Magmaris™ resorbable magnesium scaffold: state-of-art review

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Bioresorbable scaffolds (BRS) have been advocated as the ‘fourth revolution’ in interventional cardiology because they could provide temporary scaffolding and then ‘disappear’ (resorb) potentially significantly improving coronary artery disease treatment. BRS technology has gradually matured, and there are many devices available worldwide, which are currently undergoing preclinical or clinical testing. Due to the concerns related to polylactide scaffolds, magnesium alloy is now one of the most promising resorbable technologies despite available evidences on its performances *in vivo* are limited to small observational studies. In this state-of-art review we present Magmaris™ (Biotronik AG, Buelach, Switzerland) magnesium-based BRS from bench to bedside, reviewing to date available clinical trial data and current recommendations for its optimal use in clinical practice.

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In 1986, coronary angioplasty saw its first big revolution with the introduction of metallic stents to cover the treated lesion, offering a mechanical solution to dissection, elastic recoil and late remodeling, the main problems hampering the results of balloon angioplasty [1,2]. However, these bare metal stents still induced neointimal proliferation in response to the implantation of a foreign body leading to in-stent restenosis [3]. The introduction of active pharmaceutical coating, which eluted cytostatic and cytotoxic drugs, improved this vessel-supporting technology, greatly reducing the in-stent neointimal proliferation [4]. Despite some troubles due to hypersensitive reaction mediated by eosinophils, lack of endothelialization and late and very late stent thrombosis [5,6], continuous improvements made metallic drug-eluting stents (DES) the current gold standard in percutaneous myocardial revascularization, with remarkable results at long-term follow-up [7]. Today the major concerns regarding their use are the reduction of side-branch flow, the hindrance of positive vascular remodeling, a risk of neoatherosclerosis and the absent restoration of significant vasomotion. Furthermore, once implanted they will permanently interfere with future surgical revascularization and noninvasive imaging [8].

Bioresorbable scaffolds (BRS) have been developed to theoretically overcome most limitations, as they should provide temporary scaffolding and then disappear. They have been therefore advocated as the fourth revolution in interventional cardiology and have the potential to significantly improve coronary artery disease treatment [9,10]. BRS technology has gradually matured, and there are many devices available worldwide, which are currently undergoing preclinical or clinical testing [8,11]. Due to the concerns related to polylactide scaffolds [12], magnesium alloy remains as one of the most promising resorbable technologies field despite available evidence being limited to small observational studies. Initial results appear more than encouraging, but bearing in mind the lesson from

the Absorb, the Task Force of the new 2018 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization [13] endorses the recommendation of the recent ESC/European Association for Percutaneous Cardiovascular Interventions (EAPCI) document on bioresorbable scaffolds that any BRS should not be used outside well-controlled clinical studies [14], giving a strong III C level indication. The aim of this review is to describe available data on the Magmaris™ (Biotronik AG, Bülach, Switzerland) magnesium-based Magmaris resorbable magnesium scaffold (RMS) in this controversial era.

Device characteristics

Magmaris is a metallic, resorbable, sirolimus-eluting scaffold, which is delivered on a rapid-exchange system customized from the same company Orsiro™ (Biotronik AG, Bülach, Switzerland) platform. It is compatible with a six French (Fr) guide thanks to its crossing profile of 1.5 mm.

The backbone is made of an absorbable magnesium mixed with rare earth metals. Due to its complete radiolucency, it is equipped with two radiopaque tantalum markers (silicon covered to avoid electrochemical interactions with the magnesium alloy) at the distal and proximal end [15].

It has an open cell design with six crown and two links in the axial direction. The square-shaped struts are 150 µm in thickness × 150 µm in width (still thick in comparison with current DES technology), and they are electropolished, a process that produces soft, rounded edges, which contributes for improved trackability, deliverability and flow dynamics [16]. This Magmaris strut profile could theoretically alleviate shear stress disturbance if compared, for instance, with the unpolished, sharp edges of Absorb [17].

Currently available scaffold sizes are 3.0 and 3.5 mm diameter, and 15, 20 and 25 mm lengths. Nominal and burst pressures are 10 and 16 atmosphere (atm), and the diameter can be safely expanded up to a maximum of 0.6 mm above the nominal inner diameter.

Magnesium's properties & its benefits as scaffold component

Interest in magnesium alloy found its rationale in both biological and mechanical properties. From a biological point-of-view, magnesium is well-known as an essential mineral involved in many physiological functions. Usually, the western diet provides enough magnesium intake to avoid serious deficiency but nevertheless it seems not to be high enough to establish high normal serum magnesium concentrations, which have been demonstrated to be protective against various diseases. It can be stored in the bone structure or excreted in the urine throughout the kidney regulation or by the digestive system [18].

