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# Medical Device Material Performance Study

# Poly Lactic-co-Glycolic Acid [P(L/G)A] Safety Profile

*Prepared for*
**U.S. FDA Center for Devices and Radiological Health**

*Submitted to*

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# Executive Summary

### Key Points

1. Searches identified 3,062 citations; 113 articles were selected for inclusion.
2. The local response reported in the largest number of studies was inflammation (usually mild) with moderate quality of evidence supporting this finding. In-stent restenosis and stent thrombosis were reported for coronary drug-eluting stents/scaffolds and associated with low quality of evidence. Other local responses for P(L/G)G devices were associated with low or very low quality of evidence.
3. A local host response or device event could occur at any time with incidents reported within 1-day postimplantation or up to 5 years afterward. An Inflammatory response could be transient or chronic.
4. No studies that met inclusion criteria reported systemic reactions to P(L/G)A devices.
5. ECRI's surveillance data indicated that various types of complications associated with P(L/G)A devices closure devices including deployment system malfunction (16%), hematoma (15%), device malfunction (15%), and infection (12%). Harm occurred in 39% of all complications, and the majority of these events were associated with harm scores ranging from E (temporary harm) to G (permanent harm).
6. Evidence gaps:
    a. With the exception of mild inflammatory response, the quality of evidence supporting reported local host response was low. There was no evidence of systemic responses.
    b. Local host responses for all devices. The quality of evidence for all reported local host responses ranged from low to very low.
    c. Systemic manifestations for all devices. The quality of evidence for all reported systemic manifestations was very low (no evidence).
    d. Overall, the literature for P(L/G)A generally lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses.

## Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. 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 the poly lactic-co-glycolic acid [P(L/G)A]. 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 P(L/G)A?

The local response consistent across device categories was an inflammatory response that was mild in most cases. Other reported events were more specific to different device categories (see specific events for coronary stents/scaffolds under 1a below). ECRI surveillance data revealed various types of complications associated with P(L/G)A devices/closure devices, including deployment system malfunction (16%), hematoma (15%), device malfunction (15%), and infection (12%). Harm occurred in 39% of these events, and the majority of these events were associated with harm scores ranging from E (temporary harm) to G (permanent harm).

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

i. Coronary drug-eluting stents/scaffolds had the largest literature base. Local responses/device events included in-stent restenosis (ISR), stent thrombosis (ST), and chronic inflammation.
ii. Other device categories reported some local inflammatory responses (including foreign body reaction).
iii. The overall quality of evidence related to local host responses was moderate to very low, with variation across different device categories.
iv. No evidence was found regarding local host responses for drug-eluting peripheral transluminal angioplasty catheters and vascular closure devices.

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

i. A local host response or device event could occur at any time with incidents reported within 1 day postimplantation or up to 5 years afterward. An inflammatory response could be transient or chronic.

## 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?*

No studies reported data on whether there are systemic manifestations related to P(L/G)A devices. The quality of evidence is therefore very low.

*b. What are the likely systemic manifestations?*

No systemic manifestations were reported in the literature, which suggests that such manifestations are either very rare or not a problem with P(L/G)A devices.

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

See above.

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

See above.

## 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?

Since no studies reported systemic manifestations, there was no evidence to address this question.

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

Since no studies reported systemic manifestations, there was no evidence to address this question.

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

All gaps listed here indicate could benefit from future research.

i. With the exception of mild inflammatory response, the quality of evidence supporting reported local host reponses was low. There was no evidence on whether there are systemic responses.
ii. Local host responses for all devices. The quality of evidence for all reported local host responses ranged from low to very low.
iii. Systemic manifestations for all devices. The quality of evidence for all reported systemic manifestations was very low (no evidence).
iv. Overall, the literature for P(L/G)A generally lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses.

## Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials were selected by FDA based on current priority. For 2020, the following six materials were chosen:

1. Siloxane (Si)
2. Polypropylene (PP)
3. Polyether ether ketone (PEEK)
4. Poly(lactic-co-glycolic acid) (PLGA)
5. Polyurethane (PUR)
6. Polyethylene terephthalate (PET)

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 the material?
    - Over what time course does this local host response appear?
    - Can that response vary by location or type of tissue the device is implanted in or near?
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    - What evidence exists to suggest or support this?
        - In-vivo/clinical studies/reports?
        - Bench or in-vitro studies?
    - What are the likely systemic manifestations?
    - What is the observed timeline(s) for the systemic manifestations?
    - 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/research are 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 six 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 have 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 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 non-clinical 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 from 2010 to 2020 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 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 prelude harm.

Category E (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Category F (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, Harm)

An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, Harm)

An error occurred that required intervention necessary to sustain life.

Category I (Error, Death)

An error occurred that may have contributed to or resulted in the patient's death.

Definitions

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

Monitoring – To observe or record relevant physiological or psychological signs

Intervention – May include change in therapy or active medical/surgical treatment

Intervention Necessary to Sustain Life – Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

## Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident

simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

## Problem Reporting Network (PRN)

For more than 50 years, ECRI's 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 – Poly Lactic-co-Glycolic Acid

Full Name: Poly Lactic-co-Glycolic Acid

CAS Registry Number: 26780-50-7, 34346-01-5

## Search Overview

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of poly lactic-co-glycolic acid [P(L/G)A] used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of P(L/G)A. 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 P(L/G)A provided by FDA to guide ECRI searches*

| Regulatory Description | Pro Code | Class |
|---|---|---|
| Absorbable Coronary Drug-Eluting Stent | PNY | III |
| Coronary Drug-Eluting Stent/Scaffold | NIQ | III |
| Device, Hemostasis, Vascular | MGB | III |
| Drug-Eluting Peripheral Transluminal Angioplasty Catheter | ONU | III |
| Fastener, Fixation, Biodegradable, Soft Tissue | MAI | II |
| Pin, Fixation, Smooth | HTY | II |
| Screw, Fixation, Bone | HWC | II |
| Vascular Grafts* | MAL, DSY, MIH | III |

* No FDA-approved products

## Systematic Review Safety Brief

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of P(L/G)A. 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 findings is shown in Table 2. We then turn to a detailed discussion of research on P(L/G)A as a material as well as research on the various device categories.

*Table 2: Summary of primary findings from our systematic review*

| **Application** | **Local host responses/device events** | **Quality of evidence (local responses)** | **Systemic responses** | **Quality of evidence (systemic responses)** |
|---|---|---|---|---|
| P(L/G)A as a material<br>(2 human studies, 35 animal studies) | Mild inflammatory response, moderate inflammation, foreign body reaction, dysphagia, extruded grafts, restenosis, necrosis, fibrous capsules | Moderate for inflammatory response<br>Low for all other outcomes | Not investigated | Very low (no evidence) |
| Coronary drug-eluting stent/ scaffold<br>(11 human studies, 38 animal studies) | Chronic inflammation, stent thrombosis, in-stent restenosis | Low for all responses/events | Not investigated | Very low (no evidence) |
| Screw, fixation, bone (6 human studies, 4 animal studies) | Cysts, edema, tunnel widening, malocclusion, malunion, foreign body reaction, inflammation, edema | Very low for all responses/events | Not investigated | Very low (no evidence) |
| Fastener, fixation, biodegradeable soft tissue<br>(1 human systematic review, 3 animal studies) | Treatment failure, foreign body reaction | Low for treatment failure<br>Very low for foreign body reaction | Not investigated | Very low (no evidence) |
| Pin, fixation<br>(2 human studies, 3 animal studies) | Foreign body reaction, bone marrow edema, local inflammation | Very low for all responses | Not investigated | Very low (no evidence) |
| Vascular graft | Inflammatory response | Low | Not investigated | Very low (no evidence) |

| Application | Local host responses/device events | Quality of evidence (local responses) | Systemic responses | Quality of evidence (systemic responses) |
|---|---|---|---|---|
| (8 animal studies) | | | | |
| Drug-eluting peripheral transluminal angioplasty catheter and vascular closure devices<br><br>(no studies) | No evidence | Very low | Not investigated | Very low |

**P(L/G)A as a material:** 37 studies (2 human studies, 35 animal studies).[1-37] The human studies were both cohort studies.[1-2] The animal studies included 12 randomized controlled trials (RCTs),[6-10,14-15,18-19,24-25,27] 17 non-RCTs,[13,16-17,20-23,26,28-33,35-37] and 6 case series.[3-5,11-12,34] For further information, see Tables 1 and 2 in Appendix D.

*Local host responses (human studies)*: 1 prospective cohort study examined a poly-L-D-lactide (PLDLA) joint scaffold in 23 individuals (87% female). Authors reported that 7 (30%) patients developed clinically manifested foreign-body reaction between 6 and 12 months postoperatively.[1] 1 cohort study retrospectively compared a bioabsorbable anterior cervical plate (bACP) with polylactic acid (PLA) in 14 individuals versus a metal ACP with a Titanium mesh cage in 15 individuals. At 2 weeks, complications with bACP included extruded grafts in 3 (21%) individuals, and dysphagia in 2 (14%) individuals.[2]

*Systemic responses (human studies)*: No studies investigated whether there are systemic responses to P(L/G)A as a material.

*Local host responses (animal studies)*: The animal studies examined a variety of P(L/G)A formulations in matrices such as scaffolds, nanoparticles, and implants. Materials were either injected or implanted; subcutaneous placement was the most commonly used route.

Thrombosis was not observed, while restenosis was only reported in 1 RCT.[18] This study reported significantly less restenosis with P(L/G)A-loaded bilayered nanoparticle (NP) and vascular endothelial growth factor (VEGF) NP versus blank NPs and paclitaxel (PTX) NPs (all NPs were delivered via balloon angioplasty).

RCTs described visible necrosis on a P(L/G)A scaffold by 4 weeks,[6] but no necrosis with a PLLA-TMC-GA copolymer (PLTG) by 12 weeks.[7] Necrosis was not visible in a non-RCT examining a calcium hydroxyapatite scaffold covered with P(L/G)A up to 12 weeks.[17] 1 RCT examining scaffolds with PLGA versus PLGA plus recombinant human bone morphogenetic protein type 2 (rhBMP-2) versus P(L/G)A plus rhBMP-2 plus adipose-derived stem cells (ASCs) described hyaline necrosis in scaffolds with ASCs and coagulative necrosis in scaffolds without ASCs.[19]

Severe inflammation from P(L/G)A was not reported in any study. Moderate inflammation (including presence of macrophages and plasma cells, lymphocytes, thick fibrous capsule) was reported only in 1 case series in two samples of PLLA/bioactive glass bone plate at 4 weeks, and 1 sample at 8 weeks.[5]

Mild inflammatory responses including neutrophils, macrophages, and multinucleated foreign body giant cells were more commonly reported. 1 study reported a peak in neutrophils within 7 days with P(L/G)A, and a peak in lymphocytes at 14 and 21 days.[36] Another study reported an increase in number of neutrophils at 4 weeks with P(L/G)A.[24] Presence of eosinophils was reported only in 2 studies.[11,32]

Thick fibrous capsules were visible as early as 2 weeks on a PGA/PLA scaffold in 1 study.[20] Another study reported fibrous connective tissue and a thicker capsule wall were observed at 4 weeks with a PLLA-TMC-GA copolymer.[7]

Thicker fibrous capsules with P(L/G)A versus other NPs at 2 months were reported in 1 RCT.[15] Lastly, 1 study described a tri-layer P(L/G)A/silk fibrin graft was encapsulated by cells and fibrous tissue at 10 weeks.[12]

One study described P(L/G)A implants encapsulated by a typical fibrous capsule with a very high density of collagen at the P(L/G)A-tissue interface, and a subsequent decrease in collagen density with increasing distance from the implant by 16 weeks.[24] Unorganized bundles of collagen with P(L/G)A scaffold at 8 weeks were reported in 1 RCT.[9]

Cytokine expressions of collagen I and III,[9] IL-6,[10,31] CD68,[6,20,35] tumor necrosis factor alpha (TNF-α),[31,35] matrix metalloproteinases (MMPs),[8,15,27] and C-reactive proteins (CRPs)[18,27] were reported in several studies.

One non-RCT reported an increased level of IL-6 from day 1 to day 3 in 3 PLLA groups followed by weekly declines in expression.[31] A significantly higher expression of IL-6 was reported at 4 weeks and 8 weeks with PLLA versus a PLLA/amorphous calcium phosphate scaffold in 1 RCT.[10]

A thin P(L/G)A film helped attenuate inflammation up to 8 weeks in 1 controlled study.[35] Authors noted that the percent of CD68 positive cells and TNF-α was significantly lower in a scaffold containing a thin P(L/G)A film with gelatin sponge (GS) plus mesenchymal cells (MSCs) versus scaffolds with only GS or no GS. CD68-positive cells were "widespread and significantly more numerous" on PGA/PLA scaffolds versus bare metal stents versus auricular chondrocyte from 72 hours to 4 weeks in 1 study.[20]

An increase in MMPs by 6 weeks with PLGA implants were reported in 1 RCT.[8] Another RCT reported significantly higher MMP-9 level with P(L/G)A versus other NPs.[15] CRP levels were lowest with P(L/G)A-loaded bilayered NP versus VEGF NP versus blank NPs and PTX NPs (CRP level: 42.3±8.6% bilayered NP, 47.9±9.86% VEGF NP, 61.7±18.5% blank NP, 58,2±15% PTX NP, 65.7±12.6% saline).[18] Lastly, another RCT reported similar positive expression indices of MMP-2 and CRP between P(L/G)A/empty NPs versus P(L/G)A/VEGF NPs versus controls.[27]

*Systemic responses (animal studies)*: No studies investigated whether there are systemic responses to P(L/G)A as a material.

*Overall quality of evidence*: Animal studies (RCTs and observational designs) comprised the majority of evidence, and several reported evidence of a mild inflammatory response to P(L/G)A. Comparative studies showed differences in inflammatory responses between different platforms and implants, so the quality of evidence for mild inflammatory response is moderate. The evidence for all other outcomes is low. The quality of evidence for systemic responses is very low (due to no evidence).

## Coronary Drug-eluting Stent/Scaffold: 49 studies (11 human studies, 38 animal studies).[38-86]

The human studies included 6 RCTs,[38,42,43,45-47] 3 single-arm cohort studies,[39,44,48] and 2 case series.[40-41] The animal studies included 17 RCTS,[49,56,59-60,62-65,67-69,73-76,79,81] 20 controlled observational studies,[50-55,57-58,61,66,71-72,77-78,80,82-86] and 1 case series.[70] For further information, see Table 3 and 4 in Appendix D.

*Local host responses (human studies)*. Definite or probable stent thrombosis (ST) in approximately 1% of patients with a PLGA polymer was reported in four studies.[39,42,43,45] Thrombosis occurred as early as 24 hours in 1 study,[39] and as late as 12 months in 2 studies.[42,43] In-stent neoatherosclerosis (NA), a cause of late stent thrombosis and restenosis,[38] was the focus of 1 RCT. At 24 months, the study reported no significant difference in NA between an everolimus-eluting stent (EES) and a zotarolimus-eluting stent (ZES). Individual components suggestive of NA were similarly low or not present (e.g., lipid laden neointima).[38]

In-stent restenosis (ISR) was observed from 30 days to 58 months in 5 studies.[43-45,47-48] 2 RCTs reported higher binary restenosis with sirolimus-eluting stents (SESs) vs. biolimus-eluting stents[43] or ZESs.[45] 1 RCT reported significantly lower binary restenosis with CoStar stents vs. bare metal stents (BMSs).[47] Two cohort studies reported binary restenosis rates of 5.2%[48] and 28.5%.[44]

Additional angiographic results included reports on late lumen loss (LLL), a surrogate endpoint of restenosis. 2 case series reported in-scaffold LLL (mean±SD) of 0.15±0.23 mm at 6 months [40] and in-stent LLL of 0.03±0.24 mm at 12 months.[41]

Strut malapposition, a major cause of ST, was reported in three studies.[46-48] 1 RCT[46] reported no significant difference in malapposed struts with a P(L/G)A polymer with electro-grafting base layer SES versus a PLA-polymer

SES, while 1 cohort reported malappositions occurred in 2 (3.2%) patients after stent placement and at 9 months.[48] Mean number of malappositions per P(L/G)A stent were 1.4±0.5 in 1 case series.[41]

*Systemic responses (human studies)*: No studies investigated whether there are systemic responses to coronary drug-eluting stents (DESs)/scaffolds.

*Local host responses (animal studies)*: 16 studies (7 RCTs,[56,59,64,65,67,73,75] 9 comparative[50,52,54,57,58,61,71,78,84]) reported ST and/or ISR with a P(L/G)A polymer.

One RCT each compared PLGA- and PLA-coated stents with a DES containing modified magnesium hydroxide,[56] a dextran coated-SES,[59] and rapamycin DES.[65] The first RCT reported a significantly higher ISR rate (20.5% vs. 14.1%) and inflammation score (1.1 vs. 0.1) with a sirolimus-loaded PLGA-coated DES versus a DES containing modified magnesium hydroxide at 28 days.[56] The second RCT reported equal restenosis with a PLA-coated SES and a dextran-coated SES, but significantly higher inflammation and higher number of macrophages with PLA-coated stents at 4 weeks.[59] The third RCT reported no ST or ISR with MgZnYNd rapamycin DES with PLGA vs. a stainless steel (SS) stent system up to 6 months.[65] Lastly, use of a PLLA brushed-modified SES resulted in significantly lower area restenosis (28.5±7%) vs. unmodified SES (50.7±10%) and BMS (70±10%) at 28 days.[64]

Three RCTs reported on the addition of paclitaxel to P(L/G)A coronary stents. Two RCTs reported benefits from PowerStent Absorb coated with a layer of paclitaxel blended in the biodegradable carrier PLGA.[73,75] The first RCT indicated significant reductions in restenosis with PowerStent vs. PLLA/amorphous calcium phosphate (ACP) at 1 month. Angiographic results in this trial indicated a mottled texture of the PLLA interior wall vs. a smooth arterial wall with PowerStent.[75] The second RCT reported limited restenosis formation between PowerStent and Taxus DES; however, milder neointimal hyperplasia was reported with PowerStent at 6 months.[73] Lastly, 1 RCT reported higher ISR with PLA plus simvastatin-coated stents (1.04) vs. PLA (0.73) vs. PLA plus paclitaxel (0.67) at 7 days.[67]

The comparative trials reported significantly higher restenosis with 316L SS stents (outer coating with PLGA) vs. asymmetrical dual coating at 12 weeks,[54] and no ST with PLGA stents and PLLA scaffolds in 2 studies.[52,61] In addition, 2 studies reported that a PLGA copolymer with paclitaxel[57] and rapamycin[58] were protective for restenosis. Results for PLGA/ACP copolymers varied. While 1 study reported significantly reduced restenosis with PLGA/ACP-coated stents (vs. PLGA and polyethylene-co-vinyl acetate/poly-n-butyl methacrylate [PEVA/PBMA]),[78] another study excluded 13 rats from further analysis because of acute thrombosis from a SS stent coated with PLGA/ACP copolymer.[84]

Lastly, results from 1 case series[70] examining a mixture of PLGA/NCO-sP(EO-stat-PO) polymer indicated chronic inflammation from 1 to 3 months was exhibited by macrophages and Langham giant cells with horseshoe nuclei arrangement.

Signs of chronic inflammation (e.g., eosinophils, macrophages, giant cells) and acute inflammation (e.g., surface monocytes, neutrophils) were commonly reported. Inflammation scores (e.g. based on percent of inflammatory cells present) were reported in 9 studies.[56,57,60,61,63,64,81,78,83]

*Systemic responses (animal studies)*: No studies investigated whether there are systemic responses to coronary drug-eluting stents/scaffolds.

*Overall quality of evidence*: Although several human studies reported ST and ISR in a small percentage of patients with stents containing P(L/G)A, most compared different drugs eluted from the stents rather than PLGA to other materials. Also, some stents included other materials in the stent platform. Therefore, the association between PLGA and ST/ISR remains unclear, so the quality of evidence is low. Some animal studies reported signs of chronic inflammation related to PLGA stents, but since few of them provided an adequate comparator the quality of evidence for chronic inflammation is low. Since no studies reported systemic responses, the quality of evidence for systemic responses is very low.

**Screw, Fixation, Bone**: 6 human studies (1 systematic review,[87] 4 observational comparative studies,[89-92] 1 case series[88]) and 4 animal studies (1 observational comparative study,[93] 3 case series[94-96]). For further information, see Tables 5 and 6 in Appendix D.

*Local host responses*: 5 human studies reported local responses occurring from 1 month to 3 years following implantation. Cysts, edema, and tunnel widening were each reported in 2 human studies. Inflammation, malocclusion, and malunion were each reported in 1 human study. Of the human studies, the case series was the only study in which an adverse local response was not observed.

3 animal studies reported local responses occurring from 1 to 3 months following implant. 2 studies reported foreign body reaction, and 1 of those also reported inflammation. Another animal study reported edema, and 1 animal study reported observing no adverse reactions.

*Systemic responses*: No studies investigated whether there are systemic responses to PLGA bone screws.

*Overall quality of evidence*: Since the evidence base consisted of observational studies, and few studies reported the same local host responses, the quality of evidence is very low. The quality of evidence for systemic responses was also very low (due to no evidence).

**Fastener, Fixation, Biodegradeable Soft Tissue:** 1 systemic review (SR) of human studies, and 3 animal studies (1 RCT, 2 observational comparative studies). For further information, see Tables 7 and 8 in Appendix D.

*Local host responses*: The SR of human studies compared bioabsorbable poly-L-lactic acid or polyglycolic acid screws versus metallic interference screws for graft fixation in anterior cruciate ligament reconstruction. The SR reported failure of treatment and adverse events including symptomatic foreign body reactions (1 patient in 1 study). Twice as many treatment failures occurred in the bioabsorbable screw group (60/451 versus 29/434; RR 1.94, 95% CI 1.29 to 2.93; p = 0.001) during a mean follow-up ranging from 13 to 28 months.

Of the 3 animal studies, the RCT reported no adverse reactions or immune responses to a vented suture anchor with PLGA scaffold in an infraspinatus tendon acute transection/repair sheep model. However, the 2 observational comparative studies reported foreign body responses occurring between 1 and 12 months. In 1 study PDLLA plates produced a foreign body response in rabbits while PLGA plates did not. Conversely, the other study reported that in dogs, PLGA scaffolds produced a more significant local immune response than PLLA scaffolds.

*Systemic responses*: No studies investigated whether there are systemic responses to P(L/G)A fixation in biodegradeable soft tissue.

*Overall quality of evidence*: The quality of evidence supporting treatment failure or device-related adverse events in humans based on 1 systematic review is low. The evidence supporting foreign body reactions in animals is based on small, mostly observational studies with somewhat inconsistent findings, so the quality of evidence is very low. The quality of evidence for systemic responses was also very low (due to no evidence).

**Pin, Fixation**: 2 human studies (2 cohort studies) and 3 animal studies (1 RCT, 2 comparative studies). For further information, see Tables 9 and 10 in Appendix D.

