (2.6%); Sapien XT: 4 (3.3%), p=0.74;

Stroke, n (%): CoreValve: 19 (16.5%); Sapien XT: 21 (17.5%), p=0.73;

Repeat hospitalization, n (%): CoreValve: 26 (22.5%); Sapien XT: 30 (28.9%), p=0.75;

Timing of adverse effects: 5 years

Factors that predict response: NR

9.3 Source Citation: Nappi et al. 2020[26]

Study Design: Systematic Review

Device or Material: MitraClip (Abbott Laboratories, AbbottPark, Illinois) + OMT vs. OMT alone (other comparisons within study not described; no material of interest)

Contact Duration: Between 12 months and 19.6 months

Dose: NR

Frequency/Duration: Single surgery

Response: Composite Endpoint, Hospital Mortality, Long-Term Mortality, Readmission, Reoperation

Patient characteristics (gender, mean age): Mean age range: MitraClip + OMT: 70.1 to 71.7; OMT alone: 70.6 to 72.8; Percent Male: MitraClip + OMT: 66.6% to 78.9%; OMT: 61.5% to 70.4%

Number per Group: MitraClip + OMT: 454; OMT Alone: 464

Observed adverse effects: MitraClip + OMT vs OMT Alone: Composite Endpoint: OR 0.39 (95% CI: 0.09 to 1.73, I^2=96%), Hospital Mortality: OR 3.35 (95% CI: 0.25 to 44.7, I^2=65%), Long-Term Mortality: OR 0.77 (95% CI: 0.40 to 1.49, I^2=77%), Readmission: OR 0.35 (95% CI: 0.04 to 3.06, I^2=98%), Reoperation: OR 0.40 (95% CI: 0.22 to 0.72, I^2=22%, favors Mitraclip + OMT)

Timing of adverse effects: Between 12 months and 19.6 months

Factors that predict response: NR

9.4 Source Citation: Sun et al. 2020[19]

Study Design: Systematic Review

Device or Material: Nitinol: Evolut R vs. Nitinol: CoreValve

Contact Duration: Up to 30 days

Dose: NR

Frequency/Duration: Single implantation

Response: Device Failure; MI, Moderate/Severe PVR, MVC, PPI, Severe Bleeding, AKI, Mortality, Stroke/TIA

Patient characteristics (gender, mean age): Mean age range: Evolut R: 81 to 83; CoreValve: 82 to 84; Percent Male: Evolut R: 28% to 38%; CoreValve: 29% to 43%

Number per Group: Evolut R (n=4597) vs. CoreValve (n=6,933) (6 NRCSs)

Observed adverse effects: AEs were meta-analyzed with observations less than 1 favoring Evolut R, and observations greater than 1 favoring CoreValve. Results are displayed below:

Device Failure: RR: 0.33 (4 studies, n=10335, 95% CI: 0.11 to 0.96, I^2=60%); MI: RR 0.43 (5 studies, n=11379, 95% CI: 0.21 to 0.87, I^2=0%); Moderate/Severe PVR: RR: 0.67 (6 studies, n=11530, 95% CI: 0.46 to 0.98, I^2=57%); MVC: RR: 0.57 (5 studies, n=11384, 95% CI: 0.27 to 1.17, I^2=78%); PPI: RR: 0.87 (6 studies, n=11504, 95% CI: 0.76 to 1.00, I^2=26%); Severe Bleeding: RR: 0.57 (6 studies, n=11384, 95% CI: 0.33 to 1.01, I^2=82%); AKI: RR: 0.58 (5 studies, n=1914, 95% CI: 0.42 to 0.80, I^2=0%); Mortality: RR 0.68 (6 studies, n=11530, 95% CI: 0.42 to 1.08, I^2=25%); Stroke/TIA: RR: 1.08 (6 studies, n=11530, 95% CI: 0.89 to 1.30, I^2=0%)

Timing of adverse effects: Up to 30 days

Factors that predict response: NR

9.5 Source Citation: Chatzistergiou et al. 2019[20]

Study Design: Systematic Review

Device or Material: MitraClip (Abbott Laboratories, AbbottPark, Illinois)

Contact Duration: 30 days to 12 months

Dose: NR

Frequency/Duration: Single implantation

Response: Successful Implantation, 30-Day Mortality, 12-Month Mortality

Patient characteristics (gender, mean age): Mean age: 71 years (SD 10); Percent male: 71%

Number per Group: MitraClip (n=2383, 28 studies)

Observed adverse effects: Successful implantation reported by 91.1% (1798 events, 18 studies) of patients. Mortality rates were 2.95% (62 events, 24 studies) at 30-day follow-up which increased to 18.86% (249 events, 10 studies) at 12 months.

Timing of adverse effects: 30 days to 12 months

Factors that predict response: NR

9.6 Source Citation: Rahhab et al. 2019[21]

Study Design: Systematic Review

Device or Material: Nitinol-based (CoreValve, Evolut R) and non-nitinol (Edwards Sapien, Edwards Sapien XT, Edwards Sapien 3)

Contact Duration: Up to 30 days

Dose: NR

Frequency/Duration: Single implantation

Response: MVC Rate

Patient characteristics (gender, mean age): Pooled means for all devices: Mean age of 82.6 years and 43.9% male

Number per Group: CoreValve (n=4836, 7 SASs), Evolut R (n=2103, 5 SASs), Sapien (n=983, 3 SASs), Sapien XT (n=3405, 5 SASs), Sapien 3 (n=1245, 3 SASs)

Observed adverse effects: All effect sizes are pooled rates of MVCs for studies reporting one sample proportions. Sapien: ES 15.18% (3 SASs, 95% CI: 12.62% to 17.93%, I^2=0.00%, p=0.81); Sapien XT: ES 8.48% (95% CI: 7.56% to 9.45%, I^2=0.00%, p=0.73); Sapien 3: ES 4.48 % (95% CI: 2.21% to 7.50%, I^2=63.48%, p=0.065)**;** CoreValve: ES 7.97% (95% CI: 7.20% to 8.80%, I^2=39.49%, p=0.13); Evolut R: ES 5.98% (95% CI: 3.98% to 8.36%, I^2=73.22%, p=0.0048)

Timing of adverse effects: Up to 30 days

Factors that predict response: NR

9.7 Source Citation: Zhan et al. 2019[22]

Study Design: Systematic Review

Device or Material: CoreValve

Contact Duration: 30 days to 2 years

Dose: NR

Frequency/Duration: Single surgery

Response: aortic regurgitation, PPI, VCs, AKI, Mortality (30 days, 1-year)

Patient characteristics (gender, mean age): Mean age range: TF: 80.2 to 83 years; TAx: 75.5 to 83 years; Percent male range: TF: 44.9% to 58.9%; TAx: 50.0% to 68.1%

Number per Group: TF Approach (n=1414) vs. TAx Approach (n=489) (5 studies)

Observed adverse effects: aortic regurgitation: TF vs. TAx: OR 1.03 (4 studies, n=1780, 95% CI: 0.71 to 1.49, I^2=0%); PPI: OR 1.12 (5 studies, n=1903, 95% CI: 0.86 to 1.46, I^2=0%); VCs: OR 1.08 (5 studies, n=1903, 95% CI: 0.71 to 1.65, I^2=0%)

AKI: TF vs. TAx: OR 1.63 (3 studies, n=978, 95% CI: 1.01 to 2.62, I^2=0%, favors TAx); 30-Day Mortality: OR 1.30 (5 studies, n=1903, 95% CI: 0.78 to 2.17, I^2=0%); 1-Year Mortality: OR 0.76 (3 studies, n=1343, 95% CI: 0.50 to 1.16, I^2=46%)

Timing of adverse effects: 30 days to 2 years

Factors that predict response: NR

9.8 Source Citation: Alkhouli et al. 2018[23]

Study Design: Systematic Review

Device or Material: Nitinol: Watchman, Nitinol: Amplatzer Cardiac Plug, Nitinol or Non-Nitinol: Other

Contact Duration: Up to 365 days

Dose: NR

Frequency/Duration: Single surgery

Response: DRT, DRT-Associated Event

Patient characteristics (gender, mean age): Mean age: 72.97 (SD 9.22); Percent male: 60%

Number per Group: Watchman (n=4,443 patients at follow-up), Amplatzer (n=2,744 patients at follow-up), Other (n=982 patients at follow-up)

Observed adverse effects: DRT-Incidence, n/N (%): Watchman: 138/4443 (3.1%), Amplatzer: 100/2744 (3.6%), Other: 24/982 (2.4%); DRT-Associated Events: Watchman: 22/138 (16%), Amplatzer: 8/100 (8%), Other: 0/24 (0%)

Timing of adverse effects: Up to 365 days

Factors that predict response: NR

9.9 Source Citation: Baman et al. 2018[24]

Study Design: Systematic Review

Device or Material: Nitinol: Watchman (also contains registry data on Watchman, Lariat, and Amplatzer, but superseded by Alkhouli et al. 2018[23])

Contact Duration: Follow-up between 11.8 months and 18 months

Dose: NR

Frequency/Duration: Single implantation

Response: Device Embolization, Implantation Success, Major Bleeding, Pericardial Effusion, Procedure-Related Death, Procedure-Related Stroke

Patient characteristics (gender, mean age): Mean age: 72.8 years; Percent male between 70.0% and 70.5%

Number per Group: Watchman (1114 patients, 2 RCTs)

Observed adverse effects: The efficacy endpoints were pooled only for Watchman since one RCT (PREVAIL) trial only measured safety endpoints in the Watchman group. All event rates for patients with Watchman devices are as follows: device embolization: 0.6%, implantation success: 92.5%, major bleeding: 2.4%, pericardial effusion: 3.2%, procedure-related death: 0%, procedure-related stroke: 0.8%

Timing of adverse effects: Follow-up between 11.8 months and 18 months

Factors that predict response: NR

9.10 Source Citation: Meco et al. 2018[25]

Study Design: Systematic Review

Device or Material: Nitinol: Perceval vs. Non-Nitinol: Conventional Bioprosthesis

Contact Duration: Perceval: 18.25 months (SD 10.5); Conventional Bioprosthesis: 38.3 months (SD 13.1)

Dose: Mean prosthesis size in mm (SD): Perceval: 23.42 (SD 1.73), Conventional Bioprosthesis: 22.8 (SD 1.86)

Frequency/Duration: Single surgery

Response: Paravalvular Leak, PPI, AKI, Mortality (postoperative, 30-day, 1-year), Stroke

Patient characteristics (gender, mean age): Mean age (SD): Perceval: 77.7 years (4.6), Conventional Bioprosthesis: 75.9 (SD 5.9); Percent Female: 56% for both groups

Number per Group: Perceval: 639, Conventional Bioprosthesis: 760

Observed adverse effects: Paravalvular Leak: Perceval (3.1%) vs conventional bioprosthesis (1.6%): OR 2.52 (95% CI: 0.60 to 1.06, P=0.21, I^2=57%)

PPI: Perceval (7.9%) vs conventional bioprosthesis (3.1%) (5 studies): OR 2.45 (95% CI: 1.44 to 4.17, P=0.001, I^2=0%, favors conventional bioprosthesis);

AKI: Perceval (2.7%) vs conventional bioprosthesis (5.5%) (5 studies): OR 0.45 (95% CI: 0.25 to 0.80, P=0.007, I^2=18%)

Postoperative Mortality: Perceval (n=445) vs conventional bioprosthesis (n=537) (4 studies): OR 0.97 (95% CI: 0.54 to 1.74, I^2=0%);

30-Day Mortality: Perceval (2.8%) vs conventional bioprosthesis (2.7%) : OR 0.99 (0.52 to 1.88, P=0.98));

1-Year Survival: Perceval (n=308) vs conventional bioprosthesis (n=462) (4 studies): OR 0.74 (95% CI: 0.34 to 1.62, I^2=0%);

Stroke: Perceval (2.3%) vs conventional bioprosthesis (1.7%): OR 1.34 (95% CI: 0.56 to 3.21, P=0.51);

Timing of adverse effects: Perceval: 18.25 months (SD 10.5); Conventional Bioprosthesis: 38.3 months (SD 13.1). Mortality described at post-operation, 30 day, and 1 year intervals. All other measures measured at the end of follow-up.

Factors that predict response: NR

ADO II: Amplatzer Duct Occluder II; AF/AFL: atrial fibrillation/flutter; AKI: acute kidney injury; BVD: bioprosthetic valve dysfunction; CI: confidence interval; DRT: device-related thrombus; ES: effect size; MI: myocardial infarction; MT: medical therapy; MVC: major vascular complication; NDO: non-disc occlude; NR: not reported; NRCS: non-randomized controlled study; NSVD: nonstructural valve deterioration; OMT: optimal medical treatment; OR: odds ratio; PFO: patent foramen ovale; PPI: postoperative pacemaker implantation; PPM: patient-prosthesis mismatch; PVL: paravalvular leaks; PVR: paravalvular regurgitation; RCT: randomized controlled trial; RR: relative risk; SAS: single-arm study; SD: standard deviation; SVD: structural valve deterioration; TAx: transaxillary; TF: transfemoral; TIA: transient ischemic attack; VC: vascular complication;

Table 10: Cardiovascular Pacemakers/PICCs - Health Effect (In Vivo) Human Studies

10.1 Source Citation: Ngo et al. 2021[29]

Study Design: SR

Device or Material: Leadless Pacemakers Nanostim (Abbott Medical, Abbott Park, IL, USA) vs. Micra (Medtronic, Minneapolis, MN, USA) (both contained nitinol)

Contact Duration: 3 months after implant up to 1 year

Dose: NA

Frequency/Duration: Single administration

Response: Device or procedure-related complications, implant success rate

Patient characteristics (gender, mean age):

Number per Group: 36 studies with most (69.4%) reporting outcomes for Micra. Five studies (13.9%) contained outcomes data for Nanostim, five studies (13.9%) for both devices, and one study (2.8%) did not report the device type.

Observed adverse effects For Micra, the pooled incidence of complications at 90 days (n=1608) was 0.46% (95% CI, 0.08%–1.05%) and at 1 year (n=3194) was 1.77% (95% CI, 0.76%–3.07%). In 5 studies with up to 1-year follow-up, Micra was associated with 51% lower odds of complications compared with transvenous pacemakers (3.30% versus 7.43%; odds ratio [OR], 0.49; 95% CI, 0.34–0.70). The reported implant success rate for patients receiving Micra was 99.85% (95% CI: 99.59% to 99.99%), whereas the rate for patients receiving Nanostim was 97.12% (95% CI: 95.86% to 98.20%).

Timing of adverse effects: 3 months after implant up to 1 year

Factors that predict response: NR

10.2 Source Citation: Garg et al. 2020[31]

Study Design: Nonrandomized comparative study

Device or Material: Nitinol: Micra transcatheter pacemaker vs non-nitinol: TV-PPM

Contact Duration: implantation through 36 months

Dose: NA

Frequency/Duration: single administration

Response: Major complications, Mortality

Patient characteristics (gender, mean age): Group 1: Micra (TV-PPM precluded): 221 (40.6%) female, 71.6 ± 14.3 years; Group 2: Micra (TV-PPM nonprecluded): 901 (39.7%) female, 76.7 ± 12.1 years; Group 3: Control: 242 (47.0%) female, 77.9 ± 11.6 years

Number per Group: A total of 2817 patients underwent a Micra implantation attempt, of whom 546 (19%) patients were deemed ineligible for TV-PPM implantation for reasons such as venous access issues or prior device infections. 2268 patients were not precluded (preclusion status was not reported for 3 patients).
551 patients were in the historical TV-PPM control group.

Observed adverse effects: The major complication rate through 36 months was similar between the 2 Micra groups (non-precluded: 3.81% vs precluded: 4.30%; *P*=.40). Specific adverse event rates for acute and total complications also showed no statistical differences. All event rates are displayed below:

Acute cardiac effusion/perforation, n (%): Micra (TV-PPM preclude): 4 (0.73%), Micra (TV-PPM non-precluded): 18 (0.79%), p=1.00.