Consequently, a magnesium BRS has in itself the potential to provide enough radial strength to support the wall of an atherosclerotic vessel after angioplasty. Nevertheless, we must remember that the radial force of current cobalt-chromium stents is bigger, and this is the reason for higher strut thickness of Magmaris scaffold [19]. Consequently, the potential lack of radial force should be a constant warning to avoid calcified lesions. Other characteristics of the magnesium scaffolds are also similar to stainless steel stents, including the low elastic recoil (<8%), high collapse pressure (from 0.8 to 1.5 bar of the last Magmaris scaffold) and the minimum amount of shortening after inflation (that is <5%) [20]. They therefore offer a good radial strength with high compliance to the vessel geometry and low acute recoil, which in the end permits implantation of the Magmaris scaffold with a single-step inflation.

Furthermore, in the world of absorbable scaffold, a metallic structure when compared with poly-L-lactic (PLLA) scaffolds competitors (Absorb GT1 and DESolve) improves trackability (which in turn means a 29% reduction in the peak force needed to track through a tortuous vessel), pushability (with a 34% increase in the force transmitted from the hub to the tip) and ensures lesser acute recoil [20].

What is really interesting for the magnesium scaffold is the complete different chemical process that is the basis of its reabsorption if compared with PLLA scaffolds. Actually, the metallic struts are replaced by an amorphous footprint of calcium phosphate [21], and 95% of the magnesium is completely resorbed within the first 12 months [15].

Furthermore, the release of magnesium ions not only has no side effects but it could have some adjunctive positive consequences: for instance, the well-known magnesium antiarrhythmic properties [22] and the reduction in ischemia-reperfusion injury experimentally documented [23] might be protective for the ischemic myocardium. Also, it has been documented the magnesium inhibition of the endothelin-1 production, which may prevent endothelin-induced vasoconstriction [24,25].

Finally, some experiments in animal models have shown potential antithrombotic properties due to the electronegative charge during degradation [26,27] and *in vitro* tests of magnesium-based RMS also showed a decreased smooth muscle cell proliferation and an increased endothelial cell proliferation, which in turn may be speculative

Figure 1. Different stages of Magmaris™ resorption process in three different patients. Each colored column represents a different patient-reporting baseline, angiographic result and optical coherence tomography results. Red group: immediate acute result after successful implantation of two overlapped BRS Magmaris 3.5 mm × 25 mm in proximal mid right coronary artery. Yellow group: three months results after successful implantation of three overlapped BRS Magmaris (3 mm × 25 mm; 3 mm × 25 mm; 3.5 × 25 mm) in mid-distal left anterior descending. Green group: one year results after successful implantation of one BRS Magmaris 3 mm × 25 mm on distal circumflex. BRS: Bioresorbable scaffold; OCT: Optical coherence tomography.

of reduced risk of late restenosis [28]. In order to investigate the qualitative and temporal course of degradation, Joner *et al.* recently published a paper about the reabsorption process of the drug-eluting absorbable magnesium scaffold (DREAMS) scaffolds in juvenile swine [29]. Optical coherence tomography (OCT) was identified as a useful imaging tool to delineate strut degradation as a function of time: in this animal study DREAMS struts elicit complete translucence in the absence of optical shadowing acutely after implantation, and slowly convert into dissolved black and bright boxes as bioabsorption progresses.

Figure 1 depicts angiographic and OCT imaging of different stages of Magmaris reabsorption process in three different patients.

Not only magnesium: the polymeric coating

Magmaris is not a bare magnesium scaffold, it is completely coated by a 7 µm layer of the same biodegradable PLLA used for the Orsiro stent loaded with sirolimus, at a dose of 1.4 µg/mm² of scaffold surface; 70% of sirolimus is released after 90 days. The PLLA coating degradation process instead is longer than 24 months, since the PLLA undergoes a long (three steps) hydrolytic degeneration to lactic acid [15].

The first step is polymer hydration, due to water diffusion that hydrolyzes the ester bonds; then, the second step is the scission of the ties that connect the amorphous phase to the crystalline phase, leading to structural discontinuities (and radial strength decrease); finally, in the third step, the short polymer chains, which have previously been hydrolyzed, diffuse out of the coating, leading to progressive loss of mass: these small particles are

then transformed by the surrounding macrophages from lactic acid monomers into lactates, which once enter the Krebs's cycle are finally metabolized to CO₂ and H₂O.

The poly-L-lactic acid bioresorbable scaffold: a lesson to learn?

The Absorb BVS is the most widely clinically utilized and studied PLLA bioresorbable scaffold. It consists of a PLLA scaffold coated with a layer of everolimus-eluting poly-D, L-lactic acid. Like Magmaris, the strut thickness of the Absorb BVS is about 150 microns [30] but it can take up to 4 years to fully resorb [31].