*Local host responses*: Both human studies reported local responses, 1 discussing the presence of foreign body reaction the other reporting bone marrow edema. The first study reported no foreign body reaction or adverse events during the 12 week follow-up, and the other study suggested the pins may reduce the level of bone marrow edema within 6 months.

All 3 animal studies reported local host responses during a 4 to 24 week follow-up. 2 studies reported on local inflammation, with 1 study detailing specific markers like IL-6 levels, lymphocytes %, monocytes %, and neutrophil granulocytes, eosinophil, basophile granulocytes %. 1 study reported on tissue necrosis. The three studies presented inconsistent evidence on local host responses.

*Systemic responses*: No studies investigated whether there are systemic responses to P(L/G)A pins.

*Overall quality of evidence*: The evidence supporting local response to pins was inconsistent, and four of five studies were observational; the quality of evidence was therefore very low. The quality of evidence for systemic responses was also very low (due to no evidence).

**Vascular Graft**: No human studies; 8 animal studies (7 observational comparative studies,[106-108, 110-113] 1 case series[109]).

*Local host responses*: 6 out of 8 animal studies reported inflammatory responses ranging from mild to strong. The responses were measured at different times across studies, ranging from 1 week to 18 months. 1 study reported that PLGA/PGCL scaffolds induced a strong or significant inflammatory response at 30 to 90 days. Two studies reported thrombosis in mice (and 1 rabbit) at 3 days to 8 weeks following implantation.

*Systemic responses*: No studies reported whether there are systemic responses to P(L/G)A vascular grafts.

*Overall quality of evidence*: Animal studies provided consistent evidence of inflammatory responses although the intensity of the response varied among difference studies. The quality of evidence for local responses is low. For systemic responses the quality of evidence is very low (no evidence).

**Drug-eluting Peripheral Transluminal Angioplasty Catheter and Vascular Closure Devices:** We did not identify any human or animal studies that evaluated these devices.

## ECRI Surveillance Data

ECRI surveillance data comprise ECRI PSO event reports, accident investigations, 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.

The types and severity of complications reported within surveillance data for P(L/G)A vary across devices of interest. PSO reports indicate that closure devices and vascular grafts have the highest number of complications. PSO reports show that closure device complications are primarily device malfunctions/failures while vascular graft complications are mainly infection and thrombosis. PRN reports demonstrate that coronary DES complications include failure of balloon to deflate, balloon separating from stent, and broken distal tips. Additionally, bone fixation screw complications are mostly associated with breakage. The majority of ECRI alerts were unrelated to host responses to P(L/G)A and involved manufacturing, packaging, and device labeling errors. However, these reports detail sterility concerns across all device categories as well as warnings regarding myocardial infarction and thrombosis associated with coronary DESs.

## Patient Safety Organization

Search Results: ECRI PSO identified 721 reports that involved P(L/G)A materials that occurred between 1/2007 and 7/2020. 123 of these involved complications. The event review identified the top 5 complications (Table 3), including 1) Deployment system malfunction – 20 (16.3%), 2) Hematoma - 18 (14.6 %), T-2) Device malfunction/failure - 18 (14.6%), 3) Infection - 15 (12.2%), 4) Thrombosis - 10 (8.1%), T-4) Device fracture - 10 (8.1%) and 5) Vascular insufficiency - 9 (7.3%). Harm occurred in 39% of the events, and the majority these events were associated with harm scores ranging from E through G (Table 4). Events with harm score E resulted in temporary harm to the patient; incidents with harm score F resulted in prolonged hospitalization. Harm score G indicates permanent harm. Closure device and vascular graft complications were the two most commonly reported. Vascular grafts have a higher percentage of serious reports including death (harm score I, 5%) and prolonged harm (harm score F, 15%). Closure devices and vascular grafts have similar percentage of incidents resulting in temporary harm (harm scare E, 25%) while closure devices have more reports associated with no harm (harm score C, 20%).

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

*Table 3: Complications in P(L/G)A-related PSO event reports*

| Complications | Absorable/ Resorbable materials | AV graft | Closure Device | Coronary drug-eluting stent/ scaffold | Vascular Graft | Total |
|---|---|---|---|---|---|---|
| Deployment system malfunction | 1 | | 12 | 2 | 5 | 20 |
| Hematoma | | 3 | 10 | 4 | 1 | 18 |
| Device malfunction/failure | | | 15 | 3 | | 18 |
| Infection | | 3 | 1 | | 11 | 15 |
| Thrombosis | | 2 | 1 | 1 | 6 | 10 |
| Device fracture | 7 | | | 1 | 2 | 10 |
| Vascular insufficiency | 1 | | 5 | | 3 | 9 |
| Pseudoaneurysm | | | 3 | | 2 | 5 |
| Bleeding | | | 3 | | 2 | 5 |

| Complications | Absorable/ Resorbable materials | AV graft | Closure Device | Coronary drug-eluting stent/ scaffold | Vascular Graft | Total |
|---|---|---|---|---|---|---|
| Iatrogenic Injury | | | | 1 | 3 | 4 |
| Clotted graft | | 2 | | | | 2 |
| Retained foreign body | | | | | 2 | 2 |
| Clinical Manifestations | 1 | | 1 | | | 2 |
| Migration | | | | 1 | | 1 |
| Wound dehiscence | 1 | | | | | 1 |
| Loss of motor function | | | | | 1 | 1 |
| **Total** | **11** | **10** | **51** | **13** | **38** | **123** |

*Table 4: Harm score associated with P(L/G)A-related event reports.*

| Harm Scores (NCC-MERP) | | Absorable/ Resorbable materials | AV graft | Closure Device | Coronary drug-eluting stent/ scaffold | Vascular Graft | Total |
|---|---|---|---|---|---|---|---|
| **A** | No Error | -- | -- | 1 | 1 | 1 | 3 |
| **B1** | Error, No Harm | -- | -- | -- | 1 | -- | 1 |
| **B2** | Error, No Harm | 1 | -- | -- | -- | -- | 1 |
| **C** | Error, No Harm | 5 | -- | 10 | 3 | 4 | 22 |
| **D** | Error, No Harm | -- | 2 | 5 | 4 | 4 | 15 |
| **E** | Error, Harm | 2 | 5 | 13 | 3 | 9 | 32 |
| **F** | Error, Ha | -- | 1 | 3 | -- | 6 | 10 |
| **G** | Error, Ha | -- | -- | 1 | -- | 1 | 2 |
| **H** | Error, Ha | -- | -- | -- | -- | 1 | 1 |
| **I** | Error, Death | -- | -- | -- | 1 | 2 | 3 |
| **NULL*** | | 3 | 2 | 18 | | 10 | 33 |
| **Total** | | **11** | **10** | **51** | **13** | **38** | **123** |

**Harm score was not reported*

## Accident Investigations

Search Criteria: Stent and coronary, drug-eluting, scaffold, bone screw, transluminal angioplasty catheter, anchor, fastener, suture anchor, fixation pin, resorbable, vacular graft, PGA, PLA

Search Results: 1 investigation was recovered as summarized in Table 5 and included in Appendix F. The reported patient incident was associated, in part, with device misuse, including excessive force during sling anchor placement and inserting mesh fixation screws into bone instead of collagenous structures – both of which increase the likelihood of a host response.This investigation is redacted and included in Appendix F.

*Table 5: Accident investigations of patient incidents involving P(L/G)A.*

| Device Type | # Investigations | Reported Problem and Findings (number of investigations) |
|---|---|---|
| Fastener, Fixation, Biodegradable, Soft Tissue (MAI) | 1 | *Rupture / tear of mesh* – iatrogenic at implantation |

## ECRI Problem Reports

Search Criteria: Fastener, screws, graft, stent, drug eluding, pin, anchor, vascular closure device, tack, absorbable and suture

Search Results: The search returned 15 reports submitted by ECRI members (Table 6). The reports detail device failures from breaking or not performing as intended, leading to safety concerns detailed as delayed procedures, prolonged surgeries, and additional patient imaging.

All problems reports are redacted and included in Appendix F.

*Table 6: ECRI Problem Report Summary*

| Device Type | # Problem Reports | Reported Problem and ECRI Findings |
|---|---|---|
| Coronary Drug-Eluting Stent/Scaffold(NIQ) | 5 | Failure of balloon to deflate, balloon separating from stent, tip broke off |
| Screw, fixation, bone(HWC) | 9 | Breakage and cold welded |
| Fastener, Fixation Biodegradable Soft Tissue(MAI) | 1 | Needle Disengaged |

## Alerts

Search Criteria: Specific devices and search terms are included in Appendix G.

Search Results: The search returned 112 manufacturer or regulatory agencies issued alerts describing problems with labeling, manufacturing, sterility, IFU updates, questionable regulatory markings, warnings of possible myocardial infarction, adverse cardiac events, or tissue swelling, summarized in Table 7.

*Table 7: Summary of regulatory and manufacturer alerts*

| Device Type | # Alerts | Problems |
|---|---|---|
| Coronary Drug-Eluting Stent/Scaffold (NIQ) | 3 FDA warning notifications<br>1 MHRA warning notifications<br>15 manufacturer-issued | • Labeling error<br>• IFU<br>• Manufacturing error<br>• Warning of myocardial infarction<br>• Warning of thrombosis |
| Coronary Drug-Eluting Stent/Scaffold (PNY) | 1 FDA warning notifications<br>1 manufacturer-issued | • Warning of increased adverse cardiac events<br>• IFU update to reduce risks of thrombosis |
| Drug-Eluting Peripheral Transluminal Angioplasty Catheter (ONU) | 2 manufacturer-issued | • IFU update to include warnings<br>• Sterility maybe compromised |
| Screw, fixation, bone Pin, Fixation (HWC, HTY) | 6 manufacturer-issued | • Manufacturing problem<br>• Labeling error<br>• IFU update |
| Screw, fixation, bone Fastener, Fixation Biodegradable Soft Tissue; Pin, Fixation (HWC, MAI, HTY) | 4 manufacturer-issued | • Sterility concern<br>• Packaging error<br>• Manufacturing problem |
| Screw, fixation, bone (HWC) | 57 manufacturer-issued | • Manufacturing problems<br>• Labeling/packaging error<br>• Sterility concern<br>• IFU update<br>• Indications of use not cleared in CA and US<br>• Documentation errors |
| Screw, fixation, bone Fastener, Fixation Biodegradable Soft Tissue; (HWC, MAI) | 6 manufacturer-issued | • Manufacturing/assembly problems<br>• Sterility concern<br>• Product may have invalid CE mark |
| Fixation Biodegradable Soft Tissue (MAI) | 15 manufacturer-issued | • Manufacturing problems<br>• Labeling error<br>• Packaged error<br>• Sterility concern<br>• Warning of tissue swelling |
| Vascular Closure Devices (MGB) | 1 manufacturer-issued | • Sterility concern |

## Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of P(L/G)A. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is also 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.

Overall, the literature for P(L/G)A generally lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses.

**P(L/G)A as a material:** Mild inflammation was the most commonly reported local response. Although the evidence is unclear about the extent of association between P(L/G)A and inflammation (the response could be partly due to the procedures), differences in inflammatory responses between different platforms and implants suggest the the material is at least partly the cause of the response. However, the evidence for all other reported local responses is of low quality. None of the studies reported whether there were systemic responses. Based on the results of ECRI's search, there is a gap in the literature regarding the local and systemic host response to P(L/G)A as a material, indicating areas of potential future research.

**Coronary Drug-Eluting Stent/Scaffold:** There is some evidence of chronic inflammation (low quality) and no studies reported whether there was systemic response to coronary drug-eluting stents/scaffolds.

**Screw, Fixation, Bone:** Evidence of local host responses to P(L/G)A consisted of observational studies and varied (very low evidence quality) and no studies (very low evidence quality) reported whether there were systemic responses. Examples of reported local host responses include cysts, edema, and inflammation.

**Fastener, Fixation, Biodegradeable Soft Tissue:** Only 4 studies (1 human and 3 animal studies) met the search criteria. Evidence of treatment failure and device-related adverse events were of low quality while no studies reported whether there were systemic responses (very low evidence quality).

**Pin, Fixation:** Only 5 studies (2 human cohort and 3 animal studes) met the search criteria. Evidence of local host reponse was inconsistent (very low quality) with reports of local inflammation and foreign body reactions. No studies reported whether there were systemic responses (very low evidence quality).

**Vascular Graft:** The evidence base consisted of 8 animal studies, 7 of them being observational studies. There were no identified human studies. There is consistent, low-quality evidence of inflammation response with varying degrees of intensity across the animal studies. No studies reported whether there were systemic responses (very low evidence quality).

**Drug-Eluting Peripheral Transluminal Angioplasty Catheter and Vascular Closure Devices:** No human or animal studies evaluated these devices.

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

## Inclusion Criteria

1. English language publication
2. Published between January 2010 and September 2020
3. Human and animal studies
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of P(L/G)A 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 providing relevant data.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – 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)?
6. Is there evidence of a **dose response or time response** (e.g., do 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. 1 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 1 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 1 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.

| Set Number | Concept | Search statement |
|---|---|---|
| 1 | **P(L/G)A** | 'polylactic acid'/exp OR 'polylactide'/exp OR 'polylactic acid' OR 'lactic acid polymer' OR 'poly lactic acid' OR 'poly l lactic acid' OR 'poly levo lactic acid' OR 'poly llactic acid' OR 'poly dextro levo lactide' OR 'poly d l lactide' OR 'poly dl lactide' OR 'poly d-l-lactic acid*' OR 'poly dl-lactic acid' OR 'polylactate acrylate' OR 'plla' OR 'pdla' OR 'pdlla' OR 'pldlla' OR 'pldla' OR 'polyglycolic acid'/exp OR 'plga'/exp OR 'polyglactin'/exp OR 'glycolic acid polymer' OR 'polyglycolic acid' OR 'poly glycolic acid' OR 'poly l-glycolic acid' OR 'polyglycolide' OR 'poly glycolide' OR 'polyglycollic' OR 'glycolic acid lactic' OR 'glycolic lactic acid' OR 'glycolide lactide' OR 'lactic acid glycolic' OR 'lactide glycolide' OR 'lactide coglycolide' OR 'poly d l-lactic-co-glycolic' OR 'poly d l-lactic-co-glycolide' OR 'poly d l-lactic-coglycolic' OR 'poly d l-lactic-coglycolide' OR 'poly d l-lactic glycolic' OR 'poly lactic acid co glycolic acid' OR 'poly lactic acid glycolic acid' OR 'poly lactic co glycolic acid' OR 'poly lactide co glycolide' OR 'poly l lactide co glycolide' OR 'polyglactin' OR 'polylactic acid-polyglycolic acid' OR 'polylactic co glycolic acid' OR 'polylactide co glycolide' OR 'poly lactate-co-glycolate' |
| 2 | P(L/G)A trade names | 'bioresorbable vascular scaffold*':ab,dn,ti,kw OR 'absorb bvs':ab,dn,ti,kw OR synergy:dn OR ((synergy NEAR/5 stent*):ab,ti,dn,kw) OR ('manta':ab,dn,kw,ti NOT 'elasmobranch') OR 'exoseal':ab,dn,kw,ti OR 'exo-seal':ab,dn,kw,ti OR 'closer':dn OR (activanail OR activapin OR activascrew OR bilok OR 'bio statak' OR bioactif OR biobsorb OR biocryl OR 'bio-eurolig' OR biofix OR 'bioknotless' OR 'bio-pin' OR 'bio-post' OR bioraptor OR bioscrew OR biosorb OR biostatak OR biosteon OR biostinger OR biosure OR biotrak OR 'bio-transfix' OR 'compositcp' OR 'drilac' OR endofix OR endopearl OR endosorb OR endotine OR fixone OR fixsorb OR graftlok OR gryphon OR healix OR hexalon OR 'inion gtr' OR 'inion otps' OR |

| | | |
|---|---|---|
| | | lactoscrew OR lactosorb* OR 'ligafix' OR 'matryx' OR milagro OR ossiofiber OR osteoraptor OR osteotrans OR panaloc OR panalok OR phusiline OR 'rapidloc' OR rapidsorb OR regenesorb OR rigidfix OR rotium OR 'sd sorb' OR smartanchor OR 'smartpin' OR smartscrew OR smarttack OR SofThread OR 'sonicpin' OR sysorb OR trinion):ab,dn,ti,kw |
| **3** | **Combine sets** | **#1 OR #2** |
| 4 | Limit by language and publication date | #3 AND [english]/lim AND [2010–2020]/py |
| 5 | Limit by publication type | #4 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) |

**Devices**

| | | |
|---|---|---|
| 6 | DES/Absorb | 'stent'/exp OR 'drug eluting stent'/exp OR 'bioresorbable vascular stent'/exp OR stent* OR 'drug eluting' OR synergy:ti,ab,dn OR (bioabsorbab* OR bioresorb* OR absorb* OR biodegrad*) NEAR/3 (scaffold* OR stent*) |
| 7 | PTCA | 'percutaneous transluminal angioplasty balloon'/exp OR 'percutaneous transluminal angioplasty'/exp OR 'ptca catheter'/exp OR 'balloon catheter'/exp OR 'drug-coated balloon'/exp OR 'drug coated balloon angioplasty'/exp OR 'balloon'/exp OR 'drug coated' OR balloon* OR ((bioabsorbab* OR bioresorb* OR absorb* OR biodegrad* OR bio-absorbab* OR bio-resorb* OR bio-degrad* OR resorb*) NEAR/3 catheter*) |
| 8 | Vascular Closure | 'vascular closure device'/exp OR 'vascular closure device*' OR 'vascular haemostasis device*' OR 'vascular hemostasis device*' |
| 9 | Vascular Graft | 'blood vessel graft'/exp OR 'blood vessel prosthesis'/exp OR 'prosthetic vascular graft'/exp OR 'blood vessel prosthesis' OR 'vascular graft' OR 'vascular prosthesis' OR (vascular NEAR/4 'graft prosthesis') |
| 10 | Fixation: Fasteners, Pins, Screws, Anchors | 'hard tissue biodegradable fixation fastener'/exp OR 'soft tissue biodegradable fixation fastener'/exp OR 'biodegradable fixation fastener'/exp OR 'bone pin'/exp OR 'bone screw'/exp OR 'bone implant'/exp OR 'suture anchor'/exp OR 'internal fixator'/exp OR 'spine fixation device'/exp OR 'cranioplasty plate fastener'/de OR 'pedicle screw fixation device'/de OR 'bone screw' OR 'bone prosthesis' OR 'fixation device' OR 'cranioplasty plate fastener' OR ((bioabsorbab* OR bioresorb* OR absorb* OR biodegrad* OR bio-absorbab* OR bio-resorb* OR bio-degrad* OR resorb*) NEAR/4 (fixat* OR fasten* OR screw OR screws OR anchor OR anchors OR pin OR pins OR implant OR implants)) |

**Material Response**

| | | |
|---|---|---|
| 12 | | 'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation' |
| 13 | | 'degradation'/exp OR degradation OR degrad* OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep* |
| 14 | | Leachable* OR extractable* |

| | | |
|---|---|---|
| 15 | | (swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat*) NEAR/3 (implant* OR pin* OR anchor* OR screw*) |
| 16 | | 'mechanics'/exp<br>[see Emtree explosions section at the end of the strategy] |
| 17 | | 'device material'/exp/mj |
| 18 | | 'Biomedical and dental materials'/exp/mj |
| **19** | **Combine sets** | **#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18** |

**Host Response**

| | | |
|---|---|---|
| 20 | | Host NEAR/2 (reaction* OR response*) |
| 21 | | 'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti |
| 22 | | 'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj |
| 23 | | Immun*:ti OR autoimmun*:ti OR hypersens*:ti |
| 24 | | 'inflammation'/exp OR inflamm*:ti |
| 25 | | 'foreign body reaction' OR granuloma* OR 'foreign body'/exp |
| 26 | | ('adhesion'/exp OR 'tissue adhesion'/exp OR 'biomechanics'/exp OR biocompat*) |
| 27 | | (protrude* OR protrus*) |
| 28 | | Migrate OR migration OR evaginat* OR subsidence |
| 29 | | 'graft dysfunction'/exp OR (graft NEAR/3 (fail* OR reject* OR dysfunction OR occlusion OR necrosis)) |
| 30 | | 'stent complication'/exp OR 'vascular fibrosis'/exp OR 'in-stent restenosis'/exp OR restenosis OR neointima* |
| 31 | **Combine sets** | **#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30** |

| | | |
|---|---|---|
| 32 | By periodical title | (material* OR biomaterial*):jt |
| 33 | | (‘physical parameters’/exp/mj OR ‘mechanics’/exp/mj) AND ([humans]/lim OR [animals]/lim) |
| **34** | **Combine sets** | **#32 AND #33** |

**Particles**

| | | |
|---|---|---|
| 35 | Micro/nano particles | 'microsphere'/exp OR 'nanoparticle'/exp OR microsphere* OR particulate* OR microparticle* OR nanoparticle* |
| 36 | Drug delivery | 'drug delivery system'/exp OR 'drug administration'/exp OR 'injection'/exp OR 'medication therapy management'/exp OR 'drug delivery' OR 'drug administration' OR bolus OR inject* |
| 37 | Stent drugs | 'rapamycin'/exp OR 'mammalian target of rapamycin inhibitor'/exp OR biolimus OR umirolimus OR corolimus OR everolimus OR zortress OR afinitor OR votubia OR evertor OR novolimus OR pimecrolimus OR elidel OR ridaforolimus OR ap23573 OR 'mk-8669' OR mk8669 OR deforolimus OR sirolimus OR rapamune OR tacrolimus OR protopic OR prograf OR temsirolimus OR 'cci-779' OR cci779 OR torisel OR zotarolimus OR 'abt-578' OR abt578 OR rapamycin OR taxol |
| 38 | Injury location | 'blood vessel injury'/exp OR 'bone injury'/exp OR 'joint injury'/exp |
| **39** | **Combine sets** | **(#35 OR #36) AND (#37 OR#38)** |
| **40** | **P(L/G)A AND Devices AND Material Response** | **#5 AND #11 AND #19** |
| **41** | **P(L/G)A AND Devices AND Host Response** | **#5 AND #11 AND #31** |
| **42** | **P(L/G)A AND Devices AND alternate** | **#5 AND #11 AND #34** |
| **43** | **P(L/G)A AND AND Material Response AND Host Response** | **#5 AND #19 AND #31** |
| **44** | **P(L/G)A AND Material Response AND** | **#5 AND #19 AND #31 AND #39** |

| | | |
|---|---|---|
| | **Host Response AND Particles** | |
| **45** | **Combine all** | **#40 OR #41 OR #42 OR #43 OR #44** |

**Example Embase Explosion**

Mechanics/exp

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

- Organ weight
    - Brain weight
    - Ear weight
    - Heart weight
    - Liver weight
    - Lung weight
    - Placenta weight
    - Spleen weight
    - Testis weight
    - Thyroid weight
    - Uterus weight
- Seed weight
- Tablet weight
- Thrombus weight

- Weightlessness

- Hydrodynamics
    - Hypertonic solution
    - Hypotonic solution
    - Isotonic solution
    - Osmolality
        - Hyperosmolality
        - Hypoosmolality
        - Plasma osmolality
        - Serum osmolality
        - Urine osmolality
    - Osmolarity
        - Blood osmolarity
        - Hyperosmolarity
        - Hypoosmolarity
        - Plasma osmolarity
        - Serum osmolarity
        - Tear osmolarity
        - Urine osmolarity
    - Osmosis
        - Electroosmotic
        - Osmotic stress
            - Hyperosmotic stress
            - Hypoosmotic stress
- Photodynamics
    - Photoactivation
        - Photoreactivation
    - Photodegradation
    - Photoreactivity
        - Photocytotoxicity
        - Photosensitivity
        - Photosensitization
        - Phototaxis
        - Phototoxicity
    - Photostimulation
- Proton motive force
- Shock wave
    - High-energy shock wave
- Stress strain relationship
- Thermodynamics
    - Adiabaticity

        - Enthalpy
        - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress

    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity

Viscoelasticity

# Appendix C: Study Flow Diagram

I. 3, 062 Citations Identified by Searches
   a. **2,055 Citations Excluded at the Title Level** - Citations excluded at this level were off-topic or not published in English.
   b. 1,007 Abstracts Reviewed
      i. **Citations Excluded at the Abstract Level -** Citations excluded at this level were not a study design of interest, clearly did not address a key question, did not report on a device of interest, or did not report an outcome of interest.
      ii. **210 Citations Excluded at 1st Pass Full Article Level**; Articles excluded at this level did not: address any key question, meet inclusion criteria for study design, include a device of interest or report an outcome of interest; 3 articles were unavailable.
         1. 123 Articles Reviewed
         2. **10 Citations Excluded at 2nd Pass Full Article Level** - Upon further review, these studies did not report an outcome of interest, did not address a key question, did not include a device of interest, or were superseded by an included systematic review (i.e. the study was represented in a systematic review that was already included).
            a. 113 Included Studies

# Appendix D. Evidence Tables

*Table 8: P(L/G)A as a Material – Health Effect (In Vivo) Human Studies*

***Local Response/Toxicity***

Source Citation: Mattila and Waris 2016[1]

Study Design: Prospective cohort

Device or Material: PLDLA joint scaffold (RedJoint Scaffdex)

Contact Duration: 3, 6, 12 months

Dose: 14 mm, 16 mm, 18 mm, or 20 mm in diameter, 4.5 mm in height

Frequency/Duration: Single operation

Response: Foreign-body reaction

Patient characteristics (gender, mean age): 87% female, median 55 years.

