MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Magnesium Safety Profile

Report Details

Date of Submission

March 3, 2021

Prepared For

U.S. FDA Center for Devices and Radiological Health

Submitted to

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Executive Summary

Key Points

1. Searches identified 1,139 citations; 50 articles were selected for inclusion.
2. The local response reported in the largest number of studies was local inflammation, and it was associated with low or very low quality of evidence. Thrombosis and restenosis were most often reported in studies of coronary scaffolds/stents, and quality of evidence was low. Other local responses for magnesium (Mg) devices were associated with low or very low quality of evidence.
3. No studies that met inclusion criteria investigated or reported systemic reactions to Mg devices.
4. There are no Mg devices that are US FDA-cleared; thus there were no complication data in the ECRI surveillance databases. One international alert was retrieved related to mislabeling.
5. Evidence gaps:
    a. Long term randomized controlled trial human studies for local response to Mg as a material and for all device categories.
    b. Systemic response studies for Mg as a material and for all device categories.
    c. Event reports regarding complications with Mg devices.

Overview - Magnesium

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, with the understanding that there are currently no US FDA-cleared medical devices made from magnesium (Mg). This report focuses on answering 5 key questions provided by FDA and summarized below, regarding a host's local and systemic response to Mg. 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 Mg?

Local responses/device events varied somewhat across different device categories and between human and animal studies (see specific responses/events under 1a. below). However, inflammation was consistently reported across almost all device categories. There were no ECRI surveillance data, with the exception of one international alert related to mislabeling.

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

i. Studies of Mg as a material evaluated implantation of Mg alloy clips and pins in mice and rats, and both studies reported local inflammation. Only one study reported foreign body response, and fragmentation and scattering of Mg clips around extraperitoneal tissue.
ii. Several human studies of the Magmaris coronary scaffold reported thrombosis and restenosis. Other events reported in fewer studies included cardiac death/death, target vessel myocardial infarction (MI)/MI, scaffold recoil, and malapposed struts.
iii. Studies of orthopedic fixation (screw/pin/clip/nail/plate) reported the rare occurrence of femoral vein thrombosis from a screw and migration of a MAGNEZIS pin. Superficial wound-healing problems and screw penetration also infrequently occurred, while local inflammation occurred more frequently.
iv. Studies of orthopedic implants reported lameness and subcutaneous emphysema as a rare occurrence.

v. One study of biliary stents reported local inflammation, severe stent corrosion, and damaged stent integrity.
vi. The overall quality of evidence related to local host responses was low to very low, with variation across different device categories.
vii. Very little evidence was included regarding local host responses for Mg material exposure, orthopedic implants, and biliary stents.
viii. No evidence was included regarding local host responses for vascular closure devices.

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

i. Follow-up time varied for different device categories and outcomes. Studies evaluated inflammation and other events following Mg material exposure at 3 weeks and 12 weeks. Studies evaluating the Magmaris coronary scaffold reported complications such as thrombosis and restenosis occurring from 20 minutes to 4 months postimplantation. Other events such as scaffold recoil and malapposed struts occurred immediately postimplantation up to 12 months postimplantation. Studies evaluating orthopedic fixation reported femoral vein thrombosis and pin migration occurring immediately to 11 weeks postimplantation. Other local responses/events (e.g., screw penetration, synovitis, superficial wound-healing problems) occurred from 1 week to 6 months postimplantation. Studies evaluating orthopedic implants reported complications such as lameness and subcutaneous emphysema from 4 weeks to 8 weeks postimplantation. Lastly, studies of biliary stents reported local responses/events (e.g., stent corrosion, peeling) from 1 week to 6 months.

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

Three studies investigated, but did not identify, persistent or exaggerated immune responses that may lead to systemic signs or symptoms related to Mg devices.

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

No included studies investigated whether there are patient-related factors that may affect a 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?**

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

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

The gaps listed here could benefit from future research.

a. Long-term human randomized controlled trials (RCTs) for Mg as a material and all Mg device categories.
b. Studies on systemic response, including those on patient or material factors, for Mg as a material and all Mg device categories.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. If a "topic" was chosen rather than a type of material the process is referred to as a *Deep Dive*. The systematic review for a material 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 for Materials

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

Similarly, the systematic review for a Deep Dive topic was guided by a specific question, mutually agreed upon by FDA and ECRI, which defined the topic of interest and guided the searches.

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

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2010 and 2021 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

<u>Material Response</u>

Strength
Embrittlement
Degradation
Migration
Delamination
Leaching

Host Response

i) Local:

Inflammation
Sensitization
Irritation
    Scarring/ fibrosis
Keloid formation
Contracture
Ingrowth
    Erosion
ii) Systemic:

Cancer (lymphoma)
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. Text mining, logistic regression, and a search for "random" and "systematic" in titles and abstracts were used to prioritize only the top 35%-40% of the identified literature. This subset was screened against the inclusion criteria, first by title/abstract review, and then by full article review. An evidence prioritization scheme was used to ensure the inclusion of approximately 50 studies. Data were extracted from the resulting articles.

ECRI Surveillance Search Strategy

There are 4 key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

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

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2020, unless otherwise noted.

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

Category A (No Error)

Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)

An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)

An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)

An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)

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

Category F (Error, harm)

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

Category G (Error, harm)

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

Category H (Error, harm)

An error occurred that required intervention necessary to sustain life.

Category I (Error, death)

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

Definitions

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

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

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

Intervention necessary to sustain life: includes cardiovascular and respiratory support (eg CPR, defibrillation, intubation).

Accident Investigation

ECRI has performed thousands of independent medical device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - Magnesium

Full Name: Magnesium
CAS Registry Number: 7439-95-4

Systematic Review Safety Brief

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of magnesium (Mg) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of Mg. 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 Mg Provided by FDA to Guide ECRI Searches.

Regulatory Description	**Product Code***	**Class***
Coronary Stent/Scaffold	N/A	N/A
Orthopedic Fixation Device (bone screw, pin, clip, nail, plate)	N/A	N/A
Orthopedic Implant	N/A	N/A
Biliary Stent	N/A	N/A
Vascular Closure	N/A	N/A

**NOTE: None of these Mg devices are US FDA-cleared.*

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 data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on Mg 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)
Magnesium as a material (2 animal studies)	Local inflammation, Foreign body response	Very low	No studies investigated systemic responses	Very low
Coronary scaffold/stent (16 human and 2 animal studies)	Thrombosis, Restenosis	Low	Not investigated, except in 1 study that stated there were no systemic responses	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Orthopedic fixation (screw, pin, clip, nail, plate) (9 human and 18 animal studies)	Thrombosis, Migration, Local inflammation	Low	Not investigated , except in 2 studies that stated there were no systemic responses	Very low
Orthopedic implant (2 animal studies)	Lameness, Subcutaneous emphysema	Very low	No studies investigated systemic responses	Very low
Biliary stent (1 animal study)	Local inflammation	Very low	The study did not investigate systemic responses	Very low
Vascular closure (no studies)	No studies	Very low (no evidence)	No studies	Very low (no evidence)

Magnesium as a Material

Two animal studies. (1 nonrandomized comparative study[1] and 1 randomized controlled trial [RCT][2]). For further information, see Table 2 in Appendix D.

Local Host Responses (human studies)

We did not identify any human studies investigating local host responses for Mg as a material.

Systemic Responses (human studies)

We did not identify any human studies investigating systemic responses for Mg as a material.

Local Host Responses (animal studies)

One nonrandomized comparative study compared implantation of 2 Mg alloy clips composed of zinc/calcium (Mg-Zn-Ca) with 6wt% zinc (Mg-6Zn) in 30 mice. Results with Mg-6Zn clips indicated massive swelling of extraperitoneal area due to gas accumulation up to 2 weeks. At 2 weeks, the swelling had diminished, but foreign body granulomas were detected, and clips were fragmented and scattered on the extraperitoneal tissue. No swelling or fragments were reported around the Mg-Zn-Ca clips which became thinner but held their 'U' shape after 12 weeks implant.[1]

One RCT in rats compared Mg-6Zn with a titanium (Ti) alloy composed of aluminum and vanadium (Ti-3Al-2.5V). Mg-6Zn pins implanted in the abdomen of rats started to degrade at postoperative week 1.

Systemic Responses (animal studies)

We did not identify any studies investigating systemic responses to Mg-based biliary stents.

Overall Quality of Evidence

The 2 animal studies, both with control groups, were inconsistent in reporting granuloma, and these findings are inconsistent with findings from other Mg devices used in humans (coronary scaffold/stent, orthopedic fixation). We rated the quality of evidence supporting local host response to Mg as a material as very low. Since systemic responses were not investigated in any study, the quality of evidence is also very low.

Coronary Stent/Scaffold

18 studies (16 human studies, 2 animal studies).[3-20]

The human studies included 1 RCT,[3] 2 pooled data analyses,[4,5] 13 single-arm studies.[6-14,15-18] The animal studies included 2 RCTs.[19,20] For further information, see Table 3 and Table 4 in Appendix D.

Local host responses (human studies)

Use of 1st-generation Mg-based bioresorbable scaffold Magmaris (BIOTRONIK Ag) was reported in 2 studies.[13,14] Follow-up of 46 individuals with *de novo* coronary lesions was examined in BIOSOLVE I at 1 year[14] and 3 years.[13] Maximum dose of Mg was 8.5 µg. While thrombosis was not a reported outcome, the study did report strut malappositions, which is a major cause of thrombosis. A 1-year optical coherence tomography study of 5,791 struts in 7 patients indicated incompletely apposed struts in 4.1% postoperatively.[14] At 6 months, persistent incomplete apposition occurred in 0.6% of struts, and 2.2% had late acquired incomplete strut apposition. At 12 months, persistent incomplete strut apposition and late acquired incomplete strut apposition was observed in 0.1% each. At 3-year follow-up, higher late lumen loss (LLL), a surrogate endpoint of restenosis, was observed at 1 year vs. 3 years.[13]

Use of 2nd-generation Magmaris was reported in the remaining 14 studies. Thickness and width of the Magmaris scaffold was mostly reported as 150 µm. Definite or probable thrombosis was reported in 4 studies, and the rates varied from 0.5% to 16.6%.[3,9,12,15] One RCT reported similar rates of thrombosis with Magmaris implant (1.4%, 1 of 74 patients) and a sirolimus-eluting stent (2.6%, 2 of 76 patients).[3] Myocardial infarction (MI) related to device thrombosis was slightly higher with SES (2.6% vs. 1.4%).