Initially, Absorb BVS studies were limited to patients with stable angina and largely excluded complicated lesion characteristics [32]. After CE mark approval, real-world registry data began to highlight an excess of scaffold thrombosis (ScT) [33,34], particularly in the setting of acute coronary syndromes [35]. Finally, a comprehensive systematic review and meta-analysis including over 10,000 patients clearly reported a twofold increase in the rate of both myocardial infarction and definite or probable ScT compared with DES [36]. Similarly, ABSORB III trial documented a trend toward more target lesion failure at 12 months compared with DES [9] and the AIDA trial [37] showed a fourfold increase in the rate of definite or probable ScT. Consequently, Abbott Vascular decided to restrict the use of Absorb BVS in Europe only to patients enrolled in registered trial. This device was finally withdrawn from the market.

Magmaris: from bench to bedside

The history of biodegradable magnesium scaffolds started in 2003 with animal model and scaffolds made of AE21 magnesium alloy and WE43 magnesium alloy showing negligible inflammatory response, positive remodeling and a fast endothelialization process [26,38,39].

The WE43 magnesium alloy Lektom Magic scaffold (Biotronik AG, Bülach, Switzerland) was further improved and became the first version of the absorbable metallic stent (AMS1, Biotronik, Berlin, Germany). It was essentially a slotted tube stent made of WE43 magnesium alloy, with neither polymer coating nor drug that from 2005 was tested in humans to treat lower limb disease [40] as well as aortic and pulmonary arterial disease in pediatric patients [41,42].

Finally, in 2007 the PROGRESS-AMS clinical trial became the first prospective nonrandomized multicenter study on magnesium-made RMS in coronary artery disease [43]. The AMS1 showed a good safety profile, but in-scaffold late lumen loss (LLL) was high, suggesting a need for slower scaffold absorption together with an antiproliferative drug elution [43,44], conveying to the AMS2.

In this regard, the refinement of the absorbable metal scaffold then led to development of the AMS3 – later renamed DREAMS 1G device – with an improved alloy composition and strut geometry for better scaffolding properties. Moreover, to counteract the neointimal proliferative response, a 1 µm paclitaxel-eluting, bioresorbable polymer matrix made of poly lactic-co-glycolic acid was added. The absorption was longer, 9–12 months, and a higher collapse pressure was achieved [15].

DREAMS 1G was tested in the first-in-man BIOSOLVE-I study [45] and showed a favorable safety profile and significantly improved angiographic performance measures compared with its bare absorbable metal scaffold predecessor. In this prospective nonrandomized study 47 DREAMS 1G stents were implanted in single *de novo* lesions for silent ischemia, stable or unstable angina, and dual antiplatelet therapy (DAPT) was recommended for at least 6 months. After 3 years of follow-up, a 4% target lesion failure (TLF) was observed, while a 4.3% ischemia-driven target lesion revascularization (TLR) and 2.2% target vessel myocardial infarction were reported. No cardiac death (CD) or ScT was observed.

Finally, a further refinement named DREAMS 2G brought scaffold evolution to the current Magmaris, whose structural characteristics are fully explained below. Structurally if compared with DREAMS 1G, Magmaris has an optimized scaffold backbone design with more flexibility and higher radial force. Additionally, the drug-polymer coating has changed from paclitaxel to sirolimus in combination with a bioresorbable poly-L-lactide acid polymer (the same BIOLute coating used for the Orsiro DES) to more effectively decrease neointimal formation [46].

DREAMS 2G was then tested in the first-in-man prospective, multicentric, nonrandomized BIOSOLVE-II study [47] on 121 patients with stable or unstable angina or silent ischemia and in which *de novo* lesions were treated with 125 DREAMS 2G (four patients received two BRS). Interestingly – compared with the BIOSOLVE-I – in this study longer lesions (length 12.6 ± 4.5 mm) with smaller diameter (reference vessel diameter 2.68 mm^2 , range 2.2–3.7 mm) were treated. Device sizes were 2.5×20 mm, 3.0×20 mm and 3.5×25 mm. DAPT was recommended for at least 6 months. In this study a second DREAMS 2G was implanted in four (3%) patients

(three due to dissection and one because of an underestimation of lesion length), while three (2%) patients received a nonstudy device (two in order to cover dissections and one because DREAMS 2G could not cover the lesion completely).