Number per group: 23

Observations on adverse effects: 7 (30%) patients developed clinically manifested foreign-body reaction.

Timing of adverse effects: Between 6 and 12 months.

Factors that predict response: Excessive mechanical cyclic implant loading.

Source Citation: Lebl et al. 2011[2]

Study Design: Retrospective comparative cohort

Device or Material: bACP with PLA vs. mACP with Ti mesh cage (Synthes)

Contact Duration: Mean followup (months): 11.4 bACP, 16.0 mACP

Dose: 25 x 27 x 19 x 2 mm

Frequency/Duration: Single level

Response: Dysphagia, Extrusion

Patient characteristics (gender, mean age): bACP: 50% male, 48.8 years. mACP: 60% female, 50.5 years.

Number per group: 14 bACP, 15 mACP.

Observations on adverse effects: Complications at 2 weeks with bACP included 3 (21%) extruded grafts, and 2 (14%) dysphagia (1 due to sterile fluid collection).

Timing of adverse effects: 2 weeks

Factors that predict response: NR

ACP: anterior cervical plate; bACP: bioabsorbable ACP; mACP: metal ACP; NR: not reported; PLA: polylactic acid; PLDLA: poly-L-D-lactide; mm: millimeters; Ti: titanium

*Table 9: P(L/G)A as a Material – Health Effect (In Vivo) Animal Studies*

***Local Response/Toxicity***

Source Citation: Fukunishi et al. 2020[3]

Study Design: Case series

Device or Material: PGA/PLCL vascular graft

Route: Abdominal aorta (rat), carotid artery (sheep)

Dose: Rat: 0.6 mm internal diameter x 3 mm length; sheep: internal diameter 12 mm x 15 mm length

Frequency/Duration: Single administration

Response: Macrophage infiltration

Species (strain): Rat (strain NR), sheep (strain NR)

Gender: NR

Number per group: 5 rat, 3 sheep

Observations on adverse effects: Microphage infiltration higher with sheep model (47.3±16.6 cell/HPF) vs. rat model (20.0±4.5 cells/HPF).

Timing of adverse effects: 6 months.

Factors that predict response: Size of implant.

Source Citation: Melnick et al. 2020[4]

Study Design: Case series

Device or Material: Sirolimus-eluting bioresorbable scaffolds (Credence BRS, Meril Life Sciences)

Route: Iliofemoral artery

Dose: 1.25 μg/mm$^2$; 5 x 15 mm, 5 x 17 mm, 6 x 15 mm, and 6 x 17 mm

Frequency/Duration: Single administration

Response: Adventitia inflammation, Neointima inflammation

Species (strain): Miniswine (Yucatan).

Gender: NR

Number per group: 7

Observations on adverse effects: Neointimal and adventitial inflammation were minimal at 2 years and absent at 3.3 years [Neointimal inflammation: 1.50±0.71 at 90 days, 0.35±0.49 at 180 days, 0.35±0.49 at 2 years, 0.00 at 3.3 years. Adventitial inflammation: 0.30±0.00 at 90 days, 0.15±0.21 at 180 days, 0.35±0.49 at 2 years, 0.00 at 3.3 years]. No malappositions or thrombosis were observed.

Timing of adverse effects: up to 3.3 years.

Factors that predict response: Sustained patency.

Source Citation: Zargar Kharazi et al. 2020[5]

Study Design: Case series

Device or Material: PLLA/BG bone plate; PLLA from Boehringer Ingelheim Pharma

Route: Subcutaneous tissue

Dose: 10 x 10 x 3 mm

Frequency/Duration: Single administration

Response: Fibroblasts, Fibrous capsule, Giant cells, Inflammatory cells, Macrophage, Plasma cells

Species (strain): Rabbits (New Zealand white).

Gender: Male

Number per group: 10 rabbits, three samples in $4^{th}$ and $8^{th}$ weeks.

Observations on adverse effects: Severe inflammation was not observed. Moderate inflammation (presence of macrophage and plasma cells, aggregates of lymphoctyes and granulocyte cells) was observed in 1 sample at 8 weeks, and 2 samples at 4 weeks (mean inflammation score 0.8). Mild inflammation (presence of macrophage and plasma cells, >30 inflammatory cells and 10-30 fibroblasts) was observed in 3 samples at 8 weeks and 8 samples at 4 weeks. Inflammatory response included giant cells and fibrous capsules (thicker capsule in cells with moderate inflammation).

Timing of adverse effects: 4 and 8 weeks.

Factors that predict response: Strength of plate, role of hydrolysis in degradation.

Source Citation: Shen et al. 2019[6]

Study Design: RCT

Device or Material: PLGA vs. 0.3 CTS/PLGA vs. 0.5 CTS/PLGA vs. control; CTS/PLGA from Daigang Biomaterials

Route: Subcutaneous tissue

Dose: 1 x 1 cm

Frequency/Duration: Single administration

Response: CD68-positive cells, Foreign body giant cells (FBGCs), Inflammatory cells

Species (strain): Rats (Shanghai).

Gender: NR

Number per group: 3

Observations on adverse effects: At 2 and 4 weeks, more macrophages and multinucleated FBGCs with giant cell bodies formed around PLGA fibers vs. CTS/PLGA. Necrosis visible on PLGA scaffold. Fewer CD68-positive cells (macrophages and FBGCs) were visible with 0.5 CTS/PLGA.

Timing of adverse effects: 2 and 4 weeks.

Factors that predict response: CTS had an acid-neutralizing effect**.**

Source Citation: Sun et al. 2019[7]

Study Design: RCT

Device or Material: PLLA-TMC-GA copolymer (PLTG); 3D printing

Route: Subcutaneous tissue

Dose: NR

Frequency/Duration: Single administration

Response: Edema, Fibroblasts, Fibrous connective tissue, Hyperplasia, Inflammatory cells, Lymphocytes, Macrophages, Neutrophils, Thicker capsule wall

Species (strain): Rabbit (New Zealand White).

Gender: NR

Number per group: 6

Observations on adverse effects: No necrosis was observed. PLLA component: At 1 week, edema, neutrophils, fibroblasts, and macrophages were observed. At 4 weeks, fibrous connective tissue and thicker capsule wall, neovascular and scattered lymphocytes were observed. At 8 weeks, hyperplasia and a large number of inflammatory cells were visible. At 12 weeks, inflammation decreased. At 16 weeks, no inflammation was visible. Better histocompatibility with PLTG vs. PLLA.

Timing of adverse effects: 1 week to 12 weeks.

Factors that predict response: Poly-TMC has no acidity and causes no inflammation. Poly-GA adds additional strength.

Source Citation: Welch et al. 2019[8]

Study Design: RCT

Device or Material: Polypropylene implant with PLGA vs. PLGA+B7-33 dip-coating

Route: Subcutaneous tissue

Dose: 1 x 1 cm. 1 mm thick

Frequency/Duration: Single administration

Response: Capsule thickness, MMPs, Total cell count

Species (strain): Mice (C57BL/6).

Gender: Female

Number per group: 2 per group/time point.

Observations on adverse effects: Benefits to adding B7-33 included a significant reduction in capsule thickness vs. PLGA (at 2 weeks, capsule thickness reduced by 58.5%, at 6 weeks thickness was reduced by 49.2%) and a significant reduction in total cell count within the capsule (50.5% at week 2, and 30.8% at 6 weeks). Inflammatory response included an increase in MMP.

Timing of adverse effects: 2 weeks and 6 weeks.

Factors that predict response: Antifibrotic effect of controlled release of B7-33 peptide.

Source Citation: Zhao et al. 2019[9]

Study Design: RCT

Device or Material: PLGA scaffold vs. PLGA/bFGF fibrin gel vs. PLGA/MSC vs. PLGA/MSCs/bFGF vs. control; PLGA yarns from Foryou Medical Devices Co.

Route: Achilles tendon

Dose: 3 x 10 mm

Frequency/Duration: Single administration

Response: Collagen I and III expression, Fibroblast-like cells, Inflammation, Modulus, Muscle fiber area, Unorganized bundles of collagen

Species (strain): Rat (Sprague-Dawley).

Gender: Female.

Number per group: 15

Observations on adverse effects: Histological score (fiber structure, fiber arrangement, rounding of nuclear, inflammation, vascularity, cell population) significantly lower in PLGA/MSCs/bFGF group vs. control at 2 weeks (13.3 control, 8.9 PLGA/MSCs/bFGF) and 8 weeks (10.2 control, 4.16 PLGA/MSCs/bFGF**).** Percentage of muscle fiber area highest to lowest: PLGA/MSCs, PLGA, PLGA/bFGF, PLGA/MSCs/bFGF, control (significant difference PLGA/MSCs vs PLGA/bFGF and PLGA/MSCs). Percentage of fibroblast-like cells highest to lowest: PLGA/MSCs/bFGF, PLGA/bFGF, PLGA/MSCs, PLGA, control (significant difference PLGA/MSCs/bFGF vs. all other groups). At 8 weeks, regenerated tissue in control and PLGA groups was filled with unorganized bundles of collagen.

Timing of adverse effects: 2 weeks and 8 weeks.

Factors that predict response: Modulus and maximum force of PLGA/MSCs/bFGF, sustained release of bFGF.

Source Citation: Feng et al. 2018[10]

Study Design: RCT

Device or Material: PLLA/ACP scaffold vs. PLLA

Route: Back muscle

Dose: 5 x 3 mm

Frequency/Duration: Single administration

Response: IL-6 expression level, Inflammatory cell count, Positive expression index of NF-KB

Species (strain): Rat (Sprague-Dawley).

Gender: Male

Number per group: 24 (96 scaffolds).

Observations on adverse effects: Significantly higher inflammatory cell count with PLLA vs. PLLA/ACP at 4 weeks (52.54±11.07 PLLA, 37.32±5.66 PLLA/ACP) and 12 weeks (57.86±11.03 PLLA, 34.13±6.01 PLLA/ACP). Significantly higher expression index of NF-KB (49.7±6.88 PLLA, 36.7±6.84 PLLA/ACP at 4 weeks; 52.6± 8.83 PLLA, 32.65±5.99 PLLA/ACP at 8 weeks) and expression level of IL-6 with PLLA.

Timing of adverse effects: 4 weeks and 12 weeks.

Factors that predict response: Alkalinity of ACP neutralized the acidic metabolites of PLLA. Small amount of ACP (ratio 98:2) suppressed the procalcification activity of PLLA**.**

Source Citation: Nikoubashman et al. 2018[11]

Study Design: Case series

Device or Material: PLGA 85/15 stent (Purac Biochem B.V.)

Route: Subclavian artery

Dose: 5 x 30 mm

Frequency/Duration: Single administration

Response: Fibrotic tissue, Granulocytes, Lymphocytes

Species (strain): Porcine (Minipigs).

Gender: Female

Number per group: 3

Observations on adverse effects: No stent thrombosis or stenosis observed. At 6 months, prominent inflammatory, fibrotic tissue was observed (predominantly lymphocytic and granulomatous; eosinophilic granulocytes in 1 animal).

Timing of adverse effects: mean 4.8±2.5 months.

Factors that predict response: Stent fragmentation.

Source Citation: Wu et al. 2018[12]

Study Design: Case series

Device or Material: Tri-layer vascular graft with PLGA/SF and PLCL/COL; PLGA and PLCL from Jinan Daigang Biomaterial Co., Ltd)

Route: Subcutaneous tissue

Dose: 4 x 10 mm

Frequency/Duration: Single administration

Response: Fibrous encapsulation, Graft degradation

Species (strain): Mice (nude).

Gender: Male

Number per group: 10

Observations on adverse effects: No thrombosis was observed. At week 6, graft degradation occurred which contributed to cell infiltration. At 10 weeks, cells infiltrated into the entire graft and the graft was wrapped by the regenerated tissues surrounding the graft wall. Fragments of graft layers were encapsulated by cells and fibrous tissue. Regenerated tissue and collagen fibers helped maintain the graft structure.

Timing of adverse effects: 10 weeks

Factors that predict response: Inner and outer layers of PLCL/collagen fibers maintained the tubular structure. The porosity of the PLGA/SF fibers supported cell infiltration into the scaffold interior.

Source Citation: Yang et al. 2018[13]

Study Design: Non-randomized comparative

Device or Material: PLGA/HA/HACC scaffold vs. PLGA (P) vs. PLGA/HA (P/HA) vs. HACC-grafted PLGA (P/H); 3D-printed composite scaffolds

Route: Infected femoral defect

Dose: 6 x 4 mm

Frequency/Duration: Single administration

Response: Condyle abscesses, Inflammatory cell infiltration, Joint deformity, Scaffold degradation

Species (strain): Rats (Sprague Dawley), Rabbits (New Zealand white).

Gender: Female

Number per group: 20 rats. 9 rabbits.

Observations on adverse effects: In rats, inflammatory cell infiltration, joint deformity, condyle abscesses were observed but noted as bone infection signs in all groups but PLGA/HA/HACC. In rabbits, scaffold degradation of varying degrees was visible in groups P, P/HA, and P/H again noting influence of infection; degradation of P faster than P/H.

Timing of adverse effects: 8 weeks

Factors that predict response: HA slowed degradation.

Source Citation: Bao et al. 2017[14]

Study Design: RCT

Device or Material: Mg-PLGA-rhbFGF implants vs. PLGA-rhbFGF vs. non-surgery vs. control

Route: Femoral artery

Dose: NR

Frequency/Duration: Single administration

Response: Implant degradation

Species (strain): Rats (Wistar).

Gender: Male

Number per group: 6

Observations on adverse effects: No paralysis, gangrene, or ulcers were observed. PLGA-rhbFGF implant and outer PLGA layer of Mg-PLGA-rhbFGF were noted as being in a "slag-like state" and difficult to obtain. At 6 weeks, further analysis of Mg-PLGA-rhbFGF implant indicated that 64.8% of the implant had been degraded. Hemolysis rates (3.9% Mg, 3.2% PLGA, and 3.6% Mg-PLGA) were lower than national/international standard of 5%.

Timing of adverse effects: 6 weeks

Factors that predict response: Hemolytic activity of biomaterials.

Source Citation: Dou et al. 2017[15]

Study Design: RCT

Device or Material: PLGA NP vs. Ac-bCD NP vs. Ox-bCD NP vs. control; PLGA from Polysciences, Inc.

Route: Hind paw, aorta

Dose: 5 mg/mL

Frequency/Duration: Single administration

Response: Fibrous caps, Inflammatory response, Microphages, MMP-9 level, Necrotic area, SMC

Species (strain): Mice (C57BL/6, ApoE$^{-/-}$).

Gender: Male

Number per group: 10

Observations on adverse effects: In hind paws, more significant inflammatory response after injection of PLGA vs. Ac-bCD and Ox-bCD. In aortic roots, significantly decreased necrotic areas in all treatment groups vs. control; 34.4% reduction in mean area of necrotic cores with PLGA vs. 53.8% reduction with Ac-bCD and 57.5% Ox-bCD. Thicker fibrous caps with PLGA. Significantly more macrophages, relative MMP-9 level, and relative number of SMCs with PLGA vs other NPs.

Timing of adverse effects: 2 months

Factors that predict response: NPs responsive to mildly acidic or abnormal ROS microenvironments vs NPs based on polyester PLGA.

Source Citation: Izuhara et al. 2017[16]

Study Design: Non-randomized comparative

Device or Material: miR-126 incorporated PLGA NP-coated stents vs. control RNA NP-coated

Route: Iliac artery

Dose: miR-126: 33.4±0.79 μg per stent; control: 44.6±1.27

Frequency/Duration: Single administration

Response: Neointimal hyperplasia

Species (strain): Rabbit (Japanese white).

Gender: Male

Number per group: 8

Observations on adverse effects: Significantly inhibited development of neointimal hyperplasia with PLGA-coating.

Timing of adverse effects: 4 weeks

Factors that predict response: Induction of miR-126 by poly PLGA NPs

Source Citation: Jokanovi et al. 2017[17]

Study Design: Non-randomized comparative

Device or Material: Calcium HA scaffold covered with PLGA (ALBO-OS) vs. Geistlich Bio-Oss vs. control

Route: Middle skull base

Dose: 6 mm in diameter

Frequency/Duration: Single administration

Response: Fibroplasia, Foreign body giant cells, Granulocyte, Macrophages, Monocytes, Plasma cells

Species (strain): Rabbits (New Zealand white).

Gender: 10 each gender.

Number per group: 20 ALBO-OS, 14 Bio-Oss, 10 controls.

Observations on adverse effects: Advantages with PLGA included lower number of foreign body giant cells, lowest percentage of macrophages, no necrosis or fibroplasia (moderately thick bands with Bio-Oss). Number of granulocytes and monocytes similar across groups.

Timing of adverse effects: 12 weeks.

Factors that predict response: ALBO-OS was a non-irritant and displayed higher porosity

Source Citation: Zhu et al. 2017[18]

Study Design: RCT

Device or Material: Blank NPs vs. VEGF NPs vs. PTX NPs vs. PLGA-loaded bilayered NPs vs. saline; PLGA from Birmingham Polymer Co.

Route: Aortic wall

Dose: NP concentration: 200 µg/ml

Frequency/Duration: Single administration

Response: CRP level, Restenosis, Smooth muscle cell proliferation

Species (strain): Rabbits (New Zealand white).

Gender: Both

Number per group: 8

Observations on adverse effects: Significantly less restenosis with bilayered NP and VEGF NP. Inhibition of smooth muscle cell proliferation and lowest CRP level with bilayered NP (CRP level: 42.3±8.6% bilayered NP, 65.7±12.6% saline, 61.7±18.5% blank NP, 58.2±15% PTX NP, 47.9±9.86% VEGF NP).

Timing of adverse effects: 28 days

Factors that predict response: Ability of bilayered NPs to sequentially release VEGF and PTX

Source Citation: Cruz et al. 2016[19]

Study Design: RCT

Device or Material: PLGA vs. PLGA plus rhBMP-2 vs. PLGA plus rhBMP-2 plus ASC scaffolds

Route: Muscle tissue

Dose: PLGA (0.5 $cm^3$ scaffolds of PLGA), rhBMP-2 (2.5 µg), ASC (1 x $10^6$ ASCs/20 uL)

Frequency/Duration: Single administration

Response: Coagulative necrosis, Giant cells, Hyaline necrosis, Inflammatory foci

Species (strain): Dog (Beagles).

Gender: NR

Number per group: 6

Observations on adverse effects: Benefits to PLGA+rhBMP-2+ASCs included promoting smallest number of inflammatory foci (number of structures: 18 PLGA+ASCs, 29 PLGA, 43 PLGA+rhBMP-2) and smallest number of giant cells (number of structures: 153 PLGA+ASCs vs. 261 PLGA+rhBMP-2 vs. 291 PLGA). Hyaline necrosis was observed with ASCs while coagulative necrosis was observed in scaffolds without ASCs.

Timing of adverse effects: 45 days

Factors that predict response: ASCs decreased the inflammatory response induced by low dose rhBMP-2.

Source Citation: Ding et al. 2016[20]

Study Design: Non-randomized comparative

Device or Material: PGA/PLA scaffold (BMSCs vs. ACs vs. BMSCs plus ACs vs. control (no cells)); unwoven PGA fibers from National Tissue Engineering Research Center, 0.5% PLA from Sigma Aldrich

Route: Subcutaneous tissue

Dose: PGA fibers: 13 mm diameter and 1.5 mm thickness; 0.5% PLA; density of materials 6 x $10^7$ cells per mL onto each scaffold

Frequency/Duration: Single administration

Response: CD-68 positive cells, Construct damage, Encapsulated fibrous tissue, Foreign body multinucleated giant cells

Species (strain): Pigs (NR).

Gender: NR

Number per group: 12

Observations on adverse effects: Thick fibrous capsules visible at 2 weeks on all scaffolds. Number of foreign body multinucleated giant cells lowest with BMSC at 2 weeks (estimated from Figure 3: 26 PGA/PLA, 22 AC, 19 1:1, 11 BMSC) and 8 weeks (estimated from Figure 3: 25 AC, 21 1:1, 19 PGA/PLA, 13 BMSC). CD68-positive cells (pan-macrophage cell surface marker) were "widespread and significantly more numerous" on PGA/PLA scaffold from 72 hours to 4 weeks. At 8 weeks, residual PGA fibers observed in all groups.

Timing of adverse effects: 2, 4 and 8 weeks.

Factors that predict response: Increased M2 polarization of macrophages with BMSC suppressed inflammation.