Acute events at groin puncture site, n (%): Micra (TV-PPM preclude): 3 (0.55%), Micra (TV-PPM non-precluded): 13 (0.57%), p=1.00.

Acute thrombosis, n (%): Micra (TV-PPM preclude): 1 (0.18%), Micra (TV-PPM non-precluded): 4 (0.18%), p=1.00.

Acute pacing issues, n (%): Micra (TV-PPM preclude): 4 (0.73%), Micra (TV-PPM non-precluded): 15 (0.66%), p=0.78.

Acute cardiac rhythm disorder, n (%): Micra (TV-PPM preclude): 0 (0%), Micra (TV-PPM non-precluded): 1 (0.04%), p=1.00.

Acute infection, n (%): Micra (TV-PPM preclude): 2 (0.37%), Micra (TV-PPM non-precluded): 1 (0.04%), p=0.098.

Total cardiac effusion/perforation, n (%): Micra (TV-PPM preclude): 4 (0.74%), Micra (TV-PPM non-precluded): 19 (0.84%), p=0.80.

Total events at groin puncture site, n (%): Micra (TV-PPM preclude): 4 (0.76%), Micra (TV-PPM non-precluded): 14 (0.63%), p=0.72.

Total thrombosis, n (%): Micra (TV-PPM preclude): 1 (0.19%), Micra (TV-PPM non-precluded): 4 (0.18%), p=0.84.

Total pacing issues, n (%): Micra (TV-PPM preclude): 4 (0.83%), Micra (TV-PPM non-precluded): 21 (1.01 %), p=0.50.

Total cardiac rhythm disorder, n (%): Micra (TV-PPM preclude): 1 (0.21%), Micra (TV-PPM non-precluded): 2 (0.1%), p=0.69.

Total infection, n (%): Micra (TV-PPM preclude): 3 (0.62%), Micra (TV-PPM non-precluded): 2 (0.10%), p=0.083.

Both acute mortality (2.75% vs 1.32%; *P*=.022) and total mortality at 36 months (38.1% vs 20.6%; *P*<.001) were statistically higher in the precluded group than in the non-precluded group. Mortality was similar among non-precluded patients and patients implanted with a non-nitinol TV-PPM (control group).

Timing of adverse effects: implantation through 36 months

Factors that predict response: In multivariate predictors of mortality in patients receiving Micra, the covariates preclusion for transvenous pacing, age, BMI, CHF, COPD, diabetes, and renal dysfunction requiring dialysis all had significant associations. The same covariates along with AT/AF history and CAD showed significant associations in univariate analyses.

10.3 Source Citation: Goossens et al. 2018[30]

Study Design: RCT

Device or Material: SecurAcath (Nitinol) versus StatLock (non-nitinol) peripherally inserted central catheters (PICCs)

Contact Duration: Up to 180 days

Dose: NA

Frequency/Duration: Single administration

Response: bleeding/oozing/hematoma, catheter migration, leakage and loose dressing, medical adhesive-related skin injuries, pain at exit site, pain scores

Patient characteristics (gender, mean age): Females: 29/53 (StatLock); 21/52

(SecurAcath); Median age: 62 (StatLock); 64 (SecurAcath)

Number per Group: 105 patients: 53 (StatLock) 52 (SecurAcath); Dressing changes: 161 (StatLock); 164 (SecurAcath)

Observed adverse effects: Patient pain scores: Higher with SecurAcath than with StatLock at insertion (P=0.02) and at removal (P<0.001), however, no statistical difference was seen during the dressing change or during the dwell time. Adverse events at dressing change (no statistical differences between groups): *Bleeding/oozing/hematoma* 13% StatLock, 24% SecurAcath; *Pain at exit site* 9.9% StatLock, 10.4% SecurAcath; *Signs of exit site infection* 6.2% StatLock, 7% SecurAcath; *Medical adhesive-related skin injuries* 6% (StatLock), 7% SecurAcath; *Catheter migration (≥3cm)* 1% StatLock, 1% SecurAcath; *Leakage and loose dressing* 5% StatLock; 0% SecurAcath

Timing of adverse effects: Most adverse events occurred during the dressing changes, which was a median time of 7.3 minutes (95% CI: 6.4 minutes to 8.3 minutes) for StatLock and 4.3 minutes (95% CI: 3.8 minutes to 4.9 minutes) for SecurAcath. Patient pain scores were recorded at insertion, during dressing change, during dwell time, and at removal (or up to 180 days).

Factors that predict response: There is a learning curve for placement and removal of SecurAcath.

AF: atrial fibrillation; AT: atrial tachyarrhythmia; BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; CI: confidence interval; COPD: chronic obstructive pulmonary disease; NA: not applicable; RCT: randomized controlled trial; SR: systematic review; TV-PPM: transvenous permanent pacemaker

Table 11: Cosmetic - Health Effect (In Vivo) Human Studies

11.1 Source Citation: Kang and Kerstein 2016[32]

Study Design: Single arm

Device or Material: Nitinol earFold™ implantable clip system (Contract Medical International GmbH, Dresden, Germany) to treat prominent ears

Contact Duration: 18 months to 47 months

Dose: NR

Frequency/Duration: single administration

Response: bruising, erosion/extrusion, hypertrophic scarring, infection, pain, sensitivity, swelling

Patient characteristics (gender, mean age): 56% female, mean 24 years (range 7 to 57)

Number per Group: 39 patients (131 implants for 75 ears)

Observed adverse effects:

Bruising and swelling: 39 (100%) patients which increased within a few hours of treatment and subsided within 7 days of treatment

Temporary sensitivity to the implant: "most patients" when lying on their side, which disappeared in all patients by 12 weeks

Pain: number of patients not provided

Erosion/extrusion of the skin over the implant: 5 (13%) patients, 7 implants

Infection: 2 (5.1%) patients

Hypertrophic scarring associated with the incisions to insert the implant: 2 (5.1%) patients

Timing of adverse effects: all within 12 months of placement

Factors that predict response: NR

Table 12: Nitinol ENT - Health Effect (In Vivo) Human Studies

12.1 Source Citation: Serio et al. 2014[33]

Study Design: Nonrandomized comparative study

Device or Material: Silicone (Poliflex, Dumon); Metallic (Nitinol, Jomed, Multilink, Palmaz)

Contact Duration: Median duration in days (range): Silicone: 66 (1 to 1489); Metallic: 57.1 (1.1 to 145.4)

Dose: NR

Frequency/Duration: Mean stents per patient (SD): Silicone: 2.6 (1.9); Metallic: 1.3 (0.7)

Response: Breakage, major granulations requrining stent replacement, minor granulations, mucosal tear, ovalizations requiring dilations, stent dislocation

Patient characteristics (gender, mean age): Median age at first insertion, years (range):

Number per Group: 100 patients with 48 receiving silicone stents and 66 receiving silicone stents. A total of 232 stents were implanted with 112 silicone and 120 metallic. Silicone stents included 82 Dumon and 30 Poliflex, whereas, metallic included 69 Jomed, 20 Palmaz, 17 Multilink, and 14 Nitinol.

Observed adverse effects: Breakage: Nitinol 0 (0%), Poliflex 0 (0%), Dumon 0 (0%), Jomed 1 (1%), Multilink 0 (0%), Palmaz 1 (5%)

Major granulation (requiring stent replacement): Nitinol 1 (7%), Poliflex 5 (17%), Dumon 8 (10%), Jomed 0 (0%), Multilink 0 (0%), Palmaz 0 (0%)

Minor granulations: Nitinol 6 (43%), Poliflex 9 (30%), Dumon 22 (27%), Jomed 6 (9%), Multilink 2 (12%), Palmaz 1 (5%)

Mucosal tear: Nitinol 0 (0%), Poliflex 0 (0%), Dumon 0 (0%), Jomed 0 (0%), Multilink 1 (6%), Palmaz 0 (0%)

Ovalizations (requiring dilatations): Nitinol 0 (0%), Poliflex 0 (0%), Dumon 0 (0%), Jomed 53 (77%), Multilink 8 (47%), Palmaz 14 (70%)

Stent dislocation: Nitinol 4 (29%), Poliflex 10 (33%), Dumon 34 (41%), Jomed 0 (0%), Multilink 1 (6%), Palmaz 0 (0%)

Timing of adverse effects: Median duration in days (range): Silicone: 66 (1 to 1489); Metallic: 57.1 (1.1 to 145.4)

Factors that predict response: NR

Table 13: Nitinol Biliary Stent - Health Effect (In Vivo) Human Studies

13.1 Source Citation: Mohan et al. 2019[34]

Study Design: SR

Device or Material: Lumen-apposing metal stents (LAMS), AXIOS (Xlumena Inc., Mountain View, CA, USA) and Spaxus (Taewoong-Medical Co., Ilsan, Korea) stents, both are made of nitinol wire and fully covered with silicon.

Contact Duration: Follow-up ranged from 1 day to 411 days.

Dose: NR

Frequency/Duration: Single administration

Response: Bile leak, perforation, stent occlusion, stent migration and cholecystitis and/or cholangitis.

Patient characteristics (gender, mean age): male 37% to 65%, age range 25 to 93 years.

Number per Group: 393 patients (8 cohort studies)

Observed adverse effects: Adverse event rate for LAMS was 12.7% (95% CI 8.4-18.7), as compared to 17.5% (95% CI 10.2-28.2) for other SEMS (6 studies, 154 patients). Not significantly different. Bleeding 4.2%, bile leak 2.4%, stent occlusion 5.2%, perforation 2.3%, stent migration 3.2%. Rate of recurrent cholecystitis and/or cholangitis (6 studies, 301 patients, 11 events) was 4.6% (95% CI 2.6-8.0).

Timing of adverse effects: 1 to 411 days

Factors that predict response: NR

13.2 Source Citation: Dhondt et al. 2020[35]

Study Design: RCT

Device or Material: Covered stent - VIABIL endoprosthesis (W.L. Gore & Associates), an ePTFE-FEP–coated nitinol stent with antimigration anchoring fins. Uncovered stent - ZA biliary stent (Cook Europe, Limerick, Ireland), which is a handwoven nitinol SEMS with a Z-configuration and the laser-cut nitinol Zilver SEMS.

Contact Duration: median patency durations were 308 days (95% confidence interval [CI], 178–438 days) for covered stents and 442 days (95% CI, 172–712 days) for uncovered stents

Dose: NR

Frequency/Duration: Single stent

Response: Percutaneous bile leakage, Hemorrhage, Cholangitis, Cholecystitis, sepsis and septic shock, mortality at 30 days.

Patient characteristics (gender, mean age): Covered mean 68 years (30 male, 43 female), mean 69 years uncovered (34 male, 44 female).

Number per Group: 154 patients with malignant biliary obstruction, 73 covered patients, 78 uncovered patients.

Observed adverse effects: Complications and 30-day mortality were not statistically different between stent groups in the present study. Major complications – Covered 1 cardiac, 1 renal, 1 cholecystitis, 1 sepsis, 1 septic shock, mortality at 30 days 25%; uncovered 2 cardiac, 1 sepsis, 2 septic shock, mortality at 30 days 24%.

Timing of adverse effects: Estimated median survival durations in patients with covered and uncovered stents were 96 days (95% CI, 68– 124 d) and 75 days (95% CI, 42–108 d), respectively (P = .6). Timing of adverse events was not reported.

Factors that predict response: NR

13.3 Source Citation: Seo et al. 2019[36]

Study Design: RCT

Device or Material: WallFlex Biliary RX Fully Covered and Uncovered Stent, (Boston Scientific, Marlborough, Mass)

Contact Duration: up to 1 year

Dose: NR

Frequency/Duration: single stent

Response: Death, stent migration, stent occlusion due to tumor ingrowth, and acute cholecystitis.

Patient characteristics (gender, mean age): 111 patients with pancreatic cancer. Covered male 55.9%, 67 years; uncovered male 55%, 65 years.

Number per Group: Covered 59, uncovered 60

Observed adverse effects: Covered - acute cholecystitis 9.3%, acute pancreatitis 1.7%, cholangitis 15.3%, GI hemorrhage 1.7%, abdominal pain 1.7%, common bile duct obstruction 3.4%. Uncovered - acute cholecystitis 4.8%, acute pancreatitis 0%, cholangitis 13.3%, GI hemorrhage 0%, abdominal pain 3.3%, common bile duct obstruction 1.7%. No difference between stent groups. Comparing the covered and uncovered groups, there were significant differences in the reasons for self-expanding metal stents failure between the groups, notably tumor ingrowth in 0% and 16.7% ($P < .01$), and stent migration in 6.8% and 0% ($P = .03$), respectively.

Timing of adverse effects: up to 1 year, no specific timing was reported.

Factors that predict response: NR

13.4 Source Citation: Conio et al. 2018[37]

Study Design: RCT

Device or Material: Fully covered (Niti-S biliary ComVi, Taewoong Medical Co Ltd, Goyang-si, Gyeonggi-do, Korea) and self-conformable uncovered (Niti-S D-type, Taewoong Medical Co Ltd).

Contact Duration: patients were followed up to 6 months.

Dose: NR

Frequency/Duration: Single administration

Response: Occlusion, cholecystitis, migration

Patient characteristics (gender, mean age): Covered 50% male, median 77.5 years; uncovered 46.3% male, median 80 years.

Number per Group: 78 covered, 80 uncovered

Observed adverse effects: Adverse events occurred with 19 covered (26.4%) and 10 uncovered (13.2%); $P = .061$. Covered – occlusion 16.7%, cholangitis because of stent occlusion 8.3%, cholecystitis 2.8%, migration 6.9%. Uncovered - occlusion 13.2%, cholangitis because of stent occlusion 7.9%, cholecystitis 0%, migration 0%.

Timing of adverse effects: No specific times were reported. Median follow-up was 99.5 days for covered, and 108 for uncovered.

Factors that predict response: NR

13.5 Source Citation: Martins et al. 2018[38]

Study Design: RCT

Device or Material: fully covered self-expandable metal stents (cSEMSs) Wallflex, Boston Scientific compared with plastic stents (no manufacturer reported). Patients underwent regular endoscopic retrograde cholangiopancreatography (ERCP) after liver transplant.

Contact Duration: up to 1 year. Covered stent in place for a mean 158.5 days. Plastic stents were exchanged every 3 months over 1 year.

Dose: NR

Frequency/Duration: Patients were randomized to single covered stents for 6 months or to plastic stent placement, exchanged every 3 months over 1 year.

Response: Major adverse events - bleeding, acute pancreatitis, severe cardiopulmonary distress, minor - pain, stent migration or clogging, mild cardiopulmonary distress.

Patient characteristics (gender, mean age): Covered 73% male, mean 52.9 years; plastic stent 69%, mean 50.4 years

Number per Group: Covered n = 30, plastic n = 29

Observed adverse effects: Adverse events occurred in 23.3% and 6.4% of ERCPs in the covered and plastic groups, respectively (P < .01). Acute pancreatitis 13.3% covered, 2.1% plastic (p < 0.01). Severe abdominal pain, requiring hospital admission – 6.3% covered, 0.7% plastic. Migration – 10% covered, 2.8% plastic.

Timing of adverse effects: NR

Factors that predict response: "The discrepancy in the acute pancreatitis rate was attributed to the initial decision to not perform sphincterotomy before [covered stent] deployment."

13.6 Source Citation: Lee et al. 2016[39]

Study Design: RCT

Device or Material: Covered ComVi stent (Niti-S stent, ComVi type, Taewoong Medical Inc, Korea) and an uncovered nitinol metal stent (HANAROSTENT, M.I. Tech Co., Ltd., Korea).

Contact Duration: Median follow-up period was 112 days (range, 7–512 days).