After 6-month follow-up a 3.3% TLF was reported: one target vessel myocardial infarction (0.8%) that was actually due to periprocedural temporary no-reflow, one death for unknown causes classified as CD and possible ScT (0.8%), and two clinically driven TLR (1.7%) for restenosis (on the whole, the stent showed an LLL of 0.44 ± 0.36 mm) and one death because of cancer. No definite or probable ScT was therefore recorded. The first 30 consecutive patients of this study entered the imaging substudy, which showed with IntraVascular UltraSound (IVUS) a preservation of the scaffold area with a negligible neointimal hyperplasia area (0.08 mm^2). Much more interesting, when the same patients received OCT evaluation, it did not detect any malapposed or uncovered struts. Finally, 25 patients received vasomotion assessment with intracoronary acetylcholine and nitrate injection that showed an initial vasomotion recovery already after 6 months (i.e., $\geq 3.0\%$ change in mean lumen diameter) in 20 patients (80%).

At 1-year follow-up [48] 42 patients received angiographic evaluation, which showed an in-scaffold LLL of 0.39 ± 0.27 mm. TLF at 1-year was 3.4% and no further events had occurred beyond the first assessment at 6-month follow-up. No statistically significant differences were observed in the baseline characteristics between this subgroup and the overall patient population.

11 patients of the imaging (IVUS/OCT) group showed no differences in 6- and 12-month IVUS parameters, except for the number of patients with incomplete strut apposition, which was reduced to zero at 12 months. By OCT the unabsorbed struts at 6 months showed complete absorption and the median minimal lumen area slightly decreased (from 4.58 to 4.19 mm^2 ; $p = 0.032$). No intraluminal mass was observed at any time.

14 patients had a new vasomotion assessment, which showed a similar response to that observed at 6 months (79%). Excitingly, the percentage postacetylcholine and nitrate improved to 6.7%. These findings were relevant as almost 95% of the magnesium scaffold is expected to be absorbed within 12 months. Whether this incremental gain in vasomotion capacity will translate into beneficial clinical outcome remains to be determined in dedicated clinical trials.

To sum up, as the angiographic performance measures of DREAMS 2G improved compared with the precursors, the safety profile remained good, with only one CD and one target vessel myocardial infarction. Also, the rate of clinically driven TLR declined (from 4.3% for DREAMS 1G in BIOSOLVE-I to 1.7% for DREAMS 2G in BIOSOLVE II) and no definite or probable ScT was observed.

BIOSOLVE-III was a pivotal study [48] primarily designed to assess the acute performance (in-hospital procedural success) of Magmaris implantation in a cohort of 61 patients. TLF rate up to 36 months was the secondary end point. After the end of the BIOSOLVE-III study, a pooled analysis with a total of 184 patients with 189 lesions who were enrolled in both BIOSOLVE-II and BIOSOLVE-III trials was published [49]. This report includes pooled follow-up data at 6 months and BIOSOLVE-II data at 24 months: lesion length was 12.5 ± 5.1 mm and with reference diameters of 2.7 ± 0.4 mm. Procedural success was obtained in 97.8%. At 6 months, the composite clinical end point target lesion failure was 3.3% (95% CI: 1.2–7.1), based on two CDs (1.1%, one unknown that was classified as possible thrombosis and one not device related), one target vessel myocardial infarction (0.6%) and three clinically driven TLR (1.7%). For BIOSOLVE-II at 24 months, the TLF rate was 5.9% (95% CI: 2.4–11.8), based on two CDs (1.7%), one target vessel myocardial infarction (0.9%) and four target lesion revascularisations (3.4%). There was no definite or probable ScT. Interestingly, in BIOSOLVE-III there were significantly more type B2/C lesions than in BIOSOLVE-II (80.3 vs 43.4%; $p < 0.0001$) and significantly more moderate-to-severe calcifications (24.2 vs 10.7%; $p = 0.014$). At 12 months, there was no difference in LLL between the two studies: it was 0.39 ± 0.34 mm in scaffold in the overall population [50].

Clinical outcomes for DREAMS 2G compare well with other polymeric scaffolds in which a similar composite end point (CD, myocardial infarction, coronary artery bypass graft surgery or clinically driven target lesion failure) occurred in 2–5% of patients [51,52]. The clinically driven rate of TLR for DREAMS 2G was 1.7%, versus 0–6.3% for polymeric scaffolds [51,52]. Furthermore, Hideo-Kajita *et al.* presented at ACC 2018 the results of an intention-to-treat analysis in which 482 patients were included, with 184 patients in the Magmaris group ($n = 189$ lesions) and 298 patients in the Orsiro group ($n = 332$ lesions) [53]. Despite some methodological pitfalls (it is a comparison between one randomized controlled trial and two single arm registries and is underpowered for main effects), the results generate the hypothesis that Magmaris is directed toward DES-like performances, with TLF at 6-months of 5.4% (vs 3.1% in Orsiro group; $p = 0.21$) [53].

Table 1. Magnesium-made scaffold clinical trial program.

