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Early- and Long-Term Intravascular Ultrasound and Angiographic Findings After Bioabsorbable Magnesium Stent Implantation in Human Coronary Arteries

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Objectives This study aimed to evaluate the degradation rate and long-term vascular responses to the absorbable metal stent (AMS).

Background The AMS demonstrated feasibility and safety at 4 months in human coronary arteries.

Methods The PROGRESS-AMS (Clinical Performance and Angiographic Results of Coronary Stenting) was a prospective, multicenter clinical trial of 63 patients with coronary artery disease who underwent AMS implantation. Angiography and intravascular ultrasound (IVUS) were conducted immediately after AMS deployment and at 4 months. Eight patients who did not require repeat revascularization at 4 months underwent late angiographic and IVUS follow-up from 12 to 28 months.

Results The AMS was well-expanded upon deployment without immediate recoil. The major contributors for restenosis as detected by IVUS at 4 months were: decrease of external elastic membrane volume (42%), extra-stent neointima (13%), and intra-stent neointima (45%). From 4 months to late follow-up, paired IVUS analysis demonstrated complete stent degradation with durability of the 4-month IVUS indexes. The neointima was reduced by 3.6 $\pm$ 5.2 mm^3, with an increase in the stent cross sectional area of 0.5 $\pm$ 1.0 mm^2 (p = NS). The median in-stent minimal lumen diameter was increased from 1.87 to 2.17 mm at long-term follow-up. The median angiographic late loss was reduced from 0.62 to 0.40 mm by quantitative coronary angiography from 4 months to late follow-up.

Conclusions Intravascular ultrasound imaging supports the safety profile of AMS with degradation at 4 months and maintains durability of the results without any early or late adverse findings. Slower degradation is warranted to provide sufficient radial force to improve long-term patency rates of the AMS. (J Am Coll Cardiol Intv 2009;2:312–20) © 2009 by the American College of Cardiology Foundation

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Coronary stents are used as a mechanical means to overcome the major limitations of balloon angioplasty with enabling scaffolding and the prevention of early recoil and late vascular remodeling (1,2). The major limitations of stents are chronic inflammation, thrombosis, and restenosis, in association with artifact in noninvasive imaging of computerized tomography (CT) or magnetic resonance imaging (MRI) (3–5). Drug-eluting stents (DES) were introduced to minimize the restenosis and revascularization rates of metallic stents (6–9). However, DES were reported to be associated with delayed healing, inflammation, hypersensitivity to the drug or to the polymer, and endothelial dysfunction, which have contributed to the late thrombosis and perhaps mortality and mandated prolonged dual antiplatelet therapy (10–13). Nevertheless, the need for scaffolding is temporary and limited to the intervention and shortly thereafter, until healing and re-endothelialization is obtained. Beyond that, no utility or advantage for stents has been demonstrated, and their presence could be a nidus for late thrombosis and chronic inflammation.

Absorbable metal stents (AMS) were designed to overcome these drawbacks. Animal experiments demonstrated complete and rapid re-endothelialization, low neointima proliferation, and less inflammation when compared with metallic stents (14,15). The AMS are not associated with any imaging artifact with CT or MRI (16,17). The AMS initial clinical experience was in tibial arteries and demonstrated an excellent safety profile and acceptable patency rates at 24 months (18,19). This led to the initiation of the first trial to treat human coronary lesions with AMS, named PROGRESS-AMS (Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents) (20).

The PROGRESS-AMS study demonstrated that biodegradable magnesium stents can be implanted safely and that the stents degraded as intended without stent thrombosis, myocardial infarction, or death at 1 year (20). However, the study was associated with high angiographic restenosis rates of in-stent diameter stenosis (DS) (48.2 ± 17.0%) and in-segment late loss (0.83 ± 0.51 mm), which led to ischemic-driven target lesion revascularization of 23.8% at 4 months and 27.9% at 1 year. The objective of this study was to evaluate the mechanisms that contributed to restenosis of the AMS and the long-term arterial responses both inside and outside the stent as long as 28 months after implantation of the AMS by using serial quantitative angiographic and IVUS analysis in event-free patients.

Methods

The PROGRESS-AMS clinical trial was designed as a nonrandomized, prospective, multicenter trial to evaluate the efficacy and safety of an absorbable magnesium alloy stent (BIOTRONIK AG, Zurich, Switzerland) (20). The magnesium AMS geometrical design and mechanical properties have been described previously (14–17).