Dose: NR

Frequency/Duration: Single administration

Response: Occlusion, cholangitis

Patient characteristics (gender, mean age): Covered 73% male, mean 69 years; uncovered 62%, mean 65.5 years

Number per Group: Covered n = 22, uncovered n = 21

Observed adverse effects: Covered – 72.7% occlusion, 50% cholangitis; uncovered 66.7% occlusion, 47.6% cholangitis. No significant differences.

Timing of adverse effects: NR

Factors that predict response: NR

13.7 Source Citation: Yang et al.[40]

Study Design: RCT

Device or Material: partially covered or uncovered BONASTENT (Standard Sci-Tech Inc, Seoul, South Korea)

Contact Duration: 1 year follow-up

Dose: NR

Frequency/Duration: Single administration

Response: Stent dysfunction, pancreatitis, and cholecystitis.

Patient characteristics (gender, mean age): Covered 67%, man 68.7 years; uncovered 58%, mean 68.0 years

Number per Group: Covered n = 51, uncovered n = 52

Observed adverse effects: "The rate of overall adverse events following SEMS placement was 47.1% in the partially covered group and 38.5% in the uncovered group (p = 0.378)." Covered – stent dysfunction 33.3%, pancreatitis 5.9%, cholecystitis 11.1%; uncovered - stent dysfunction 28.8%, pancreatitis 0.0%, cholecystitis 6.0%

Timing of adverse effects: NR

Factors that predict response:

13.8 Source Citation: Soderlund et al. 2014[41]

Study Design: RCT

Device or Material: Steel alloy (Wallstent; Boston Scientific Nordic AB, Helsingborg, Sweden), nitinol alloy (Wallflex; Boston Scientific Nordic AB)

Contact Duration: Patient median survival times were 137 days and 120 days in the steel and nitinol stent groups, respectively (P= 0.25).

Dose: NR

Frequency/Duration: Single administration

Response: Pancreatitis, cholangitis, cholecystitis

Patient characteristics (gender, mean age): Steel 55% male, median 78 years; nitinol 45%, median 78 years.

Number per Group: Steel n = 169, nitinol n = 180

Observed adverse effects: Steel – pancreatitis 1.5%, cholecystitis 1.5%, cholangitis 2%; nitinol - pancreatitis 1.0%, cholecystitis 1.5%, cholangitis 2.5%

Timing of adverse effects: NR

Factors that predict response: NR

13.9 Source Citation: Lee et al. 2014[42]

Study Design: RCT

Device or Material: Zilver self-expanding stent (Cook, Inc, Bloomington, Indiana), which is made of nitinol, was used for the uncovered stent group. The Niti-S stent, ComVi type (Taewoong Medical Co, Ltd, Seoul, Korea), which is made with a biocompatible polytetrafluoroethylene membrane and nitinol stent mesh, was used for the covered stent group.

Contact Duration: Mean follow-up was 170 days

Dose: NR

Frequency/Duration: Single administration

Response: Pancreatitis, cholecystitis

Patient characteristics (gender, mean age): Covered mean 62.1 years, male 45%; uncovered mean 63.2 years, male 45%

Number per Group: Covered n = 20, uncovered n = 20

Observed adverse effects: "Major complications occurred in 5% of patients in the covered stent group and none of the patients in the uncovered stent group." No pancreatitis occurred in patients in either stent group. One patient in the covered stent group developed acute cholecystitis.

Timing of adverse effects: NR

Factors that predict response: NR

13.10 Source Citation: Kitano et al. 2013[43]

Study Design: RCT

Device or Material: Covered or uncovered stents (Wallflex biliary RX stent, Boston Scientific, Natick, MA)

Contact Duration: Mean follow-up was 233 days. Median survival was 285 and 222 days in the covered and uncovered groups, respectively

Dose: NR

Frequency/Duration: Single administration

Response: Pancreatitis, cholecystitis, migration

Patient characteristics (gender, mean age): Covered male 42%, mean 70.6 years; uncovered male 48.3%, mean 68.7 years

Number per Group: Covered n = 60, uncovered n = 60

Observed adverse effects: Acute pancreatitis occurred in only one patient, who had received a covered stent. Acute cholecystitis occurred in only one patient, who had received a covered stent, and in two patients in the uncovered stent group. There was no significant difference in the incidence of serious adverse events between the two groups.

Timing of adverse effects: NR

Factors that predict response: NR

Abbreviations: CI = confidence interval; ePTFE = expanded polytetrafluoroethylene; FEP = fluorinated ethylene propylene; LAMS = Lumen-apposing metal stents; RBO = recurrent biliary obstruction; RR = risk ratio; SEMS = self-expandable metal stent

Table 14: Nitinol Gastro - Pancreatic - Health Effect (In Vivo) Human Studies

14.1 Source Citation: Kayal et al. 2021[44]

Study Design: Nonrandomized comparative study

Device or Material: Nitinol: LAMS (Hot Axios, Boston Scientific Corporation, Marlborough, USA), Nitinol: FCSEMS (Wallflex stent, Boston Scientific Corporation, Marlborough, USA or Niti stent, Taewoong-Medical, Ilsan, Korea), Non-Nitinol: DPPS (Zimmon biliary stent, Cook Medical, Winston-Salem, USA)

Contact Duration: Up to 3 months, LAMS were removed 2-4 weeks after insertion

Dose: DPPS: 7-9 cm x 10 cm diameter, FCSEMS: 4 cm x 10 mm, LAMS: 10 mm x 15 mm

Frequency/Duration: Implantation with one or two stents

Response: Abscess, bleeding, cyst leak, migration, pain, perforation, splenic laceration

Patient characteristics (gender, mean age): Median age in years (IQR): DPPS: 60 (52-74), FCSEMS: 50 (37-56), LAMS: 51 (40-62); Female, n (%): DPPS: 5 (41.7%), FCSEMS: 10 (52.6%), LAMS: 9 (33.3%)

Number per Group: DPPS: 12, FCSEMS: 19, LAMS: 27

Observed adverse effects: Early AEs (up to 14 days), n (%): Bleeding: DPPS: 2 (16.6%), FCSEMS: 1 (5.3%), LAMS: 0 (0%); Cyst leak: DPPS: 0 (0%), FCSEMS: 0 (0%), LAMS: 0 (0%); Migration/Perforation: DPPS: 1 (8.3%), FCSEMS: 1 (5.3%), LAMS: 0 (0%); Pain: DPPS: 1 (8.3%), FCSEMS: 0 (0%), LAMS: 0 (0%)

Late AEs (after 14 days), n (%): Bleeding: DPPS: 0 (0%), FCSEMS: 2 (10.5%), LAMS: 1 (3.7%), Migration: DPPS: 0 (0%), FCSEMS: 3 (15.8%), LAMS: 0 (0%); Perforation: DPPS: 1 (8.3%), FCSEMS: 0 (0%), LAMS: 0 (0%); Pain: DPPS: 1 (8.3%), FCSEMS: 0 (0%), LAMS: 0 (0%); Abscess: DPPS: 0 (0%), FCSEMS: 1 (5.3%), LAMS: 0 (0%); Splenic laceration: DPPS: 0 (0%), FCSEMS: 0 (0%), LAMS: 1 (3.7%)

Timing of adverse effects: AEs divided into early (up to 14 days) or late (after 14 days) classifiers.

Factors that predict response: NR

14.2 Source Citation: Abu Dayyeh et al. 2018[47]

Study Design: Nonrandomized comparative study

Device or Material: Nitinol: LC-SEMS (Axios or Niti-S), Non-nitinol: DPPS

Contact Duration: Patients followed until WON resolution: median 8 weeks (IQR 6-12)

Dose: LC-SEMS: Axios 15 mm, Niti-S 18 mm, or Niti-S 20 mm; DPPS: 7Fr or 10 Fr

Frequency/Duration: Single implantation

Response: Abdominal compartment syndrome, bleeding requiring endoscopic intervention, bleeding requiring IR, bleeding requiring surgery, gastric varices, migration of stents, perforation managed non-surgically, perforation requiring surgery, portal vein thrombosis, sepsis (ICU transfer), SMV thrombosis, splenic vein thrombosis, stent occlusion, Mortality, new-onset DM

Patient characteristics (gender, mean age): Mean age in years (SD): DPPS: 59.7 (15), LC-SEMS: 52.7 (17); Male, n (%): DPPS: 28 (78%), LC-SEMS: 45 (78%)

Number per Group: DPPS: 36, LC-SEMS: 58

Observed adverse effects: Abdominal compartment syndrome, n (%): DPPS: 0 (0%), LC-SEMS: 1 (2%), p=0.08.

Bleeding requiring endoscopic intervention, n (%): DPPS: 5 (14%), LC-SEMS: 1 (2%), p=0.02, favors LC-SEMS.

Bleeding requiring IR, n (%): DPPS: 2 (6%), LC-SEMS: 2 (3%), p=0.63.

Bleeding requiring surgery, n (%): DPPS: 0 (0%), LC-SEMS: 1 (2%), p=0.42.

Gastric varices, n (%): DPPS: 3 (8%), LC-SEMS: 5 (9%), p=0.96.

Migration of stents, n (%): DPPS: 7 (19%), LC-SEMS: 12 (21%), p=0.80.

Perforation managed non-surgically, n (%): DPPS: 3 (8%), LC-SEMS: 1 (2%), p=0.07.

Perforation requiring surgery, n (%): DPPS: 0 (0%), LC-SEMS: 0 (0%), p>0.99.

Portal vein thrombosis, n (%): DPPS: 4 (11%), LC-SEMS: 4 (7%), p=0.48.

Sepsis (ICU transfer), n (%): DPPS: 2 (6%), LC-SEMS: 2 (3%), p=0.63.

SMV thrombosis, n (%): DPPS: 3 (8%), LC-SEMS: 5 (9%), p=0.96.

Splenic vein thrombosis, n (%): DPPS: 4 (11%), LC-SEMS: 8 (14%), p=0.70.

Stent occlusion, n (%): DPPS: 1 (3%), LC-SEMS: 2 (3%), p=0.85.

Mortality, n (%): DPPS: 2 (6%), LC-SEMS: 1 (2%), p=0.31.

New-onset DM, n (%): DPPS: 1 (3%), LC-SEMS: 2 (3%), p=0.85.

Timing of adverse effects: Patients followed until WON resolution: median 8 weeks (IQR 6-12)

Factors that predict response: NR

14.3 Source Citation: Law et al. 2018[46]

Study Design: Nonrandomized comparative study

Device or Material: Nitinol: FCSEMS (Wallflex or Hanarostent) or Nitinol: LAMS (Axios)

Contact Duration: FCSEMS: 9 weeks (SD 5), LAMS: 10 weeks (SD 4.5)

Dose: FCSEMS: 10 x 60 mm, Axios: 15 x 10 mm or 10 x 10 mm

Frequency/Duration: Single implantation

Response: Bleeding, dislodged during necrosectomy, recurrence, spontaneous migration, stent revision, technical success

Patient characteristics (gender, mean age): Mean age in years (SD): FCSEMS: 66 (32), LAMS: 70 (26); Male, n (%): FCSEMS: 13 (59.1%), LAMS: 32 (69.6%)

Number per Group: FCSEMS: 22, LAMS: 46

Observed adverse effects: Bleeding: FCSEMS: 2 (9.1%), LAMS: 9 (19.6%); dislodged during necrosectomy: FCSEMS: 2 (9.1%), LAMS: 3 (6.5%); recurrence: FCSEMS: 0 (0%), LAMS: 3 (6.5%); spontaneous migration: FCSEMS: 1 (4.5%), LAMS: 6 (13.0%); stent revision: FCSEMS: 3 (13.6%), LAMS: 15 (32.6%); technical success: FCSEMS: 22 (100%), LAMS: 43 (93.5%)

Timing of adverse effects: FCSEMS: 9 weeks (SD 5), LAMS: 10 weeks (SD 4.5)

Factors that predict response: NR

14.4 Source Citation: Wang et al. 2018[45]

Study Design: Nonrandomized comparative study

Device or Material: Non-Nitinol: DPPS (Cook Medical), Nitinol: FCSEMS (Wallflex, Boston Scientific), Nitinol: LAMS (Micro-Tech)

Contact Duration: Stents removed within 3 to 8 weeks

Dose: DPPS: 7F or 10F, FCSEMS: 10 x 40 mm, LAMS: 16 mm inner diameter, 20 mm length

Frequency/Duration: Single or multiple stents

Response: Bleeding, migration, occlusion/infection, recurrence, re-intervention, technical success, Mortality

Patient characteristics (gender, mean age): Mean age in years (SD): DPPS: 46.6 (15.9), FCSEMS: 49.7 (9.9), LAMS: 45.4 (14.4); Female, n: DPPS: 26, FCSEMS: 12, LAMS: 18

Number per Group: DPPS: 52, FCSEMS: 27, LAMS: 70

Observed adverse effects: End of follow-up: Technical success: DPPS: 58 (93.5%), FCSEMS: 27 (96.4%), LAMS: 66 (94.3%); re-intervention: DPPS: 7 (13.5%), FCSEMS: 7 (25.9%), LAMS: 18 (27.7%); recurrence: DPPS: 6 (13.6%), FCSEMS: 5 (21.7%), LAMS: 5 (8.6%), Mortality: DPPS: 0, FCSEMs: 0, LAMS: 2

Early AEs, n/N (within 2 weeks): occlusion/infection: DPPS: 9/52, FCSEMS: 5/27, LAMS: 12/65; bleeding: DPPS: 4/52, FCSEMS: 2/27, LAMS: 3/65; migration: DPPS: 0/52, FCSEMS: 3/27, LAMS: 1/65

Late AEs, n/N (>2 weeks): occlusion/infection: DPPS: 3/52, FCSEMS: 0/27, LAMS: 1/65; bleeding: DPPS: 0/52, FCSEMS: 1/27, LAMS: 1/65; migration: DPPS: 10/52, FCSEMS: 3/27, LAMS: 1/65

Timing of adverse effects: AEs divided into early and late subgroups, or AEs described as cumulative until the end of follow-up (6 months)

Factors that predict response: NR

14.5 Source Citation: Bekkali et al. 2017[48]

Study Design: Nonrandomized comparative study

Device or Material: Nitinol: BFMS (NAGI; Taewoong Medical, Gyenoggi-do, Korea), Nitinol: LAMS (Hot AXIOS, Boston Scientific)

Contact Duration: Up to 30 days

Dose: BFMS: 14- or 16-mm diameter and 20- or 30-mm length; LAMS: 15 x 10 mm

Frequency/Duration: Single or multiple implantation

Response: Additional percutaneous drain, clinically significant stent migration, dislodged stent during necrosectomy, percutaneous drainage post-EUS, percutaneous drainage prior to EUS, stent deployment failure, stent misplacement, surgical debridement, Mortality

Patient characteristics (gender, mean age): Median age (range): BFMS: 63 (11 to 81), LAMS: 57 (19 to 81); Male, n (%): BFMS: 27 (67.5%), LAMS: 18 (56.3%)

Number per Group: BFMS: 40 patients (44 stents), LAMS: 32 patients (33 stents)

Observed adverse effects: Additional percutaneous drain, n: BFMS: 3, LAMS: 4, p=0.45.

Clinically significant stent migration, n: BFMS: 2, LAMS: 0, p=0.50.

Dislodged stent during necrosectomy, n: BFMS: 5, LAMS: 3, p>0.99.

Percutaneous drainage post-EUS, n: BFMS: 3, LAMS: 4, p=0.70.

Percutaneous drainage prior to EUS, n: BFMS: 9, LAMS: 7, p>0.99.

Stent deployment failure, n: BFMS: 2, LAMS: 0, p=0.50.

Stent misplacement, n: BFMS: 2, LAMS: 1, p>0.99.

Surgical debridement, n: BFMS: 2, LAMS: 0, p=0.50.