Study name	Study type	Study design	Patients	Status	1° end point	Conclusion	Device used	Ref.
PROGRESS-AMS	First-in-man	Retrospective, multicenter	63	Completed	Composite of CD, nonfatal MI and CD-TLR at 4 months	No CD, nonfatal MI. CD-TLR up by 26.7% at 12 month. TLR 45%	Absorbable metallic scaffold (AMS1)	[43]
BIOSOLVE-I	First-in-man	Prospective, multicenter (Europe + Switzerland)	46	Completed	TLF (composite of CD, TV-MI and CD-TLR) at 6 and 12 months	Excellent long-term outcomes at 3 years with a low TLF rate and no CD or scaffold thrombosis. No TLF events were observed after the first year	DREAMS 1G (AMS3) – Paclitaxel-eluting, bioresorbable polymer matrix made of poly lactic-co-glycolic acid	[45]
BIOSOLVE-II	First-in-man	Prospective, multicenter (worldwide)	123	36 m FUP available	In-segment LLL at 6 months	Magmaris demonstrated a favorable safety and performance until 36-month follow-up. The rate of definite/probable scaffold thrombosis remained at 0% at 36 months	DREAMS 2G Magmaris – sirolimus eluted in combination with a bioresorbable poly-L-lactide acid polymer	[47]
BIOSOLVE-III	Pivotal trial	Prospective, multicenter (Europe + Switzerland)	61	6 m FUP available	In-hospital procedural success	CD 1.1%. TLF = 3.3%. CD-TLR 1.7%. Absence of definite or probable scaffold thrombosis	DREAMS 2G Magmaris – sirolimus eluted in combination with a bioresorbable poly-L-lactide acid polymer	[49]
BIOSOLVE-IV	Postmarket trial	Prospective, multicenter (worldwide)	1065	Enrolling	TLF (composite of CD, TV-MI and TLR) at 12 months	Available of first 400 points up to 1 year [†] : CD = 0; CD-TLR = 4.3%; TV-MI = 0.8%; definite or probable scaffold thrombosis = 0.3% (n = 1)	DREAMS 2G Magmaris – sirolimus eluted in combination with a bioresorbable poly-L-lactide acid polymer	[55]

[†]Presented at EuroPCR 2018 Congress, Paris, France.

CD: Cardiac death; CD-TLR: Clinically driven-target lesion revascularization; DREAMS: Drug-eluting absorbable magnesium scaffold; FUP: Follow-up; LLL: Late lumen loss; MI: Myocardial infarction; TLF: Target lesion failure; TLR: Target lesion revascularization; TV: Target vessel; TV-MI: Target vessel myocardial infarction.

Other studies will shed further light on these findings. The BIOSOLVE-IV trial (ClinicalTrials.gov identifier: NCT02817802) [54], is a postmarket surveillance, prospective, multicentric registry aimed to test the clinical performance and long-term safety of Magmaris in patients with symptomatic CAD and single *de novo* native coronary artery lesions. Presenting the results of the first 400 patients from the cohort of 1065 patients included in the BIOSOLVE-IV registry at TCT 2018, Lee *et al.* reported that the 12-month rate of TLF was 4.3%, which was up from 2.5% at 6 months [55]. Among these there were no CDs, and only one reported case of definite/probable ScT, which occurred early. The thrombotic event occurred in a non-ST segment elevation myocardial infarction patient with three vessel disease where Magmaris was implanted in a heavily calcified coronary artery and who stopped DAPT to undergo a minimally invasive direct coronary artery bypass surgery 4 days after Magmaris implantation.

This study targets a real-world population with few exclusion criteria (pregnancy, allergy and dialysis) and includes also non-ST segment elevation myocardial infarction patients and complex lesions with the exception of chronic total occlusions. Inclusion criteria are target lesion stenosis >50% and <100%, and thrombolysis in myocardial infarction flow ≥ 1 . Currently, it is still enrolling patients in over 120 centers across 30 countries, and although it was initially planned to enroll 1065 patients in the BIOSOLVE-IV registry, Biotronik has decided to increase enrollment by an additional 1000 patients, with study completion in 2023 to allow for long-term clinical follow-up. BIOTRONIK's clinical trial program from PROGRESS-AMS to BIOSOLVE-IV registry is shown in Table 1.