Two single-arm studies reported interim small side branch occlusion in 2 (3.9%) cases perioperatively[11] and thrombosis in 5 patients (0.5%) at postoperative days 6 to 95.[9] Another single-arm study reported cardiac death and possible scaffold thrombosis at postoperative day 134 in 1 patient.[12] Lastly, one single-arm study reported thrombus in 1 (16.6%) patient and in-scaffold tissue prolapse in 2 (33.3%) patients.[15]

Restenosis was reported in 5 studies.[3,6,16-18] One RCT reported significantly higher binary restenosis and LLL with Magmaris vs. Orsiro.[3] In-stent restenosis was reported in 2 patients registered in the CardioHULA registry.[6] One study of 6 patients reported a binary restenosis rate of 33.3%.[16] High-grade restenosis in the vessel segment and distal edge dissection occurred in 2 patients each in another single-arm study. Restenosis occurred at 3 and 4 months postimplantation, while distal edge dissection occurred before and after balloon post dilatation.[17] Lastly, early restenosis occurred at 102 days postimplantation in 1 of 18 patients with ST elevation MI.[18]

Late lumen loss was reported in an additional 3 studies.[7,8,15] One single-arm study reported slight increases in LLL and diameter stenosis between 1 and 3 years.[7] One single-arm study reported mild in-scaffold LLL and underlying plaque growth with necrotic plaque in 4.8% of analyzed plaque.[15] One single-arm study reported scaffold LLL ≥0.5 mm was due to scaffold recoil (82.8%), and neointimal hyperplasia (3.4%).[8] Acute recoil and incomplete strut apposition was 5.34±3.99% and 3.16±4.22%, respectively in a study of 6 patients with coronary artery disease.[16] Lastly, an analysis of 201 struts identified malapposed struts in 1.93% post-procedure.[7]

One study comparing data from 184 individuals from BIOSOLVE II-III study (Magmaris) with 298 individuals from BIOFLOW II (Orsiro) reported no significant differences between Magmaris and Orsiro for cardiac death (1.1% Magmaris, 0.7% Orsiro), target vessel MI (3.3% Magmaris, 2.7% Orsiro), death (1.6% Magmaris, 1.0% Orsiro), or MI (4.3% Magmaris, 3.0% Orsiro). No definite or probable stent thrombosis was reported.[4] Another study pooling data from BIOSOLVE II-III cohorts reported incomplete strut apposition post-procedure and significant neointimal hyperplasia in 1 patient at 84 days.[5] Lastly, local response was not observed in any of 69 individuals (MAGIC registry) up to 9 months follow-up.[10]

Systemic responses (human studies)

We did not identify any human studies investigating systemic responses to Mg-based coronary stents/scaffolds.

Local host responses (animal studies)

Two RCTS examined biodegradable Mg alloy stents (BMAS).[19,20] The first RCT compared BMAS with 316L stainless steel stents and controls in 24 New Zealand white rabbits undergoing vein graft transplantation and stent implantation. Stent strut diameter was reported as 155±65 mm. BMAS structure was incomplete within 2 to 3 months with complete degradation by 4 months. Hematoxylin and eosin staining showed irregular cracks in the stent wires and a tendency to degrade from the circumference to the center.[19]

The second RCT reported mild neointimal hyperplasia 2 to 4 weeks postimplantation of a 99% Mg-Al-Zn alloy (dosage 100 to 150 µm), but no significant inflammatory cell infiltration vs. untreated dogs up to 28 days. Complete degradation was reported by 1 week with no recoil or early thrombosis observed.[20]

Systemic responses (animal studies)

One animal study investigated, but did not identify, systemic responses to Mg-based coronary stents/scaffolds.

Overall quality of evidence:

The evidence base was large, but the bulk of the studies were uncontrolled single-arm studies. Five studies reported definite/probable thrombosis and 5 studies reported restenosis, but these outcomes rarely occurred (affecting few patients in the studies that reported them), and we rated the quality of evidence supporting them is low. For other outcomes reported in fewer studies, we rated the quality of evidence as very low.

Orthopedic Fixation Device (bone screw, pin, clip, nail, plate)

27 studies (9 human studies, 18 animal studies).[21-47]

The human studies included 3 RCTs,[21-23] 1 nonrandomized comparative study,[24] and 5 single-arm studies.[25-29] The animal studies included 11 RCTs,[30-40] 6 nonrandomized comparative studies,[41-46] and 1 single-arm study.[47] For further information, see Table 5 and Table 6 in Appendix D.

Local host responses (human studies)

The human studies evaluated screws in 8 studies[21-28] and pins in 1 study.[29]

Screws: MAGNEZIX compression screws (Syntellix AG) were evaluated in 5 studies.[21,23-26] Three RCTs compared MAGNEZIX compression screws with Ti compression screws.[21,23,24] The first RCT (n=14) reported radiologic metallic debris and corresponding artifacts on MRI in 3 patients with Mg screws; fewer artifacts than Ti screws. No significant differences were reported for pooled median scores for edema (1.0 Mg, 1.5 Ti), and soft-tissue reaction (1.0 each) up to mean 3.1 years.[21] The second RCT (n=26) reported superficial wound-healing problems in 3 patients (2 Mg, 1 Ti) up to 6 months.[23] A 3rd nonrandomized comparative study (n=48) reported that degradation of Mg screws was completed by 12 months when implanted for medial malleolar fractures.[24]

One single-arm study (n=6) reported tenderness on palpation at operation site and joint in 2 patients up to 3 months after implantation of MAGNEZIX for mandibular condyle fractures. Penetration of screw tip through the condylar surface also occurred at 6 months in 1 patient with degradation of materials by 12 months precluding implant removal.[25] Lastly, one single-arm study (n=5, 6 fractures) reported screw breakage 1 day postoperatively due to patient fall.[26]

Responses in 3 remaining studies included postoperative unilateral femoral vein thrombosis from a biodegradable Mg screw,[28] femoral head collapse from a screw with high-purity (HP) Mg in 2 (8.7%) patients,[22] and no local response from placement of Mg alloys for 28 hand and wrist fractures.[27]

Pins: Of 67 MAGNEZIX pins (Syntellix AG) implanted in 19 individuals, a broken pin migrated into the knee joint in 1 patient 11 weeks postoperatively and required revision surgery. Radiolucent areas observed around the pins in all patients at 6 weeks decreased by 6 months, and were no longer detectable at 12 months.[29]

Systemic responses (human studies)

One human study investigated, but did not identify, systemic responses to orthopedic fixation devices.

Local host responses (animal studies)

The 18 animal studies examined screws in 5 studies,[30-32,41,42] pins in 10 studies,[33-38,43-45,47] and plugs, nails, and plates in 1 study each.[39,40,46]

Screws: Of the 5 studies examining screws, 3 studies examined HP Mg.[31,41,42] One study reported HP Mg corrosion was higher when the femoral diaphysis was co-implanted with Ti screws vs. co-implantation with another Mg screw.[41] A second study reported that soft-tissue swelling around the knee at 3 weeks had vanished by 6 weeks.[42] A 3rd study reported a reduction of HP Mg screws of approximately 24.6% in weight within the first 4 weeks, with 39.2% in weight remaining after 24 weeks.[31]

Two RCTs compared Mg alloy screws with Ti alloy screws[30] or surgical steel screws.[32] Gas liberation was most prominent 4 weeks post-anterior cruciate ligament reconstruction with significant decreases by 24 weeks in 1 RCT. A focal infiltration of macrophages and granulocytes in the tendon tissue was noted in 1 section with a Mg alloy and in 2 sections with a Ti alloy.[30] Tibia implants in another RCT resulted in moderate inflammation from both Mg alloy and surgical steel screws.[32]

Pins: Ten studies examined pins composed of Mg alloys,[33-38,43-45,47] with 5 studies comparing Mg alloys with Ti alloys or poly-L-lactic acid.[35,36,38,43,44]

Responses from Mg alloy screws included degradation of a Mg10Gd alloy at 4 weeks with pins integrated into small pieces by 12 weeks.[47] One RCT reported degradation at 6 weeks with a degradation rate of Mg alloy of 0.91 mm per year (range 0.77 to 1.22 mm) vs. pure Mg rate of 1.80 mm per year (range 1.43 to 2.26 mm) when placed in distal femurs.[33] A second RCT reported HP Mg and Mg-1Ca and Mg-2Zn alloys caused a slight inflammatory response in the initial 3 days, with lymphocytes rarely observed.[34]

A 3rd RCT questioned the biocompatibility of Mg alloys with (ZEK100) and without (AX30) rare earth elements after degradation induced an unfavorable osteoclastogenic resorption of bone and a rushed reactive formation of new bone periosteally.[37] One nonrandomized comparative study reported good biocompatibility of 2 different Mg-Zn alloys with gas evolution being unproblematic. ZX50 (5% Zn) pins started to corrode immediately after implantation and exhibited surface pits already within the first week and were associated with gas release. WZ21 pins (1% Zn, 2% Y) decreased only moderately during the initial months after implantation.[45] WZ42 alloy pins and Ti6A14V alloy pins were all broken by 2 weeks in one study, which may have been because of the movement stress of rats. Progressive pin degradation was observed at 8 and 14 weeks.[43]

Four different Mg alloys examined in 1 study indicated the highest inflammatory reaction in LANd442 (4% lithium, 4% aluminum, 2% neodymium) and ZEK100 (1% zinc, <1% rare earth, <1% zirconium) groups, in which significant necrotic changes in the peri-implant area were combined with intensive inflammation and periostitis as well as with a high amount of gas bubbles. LAE442 (4% lithium, 4% aluminum, 2% rare earth) showed the lowest rates of bone reaction and the lowest level of inflammation.[44] The remaining studies examining pins reported mild synovitis at week 1 from a MgYREZr alloy,[36] no local response from a MgYNdHRE alloy,[38] and less than 10% of the original volume of a Mg–1.0Ca–0.5Sr alloy at 6 weeks.[35]

Cylinders/Nails/Plates: Femur implants of HP Mg cylinders and Mg2%Ag alloy nails degraded "rapidly"[39] and "as early as 30 days"[46] in 2 studies, respectively. Corrosion of Mg–1.0Al plates was fastest in the head, followed by the back then the femur in a study examining 4 different placements of alloys. Area of the gas cavities was significantly decreased at all implantation sites from 2 to 4 weeks after implantation ($p < 0.05$), and was significantly larger in the head than in the back and femur at all time points ($p < 0.05$). Mild inflammation and foreign body reaction were also reported.[40]

Systemic responses (animal studies)

One animal study investigated, but did not identify, systemic responses to orthopedic fixation devices.

Overall quality of evidence

The evidence base was large, and the bulk of the studies had control groups. One study reported thrombosis and migration, but these outcomes rarely occurred (affecting only 1 patient in the studies that reported them), but in agreement with human studies reported in other devices (coronary scaffold/stent).We rated the quality of evidence is low. For other outcomes reported in very few studies, the quality of evidence is very low.