Mortality, n: BFMS: 3, LAMS: 1

Timing of adverse effects: Up to 30 days

Factors that predict response: NR

14.6 Source Citation: Siddiqui et al. 2017[49]

Study Design: Nonrandomized comparative study

Device or Material: Non-Nitinol: DPPS, Nitinol: FCSEMS (Wallflex, BSC, Marlborough, Massachusetts or Viabil, Gore, Utitca, NY), Nitinol: LAMS (Hot AXIOS, Boston Scientific)

Contact Duration: 6 months

Dose: DPPS: 2 10F stents, FCSEMS: 10 x 40 mm or 10 x 60 mm, LAMS: 15 x 10 mm or 10 x 10 mm

Frequency/Duration: DPPS: 2 stents, FCSEMS: single stent + DPPS stent, LAMS: single stent

Response: Bleeding, perforation, stent migration, stent occlusion leading to infection, suprainfection, technical success

Patient characteristics (gender, mean age): Mean age in years: DPPS: 56.3, FCSEMS: 51.9, LAMS: 51.5; Female, n: DPPS: 38, FCSEMS: 26, LAMS: 9

Number per Group: DPPS: 106, FCSEMS: 121, LAMS: 86

Observed adverse effects: Technical success occurred in 99.05% of DPPS stents, 100% of FCSEMS stents, and 97.7% of LAMS stents. The following AEs were classified as early or late based on timing. Early adverse events (within 1 week of procedure): bleeding, n: DPPS: 2, FCSEMS: 0, LAMS: 6, p=0.006, significant differences between groups; suprainfection, n: DPPS: 5, FCSEMS: 1, LAMS: 1, p=0.1; perforation, n: DPPS: 1, FCSEMS: 1, LAMS: 3, p=0.25. Late AEs (after 1 week): stent occlusion leading to infection, n: DPPS: 23, FCSEMS: 26, LAMS: 3, p=0.0006, differences between groups; stent migration, n: DPPS: 3, FCSEMS: 7, LAMS: 0, p=0.063.

Timing of adverse effects: Technical success was assessed at 6-month follow-up. Adverse events were classified as early if they occurred within 7 days, and late AEs occurred between 7 days and 6 months.

Factors that predict response: Regarding predictors of all adverse events (early and late), FCSEMSs had lower overall adverse events compared with DP stents (OR, 11.8; 95% CI, 2.5-54; P Z .002) and LAMS (OR, 6.5; 95% CI, 1.3-32.2; P Z .02) even when adjusting for sex, age, cyst size, and number of endoscopic sessions.

14.7 Source Citation: Sharaiha et al. 2015[50]

Study Design: Nonrandomized comparative study

Device or Material: Nitinol: FCSEMS (Wallflex, Boston Scientific or Viabil, Gore), Non-Nitinol: DPPS

Contact Duration: Up to 12 months

Dose: FCSEMS: 10 x 40 mm or 10 x 60 mm

Frequency/Duration: DPPS: 2 stents, FCSEMS: 1 nitinol stent and 1 DPPS

Response: Bleeding, infection, migration, occlusion, perforation

Patient characteristics (gender, mean age): Mean age in years (SD): FCSEMS: 53.2 (16), DPPS: 52.2 (17); Female, n (%): FCSEMS: 50 (45%), DPPS: 36 (31%)

Number per Group: FCSEMS: 112, DPPS: 118

Observed adverse effects: Early AEs (within 30 days): Occlusion: FCSEMS: 4; DPPS: 8; Migration: FCSEMS: 1, DPPS: 1; Infection: FCSEMS: 6, DPPS: 16, Perforation: FCSEMS: 2, DPPS: 5; Bleeding: FCSEMS: 3, DPPS: 6. Significant differences seen between groups favoring FCSEMS for overall early AEs (p=0.008)

Late AEs (after 30 days): Occlusion: FCSEMS: 2, DPPS: 1, p=0.735.

Timing of adverse effects: Early AEs occurred within 30 days, and late AEs occurred between 30 days and 12 months.

Factors that predict response: Greater number of endoscopy sessions was a predictor of higher AEs (OR 1.81, 95% CI: 1.14 to 2.86, p=0.01). No other covariates (sex, age, date of enrollment, and cyst size) predicted higher AEs.

BFMS: bi-flagged metal stent; CI: confidence interval; DM: diabetes mellitus; DPPS: double pigtail plastic stent; EUS: endoscopic ultrasound; FCSEMS: fully covered self-exposing metal stent; ICU: intensive care unit; IQR: interquartile range; IR: interventional radiology; LAMS: lumen-apposing metal stent; LC-SEMS: large-caliber fully covered self-expandable metal stents; NR: not reported; OR: odds ratio; SD: standard deviation; SMV: superior mesenteric vein; WON: walled-off necrosis

Table 15: Gastrointestinal – stomach/colon/rectum - Health Effect (In Vivo) Human Studies

15.1 Source Citation: Hamid et al. 2021[52]

Study Design: Systematic review of self-expandable metallic stent (SEMS); 23 single-arm studies (11 studies exclusively used nitinol stents, 12 studies used nitinol and non-nitinol stents) to manage sleeve gastrectomy leak

Device or Material: nitinol stents included Ultraflex and Wallflex (Boston Scientific, Marlborough, MA), Niti-S (Taewong Medical, Korea), Hanaro ECBB, Hanaro GastroSeal, Hanaro, Hanaro colorectal and Choo (M.I. Tech, Korea), Hanarostent (Life Partner Europe, France), Alimaxx-ES (Merit Medical, USA), Endoflex (Endotechniek, Germany), Evolution (Cook Medical, Bloomington, IN), and Alveolus (Alveolus, USA)

Contact Duration: mean 8.4 months

Dose: NR

Frequency/Duration: NR

Response: migration (dislocation requiring repositioning or extraction)

Patient characteristics (gender, mean age): 58% females, 38 years

Number per Group: 130 patients were enrolled in studies exclusively receiving nitinol stents

Observed adverse effects: Migration occurred in:

0%: 3 studies (n=19) with Hanaroo ECBB, Hanaroo, and Hanarostent

10 to 20%: 3 studies (n=35) with Wallflex, Hanaro, Hanaro colorectal, Choo, Endoflex

20 to 25%: 2 studies (n=45) with Hanaroo ECBB and Hanaro GastroSeal

37%: 1 study (n=19) with Hanaro

60%: 1 study (n=5) with Wallflex and Alimaxx-ES

86%: 1 study (n=7) with Hanaro ECBB

While bleeding (4), perforation (3), intractable symptoms (9), device malfunction (7) and device-related mortality (1) occurred, data was not reported separately for nitinol and non-nitinol devices.

Timing of adverse effects: NR

Factors that predict response: NR

15.2 Source Citation: Jang et al. 2019[58]

Study Design: Nonrandomized comparative

Device or Material: endoscopic placement of SEMS with WallFlex duodenal stent or Evolution duodenal stent vs. gastrojejunostomy (GJ) for palliation of malignant gastric outlet obstruction (GOO)

Contact Duration: mean days 119 SEMS, 193 GJ

Dose: NR

Frequency/Duration: NR

Response: aspiration, perforation, bleeding

Patient characteristics (gender, mean age): 45% female, 66.8±13.1 years

Number per Group: 183 SEMS, 127 GJ

Observed adverse effects: Overall rate of adverse outcomes was significantly higher with GJ (16.6% vs 6.4%).

Aspiration: 5 SEMS, 6 GJ

Bleeding: 4 SEMS, 8 GJ

Perforation/leak: 5 SEMS, 4 GJ

Intraoperative death: 1 GJ

Timing of adverse effects: NR

Factors that predict response: NR

15.3 Source Citation: Ahn et al. 2016[59]

Study Design: Nonrandomized comparative

Device or Material: endoscopic SEMS with Hanarostent (M.I. Tech, Seoul, South Korea) and Bonastent (Standard Sci-Tech, Seoul, South Korea) vs. palliative surgery (68.3% primary resection with anastomosis, 12.2% bypass, 9.8% each colostomy or ileostomy, and Hartmann's operation) in patients with unresectable colorectal cancer obstruction

Contact Duration (days): 247.5 (2 to 899) SEMS, 319.1 (9 to 1636) surgery

Dose: NR

Frequency/Duration: 5 patients required an additional stent within 30 days of 1st placement. 5 patients required a 2nd stent placement, and 3 patients required a 3rd stent placement after 30 days of 1st stent placement.

Response: colonic perforation, death due to bleeding, inappropriate stent expansion, stent migration, stent obstruction caused by tumor ingrowth/outgrowth, stoma

Patient characteristics (gender, mean age): 61% male; 67.3 SEMS, 64.3 surgery

Number per Group: 73 SEMS, 41 palliative surgeries

Observed adverse effects:

30-day adverse events with SEMS: 3 (4.1%) stent migration, 2 (2.7%) inappropriate stent expansion, 1 stent obstruction caused by tumor ingrowth, and 2 colonic perforations.

Late AEs (>30 days) with SEMS: 12 (16.4%) obstruction caused by tumor ingrowth (n=10) or tumor outgrowth (n=2), 2 migration, 1 death due to postoperative bleeding, 6 (8.2%) late colonic perforation.

Late AEs (SEMS vs surgery): stoma in 13/73 (17.8%) SEMS, 10/41 24.4% surgery; p=0.401.

Late AEs with surgery occurred in 4 patients (2 postoperative ileus, 2 intestinal obstruction); no deaths occurred. Late AE rate was significantly higher with SEMS (27.4% vs. 9.8%; p=0.005).

Timing of adverse effects: With SEMS, early colonic perforation (n=2) developed on days 14 and 15, while late colonic perforation (n=6) occurred on days 125, 202, 333, 403, 507, and 629.

Factors that predict response: NR.

15.4 Source Citation: Li et al. 2016[53]

Study Design: Systematic review of 8 RCTs

Device or Material: Niti memory shape device as a compression anastomosis clip (CAC) or ring (CAR) vs. stapler for gastrointestinal and colorectal anastomosis

Contact Duration (days): Time to expel for CAC was 5 to 7 (2 studies), 7 to 10 (1 study), 11±2.5 (1 study), 10 to 30 (1 study), and 15.1± 6.04; time to expel for CAR was mean 11.3±8.9 (1 study); followup mostly 6 months for CAC, 3 months for CAR

Dose: compression power of 400 g/cm^2 with CAC

Frequency/Duration: NR

Response: abscess, hematoma, obstruction, device malfunction, anastomotic leakage

Patient characteristics (gender, mean age): NR

Number per Group: 287 Niti CAC vs. stapler (7 RCTs), 60 Niti CAR vs. stapler (1 RCT)

Observed adverse effects:

CAC vs. stapler: Fewer postoperative complications with CAC (4 CAC, 7 staplers; Odds ratio 0.55 (95% CI: 0.16 to 1.9, p=0.34).

Obstruction: 2 CAC (adherent intestinal obstruction distant from the anastomosis site, small bowel obstruction), 3 staplers (small bowel obstruction, 2 adhesion obstruction in small bowel)

Hematoma (left subphrenic-infected): 1 CAC

Abscess: 1 CAC (subphrenic), 1 stapler (intraabdominal)

Device malfunction: 2 CAC. 2 anastomosis clips did not expel with stool in 1 study. One patient who died 35 days after surgery did not expel the ring. The clip was removed by gastroscopy in 1 patient with adhesive ileus on postoperative day 16.

Wound infection, anastomotic bleeding, and pseudomembranous colitis occurred in 1 patient each with stapler.

CAR vs. stapler: anastomotic leakage after low anterior resection in 1 patient in each group.

Timing of adverse effects: NR.

Factors that predict response: NR.

15.5 Source Citation: Li et al. 2014[54]

Study Design: Randomized controlled trial

Device or Material: Niti S Colorectal Stent (Taewoong Medical Inc., Gimpo-si, Korea) vs. transanal drainage tube (TDT) for decompression of acute left-sided malignant colorectal obstruction

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: No complications

Patient characteristics (gender, mean age): 62% male, 73.3 Niti S, 72.6 TDT

Number per Group: 16 Niti S, 13 TDT

Observed adverse effects: 1 perforation was reported in the TDT arm.

Timing of adverse effects: Not applicable (N/A)

Factors that predict response: NR

15.6 Source Citation: Van Halsema et al. 2014[51]

Study Design: Systematic review of 86 studies

Device or Material: uncovered nitinol colorectal stents: Comvi Stent (Taewoong Medical Co; Gimpo, South Korea), Hanarostent (M.I. Tech; Seoul, Korea), (Taewoong Medical Co), Niti-S D-type colorectal stent (Taewoong Medical Co), Ultraflex Precision colonic stent (Boston Scientific), and WallFlex colonic stent (Boston Scientific); vs. a covered nitinol stent: Niti-S colorectal covered with polyurethane; vs. non-nitinol stents: Dual stent, Wallstent

Contact Duration: days until perforation: 0 (29%), 1 to 3 (23.3%), 4 to 7 (14.2%), 8 to 14 (10.8%), 15 to 30 (6.8%), >30 (15.9%)

Dose: NR

Frequency/Duration: 8 patients had restenting

Response: perforation

Patient characteristics (gender, mean age): NR

Number per Group:

1496 uncovered nitinol stents including 126 Comvi, 388 Hararostent, 221 Niti-S D-type, 338 Ultraflex, 423 WallFlex.

125 covered nitinol stents: 125 Niti-S covered colorectal

1242 non-nitinol stents including, 283 Dual stents, and 959 Wallstents.

Observed adverse effects:

Perforation with uncovered nitinol stents: 10.9% WallFlex, 10.8% Comvi, 10.3% Niti-S D-type, 7.2% Ultraflex, 4.7% Hanarostent.

Perforation with a covered nitinol stent: 3.1% Niti-S covered colorectal

Perforation with non-nitinol stents: 7.7% Wallstent, 8.7% Dual stent.

Timing of adverse effects: Some nitinol stents had delayed perforation (36.4% WallFlex stents and 25% Comvi stents).

Factors that predict response: NR

15.7 Source Citation: Gianotti et al. 2013[57]

Study Design: Nonrandomized controlled trial

Device or Material: nitinol self-expandable metallic stents (SEMS) with Hanarostent (M.I. Tech Co., Gyeonggi-Do, Korea) vs. immediate surgery without stenting (NO-SEMS) for large-bowel obstruction

Contact Duration: 37 to 350 days

Dose: NR

Frequency/Duration: 10 patients underwent stent replacement

Response: abdominal-rectal pain, anastomotic leak, bowel perforation, colorectal bleeding, incisional hernia, migration, new episodes of intestinal obstruction, peritonitis, recurrent abdominal pain, stoma formation, tenesmus

Patient characteristics (gender, mean age): SEMS: 65.4% male, 25 to 96 years; NO-SEMS: 56.9% male, 40 to 86 years

Number per Group: 81 SEMS (49 stenting as a bridge to elective surgery; 34 for definitive palliation); 51 no stenting (NO-SEMS)

Observed adverse effects:

SEMS: short-term complications (n=81): 6 (7.4%) abdominal-rectal pain, 4 (4.9%) migration, 3 (3.7%) colorectal bleeding, 1 (1.2%) bowel perforation, and 1 (1.2%) tenesmus (cramping rectal pain).

SEMS: long-term complications (n=32) 1 (3.1%) bowel perforation, 4 (12.5%) SEMS migration**,** 7 (21.9%) tenesmus, 7 (21.9%) recurrent abdominal pain, and 8 (25%) colorectal bleeding. Complications occurred at median interval of 116 days from stent placement (range, 37 to 350 days).

SEMS as a bridge to surgery vs. NO-SEMS up to median 43 months:

Short-term complications (49 SEMS, 51 NO-SEMS): anastomotic leak (6 (12.2%) SEMS, 10 (19.6%) NO-SEMS; p=0.415), and peritonitis (2 (4.1%) SEMS, 5 (9.8%) NO-SEMS; p=0.436).