Until now, there have been no studies designed specifically to evaluate the angiographic and clinical performance of these devices in coronary bifurcations. The aim of the BIFSORB Pilot Study II (ClinicalTrials.gov identifier: NCT03027856) is to investigate the feasibility and safety of the Magmaris for treatment of coronary bifurcation lesions. Eligible patients with a bifurcation lesion are treated by the provisional technique with mandatory jailing of

the side branch and provisional opening of side branch ostium by the mini-kiss technique in case of severe pinching or thrombolysis in myocardial infarction flow <3. Proximal postdilatation is mandatory. At baseline, the target lesion is assessed by OCT before, during and after implantation of the Magmaris. OCT assessment is performed again after 1 and at 12-month follow-up, or before if the patient is readmitted with a possible TLF. It started in September 2016 enrolling 20 patients. Primary outcome was a composite of major procedural and non-procedural myocardial infarction, target lesion failure and cardiac death. An OCT evaluation was performed in case of adverse vessel wall features. Other investigator-initiated trials are ongoing and results are awaited.

When should I place a Magmaris scaffold?

Magmaris received Conformité Européenne (CE) mark approval in June 2016. A panel of the experts involved in the first studies with absorbable metallic stent-DREAMS scaffolds produced a consensus document just before Magmaris European market launch in June 2016 [56]. Previously, the device had not been used outside controlled clinical trials, and despite a quick spread among catheterization laboratories, current experience is still limited especially regarding long-term follow-up.

The panel recognized that this technology was – and still actually is – in its infancy, and kept in mind the experience gained with Absorb, whose unrestricted use at launch allowed some implantation pitfalls, which in turn probably contributed to a higher than expected ScT rate. Current ESC guidelines [13] extend this caution, and credited a class III recommendation for implant of Magmaris scaffold in patients who are not recruited in clinical trial with adequate follow-up.

They stated therefore that, at least initially, Magmaris implantation should be limited to patients with long life expectancy, and with stable, short *de novo* lesions, which can be adequately predilated and that have good likelihood to regain vasomotion. Magmaris implantation must be avoided in the settings in which the returning of vasomotion could not be expected (e.g., saphenous grafts, in-stent restenoses, previous stents in the same vessel, heavy calcification), as well if there is remaining thrombus at the lesion site or if optimal sizing with the use of IVUS could not be obtained [17]. Furthermore, for the time being Magmaris must be avoided in left main lesions, in ostial lesions and in lesions with complex anatomy (heavy calcification; challenging tortuosity or angulation; diffuse, long disease and bifurcation). In this last setting, a novel preclinical study by Bennett *et al.* investigated the feasibility of performing complex bifurcation stenting with Magmaris in nondiseased aortoiliac bifurcations of 25 rabbits [57]. They used provisional (PS; n = 5), culotte (n = 6), mini-crush (n = 6) or T and protrusion (TAP; n = 8) stenting technique and concluded that bifurcation stenting using Magmaris appears feasible, and PS with additional TAP, if needed, seems a reasonable approach, since they observed that Proximal Optimization (POT), Side Branch (SB) opening and final kissing-balloon post-dilatation generated good results on angiography, OCT and Micro Computed Tomography (micro-CT) in all PS procedures, with no strut fractures. Whenever a two-stent technique is planned, TAP appears most favorable while mini-crush and culotte stenting should probably be avoided. These conclusions came from the observation that following two-stent procedures with the Magmaris, strut fractures were present at the bifurcation in 7 out of 20 (35%) procedures (clinical importance of strut fractures is currently unknown). Moreover, a culotte strategy with the Magmaris left the patient with a double layer of thick scaffold struts in the proximal main vessel and bifurcation core, increasing the risk of malapposition.

In ST-elevation myocardial infarction (STEMI) patients, the Magmaris is not currently recommended due to lack of data and concern about further platelets activation from thick struts. Ongoing clinical trials (MAGSTEMI) are, however, evaluating the performance of Magmaris in STEMI patients in comparison with Orsiro. Regarding other acute coronary syndrome settings, a recent case report suggests the possibility to take advantage of resorbable magnesium scaffold to treat spontaneous coronary dissection, in order to obtain long-term restoration of coronary vasomotion [58,59]. Finally, patients who cannot comply with current ESC/EAPCI DAPT recommendations for stable lesions must not be treated with Magmaris scaffold [14].

Multiple reports highlighted the possibility of in-stent restenosis due to partial collapse of the magnesium scaffold. It has been described after 7 months in a 65-year-old patient after implantation of Magmaris in a calcified lesion [60] and after 10 weeks in a 45-year-old patient with a type A lesion, confirmed by OCT analysis [61] and in another case confirmed by IVUS after 2 months [62]. These early scaffold collapses are due to insufficient radial strength. As stated by authors, correct implantation techniques in terms of sizing, predilatation and postdilatation were followed in all the three cases although presence of calcifications of the lesion with the need of the use of scoring balloon might justify the first case and imaging was not used to guide implantation in the second case. Nevertheless, consequences of spasm once the scaffold has been applied could not be excluded and they actually

could affect a degrading BRS, which is still physically present, but lacks very early any residual radial strength. This concept should therefore even more be kept in mind while following all the correct points of the implantation technique.