Other Orthopedic Implants

2 animal studies. (2 RCTs[48,49]).-For further information, see Table 7 in Appendix D.

Local host responses (human studies)

We did not include any human studies reporting local host responses to Mg-based orthopedic implants.

Systemic responses (human studies)

We did not include any human studies reporting systemic responses to Mg-based orthopedic implants.

Local host responses (animal studies)

One RCT compared an Mg alloy implant (LAE442) with two different pore sizes (pore size of 400 µm [p400], pore size of 500 µm [p500]). Resorbable β-tricalcium phosphate (β-TCP) was used as control. 40 total scaffolds were placed in the greater trochanter of the femur with tissue collected at 6, 12, 24, and 36 weeks. Both LAE442 scaffolds displayed increased gas formation through week 20 with subsequent decreases to a moderate amount in week 36. p400 and p500 showed volume decreases of 15.9% and 11.1%, respectively, while ß-TCP lost 74.6% of its initial volume by week 36.[48]

Another RCT compared 2 Mg alloys (LAE442, LANd442) with a non-resorbable Ti alloy. 28 total implants were placed in the medullary cavity of the tibia with tissue collected at 4 and 8 weeks. Redness, swelling and coarse peripheral augmentation were observed at most implant sites. Wound dehiscence (LAE442), mild subcutaneous emphysema (LAE442, LANd442), and low-grade lameness (LANd442) were reported in 1 to 4 rabbit legs. Gas bubbles were visible from 1 week to 8 weeks with both Mg alloys. At 4 weeks, degradation of materials was similar (median value of 0.0). At 8 weeks, degradation was higher with LANd442 vs. both LAE442 and Ti implants, which appeared almost unchanged.[49]

Systemic responses (animal studies)

None of the animal studies investigated whether there were systemic responses to Mg-based orthopedic implants.

Overall quality of evidence

The 2 animal studies, both with control groups, were inconsistent in reporting lameness and subcutaneous emphysema, and these findings are inconsistent with findings from other Mg devices (coronary scaffold/stent, orthopedic fixation) used in humans. Considering these factors, we rated the quality of evidence supporting local host response as very low.

Biliary Stent

1 animal study. (1 single-arm study[50]).-For further information, see Table 8 in Appendix D.

Local host responses (human studies)

No included human studies reported whether there were local host responses to Mg-based biliary stents.

Systemic responses (human studies)

No included human studies reported whether there were systemic responses to Mg-based biliary stents.

Local host responses (animal studies)

One single-arm study examined 15 biliary stents composed of the Mg alloy AZ31. Results indicated severe corrosion, damaged stent structure, with some parts of the stent peeling off by 3 months. Increased levels of white blood cells and serum Mg concentration were noted at 1 and 4 weeks, respectively. Histological evaluation of the bile duct at 1 month indicated papillary hyperplasia, fibrous hyperplasia, and infiltration by lymphocytes and eosinophils. At 6 months, papillary hyperplasia continued to be detected in the bile duct and was also detected in the gall bladder. Additional inflammatory responses included cholangiectasis in the liver (1 rabbit) at 3 months, calcified fragments in the gall bladder at 1 and 3 months, and mucosal chronic inflammation in the duodenum.

Systemic responses (animal studies)

We did not identify any studies reporting systemic responses to Mg-based biliary stents.

Overall quality of evidence

The evidence base consisted of 1 uncontrolled animal study. This study reported papillary hyperplasia, which was inconsistent with findings from other Mg devices (coronary scaffold/stent, orthopedic fixation) used in humans. We rated the quality of the evidence supporting local host response is very low.

Vascular Closure

Our literature searches did not identify any studies of these devices that met inclusion criteria.

ECRI Surveillance Data

As magnesium devices are not US FDA-cleared, there were no complications reported in our surveillance data. There was one international manufacturer Alert retrieved related to a mislabeling problem.

Patient Safety Organization

Search Criteria: Biotronic Magmaris, Syntellix Magnesix, Transluminal Technologies Velox, U&L Company Resomet, QualiMed Unity, Magnesium

Search Results: ECRI PSO identified 266 reports that occurred between 6/2005 and 5/2020 and contained the keyword "magnesium"; however, none of these involved complications with devices made from Mg.

Accident Investigations

Search Criteria: None. There were no Mg devices approved for use in the U.S.

Search Results: There were no investigations pertaining to the Mg device categories.

ECRI Problem Reports

Search Criteria: None. There were no Mg devices approved for use in the U.S.

Search Results: There were no problem reports pertaining to the Mg device categories.

Healthcare Technology Alerts

Search Criteria: Biotronic Magmaris, Syntellix Magnesix, Transluminal Technologies Velox, U&L Company Resomet, QualiMed Unity, Magnesium

Search Results: The search returned 1 manufacturer-issued alert describing a mislabeling problem, summarized in Table 7.

Table 3: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
Bone Screw	1 Manufacturer-issued (Syntellix)	Mislabeling product sizes

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of the material of interest. In this case there were no surveillance data as these devices are not US FDA-cleared. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

Magnesium as a material

There were only two animal studies and no human studies that reported on Mg as a material. While the quality of evidence was low, the reported complication with Mg-6Zn clips was substantial. Additional research is indicated if considering these clips or other devices made of the Mg-6Zn alloy in human studies.

Coronary Stent/Scaffold

There were 18 studies reporting local responses. Of the 16 human studies, a majority were single-arm design with limited reporting of outcomes. Additional RCTs are indicated to expand on the evidence base before conclusions can be made on the biocompatibility of these devices. There were no human studies on systemic responses to Mg coronary stents or scaffolds indicating a need for additional research in these areas.

Orthopedic Fixation Device (bone screw, pin, clip, nail, plate)

The evidence base was large, and the bulk of the studies had control groups. Complications in the animal and human studies for pins and screws were rare, but in agreement with the types of complications reported in other devices (coronary scaffold/stent). Longer-term RCT human studies are indicated. There were no human studies on cylinders/nails/plates. The animal studies for these reported only mild inflammation and foreign body reaction. Further research to include human studies is indicated.

Other Orthopedic Implants

There were only two animal studies included for orthopedic bone scaffolds. These studies were associated with very low quality of evidence given inconsistency in reporting lameness and subcutaneous emphysema. Also these findings are inconsistent with findings from studies of other Mg devices. Future research, including human studies, is indicated in these areas.

Biliary Stent

The one small animal study for magnesium biliary stents reported outcomes related to implantation of an AZ31 magnesium alloy stent. The complications were both local and systemic, indicating an area of needed research. Other alloys could be considered. There were no human studies for biliary stents, which clearly is indicated before widespread adoption of magnesium biliary stents.

Vascular Closure

There were no studies that met inclusion criteria for magnesium vascular closure devices, indicating an area of future research.

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

Inclusion Criteria

1. English language publication
2. Published between January 2010 and December 10, 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 Mg 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 represented 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** – how many systematic reviews and individual studies provide relevant data?
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – in human and animal studies, what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time) and the possible number of patients likely to have harms?
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)? Animal studies are indirect but may provide the best evidence for the material itself.
6. Is there evidence of a **dose response or time response** (e.g., adverse effects increase with longer exposure time)?

Appendix B. Search Summary

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

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

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

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

Literature Search for Magnesium

Material (Set Number 1-4)

Set Number	Concept	Search Statement
1	Magnesium	('magnesium'/exp OR 'magnesium derivative'/de OR 'magnesium ion'/de) AND (alloy* OR composite* OR metal* OR implant* OR biomaterial*) OR 'magnesium implant' OR ((magnesium OR mg* OR az91* OR az93* OR az31* OR 'zx00' OR 'mg-y' OR 'mg-re*' OR 'mg-zn*' OR 'mg sr*' OR 'mg–y*' OR 'mg-nd*' OR 'mg-al*' OR 'mg-mn*' OR 'mg–2ag*' OR 'zn-al-mg*' OR 'fe-mg*') NEAR/3 (alloy* OR composite* OR metal* OR implant* OR biomaterial* OR based OR uncoated OR coated OR material)) OR 'pure mg' OR 'pure magnesium' OR 'high-purity magnesium' OR 'hp mg' OR 'hf mg' OR 'mg ti' OR 'biomg' OR mg12zny* OR 'zek100'

Set Number	Concept	Search Statement
2	Bioresorbable Mg devices	magmaris OR 'mg-brs' OR 'bioabsorbable metallic stent' OR 'absorbable metal stent' OR 'biodegradable magnesium stent' OR 'absorbable metallic stent' OR (('biodegradable implant' OR 'bioresorbable scaffold' OR 'ams' OR 'ams-1' OR 'ams-2' OR 'dreams' OR biosolve* OR magstemi OR bestmag OR 'solve-acs' OR 'sherpa-magic') AND magnesium) OR magnezix OR mgyrezr OR 'japan medical device technology mg scaffold' OR jdbm* OR 'unity b' OR 'unity hybrid' OR 'velox cd' OR resomet OR 'kresomet' OR 'k-met'
3	Combine and Limit by language and publication date	(#1 OR #2) AND [english]/lim AND [2010-2020]/py
4	Limit by publication type	#3 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response (Set numbers 5-15).

Set Number	Concept	Search Statement
5		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
6		'degradation'/exp OR degrad* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorbable OR adsorbable 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* OR evaginat* OR subsidence
7		'corrosion'/exp OR corrosion OR biocorros* OR biocorrodible OR 'bio-corrosion' OR pitt* OR crack* OR galvanic*
8		Leachable* OR extractable*
9		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat*) NEAR/3 (implant* OR pin* OR plate* OR anchor* OR screw* OR mesh OR wire* OR microwire* OR scaffold* OR stent*)

Set Number	Concept	Search Statement
10		'gas evolution'/exp OR dissolution OR ((hydrogen OR 'h2' OR gas) NEAR/2 (pocket OR cavity OR cavities OR void* OR formation OR production OR releas* OR bubble* OR exposure OR concentration))
11		'mechanics'/exp
12		'device material'/exp/mj
13		'Biomedical and dental materials'/exp/mj
14	Combine sets	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15	**Mg + Material Response**	**#4 AND #14**

Host Response (Set numbers 16-26)

Set Number	Concept	Search Statement
16		Host NEAR/2 (reaction* OR response*)
17		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
18		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
19		Immun*:ti OR autoimmun*:ti OR hypersens*:ti
20		'inflammation'/exp OR inflamm*
21		'foreign body' OR granuloma* OR 'foreign body'/exp OR (fibro*NEAR/2 capsule*)
22		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'bone response'
23		(protrude* OR protrus*)
24		osteolysis' OR 'volume loss' OR 'bone regeneration'/exp
25		'thrombosis'/exp OR 'stenosis, occlusion and obstruction'/exp OR 'stent complication'/exp OR restenosis OR thromb*
26	Combine sets	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25