Long-term complications (48 SEMS, 50 NO-SEMS): statistically significantly lower definitive stoma formation (3 (6.3%) SEMS, 13 (26%) NO-SEMS; p=0.012), and incisional hernia (3 (6.3%) SEMS, 11 (22%) NO-SEMS; p=0.04) with SEMS. No significant differences were reported for recurrent abdominal pain (6 (12.5%) SEMS, 12 (24%) NO-SEMS; p=0.193), colorectal bleeding (4 (8.3%) SEMS, 6 (12%) NO-SEMS; p=0.74), new episodes of intestinal obstruction (3 (6.3%) SEMS, 5 (10%) NO-SEMS; p=0.715), and tenesmus (4 (8.3%) SEMS, 4 (8%) NO-SEMS; p=1.00).

Timing of adverse effects: stent-related complications occurred from 37 to 350 days

Factors that predict response: NR

15.8 Source Citation: Sauer et al. 2013[56]

Study Design: Randomized controlled trial

Device or Material: Nitinol endoluminal mechanical device (Satisphere) vs. control for treatment of obesity

Contact Duration: device removal at 3 months

Dose: NR

Frequency/Duration: single administration

Response: abdominal pain, migration (study prematurely terminated because of this complication)

Patient characteristics (gender, mean age): 65% female, 42.9 years

Number per Group: 21 Satisphere, 10 controls

Observed adverse effects: Satisphere migration occurred in 10 (48%) patients; emergency surgery required in 2 patients. Abdominal pain occurred in 1 (5%) patient with Satisphere.

Timing of adverse effects: Migration <3 months. Abdominal pain after 2 months.

Factors that predict response: NR

15.9 Source Citation: Hur et al. 2011[55]

Study Design: Randomized controlled trial

Device or Material: CAC with NiTi Hand CAC™ 30 (Niti™ Surgical Solution, Netanya, Israel) vs. hand suture technique (control) for jejunojejunostomy in gastric cancer surgery

Contact Duration: 4 to 21 days

Dose: NR

Frequency/Duration: reanastomosis in 2 patients due to leakage at the jejunojejunostomy site

Response: Esophagojejunostomy (EJ) bleeding, EJ leakage, fluid collection, foreign body, jejunojejunostomy leakage

Patient characteristics (gender, mean age): 75% male, median 53 years (range 25-82)

Number per Group: 20 CAC, 24 controls

Observed adverse effects:

EJ leakage: 1 CAC, 2 hand suture

EJ bleeding: 1 CAC

Fluid collection: 2 CAC, 2 hand suture

Jejunojejunostomy leakage: 2 CAC

Foreign body: 1 CAC

The following complications only occurred in the hand suture group: pancreas leakage (2), colon perforation (1), and wound infection (1).

Timing of adverse effects: Jejunojejunostomy leakage occurred "in the early period."

Factors that predict response: NR

15.10 Source Citation: Park et al. 2011[60]

Study Design: Nonrandomized comparative

Device or Material: Uncovered nitinol stents (Niti-S, Bonastent), and covered nitinol stents (Niti-S with polyurethane membrane and Bonastent with silicone membrane), and uncovered non-nitinol stents (Wallstent with Elgiloy - a cobalt, chromium, nickel alloy), for malignant colorectal obstruction

Contact Duration: up to 630 days

Dose: NR

Frequency/Duration: restenting in 13 patients

Response: migration, occlusion (obstruction by tumor ingrowth or overgrowth), patency

Patient characteristics (gender, mean age): uncovered nitinol: 50% male, 66 years; uncovered non-nitinol: 52% male, 65 years

Number per Group: 69 uncovered stents including 42 nitinol (20 Niti-S, 22 Bonastent, 4 Hanarostent excluded from analysis), and 27 non-nitinol (Wallstent); 30 covered nitinol (24 Niti-S, 6 Bonastent)

Observed adverse effects:

Migration: 3/42 (7.1%) uncovered nitinol, 5/27 (18.5%) covered nitinol (4 Niti-S, 1 Bonastent), and 7/27 (25.9%) non-nitinol; significantly lower migration with uncovered nitinol vs. non-nitinol (p=0.037).

Occlusion: 3/42 (7%) uncovered nitinol, 1/30 (3.3%) covered nitinol, 3/27 (11.1%) non-nitinol; p=0.761 for uncovered nitinol vs. non-nitinol.

Stent patency up to death: 35/42 (83%) nitinol, 17/27 (63%) non-nitinol; p=0.065.

Procedure-related perforation in 1 patient with covered nitinol.

Timing of adverse effects: Time to occlusion with uncovered nitinol stents was 69 days, 150 days, and 169 days. Mean time to migration ~28 days.

Factors that predict response: Of uncovered nitinol (Niti-S and Bonastent) and non-nitinol stents (Wallstent), no migration occurred with Bonastent which has a flared end and larger diameter vs. Wallstent and Niti-S which have no flared end and smaller diameters.

Table 16: Gastro Throat - Health Effect (In Vivo) Human Studies

16.1 Source Citation: Kappelle et al. 2019[64]

Study Design: RCT

Device or Material: Nitinol: FCSEMS (Wallflex, BSC, Marlboro, Massachusetts) vs. Non-Nitinol: BD

Contact Duration: Stents removed per-protocol at 8 weeks or sooner if complications occurred.

Dose: Stent sizes were 18-mm body diameter and 103-, 123-, or 153-mm length; or 23-mm body diameter with 105-, 125-, or 155-mm length.

Frequency/Duration: FCSEMS: Single implantation, removed at 8 weeks and dilation procedures as needed (mean number of re-interventions 5.4 [SD 5.4]); BD: Dilation in one to four sessions, per standard treatment (mean number of re-interventions 2.7 [SD 2.6])

Response: Aspiration, cervical pain, dysphagia recurrence, epigastric pain, foreign body sensation, stent-related GI reflux, thoracic pain

Patient characteristics (gender, mean age): Mean age (SD): FCSEMS: 66.6 (6.3), BD: 66.6 (7.7); Percent male, n (%): FCSEMS: 6/9 (66.7%), BD: 6/9 (66.7%)

Number per Group: FCSEMS: 9; BD: 9

Observed adverse effects: Aspiration, n (%): BD: 0; FCSEMS: 1

Cervical pain: BD: 0; FCSEMS: 1

Epigastric pain: BD: 0; FCSEMS: 1

Foreign body sensation: BD: 0; FCSEMS: 1

Re-intervention due to dysphagia, number of dilations (%): BD: 23/26 (88.5%), FCSEMS: 49/50 (98.0%), p=0.113

Stent-related GI reflux: BD: 0; FCSEMS: 1

Thoracic pain: BD: 0; FCSEMS: 1

Timing of adverse effects: Patients followed up to 12 months

Factors that predict response: a multivariate analysis of found that location of the anastomotic stricture was significantly associated with more re-interventions due to dysphagia (RR 0.7, 95% CI: 0.5 to 0.9, p=0.006)

16.2 Source Citation: Thomas et al. 2019[68]

Study Design: Nonrandomized comparative study

Device or Material: All are nitinol-based stents: WallFlex stent (BSC, Natick, Massachusetts, United States), the Endomaxx stent (Merit Medical, South Jordan, Utah, United States), and the Evolution stent (Cook Endoscopy, Winston-Salem, North Carolina, United States)

Contact Duration: Up to 4 weeks

Dose: All patients: Stent diameter: range 18 mm - 23 mm; stent length: range 70 mm - 150 mm

Frequency/Duration: Single implantation

Response: Any migration (benign strictures, malignant strictures), clinically relevant migration (benign strictures, malignant strictures)

Patient characteristics (gender, mean age): All patients: Mean age (range): 63 (21 to 94); Female, n (%): 91 (25%)

Number per Group: Wallflex: 218 (59%), Endomaxx: 96 (26%), Evolution: 55 (15%)

Observed adverse effects: Any migration (benign strictures), n/N (%): Endomaxx: 19/47 (40%), Wallflex: 24/94 (26%), Evolution: 6/20 (30%), p=0.19

Any migration (malignant strictures), n/N (%): Endomaxx: 14/49 (29%), Wallflex: 21/124 (17%), Evolution: 13/35 (37%), p=0.025

Clinically relevant migration (benign strictures), n/N (%): Endomaxx: 9/47 (19%), Wallflex: 14/94 (15%), Evolution: 5/20 (25%), p=0.52

Clinically relevant migration (malignant strictures), n/N (%): Endomaxx: 6/49 (12%), Wallflex: 9/124 (7%), Evolution: 10/35 (29%), p=0.003

Timing of adverse effects: Up to 4 weeks

Factors that predict response: NR

16.3 Source Citation: Didden et al. 2017[65]

Study Design: RCT

Device or Material: Wallflex (BSC, Natick, Massachusetts, USA) partially or fully covered nitinol stent

Contact Duration: Up to 6 months

Dose: The diameter of the stents is 18 mm, with a diameter of 23mm for both flares. Lengths of 10, 12, and 15 cm are available.

Frequency/Duration: Single implantation

Response: esophagitis, fistula, hemorrhage, mediastinitis, mild pain, pressure ulcer, recurrent obstruction, severe pain, splondylodiscitis, stridor, Fever, pneumonia

Patient characteristics (gender, mean age): Mean age in years (SD): FCSEMS: 69.2 (12.2), PCSEMS: 70.8 (11.4); Female, n: FCSEMS: 14; PCSEMS: 13

Number per Group: FCSEMS: 48; PCSEMS: 49

Observed adverse effects: Recurrent obstruction: FCSEMS: 9 events in 9 patients (19%); PCSEMS: 11 events in 11 patients (22%), p=0.65. Recurrent obstruction events occurred within 6 months. Major AEs and minor AEs were divided by number of events occurring early (within 7 days) or late (after 7 days). Event counts are as follows: Major AEs (early): severe pain: FCSEMS: 8, PCSEMS: 8; mediastinitis: FCSEMS: 0, PCSEMS: 1; stridor: FCSEMS: 2, PCSEMS: 0, pneumonia: FCSEMS: 0, PCSEMS: 3.

Major AEs (late): hemorrhage: FCSEMS: 4, PCSEMS: 5; severe pain: FCSEMS: 1, PCSEMS: 1; fistula: FCSEMS: 0, PCSEMS: 3; spondylodiscitis: FCSEMS: 1, PCSEMS: 0; pressure ulcer: FCSEMS: 1, PCSEMS: 0, pneumonia: FCSEMS: 4, PCSEMS: 6.

Minor AEs (early): mild pain: FCSEMS: 1, PCSEMS: 1; esophagitis: FCSEMS: 0, PCSEMS: 1, fever: FCSEMS: 1, PCSEMS: 1.

Minor AEs (late): mild pain: FCSEMS: 1, PCSEMS: 0, fever: FCSEMS: 0, PCSEMS: 1.

Timing of adverse effects: AEs specified as early (within 7 days) or late (between 7 days and 6 months) for most responses, except for recurrent obstruction which occurred up to 6 months follow-up.

Factors that predict response: Univariate Cox regression analaysis of covariates found females to have higher rates of recurrent obstruction (p=0.04), however, the covariate was non-significant (p=0.08) in a multivariable analysis. When analyzing the outcome of recurrent obstruction and/or major AEs as a cumulative endpoint, female sex and proximal stricture were significantly associated with higher rates compared to events for male sex and mild or distal location. All other covariates (age, WHO score, prior chemotherapy and/or radiotherapy, post-SEMS chemotherapy, type of covering, length of SEMS) all had non-significant associations.

16.4 Source Citation: Persson et al. 2017[66]

Study Design: RCT

Device or Material: All are nitinol-based stents: Wallflex (BSC, Natick, Massachusetts, USA) fully covered stent or Ultraflex (BSC, Natick, Massachusetts, USA) partially covered stent

Contact Duration: FCSEMS: Mean 130 days (range 14 to 430 days); PCSEMS: Mean 120 days (range 5 to 820 days)

Dose: Ultraflex: proximal flare of 23 mm and an inner body diameter of 18 mm. It was available in three lengths: 100, 120, and 150 mm. Wallflex: body diameter of the stent used was 18 mm, and the flare diameters were 25 mm proximally, and 23 mm distally. This stent was available in three lengths: 103, 123, and 153 mm.

Frequency/Duration: Single implantation

Response: endoscopic re-interventions, perforation at stent insertion, stent migration, Survival

Patient characteristics (gender, mean age): Median age (range): FCSEMS: 71.2 (56.8 to 91.0), PCSEMS: 72.2 (48.2 to 91.0); Female, n (%): FCSEMS: 13 (27.1%), PCSEMS: 11 (23.4%)

Number per Group: FCSEMS: 48, PCSEMS: 47

Observed adverse effects: Endoscopic re-interventions, n (%): FCSEMS: 8 (18.6%), PCSEMS: 15 (34.9%), p=0.083

Perforation at stent insertion, n: FCSEMS: 0; PCSEMS: 1

Stent migration > 20 mm, n (%): FCSEMS: 9 (20.0%), PCSEMS: 16 (37.2%), p=0.068

Kaplan–Meier analysis with the log-rank test showed no significant differences in survival between the groups (FCSEMS mean 130 days vs. PCSEMS mean 120 days, p = 0.53).

Timing of adverse effects: Perforation occurred at day 0, endoscopic re-interventions were followed up until 3 months and stent migration > 20 mm were followed for the patient's lifespan post-surgery. Stent migration > 20 mm and endoscopic re-interventions also contained data at 1 week, at 1 month, and at 3 months. Data is displayed here: Stent migration, (at 1 week): FCSEMS: 4, PCSEMS: 4; stent migration (at 1 month): FCSEMS: 1, PCSEMS: 3; stent migration (at 3 months): FCSEMS: 1, PCSEMS: 4; endoscopic re-interventions (at 1 week): FCSEMS: 5 (11.6%), PCSEMS: 6 (13.9%); endoscopic re-interventions (at 1 month): FCSEMS: 2 (6.7%), PCSEMS: 5 (15.6%); endoscopic re-interventions (at 3 months): FCSEMS: 1 (8.3%), PCSEMS: 4 (25.0%). Survival FCSEMS: Mean 130 days (range 14 to 430 days); PCSEMS: Mean 120 days (range 5 to 820 days).

Factors that predict response: NR

16.5 Source Citation: Hussain et al. 2016[61]

Study Design: Systematic Review

Device or Material: NiTi-S (Taewoong Medical, Seoul, South Korea)

Contact Duration: Median follow-up between 2 months and 6 months

Dose: NR

Frequency/Duration: Single implantation

Response: Migration, overall complications, technical success, tumor overgrowth

Patient characteristics (gender, mean age): Mean age range: 65 to 72 years; Percent Male Range: 60% to 94%

Number per Group: 250 patients (1 RCT, 4 prospective cohort studies, 1 retrospective cohort studies)

Observed adverse effects: Migration: Proportion, RE: 4.7% (6 studies, n=250, 95% CI: 2.5% to 7.7%, I^2=0.0%)

Overall complications: Proportion, RE: 27.6% (6 studies, n=250, 95% CI: 20.7% to 35.2%, I^2=41.9%)

Technical success: Proportion, RE: 97.2% (6 studies, n=250, 95% CI: 94.8% to 98.9%, I^2=5.8%)

Tumor overgrowth: Proportion, RE: 11.2% % (6 studies, n=250, 95% CI: 3.7% to 22.1%, I^2=82.2%)

Timing of adverse effects: Median follow-up between 2 months and 6 months

Factors that predict response: NR

16.6 Source Citation: Jang et al. 2016[69]

Study Design: Nonrandomized comparative study

Device or Material: All are nitinol-based stents: Fully covered or partially covered WallFlex (BSC), Evolution (Cook Medical, Bloomington, Indiana, USA), Hanaro [M.I.Tech, Pyeongtaek, Korea], or Niti-S [Taewoong Medical]); size was determined by the performing endoscopist.