Interestingly, regardless of the scaffold collapse leading to restenosis and recurrent angina, the absence of thrombus formation is an important observation supporting low thrombogenicity of the magnesium scaffold as has been suggested by recent preclinical studies [63].

How should I place a Magmaris scaffold?

Due to the bad experience with the first Absorb generation, and bearing in mind the recommendation of the latest guidelines [13], which stress the need of careful implant of BRS, imaging-guided implantation is highly recommended. It permits to precisely assess the vessel size, to detect any significant calcification (that are still an unfavorable subset for any BRS), and to assess how postdilatation worked (postdilatation with a balloon up to 0.5 mm bigger than the initial scaffold is mandatory).

As above mentioned, the Magmaris instructions-for-use recommend to implant in vessel from 2.7 to 3.7 mm (using a 3.0-mm scaffold for vessel diameter 2.7–3.2 mm and a 3.5 mm scaffold for vessel diameter 3.2–3.7 mm).

The careful preparation is the key for a successful deployment, so the predilatation is essential since the Magmaris scaffolds must not be implanted if a complete expansion of the predilatation balloon is not achieved (or if remains a residual stenosis >20% after the predilatation). After this step, the Magmaris may be released through a single-step inflation like a normal metallic DES.

Postdilatation should always be performed regardless of the imaging after the stent delivery. It must be done with a noncompliant balloon of the same nominal size of the scaffold (or up to 0.5 mm larger), inflated to a pressure >16 atm: as per instructions for use (IFU), the upsizing of the device must be limited to 0.6 mm over the nominal size.

Although a planned overlap should be avoided if possible, a second Magmaris could be implanted if needed in bail out situations: in this case they have to be juxtaposed (i.e., a scaffold-to-scaffold strategy in order to avoid any gap and overlap). If a DES is placed as the second stent, a DES with a passivated surface to prevent any electrochemical interaction, for example, Orsiro with its proBIO coating could be considered: in line with the manufacturer and a consensus document from an expert panel [56].

The anticoagulation regimen during Magmaris implantation and DAPT regimen are similar to the ones used for DES [64]. A minimum of 6 months is required for stable patients based on the result of the BIOSOLVE-II study [65], but in the currently ESC/EAPCI guidelines for myocardial revascularization, the length of suggested DAPT after implantation of a BRS has been prolonged to up to 3 years, despite this recommendation is mainly based on the Absorb data [13]. This is a further prolongation of the suggested length of DAPT from the 12 months of the previous 2017 ESC-focused update on DAPT in coronary artery disease [66]. However, this recommendation is actually moderated for patients receiving a Magmaris by a IIa indication to do at least 12 months (both in stable and acute coronary syndrome patients) and then assess the individual bleeding and ischemic risk and the presumed full absorption of the BRS, thus recognizing the intrinsic differences between poly-lactide and magnesium alloy scaffolds [13].

If subsequent follow-up of patients treated with a Magmaris scaffold is performed, coronary imaging is recommended but knowing what to expect: at 12 months, elution of magnesium from the metallic backbone is usually completed, magnesium has been converted to amorphous calcium phosphate with high water content, which is not discernible by OCT but to some extent by IVUS. Actually, amorphous calcium phosphate has not the echo shadowing that is instead typical of true vessel calcifications [49]. Further OCT imaging studies are needed to inform us whether detailed investigation of strut degradation is feasible following implantation of DREAMS 2G.

Conclusion

Magmaris is a BRS currently limited in Europe inside clinical trials for patients with *de novo* lesions, which closely match the available scaffold sizes, and it is not recommended in STEMI, cardiogenic shock, saphenous vein grafts, or in patients with poor medical compliance or contraindications to DAPT. Using it in the indicated settings the contemporary instrumental and clinical data of the device are encouraging. Ever since its CE launch in June 2016, Magmaris has been implanted by >650 physicians in over 350 hospitals across 45 countries [48,55]. As part of the postmarket evaluation Magnesium 2000 program, >2000 Magmaris cases were evaluated in a range of performance criteria, and the recent presentation of the BIOSOLVE-IV trial has shown that when considering the IFU and

proper indication, Magmaris shows performance rates at 12 months that are comparable to second-generation DESs [55]. The ESC-EAPCI report on the evaluation of coronary stents reported the following average event rates for new-generation DES at 9–12 months [6,10]: CD 1.0%, myocardial infarction 2.89%, TLR 2.91% and definite stent thrombosis 0.47%. The 6- and even 24-month data of Magmaris are comparable [45,46,54,65]. In particular, the CD rate was 1.1% at 6 months for the pooled analysis and 1.7% at 24 months for BIOSOLVE-II, while the corresponding rates of myocardial infarction were 0.6 and 0.9%, and of TLR 1.7% and 3.4%, respectively. Magmaris, therefore, appears as a safe and effective therapy for patients with coronary artery disease as long as it is properly employed focusing on the ‘4 Ps’: patient selection, proper sizing, predilatation and postdilatation. In the registries 98.8% of scaffolds are successfully deployed, and after 3 years of clinical follow-up in the BIOSOLVE-II trial there was 0% incidence of definite or probable ScT with Magmaris and still no reports of definite ScT are reported in literature [49,67]. To date there is only one reported case of definite/probable ScT, which occurred early in BIOSOLVE-IV trial [55].