Combination Sets (27-29)

Set Number	Concept	Search Statement
27	Combine sets **Mg+ Material** **Response+ Host Response**	#15 AND #26
28	**Mg device + Host response**	(#2 AND #4) AND #26
29	**Final set**	**#27 OR #28**

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

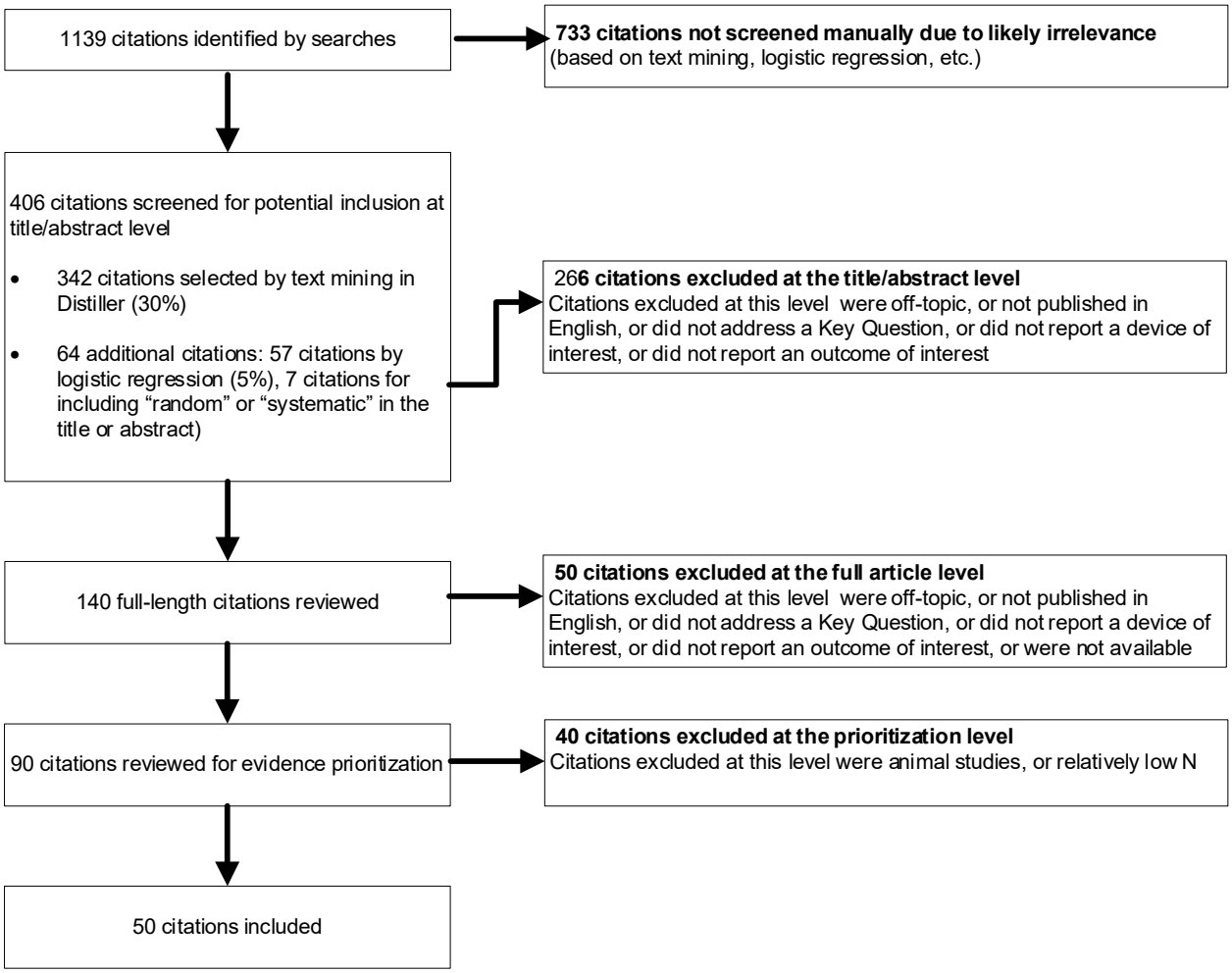
        - Gestational weight gain
      - Body weight loss
        - Emaciation
      - Body weight control
      - Fetus weight
      - Ideal body weight
      - Lean body weight
      - Live weight gain
    - Dry weight
    - Fresh weight
    - Molecular weight
    - Organ weight
      - Brain weight
      - 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



Appendix D. Evidence Tables

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

Local Response/Toxicity

Source citation: Ikeo et al. 2016[1]

Study Design: Nonrandomized comparative

Device or Material: 2 Mg alloy clips (Mg-Zn-Ca and Mg-6Zn)

Route: Subcutaneous

Dose: 4 mm diameter

Frequency/ Duration: Single administration. Tissue collected at 1, 2, 4, 8, and 12 weeks

Response: Fragmentation, Gas accumulation, Inflammation

Species (strain): Mice (C57BL).

Gender: Male.

Number per group: 3 each group/each time point (total 30).

Observed adverse effects: Massive swelling of extraperitoneal area due to gas accumulation up to 2 weeks with Mg-6Zn clips. At 2 weeks, the gas cavity had diminished, foreign body granulomas were observed, and clips were fragmented and scattered on the extraperitoneal tissue. No swelling or fragments around Mg-Zn-Ca clips, which became thinner but held their 'U' shape after 12 weeks implant.

Timing of adverse effects: 1 to 12 weeks.

Factors that predict response: NR.

Source citation: Yan et al. 2014[2]

Study Design: RCT

Device or Material: Mg alloy Mg-6Zn (6 wt% Zn), School of Materials Science and Engineering at Shanghai Jiao Tong University); vs. Ti alloy Ti-3Al-2.5V (Ethicon pins) vs. negative control

Route: Abdomen

Dose: Pins sized 5 x 1 x 1 mm, Mg and Ti both HP

Frequency/ Duration: Single administration Tissue collected at 1, 2, and 3 weeks

Response: Corrosion/degradation, TNF- α expression, Inflammation

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

Gender: Male.

Number per group: 18 (54 total).

Observed adverse effects: Mg-6Zn implants started to degrade at 1 week with no gas bubbles observed around the implants (may be too small to observe). No dynamic inflammatory cell infiltration was observed in the cecum at the implant region. The Mg–6Zn alloy reduced the expression of the tumor necrosis factor (TNF-*α*) at different stages and decreased inflammatory response which may have been related to the zinc inhibiting TNF-*α*."

Timing of adverse effects: 1 week to 3 weeks.

Factors that predict response: NR.

Al: aluminum; HP: high purity; NR: not reported; RCT: randomized controlled trial; TNF-α: tumor necrosis factor alpha; V: vanadium; wt%: percentage by weight; Zn: zinc

Source citation: Abellas-Sequeiros et al. 2020[6]

Study Design: Single arm (CardioHULA registry)

Device or Material: Bioresorbable scaffold Magmaris (BIOTRONIK AG)

Contact Duration: 1 year

Dose: NR

Frequency/ Duration: 88% single administration, 12% double administration

Response: In-stent restenosis

Patient characteristics (gender, mean age): 86% male, 58 years.

Number per group: 42 (19 effort angina, 22 NSTEMI, 1 STEMI).

Observed adverse effects: In-stent restenosis in 2 patients. No cardiac death, MI, or stent thrombosis was reported.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source citation: Haude et al. 2020[7]

Study Design: Single arm (BIOSOLVE II)

Device or Material: Bioresorbable scaffold Magmaris (BIOTRONIK AG)

Contact Duration: 3 years

Dose: Thickness and width of 150 µm

Frequency/ Duration: Single administration

Response: Increased diameter stenosis, LLL, Malapposed struts

Patient characteristics (gender, mean age): 60% male, 66 years.

Number per group: 117 with de novo coronary lesions.

Observed adverse effects: No definite or probable scaffold thrombosis. Optical coherence tomography assessment of 201 struts indicated malapposed struts in 1.93% post-procedure. Between 1 and 3 years, slight increases in LLL and diameter stenosis were reported (n=25).

Timing of adverse effects: N/A.

Factors that predict response: NR.

Source citation: Hideo-Kajita et al. 2020[4]

Study Design: Pooled data analysis (Biosolve II-III and Bioflow II)

Device or Material: Magmaris vs. SES stent (Orsiro, BIOTRONIK Ag)

Contact Duration: 1 year

Dose: 150 µm Magmaris, 60 to 80 µm Orsiro

Frequency/ Duration: Single administration

Response: Cardiac death, Death, MI, Target vessel MI

Patient characteristics (gender, mean age): 63% male, 65 years.

Number per group: 482 (184 Magmaris with 12.5% unstable angina, 298 Orsiro with 19.5% unstable angina).

Observed adverse effects: No significant differences between Magmaris and Orsiro for cardiac death (p=0.640), target vessel MI (p=0.783), death (p=0.387), or MI (p=0.459). No definite or probable stent thrombosis in any patients.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source citation: Salinas et al. 2020[15]

Study Design: Single arm

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 1 year

Dose: NR

Frequency/ Duration: Single administration

Response: In-scaffold tissue prolapse, LLL, Thrombus

Patient characteristics (gender, mean age): 12.5% female, 58.5 years.

Number per group: 8 (2 STEMI, 2 NSTEMI, 2 unstable angina, 2 stable angina).

Observed adverse effects: Intracoronary imaging (n=6) detected thrombus in 1 (16.6%) patient and in-scaffold tissue prolapse in 2 (33.33%) patients. CCTA indicated mild in-scaffold LLL and underlying plaque growth. Necrotic plaque was observed in 4.78% of analyzed plaque.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source citation: Tovar Forero et al. 2020[16]

Study Design: Single arm

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 4 to 12 months

Dose: NR

Frequency/ Duration: Single administration

Response: Acute recoil, Binary restenosis, Incomplete strut apposition, Premature scaffold degradation, Significant reductions in MLA and scaffold area at MLA site

Patient characteristics (gender, mean age): 50% male, 57.2 years.

Number per group: 6 with stable angina and noncomplex single-vessel coronary artery disease.

Observed adverse effects: Fast and heterogenous scaffold degradation resulted in a significant reduction in both MLA (43.44±28.62) and scaffold area at the MLA site (38.20±25.74%). Binary restenosis rate was 33.3%. Acute recoil was 5.34±3.99%. Incomplete strut apposition was 3.16±4.22%.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source citation: Ueki et al. 2020[8]

Study Design: Single arm (Biosolve II)

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 1 year

Dose: 150 µm

Frequency/ Duration: Single administration

Response: NIH, Stent recoil

Patient characteristics (gender, mean age): 63% male, 65 years.