Source Citation: Kimishima et al. 2016[21]

Study Design: Non-randomized comparative

Device or Material: GFLX-loaded PLGA and βTCP (0, 1, and 10 wt %) vs. 10 wt % GFLX-PLGA; resorbable collagen membrane (BioMend; Zimmer Dental Inc.) was filled with materials

Route: Mandible

Dose: Cavity of 2 mm diameter x 2 mm depth; GFLX total dose per rabbit: 4.3±1.3 mg

Frequency/Duration: Single administration

Response: Infiltration of neutrophils and lymphocytes

Species (strain): Rabbits (New Zealand white).

Gender: Male.

Number per group: 5

Observations on adverse effects: At 4 weeks, inflammation inside and outside the debrided area was lowest with 10 wt % GFLX composite (percent inflamed: 100% controls, 70% of 1 wt % GFLX composite, 20% of 10 wt % GFLX composite).

Timing of adverse effects: 4 weeks.

Factors that predict response: Rapid degradation of 10 wt % GFLX composite**.**

Source Citation: Thiem et al. 2016[22]

Study Design: Non-randomized comparative

Device or Material: Gelatin-PLGA scaffolds vs. Ethisorb scaffolds

Route: Subcutaneous tissue

Dose: Diameter: 8 mm, height: 2 mm)

Frequency/Duration: Single administration

Response: Degradation, Foreign body reactions -macrophages, foreign body giant cells, Inflammation, polymorphonuclear cells, lymphocytes, and plasma cells, Necrosis - neovascularization, fat infiltration and fibrosis

Species (strain): Wistar rat.

Gender: Female

Number per group: 42

Observations on adverse effects: The between group comparison revealed the presence of polymorphonuclear cells and lymphocytes after 2 weeks as well as lymphocytes and plasma cells after 4 weeks in both groups. The amount of macrophages and foreign body giant cells was significantly lower in the test group after 2 and 4 weeks. The scores for the tissue reaction (fibrosis, neovascularization, necrosis, fat infiltration) were almost equal and not significantly different, so that the overall score for the test material was lower than for the reference material at 2 and 4 weeks. This result reveals a lower tissue irritation caused by the scaffold material compared to the reference material. Finally, there was no indication of systemic inflammation or any other adverse systemic effect induced by the implantation procedure or the implanted materials.

Timing of adverse effects: 2 to 26 weeks

Factors that predict response: NR

Source Citation: Baker et al. 2015[23]

Study Design: Non-randomized comparative

Device or Material: PDLA-nanoclay particulate (A or B) vs. pure PDLA vs. PDLA filled with HA vs. saline

Route: Subcutaneous pouch

Dose: 100 mg of particles

Frequency/Duration: Single administration

Response: Pro-inflammatory cytokines, including interleukin-1beta (IL-1β), interferongamma (IFN-γ), and granulocyte/macrophage-colony stimulating factor (GM-CSF)

Species (strain): Balb/C mice.

Gender: Female

Number per group: 5

Observations on adverse effects: All mice that underwent implantation of particulate showed measurable amounts of pro-inflammatory cytokines.MiP-2 expression was largest for PDLA-30B nanocomposite samples (2,770.0 pg/mL ± 1,304.3 pg/mL). This value was not statistically significant when compared to PDLA-93A ($p = 1.00$; 2312.4 ± 697.0 pg/mL), or PDLA-HA particulate ($p = 1.00$; 2119.1 ± 542.8 pg/mL). PDLA (no filler) particulate induced the highest expression of IFN-γ (175.9 ± 15.9 pg/mL). No statistically significant differences were found with respect to IFN-γ expression between treatment groups and controls. PDLA-HA particulate yielded the greatest expression of IL-1β (250.4 ± 111.3 pg/mL), though there was no significant difference when compared to PDLA ($p = 0.139$; 111.5 ± 76.1 pg/mL), PDLA-93A ($p = 1.00$; 195.3 ± 79.0 pg/mL), or PDLA-30B ($p = 1.00$; 184.8 ± 61.6 pg/mL). With regard to GM-CSF expression, PDLA-HA particulate yielded the

highest expression (20.0 ± 9.8 pg/mL) without a significant difference found between any treatment groups, or with controls.

Timing of adverse effects: 48 hours

Factors that predict response: NR

Source Citation: Baker et al. 2015[23]

Study Design: Non-randomized comparative

Device or Material: PDLA vs. PDLA + rhBMP-2 vs. PDLA-93A vs. PDLA-93A + rhBMP-2

Route: Intramuscular

Dose: NR

Frequency/Duration: Single administration

Response: Foreign body reactions, Inflammatory infiltrate

Species (strain): Balb/C mice.

Gender: Female

Number per group: 9

Observations on adverse effects: No outward observable signs of deep infection or foreign body response were noted. While mineralized tissue was most pronounced on the periphery of the discs, both osteoid and mineralized tissue were present in the interior regions of the samples, indicating that cells were able to infiltrate the 3-dimensional structure of both PDLA and PDLA-93A constructs. Small blood vessels were also present in the interior regions of the samples, especially at later time points. No significant foreign body reactions or inflammatory infiltrate were observed in any of the samples. At 2 weeks, the PDLA samples showed the greatest amount of osteoid, while the PDLA constructs with rhBMP-2 demonstrated the greatest amount of mineralized tissue. The differences in mineralized tissue between PDLA and PDLA-93A ($p = 1.00$), and PDLA-BMP and PDLA-93A-BMP ($p = 1.00$) were not statistically significant at this early time point. The presence of rhBMP-2 did significantly impact the amount of mineralized tissue observed for pure (PDLA-BMP vs. PDLA; $P < 0.001$) and nanocomposites (PDLA-93A-BMP vs. PDLA-93A; $P < 0.001$) constructs at 2 weeks. No significant differences in the percentage of osteoid were observed either as a function of construct type (PDLA vs. PDLA-93A; $p = 1.00$), or presence of rhBMP-2. At 4 weeks, an increase in mineralized tissue was observed with rhBMP-2-containing constructs demonstrating the highest amount. While no statistically significant difference in the percentage of mineralized tissue between PDLA and PDLA-93A constructs ($p = 0.755$) was found at this time point, there was a significant difference between PDLA-BMP and PDLA-93A-BMP constructs ($P < 0.001$), with PDLA-BMP constructs displaying a greater amount. At 6 weeks, a decrease in the percentage of mineralized tissue was observed. No statistically significant difference was observed between the PDLA and PDLA-93A specimens ($p = 1.00$), or the PDLA-BMP and PDLA-93A-BMP specimens ($p = 1.00$). There was a statistically significant difference in the percentage of osteoid between the PDLA and PDLA-BMP specimens ($p = 0.032$) and the PDLA-BMP and PDLA-93A specimens ($p = 0.001$) at 6 weeks.

Timing of adverse effects: 2 to 6 weeks

Factors that predict response: NR

Source Citation: Chandorkar et al. 2015[24]

Study Design: RCT

Device or Material: PGLA vs. biodegradable salicylic acid releasing polyester (SAP)

Route: Subcutaneous tissue

Dose: PLGA discs of ~9.8 mm diameter and ~1.4 mm thickness

Frequency/Duration: Single administration

Response: Foreign body response, Inflammation, Leakage, Proinflammatory cytokines (tumor necrosis factor-α and interleukin-1β)

Species (strain): BALB/c mice.

Gender: Male

Number per group: 18

Observations on adverse effects: There was no mortality or morbidity. Anomalies such as ulceration, pus, or discharge of exudate were not observed at the sites of implantation, and the wounds healed within 3 weeks, as observed externally. No evidence of infection or necrosis was observed. A mild inflammatory response was observed in the subcutaneous tissue surrounding the SAP and PLGA implants at the end of 2 weeks. The tissue−SAP interface showed a lower number of inflammatory cells as compared to that for PLGA. As part of the acute inflammatory response to the implants, neutrophils were observed in the surrounding tissue. The observed decrease in their density was statistically significant ($p < 0.05$) at 16 weeks compared to that at 2 and 4 weeks post-implantation for SAP implanted animals. In PLGA-implanted animals, however, the number of neutrophils was seen to increase at 4 weeks, which was also statistically significant ($p < 0.05$) with respect to that at 2 weeks. Macrophage density around the SAP implant was higher than that for PLGA at 2 weeks ($p < 0.05$), it decreased significantly by 16 weeks ($p < 0.05$) and was similar to that for the PLGA implant at 16 weeks. Foreign body giant cells were also observed near the implant surface at 2 and 4 weeks postimplantation. Fibroblasts were observed at every time point. The fibroblast density observed for SAP at 2 weeks was higher than that for PLGA ($p < 0.05$). A remarkable decrease in fibroblast density was observed for SAP at 4 and 16 weeks ($p < 0.05$) compared to that at 2 weeks postimplantation. TNF-α decreased with time in the serum from SAP implanted animals, from 10.88 ± 0.83 pg/mL at 2 weeks to 1.75 ± 0.26 pg/mL at 16 weeks, which was statistically significant ($p < 0.05$). At 16 weeks, the serum concentration of TNF-α in PLGA-implanted animals (11.35 ±1.63 pg/mL) was significantly higher ($p < 0.05$) than that in SAP-implanted animals. The measured serum IL-1β concentration in SAP- and PLGA-implanted animals did not show levels elevated above that of normal serum or any statistically significant difference. Collagen: PLGA implant was encapsulated by a typical fibrous capsule with very high density of collagen at PLGA−tissue interface, and a subsequent decrease in collagen density was observed with increasing distance from the implant. However, the encapsulation surrounding the SAP implant showed uniformly distributed collagen with cells, representing a normal connective tissue-like structure. This difference between SAP and PLGA was statistically significant at the interface for all time points ($p < 0.001$).

Timing of adverse effects: 2 to 16 weeks

Factors that predict response: NR

Source Citation: Chang et al. 2015[25]

Study Design: RCT

Device or Material: Cell-free porous PLGA graft with and without early loading exercise vs. empty defect with or without early loading exercise vs. sham (not drilled to create a defect)

Route: Subcutaneous tissue/femoral trochlear groove

Dose: 3 mm in diameter and 3 mm in depth

Frequency/Duration: Single administration

Response: Inflammatory response (plasma cells, lymphocytes, and multinucleated giant cells), Osteophytes Surface, Synovitis

Species (strain): Rabbits (New Zealand white).

Gender: Male

Number per group: 60 knees total: PLGA/with or without exercise (16 knees each) and empty defect operation/with or without exercise groups (12 knees each) and sham (4 knees).

Observations on adverse effects: None of the sedentary or exercise knees developed synovitis, formed osteophytes, or became infected at either 6 or 12 weeks after surgery. The PLGA plus exercise group regenerated a smooth articular surface, with transparent new hyaline-like tissue soundly integrated with the neighboring cartilage, but the other groups remained distinct at the margins, showing fibrous or opaque tissues. None of the rabbits in the sedentary and exercise groups had signs of infection, joint swelling, or limited range of motion at 6 and 12 weeks after surgery. At week 6, the repaired joints in the exercise groups initiated more tissue coverage with visible chondroblasts and few chondrocytes in the defects, whereas the sedentary groups had disorganized and irregular surfaces, and the defect sites were covered with fibrous tissue containing fibroblast-like cells. In particular, the synovial-like lining cells migrating over the regenerating tissue were observed in the PGLA plus exercise group. More chondroblasts had migrated into the center of the repaired tissue in the PGLA groups than in the empty defect groups. The empty defect and PGLA groups revealed the presence of plasma cells, lymphocytes, and multinucleated giant cells in the reparative sites. The empty defect sedentary group manifested visible hemorrhage. The PGLA plus exercise group had a modest inflammatory response, filled with more osteoid matrix, and appeared to form a vasculature. The PGLA plus exercise group had markedly higher levels of GAG in both neo-formed tissue and adjacent cartilage and clearly expressed both COL II and endogenous growth factor TGF-b1 as well as showing modest expression levels of COL I, COL X, TNF-α and IL-6 in the repaired region. The integration between hosts was distinct, and the PLGA grafts still remained clearly distinguishable. The empty defect groups had little GAG in the neo-formed tissue and adjacent cartilage and higher levels of COL I, COL X, TNF-α and IL-6 in addition to lower TGF-b1 expression. At 12 weeks, in the PLGA plus exercise group inflammatory cells were minimally present in the defects, and COL I, COL X, TNF-α and IL-6 were observed to be modest. At week 12, the histological assessments in the PGI-TRE group revealed by far the best surface morphology (i.e., neo-formed hyaline cartilage), bone bonding, and GAG content. The PGI-TRE group showed a notably lower level of inflammation than the other groups at both 6 and 12 weeks.

Timing of adverse effects: 6 and 12 weeks.

Factors that predict response: Exercise

Source Citation: Pereira et al. 2015[26]

Study Design: Non-randomized comparative

Device or Material: Thalidomide (THD) -loaded PLGA implants at different doses (25%, 50%, or 75% w/w) of medication vs. PLGA alone

Route: Subcutaneous tissue

Dose: NR

Frequency/Duration: Single administration

Response: Degradation, Inflammation

Species (strain): Mice ISwiss).

Gender: Female

Number per group: 6

Observations on adverse effects: No signs of degradation at any time point for implants with medication. For the implants containing only the polymer, a gradual loss of the cylindrical conformation was observed from day 3, presenting as less rigid with a decrease in length. There was no sign of exudate or ulceration in mice with PLGA plus medication. A high burst release percentage was observed for the implants with higher doses of medication. After the initial burst release, there was a stage in which the drug release became slower due to the interaction of the drug with the polymer matrix, which depends on the polymer degradation rate. That phase dependent on polymer matrix degradation was slower for the implant containing 25% (w/w) THD. An increase in the DPR was observed with the progress of the study, particularly within 28 days, which may be due to the erosion of the polymer hindering the recovery of all fragments. At the day 28 it remained 83.6%, 44.5%, and 43.9% of the initial THD in the implants, respectively for the 25% (w/w), 50% (w/w), and 75% (w/w) THD. No signs of an aggressive inflammatory process were evident in any of the implants. A fibrous capsule surrounding implants could be noted. For non-drug containing implants, a fibrous capsule lining a cavity in which the implant was isolated was observed. Inside this capsule, immune cells involved in the response of the body to the presence of the implant were observed. The presence of lymphocytes, macrophages, and giant cells was noted. A giant cell that phagocyted a fragment of the implant, and some cells with nuclei in pyknosis and karyorrhexis were noted. For drug-containing (75%) implants, a thinner fibrous capsule than that observed in the implant without drug was noted. Also, there was a mild inflammatory response with many cells with nuclei in pyknosis and karyorrhexis. The 75% drug implant was positive for the presence of lymphocytes, macrophages, and giant cells, but to a lesser extent than non-drug-containing implants.

Timing of adverse effects: Up to 28 days postimplantation.

Factors that predict response: Amount or presence of THD.

Source Citation: Xie et al. 2015[27]

Study Design: RCT

Device or Material: PLGA/empty NPs group vs. PLGA/VEGF NPs vs. saline vs. no treatment at all

Route: Abdominal aorta for restenosis, delivery by GENIE Catheter

Dose: 200 mg of PGLA was used in the NPs, average diameter of the NPs was 78.82 nm

Frequency/Duration: Single administration

Response: Collagen, Degradation, Inflammation, Smooth muscle

Species (strain): Rabbits (New Zealand white).

Gender: Male

Number per group: 6 per implant group and 2 that received no treatment.

Observations on adverse effects: **:** In the control and empty NP groups, partially denuded endothelial cells with intimal thickening and hyperplasia of foam cells, smooth muscle cells, and fibrous tissue, as well as the rupture of the internal elastic lamina were observed. By contrast, these pathological changes were rarely observed in the VEGF NPs group at day 28 after balloon injury. The VEGF NP group exhibited a decreased neointimal area (VEGF NPs, 0.19±0.11 mm2 vs. empty NPs, 0.48±0.08 mm2 and controls, 0.49±0.09 mm2; $p < 0.001$) and a decreased proliferation index (VEGF NPs, 0.13±0.06 vs. empty NPs, 0.32±0.05 and controls, 0.32±0.03; $p < 0.001$) when compared with the 2 other groups. Small amounts of type III and type II collagen were observed in the media and adventitia of the vessel walls from the 3 groups. For the intima examination, VEGF NPs group showed decreases in the positive expression index (PEI) of α-actin, a measure of

smooth muscle cells, (VEGF NPs, 34.7±9.6% vs. empty NPs, 65.7±16.2% and controls, 65.0±21.3%; p = 0.001) and PCNA, or cell proliferation, (VEGF NPs, 21.0±8.6% vs. empty NPs, 69.5±13.7% and controls, 63.0±17.3%; p <0.001), and an increase in the PEI of VEGF (VEGF NPs, 45.8±10.5% vs. empty NPs, 27.5±12.5% and controls, 25.7±10.2%; p = 0.01). The PEIs of MMP-2 (degradation and cell migration), TIMP-2 (inhibits MMP-2) and CRP were similar among the 3 groups.

Timing of adverse effects: Up to 28 days.

Factors that predict response: NR

Source Citation: Zhan and Shen 2015[28]

Study Design: Non-randomized comparative

Device or Material: PLGA

Route: particles containing 5 μg of gD antigen

Dose: Subcutaneous

Frequency/Duration: Two administrations (time 0 and booster dose 2 weeks later)

Response: Inflammation

Species (strain): **Mice** (C57BL/6).

Gender: Female

Number per group: 4

Observations on adverse effects: BMA-AA (BA3, molar ratio 3:1) and BMA-DMAEMA (BD1, molar ratio 1:1) were used to fabricate particles of DA1-5 (blended particles containing PLGA and BMA copolymers). The pH-dependent glycoprotein D (gD) release from gD-loaded particles was consistent with that of myoglobin (MGB)-loaded particles except BD5. gD-loaded DA5 particles released less than 10% at pH 7.4 and 40% total proteins at acidic pHs compared to more than 60% for MGB-loaded DA5 particles. This difference was likely due to that the molecular weight of gD was nearly 4 times greater than MGB. Antibody responses and primary antigen-specific T cell responses in mouse spleens: Particle DA3 achieved the highest antigen-specific immunoglobulin G (IgG) titer among all 3 formulations after 5 d post-boost immunization. The antigen-specific CD4+ and CD8+ T cells in spleen were quantified by detecting intracellular IFNγ+ T cells. A significant higher level of IFNγ+ CD4+ T cells (3.7%) was detected in DA3-treated mice than DA5 ($p < 0.05$) and DA1-treated mice. Though the difference in the level of IFNγ+ CD8+ (2.9%) T cells within 3 groups was not statistically significant, there was a trend that a higher level in DA3-treated mice than other 2 groups. Results indicate that optimization of the release of antigens at different pH environments enables optimized immune responses. Considering the particle stability and the strength of immune responses, DA3 is the most promising candidate as HSV-2 gD antigen delivery vehicles.

Timing of adverse effects: 5 days post-boost immunization

Factors that predict response: pH 4.6, 6 or 7.4. Per study authors, immune responses were dependent on the ratio of 2 charged polymers, which correlated well with the release of proteins.

Source Citation: Zhu et al. 2015[29]

Study Design: Non-randomized comparative

Device or Material: PLGA vs. MSCs-PLGA

Route: Subcutaneous tissue

Dose: NR

Frequency/Duration: Single administration

Response: Inflammation

Species (strain): Normal inbred 8-week-old BALB/c mice.

Gender: NR

Number per group: 30 total

Observations on adverse effects: At day 3, MSC co-implantation significantly reduced the proportion of mature DCs (CD11cþCD80þ, CD11cþCD86þ, and CD11cþIaþ) among the host splenocytes (*, p< 0.05; **, p < 0.01). Furthermore, the expression of pivotal cytokines for DC maturation was also inhibited by the MSCs. Compared with the PLGA film-implanted mice, the IL-12 mRNA levels dropped more than 50% and the TNF-α mRNA levels decreased more than 70% at day 3 in the MSC-PLGA construct-implanted mouse splenocytes (*, p < 0.05; **, p < 0.01). Similar effects were observed at day 7. MSCs also significantly down-regulated the CD3þCD69þ T lymphocyte proportion in the host spleens in a time-dependent manner. At day 7, MSCs significantly decreased the proportion of Th1 and Th17 cells but increased the proportion of Th2 cells and Tregs in the recipients (*, p < 0.05). Consistently, the real-time polymerase chain reaction (PCR) results showed that the MSCs down-regulated IFN-g and IL-17A expression but up-regulated IL-4 and Foxp3 expression (*, p < 0.05; **, p < 0.01). Also on Day 7, spleen nodules in the MSC-PLGA construct-implanted recipients were smaller than those in the PLGA film-implanted recipients. The mouse spleen nodules showed active hyperplasia, which suggested that the engrafted PLGA films had antigenicity and activated lymphocytes in the spleens, whereas the MSCs ameliorated the immune responses. Immune cell infiltration around the implants was observed at day 21. The implanted-PLGA film activated inflammatory cells in vivo and a fibrotic capsule formed at the implantation sites; however, no remarkable immune cell infiltration near the MSC-PLGA constructs was observed.

Timing of adverse effects: Day 3, 7, and 21

Factors that predict response: MSC

Source Citation: Huang et al. 2014[30]

Study Design: Non-randomized comparative

Device or Material: PLC vs. PCL/PLC vs. HDPE

Route: Intramuscular

Dose: 3 x 10 mm

Frequency/Duration: Single administration

Response: Inflammatory response

Species (strain): **Rabbits** (New Zealand white).

Gender: NR

Number per group: 6 rabbits total: each rabbit had 5 pieces of control sample implanted into the left paravertebral muscle and 5 pieces of test samples implanted into the right paravertebral muscle.

Observations on adverse effects: The number of inflammatory cells varied between samples, being much higher in some implant sites and in 1 individual animal, compared with others, irrespective of the implant material used. Very few tissue sites surrounding the PLC samples showed any significant inflammatory response. The average inflammatory score was 2.4±2.0 for PLC group, and 2.3±1.5 for control HDPE group, indicating a mild and comparable inflammatory response in both PLC and HDPE groups. However, tissue surrounding PCL/PLC samples in 1 individual animal showed much higher inflammatory response, that resulted in the slightly higher average inflammatory score

observed in PCL/PLC30 group (3.1±1.9), as compared to control group (1.0±0.8). Generally, noneovascularization, granuloma formation, and tissue ingrowth into the device were found in both test groups, PLC and PCL/PLC30. The average fibrous capsule thickness of the neat PLC and PCL/PLC30 implants were 55.2±71.9 and 59.8±64.2, respectively. The measured capsule thicknesses for both test groups had no statistically significant difference as compared to the 2 control groups (C1 [control sample in rabbits with PLC samples] 44.2±22.6 and C2 [control sample in rabbits with PCL/PLC30 test samples] 94.9±127.0).

Timing of adverse effects: 6 weeks.