Contact Duration: NR

Dose: NR

Frequency/Duration: Single or multiple stent placements per patients

Response: aspiration, erosion into broncho-pulmonary structures, GI bleeding, migration, migration requiring surgical retrieval

Patient characteristics (gender, mean age): Mean age in years (SD):

Number per Group: Study used many types of subgroups for comparative purposes. For baseline characteristics, patients were classified by malignant (n=55) or benign (n=30) disease. Univariable analyses were compared for a variety of factors, including manufacturer. All other serious adverse events were not compared by group, but rather, examined for the entire sample.

Observed adverse effects: Stent migration was found in 15 cases (22.4%) of Wallflex implants, 6 cases (33.3%) of Hanaro implants, 3 cases (33.3%) of Evolution implants, and 4 cases (36.4%) of Niti-S implants. Other serious adverse events for the sample included 2 cases of stent erosion, 1 case of life-threatening aspiration, 1 case of stent migration requiring surgical retrieval, and 2 cases of hemodynamically significant GI bleeding.

Timing of adverse effects: The case of aspiration occurred within 24 hours of stent placement. All other AEs occurred any time after stent implantation (no follow-up time reported in study).

Factors that predict response: A multivariable analysis of factors associated with stent migration found higher migration rates for benign than malignant lesions (OR 10.2, 95% CI: 3.0 to 34.2, $p<0.001$), distal versus midial/proximal location (OR 6.2, 95% CI: 1.7 to 22.4, $p=0.006$), and fully versus partially covered stents (OR 10.2, 95% CI: 3.0 to 34.2, $p<0.001$).

16.7 Source Citation: Coron et al. 2015[67]

Study Design: RCT

Device or Material: All nitinol-based stents: Antireflux stent (Dostent, M. I. Tech, Seoul, Korea) or conventional stent (Choostent, M. I. Tech, Seoul, Korea)

Contact Duration: Up to 18 months

Dose: 18 mm diameter, stent length ranged from 80 to 170 mm

Frequency/Duration: Single implantation

Response: Severe aspiration, stent migration, stent obstruction, Survival

Patient characteristics (gender, mean age): Mean age in years (SD): Dostent: 68.9 (11.1), Choostent: 74.1 (12.1); Female, n (%): Dostent: 4 (20.0%), Choostent: 3 (16.7%)

Number per Group: Dostent: 20, Choostent + PPI/postural advice: 18

Observed adverse effects: Five migrations occurred in patients with Dostent versus three in patients with Choostent. Four obstructions occurred in patients with Dostent versus one in patients with Choostent. No significant difference observed between groups (p=0.41) for migration, however, more overall AEs (obstructions and migrations) were observed in Dostent than Choostent (55% vs. 18%, p=0.0196). No statistical difference was found in terms of overall mortality. However, a tendency toward longer survival was noted in Dostent patients (median [95% CI]): 242 [108 to 390] vs 165 [60 to 215] days; p=0.57).

Timing of adverse effects: All local and systemic host responses were recorded up to 18 months.

Factors that predict response: NR

16.8 Source Citation: Tahiri et al. 2015[70]

Study Design: Nonrandomized comparative study

Device or Material: All nitinol-based stents: WallFlex Esophageal Stent (BSC, Natick, Massachusetts), and the Evolution Stent (Cook Medical, Bloomington Indiana)

Contact Duration: Mean in days (SD, range): 146 (26.5, 6 to 636)

Dose: NR

Frequency/Duration: Single implantation: 43 (91.5%), multiple implantation: 4 (8.5%)

Response: Tumor overgrowth

Patient characteristics (gender, mean age): Mean age in years (SD): 70.4 (9.6); Male, n (%): 38 (81%)

Number per Group: Group with 5 cm proximal tumor covering (n=32), group without 5 cm proximal tumor covering (n=15)

Observed adverse effects: Tumor overgrowth occurred in 2 patients (6.25%) with a 4 cm proximal tumor covering and 2 patients (13.3%) without a 5 cm proximal tumor covering.

Timing of adverse effects: Tumor overgrowth occurred at 10 months and 11 months after insertion for the group with a 5 cm proximal tumor covering, whereas tumor overgrowth occurred at 6 months and 7 months after insertion for the group without a 5 cm proximal tumor covering.

Factors that predict response: NR

16.9 Source Citation: Yang et al. 2014[62]

Study Design: Systematic Review

Device or Material: Nitinol: Ultraflex vs. Non-Nitinol: Wallstent

Contact Duration: NR

Dose: NR

Frequency/Duration: Single implantation

Response: Bolus obstruction, hemorrhage, migration, perforation, persistent/recurrent dysphagia, reflux, technical success, tumor overgrowth, Mortality (30-day, procedure-related)

Patient characteristics (gender, mean age): NR

Number per Group: Ultraflex (n=65) vs. Wallstent (n=55) (2 RCTs)

Observed adverse effects: Bolus obstruction: OR, FE: 0.62 (95% CI: 0.10 to 4.00, I^2=N/A)

Hemorrhage: OR, FE: 1.41 (95% CI: 0.37 to 5.33, I^2=0%)

Migration: OR, FE: 1.93 (95% CI: 0.54 to 6.87, I^2=0%)

Perforation: OR, FE: 1.29 (95% CI: 0.22 to 7.58, I^2=47%)

Persistent/recurrent dysphagia: OR, FE: 1.27 (95% CI: 0.49 to 3.31, I^2=0%)

Reflux: OR, FE: 0.61 (95% CI: 0.13 to 2.92, I^2=0%)

Technical success: OR, FE: 3.00 (95% CI: 0.12 to 76.31, I^2=N/A)

Tumor overgrowth: OR, FE: 0.27 (95% CI: 0.05 to 1.41, I^2=0%)

Mortality (30-day): OR, FE: 1.18 (95% CI: 0.44 to 3.18, I^2=0%);

Mortality (procedure-related): OR, FE: 0.97 (95% CI: 0.06 to 16.17, I^2=N/A)

Timing of adverse effects: AEs are NR follow-up. Mortality has a follow-up of 30-days; procedure-related mortality follow-up NR.

Factors that predict response: NR

16.10 Source Citation: Thomas et al. 2010[63]

Study Design: Systematic Review

Device or Material: Nitinol stents, Polyflex stents (non-nitinol)

Contact Duration: Follow-up ranged from 24 to 152 weeks

Dose: NR

Frequency/Duration: Single or multiple stents

Response: Stent migration

Patient characteristics (gender, mean age): Mean age ranged from 49 to 68 years; Gender: NR

Number per Group: 80 nitinol stents (2 studies), 119 Polyflex stents (6 studies)

Observed adverse effects: Migration: Nitinol (n=80, 2 studies): OR 0.28 (95% CI: 0.16 to 0.49); Polyflex (n=119, 6 studies): OR 0.43 (0.27 to 0.67)

Timing of adverse effects: Follow-up ranged from 24 to 152 weeks

Factors that predict response: For both Polyflex (non-nitinol) and nitinol stents combined, meta-regression analysis determined that time from insertion to removal was the only significant confounding factor (p=0.010) for migration rate. Gender (p=0.322), age (p=0.085), stricture etiology (p=0.388), stricture location (p=0.334), and stricture length (p=0.523) had no significant influence on the migration rate.

AE: adverse event; BD: bougie dilation; BSC: Boston Scientific Corporation; CI: confidence interval; FCSEMS: fully covered self-expandable metal stents; FE: fixed effects; GI: gastrointestinal; NR: not reported; OR: odds ratio; PCSEMS: partially covered self-expandable metal stents; PPI: proton-pump inhibitor; RCT: randomized controlled trial, RE: random effects; RR: relative risk; SD: standard deviation; SEMS: self-expandable metal stents; WHO: World Health Organization

Table 17: Nitinol Lung - Health Effect (In Vivo) Human Studies

17.1 Source Citation: Deslee et al. 2016[71]

Study Design: RCT

Device or Material: Nitinol Coil (PneumRx/BTG)

Contact Duration: Up to 12-months follow-up

Dose: 100mm or 125 mm sizes

Frequency/Duration: 10 coils placed in 2 bilateral lobes in 2 procedures

Response: COPD exacerbation, hemoptysis, invasive ventilation > 24 hours, pneumonia, pneumothorax, thoracic pain, Cardiovascular events, mortality

Patient characteristics (gender, mean age): Mean age (SD): Coil: 62.1 (SD 8.3); Usual Care: 61.9 (7.3); Male, n (%): Coil: 39 (78%); Usual Care: 32 (64%)

Number per Group: Bilateral coils + usual care (n=50) vs. usual care (n=50)

Observed adverse effects: Study reported non-serious AEs by number of events rather than number of patients; serious AE rates are listed below:

COPD exacerbation, n (%): Coil: 13 (26%); Usual Care: 11 (22%); Difference, %: 4 (95% CI: -13 to 21, p=0.64)

Hemoptysis, n (%): Coil: 1 (2%); Usual Care: 0 (0%); Difference, %: 2 (95% CI: -2 to 6, p=0.99)

Invasive ventilation > 24 hours, n (%): Coil: 1 (2%); Usual Care: 3 (6%); Difference, %: -4 (95% CI: -12 to 4, p =0.62)

Pneumonia, n (%): Coil: 9 (18%); Usual Care: 2 (4%); Difference, %: 14 (95% CI: 2 to 26, p=0.03)

Pneumothorax, n (%): Coil: 3 (6%); Usual Care: 1 (2%); Difference, %: 4 (95% CI: -4 to 12, p=0.62)

Thoracic pain, n (%): Coil: 2 (4%); Usual Care: 2 (4%); Difference, %: -2 (95% CI: -9 to 5, p=0.64). Note: one patient allocated to the coil study arm experienced thoracic pain before implantation. Patient is included in counts by study arm, although, the t-test adjusts for this occurrence.

Cardiovascular, n (%): Coil: 1 (2%); Usual Care: 3 (6%); Difference, %: -4 (95% CI: -12 to 4, p=0.62)

Mortality, n (%): Coil: 4 (8%); Usual Care: 3 (6%); Difference, %: 2 (95% CI: -8 to 12, p=0.99)

Timing of adverse effects: Up to 12-months follow-up for observed AEs. For coil treatment groups, one patient was recorded having pneumothorax requiring chest tube placement for more than seven days. No events of hemoptysis > 150 mL or invasive ventilation > 24 hours were observed within 24 hours for patients receiving coil treatment.

Factors that predict response: NR

Table 18: Neurovascular - Health Effects (In Vivo) Human Studies

18.1 Source Citation: Sun et al. 2021[76]

Study Design: Systematic review of 7 single-arm studies

Device or Material: Enterprise stent for intracranial atherosclerotic stenosis (ICAS)

Contact Duration: mean followup 6.3 to 25.6 months

Dose: Not reported (NR)

Frequency/Duration: NR

Response: stroke or death, hemorrhagic stroke, ischemic stroke, death, intraprocedural complications, vasospasm, hematoma in the groin, asymptomatic dissection of the stented segment, stroke or transient ischemic attack (TIA) in the territory of the qualifying artery, in-stent restenosis (ISR), symptomatic ISR

Patient characteristics (gender, mean age): age range 56.8 to 64.0

Number per Group: 557 patients (588 ICAS lesions)

Observed adverse effects:

Within 30 days of percutaneous transluminal angioplasty and stenting (PTAS): Incidence rate for stroke or death was 7.4% (95% CI: 5.5 to 10.1%); hemorrhagic stroke was 3.1% (95% CI: 1.9 to 5.0%); ischemic stroke was 4.5% (95% CI: 3.0 to 6.73%); and mortality was 1.2% (95% CI: 0.5 to 2.6%). Death was always due to hemorrhagic stroke. Pooled incidence rate for intraprocedural complications (vasospasm, hematoma in the groin, and asymptomatic dissection of the stented segment) was 2.2% (95% CI: 1.2 to 4.0%).

Beyond 30 days: Incidence rate of ischemic stroke or TIA in the territory of the qualifying artery beyond 30 days was 3.2% (95% CI: 1.1 to 9.5%). The pooled incidence rate of in-stent restenosis (ISR) and symptomatic ISR was 10.1% (95% CI: 4.6 to 22.2%) and 4.9% (95% CI: 2.9 to 8.5%), respectively. No deaths beyond 30 days were reported.

Timing of adverse effects: Within 30 days, beyond 30 days

Factors that predict response: NR

18.2 Source Citation: Essibayi et al. 2021[72]

Study Design: Systematic review of 18 single-arm studies (19 publications)

Device or Material: Woven EndoBridge (WEB; MicroVention-Terumo, Aliso Viejo, California) to treat ruptured intracranial aneurysms

Contact Duration: mean followup 3 to 15 months

Dose: NR

Frequency/Duration: 27/496 aneurysms required retreatment

Response: WEB-related clinical complication rate, hemorrhagic events, thromboembolic events, death

Patient characteristics (gender, mean age): NR, 57 years

Number per Group: 487 patients (496 ruptured aneurysms); aneurysms mostly wide-neck

Observed adverse effects: Overall WEB-related clinical complication rate was 3.2% (95% CI: 1.6 to 4.7%). 13 hemorrhagic events (2%, 95% CI: 0.8 to 3.3%) and 41 thromboembolic events (6.8%, 95% CI: 4.6 to 9%) resulted in prolonged clinical deterioration or permanent neurologic deficits. 12 patients died during the perioperative period resulting in a procedure-related mortality rate of 2.1% (0.8 to 3.3%).

Timing of adverse effects: NR

Factors that predict response: NR

18.3 Source Citation: Monteiro et al. 2021[73]

Study Design: Systematic review of 9 single-arm studies

Device or Material: WEB to treat acutely ruptured intracranial aneurysms

Contact Duration: range, 3 to 39 months

Dose: NR

Frequency/Duration: NR

Response: device protrusion, thromboembolic events, device dislodgement, device migration

Patient characteristics (gender, mean age): NR; 83% with wide-necked aneurysms

Number per Group: patients NR (377 aneurysms)

Observed adverse effects: Rate of intraprocedural device-related complications was 8.4% (95% CI: 3.6 to 13.3%). Device protrusion into the parent vessel and thromboembolic events occurred in 14 and 17 procedures, respectively. Device dislodgement and distal migration into the parent artery was reported in 1 patient. Postprocedure complication rate was 1% (95% CI: 0 to 2%) and included 3 thromboembolic events that occurred during the hospital stay.

Timing of adverse effects: 3 thromboembolic events occurred during the hospital stay.

Factors that predict response: NR

18.4 Source Citation: Pranata et al. 2021[74]

Study Design: Systematic review of 6 single-arm studies

Device or Material: PulseRider (Cerenovus, New Brunswick, NJ) to treat intracranial aneurysms

Contact Duration: 6 to 24 months

Dose: NR

Frequency/Duration: NR

Response: thrombus formation, cerebral artery strokes, delayed device thrombosis

Patient characteristics (gender, mean age): gender and age NR; 100% wide-necked aneurysms

Number per Group: 157

Observed adverse effects: Complication rate was 5% (95% CI: 1 to 8%). Complications included 3 thrombus formations, 3 procedure-related posterior cerebral artery strokes, and 1 delayed device thrombosis. No procedure/device-related death was reported.

Timing of adverse effects: device thrombosis in 1 patient was "delayed"

Factors that predict response: NR

18.5 Source Citation: Lynch et al. 2020[75]

Study Design: Systematic review of 14 single-arm studies

Device or Material: Neuroform Atlas (Stryker Neurovascular, Fremont, CA)

Contact Duration: mean 9.1 months (489 patients)

Dose: NR

Frequency/Duration: Multiple stent usage in 26% of patients.

Response: stent dislodgement/migration, morbidity, ischemic complications, stent thrombosis, early hemorrhage, mortality, permanent residual neurological deficit/disability

Patient characteristics (gender, mean age): 35.6% male, 58.2 years

Number per Group: 577 patients (593 intracranial aneurysms)

Observed adverse effects: Stent dislodgement/migration occurred in 8 patients.