Number per group: 70 (11% with unstable angina).

Observed adverse effects: Optical adherence tomography indicated in-scaffold LLL ≥0.5 mm was due to scaffold recoil (82.8%), NIH (3.4%) and mixed origin (13.8%). Late scaffold recoil was highest among fibrotic lesions.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source citation: Verheye et al. 2020[9]

Study Design: Single arm (Biosolve-IV Registry)

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 1 year

Dose: Width of 150 µm

Frequency/ Duration: Single administration

Response: Thrombosis

Patient characteristics (gender, mean age): 75% male, 61 years.

Number per group: 1,075 (1,121 lesions) with NSTEMI.

Observed adverse effects: Definite/probable scaffold thrombosis occurred in 5 patients (0.5%, 95% CI: 0.2 to 1.1); early discontinuation of antiplatelet/anticoagulation therapy in 4 patients.

Timing of adverse effects: Postoperative days 6, 10, 28, 46, and 95.

Factors that predict response: NR.

Source citation: Blachutzik et al. 2019[17]

Study Design: Single arm

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 6 months

Dose: NR

Frequency/ Duration: Single administration

Response: High-grade restenosis, Distal edge dissection

Patient characteristics (gender, mean age): 71% male, 66 years.

Number per group: 35 (40 implants). 30 patients with stable angina, 5 with NSTEMI.

Observed adverse effects: High-grade restenosis in the vessel segment and distal edge dissections occurred in 2 patients each.

Timing of adverse effects: Restenosis: 3 and 4 months postimplantation. Dissection: before and after balloon post-dilatation.

Factors that predict response: NR.

Source citation: Ielasi et al. 2019[10]

Study Design: Single arm (MAGIC registry)

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 9 months

Dose: Thickness and width of 150 µm

Frequency/ Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): Gender NR, 58 years

Number per group: 69 (24 STEMI, 45 NSTEMI).

Observed adverse effects: No cardiac death, target-vessel MI, or stent thrombosis reported.

Timing of adverse effects: N/A.

Factors that predict response: N/A.

Source citation: Sabate et al. 2019[3]

Study Design: RCT (MAGSTEMI trial)

Device or Material: Magmaris scaffold vs. SES stent (Orsiro, BIOTRONIK Ag)

Contact Duration: 1 year

Dose: 150 µm Magmaris, 60 to 80 µm Orsiro

Frequency/ Duration: Single administration

Response: Binary restenosis, LLL, MI-related with device thrombosis, Thrombosis

Patient characteristics (gender, mean age): 89% male, 58.8 MgBRS, 59.2 years SES.

Number per group: 150 with ST-segment-elevation myocardial infarction (74 MgBRS, 76 SES).

Observed adverse effects: Binary restenosis and LLL were significantly higher with MgBRS. Definite or probable device thrombosis occurred in 3 patients (1 MgBRS, 2 SES). MI-related with device thrombosis was slightly higher with SES (2.6% vs. 1.4%).

Timing of adverse effects: Thrombosis occurred 20 minutes after implantation with MgBRS.

Factors that predict response: NR

Source citation: Wlodarczak et al. 2019[11]

Study Design: Single arm (Magmaris-ACS Registry)

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 6 months

Dose: 150 µm thick, 150 µm wide

Frequency/ Duration: Single administration

Response: Occlusion, Recurrent ischemia

Patient characteristics (gender, mean age): 86% male, 63 years.

Number per group: 50 with ACS

Observed adverse effects: 2 cases (3.9%) of interim small side branch occlusion after implantation. Recurrent ischemia in 1 patient due to significant distal edge dissection to a previously implanted scaffold.

Timing of adverse effects: Perioperative occlusion. Ischemia 1 day postoperative.

Factors that predict response: NR.

Source citation: de Hemptinne et al. 2018[18]

Study Design: Single arm

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: Median 153 days (range 59 to 326)

Dose: NR

Frequency/ Duration: Single administration (15 patients), double administration (3 patients)

Response: Early restenosis, Edge dissection

Patient characteristics (gender, mean age): 78% male, 48.5 years.

Number per group: 18 with STEMI (17 for clinical follow-up).

Observed adverse effects: Edge dissection and early restenosis occurred in 1 patient.

Timing of adverse effects: Edge dissection was a procedural complication. Restenosis occurred at 102 days postimplantation.

Factors that predict response: NR.

Source citation: Haude et al. 2017[5]

Study Design: Pooled data analysis (BIOSOLVE II and BIOSOLVE III)

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 6 months (BIOSOLVE III), 24 months (BIOSOLVE II)

Dose: 150 μm thick, 150 μm wide

Frequency/ Duration: Single administration

Response: NIH, Incomplete strut apposition

Patient characteristics (gender, mean age): 64% male, 65 years.

Number per group: 184 (123 BIOSOLVE II, 61 BIOSOLVE III); unstable and documented silent ischemia in 12.5%.

Observed adverse effects: Incomplete strut apposition postprocedure and significant NIH observed in 1 patient.

Timing of adverse effects: NIH at 84 days

Factors that predict response: NR

Source citation: Haude et al. 2016[12]

Study Design: Single arm (BIOSOLVE II)

Device or Material: Magmaris (BIOTRONIK AG)

Contact Duration: 1 year

Dose: NR

Frequency/ Duration: Single administration

Response: Cardiac death and possible scaffold thrombosis

Patient characteristics (gender, mean age): 78% male, 65 years.

Number per group: 123 with de novo coronary lesions (13.8% unstable angina, 14.6% silent ischemia).

Observed adverse effects: 1 patient died of unknown cause, which was classified as cardiac death and possible scaffold thrombosis. No increase in LLL between 6 and 12 months (n=42).

Timing of adverse effects: 1 death at postoperative day 134.

Factors that predict response: NR.

Source citation: Haude et al. 2016[13]

Study Design: Single arm (BIOSOLVE I)

Device or Material: DREAMS (1st generation Magmaris, BIOTRONIK AG)

Contact Duration: 3 years

Dose: Nominal drug content 0.07 μg/mm2, maximum dose 8.5 μg

Frequency/ Duration: Single administration in all patients but 1 who required a second scaffold

Response: LLL

Patient characteristics (gender, mean age): 74% male, 65 years.

Number per group: 44 with de novo coronary lesions.

Observed adverse effects: No cardiac death or scaffold thrombosis. Higher LLL at 12 months vs. 36 months (in-scaffold: 0.51±0.46 mm vs. 0.32±0.32 mm; in-segment: 0.28±0.34 vs. 0.11±0.18).

Timing of adverse effects: N/A.

Factors that predict response: NR.

Source citation: Haude et al. 2013[14]

Study Design: Single arm (Bio BIOSOLVE I)

Device or Material: DREAMS (1st generation Magmaris, BIOTRONIK AG)

Contact Duration: 1 year

Dose: Nominal drug content 0.07 µg/mm2, maximum dose 8.5 µg

Frequency/ Duration: Single administration in all patients but 1 who required a second scaffold

Response: Incomplete strut apposition, MI, NIH, Persistent incomplete apposition

Patient characteristics (gender, mean age): 74% male, 65 years.

Number per group: 46 with de novo coronary lesions.

Observed adverse effects: No cardiac death or scaffold thrombosis. Significant differences in NIH area 12 months vs. postprocedure (MD 0.40 (95% CI: 0.25 to 0.54; p<0.0001) and 6 months vs. postprocedure (MD 0.30, 95% CI: 0.12 to 0.49; p=0.0029). One periprocedural target vessel MI. Evaluation of 5,791 struts in 7 patients indicated incompletely apposed struts in 4.1% postprocedure. At 6 months, persistent incomplete apposition occurred in 0.6% of struts, and 2.2% had late acquired incomplete strut apposition. At 12 months, 0.1% with persistent incomplete strut apposition, and 0.1% late acquired incomplete strut apposition.

Timing of adverse effects: Follow-up at 6 and 12 months.

Factors that predict response: NR

ACS: acute coronary syndrome; CCTA: cardiac computed tomography angiography; CI: confidence interval; LLL: late lumen loss; MAGIC: MAGnesIum alloy scaffold for Coronary artery disease; Mg: magnesium; MgBRS: Mg-based bioresorbable scaffold; MI: myocardial infarction; MLA: minimal lumen area; NIH: neointimal hyperplasia; NR: not reported; NSTEMI: non-ST elevation myocardial infarction; RCT: randomized controlled trial; SES: sirolimus-eluting stent; STEMI: ST elevation myocardial infarction; µg: microgram; µg/mm^2: microgram per square millimeter

Table 5: Mg Coronary Scaffold/Stent - Health Effects (In Vivo) Animal Studies

Source citation: Li et al. 201919

Study Design: RCT

Device or Material: BMAS vs. 316L stainless steel (SS) stents vs. Control (Institute of Metal Research, Chinese Academy of Sciences)

Route: Abdominal aorta

Dose: Stent specifications: 3 mm diameter and 15 mm length, stent strut diameter of 155+65mm

Frequency/ Duration: Single administration

Response: Degradation

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

Gender: NR

Number per group: 24 undergoing vein graft (VG) transplantation and stent implantation.

Observed adverse effects: No systemic toxicity, VG occlusion, stent migration or thrombosis was observed up to 4 months. Atherosclerotic plaque formation was observed between the stent and vein in 3 animals with SS. BMAS structure was incomplete within 2 to 3 months with complete degradation by 4 months. H&E staining showed irregular cracks in the stent wires, and a tendency to degrade from the circumference to the center.

Timing of adverse effects: 2 to 4 months.

Factors that predict response: NR.

Source citation: Ye et al. 2015[20]

Study Design: RCT

Device or Material: BMAS (99% Mg-Al-Zn alloy) vs. control

Route: Coronary or femoral artery

Dose: 100 to 150 µm; stent dimensions: 2 to 4 mm inner diameter, 0.08 to 0.12 mm wall thickness, 9 to 38 mm length

Frequency/ Duration: Single administration

Response: Degradation, neointimal hyperlasia

Species (strain): Dogs (hybrid).

Gender: NR

Number per group: 5 control, 5 each treated at 7 time points.

Observed adverse effects: Mild neointimal hyperplasia 2 to 4 weeks postimplantation, but no significant inflammatory cell infiltration vs. untreated dogs up to 28 days. Degradation complete by 1 week. No recoil or early thrombosis.

Timing of adverse effects: 2 to 4 weeks.

Factors that predict response: NR.