Factors that predict response: NR

Source Citation: Yuan et al. 2014[31]

Study Design: Non-randomized comparative

Device or Material: Acid-responsive ibuprofen (IBU)-loaded PLLA, ibuprofen-loaded PLLA, PLLA alone, and control

Route: Intramuscular

Dose: The diameters of fibers were 1.29±0.35, 1.35±0.28, and 1.13±0.42 μm for the PLLA, PLLA–IBU, and PLLA–IBU–SB scaffolds, respectively.

Frequency/Duration: Single administration

Response: Inflammation, Structural

Species (strain): Rats (Sprague-Dawley)

Gender: Male

Number per group: 50 total, each rat had two treatments.

Observations on adverse effects: **:** In the control group, there was a trend toward greater inflamed cells on day 3. At this stage many inflamed cells infiltrated the intermuscular septum, which led to the derangement of the intermuscular septum. In the PLLA group, burst inflamed cells appeared on day 7, and this phenomenon continued to day 14 in both the control group and the PLLA group. In the PLLA–IBU–SB group and the PLLA–IBU group, the greatest inflamed cell infiltration appeared on day 3, but to a smaller degree compared to the control group and the PLLA group. Especially for the PLLA–IBU–SB group, the control of the inflammatory reaction was better than the PLLA–IBU group. On day 7, the inflamed cell infiltration became less in the PLLA–IBU–SB and PLLA–IBU groups, and the structure of the intermuscular septum became obvious. In the control group and the PLLA group, the muscle fibers had a normal morphology and a regular arrangement on day 21, while in the PLLA–IBU–SB and PLLA–IBU groups this happened on day 14 and the muscle tissues became completely normal on day 21. In the control group, the expression of IL-6 had an increased trend from day 1 to day 3, and began to decline from day 7. In the PLLA group, the level of IL-6 increased from the first day to day 7, and then decreased weekly. In the PLLA–IBU and PLLA–IBU–SB groups, the expression of IL-6 was burst on day 3, but it was to a smaller degree compared to the control group and the PLLA group. Especially in the PLLA– IBU–SB group, the level of IL-6 began to dramatically decline from day 7. The detection of TNF-α indicated that the level of TNF-α had an increased trend from day 1 to day 3 in all groups, while from day 7 the expression became different. In the control group, the level of TNF-α was still high on day 7 and lasted until day 14, while in the other three groups the expression of TNF-α decreased weekly from day 7, and within these three groups, the PLLA–IBU–SB group had the most significant decline. The concentration of TNF-α increased in a time-dependent manner during the first 14 days in the control group, while this trend stopped on day 7 in the PLLA and PLLA–IBU groups, and in the PLLA–IBU–SB group the highest expression was on day 3 with the lowest level among all the peak values ($P < 0.05$). These results indicated that the animals treated with the acid-responsive IBU-

loaded electrospun fibrous scaffolds showed significantly lower levels of IL-6 and TNF-α compared with the other groups.

Timing of adverse effects: Through Day 21.

Factors that predict response: NR

Source Citation: Boennelycke et al. 2011[32]

Study Design: Non-randomized comparative

Device or Material Resorbable methoxypolyethyleneglycol-polylactic-co-glycolic acid polymer (MPEG-PLGA) pure, enriched with extra-cellular matrix (ECM) or estrogen, and control

Route: Subcutaneous tissue

Dose: NR

Frequency/Duration: Single administration

Response: Erosion, Inflammation

Species (strain): Rats (Sprague Dawley).

Gender: Female

Number per group: 10 rats for 3 weeks and in 10 rats for 8 weeks.

Observations on adverse effects: No erosion or evidence of infection was seen, and there were no signs of implant encapsulation. At 3 weeks, newly formed collagen and a mild to moderate inflammatory response surrounded the implants. All implants showed a high degree of biocompatibility with moderate to intense in-growth of cells. There was a tendency towards a more organized connective tissue response in implants with ECM. Implants with estrogen were scored at an intermediate level, which was slightly closer in tissue response to that of the ECM-enriched than to the pure implant. There were no significant differences in the thickness of the newly formed layer of connective tissue (older granulation tissue) surrounding the implants. Inflammatory and regeneratory cells present in all implants consisted mainly of macrophages and myofibroblasts and less frequently of multinucleated foreign body giant cells, scattered lymphocytes and plasma cells, and occasional eosinophils, basophils and neutrophils. Scores of inflammation differed significantly among different implants ($p = 0.02$). Levels were higher in those enriched with ECM than in pure implant (3.3 [3.0;3.6] vs. 3.9 [3.7;4.1]), indicating an accelerated healing process in implants with ECM. No trace of the implants remained at 8 weeks. Only early fibrosis with myofibroblasts gave evidence of the site of the previous implantation. A similar fibrous response was seen in the sham sections. There was no foreign body reaction and no signs of a lingering chronic inflammatory reaction. All possible effects of enrichment of the implant had vanished at 8 weeks. Scores for connective tissue organization, inflammation, and vascularity were approximately equal for all implants, and connective tissue organization did not differ between sham surgery and implants. Furthermore, it was not possible to detect any significant difference in the thickness of the connective tissue among the three types of implants or sham sections.

Timing of adverse effects: 3 and 8 weeks.

Factors that predict response: NR

Source Citation: Filion et al. 2011[33]

Study Design: Non-randomized comparative

Device or Material: Polyhedral oligomeric silsesquioxane (POSS) with poly(lactic acid) (PLA) POSS-SMP of a given PLA arm length (POSS-SMP-10, -20,or -40) or commercial amorphous DL-PLA pellets

Route: Subcutaneous

Dose: NR

Frequency/Duration: Single administration

Response: Collagen Degradation, Infection, Inflammation

Species (strain): Rats (Charles River SASCO-SD)

Gender: Male

Number per group: 3

Observations on adverse effects: No animals were lost or prematurely sacrificed because of substantial adverse reactions (e.g., tumor formation or unresolved infections) during the course of the study. All POSS-SMPs and PLA control elicited a mild foreign body type immune response upon subcutaneous implantation. POSS-SMP-10 harvested 4 days post implantation was surrounded by a fibrous tissue capsule where macrophages, abundant and active capillaries (as indicated by the "plump" endothelial cells lining the vessels) and lymphocytes were detected, indicative of a typical foreign body response. Greater than 80% of the cells within the newly formed fibrous tissue capsule were proliferating at this early time point. The early tissue responses to POSS-SMP-10 appeared to be milder than those observed with the PLA control, with the tissue capsule of the latter characterized with more abundant macrophages and lymphocytes, as well as the presence of neutrophils. No significant hypersensitivity reaction to either POSS-SMP-10 or the PLA control was detected, as supported by the presence of very few mast cells or eosinophils surrounding the implant. By 18 days postimplantation, a more mature fibrous tissue capsule characterized by aligned extracellular collagen fibers embedded with spindly fibroblasts surrounding both POSS-SMP-10 and the PLA control. The numbers of proliferating (Ki67 positive) cells, macrophages, lymphocytes, and blood vessels within the fibrous capsules surrounding both implants significantly decreased, but the overall immune responses to PLA remained stronger. No acute inflammatory response was detected at this time point in either POSS-SMPs or the PLA control, as supported by the absence of neutrophils. By 60 days, while the number of proliferating cells, macrophages and blood vessels surrounding the PLA control continued to decrease, the onset of the degradation of POSS-SMP-10, indicated by the opaque appearance of the once-transparent material, elicited a second inflammatory response. The small number of macrophages, proliferating fibroblasts, and blood vessels surrounding POSS-SMP-10, however, was not accompanied by lymphocytes or neutrophils. Finally, while masts cells were observed surrounding the PLA, no allergic reaction to POSS-SMP-10 was detected by 60 days. At day 164, all POSS-SMPs degraded, with the extent of the structural disintegration and the degree of the corresponding acute inflammatory tissue response inversely correlated to the PLA chain length of the nanocomposite. POSS-SMP-10 degraded the fastest. The second acute inflammatory response to the degradation was the most abundant surrounding POSS-SMP-10 at day 164, with significantly more actively proliferating capillaries, macrophages, and neutrophils detected within its tissue capsule. This second acute inflammatory response to the extensive degradation of POSS-SMP-10 was also accompanied by mild allergic/hypersensitivity reaction to the degradation products as indicated by the presence of a small number of mast cells and eosinophils. The more abundant inflammatory cell activities within the fibrous capsule of POSS-SMP-10 also led to a drop of the intensity of birefringence as its collagen alignment was more profoundly disrupted than those surrounding POSS-SMP-20 or POSS-SMP-40. None of the major viscera examined showed any evidence of chronic injury or chronic systemic immune response such as systemic foreign body type granulomatous inflammation. By 1 year, the POSS-SMP-10 implant was almost completely resorbed, with few immune cells present at the site of implantation and no signs of chronic inflammation. By 164 days, the rats did not exhibit any signs of distress or infection.

Timing of adverse effects: 4-, 18-, 60-, or 164-day post-op for histology and through 1 year for other outcomes.

Factors that predict response: Adjusting the length of the DL-PLA arms attached to the POSS core.

Source Citation: Thevenot et al. 2011[34]

Study Design: Case series

Device or Material: PLGA films (Medisorb Inc.)

Route: Subcutaneous tissue

Dose: Cromolyn: 640 ug/kg body wt/day; compound 48/80: 1 mg/kg body wt/day

Frequency/Duration: Single administration

Response: Capsule thickness, Fibrocytes, Granulocytes, Leukocytes

Species (strain): Mice (C57).

Gender: Both

Number per group: NR

Observations on adverse effects: Inflammatory cells (mostly granulocytes) started to decrease at day 4 and changed from spindle-shaped cells mostly in outer layer of implant to round and spindle-shaped throughout the matrix. At day 4, influx of $CD45^{+}/Col1^{+}$ fibrocytes and decrease in leukocytes (neutrophils, monocytes/macrophages), which had peaked on day 2. Leukocytes peaked at day 10. Capsule thickness decreases from 169 μm on day 10 to 113 μm at day 14.

Timing of adverse effects: 14 days

Factors that predict response: NR

Source Citation: Zeng et al. 2011[35]

Study Design: Non-randomized comparative

Device or Material: GS+MSC scaffold (thin PLGA film) vs. GS vs. no GS spinal cord injury (SCI)

Route: Spinal cord

Dose: Scaffolds: 2 mm length

Frequency/Duration: Single administration

Response: CD68 double positive cells, CD68 positive cells, Macrophages, Microglia, Secretion of IL-1βSecretion of TNF-a

Species (strain): R ats (Sprague-Dawley).

Gender: Female

Number per group: 6

Observations on adverse effects: More intense inflammation (infiltration of macrophages/microglia) in SCI (61.5±17.21 SCI, 16.00±9.63 GS+MSCs, 11.67±5.64 GS). Percent of CD68 double positive cells and TNF-α significantly lower with GS+MSC (34.82±13.35% GS+MSC, 88.92±4.51% GS, 89.93±6.67% SCI). Percent of IL-1β and CD68-positive cells also significantly lower with GS+MSC (13.00±4.52% GS+MSC, 74.8±6.25% GS, 78.97±14.94% SCI).

Timing of adverse effects: 1 week to 8 weeks

Factors that predict response: PLGA restricted the extent of swelling of the inner hydrophilic GS**.**

Source Citation: Kim et al. 2010[36]

Study Design: Non-randomized comparative

Device or Material: Unmodified and Arg-Gly-Asp (RGD) peptide-modified PEG/Sebacic acid (PEGSDA)-based hydrogels vs. PLGA implant

Route: Lower back

Dose: 10 mm diameter x 2 mm thickness

Frequency/Duration: Single administration

Response: Fibrous capsule, Inflammatory cells, Leukocyte concentrations, Lymphocytes, Macrophages

Neutrophils

Species (strain): Rats (Sprague Dawley)

Gender: Female

Number per group: 6

Observations on adverse effects: Total and differential leukocyte concentrations similar across groups. Initially predominant neutrophils were replaced by lymphocytes and macrophages. Significantly fewer activated inflammatory cells and fewer fibrous capsules with PEGSDA-based implants vs. PLGA implants.

Timing of adverse effects: Neutrophils peaked ≤7 days. Lymphocytes peaked at 14 and 21 days

Factors that predict response: PEGSDA hydrogels had a similar degradation profile than PLGA.

Source Citation: Park et al. 2010[37]

Study Design: Non-randomized comparative

Device or Material: PLGA scaffolds with pore sizes of 0 μm, 100 μm, 200 μm vs. no scaffold

Route: Back

Dose: NR

Frequency/Duration: Single administration

Response: Fibrous capsule, Number of monocytes, Number of polymorphonuclear leukocytes

Species (strain): Rats (Sprague Dawley).

Gender: Male

Number per group: 3. HA was used.

Observations on adverse effects: Scaffold with 200-μm pores maintained its structure for at least 4 weeks after implant, fibrous capsule appearing after 8 weeks. In the scaffold with no pores, the fibrous capsule was apparent up to 4 weeks. At 4 weeks, inflammation scores (number of monocytes and polymorphonuclear leukocytes) indicated as the pore size increased that the inflammation score slightly decreased with scores similar between control and 200-μm pores.

Timing of adverse effects: 4 weeks.

Factors that predict response: Pore size.

AC: auricular chondrocyte; Ac-bCD: acetalated b-cyclodextrin; ACP: amorphous calcium phosphate; ApoE$^{-/-}$: apolipoprotein E-deficient; ASC: adipose-derived stem cells; bFGF: basic fibroplast growth factor; BG: bioactive glass; BMA: butyl methacrylate; BMSCs: bone marrow mesenchymal stem cells; βTCP: β-tricalcium phosphate; COL: collagen; CRP: C-reactive protein; CTS/PLGA: chitosan/poly(lactide-*co*-glycolide); DPR: drug polymer ratio; ED: empty defect; GAG: glycosaminoglycan; GFLX: gatifloxacin; GS: gelatin sponge; HA: hydroxyapatite; HACC: quaternized chitosan; HDPE: high-density polyethylene; HPF: high power field; IL-1β: interleukin 1 beta; kg: kilogram; M2: alternatively activated macrophages; mg/mL: milligrams per milliliters; mg: magnesium; mm: millimeter; MMP: matrix

metalloproteinases; MMP-2: matrix metalloproteinase-2; MSCs: mesenchymal stem cells; NP: nanoparticle; NR: not reported; Ox-bCD: ROS-responsive B-CD; PCL: poly(ε-caprolactone); PCL/PLC30: molar ratio of L-lactide to ε-caprolactone in 70 to 30; PCNA: proliferating cell nuclear antigen; PDLA: poly(L, d-lactide); PGA: poly(glycolic acid); PGI: PLGA graft implant; PLA: poly(lactic acid); PLC: poly(L-lactide-co-ε-caprolactone); PLCL: poly(lactide-*co*-caprolactone); PLGA: polylactideco-glycolide; PLLA: poly L-lactic acid; PTX: paclitaxel; RCT: randomized controlled trial; rhbFGF: recombinant human basic fibroblast growth factor; rhMPP-2: recombinant human bone morphogenetic protein type 2; ROS: reactive oxygen species; SF: silk fibrin; SMC: smooth muscle cell; TIMP2: tissue inhibitor of metalloproteinases 2; TNF-a: tumor necrosis factor alpha; TRE: treadmill; µg: microgram; µm: micrometer; VEGF: vascular endothelial growth factor; w/w: weight per weight.

*Table 10: Coronary Drug-eluting Stent/Scaffold – Health Effect (In Vivo) Human Studies*

***Local Response/Toxicity***

Source Citation: Guagliumi et al. 2018[38]

Study Design: RCT

Device or Material: BP-EES (Synergy, Boston Scientific) vs. DP-ZES (Resolute Integrity, Medtronic Cardiovascular)

Contact Duration: 24 months

Dose: NR

Frequency/Duration: Single administration

Response: Calcification, In-stent NA, Lipid rich plaque, Macrophage, NA in neointima, Peristrut neovascularization, Plaque rupture, TCFA

Patient characteristics (gender, mean age): 73% and 87% male. 64±10 years both arms.

Number per group: 45 BP-EES, 45 DP-ZES.

Observations on adverse effects: At 18 months, no significant difference in percent of patients presenting frames of in-stent NA (11.6% BP-EES, 15.9% DP-ZES; p = 0.56) or frequency of NA in neointima (mean±SD: 1.1±3.1 BP-EES, 2.5±9.1; p = 0.33). Individual components suggestive of NA were similarly low or not present (e.g., lipid laden neointima, macrophages, calcium infiltration, TCFA, and/or plaque rupture). No ST was observed.

Timing of adverse effects: Up to 2 years.

Factors that predict response: Patients on high-intensity statin regimen.

Source Citation: Kereiakes et al. 2017[39]

Study Design: Cohort

Device or Material: Synergy (Boston Scientific)

Contact Duration: 24 months

Dose: 4 mm PLGA

Frequency/Duration: Single administration

Response: Definite ST

Patient characteristics (gender, mean age): 70% male, 65 years.

Number per group: 466 with diabetes.

Observations on adverse effects: Definite ST occurred early in 5 (1.1%) patients.

Timing of adverse effects: 4/5 within 24 hours, 1/5 on day 5 post-op

Factors that predict response: Thrombosis occurred only in individuals with ACS.

Source Citation: Seth et al. 2017[40]

Study Design: Case series

Device or Material: MeRes100 sirolimus-eluting bioresorbable vascular scaffold system (Meril Life Sciences)

Contact Duration: 12 months

Dose: 1.25 µg /$mm^2$

Frequency/Duration: Single administration

Response: LLL

Patient characteristics (gender, mean age): 71.3% male, 50.13±8.82 years.

Number per group: 108 (116 scaffolds).

Observations on adverse effects: In-scaffold LLL (surrogate for restenosis) was 0.15±0.23 mm with 0% binary restenosis. No scaffold recoil or thrombosis was observed up to 1 year.

Timing of adverse effects: LLL at 6 months.

Factors that predict response: NR

Source Citation: Vesga et al. 2017[41]

Study Design: Case series

Device or Material: PLGA stent (Synergy, Boston Scientific Corp.)

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response: Delayed healing, LLL, Malappositions, NIH, Strut microthrombi

Patient characteristics (gender, mean age): 59% male, 66.54 years.

Number per group: 37 (OCT strut coverage analysis: 7761 struts, 209.9±45.8 struts/stent).

Observations on adverse effects: Angiographic results at 3 months included: in-stent LLL 0.03±0.24, percentage NIH volume 7.1±4.9%, mean number of malappositions per stent of 1.4±0.5, and presence of strut microthrombi in 4 (10.8%) patients. OCT strut coverage at 3 months indicated that 1% of struts were definitely uncovered/covered with fibrin and 12.5% showed partial coverage. No restenosis or thrombosis was reported.

Timing of adverse effects: 3 months.

Factors that predict response: NR

Source Citation: von Birgelen et al. 2016[42]

Study Design: RCT

Device or Material: EES (Synergy; Boston Scientific) vs. SES (Orsiro; Biotronik) vs ZES (Resolute Integrity; Medtronic)

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response: Definite stent thrombosis, Probable stent thrombosis

Patient characteristics (gender, mean age): 72% male, 63.9±10.8.

Number per group: 1,172 EES, 1,173 ZES, 1,169 SES.

Observations on adverse effects: Definite ST occurred in ≤ 4 (<1 %) patients per arm: 4 EES, 4 SES, and 3 ZES. Probable ST occurred in ≤ 3 (<1 %) patients per arm: 1 EES, 3 ZES, and 1 SES.

Timing of adverse effects: Thrombosis was late with all stent types.

Factors that predict response: Subgroup analyses did not identify any factors that predicted target vessel failure.

Source Citation: Lemos et al. 2015[43]

Study Design: RCT

Device or Material: SES (Inspiron; Scitech) vs. biolimus-eluting (Biomatrix Flex; Biosensors Europe SA)

Contact Duration: 9 and 12 months

Dose: Total drug load (μg): sirolimus (56, 84, 102, 130 ug), biolimus (218, 280, 374, 437)

Frequency/Duration: Single administration

Response: Binary restenosis, Definite ST, LLL

Patient characteristics (gender, mean age): Sirolimus: 57.9% male, 59.9 years. Biolimus: 48.2% male, 59.9 years.

Number per group: 114 SES (132 lesions), 56 biolimus (62 lesions).

Observations on adverse effects: Angiographic results indicated no significant difference for in-stent LLL (mm): mean±SD: 0.20±0.29 SES, 0.15±0.20 biolimus or in-stent binary restenosis (3.2% SES, 1.7% biolimus). Definite ST occurred with biolimus-eluting stents (cumulative hazard 1.8, 95% CI: 0.3 to 12.9).

Timing of adverse effects: Angiographic at 9 month. Thrombosis at 12 months.

Factors that predict response: NR

Source Citation: Silingardi et al. 2015[44]

Study Design: Cohort

Device or Material: PLLA stent (Remedy, Kyoto Medical Planning)

Contact Duration: Mean months: 38.3 (range 30-58)

Dose: NR

Frequency/Duration: Single administration

Response: Asymptomatic restenosis, Symptomatic restenosis, In-stent occlusion

Patient characteristics (gender, mean age): 80% male. 71 years.

Number per group: 35

Observations on adverse effects: **:** 28.5% asymptomatic restenosis and 20% symptomatic restenosis was noted. In-stent occlusion in 1 (2.8%) patient. No stent recoil or fracture was observed.

Timing of adverse effects: Asymptomatic restenosis ≤30 days. Occlusion at 12 months.

Factors that predict response: NR

Source Citation: Wijns et al. 2015[45]

Study Design: RCT

Device or Material: SES (MiStent SES; Micell Technologies) vs. ZES (Endeavor; Medtronic Vascular, Inc.)

Contact Duration: 9 months

Dose: 2.44 μg/mm$^2$ for both

Frequency/Duration: Single administration

Response: Binary restenosis, Definite ST, LLL, Possible ST

Patient characteristics (gender, mean age): SES: 69.1% male, 65 years. ZES: 74% male, 65.1 years.

Number per group: 123 SES, 61 ZES.

Observations on adverse effects: Angiographic results indicated significantly higher LLL with ZES (-0.31 mm difference) and no significant difference in binary restenosis (4.9% SES; 1.9% ZES). 1 definite ST occurred with ZES, and 1 possible ST with SES.

Timing of adverse effects: : Thrombosis occurred early with ZES, and late with SES.

Factors that predict response: NR

Source Citation: Qian et al. 2014[46]

Study Design: RCT

Device or Material: PLGA-polymer with electro-grafting base layer SES (BuMA, SINOMED) vs. PLA-polymer SES (EXCEL SES, JW Medical Systems)

Contact Duration: 3 months

Dose: NR

Frequency/Duration: Single administration

Response: Malapposed struts, NIH, Neointimal thickness, ST

Patient characteristics (gender, mean age): 63% male, 57 years.

Number per group: 40 each arm.

Observations on adverse effects: No significant difference in in-stent LLL, percent malapposed struts, or mean neointimal thickness of stent struts. Significantly higher NIH with BuMa (mean 0.50 vs. 0.40 mm$^2$). No signs of ST.

Timing of adverse effects: 3 months.