However, the overall follow-up is still too short, and some key points should be kept in mind: first, fine tuning of the Magmaris (especially postdilatation and overlap) is rather difficult due to the lack of radiological visibility of the scaffold itself, which is little compensated by the scarce visibility of the tantalum markers. Second, despite imaging and histopathological data seem to demonstrate fast resorption and rapid endothelialization – which could nourish the finding of a zero definite/probable ScT rate to date – a confirmation by dedicated and systematic imaging studies is needed. Third, the same fast resorption might contribute to a fast loss of radial strength and decreased scaffolding properties that might rarely fail in opposing late recoil [60,61]. Fourth, despite encouraging numbers, little clinical data are available about vasomotion recovery. A perfect implantation technique is therefore the main key to obtain the most from this technology.

Available data could be useful to refine recommendations for use and new investigator-initiated trial as well as future superiority randomized trial against DES should be planned to get out the most of this promising technology. Today, caution in everyday practice is needed since, due to the lack of evidences, the recent 2018 ESC/EACTS guidelines on myocardial revascularization [13] recommend that any BRS, and Magmaris at present fall into this classification, should not be used outside well-controlled clinical studies.

We await further data from well-controlled trials to better judge the safety, efficacy and future role of RMS technology in the toolkit of an Interventional Cardiologist [68].

Disclaimer

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

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Executive summary

Background

- Bioresorbable scaffolds (BRS) have been developed to theoretically overcome most limitations, as they should provide temporary scaffolding and then disappear.

Device characteristics

- Due to the concerns related to poly-lactide scaffolds like the (poly-L-lactic acid) BVS Absorb™ or the DESSolve™, magnesium alloy remains as one of the most promising resorbable technologies. Magmaris™ is a unique device, a magnesium-made resorbable, sirolimus-eluting scaffold.

Magmaris: from bench to bedside

- Since its introduction in Europe in June 2016, Magmaris has been implanted by >650 physicians in over 350 hospitals across 45 countries. As part of the postmarket evaluation Magnesium 2000 program, >2000 Magmaris cases were evaluated in a range of performance criteria, and the recent presentation of the BIOSOLVE-IV trial has shown that when considering the instructions for use and proper indication, Magmaris shows performance rates at 12 months, which are comparable to second-generation drug-eluting stents.

How should I place a Magmaris scaffold?

- Magmaris therefore appears as a safe and effective therapy for patients with coronary artery disease as long as it is properly employed focusing on the '4 Ps': patient selection, proper sizing, predilatation and postdilatation.

When should I place a Magmaris scaffold?

- Magmaris is a BRS currently limited in Europe inside clinical trials for patients with *de novo* lesions, which closely match the available scaffold sizes, and it is not recommended in ST-elevation myocardial infarction, cardiogenic shock, saphenous vein grafts, or in patients with poor medical compliance or contraindications to dual antiplatelet therapy. To date there is only one reported case of definite/probable scaffold thrombosis, which occurred early in BIOSOLVE-IV trial. However, the overall follow-up is still too short, and some key points should be kept in mind: first, fine-tuning of the Magmaris (especially postdilatation and overlap) is rather difficult due to the lack of radiological visibility of the scaffold itself. Second, despite imaging and histopathological data seem to demonstrate fast resorption and rapid endothelialization – which could nourish the finding of a zero definite/probable scaffold thrombosis rate to date – a confirmation by dedicated and systematic imaging studies is needed. Third, the same fast resorption might contribute to a fast loss of radial strength and decreased scaffolding properties that might rarely fail in opposing late recoil. Fourth, despite encouraging numbers, little clinical data are available about vasomotion recovery. A perfect implantation technique is therefore the main key to obtain the most from this technology.

Conclusion

- Available data could be useful to refine recommendations for use, and new investigator-initiated trial as well as future superiority randomized trial against drug-eluting stents should be planned to get out the most of this promising technology. Today, caution in everyday practice is needed since, due to the lack of evidences, the recent 2018 ESC/EACTS guidelines on myocardial revascularization recommend that any BRS, and Magmaris at present fall into this classification, should not be used outside well-controlled clinical studies.

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