Al: aluminum; BMAS: biodegradable magnesium alloy stents; H&E: hematoxylin and eosin; Mg: magnesium; mm: millimeter; NR: not reported; RCT: randomized controlled trial; µm: micrometer; Zn: zinc

Table 5: Mg Orthopedic Fixation - Health Effect (In Vivo) Human Studies

Source citation: Jungesblut et al. 2020[29]

Study Design: Single arm

Device Material: Mg-based pins (MAGNEZIX, Syntellix AG)

Contact Duration: Mean months: 11.3±4.2

Dose: 1.5 mm (n=25) and 2.0 mm (n=42); length ranged from 14 to 28 mm

Frequency/ Duration: Single administration

Response: Broken pin, Implant failure, Migration, Radiolucent area around pins

Patient characteristics (gender, mean age): 52% female, 13.7 years.

Number per group: 19 with unstable osteochondritis dissecans lesions and displaced osteochondral fragments (67 pins).

Observed adverse effects: Broken pin with migration into the knee joint requiring revision surgery in 1 patient. Radiolucent area around the pins in all patients at 6 weeks, decreased size at 6 months, and no longer detectable at 12 months postoperatively.

Timing of adverse effects: Pain and implant failure at 11 weeks postoperatively.

Factors that predict response: NR.

Source citation: Leonhardt et al. 2020[25]

Study Design: Single arm

Device Material: MAGNEZIX compression screw (CS) (Syntellix AG)

Contact Duration: 1 year

Dose: 2.7 mm

Frequency/ Duration: Single administration

Response: Penetration of screw tip through the condylar surface, Tenderness

Patient characteristics (gender, mean age): 66% male, 43.2 years.

Number per group: 6 with mandibular condyle fractures.

Observed adverse effects: Penetration of 1 screw tip through the condylar surface that did not result in implant removal due to degradation by 12 months. 2 patients had tenderness on palpation at operation site and joint.

Timing of adverse effects: Tenderness up to 3 months postoperatively. Penetration of screw tip at 6 months.

Factors that predict response: NR.

Source citation: May et al. 2020[24]

Study Design: Nonrandomized comparative

Device Material: MAGNEZIX CS 3.2 mm (Syntellix AG) vs. Ti compression screw 4.0 mm or 4.5 mm partial thread cannulated screws (manufacturer NR)

Contact Duration: Mean months: 24.6±10.5 (range 12 to 53)

Dose: 3.2 mm Mg, 4.0 mm or 4.5 mm Ti

Frequency/ Duration: Single administration

Response: Degradation

Patient characteristics (gender, mean age): Mg: 69% male, 37.9 years. Ti: 56% male, 45 years.

Number per group: 23 Mg, 25 Ti with medial malleolar fractures.

Observed adverse effects: Significantly higher implant removal rate with Ti (0 Mg, 5 Ti, p=0.031; 3 due to pain, 2 due to difficulty in wearing shoes). Degradation of screws was completed by end of year 1 based on lack of gas shadows on CT/MRI.

Timing of adverse effects: Implant removal occurred from 12 to 19 months (mean 14.2±3.1 months).

Factors that predict response: NR.

Source citation: Plaass et al. 2018[21] -- Follow up of Windhagen 2013[23]

Study Design: RCT

Device Material: MAGNEZIX CS 3.2 mm (Syntellix AG) vs. Ti compression screw 3.5 (Konigsee Implantate GmbH)

Contact Duration: Mean 3.1 years

Dose: Both Herbert screws; average grain size of Mg screw: 5 µm

Frequency/ Duration: Single administration

Response: Artifacts in MRI, Edema, Persistent hallux valgus, Radiologic metallic debris, Soft-tissue reaction

Patient characteristics (gender, mean age): 100% female. 56 years Mg, 52 years Ti.

Number per group: 8 Mg, 6 Ti undergoing distal metatarsal osteotomies for symptomatic hallux valgus and full clinical/MRI follow-up at 3 years.

Observed adverse effects: Radiologic metallic debris and corresponding artifacts in MRI in 3 patients with Mg screws; fewer artifacts vs. Ti. No significant differences for pooled median scores for edema (1.0 Mg, 1.5 Ti) and soft-tissue reaction (1.0 each). No patients reported residual pain with Mg screw. Persistent hallux valgus (without pain) was reported in 1 patient with Mg screw. No reoperations were reported with Mg.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source citation: Leonhardt et al. 2017[26]

Study Design: Single arm

Device Material: MAGNEZIX CS 2.7 mm (Syntellix Ag)

Contact Duration: 3 months

Dose: 2.7 mm

Frequency/ Duration: Single administration

Response: Screw breakage

Patient characteristics (gender, mean age): NR

Number per group: 5 with 6 displaced fractures of the condylar head.

Observed adverse effects: Screw breakage in 1 patient after falling on chin; replaced with similar screw. No facial nerve palsy or swelling associated with hydrogen gas or any other complications from Mg degradation.

Timing of adverse effects: Fracture 1 day postoperatively.

Factors that predict response: NR.

Source citation: Lee et al. 2016[27]

Study Design: Single arm

Device Material: Biodegradable Mg-5wt%Ca-1wt%Zn alloy screws

Contact Duration: 1 year

Dose: NR

Frequency/ Duration: Single administration

Response: None reported.

Patient characteristics (gender, mean age): 22 male, 6 female; 20 years or older with hand and wrist fractures.

Number per group: 28 patients at 12 months.

Observed adverse effects: No adverse events reported. By 12 months after implantation, patients involved in 53 cases (53 separate screws) all returned to their everyday life and career without any sign of pain; pain VAS was ~1.38 ± 1.1.

Timing of adverse effects: N/A

Factors that predict response: NR.

Source citation: Zhao et al. 2016[22]

Study Design: RCT

Device Material: Mg-based screws (Mg with a purity of 99.99 wt% jointly designed with Dongguan Eontec Co., Ltd., China) vs. No fixation

Contact Duration: 12 months

Dose: Screw shaft was 4 mm in diameter and 40 mm in length.

Frequency/ Duration: Single administration

Response: Femoral head collapse

Patient characteristics (gender, mean age): 48 patients (29 male and 19 female) aged 30 years to 48 years with osteonecrosis of the femoral head (ONFH).

Number per group: 24 patients per group.

Observed adverse effects: Femoral head collapse: 2 patients (8.7%) in Mg group, 6 cases (24%) in control group.

Timing of adverse effects: NR.

Factors that predict response: "With degradation of Mg screw over time, no potential adverse effects were observed that could be caused by degradation products from screws on surrounding bone tissue around implants by x-ray or CT images, indicating high biocompatibility for the use of such novel Mg fixators in ONFH indications.".

Source citation: Yu et al. 2015[28]

Study Design: Single arm

Device Material: Biodegradable Mg screws (brand NR)

Contact Duration: 14 months

Dose: Pure magnesium and had a 4 mm diameter cancellous bone screw thread in distal

Frequency/ Duration: Single administration

Response: Thrombosis

Patient characteristics (gender, mean age): 58% male, 35.5 years.

Number per group: 19 with displaced femoral neck fracture.

Observed adverse effects: Unilateral femoral vein thrombosis postoperatively. No avascular necrosis of femoral head.

Timing of adverse effects: NR.

Factors that predict response: NR

Source citation: Windhagen et al. 2013[23]

Study Design: RCT

Device Material: MAGNEZIX CS 3.2 mm (Syntellix AG) vs. Ti CS 3.5 mm (Königsee Implantate GmbH)

Contact Duration: 6 months

Dose: Both Herbert screws; average grain size of Mg screw: 5 µm

Frequency/ Duration: Single administration

Response: Superficial wound-healing problems

Patient characteristics (gender, mean age): 92% female, 57 years Mg, 50 years Ti.

Number per group: 13 each (symptomatic hallux valgus).

Observed adverse effects: No foreign body reactions, osteolysis, or systemic inflammatory reactions were observed. Superficial wound-healing problems occurred in 3 patients (2 Mg, 1 Ti) and resulted in delayed wound healing. No significant differences in pain (VAS), or radiographic results. No signs of avascular necrosis or bone erosion due to development of gas cavities.

Timing of adverse effects: NR.

Factors that predict response: NR

CT: computed tomography; Mg: magnesium; mm: millimeter; MRI: magnetic resonance imaging; NR: not reported; RCT: randomized controlled trial; Ti: titanium; VAS: visual analog scale; wt%: percentage by weight; µm: micrometer;

Table 6: Mg Orthopedic Fixation - Health Effects (In Vivo) Animal Studies

Source citation: Bao et al. 2019[34]

Study Design: RCT

Device or Material: HP Mg, Mg-1Ca and Mg-2Zn

Route: Implanted in the gluteal muscle

Dose: Pin: 2 mm diameter and 2 mm thickness

Frequency/ Duration: Single administration Muscle tissue collected at 3, 10, and 28 days after implantation

Response: Inflammation

Species (strain): Sprague Dawley rats

Gender: female

Number per group: 9 rats each in 4 groups.

Observed adverse effects: Acute inflammatory reaction decreased over time as connective tissue increased.

Timing of adverse effects: over 28 days.

Factors that predict response: In vivo experiment showed that HP-Mg, Mg-1Ca alloy, and Mg-2Zn alloy implants caused a slight inflammatory response in the initial 3 days, but they were surrounded mainly by connective tissue, and lymphocytes were rarely observed at 4 weeks.

Source citation: Chou et al. 2019[43]

Study Design: Non-randomized comparative

Device or Material: WZ42 alloy pin nominal composition of Mg-4.0%Y-2.0%Zn-1.0%Zr- 0.6%Ca in wt. % vs. non-degradable Ti6Al4V

Route: Intramedullary implant in right femur after osteotomy

Dose: 15 mm length, 1.66 mm diameter

Frequency/ Duration: Single administration Bone tissue collected at 2, 8, and 14 weeks.

Response: Blood counts and serum biochemistry, Corrosion/degradation of Mg pins, Serum Mg

Species (strain): Sprague-Dawley rats.

Gender: female

Number per group: 5 rats per time period for each study group.

Observed adverse effects: Blood cell counts and serum biochemistry were normal, serum Mg were at low end of reference levels, all pins had broken by 2 weeks, progressive pin degradation continued at 8 and 14 weeks.

Timing of adverse effects: Rats were not immobilized after surgery and movement stress probably contributed to corrosion and pin breakage.

Factors that predict response:

Source citation: Liu et al. 2019[39]

Study Design: RCT

Device or Material: Mg-30 wt% scandium (Sc) alloy vs. high pure (HP)-Mg control

Route: Holes drilled in both femurs for inserting plugs

Dose: Cylinders with a dimension of 1.0 mm and 6.5 mm.

Frequency/ Duration: Single administration Tissue collected 4, 12, and 24 weeks.

Response: Corrosion/Degradation

Species (strain): Sprague-Dawley rats.

Gender: male

Number per group: 6 rats per group totaling 36.

Observed adverse effects: HP-Mg cylinders degraded rapidly.

Timing of adverse effects: by 4 weeks

Factors that predict response: Mg-30 wt%Sc alloy had less degradation than HP Mg.