Factors that predict response: NR

Source Citation: Silber et al. 2011[47]

Study Design: RCT

Device or Material: CoStar PTX-eluting stent with reservoir technology vs. UniStar BMS (both Cordos Corporation)

Contact Duration: 8 months

Dose: PLGA polymer and PTX dose of 10 μg/mm$^2$

Frequency/Duration: Single administration

Response: Binary restenosis, LLL, ST

Patient characteristics (gender, mean age): CoStar: 74.3% male, 64.9 years. UniStar: 68.9% male, 66.2 years.

Number per group: 152 CoStar DES, 151 UniStar BMS.

Observations on adverse effects: **:** Both in-stent and in-segment binary restenosis and LLL were significantly lower with CoStar. ST occurred in one (0.7%) patient with UniStar BMS.

Timing of adverse effects: ST at 7 days.

Factors that predict response: NR

Source Citation: Grube et al. 2010[48]

Study Design: Cohort

Device or Material: PLA and PTX- coated BMS (Liberté, Boston Scientific)

Contact Duration: 9 months

Dose: 9.2 µg of PLA and PTX per 16-mm stent

Frequency/Duration: Single administration

Response: Binary restenosis, LLL, NIH, Stent malappositions

Patient characteristics (gender, mean age): 83% male, 65.6 years

Number per group: 103 (127 lesions).

Observations on adverse effects: At 9 months, in-stent binary restenosis was 5.2%, and in-stent LLL was 0.33±0.45 mm. Percentage of NIH volume was low (11.4±11.2%). Stent malappositions occurred in 2 (3.2%) patients after stent placement and at 9 months. No stent thrombosis was observed.

Timing of adverse effects: 30 days and 9 months.

Factors that predict response: NR

ACS: acute coronary syndrome; BMS: bare-metal stent; BP: biodegradable polymer; DP: durable polymer; EES: everolimus-eluting stent; LLL: late lumen loss; mm: millimeter; $mm^2$: square millimeter; NA: neoatherosclerosis; NIH: neointimal hyperplasia; NR: not reported; PLA: polylactide or polylactic acid; PLGA: poly(DL-lactide-co-glycolide); PLLA: poly-L-lactic acid; PTX: paclitaxel; RCT: randomized controlled trial; SD: standard deviation; SES: sirolimus-eluting stent; ST: stent thrombosis; TCFA: thin-cap fibroatheroma; µg: microgram; ZES: zotarolimus-eluting stents

*Table 11: Coronary Drug-eluting Stent/Scaffold – Health Effect (In Vivo) Animal Studies*

### *Local Response/Toxicity*

Source Citation: Deng et al. 2020[49]

Study Design: RCT

Device or Material: PLGA-FK506-NP vs. FK506 vs. Isograft vs. PBS; PLGA from Sigma-Aldrich

Route: Coronary artery

Dose: NR

Frequency/Duration: Single administration

Response: Inhibition of cytokine secretion, Lymphocyte infiltration

Species (strain): Rats (Lewis and Brown Norway).

Gender: Male

Number per group: 6

Observations on adverse effects: Acute rejection grades at postoperative day 7: PLGA-treated: grades 1R or 2R acute rejection (mild/moderate lymphocyte infiltration); isograft: grade OR (no lymphocyte infiltration or myocyte damage); PBS: grade 3R (massive lymphocyte infiltration, myocyte necrosis, scattered hemorrhage, and severe vasculopathy). PLGA inhibited the secretion of CD3+ T lymphocytes, and IL-2 and IFN-$\gamma$ cytokines; PLGA significantly reduced secretion of IL-2 and IFN-$\gamma$ vs. PBS.

Timing of adverse effects: 28 days.

Factors that predict response: NR

Source Citation: Hou et al. 2020[50]

Study Design: Comparative

Device or Material: BMS (Beijing Amsinomed Medical) vs. PLLA stents (Beijing Medical Technology)

Route: Carotid artery

Dose: 2 x 12 mm

Frequency/Duration: Single administration

Response: In-stent stenosis, OPN expression, Pro-fibrotic genes (Collagen-1, Collagen-3, MMP2, MMP9)

Species (strain): Rabbits. (New Zealand white).

Gender: Male

Number per group: 3

Observations on adverse effects: PLLA stents displayed severe in-stent stenosis (50% at 3 months, 55% at 6 months). Expression of fibrosis-related gene OPN was significantly higher with PLLA. In addition, pro-fibrotic genes (Collagen-1, Collagen-3, MMP2, MMP9) were upregulated in PLLA stents.

Timing of adverse effects: 3 and 6 months.

Factors that predict response: PLLA degradation.

Source Citation: Uurto et al. 2015[51]

Study Design: Comparative

Device or Material: Muraglitazar-eluting PLA96 stents vs. PLA96 stents (Purac Biochem)

Route: Iliac arteries

Dose: Scaffolds: 500 µg±70 per stent

Frequency/Duration: Single administration

Response: Inflammation, Intimal hyperplasia, Migration, Occlusion, Vascular injury

Species (strain): Swine (laboratory-bred).

Gender: Male

Number per group: 10

Observations on adverse effects: Both stent types showed mild inflammation (1.05±0.17 muraglitazar-eluting, 1.23±0.19 control) and minimal vascular injury (0.7±0.01 muraglitazar-eluting, 0.8±0.01 control). More intimal hyperplasia present with control (557 µm ±122 control, 361 µm±32 muraglitazar-eluting). 1 occluded stent and 1 migrated stent with control PLA96.

Timing of adverse effects: 28 days

Factors that predict response: Radial force of the stent was higher at the middle of the stent vs. ends of stent**.**

Source Citation: Lee et al. 2019[52]

Study Design: Comparative

Device or Material: PLGA stents (Resomer RG 503) vs. hybrid vildagliptin/PLGA (low dose and high dose)

Route: Abdominal aorta

Dose: NR

Frequency/Duration: Single administration

Response: Extended intercellular spaces, Higher local expression of collagen I, Irregular size of endothelial cells, poorly aligned stent surface, Significant intimal hyperplasia, Uneven intercellular spaces

Species (strain): Rabbits (New Zealand White).

Gender: Male

Number per group: 10

Observations on adverse effects: At 8 weeks, extended and uneven intercellular spaces, irregular size of endothelial cells, and poorly aligned surfaces with PLGA stents. Significant intimal hyperplasia (around 200 µm thickness) and higher local expression of collagen I was observed with PLGA stents at 8 weeks. No in-stent thrombosis was observed at 2 months with any stent type.

Timing of adverse effects: 8 weeks

Factors that predict response: NR

Source Citation: Nishio et al. 2019[53]

Study Design: Comparative

Device or Material: PBS vs. control microRNA (cont-miR)-loaded PLGA NP solution vs. miR–145-loaded PLGA NP solution

Route: Ipsilateral carotid artery

Dose: 0.5 mg/mL

Frequency/Duration: Single administration

Response: Ki-67 positive cells, CD40 expression, NF-kB expression, Suppression of neointimal thickening

Species (strain): Rabbits (Japanese white)

Gender: Male

Number per group: 8

Observations on adverse effects: Short-term use of miR-145-loaded PLGA NP resulted in significantly fewer Ki-67-positive cells in the neointima (indicating reduced VSMC proliferation), and significantly reduced expression of CD40 and NF-kB vs. cont-miR.

Timing of adverse effects: 2 weeks

Factors that predict response: Local sustained release of miR-145 with PLGA NPs.

Source Citation: Wang et al. 2019[54]

Study Design: Comparative

Device or Material: 316 L SS (inner coating of CSC, outer coating of CSC plus PLGA) vs. ADC

Route: Left common carotid artery

Dose: 1 mg/mL

Frequency/Duration: Single administration

Response: Blood components adhering to endothelium, Fibrous tissue, NIH, Restenosis

Species (strain): Rabbits (NR)

Gender: NR

Number per group: 3

Observations on adverse effects: At 4 weeks, blood components had adhered to the endothelium on the 316 L SS stents, and NIH was significantly higher vs. ADC stents. At 12 weeks, appearance of fibrous tissue-like materials and significantly higher restenosis with 316L SS stents.

Timing of adverse effects: 4 and 12 weeks

Factors that predict response: Asymmetrical dual drug coating

Source Citation: Lee et al. 2018[55]

Study Design: Comparative

Device or Material: PLGA/ticagrelor vs. PLGA/sirolimus-eluting nanofibrous stents

Route: Descending abdominal aorta

Dose: 240/40 mg PLGA/tica and PLGA/sirolimus

Frequency/Duration: Single administration

Response: None reported

Species (strain): Rabbits (New Zealand White).

Gender: Male

Number per group: 12

Observations on adverse effects: No intimal hyperplasia or inflammation response was noted with either stent, although re-endothelialization onto strut surfaces was significantly higher with ticagrelor (coverage: 96.4% ticagrelor, 89% sirolimus).

Timing of adverse effects: 4 weeks

Factors that predict response: NR

Source Citation: Lih et al. 2018[56]

Study Design: RCT

Device or Material: Sirolimus-loaded PLGA-coated, (DES control) and sirolimus-loaded PLGA/RA15-Mg-OLA5-coated (DES/RA-Mg-OLA)

Route: Coronary artery

Dose: Scaffolds: NR

Frequency/Duration: Single administration

Response: Fibrin infiltrates, Inflammatory cells, ISR, Neointimal areas, Stenosis areas

Species (strain): Pig (NR).

Gender: NR

Number per group: 10

Observations on adverse effects: Significantly higher inflammation score (1.1 vs. 0.1), ISR rate (20.5% vs. 14.1%), stenosis score (percent stenosis area: 63% vs. 21.5%), neointima areas (1.99 $mm^2$ vs. 0.80 $mm^2$), and fibrin infiltrates (score 1.7 vs. 0.7) with DES control.

Timing of adverse effects: 28 days.

Factors that predict response: NR

Source Citation: Bae et al. 2017[57]

Study Design: Comparative

Device or Material: Hyaluronic acid (HA) vs. BMS vs. HA-coated paclitaxel (H-PTX) vs. PLGA PTX-eluting stent (P-PTX)

Route: Coronary artery

Dose: NR

Frequency/Duration: Single administration

Response: Injury scores, Inflammation score, Lumen area, Restenosis

Species (strain): Pigs (NR).

Gender: Male

Number per group:

Observations on adverse effects: Percent area restenosis was lowest with PTX (14.8 H-PTX, 15.8 P-PTX, 24.1 HA, 39.3 BMS). Inflammation score of PLGA was significantly higher vs. other stent types (1.9 P-PTX, 0.9 BMS, 0.9 HA, 1.1 H-PTX). Lumen areas higher with PTX (4.0 H-PTX, 4.1 P-PTX, 2.8 BMS, 3.2 HA). No significant differences in injury scores.

Timing of adverse effects: 4 weeks

Factors that predict response: NR

Source Citation: Hu et al. 2017[58]

Study Design: Comparative

Device or Material: 316L SS stents vs. SZ-21/VEGF/ RAPA stents both containing PLLA

Route: Left carotid artery

Dose: NR

Frequency/Duration: Single administration

Response: Intimal hyperplasia, Macrophages, Restenosis

Species (strain): Rabbits (New Zealand white).

Gender: Male

Number per group: 4

Observations on adverse effects: Higher number of macrophages with 316L from 1 week to 12 weeks (significantly different at 1 week). Excessive intimal hyperplasia with 316L at 4 weeks. Significantly more restenosis with 316L at 12 weeks. Increase in restenosis rates (4 vs. 12 weeks): 25.27% to 58.8% 316L vs. 12.8% to 15.8% SZ-21.

Timing of adverse effects: 1, 4, and 12 weeks.

Factors that predict response: NR

Source Citation: Lee et al. 2017[59]

Study Design: RCT

Device or Material: Dextran-coated SES (DSS) vs. PLA-coated SES (PSS) vs. BMS

Route: Coronary artery

Dose: Coating 20 mg/mL to 4 μm thickness

Frequency/Duration: Single administration

Response: Inflammation, Injury score, Internal elastic lamina, Lumen area, Macrophages, Restenosis

Species (strain): Pigs (NR)

Gender: Male

Number per group: 10

Observations on adverse effects: Inflammation significantly higher with PSS (1.5±0.18 PSS, 0.7±0.12 BMS, 0.7±0.21 DSS); higher numbers of macrophages with PSS. Restenosis was similarly inhibited in SES stents vs. BMS (percent area restenosis: 34.8 BMS, 26.2 DSS, 25.1 PSS). No significant differences in injury score, internal elastic lamina, and lumen area. Stenosis highest in BMS.

Timing of adverse effects: 4 weeks

Factors that predict response: NR

Source Citation: Mori et al. 2017[60]

Study Design: RCT

Device or Material: BMS (Kaname; Terumo) vs. DP-EES (Xience; Abbott Vascular) vs. BP-SES (Ultimaster; Terumo)

Route: Iliac artery

Dose: Sirolimus 0.8 µg/mm2, everolimus 1.0 µg/$mm^2$, BMS NR

Frequency/Duration: Single administration

Response: Giant cells, Inflammation, Injury score, Lumen area, Monocytes, Neointimal area, Stenosis

Species (strain): Rabbits (New Zealand white).

Gender: Male

Number per group: 8 arteries BP-SES, 4 arteries each DP-EES and BMS.

Observations on adverse effects: At 28 days, significantly higher inflammation score (0.7 vs. 0.3) with BP-SES (vs. BMS). At 28 days, significantly higher stenosis (15.7% BMS, 10.1% BP-SES), neointimal area (0.99 mm, 0.67), and struts with giant cells (41% vs. 33%) with BMS; smaller lumen area with BMS (5.3 $mm^2$ vs. 6.0 $mm^2$). Significant differences between DP-EES and BP-SES only for injury score (higher with SES). At 120 days, significantly more surface monocytes (n/$mm^2$) with DP-EES vs. BP-SES (497 vs 201).

Timing of adverse effects: 28, 45, and 120 days.

Factors that predict response: NR

Source Citation: Sekimoto et al. 2017[61]

Study Design: Comparative

Device or Material: PLLA scaffolds (Igaki-Tamai stent (ITS), Kyoto Medical Planning Co.) vs. BMS

Route: Iliac arteries

Dose: NR

Frequency/Duration: Single administration

Response: Inflammation score, Injury score

Species (strain): Pig (Miniature)

Gender: Male

Number per group: 5

Observations on adverse effects: Mean inflammation score and injury score higher with ITS (not significant): inflammation score (0.073±0.021 ITS vs. 0.027±0.010 BMS), injury score (0.053±0.014 ITS, 0.023±0.009 BMS). No malappositions, thrombosis, or dissection.

Timing of adverse effects: 6 weeks.

Factors that predict response: NR

Source Citation: Shi et al. 2017[62]

Study Design: RCT

Device or Material: PDLLA/RAPA vs. Firebird 2 (Microport Endovascular Co. Ltd)

Route: Coronary arteries

Dose: 1.40±0.20 µg/$mm^2$

Frequency/Duration: Single administration

Response: None reported

Species (strain): Minipig (Bama).

Gender: Both

Number per group: 9

Observations on adverse effects: No malappositions, restenosis, ST, neointimal hyperplasia, or recoil.

Timing of adverse effects: 3 months

Factors that predict response: NR

Source Citation: Wang et al. 2017[63]

Study Design: RCT

Device or Material: Bioresorbable vascular scaffolds (BVS)(Power Scaffold (TT Medical Inc.) vs. SES (Helios stent; Kinhely Bio-tech co., Ltd.)

Route: Coronary arteries

Dose: NR

Frequency/Duration: Single administration

Response: Inflammation, Injury score, Lumen loss

Species (strain): Minipigs (Chinese).

Gender: Both

Number per group: 24 (6 per arm each follow-up).

Observations on adverse effects: No significant difference in lumen lost, inflammation score, or injury score at 180 days.

Timing of adverse effects: 14 days to 180 days

Factors that predict response: NR

Source Citation: Bedair et al. 2016[64]

Study Design: RCT

Device or Material: BMS (Bio-Alpha Corp.) vs. unmodified SES vs. PLLA brush-modified SES; PDLLA from Lakeshore Biomaterials, Sirolimus from LC-laboratories

Route: Coronary arteries

Dose: NR

Frequency/Duration: Single administration

Response: Inflammation, Injury score, Lumen loss, Restenosis

Species (strain): Pigs (NR).

Gender: Male

Number per group: NR

Observations on adverse effects: Results for PLLA brush-modified SES indicated 1) the most lumen area at 28 days; 2) significant reductions in inflammation score vs. BMS (0.479±0.59 PLLA, 1.8±0.2 BMS); and 3) significantly lower area restenosis (28.5±7%) vs BMS (70±10%) and unmodified SES (50.7±10%). No significant differences were noted for injury score.

Timing of adverse effects: 28 days.

Factors that predict response: NR

Source Citation: Liu et al. 2016[65]

Study Design: RCT

Device or Material: MgZnYNd rapamycin DES (with PLGA) vs. SS stent system (BuMA, Sinomed)

Route: Coronary arteries

Dose: BuMA: 3.0 x 15.0 mm

Frequency/Duration: Single administration

Response: Inflammatory cells

Species (strain): Minipigs (Gottinger).

Gender: Both

Number per group: 10

Observations on adverse effects: No ST, ISR, or in-stent injury. Inflammatory cells visible with both stents; fewer cells near MgZnYNd stent.

Timing of adverse effects: 3 and 6 months.

Factors that predict response: NR

Source Citation: Orlik et al. 2016[66]

Study Design: Comparative

Device or Material: BP-SES (Alex, Balton Company) vs. BPS; both with PLA

Route: Coronary arteries

Dose: Scaffolds: Polymer on stent day 1: µg (IQR) 5.48 (5.38-5.56)

Frequency/Duration: Single administration

Response: None reported

Species (strain): Swine (domestic).

Gender: Both

Number per group: 36 BP-SES, 18 BPS.

Observations on adverse effects: No peristrut inflammation, ST, necrosis, ISR, no FBGCs.

Timing of adverse effects: 1 to 56 days.

Factors that predict response: NR

Source Citation: Scoutaris et al. 2016[67]

Study Design: RCT

Device or Material: Presillion BMS (negative control, Abbott Vascular) vs. Cypher (positive control; Cordis) vs. SMV/PLA (SMV from Sigma-Aldrich, PLA Resomer 205 from Evonic) vs. PTX/PLA stents (PTX from INRESA)

Route: Aorta

Dose: BMS: 2.5 x 14 mm, PLA coated: 2.5 x 14 mm

Frequency/Duration: Single administration

Response: Cytokine expression, ISR

Species (strain): Rats (Wistar)

Gender: Male

Number per group: 3

Observations on adverse effects: ISR (ratio neointima area to media area) highest to lowest: 1.04 PLA/SMV, 0.73 PLA, 0.72 BMS, 0.67 PCX/PLA, 0.6 Cypher. No significant difference between PLA coatings vs. BMS for all cytokine expression tested (e.g., IL-6, TNFa).

Timing of adverse effects: 7 days

Factors that predict response: NR

Source Citation: Zhang et al. 2016[68]

Study Design: RCT

Device or Material: BPSES-A, BPSES-C, BMS, BPS

Route: Coronary arteries

Dose: PLGA/Sirolimus: 1.40±0.20 μg/$mm^2$

Frequency/Duration: Single administration

Response: Inflammatory cells, LLL

Species (strain): Pig (NR)

Gender: NR

Number per group: 38 pigs (75 stents: 25 BPSES-A, 25 BPSES-C, 20 BMS, 5 BPS).

Observations on adverse effects: LLL highest to lowest: BPS>BMS>BPSES-C equivalent to BPSES-A at 4 weeks; BPSES-A equivalent with BPSES-C at 12 weeks; BMS>BPSES-C>BPSES-A at 24 weeks. Inflammatory cells remained in BPSES-C stents at 12 and 24 weeks; significantly better healing with BMS at 24 weeks vs. covered stents.

Timing of adverse effects: 4 weeks to 24 weeks

Factors that predict response: NR

Source Citation: Buszman et al. 2015[69]

Study Design: RCT

Device or Material: Elevated sirolimus dose and fast release kinetics (ed-frSES; Alex) vs. frSES vs. BMS (Coflexus)

Route: Coronary arteries

Dose: PLGA/Sirolimus: total mass on 3.0 x 15 mm stent ≤ 360 μg

Frequency/Duration: Single administration

Response: Adventitial inflammation, Injury, NIH

Species (strain): Swine (NR)

Gender: Both

Number per group: 7 stents ed-frSES, 8 frSES, 4 BMS.

Observations on adverse effects: Peristrut inflammation was not observed. Adventitial inflammation was moderate (0 ed-frSES, 0.21 frSES, 0.18 BMS), and injury was similar (0.54 ed-frSES and frSES, 0.52 BMS). NIH (measured by LLL and percentage diameter stenosis) was lowest with ed-frSES.

Timing of adverse effects: 28 days for LLL

Factors that predict response: NR

Source Citation: Simon-Yarza et al. 2015[70]

Study Design: Case series

Device or Material: PLGA/NCO-sP(EO-stat-PO) scaffold

Route: Coronary arteries

Dose: NR

Frequency/Duration: Single administration

Response: Langham giant cells, Macrophages

Species (strain): Rat (Sprague Dawley).

Gender: Female

Number per group: 2

Observations on adverse effects: Initial acute inflammation followed by chronic inflammation (macrophages and Langham giant cells with horseshoe nuclei arrangement).

Timing of adverse effects: Acute inflammation at 24 hours and 1 week, chronic inflammation at 1 and 3 months.

Factors that predict response: NR

Source Citation: Veeram Reddy et al. 2015[71]

Study Design: Comparative

Device or Material: Double-opposing helical (DH) PLLA stents with LMW (PL-18) vs. DH-PLLA with MMW (PL-32) vs. metal stents; PLLA from PURAC, metal stents from Cordis Endovascular

Route: Descending aorta

Dose: 3 x 15 mm

Frequency/Duration: Single administration

Response: Immature smooth muscle cells, ISR

Species (strain): Rabbits (New Zealand white).

Gender: Female

Number per group: 7 LWM, 3 MMW, 7 metal

Observations on adverse effects: No acute ST or malappositions. Minimal luminal loss from ISR; no significant flow difference between PLLA and metal stents. Minimal number of immature smooth muscle cells in neointima with LMW and MMW stents.

Timing of adverse effects: 9 months.

Factors that predict response: NR

Source Citation: Wilson et al. 2015[72]

Study Design: Comparative

Device or Material: Synergy EES stent (Boston Scientific) with PLGA polymer vs. 1x Polymer (=polymer, no drug) vs. 3x Polymer (no drug) vs. BM OMEGA (identical alloy to Synergy) vs. BM Synergy (no polymer or drug)

Route: Internal thoracic arteries

Dose: PLGA: 58.6 µg and 170.3 µg

Frequency/Duration: Single administration

Response: Eosinophils, Inflammation, Macrophages, Multinucleated giant cells producing granulomas

Species (strain): Swine (domestic Yorkshire cross)

Gender: NR

Number per group: 5 to 11 stents/device each time point.