Periprocedural complications: Under 30-day morbidity was 3.6% (31/577; 95% CI: 1.9 to 5.2%) with ischemic complications sustained during or within 30-days after the procedure in 2.9% (23/577; 95% CI: 1.5 to 4.2%). Stent thrombosis occurred in 1.1% (9/577; 95% CI: 0.03 to 2%), and 30-day/early hemorrhage occurred in 1.0% (4/577; 95% CI: 0.02 to 1.8%).

Delayed and overall complications at mean 9.1 months followup included overall mortality in 1.8% (12/519; 95% CI: 0.07 to 2.9%), permanent residual neurological deficit or disability in 2.7% (23/489; 95% CI: 0.08 to 4.5%), delayed complications in 1.1% (10/489; 95% CI: 0.02 to 2%), and overall complications in 6.2% (40/489; 95% CI: 0.03 to 9%).

Overall, patients receiving multiple stents (vs. single stents) had increased rates of perioperative symptomatic morbidity (10.6% vs. 2.7%), ischemia (8.24% vs. 1.3%), stent thrombosis (3.5% vs. 0%), and hemorrhage (2.3% vs. 1.3%). Increased rates of late complications including permanent disability (11.8% vs. 0%), delayed complications (1.5% vs. 0%), and overall complications (13.2% vs. 2.7%) were also noted with multiple stents.

Timing of adverse effects: periprocedural/early (within 30 days after treatment), delayed (after 30 days).

Factors that predict response: NR

18.6 Source Citation: Cagnazzo et al. 2019[77]

Study Design: Systematic review of 27 single-arm studies

Device or Material: Y-stent assisted coiling (Y-SAC) with 2 stent placements. Stent usage was Enterprise (476/1060, 45%), Neuroform (332/1060, 31.3%), LVIS stents (MicroVention, Tustin, CA; 132/1060, 12.5%), Solitaire (Covidien, Irvine, CA; 66/1060, 6.2%), and Acclino flex stents (Acandis, Pforzheim, Germany; 54/1060, 5%).

Contact Duration: radiologic f/u (mean 14 months; range 6 to 24 months), clinical f/u (mean 17 months; range 3 to 30)

Dose: NR

Frequency/Duration: NR

Response: treatment-related complications, periprocedural complications, in-stent occlusion, ischemic events, treatment-related mortality, ischemic/thromboembolic events, hemorrhagic events, acute in-stent thrombosis, and chronic in-stent thrombosis.

Patient characteristics (gender, mean age): 36% male, 56.6 years

Number per Group: 744 patients (750 aneurysms)

Observed adverse effects: The overall treatment-related complication rate was 8.9% (95% CI: 5.8 to 12.1%) with more complications occurring within 30 days (6.7%, 95% CI: 4 to 9%), versus after 30 days (2.1%, 95% CI: 1 to 3%). The rate of periprocedural treatment-related morbidity and mortality was 2.4% (95% CI: 1.2 to 3.7%) and 1.1% (95% CI: 0.3 to 1.9%), respectively.

Treatment-related complications included ischemic/thromboembolic events (6.5%, 95% CI: 3 to 7.6%), hemorrhagic events (2%, 95% CI: 0.7 to 3%), acute in-stent thrombosis (2.1%, 95% CI: 1.6 to 6%), and chronic in-stent stenosis (2.3%, 95% CI: 0.6 to 4%). Delayed complications included 3 cases of in-stent occlusion, and 5 ischemic events.

The complication rate for Enterprise stents (6.5%, 95% CI: 1.6 to 11%) was lower versus Neuroform (14%, 95% CI: 5 to 26%), and LVIS braided stents (11%, 95% CI: 3 to 20%). Rates were not reported for Solitaire and Acclino flex stents.

Timing of adverse effects: periprocedural/early (within 30 days of treatment), delayed (after 30 days).

Factors that predict response: NR

18.7 Source Citation: Granja et al. 2019[78]

Study Design: Systematic review of 18 single-arm studies

Device or Material: Y-SAC with 2 stent placements. Stents included Acclino, Enterprise (Codman Neurovascular, Raynham, MA), Leo Baby (Balt Extrusion, Montmorency, France), Neuroform (Boston Scientific, Fremont, CA) and Solitaire (Medtronic, Irvine, CA). Y-stent configurations were 116 Neuroform-Neuroform, 52 Neuroform-Enterprise, 100 Enterprise-x2, 7 Solitaire-x2, 2 Neuroform-Solitaire, 11 Solitaire-Enterprise, 3 LeoBaby-x2, 2 Enterprise-LeoBaby, 6 Acandis-x2, 1 AcandisFlex-x2

Contact Duration: angiographic followup: mean 18 months (range, 0-115)

Dose: NR

Frequency/Duration: NR

Response: in-stent thrombosis, stroke, mortality, permanent neurological deficit

Patient characteristics (gender, mean age): 64% female, 56.2 years; 89% with wide-neck aneurysms

Number per Group: 327 patients (343 aneurysms)

Observed adverse effects: In-stent thrombosis at angiographic follow-up was observed in 8 patients (6%, 95% CI: 1.9 to 10%), equally due to open-open and closed-closed Y-stent configurations. The procedure-related stroke rate and mortality rate were 12% (n=12; 95% CI: 4.3 to 15%) and 2% (n=7; 95% CI: 0.6 to 3.8%), respectively. The permanent neurological deficit rate was 4% (n=10; 95% CI: 0.2 to 4.5%).

Timing of adverse effects: NR

Factors that predict response: NR

18.8 Source Citation: Cagnazzo et al. 2018[80]

Study Design: Systematic review of 35 single-arm studies

Device or Material: Self-expandable braided stents (LEO and LVIS) to treat intracranial aneurysms

Contact Duration: mean followup: 10.4 months radiologic, 12 months clinical

Dose: NR

Frequency/Duration: 33.5% LEO stents, 62.5% LVIS

Response: ischemic/thromboembolic events, in-stent thrombosis, hemorrhagic/hematoma events, mortality

Patient characteristics (gender, mean age): 0.47 male/female ratio, 54.5 years

Number per Group: 1426 patients (1518 intracranial aneurysms)

Observed adverse effects (all treatment-related complications):

Overall treatment-related complication rate was 7.4% (107/1317; 95% CI: 5 to 9%) with significantly higher rates with LEO stents vs. LVIS stents (10.5% vs. 5.3%; p=.001).

Overall permanent complication rate was 1.5% (30/1324; 95% CI: 0.9 to 2%) with significantly higher rates with LEO stents vs. LVIS stents (2.7% vs. 1.3%; p=.002).

Higher rates of periprocedural/early events were reported vs. delayed events (5% vs. 1%) with complications occurring more frequently with LEO stents (7% vs. 3.4% early events, 2.5% vs. 0.8% delayed events).

Ischemic/thromboembolic events (48/1324; 2.4%; 95% CI: 1.5–3.4%) and in-stent thrombosis (35/1324 = 1.5%; 95% CI: 0.6%–1.7%) were the most common complications followed by hemorrhagic/hematoma (1/1324; 0.5%, 95% CI: 0.3 to 1.1%). Rates by stent type included ischemic/thromboembolic (3.6% LEO, 1.6% LVIS), in-stent thrombosis (3.2% LEO, 0.8% LVIS), and hemorrhagic/hematoma (0.9% LEO, 0% LVIS).

Treatment-related mortality was similar between LEO and LVIS stents (0.7% LEO, 0.8% LVIS).

Timing of adverse effects: periprocedural/early events (within 30 days), delayed events (after 30 days)

Factors that predict response: NR

18.9 Source Citation: Zhang et al. 2017[81]

Study Design: Systematic review of 9 single-arm studies

Device or Material: Low-profile Visualized Intraluminal Support (LVIS); LVIS Junior stent (5 studies), LVIS stent (1 study), LVIS and LVIS Junior stents (3 studies)

Contact Duration: mean angiographic followup, mean 5.6 months (mean range 4.2 to 7.8)

Dose: NR

Frequency/Duration: NR

Response: morbidity, thromboembolic events, hemorrhagic/hematoma events

Patient characteristics (gender, mean age): 59.3% female, 55.4 years, mostly wide-necked aneurysms

Number per Group: 384 patients (390 aneurysms)

Observed adverse effects: The procedure-related complication rate was 6.5% (95% CI 4.1 to 9.0%) and the procedure-related morbidity rate was 1.4% (95% CI 0.2 to 2.6%). The thromboembolic event rate was 4.9% (95% CI 1.9 to 7.9%), with 2.4% (95% CI 0.9 to 3.9%) experiencing symptomatic thromboembolic events and 1.4% (95% CI 0.2 to 2.5%) experiencing in-stent thrombosis.

The hemorrhagic event rate was 2.1% (95% CI 0.7 to 3.5%), including 0.9% (95% CI 0 to 1.8%) experiencing neurologic hemorrhagic complications (i.e., intracranial hematomas) and 1.9% (95% CI 0.5 to 3.2%) experiencing non-neurologic hemorrhagic complications (i.e., groin hematomas). The procedural-related mortality rate was 0%.

Timing of adverse effects: NR

Factors that predict response: NR

18.10 Source Citation: Phan et al. 2016[79]

Study Design: Systematic review of 14 nonrandomized comparative studies

Device or Material: SAC with Neuroform (12 studies), Enterprise (8 studies), Solitaire (2 studies), Wingspan (Stryker Neurovascular, Kalamazoo, MI; 2 studies), LEO (3 studies) versus coiling only.

Contact Duration: mean followup 9.7 months to >36 months

Dose: NR

Frequency/Duration: 1 brand (2 studies), combination of ≥2 stents (12 studies)

Response: all-complications, permanent complications, thrombotic complications, mortality

Patient characteristics (gender, mean age): % males: 23.7 SAC, 26.4 coiling only; age: 56.3 SAC, 55.4 years coiling only

Number per Group: 2698 SAC, 29388 coiling only

Observed adverse effects: No significant difference was reported for all-complications (7 studies: 12.2% SAC, 12.0% coiling only; OR 1.08, 95% CI: 0.79 to 1.47), permanent complications (4 studies: 4.1% SAC, 3.5% coiling only; OR 1.50, 95% CI: 0.97 to 2.34), or thrombotic complications (7 studies: 4.5% SAC, 4.1% coiling only; OR 1.18, 95% CI: 0.68 to 2.03).

Mortality was significantly higher with SAC versus coiling (9 studies: 1.4% SAC, 0.2% coiling only; OR 2.16, 95% CI: 1.33 to 3.52), however this rate was mostly driven by 1 study with significantly larger aneurysm sizes in stented patients. Authors noted that mortality was higher in studies using Leo stents (11.1%) vs. Neuroform (3.0%) or Enterprise (5.3%).

Timing of adverse effects: NR

Factors that predict response: NR

Table 19: Nitinol Ophthalmic - Health Effect (In Vivo) Human Studies

19.1 Source Citation: Samuelson et al. 2018[82]

Study Design: RCT

Device or Material: Hydrus Microstent (Ivantis, Inc, Irvine, CA) vs. no stent

Contact Duration: Up to 24 months

Dose: NR

Frequency/Duration:

Response: BCVA loss ≥ 2 lines ≥ 3 months, Conjunctivitis, Corneal abrasion, Corneal edema, Cystoid macular edema, Device malposition, Elevated IOP ≥ 10 mmHg over baseline, Epiretinal membrane, Hyphema obscuring the surgeon's view, Laser membranectomy/synechialysis, Layered hyphema > 2 mm after 1 day, Nonobstructive Device obstruction/focal PAS, Obstructive Device obstruction/focal PAS, Paracentesis, SLT/trabeculoplasty, Subconjunctival hemorrhage, Surgical re-intervention in study eye, Uveitis/iritis requiring steroids, Tube shunt/trabeculectomy, Worsening of VF MD by 2.5 dB,

Patient characteristics (gender, mean age): Mean age (SD): Microstent: 71.1 (7.9); no stent: 71.2 (7.6); Female, n (%): Microstent: 206 (55.8%); no stent: 105 (56.1%)

Number per Group: Microstent (n=369 eyes), no stent (n=187 eyes)

Observed adverse effects: BCVA loss ≥ 2 lines ≥ 3 months: Microstent: 1.4%, no stent: 1.6%.

Conjunctivitis: Microstent: 5.7%, no stent: 7.0%.

Corneal abrasion: Microstent: 1.1%, no stent: 0%.

Corneal edema: Microstent: 1.4%, no stent: 0%.

Cystoid macular edema: Microstent: 2.2%, no stent: 2.1%.

Device malposition: Microstent: 1.6%, no stent: 0%.

Elevated IOP ≥ 10 mmHg over baseline: Microstent: 0.5%, no stent: 2.7%.

Epiretinal membrane: Microstent: 1.6%, no stent: 1.6%.

Hyphema obscuring the surgeon's view: Microstent: 1.1%, no stent: 0%.

Laser membranectomy/synechialysis: Microstent: 0.8%, no stent: 0%.

Layered hyphema > 2 mm after 1 day: Microstent: 0.5%, no stent: 0.5%.

Nonobstructive Device Obstruction/Focal PAS: Microstent: 0.5%, no stent: 2.7%.

Obstructive Device Obstruction/Focal PAS: Microstent: 0.5%, no stent: 2.7%.

Paracentesis: Microstent: 0.3%, no stent: 1.0%.

SLT/trabeculoplasty: Microstent: 0%, no stent: 0.5%.

Subconjunctival hemorrhage: Microstent: 2.4%, no stent: 0%.

Surgical re-intervention in study eye: Microstent: 2.4%, no stent: 4.8%.

Tube shunt/trabeculectomy: Microstent: 0%, no stent: 2.1%.

Uveitis/iritis requiring steroids: Microstent: 5.6%, no stent: 3.7%.

Worsening of VF MD by 2.5 dB: Microstent: 4.3%, no stent: 5.3

Timing of adverse effects: Up to 24 months

Factors that predict response: NR

19.2 Source Citation: Fea et al. 2017[84]

Study Design: Nonrandomized comparative study

Device or Material: Hydrus Microstent (Ivantis, Inc, Irvine, CA) vs. selective laser trabeculoplasty

Contact Duration: Up to 12 months

Dose: NR

Frequency/Duration: Single surgery

Response: Post-operative IOP spikes, Temporary reduction of visual activity

Patient characteristics (gender, mean age): Mean age (SD): SLT: 69.0 (11.28); Microstent: 70.8 (11.83); Percent female, n/N (%): SLT: 16/25 (64%); Microstent: 13/31 (42%)

Number per Group: Microstent (n=31), SLT (n=25)

Observed adverse effects: Post-operative IOP spikes: Microstent: 3; SLT: 0; Temporary reduction of visual activity: Microstent: 2; SLT: 0

Timing of adverse effects: Post-operative IOP spikes resolved within one week. Temporary reduction of visual activity occurred within 12-month follow-up.