Source citation: Yu et al. 2018[33]

Study Design: RCT

Device or Material: Biodegradable Mg-argentum (Ag)-yttrium (Y) alloy vs. pure MG and stainless steel

Route: Holes drilled in distal femurs for implants

Dose: Pin size not described

Frequency/ Duration: Single administration, Tissue collected at 6 weeks.

Response: Corrosion/Degradation

Species (strain): Sprague-Dawley rats.

Gender: NR

Number per group: 36 total

Observed adverse effects: Degradation rate of alloy was 0.91 mm per year, (range 0.77– 1.22 mm), and pure-Mg 1.80 mm per year (range 1.43–2.26 mm). Bone formation was greater in Mg group.

Timing of adverse effects: 6 weeks.

Factors that predict response: Corrosion rate of Mg-Ag-Y alloy was significantly lower than pure-Mg, due to the addition of Y element.

Source citation: Hou et al. 2017[41]

Study Design: Nonrandomized comparative

Device or Material: HP Mg and Ti screws

Route: Implanted in femoral diaphysis

Dose: Outer diameter 2.0 mm, inner diameter 1.6 mm, screw pitch 0.6 mm and length 10.0 mm

Frequency/ Duration: Single administration Tissue collected at 2, 4, and 8 weeks.

Response: Corrosion/Degradation

Species (strain): Sprague-Dawley rats.

Gender: male

Number per group: 72 total, 6 rats per group and time period; 4 intervention groups and 3 time periods.

Observed adverse effects: HP Mg corrosion was higher when co-implanted with Ti screws vs. co-implanted with another Mg screw.

Timing of adverse effects: up to 12 weeks.

Factors that predict response: The electrically conductive blood vessels connected Mg and Ti screws, together with body fluid, formed a galvanic-like cell that accelerated corrosion.

Source citation: Myrissa et al. 2017[47]

Study Design: Single arm

Device or Material: Mg10Gadolinium (Gd) pins

Route: Transcortically in the femoral bones

Dose: 2 pins: 1.6 mm diameter and 8 mm length

Frequency/ Duration: Single administration, Tissue collected at 4, 12, 24 and 36 weeks.

Response: Corrosion/Degradation

Species (strain): Sprague-Dawley rats.

Gender: male

Number per group: 48 total, 24 implant, 24 sham.

Observed adverse effects: Mg10Gd alloy pin volume loss was significantly increased at 4 weeks. Pins disintegrated into small pieces by 12 weeks. Mg did not accumulate in organs or serum at any time point.

Timing of adverse effects: Degradation apparent by 4 weeks.

Factors that predict response: NR

Source citation: Berglund et al. 2016[35]

Study Design: RCT

Device or Material: Mg–1.0 wt% Ca–0.5 wt% Sr alloy pins vs. PLLA vs. healthy controls

Route: Implanted in tibia

Dose: Pin: 0.8 mm diameter

Frequency/ Duration: Single administration Tissue collected at 3 and 6 weeks.

Response: Corrosion/Degradation, Gas generation

Species (strain): Sprague-Dawley rats.

Gender: male

Number per group: 24 total, divided into 5 groups of 4 to 6 rats (Mg at 1 week, 3 weeks, and 6 weeks; PLLA, and controls).

Observed adverse effects: Almost completely degraded at 6 weeks with less than 10% of the original volume present. Replaced by bone during degradation. Gas resulting from the degradation process of the alloys, as represented by voids, and the associated tissue response were seen at 1 week and 3 weeks but not by 6 weeks. No evidence of bone fracture due to gas. Mild inflammatory response was noted.

Timing of adverse effects: 1 to 3 weeks

Factors that predict response: NR

Source citation: Cheng et al. 2016[42]

Study Design: Nonrandomized comparative

Device or Material: HP Mg screw compared to Ti

Route: Reconstruction of anterior cruciate ligament (ACL)

Dose: Length 12 mm, shaft outer diameter 2.7 mm and shaft inner diameter 2.1 mm

Frequency/ Duration: Single administration Femur-tendon graft-tibia complex retrieved at 3, 6, 9 and 12 weeks.

Response: Local inflammatory response, Tissue regrowth

Species (strain): New Zealand white rabbits.

Gender: male

Number per group: 60 total (n per group NR).

Observed adverse effects: No sign of host reaction in X-ray scanning. Soft-tissue swelling around the knee was found with Mg at 3 weeks. At 6 weeks, the swelling vanished. HP Mg screws demonstrated good biocompatibility, with no signs of osteolysis, deformity or dislocation. Tendon bone healing was relatively better in the HP Mg group than in the Ti group ($P < 0.01$).

Timing of adverse effects: 3 to 6 weeks

Factors that predict response: Stimulation of bone morphogenic protein-2 and vascular endothelial growth factor by Mg ions was responsible for the fibrochondrogenesis of Mg materials.

Source citation: Diekmann et al. 2016[30]

Study Design: RCT

Device or Material: Mg alloy MgYREZr compared to Ti alloy screw

Route: Reconstruction of ACL

Dose: Screw: length 10 mm and an external diameter 2.6 mm with a thread pitch of 0.8 mm.

Frequency/ Duration: Single administration Tissue collected 4, 12, and 24 weeks.

Response: Corrosion/Degradation, Gas generation, Inflammation

Species (strain): New Zealand white rabbit.

Gender: female

Number per group: 18 each in 2 groups, 6 for each time period.

Observed adverse effects: Gas liberation was most prominent 4 weeks after implantation and was significantly decreased by 24 weeks. No inflammation was noted. "The pathological evaluations of these two groups demonstrated that there was no evidence of inflammatory reactions, fibrosis, or necrosis. There was only a focal infiltration of macrophages and granulocytes in the tendon tissue in one section of the magnesium group and two sections of the titanium group." "The general degradation rate of the implanted magnesium alloy was 0.17 mm a^{-1} based on the values of the 24-week group."

Timing of adverse effects: 4 to 24 weeks

Factors that predict response: NR

Source citation: Jahn et al. 2016[46]

Study Design: Non-randomized comparative

Device or Material: Intramedullary Mg2%Ag alloy nails compared with steel implant or no implant

Route: Implanted Mg2Ag nails into the non-fractured femur and fractured femur

Dose: 0.8 mm diameter

Frequency/ Duration: Single administration Tissue collected 30, 60, and 210 days for nonfracture study and 7, 14, 21 and 133 day fracture study

Response: Corrosion/Degradation, New bone growth

Species (strain): C57Bl/6J wild type mice.

Gender: male

Number per group: 4 mice per group and time point for nonfracture study and 6 to 11 mice per time point for fracture repair study

Observed adverse effects: Degradation was seen as early as 30 days. A considerable degradation of Mg2Ag implants was seen 210 days after implantation. Callus was fully developed already by day 14 in mice in which the fracture was stabilized by a Mg2Ag pin, a time point at which callus formation just started to begin in the control group. No adverse events.

Timing of adverse effects: 30 to 210 days

Factors that predict response: Mg stimulated bone formation while inhibiting bone resorption, leading to an augmented callus formation during fracture healing. Mg2Ag implants degraded within a reasonable period of time without causing systemic adverse effects.

Source citation: Miura et al. 2016[40]

Study Design: RCT

Device or Material: Plates: Mg-1.03% Al-0.006% Zn-0.006% Mn-0.003% Si-0.002% Cu-0.001% Fe, compared with Ti

Route: Implanted in head, back adipose tissue and femur

Dose: 2 mm × 3 mm × 0.5 mm plates

Frequency/ Duration: Single administration Tissue collected at 1, 2, and 4 weeks.

Response: Corrosion/Degradation, Foreign body reaction, Gas production, Mild inflammation

Species (strain): Wistar rats.

Gender: male

Number per group: 54 total divided into 3 groups, 18 per group.

Observed adverse effects: "In the head and back, the volume losses significantly increased at 4 weeks compared with those at 1 and 2 weeks after implantation ($p < 0.05$), whereas in the femur, no significant difference was found between time periods. Among the implantation sites, the Mg alloy plates were corroded fastest in the head, followed by in the back, and then, in the femur." "Area of the gas cavities was significantly decreased at all implantation sites from 2 to 4 weeks after implantation ($p < 0.05$), and was significantly larger in the head than in the back and femur at all time points ($p < 0.05$)." "Tissues surrounding the Mg alloy and Ti plates showed normal wound healing processes with only mild inflammation and foreign body reaction."

Timing of adverse effects: 1 to 4 weeks

Factors that predict response: "At the implantation sites in vivo, tissue fluid and blood plasma around Mg alloys act as an electrolyte, with the circulation of tissue fluid depending on the number of blood vessels and level of blood flow. It has also been reported that the corrosion rates vary depending on the site of implantation."

Source citation: Han et al. 2015[31]

Study Design: RCT

Device or Material: HP-Mg screw compared with PLLA screw

Route: Femoral intracondylar fracture model

Dose: Single screw: major diameter 2.7 mm, a core diameter 2.1 mm, a pitch 1 mm and a length 27 mm

Frequency/ Duration: Single administration Tissue collected at 4, 8, 16 and 24 weeks.

Response: Corrosion/Degradation, Inflammation

Species (strain): New Zealand white rabbits.

Gender: NR

Number per group: n = 24 HP Mg, n = 12 PLLA.

Observed adverse effects: Good biocompatibility of HP Mg screws wtih no severe inflammatory response in the degradation of HP Mg screws. Rigid fixation in fracture healing process provided by both HP Mg screws and PLLA screws. There was a great decrease in HP Mg screw volume from 16 weeks. There was a reduction of approximately 24.6% in weight for the Mg HP screws within the first 4 weeks, and 39.2% remained after 24 weeks. HP Mg screws performed corrosion rate of 1.38 ± 0.03 mm per year at 4 weeks post operation, then decreased to 0.57 ± 0.03 mm per year.

Timing of adverse effects: 4 to 24 weeks

Factors that predict response: NR

Source citation: Bondarenko et al. 2014[44]

Study Design: Non-randomized comparative

Device or Material: 4 different Mg alloys compared with Ti pins

Route: Intramedullary tibia implant

Dose: 25 mm length and 2.5 mm diameter

Frequency/ Duration: Single administration Tissue collected at 3 and 6 months.

Response: Histologic (necrosis, inflammation, bone growth)

Species (strain): New Zealand white rabbits.

Gender: female

Number per group: 5 for each group and time point.

Observed adverse effects: Highest inflammatory reaction in LANd442 (4% lithium, 4% aluminium, 2% neodymium) and ZEK100 (1% Zinc, <1% rare earth, <1% zirconium) groups, where significant necrotic changes in the peri-implant area were combined with intensive inflammation and periostitis as well as with high amount of gas bubbles. LAE442 (4% lithium, 4% aluminium, 2% rare earth) showed the lowest rates of bone reaction and the lowest level of inflammation.