Observations on adverse effects: Inflammation observed at day 5 in all groups. At day 28, significantly less inflammation with 3x Polymer vs. BM Synergy or BM Omega. Between 28 days and 90 days, hypersensitivity reactions including numerous parastrut eosinophils and macrophages, and multinucleated giant cells producing granulomas were noted in all stent types but 3x Polymer.

Timing of adverse effects: Inflammation Day 5 to day 90.

Factors that predict response: NR

Source Citation: Xiao et al. 2015[73]

Study Design: RCT

Device or Material: PowerStent Absorb DES with PLGA (VasoTech Inc.) vs. TAXUS DES stent (Boston Scientific Company)

Route: Coronary arteries

Dose: PowerStent: 3 x 13 mm (PLGA ~ 20 µm thick); TAXUS: 3 x 16 mm

Frequency/Duration: Single administration

Response: Inflammatory cells, NIH, Restenosis, Stent recoil

Species (strain): Pigs (Tibet miniature).

Gender: Both

Number per group: 6

Observations on adverse effects: NIH was mild with PowerStent; no or few inflammatory cells visible at 6 months. Restenosis formation and stent recoil was limited with both stent types.

Timing of adverse effects: 6 months

Factors that predict response: NR

Source Citation: Castellano et al. 2014[74]

Study Design: RCT

Device or Material: Poly(3-hydroxybutyrate) (PHB) vs. poly(e-caprolactone) (PCL) vs. silk PLA (PLA) vs. polyamide (PA) vs. control of bovine-derived nonporous collagen (Col) scaffolds

Route: Coronary artery

Dose: NR

Frequency/Duration: Single administration

Response: Granulomatous reaction, Inflammation, Mononuclear cells, Multinucleated giant cells, Vascular congestion

Species (strain): Rats (Wistar).

Gender: Male

Number per group: 6

Observations on adverse effects: Multinucleated giant cells were visible in all biomaterials. Exacerbated cell infiltration composed of mononuclear cells with PLA. Foreign body response with PLA at 8 weeks: strong presence of granulomatous reaction; moderate presence of biomaterial integrity and vascular congestion; slight presence of inflammatory infiltrate, and no presence of hemorrhage or epicardial fibrosis. Inflammatory response was resolved with PHB and Col by 8 weeks.

Timing of adverse effects: 8 weeks

Factors that predict response: NR

Source Citation: Lan et al. 2014[75]

Study Design: RCT

Device or Material: PLLA/ACP vs. PowerStent Absorb

Route: Coronary arteries

Dose: PLLA: 103.28±3.1 in-stent, 92±6.9 on-surface; PowerStent: 102.86±2.0 in-stent, 87±5 on-surface

Frequency/Duration: Single administration

Response: Inflammation, Mottled inner arterial wall, Recoil, Restenosis

Species (strain): Swine (miniature).

Gender: Both

Number per group: 6

Observations on adverse effects: Benefits with PowerStent included significant reductions in restenosis vs. PLLA/ACP (44.49±10.59% vs. 64.47±16.2%), significantly less stent recoil (21.57±5.36% vs. 33.81±11.49%), and significantly less inflammation (3.01±0.62 vs. 4.07±0.86). Angiography indicated mottled texture of PLLA inner arterial wall vs. smooth arterial wall with PowerStent.

Timing of adverse effects: 1 month

Factors that predict response: NR

Source Citation: Lee et al. 2014[76]

Study Design: RCT

Device or Material: 2 hybrid stents with PLGA nanofibers (Resomer RG 503, Boehringer Ingelheim) at 2 different doses vs. control

Route: Abdominal aorta

Dose: Group A: 25 μg/mm2, Group B: 5 μg/mm2, Group C: control

Frequency/Duration: Single administration

Response: Adhered monocytes, Adhered platelets, Inflammation response, Vascular injury

Species (strain): Rabbit (New Zealand white).

Gender: Male

Number per group: 12 Group A and B, 24 Group C.

Observations on adverse effects: At 2 and 4 weeks follow-up, the inflammation response was significantly lower with PLGA (both doses) vs. control. Vascular injury scores were comparable. Number of adhered platelets significantly lower with PLGA vs controls; adhered monocytes in Group A (higher dose of PLGA) were significantly lower vs. Group B (lower dose of PLGA) and controls.

Timing of adverse effects: 2 and 4 weeks

Factors that predict response: NR

Source Citation: Watanabe et al. 2014[77]

Study Design: Comparative

Device or Material: PLA with ONO-1301 solution vs. without ONO-1301 solution; stainless Gianturco Z stents from Cook

Route: Descending thoracic aorta

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Species (strain): Dogs (Mongrel)

Gender: NR

Number per group: 6

Observations on adverse effects: No stent migration or embolic events observed.

Timing of adverse effects: 3 months

Factors that predict response: NR

Source Citation: Zheng et al. 2014[78]

Study Design: Comparative

Device or Material: PEVA/PBMA vs. PLGA or PLGA/ACP

Route: Abdominal aorta

Dose: Mean coating 30±10 μm

Frequency/Duration: Single administration

Response: Inflammation, Restenosis

Species (strain): Rats (Sprague Dawley).

Gender: Male

Number per group: 18 each composite, 9 PLGA.

Observations on adverse effects: At 1 month, PLGA/ACP coated stents had significantly reduced restenosis and significantly reduced inflammation vs. PEVA/PBMA and PLGA. At 3 months, a significantly lower

inflammation score with PLGA/ACP vs. PEVA/PBMA (1.33 vs. 2.27); no significant difference in restenosis.

Timing of adverse effects: 1 and 3 months.

Factors that predict response: NR

Source Citation: Zago et al. 2013[79]

Study Design: RCT

Device or Material: PTCA-NC alone (control) vs. PTCA-NC plus PDLLA-based nanoparticle formulation (anionic 1) vs. PTCA-NC + polylactic-co-glycolic acid-based nanoparticle formulation (anionic 2) vs. Eudragit RS nanoparticle formulation (cationic)

Route: Coronary arteries

Dose: 3.0 x 16 mm 316L stainless stents

Frequency/Duration: Single administration

Response: Luminal loss, Neointimal hyperplasia

Species (strain): Pigs (large white)

Gender: NR

Number per group: 4

Observations on adverse effects: Luminal volume (LV) loss and percent variation in LV loss were significantly higher in control group vs. all treatment groups; most benefit with anionic formulations. Anionic 1 formulation (with PDLLA) displayed the lowest percentage in NIH volume gain.

Timing of adverse effects: 28 days

Factors that predict response: NR

Source Citation: Carlyle et al. 2012[80]

Study Design: Comparative

Device or Material: AC-SES with PLGA (MiStent Sirolimus Eluting Absorbable Polymer Coronary Stent System; Micell Technologies, Inc.) vs. Vision BMS (Abbott Vascular)

Route: Coronary arteries

Dose: Target drug load of 2.44 μg/mm$^2$; 3.0 x 15 mm stent

Frequency/Duration: Single administration

Response: Inflammatory response, Neointimal area, NIH, Neointimal thickness, Percent stenosis

Species (strain): Mini-swine (Yucatan).

Gender: NR

Number per group: 8 stents/pairs each stent type and time point.

Observations on adverse effects: Reduced inflammatory response and neointimal hyperplasia with overlapping AC-SES stents vs. overlapping BMS stents at 30 and 90 days. At 30 days, significantly lower neointimal area (1.38 mm vs. 2.26 mm), area % stenosis (22% vs. 35%), and neointimal thickness (0.17 mm vs. 028 mm) with AC-SES with PLGA.

Timing of adverse effects: 30 days

Factors that predict response: NR

Source Citation: Koppara et al. 2012[81]

Study Design: RCT: Polymer selection study

Device or Material: PEVA/PBMA SES vs. PUR SES vs. PLLA SES vs. PLGA SES vs. BMS (PRO-Kinetic Energy (Biotronik AG)

Route: Coronary arteries

Dose: PLLA SES: 6.2 µg/mm, PLGA SES: 8.8 µg/mm, PEVA/PBMA: 8.6 µg/mm, PUR SES: 6.2 µg/mm

Frequency/Duration: Single administration

Response: Inflammation score

Species (strain): Pigs (domestic farm).

Gender: NR

Number per group: 11 PEVA/PBMA, 9 PUR SES, 10 PLLA SES, 10 PLGA SES, 10 BMS.

Observations on adverse effects: Inflammation scores significantly higher with SES vs. BMS (0.8±0.8 BMS, 1.4±0.7 PEVA/PBMA, 1.5±0.7 PUR SES, 1.0±0.7 PLLA SES, 1.1±0.2 PLGA SES). Percent area stenosis (23.1±15.6 PLLA SES, 26.8±10.6 PLGA SES, 30.0±18.2 BMS, 33.1±13.1 PUR SES, 39.9±19.7 PEVA/PMA SES) and neointimal area (1.3±0.7 PLLA SES, 1.4±0.4 PLGA SES, 1.7±1.1 BMS, 1.8±0.7 PUR SES, 2.2±1.1 PEVA/PBMA SES) lowest with PLLA SES.

Timing of adverse effects: 28 days

Factors that predict response: NR

Source Citation: Koppara et al. 2012[81]

Study Design: RCT: Proof-of-principle study

Device or Material: PLLA SES vs. PEVA/PBMA (Cypher; Cordis Corp) vs. PLLA SES overlap

Route: Coronary arteries

Dose: Cypher: 1.4 µg/mm2 sirolimus

Frequency/Duration: Single administration

Response: Giant cells, Inflammation scores

Species (strain): Swine (Yucatan miniature)

Gender: Female

Number per group: 10 PLLA SES, 10 Cypher, 9 PLLA SES at 28 days; PLLA SES vs. Cypher at 90 days and 180 days.

Observations on adverse effects: Inflammation scores significantly higher with Cypher vs. PLLA SES at 28 days (1.1 Cypher, 0.2 PLLA SES) and 90 days (1.5 Cypher, 0.5 PLLA SES); no significant difference at 180 days (1.1 Cypher, 0.5 PLLA SES). At 90 days, PLLA SES displayed moderate inflammation driven by giant cells; cypher inflammation noted by excessive chronic leukocyte infiltration (neutrophils and eosinophils). Inflammation similar in overlapping stented segments vs. adjacent single stented segment for PLLA SES.

Timing of adverse effects: 28, 90, and 180 days.

Factors that predict response: NR

Source Citation: Wilson et al. 2012[82]

Study Design: Comparative

Device or Material: Element (BSC) bare metal or polymer-only stent vs. Synergy EES with PLGA vs. Promus (Xience V) EES; Abbott Vascular)

Route: Coronary arteries

Dose: Synergy with PLGA: 150 µg total coat weight

Frequency/Duration: Single administration

Response: Abundant eosinophils, Granuloma formation, Severe inflammatory reaction

Species (strain): Swine (NR)

Gender: NR

Number per group: NR (161 stents)

Observations on adverse effects: No significant difference in inflammation (mostly minimal to mild) across stent types up to 360 days. Severe inflammatory reactions (granuloma formation with abundant eosinophils) were infrequently observed for all groups except bare metal Element stent.

Timing of adverse effects: 30 to 360 days

Factors that predict response: NR

Source Citation: Kim et al. 2011[83]

Study Design: Comparative

Device or Material: BMS vs. PLGA-coated BMS vs. Sirolimus/PLGA DES (Sirolimus: PLGA 20:80 and 33:67)

Route: Coronary arteries

Dose: Sirolimus loaded stent: 8.3 µg/mm$^2$

Frequency/Duration: Single administration

Response: Inflammation score, Injury score, NIH, Stenosis

Species (strain): Swine (farm)

Gender: NR

Number per group: 32 stents in 16 pigs

Observations on adverse effects: Inflammation scores (range 0.99 to 1.05) and injury scores (range 1.71 to 1.85) were similar across groups. Benefits to SES vs. controls (both BMS) included significantly decreased neointimal area, percent diameter stenosis significantly less, NIH area significantly smaller, and area stenosis significantly lower.

Timing of adverse effects: 4 weeks

Factors that predict response: NR

Source Citation: Oyamada et al. 2011[84]

Study Design: Comparative

Device or Material: 316L SS coated with PLGA/ACP copolymer (VasoTech, Inc.)

Route: Abdominal aorta vs trans-iliac approach

Dose: NR

Frequency/Duration: Single administration

Response: Restenosis, ST

Species (strain): Rats (Sprague Dawley).

Gender: Male

Number per group: 6 each time point

Observations on adverse effects: Acute thrombosis observed in 13 rats (excluded from further analysis). In-stent restenosis was observed (~10% at 1 week, ~12% at 2 weeks, ~20% at 4 weeks, ~25% at 12 weeks; displayed in Figure 4).

Timing of adverse effects: 1 week to 12 weeks

Factors that predict response: NR

Source Citation: Di Felice et al. 2010[85]

Study Design: Comparative

Device or Material: Customized PDLLA composite scaffold vs. Open-pore polylactic acid (OPLA; BD BioSciences)

Route: Dorsal subcutaneous region

Dose: Scaffolds: NR

Frequency/Duration: Single administration

Response: Less defined capsule, Macrophages, Necrosis

Species (strain): Mice (athymic Nude-Foxn1$^{nu}$).

Gender: Female

Number per group: 5 scaffolds overall.

Observations on adverse effects: Less defined capsule, presence of macrophages, and areas of necrosis with PDLLA.

Timing of adverse effects: 21 days

Factors that predict response: NR

Source Citation: Zamiri et al. 2010[86]

Study Design: Comparative

Device or Material: 10:90 PLGA vs. 85:15 PLGA vs. polydioxanone (PDO) vs. PLA control

Route: Coronary arteries

Dose: Scaffolds: NR

Frequency/Duration: Single administration

Response: FBGC, Fibroblasts, Inflammatory response, Injury, Macrophages, Stenosis

Species (strain): Pigs (Yucatan)

Gender: NR

Number per group: 5

Observations on adverse effects: **:** Highest inflammatory response (consisting of 1-2 cell layers of macrophages, fibroblasts, and FBGCs) with 10:90 PLGA at 30 days, but minimal inflammation at 90 days. Stenosis was observed in all stent types at 30 and 90 days; no significant difference between stent types. Mild injury observed at 30 days; 0 injury score for all stents at 90 days.

Timing of adverse effects: 30 and 90 days

Factors that predict response: NR

ACP: amorphous calcium phosphate; AC-SES: absorbable coating-sirolimus-eluting stent; ADC: asymmetrical dual coating; BMS: bare metal stent; BP-SES: biodegradable polymer sirolimus-eluting stents; BPS: biodegradable polymer-only coated stent; BPSES-A: asymmetric biodegradable drug eluting PLGA/SES; BPSES-C: conventional drug eluting coating; CSC: Chitosan-loaded monoclonal platelet glycoprotein IIIa receptor antibody SZ-21 coating; DES: drug-eluting stent; DP-EES: durable polymer everolimus-eluting stents; EES: everolimus-eluting stent; FBGC: foreign body giant cells; IQR: interquartile range; ISR: in-stent restenosis; LLL: late lumen loss; LMW: low molecular weight; miR-145: microRNA-145; mg: milligram; mL: milliliter; mm: millimeter; MMP-2: matrix metalloproteinase-2. MMP-9: matrix metalloproteinase-9; MMW: medium molecular weight; NA: not applicable; NF-kB: nuclear factor-kappa B; NIH: neointimal hyperplasia; NP: nanoparticles; $n/mm^2$: newton per square millimeter: NR: not reported; OPN: osteopontin; PBS: phosphate-buffered saline; PDLLA: poly-D, L-lactide; PEVA/PBMA: polyethylene-co-vinyl acetate/poly-n-butyl methacrylate; PLA: polylactide or polylactic acid; PLGA: poly(DL-lactide-co-glycolide); PLLA: poly-L-lactic acid; PTCA-NC: percutaneous transluminal coronary angioplasty with a noncompliant balloon; PTX: paclitaxel; RAPA: rapamycin; RCT: randomized controlled trial; SES: sirolimus-eluting stents; SMV: simvastatin; SS: stainless stent; ST: stent thrombosis; µm: micrometer; VEGF: vascular endothelial growth factor; VSMC: vascular smooth muscle cells

*Table 12: Screw, Fixation, Bone – Health Effect (In Vivo) Human Studies*

### *Local Response/Toxicity*

Source Citation: Gareb et al. (2020)[87]

Study Design: Systematic review

Device or Material: Biodegradable (mostly Inion CPS and Bio-Sorb FX) vs. titanium osteosynthesis in maxillofacial fractures

Contact Duration: 4 to12 weeks

Dose: Screw diameters 1.5 to 2.5 mm.

Frequency/Duration: Single administration

Response: Malunion, Malocclusion, Infection

Patient characteristics (gender, mean age): Mostly male, 4 to 83 years

Number per group: 1,639 titanium, 811 biodegradable.

Observations on adverse effects: No significant difference in malunion, malocclusion, inflection, dehiscence, plate exposure, pain, abscess formation, swelling, palpability of plates and/or screws, satisfaction, operative time, revision surgery. Screw breakage at time of surgery occurred more often in biodegradeable group.

Timing of adverse effects: 4 to 12 weeks

Factors that predict response: NR

Source Citation: Kuroyanagi et al. 2018[88]

Study Design: Case series

Device or Material: Zimmer Osteotrans F-u-HA/PLLA screws to repair lateral tibial condylar fractures

Contact Duration: Mean follow-up 44 months (15 to 78).

Dose: Two 6.5 mm screws with washers. 1 patient received an additional 4.5 mm screw.

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 5 female, 2 male, 51.1 years.

Number per group: 7

Observations on adverse effects: All fractures healed. No screw breakage, osteolysis, or radiolucent zones around the screws were observed at final follow-up. No patient had infection, late aseptic tissue response, or foreign body reaction postoperatively.

Timing of adverse effects: None reported.

Factors that predict response: NR

Source Citation: Lee et al. (2017)[89]

Study Design: Comparative cohort study

Device or Material: Interference screw for ACL reconstruction. PLLA (BioRCI, Smith & Nephew), PLLA-HA (BioRCI-HA, Smith & Nephew)

Contact Duration: Mean follow-up: PLLA=32.5±5.9 months, PLLA-HA=31.0±6.1 months

Dose: One screw. 8.2±4.1mm diameter, 26.2±2.3mm length.

Frequency/Duration: Single administration

Response: Edema, Cysts, Tunnel widening

Patient characteristics (gender, mean age): PLLA: 64 male/ 22 female, 31.1±5.6 yrs. PLLA-HA: 64 male/ 22 female, 31.2±7.3 yrs.

Number per group: 86 PLLA, 86 PLLA-HA.

Observations on adverse effects: In PLLA group, 9(10.5%) had no reaction, 66 (76.7%) had edema, 11 (12.8%) had cysts. In PLLA-HA group, 63 (73.3%) had no reaction, 21 (24.4%) had edema, 2 (2.3%) had cysts. PLLA group had 41.3% increase in tibial tunnel cross sectional area (CSA), and PLLA-HA group had 27.4% increase in CSA.

Timing of adverse effects: Imaging acquired at approximately 27±3 months.

Factors that predict response: Presence of hydroxyapatite (HA).

Source Citation: Caekebeke et al. 2016[90]

Study Design: Comparative cohort study

Device or Material: PLLA interference screw (Arthrex), PEEK interference screw (OPTIMA, Arthrex) for distal biceps tendon repair

Contact Duration: Mean follow-up: 35 months (24 to 48) for PLLA, 16 months (12 to 24) for PEEK.

Dose: Single 7 x 10 mm or 8 x 12 mm screw

Frequency/Duration: Single administration

Response: Tunnel widening, Heterotopic ossification

Patient characteristics (gender, mean age): All males, PLLA 45±7 yrs, PEEK 45±10 yrs.

Number per group: PLLA = 12, PEEK = 11.

Observations on adverse effects: **:** No foreign body reactions with aseptic swelling, sinus formation, or screw breakage was encountered. CT imagine suggests the bone tunnel widened 44% in PLLA group and 38% in PEEK group. Closure of cortical bone over the bone tunnel at the radial tuberosity occurred in 2/12 PLLA patients and 3/11 PEEK patients.

Timing of adverse effects: CT images acquired 1 year postop.

Factors that predict response: NR

Source Citation: Cox et al. (2014)[91]

Study Design: Comparative cohort study

Device or Material: Interference screws. Smith & Nephew CALAXO polylactide carbonate (65% PDLGA), DePuy Synthes MILAGRO (70% PLGA)

Contact Duration: Mean (range): CALAXO - 3.1 years (2.8 to 4.0) MILAGRO to 2.9 (2.5 to 3.2)

Dose: Not stated explicitly. Likely 2 screws per patient because "all patients underwent unilateral primary ACL reconstruction… utilizing almost exclusively bone-patellar tendon-bone autograft"

Frequency/Duration: Single administration

Response: Edema, Cyst formation

Patient characteristics (gender, mean age): CALAXO: 15 male, 16 female, median age 21 years, median weight 73 kg, median height 1.73 m. MILAGRO: 18 male, 18 female, median age 21 years, median weight 74 kg, median height 1.73 m

Number per group: CALAXO: 31, MILAGRO: 36

Observations on adverse effects: No foreign body reaction was seen in >50% of subjects. Edema observed in 19% to 25% of tibias and 31% of femurs. Cysts observed in 16% to 19% of tibias and 10% to 12% of femurs.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Turvey et al. (2011)[92]

Study Design: Comparative cohort study

Device or Material: PDLLA 70/30 screws and plates in the craniomaxillofacial region. Bionx, Con Med from 1999 to 2002, then Inion Corp.

Contact Duration: Not reported

Dose: Varied widely

Frequency/Duration: 1 to 3 operations

Response: Inflammation

Patient characteristics (gender, mean age): 61% female, age 22±11 years. 88% Caucasian, 7.9% African American, 1.5% Hispanic, 1.3% Asian, 1.3% Native American.

Number per group: 745 patients total underwent 761 operations (179 Bionx, 575 Inion, 7 Macropore).

Observations on adverse effects: 14 instances of breakage (2 [1%] Bionx, 11 [2%] Inion, 1 [14%] Macropore), 31 instances of inflammation leading to failure (8 [5%] Bionx, 23 [6%] Inion, 0 Macropore).

Timing of adverse effects: NR

Factors that predict response: NR

NA: not applicable; NR: not reported; Obs: observational; PDLLA: poly-d,l-lactic acid; PLDLA: poly (L-lactide-co-D,L-lactide); PLGA: poly(lactic-co-glycolic acid); R: reliable

*Table 13: Screw, Fixation, Bone – Health Effect (In Vivo) Animal Studies*

### *Local Response/Toxicity*

Source Citation: Schaller et al. (2018)[93]

Study Design: Comparative study

Device or Material: DePuy Synthes Rapidsorb plates and screws

Route: Repair of midface osteotomy of the supraorbital rim and zygoma

Dose: 2 thin plates (6x18x.8mm), 2 thick plates (7x29x1.2mm). 12 screws (1.5 or 2 mm dia, 4 – 6mm length)

Frequency/Duration: 1 and 9 months

Response: None observed

Species (strain): skeletally mature 2 yr old Yucatan miniature pigs.