Factors that predict response: NR

19.3 Source Citation: Pfeiffer et al. 2015[83]

Study Design: RCT

Device or Material: Hydrus Microstent (Ivantis, Inc, Irvine, CA) vs. CS

Contact Duration: 1 year, 2 years

Dose: NR

Frequency/Duration: Single surgery

Response: Anterior ischemic optic neuropathy, BCVA loss >2 lines, IOP spike (>10 mmHg more than baseline, Epiretinal membrane, Focal PAS, Macular edema, Optic disc hemorrhage, Postoperative wound dehiscence, Retinal detachment, Secondary glaucoma surgery, Vitreal macular traction,

Patient characteristics (gender, mean age): Mean age (SD): Microstent + CS: 72.8 (6.6); CS alone: 71.5 (6.9); Percent male, n (%): Microstent + CS: 20 (40.0%); CS alone: 29 (58.0%)

Number per Group: Hydrus Microstent with CS (n=50) vs. CS alone (n=50)

Observed adverse effects: Anterior ischemic optic neuropathy: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 0 (0.0%);

BCVA loss >2 lines: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 1 (2.0%)

Epiretinal membrane: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 1 (2.0%)

Focal PAS: Microstent + CS (n=48): 9 (18.8%); CS (n=49): 1 (2.0%)

IOP spike (>10 mmHg more than baseline): Microstent + CS (n=48): 0 (0.0%); CS (n=49): 0 (0.0%)

Macular edema: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 0 (0.0%)

Optic disc hemorrhage: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 0 (0.0%)

Postoperative wound dehiscence: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 0 (0.0%)

Retinal detachment: Microstent + CS (n=48): 0 (0.0%); CS (n=49): 0 (0.0%)

Secondary glaucoma surgery: Microstent + CS (n=48): 1 (2.1%); CS (n=49): 2 (4.1%)

Vitreal macular traction: Microstent + CS (n=48): 1 (2.1%); CS (n=49): 0 (0.0%)

Timing of adverse effects: All of the observed effects are used for the maximum follow-up time point of 2 years. The one-year event rates are displayed below:

Anterior ischemic optic neuropathy: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 1 (2.0%)

BCVA loss >2 lines: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 3 (6.0%)

Epiretinal membrane: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 2 (4.0%)

Focal PAS: Microstent + CS (n=50): 6 (12.0%); CS (n=50): 1 (2.0%)

IOP spike (>10 mmHg more than baseline): Microstent + CS (n=50): 2 (2.0%); CS (n=50): 2 (2.0%)

Macular edema: Microstent + CS (n=50): 1 (2.0%); CS (n=50): 2 (4.0%)

Optic disc hemorrhage: Microstent + CS (n=50: 1 (2.0%); CS (n=50): 0 (0.0%)

Postoperative wound dehiscence: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 1 (2.0%)

Retinal detachment: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 1 (2.0%)

Secondary glaucoma surgery: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 0 (0.0%)

Vitreal macular traction: Microstent + CS (n=50): 0 (0.0%); CS (n=50): 1 (2.0%)

Factors that predict response: NR

BCVA: best-corrected visual acuity; CI: confidence interval; CS: cataract surgery; IOP: intraocular pressure; MD: mean deviation; NR: not reported; PAS: peripheral anterior synechiae; RCT: randomized controlled trial; SD: standard deviation; SLT: selective laser trabeculoplasty; VF: visual field

Table 20: Orthopedic - bone fixation: Health Effects (In Vivo) Human Studies

20.1 Source Citation: Favorito et al. 2021[87]

Study Design: Single-arm

Device or Material: Intramedullary nitinol cage and plate (Conventus Orthopedics, Maple Grove, MN) to treat proximal humeral fractures. The implant allows screw placement through the cage both from outside and through the plate.

Contact Duration: up to 27 months; mean f/u 91 weeks, minimum f/u 1 year

Dose: NR

Frequency/Duration: single administration

Response: avascular necrosis (AVN), transient axillary neuritis, hardware malfunction (screw breakage)

Patient characteristics (gender, mean age): 81% female, 64 years

Number per Group: 31

Observed adverse effects: Symptomatic avascular necrosis occurred in 4 (13%) patients; 3 patients underwent revisions to a shoulder arthroplasty, while 1 patient with mild AVN chose not to undergo surgery. Authors noted "a higher-than-expected rate of [AVN]" versus studies "using a similar fixation construct."

Transient axillary neuritis occurred in 2 (6.4%) patients. 1 patient underwent removal of a broken locking screw which had backed out of the cage.

Timing of adverse effects: AVN was discovered on radiographs obtained ≥1 year postoperatively in 3 patients. Radiographs of 1 patient showed no evidence of AVN at 7 months, development at 1 year and progression at 14, 18, and 27 months before undergoing arthroplasty. Mild AVN was discovered 2 years postoperatively in 1 patient.

Factors that predict response: NR

20.2 Source citation: Obrador et al. 2018[86]

Study Design: Nonrandomized comparative

Device or Material: Nitinol internal fixation device Smart Toe (Stryker Osteosynthesis, Mahwah, NJ) versus TenFuse bone allograft (Solana Surgical, Memphis, TN) versus standard K-wire for intramedullary hammertoe fixation

Contact Duration: 12 months for Smart Toe and TenFuse, K-wire removal after 6 weeks.

Dose: NR; 4 types of Smart Toe implants (16-mm, 19-mm, straight, angled)

Frequency/Duration: NR

Response: wound complications, breakage, adhesions/scar tissue in the interphalangeal joint (IPJ)

Patient characteristics (gender, mean age): 81.3% female, 62.6 years (range 20 to 81)

Number per Group: 96 patients (54 Smart Toe, 15 TenFuse, 27 K-wire), 186 toes (94 Smart Toe, 27 TenFuse, 65 K-wire)

Observed adverse effects: No significant differences were reported between groups for wound complications (e.g., dehiscence, infection) at 12 months followup (toes: 7.4% with Smart Toe and TenFuse, 4.6% with K-wire). Breakage was significantly higher with Smart Toe vs. K-wire (10.6% Smart Toe, 0 K-wire; p=.007), while no significant difference was reported between Smart Toe and TenFuse (10.6%, 0 TenFuse; p=.079). No significant between group differences were reported for adhesions/scar tissue in the IPJ (2.1% Smart Toe, 9.2% K-wire, 0% TenFuse).

Timing of adverse effects: Breakage occurred with Smart Toe prior to 12 months.

Factors that predict response: The most common Smart Toe fracture was at the distal thinner legs of the implant.

20.3 Source Citation: Guelfi et al. 2015[85]
Study Design: Systematic review of 9 studies (3 nonrandomized comparative, 6 single-arm)

Device or Material: Smart Toe with memometal nitinol (Stryker) in 5 studies, ProToe VO with stainless steel (Wright) in 1 study, Ipp On with stainless steel (Integra) in 1 study, StayFuse with titanium (Tornier) in 2 studies, K-wire vs. Smart Toe in 3 studies.

Contact Duration (months): 6, 12, ~38, and 40 with Smart Toe (NR in 1 study)

Dose: NR

Frequency/Duration: NR

Response: deformities, displaced fixation, fracture, hardware failures, malunion, non-union

Patient characteristics (gender, mean age): NR, undergoing proximal inter-phalangeal (PIP) joint arthrodesis for hammertoe

Number per Group (toes): 107 Smart Toe in single-arm studies, 101 overall for Smart Toe vs. K-wire studies, 63 ProToe, 156 Ipp On, 188 StayFuse

Observed adverse effects: Due to the limited information provided in this SR, we sought additional details from the abstracts of these individual studies. Minor complications (listed below) were described as mostly asymptomatic and radiologically identified.

Fracture: 1 nonrandomized comparative study (n=86) reported higher (non-significant) rates of fracture with Smart Toe vs. K-wire (12/58 (20.7%) vs. 2/28 (7.1%)) up to ~38 months.

Displaced fixation: 2 single-arm studies (n=45, 95 toes) reported that Smart Toe was associated with displaced fixation rates of 1.5% and 13% up to 40 months.

Malunion: 1 single-arm study (n=10, 30 toes) reported that Smart Toe was associated with a malunion rate of 7%, while another single-arm study (63 toes) reported a rate of 2.4% with ProToe, a stainless steel (SS) fixation device.

Deformities: 1 single-arm study (n=10, 30 toes) reported that Smart Toe was associated with a 23% rate of secondary contracture of the distal IPJ (mallet toe), while another study reported this deformity was found in 2% of patients after 1 year with Ipp on, a SS fixation device. 1 single-arm study (n=24, 42 toes) reported minor digital rotational deformity with Smart Toe in 1 toe at 12 months followup.

Non-union: Rates for asymptomatic non-union with Smart Toe were 1.5% and 6.7% up to 40 months.

Hardware failure: 1 single-arm study (n=35, 65 toes) reported hardware failure [not requiring revisions or hardware removal] with Smart Toe in 2 (3%) patients up to 40 months. Another single-arm study (n=24, 42 toes) reported hardware failure with Smart Toe in 5% of patients up to 12 months.

Timing of adverse effects: NR

Factors that predict response: NR

Table 21: Reproductive – Health Effect (In Vivo) Human Studies

21.1 Source Citation: Turok et al. 2020[88]

Study Design: single arm

Device or Material: nitinol and copper intrauterine device (IUD) (VeraCept, Sebela Pharmaceuticals, Roswell, GA)

Contact Duration: up to 3 years

Dose: NR

Frequency/Duration: 267 single attempts, 19 required a second attempt

Response: abdominal pain, abdominal pain lower, back pain, bacterial vaginosis, dysmenorrhea, dyspareunia, ectopic pregnancy, expulsion, hemorrhagic cyst, menorrhagia, metrorrhagia, pelvic inflammatory disease (PID), pelvic pain, postprocedural hemorrhage, procedural pain, urinary tract infection (UTI), uterine spasm, vaginal discharge, vulvovaginal mycotic infection, headache, nasopharyngitis, nausea, upper respiratory infection

Patient characteristics (gender, mean age): 100% female, 27.1 years (range 18 to 40)

Number per Group: 286

Observed adverse effects in 283 patients:

Abdominal pain: 44 (15.5%)

Abdominal pain lower: 23 (8.1%)

Back pain: 33 (11.7%)

Bacterial vaginosis: 32 (11.3%)

Dysmenorrhea: 142 (50.2%)

Dyspareunia: 21 (7.4%)

Ectopic pregnancy: 1 (0.3%) unlikely related to treatment

Expulsion (device moving part way into the vagina or all the way out of the body): 5 (1.8%)

Hemorrhagic cyst: 1 (0.3%) unlikely related to treatment

Menorrhagia: 73 (25.8%)

Metrorrhagia: 39 (13.8%)

Pelvic pain: 39 (13.8%)

PID: 1 (0.3%) unlikely related to treatment

Postprocedural hemorrhage: 21 (7.4%)

Procedural pain: 105 (37.1%)

UTI: 31 (11%)

Uterine perforations: 0

Uterine spasm: 26 (9.2%)

Vaginal discharge: 18 (6.4%)

Vulvovaginal mycotic infection: 25 (8.8%)

Authors noted that 48 (17%) patients discontinued the trial due to adverse events.

Nasopharyngitis: 61 (21.6%)

Headache: 38 (13.4%)

Upper respiratory infection: 37 (13.1%)

Nausea: 15 (5.3%)

Timing of adverse effects: 3 expulsions occurred in year 1, 2 expulsions occurred year 1 to 3; PID diagnosed at day 119; dysmenorrhea (8, 2.8%) and pelvic pain (5, 1.8%) occurred in year 2; 1 ectopic pregnancy in year 3

Factors that predict response: NR

Table 22: Urinary - Health Effect (In Vivo) Human Studies

22.1 Source Citation: Chughtai et al. 2021[90]

Study Design: RCT

Device or Material: iTind (Medi-Tate Ltd) vs sham

Contact Duration: Implant duration = 5-7 days. Follow-up = 12 months

Dose: 1 implant

Frequency/Duration: Single Administration

Response: Dysuria, Ejaculatory dysfunction, Erectile dysfunction, Hematuria, Micturition urgency, Pain, Pollakiuria, Urinary retention, Urinary tract infection, Sepsis

Patient characteristics (gender, mean age): Male, 61.1±6.5 yrs

Number per group: iTind - 118; Sham - 57

Observed adverse effects: Dysuria - 27 (22.9%) of subjects. None observed. None observed. Hematuria - 16 (13.6%). Micturition urgency - 6 (5.1%). Pain - 1 (0.8%). Pollakiuria - 8 (6.8%). Urinary retention - 7 (5.9%). UTI - 2 (1.7%). Sepsis - 1 (0.8%).

Timing of adverse effects: All effects occurred within 30 days of the initial iTind placement, except 1 case of Urinary retention and 1 case of UTI (different subjects) occurred 1 - 3 months after initial placement.

Factors that predict response: NR

22.2 Source Citation: Corrales et al. 2021[89]

Study Design: Systematic Review

Device or Material: Memokath 051 (PNN Medical), Uventa (Taewoong Medical), Allium (Allium Medical Solutions), Memotherm Stent (Bard)

Contact Duration: Mean stent duration = 9 months. Mean follow-up = 16.5 months.

Dose: 1 or 2 stents

Frequency/Duration: Single Administration

Response: Clavien-Dindo class IIIb: fistulas, Encrustation, Fungal infection, Hematuria, Intolerance, Lower abdominal pain, LUTS, Migration, Obstruction, Urinary tract infection

Patient characteristics (gender, mean age): NR

Number per group: 530 combined

Observed adverse effects: One study of 44 patients found 28% developed a class IIIb fistula. Five studies including 186 patients found an encrustation rate of 6%. One study of 55 patients found a fungal infection rate of 6%. Four studies reported hematuria in 25% of 101 patients. One study of 36 patients reported an intolerance rate of 8%. Three studies reported the occurrence of lower abdominal pain but did not give rates. Two studies including 73 patients reported 36% of them experienced lower urinary tract symptoms. 12 studies including 351 patients reported a migration rate of 17%. Six studies including 138 patients reported an obstruction rate of 9% but was mostly due to tumor progression that led to stent blockage. Three studies including 146 patients reported a UTI rate of 9%.

Timing of adverse effects: NR

Factors that predict response: NR

22.3 Source Citation: Kadner et al. 2020[91]

Study Design: Single-arm study

Device or Material: iTind (Medi-Tate Ltd)

Contact Duration: 2 years

Dose: 1 implant

Frequency/Duration: Single Administration

Response: Complications, Ejaculatory dysfunction, Erectile dysfunction

Patient characteristics (gender, mean age): Male, 65 yrs (45.5-83.7)

Number per group: 51

Observed adverse effects: No complications were reported between 1 and 2 years. No deterioration in ejaculatory abilities were observed. No deterioration in sexual abilities were observed.

Timing of adverse effects: NR

Factors that predict response: NR

22.4 Source Citation: Barbagli et al. 2017[92]

Study Design: Single-arm study

Device or Material: Memokath 044TW/0045TW (Pnn Medical)

Contact Duration: 16 months

Dose: 1 implant

Frequency/Duration:

Response: Encrustation, Hematuria, Infection, Migration, Pain, Urinary incontinence

Patient characteristics (gender, mean age): Male, 61 yrs

Number per group: 16

Observed adverse effects: One (6%) patient experienced aggressive obliterative encrustation inside the stent. At follow-up urethroscopy, four(25%) patients showed small calcifications inside the stent that required chipping by a laser. No cases of hematuria were reported. Infections occurred in 5 (31%) patients. Migration into the penile tract occurred in 1 patient (6%). The stent was removed because of pain in 5 patients (31%) 4 to 9 months after implantation. No cases of urinary incontinence were reported.

Timing of adverse effects:

Factors that predict response: Pain occurred 4 - 9 months after implantation.

22.5 Source Citation: Abdallah et al. 2013[93]

Study Design: Single-arm study

Device or Material: Memokath MK044 (Pnn Medical)

Contact Duration: Mean follow-up 17.4±6.1 months

Dose: 1 implant

Frequency/Duration: Single Administration

Response: Encrustration, Hematuria, Pain, Urethral hyperplasia, Urinary tract infection

Patient characteristics (gender, mean age): Male, 55.4±7.3 yrs

Number per group: 23

Observed adverse effects: Three patients (13%) had obstructed stents due to encrustation during the first 6 months, and needed lithotripsy to clear the encrustation, which failed in one and the stent was exchanged. Three patients (13%) had intermittent gross haematuria during the first 2 weeks after insertion. Perineal pain occurred in six patients (26%) that was transient and disappeared within a few weeks of follow-up. Urethral hyperplasia was noted in two patients (8%) who presented with lower urinary tract obstructive symptoms, and the diagnosis was confirmed by cystoscopy; they required removal of the stent. Four patients (17%) had UTIs twice or three times during the first 3 months of follow-up.

Timing of adverse effects: First 6 months Hematuria occurred in the first 2 weeks. Pain resolved within a few weeks. UTIs occurred in the first 3 months.

Factors that predict response: NR

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.