Timing of adverse effects: NR

Factors that predict response: Severity of bone reactions as well as the markers' expression depends on the type of implant, particularly on its physicochemical properties, including the corrosion rate. A lower level of bone reactions in all groups with resorbable magnesium-based implants than in the control group could be explained by lack of stable bone/implant interface.

Source citation: Ezechieli et al. 2014[36]

Study Design: RCT

Device or Material: MgYREZr or Ti6Al4V alloy pin

Route: Intercondylar femoral notch

Dose: Total length 9 mm and external diameter 2 mm

Frequency/ Duration: Single administration Tissue collected at 1, 4, and 12 weeks.

Response: Inflammation

Species (strain): New Zealand white rabbits.

Gender: female

Number per group: 18 in each group, 6 at each time point.

Observed adverse effects: All implants were well-tolerated with no inflammation or evidence of gas generation. Mild synovitis was present in weeks 1 and 4 and gone by week 12.

Timing of adverse effects: 1 to 12 weeks

Factors that predict response: Addition of rare earth element in this alloy increased biocompatibility and produced acceptable corrosive characteristics.

Source citation: Huehnerschulte et al. 2012[37]

Study Design: RCT

Device or Material: Mg alloys with (ZEK100) and without (AX30) rare earth elements

Route: Pins inserted into tibia

Dose: 2.5 mm diameter and 25 mm length

Frequency/ Duration: Single administration Tissue collected at 3 and 6 months.

Response: Biodegradation and new bone formation

Species (strain): New Zealand white rabbits.

Gender: female

Number per group: 24 total, 6 per alloy and time period.

Observed adverse effects: In areas of the bone marrow adjacent to the Mg implant, cells of an inflammatory reaction, such as macrophages and foreign body cells, were observed. Degrading ZEK100 and AX30 implants caused adverse host reactions by inducing an unfavorable osteoclastogenic resorption of bone and a rushed reactive formation of new bone periosteally. Therefore the biocompatibility of ZEK100 and AX30 is questionable.

Timing of adverse effects: NR

Factors that predict response: No effect of rare earth elements were found.

Source citation: Kraus et al. 2012[45]

Study Design: Non-randomized comparative

Device or Material: Pins made of 2 different Mg-Zn alloys

Route: Femoral pin implants

Dose: 2 pins: 1.6 mm diameter and 8 mm length

Frequency/ Duration: Single administration Tissue collected at 4, 12, 24, and 36 weeks.

Response: Degradation/gas generation

Species (strain): Sprague–Dawley rats.

Gender: male

Number per group: 32 total, 16 in each group divided over each time period.

Observed adverse effects: No inflammation. ZX50 (5% Zn) pins started to corrode immediately after implantation and exhibited surface pits already within the first week and associated with gas release. WZ21 pins (1% Zn, 2% Y) decreased only moderately during the initial months after implantation. 2.3% of the initial pin volume degraded within the first 2 months. Despite excessive gas formation, the magnesium pins did not harm bone regeneration. At smaller degradation rates, gas evolution remained unproblematic and the magnesium implants showed good biocompatibility.

Timing of adverse effects: 1 week to 2 months

Factors that predict response: NR

Source citation: Castellani et al. 2011[38]

Study Design: RCT

Device or Material: MgYNdHRE alloy compared with Ti alloy

Route: Femur implants

Dose: 1.6 mm diameter and 7 mm length

Frequency/ Duration: Single administration Tissue collected at 4, 12, and 24 weeks.

Response: Inflammation, bone growth

Species (strain): Sprague–Dawley rats.

Gender: male

Number per group: 72 total pins, divided between 2 groups and 3 time periods.

Observed adverse effects: Healing occurred uneventfully and no signs of local inflammation, gross infection or tissue reaction could be observed clinically throughout the implantation period. Enhanced bone response to the investigated Mg alloy.

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: Erdmann et al. 2010[32]

Study Design: RCT

Device or Material: Screws: Mg calcium alloy (MgCa0.8) vs. surgical steel

Route: Tibia implants

Dose: 2 screws, shaft diameter 4.0 mm, length 6.0 mm

Frequency/ Duration: Single administration Tissue collected at 2, 4, 6, and 8 weeks.

Response: Inflammation

Species (strain): New Zealand white rabbits.

Gender: female

Number per group: 40 total, 24 Mg and 16 control.

Observed adverse effects: Moderate inflammation was detected in both implant materials and resolved to a minimum during the first weeks indicating comparable biocompatibility for MgCa0.8. Inflammation was related to surgery and not the devices. Hydrogen cavities that were produced by the degrading implant did not seem to affect the host adversely as they did not influence the extent of the host response.

Timing of adverse effects: NR

Factors that predict response: NR

HP: high purity; Mg: magnesium; mm: millimeter; NR: not reported; PLLA: poly-L-lactic acid; RCT: randomized controlled trial; Ti: titanium; wt%: percentage by weight

Table 7: Mg Orthopedic Implant – Health Effects (In Vivo) Animal Studies

Source citation: Augustin et al. 2020[48]

Study Design: RCT

Device or Material: Mg alloy LAE442 (4 wt% lithium, 4 wt% aluminum, 2 wt% rare earths) with pore size of 400 µm (p400) and 500 µm (p500) vs. control (resorbable β-TCP (Cerasorb M)

Route: Hole into greater trochanter of the femur

Dose: p400: strut elements of 0.4 and 0.3 mm, porosity of 43% and a volume of 37 mm3; p500: strut elements of 0.4 and 0.5 mm, porosity of 41% and a volume of 38 mm3; β-TCP porosity of 65% with pores ≤500 µm

Frequency/ Duration: Single administration Tissue collected at 6, 12, 24, and 36 weeks

Response: Corrosion/degradation, Gas formation

Species (strain): Rabbits (Zika).

Gender: Female.

Number per group: 40 total (10 scaffolds per time group).

Observed adverse effects: Radiological evaluation indicated mild gas accumulation in the soft tissue close to the implant site in 2 animals with p500 scaffold. Gas formation visible with LAE442 up to 36 weeks with highest increase in gas up to week 2 (p400 with significantly more gas than p500 [p=0.47]). Both LAE442 scaffolds increased gas formation until week 20 with subsequent decreases to a moderate amount in week 36. By week 36, p400 and p500 showed volume decreases of 15.9% and 11.1%, respectively, with homogeneous degradation, whereas ß-TCP lost 74.6% of its initial volume.

Timing of adverse effects: Mild gas accumulation at week 4 and 6.
Factors that predict response: NR.

Source citation: Hampp et al. 2013[49]

Study Design: RCT

Device or Material: 2 Mg alloys (LAE442 (90 wt% Mg,4 wt% lithium, 4 wt% aluminum, 2 wt% rare earth) and LANd442 (based on LAE442 but 2 wt% neodymium replaced rare earth); specially produced for study) vs. Ti alloy (S+D Spezialstahl Handelsgesellschaft mbH) and controls

Route: Medullary cavity of tibia

Dose: p400: strut elements of 0.4 and 0.3 mm, porosity of 43% and a volume of 37 mm3; p500: strut elements of 0.4 and 0.5 mm, porosity of 41% and a volume of 38 mm3; β-TCP porosity of 65% with pores ≤500 µm

Frequency/ Duration: Single administration Tissue collected at 6, 12, 24, and 36 weeks

Response: Corrosion/degradation, Gas formation

Species (strain): Rabbits (Zika).

Gender: Female.

Number per group: 40 total (10 scaffolds per time group).

Observed adverse effects: Radiological evaluation indicated mild gas accumulation in the soft tissue close to the implant site in 2 animals with p500 scaffold. Gas formation visible with LAE442 up to 36 weeks with highest increase in gas up to week 2 (p400 with significantly more gas than p500 [p=0.47]). Both LAE442 scaffolds increased gas formation until week 20 with subsequent decreases to a moderate amount in week 36. By week 36, p400 and p500 showed volume decreases of 15.9% and 11.1%, respectively, with homogeneous degradation, whereas ß-TCP lost 74.6% of its initial volume.

Timing of adverse effects: Mild gas accumulation at week 4 and 6.

Factors that predict response: NR.

Table 8: Mg Biliary Stent - Health Effects (In Vivo) Animal Studies

Source citation: Liu et al. 2017[50]

Study Design: Single arm

Device or Material: Mg alloy AZ31

Route: Anterior wall of distal common bile duct

Dose: External diameter 2.2 mm, internal diameter of 1.8 mm, length 10 mm

Frequency/ Duration: Sin Single administration. Tissue collected at 1, 3 and 6 months

Response: Calcification, Cholangiectasis, Corrosion/degradation, Damaged stent integrity, Fibrous hyperplasia, Increased serum Mg level, Increased white blood cell concentration, Inflammation, Lymphocyte and eosinophil infiltration, Mucosal chronic inflammation, Papillary hyperplasia, Peeling

Species (strain): Rabbits (New England).

Gender: Male.

Number per group: 5 each time period (15 total stents).

Observed adverse effects: High-resolution 3D reconstruction: Remaining volume of 93.82±1.36% and 30.89±2.46% at 1 and 3 months, respectively. At 3 months, stents showed severe corrosion, damaged stent structure with some parts of the stent appearing to have peeled off. Full degradation was noted by 6 months with a small quantity of metallic residues and little biliary sludge in the dissected biliary duct. Non-uniform corrosion at two ends of stents resulted from flow or local inflammation. Whole blood cell analysis: White blood cell concentration significantly increased 1 week after surgery but decreased during the following period indicating an inflammatory response which disappeared at 6 months. Serum Mg level significantly increased at 4 weeks then decreased to normal.

Histological evaluation: At 1 month, H&E staining of the bile duct revealed papillary hyperplasia in the epithelium and fibrous hyperplasia in the adventitia layer, with infiltration by lymphocytes and eosinophils. Papillary hyperplasia was still detected at 3 and 6 months. At 1 month, staining of the liver indicated lymphocytes infiltration and an inflammatory response at the portal area. This inflammatory response was reduced in the liver by 3 months, however cholangiectasis was seen in 1 rabbit. Staining of the gall bladder detected calcified fragments at 1 and 3 months, and papillary hyperplasia (similar to bile duct) at 6 months. Histological results for the duodenum revealed a mucosal chronic inflammation.

Timing of adverse effects: 1, 3, and 6 months.

Factors that predict response: NR.

H&E: hematoxylin and eosin; Mg: magnesium; mm: millimeter; NR = not reported

Appendix E. References

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

There were no reports for magnesium-related devices.

Appendix G. Regulatory and Manufacturer Safety Alerts

The associated alert is provided with this report as a separate PDF.