Gender: NR

Number per group: 2 PLGA, 3 Magnesium.

Observations on adverse effects: No plate exposure, foreign body reaction, increased morbidity, allergic reactions, or changes in animal behavior.

Timing of adverse effects: NR

Data Quality: NR

Factors that predict response: NR

Source Citation: Neumann et al. (2015)[94]

Study Design: Case Series

Device or Material: SonicFusion 70:30 poly (L-lactide-co-D,L-lactide) inside a modified titanium Asnis screw (Stryker)

Route: Screws placed in femur proximal to the knee joint

Dose: Four 6.5mm dia x 60mm length screws: one screw with thread of 10mm thread and one with 20mm thread, both augmented with PLDLA. 2 un-augmented screws.

Frequency/Duration: Single administration. End points at 4, 8, and 12 weeks.

Response: Edema

Species (strain): Ovis aries

Gender: Female

Number per group: Each animal received 2 augmented screws and 2 control screws. 4 animals sacrificed at each time period (4, 8, 12 weeks), resulting in 4 of each implant type at each time period.

Observations on adverse effects: Slight to moderate signs of edemas in the 4-week group. The 8- and 12-week group did not exhibit any noticeable problems. Macroscopically, there were no signs for infection or inflammation in any group. Histologically, the 8-week group had fewer inflammatory

cell activity. No significant evidence of inflammation or infection could be observed. After 12 weeks, the augmented screws showed less inflammatory reaction than after 4 or 8 weeks.

Timing of adverse effects: 4 weeks

Factors that predict response:

Source Citation: Park et al. (2013)[95]

Study Design: Case Series

Device or Material: PLGA plate and screw

Route: Repair of mandibular body ostetomy

Dose: NA

Frequency/Duration: 2, 4, 6, 8, and 10 weeks

Response: Severe acute inflammation, foreign body reaction

Species (strain): 2.5 to 3.0 kg New Zealand white rabbits.

Gender: Male

Number per group: 25

Observations on adverse effects: No significant change in pattern of chewing, eating, and sucking were observed. Severe acute inflammation detected at 4 weeks. Inflammation and foreign body reaction reduced at 6 weeks and disappeared at 8 weeks. Healing, fibrosis, and complete bone remodeling observed at 10 weeks.

Timing of adverse effects: 4 weeks

Factors that predict response:

Source Citation: Lyons et al. (2011)[96]

Study Design: Case Series

Device or Material: 70:30 PDLLA plates and screws

Route: Anterior cervical discectomy and fusion (ACDF) at C2-C3 and C4-C5.

Dose: Each level received 4 screws (4.0mm dia) and 1 plate, which was either 17x22x2mm (C2-C3) or 17x24x2mm (C4-C5).

Frequency/Duration: 3 months

Response: Foreign body giant cell

Species (strain): Rambouillet x Columbian ewes.

Gender: NR

Number per group: 6

Observations on adverse effects: Inflammation was not frequently observed. If observed, inflammation was typically in the form of a single foreign body giant cell within the fibrous tissue adjacent to the plate.

Timing of adverse effects: 3 months

Factors that predict response:

NA = not applicable; NR = not reported; PDLLA= Poly-d,l-lactic acid; PLDLA= poly (L-lactide-co-D,L-lactide); PLGA=poly(lactic-co-glycolic acid)

*Table 14: Fastener, Fixation, Biodegradable Soft Tissue – Health Effect (In Vivo) Human Studies*

***Local Response/Toxicity***

Source Citation: Debieux et al. 2016[97]

Study Design: Systematic Review

Device or Material: Bioabsorbable versus metallic interference screws for graft fixation in anterior cruciate ligament reconstruction

Contact Duration: 3 studies: mean 13 months, mean 21 months, 28 months

Dose: Poly-L-lactic acid, or polyglycolic acid screws

Frequency/Duration: NR

Response: Failure of treatment and adverse events included symptomatic foreign body reactions

Patient characteristics (gender, mean age): NR

Number per group: 369 from 3 studies

Observations on adverse effects (brief): Three studies (Benedetto 2000; Kotani 2001; McGuire 1995) specifically referred to symptomatic foreign body reactions as an outcome. The only case, which involved a soft fluid-filled subcutaneous cyst, was reported in Benedetto 2000 (1/197 versus 0/172; Risk Ratio 2.52, 95% CI 0.10 to 60.67). Overall treatment failure was higher in the bioabsorbable screw group. Twice as many treatment failures in the bioabsorbable screw group (60/451 versus 29/434; RR 1.94, 95% CI 1.29 to 2.93; P = 0.001).

Timing of adverse effects: NR

Factors that predict response: NR

NR = not reported; RR = risk ratio.

*Table 15: Fastener, Fixation, Biodegradable Soft Tissue – Health Effect (In Vivo) Animal Studies*

***Local Response/Toxicity***

Source Citation: Easley et al. 2020[98]

Study Design: Randomized controlled trial

Device or Material: Vented suture anchor with PLGA scaffold (BioWick SureLock W Suture Anchor, Zimmer-Biomet, Warsaw, IN)

Route: Infraspinatus tendon acute transection/repair model

Dose: 1 implant

Frequency/Duration: 7 and 12 weeks

Response: No adverse reactions or immune responses

Species (strain): skeletally mature Columbia Cross sheep

Gender: female

Number per group: 14

Observations on adverse effects (brief): Histopathology did not indicate any abnormal or adverse reaction or immune response in either surgical group. Qualitatively, tendon repair progressed in an expected fashion from 7 to 12 weeks in both groups. Inflammation scores for the Treatment group at both 7 and 12 weeks were modestly reduced compared to the Control (predicate device, SureLock All-Suture Anchor; Zimmer-Biomet) groups. Minimal to mild chronic inflammation and perivascular inflammation was present in both Treatment and Control groups at both 7 and 12 weeks

Timing of adverse effects: 7 and 12 weeks.

Factors that predict response:

Source Citation: Xue et al. 2014[99]

Study Design: Comparative study

Device or Material: Bone plates: poly(D/L)lactide acid (PDLLA) (Resorb-X System, KLSMartin, Jacksonville, FL) and polylactide-co-glycolide acid (PLGA) ((Delta System, Stryker Osteosynthesis, Freiburg, Germany)

Route: Each plate was placed into a periosteal pericalvarial pocket created beneath the anterior or posterior scalp of the same rabbit.

Dose: Scaffolds: 2 implants

Frequency/Duration: 3, 6, and 12 months

Response: Foreign body response

Species (strain): Rabbits

Gender: Male

Number per group: 5

Observations on adverse effects (brief): The PDLLA plates demonstrated marked local foreign-body reactions within the implant capsule as early as 3 months after implantation, with presence of inflammatory cells and granulomatous giant cells in close association with the implant material. All local foreign-body reactions were subclinical with no corresponding tissue swelling requiring drainage. PLGA plates did not demonstrate any signs of inflammatory reactions. In addition, the

PLGA plates did not appear to resorb or integrate at 12 months. Neither PDLLA nor PLGA plates demonstrated inflammation of the soft tissue or adjacent bone outside the implant capsule.

Timing of adverse effects:

Factors that predict response: Current generation of commercial biodegradable plates is formulated to minimize this complication by altering the ratio of polylactic and polyglycolic acids.

Source Citation: Asawa et al. 2012[100]

Study Design: Comparative study

Device or Material: Biodegradable poly-L-lactic acid (PLLA) or poly-DL-lactic-co-glycolic acid (PLGA) polymer scaffolds

Route: canine autologous chondrocyte transplants using PLLA or PLGA scaffolds

Dose: 2 implants

Frequency/Duration: 1, 2, and 6 months

Response: Foreign body reaction

Species (strain): dogs

Gender: male

Number per group: 6

Observations on adverse effects (brief): The ACP-positive macrophages were significantly increased in the PLGA constructs in comparison with those of the PLLA constructs at 1 month. PLLA scaffolds were suitable for the autologous chondrocyte transplantation for cartilage tissue engineering under the immunocompetent condition, because of the retarded degradation properties and the decrease in the severe tissue reactions during the early stage of transplantation.

Timing of adverse effects: 1 and 2 months.

Factors that predict response: The biodegradation of PLGA progressed much faster than that of PLLA, and the PLGA had almost disappeared by 2 months. The degraded products of PLGA may evoke a more severe tissue reaction at this early stage of transplantation than PLLA.

NA = not applicable; NR = not reported

*Table 16: Pin, Fixation – Health Effect (In Vivo) Human Studies*

***Local Response/Toxicity***

Source Citation: Yanagibayashi et al. 2020[101]

Study Design: Cohort

Device or Material: HPLLA threaded pin (super FIXSORB-MX)

Contact Duration: Mean: 12.75 weeks

Dose: 1 pin per patient (diameters 1.5 or 2 mm, length 40 mm)

Frequency/Duration: Single operation

Response: No foreign body reaction

Patient characteristics (gender, mean age): All male, 48.6 years.

Number per group: 10 patients.

Observations on adverse effects: No adverse events or foreign body reaction.

Timing of adverse effects: Median 12 weeks.

Factors that predict response:

Source Citation: Nakasa et al. 2019[102]

Study Design: Retrospective cohort

Device or Material: PLLA pins (GRAND FIX)

Contact Duration: 3 months, 6 months, 12 months

Dose: 1 pin per patient (nail diameter 2 mm, length 15 mm)

Frequency/Duration: Single operation

Response: Bone marrow edema

Patient characteristics (gender, mean age): 58% males, 14 to 34 years.

Number per group: 12 (13 ankles)

Observations on adverse effects: Reduction in bone marrow edema.

Timing of adverse effects: After 6 months.

Factors that predict response: No osteolysis is correlated with less edema.

HPLLA: hydroxyapatite/poly-L-lactide; PLLA: poly-L-lactide; mm: millimeters

*Table 17: Pin, Fixation – Health Effect (In Vivo) Animal Studies*

***Local Response/Toxicity***

Source Citation: Morawska-Chochol et al. 2018[103]

Study Design: Comparative

Device or Material: PLA/CF/ALG fiber nail

Route: Epiphysis fixation

Dose: 2 nails per rabbit (nail diameter 2.5 mm, length 30 mm)

Frequency/Duration: 2 to 8 weeks

Response: Necrosis

Species (strain): Rabbit (Californian)

Gender: Female

Number per group: 5 for PLA fiber nails and 3 for control Kirschner wires.

Observations on adverse effects: Focal necrosis seen at 4 weeks, but compensated for by bone healing.

Timing of adverse effects: 8 weeks

Factors that predict response: NR

Source Citation: Lindtner et al. 2013[104]

Study Design: RCT

Device or Material: PLGA implant rod (Purasorb PLG8531, Purac Biochem)

Route: Transcortically inserted into the mid-diaphysis of each femoral bone

Dose: 2 rods per animal (1 in each femoral bone) (each rod 1.6 mm in diameter and 7 mm in length)

Frequency/Duration: 4 to 24 weeks

Response: Foreign-body reaction, IL-6 levels, Local inflammation, Lymphocytes %, Monocytes% Neutrophil granulocytes, eosinophil, and basophile granulocytes %

Species (strain): Rat (Sprague-Dawley)

Gender: Male

Number per group: 36 for experimental and control, each subdivided into three groups of different implantation periods (four, twelve, twenty-four weeks).

Observations on adverse effects: PLGA implants shows higher percentages of monocytes.

Timing of adverse effects: 12 weeks

Factors that predict response:

Source Citation: Annunziata et al. 2015[105]

Study Design: Comparative

Device or Material: PDLLA membranes and PDLLA pins

Route: Calvarial bone defect repair

Dose: 4 pins per membrane (1.6 mm wide, 4 mm long)

Frequency/Duration: 40 days

Response: Inflammation, Infection

Species (strain): White domestic pigs

Gender: Female

Number per group: 6 intervention per animal: negative control, non-perforated membrane only, perforated membrane only, bone only, bone + non-perforated membrane, bone + perforated membrane.

Observations on adverse effects:

Timing of adverse effects:

Factors that predict response:

ALG: alginate fibers; CF: carbon fibers; PDLLA: poly-D-L-lactic acid; PLA: poly-L-lactide; PLGA: poly(L-lactic-co-glycolic acid); RCT: randomized control trial

*Table 18: Vascular Graft – Health Effect (In Vivo) Animal Studies*

***Local Response/Toxicity***

Source Citation: Chang et al. 2018[106]

Study Design: Comparative

Device or Material: 50:50 PLGA (control group), 50:50 PLGA+propylthiouracil-coated vascular BMS (Gazella)

Route: Descending abdominal aorta

Dose: 240 mg PLGA, 40 mg propylthiouracil

Frequency/Duration: Single administration

Response: Inflammation score, Intima thickness, Endothelial cell proliferation, Vessel injury score Thyroid function

Species (strain): Rabbit (New Zealand).

Gender: Male

Number per group: 12

Observations on adverse effects (brief): No adverse effect on survival and no infections reported. At 8 weeks, vessels with PLGA and propylthiouracil-coated BMS had significantly thinner intima than the control group. Inflammation and vessel injury scores were not significantly different between groups at 8 weeks.

Timing of adverse effects: : 3-8 weeks.

Factors that predict response: NR

Date Quality: NR

Source Citation: Esguerra et al. 2010[107]

Study Design: Comparative

Device or Material: 3 mm x 3 mm section of *Acetobacter xylinum* BC, PGA (Concordia Manufacturing LLC), ePTFE (Gore-Tex)

Route: Dorsal skin layer

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory response (leukocyte infiltration and hemodynamics (adherent, rolling, or free-flowing cells)) Vessel diameter Macromolecular leakage

Species (strain): Hamster (Syrian, golden)

Gender: Female

Number per group: 5

Observations on adverse effects (brief): No adverse effect on survival and no infections reported. Leukocyte rolling and adherence were not significantly different between BC, PGA, and ePTFE groups at any time point. Vascularization was faster in the PGA and ePTFE groups compared to the BC group.

Timing of adverse effects: 30 minutes (baseline), 3, 6, 10, and 14 days.

Factors that predict response: NR

Date Quality: NR

Source Citation: Fukunishi et al. 2019[108]

Study Design: Comparative

Device or Material: Native aorta, PGA (The Secant Group), PGS-coated PGA vascular scaffold

Route: Infrarenal abdominal aorta

Dose: 15% w/w PGS solution

Frequency/Duration: Single administration

Response: Aortic stiffness, Proliferation of endothelial cells, SMC, and elastin, Total number of macrophages, Lumen diameter, Calcification area, Wall thickness, Elastin layer thickness, Scaffold area

Species (strain): Rat (Lewis)

Gender: Female

Number per group: 25 (vascular scaffold groups), NR (native aorta)

Observations on adverse effects (brief): No adverse effect on survival and no infections reported. Histological analyses of the uncoated PGA scaffolds at 1, 3, and 6 months demonstrated host SMC infiltration, endothelialization, and elastin proliferation. PGS-coated PGA scaffolds had significantly fewer pro-inflammatory M1 macrophages at 1, 3 and 6 months and greater anti-inflammatory M2 macrophages at 3 months compared to uncoated PGA scaffolds. At 1, 3, and 6 months, significantly more calcifications were observed in the uncoated PGA scaffolds compared to the PGS-coated PGA scaffolds.

Timing of adverse effects: 1-6 months

Factors that predict response: NR

Date Quality: NR

Source Citation: Liu et al. 2018[109]

Study Design: Uncontrolled case series

Device or Material: 50:50 PLGA+vancomycin-coated vascular BMS (Liberté)

Route: Infrarenal abdominal aorta

Dose: 240 mg PLGA, 40 mg vancomycin

Frequency/Duration: Single administration

Response: Inflammatory response (leukocyte infiltration), Endothelial cell proliferation

Species (strain): Rabbit (New Zealand, white).

Gender: Male

Number per group: 15

Observations on adverse effects (brief): No adverse effect on survival and no thromboembolic events reported. Leukocyte penetration into the stent was low during the study period. Endothelial cell proliferation was observed at 3 weeks and endothelial cell maturity was reported at 8 weeks of the study.

Timing of adverse effects: 1-8 weeks.

Factors that predict response: NR

Date Quality: NR

Source Citation: Liu *et al.,* 2010[110]

Study Design: Comparative

Device or Material: No graft, vein graft, vein graft with intraluminal perfusion of PLGA NP, vein graft with intraluminal perfusion of PLGA+ rapamycin+0.1% carbopol NP

Route: Common carotid artery

Dose: NR

Frequency/Duration: Single administration

Response: Intima thickness, Collagen volume index

Species (strain): Rabbit (New Zealand, albino).

Gender: NR

Number per group: 15

Observations on adverse effects (brief): Vein graft thrombosis occlusion occurred in two rabbits (one in the vein graft and one in PLGA NP vein graft groups). In the vein graft and PLGA NP vein graft groups, graft intima thickness and collagen volume index were significantly elevated compared to the PLGA+ rapamycin+0.1% carbopol NP group on day 28.

Timing of adverse effects: 28 days

Factors that predict response: NR

Date Quality: NR

Source Citation: Liu *et al.,* 2010[110]

Study Design: Comparative

Device or Material: Vein graft with intraluminal perfusion of PLGA+ rapamycin+0.1% carbopol NP

Route: Common carotid artery

Dose: 100 µg/ml, 500 µg/ml

Frequency/Duration: Single administration

Response: Thrombosis, Vein graft intraluminal concentration of PLGA+ rapamycin+0.1% carbopol NP

Species (strain): Rabbit (New Zealand, albino).

Gender: NR

Number per group: 20

Observations on adverse effects (brief): The authors reported that "one rabbit in the high-dose group died due to an anesthetic accident and one rabbit in the low-dose group was found to have thrombosis on postoperative day 3. There was not a significant difference between the low and high dose groups at any time point; rapamycin was not detected in the low or high dose groups on day 28.

Timing of adverse effects: 7-28 days

Factors that predict response: NR

Date Quality: NR

Source Citation: Sharma *et al.,* 2018[111]

Study Design: Comparative

Device or Material: 10:90 PLGA+50:50 PGCL vascular scaffold

Route: Femoral artery

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory response (inflammation score, fibrin score, presence of granuloma), Intima thickness, Vessel injury score

Species (strain): Swine (NR).

Gender: NR

Number per group: NR

Observations on adverse effects (brief): No implant migration, thrombosis, dissection or aneurysm was identified. The authors reported "histologic analysis demonstrated a significant inflammatory response and the presence of granuloma at 30 days…Overall, the biocompatibility of this implant was deemed unacceptable."

Timing of adverse effects: 30-90 days.

Factors that predict response: NR

Date Quality: NR

Source Citation: Sharma *et al.,* 2018[111]

Study Design: Comparative

Device or Material: 75:25 PLGA+ 50:50 PGCL, 75:25 PLGA+40:60 PLCL vascular scaffold

Route: Femoral artery

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory response (inflammation score, fibrin score, presence of granuloma), Endothelial cell proliferation, Intima thickness, Vessel injury score

Species (strain): Swine (NR)

Gender: NR

Number per group: NR

Observations on adverse effects (brief): The authors reported that the PLGA/PGCL scaffolds had significant *in vivo* resorption "at 90 days…. This resorption coincided with a strong inflammatory response with the presence of granuloma." The PLGA/PLCL scaffolds had significant resorption at 180 days and the authors reported "this resorption was accompanied by a modest amount of inflammation" and low vessel disruption.

Timing of adverse effects: 30-180 days.

Factors that predict response: NR

Date Quality: NR

Source Citation: Sharma *et al.,* 2018[111]

Study Design: Comparative

Device or Material: 75:25 PLGA+40:60 PLCL, 85:15 PLGA+40:60 PLCL vascular scaffold

Route: Femoral artery

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory response (inflammation score, fibrin score, presence of granuloma), Intima thickness, Vessel injury score

Species (strain): Ovine (NR).

Gender: NR

Number per group: NR

Observations on adverse effects (brief): The authors reported that in both groups "mild to moderate amount of inflammation without granuloma was present, minimal vessel injury was observed" and fibrin scores were similar.

Timing of adverse effects: 1-18 months.

Factors that predict response: NR

Date Quality: NR

Source Citation: Sugiura *et al.,* 2017[112]

Study Design: Comparative

Device or Material: PGA+50:50 PLCL+PLA (Gunze Ltd), PGA+50:50 PLCL+PLA+tropoelastin-coated vascular scaffold

Route: Infrarenal abdominal aorta

Dose: 1 mg/ml of 60 kDa tropoelastin

Frequency/Duration: Single administration

Response: Acute thrombosis, Inflammatory response (leukocyte infiltration), Wall thickness, Lumen diameter, Proliferation of endothelial cells, SMC, and PCNA

Species (strain): Mouse (C57BL/6)

Gender: Female

Number per group: 10

Observations on adverse effects (brief): In the uncoated scaffold group, two mice were sacrificed during the study period due to acute thrombosis and one mouse died from an undetermined cause. In the tropoelastin-coated scaffold group, four mice were sacrificed during the study period due to acute thrombosis. There was no graft rupture in either group. Endothelialization was similar between groups. The tropoelastin-coated scaffold group had fewer SMC and PCNA in the neointimal layer than the uncoated scaffold group.

Timing of adverse effects: 8 weeks

Factors that predict response: NR

Date Quality: NR

Source Citation: Xie *et al.*, 2015[113]

Study Design: Comparative

Device or Material: Uncoated (control group), PLGA+fibrin, PLGA+fibrin+bosentan-coated vein graft

Route: Ipsilateral carotid artery

Dose: 5% bosentan

Frequency/Duration: Single administration

Response: Intima thickness, Media thickness, Area of the intima/media

Species (strain): Rabbit (Japanese).

Gender: NR

Number per group: 10

Observations on adverse effects (brief): In the uncoated graft group, the authors reported that the "intima and media thickened significantly…and the lumen of the graft was narrow and irregular." The PLGA+fibrin and PLGA+fibrin+bosentan groups reported to have intact endothelium with a symmetric thickening of the intima and media.

Timing of adverse effects: NR

Factors that predict response: 9 weeks

Date Quality: NR

PGA: poly(glycolic acid); PGS : poly(glycerol sebacate); PLA : poly (l-lactic acid); PLGA : poly(lactic-co-glycolic acid); PGCL : poly(glycolide-co caprolactone); PLCL : poly(L-lactide-co-ε-caprolactone); BC : bacterial cellulose; ePTFE : expanded polytetrafluoroethylene; BMS : bare metal stent; NP : nanoparticles; SMC : smooth muscle cells; kDa : kilodalton; PCNA : proliferating-cell nuclear antigens; NA : not applicable; NR : not reported; Retro : retrospective; R : reliable; Dose : mg/kg/day

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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

*The associated alerts are provided with this report as a separate PDF.*

## Appendix H. P(L/G)A Alerts Search Terms

*Provided with this report as separate Excel spreadsheet.*