The methodology of the PROGRESS study was published previously (20). In brief, 63 patients in 8 centers with anginal symptoms and single de novo lesions with reference vessel diameters of 3.0 to 3.5 mm and lesion lengths ≤15 mm in native coronaries were enrolled. Seventy-one stents, 10 to 15 mm in length and 3.0 to 3.5 mm in diameter, were successfully implanted after pre-dilation in 63 patients.

IVUS analysis. Intravascular ultrasound was performed in 52 patients with a mechanical rotating element 40-MHz transducer (Atlantis IVUS catheter and Galaxy II console, Boston Scientific, Natick, Massachusetts) and in 13 patients from 2 centers with a synthetic aperture electronic system 20 MHz (Eagle Eye, Volcano, Rancho Cordova, California) with acquisition started after activation of a motorized pullback at 0.5 mm/s. All patients underwent angiographic and IVUS follow-up at 4 months. Nine patients underwent late IVUS follow-up (study ranges from 12 to 28 months). Computerized planimetry measured the reference segment external elastic membrane (EEM), stent, and lumen every millimeter within the stent. Neointima was calculated as stent minus lumen measures, whereas volumes were calculated by the summation of areas. Qualitative and quantitative IVUS assessment was performed by an independent core laboratory (Washington Hospital Center, Washington, DC). The IVUS characteristics were identified according to the criteria of the American College of Cardiology Clinical Expert Consensus document on the IVUS examinations performed before and after stenting and at follow-up (21). Quantitative measurements included EEM area, luminal area, and plaque and media area, which at follow-up could be further divided into neointimal area inside the stent struts and original plaque outside. The proximal and distal reference segments selected for analysis had the most normal-looking cross-section within 10 mm proximal and distal to the lesion. The average of the proximal and distal reference EEM and lumen cross sectional area (CSA) were used to assess stent expansion, defined as: minimal stent CSA/reference lumen CSA × 100 (21). Stent malapposition was defined as a lack of contact between any stent strut and the underlying vessel wall (22).

Long-term angiographic and IVUS analysis. The study protocol was amended to include late angiographic and IVUS long-term follow-up, to further evaluate the natural history of vascular responses to the AMS. Of the initial 63 patients,

Abbreviations and Acronyms

AMS = absorbable metal stent(s)
BMS = bare-metal stent(s)
CSA = cross sectional area
DES = drug-eluting stent(s)
DS = diameter stenosis
EEM = external elastic membrane
IVUS = intravascular ultrasound
LLL = late lumen loss
MLD = minimum lumen diameter

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9 patients without any clinical events, including revascularization, through the 28-month follow-up with serial (after procedure, 4-month, and late follow-up [12 to 28 months]) and analyzable IVUS data were selected for this substudy.

Quantitative IVUS and angiographic analysis. The quantitative coronary angiography (QCA) analyses were performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands). The serial IVUS (after procedure, 4-month, and late follow-up) procedures were performed after administration of 200 μg intracoronary nitroglycerin with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotape, and the images were digitized for analysis. Two coronary segments were subjected to coronary angiography: in-stent and -lesion. The in-stent analysis encompassed only the 10- to 15-mm-long segment covered by the stent. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion restenosis were defined as ≥50% DS at follow-up within the stent and target lesion, respectively. Minimum lumen diameter (MLD) and percent DS were measured for each segment. In-stent late lumen loss (LLL) was calculated as post-procedural MLD minus follow-up MLD. Intimal hyperplasia volume was calculated as stent volume minus luminal volume. Percent intimal hyperplasia was defined as intimal hyperplasia volume/stent volume.

Statistics. Descriptive statistics reported mean values, SD or median, and range for continuous data sets and absolute and relative frequencies for categorical data. Comparisons between the same measurements at different time points were performed with a 2-tailed paired t test or the Wilcoxon signed-rank test. A probability value <0.05 was considered statistically significant. The SAS 9.1 software (SAS, Cary, North Carolina) was used.

Results

Patients and procedural characteristics. The patient and procedural characteristics for the group that had serial (after the procedure, at 4 months, and at late follow-up) IVUS examinations compared with the entire PROGRESS study cohort are displayed in Table 1. Comparable baseline demographic and angiographic data indicate that the data in the serial IVUS cohorts are representative of the overall randomized study population (Tables 1 and 2).

Quantitative angiographic results. The baseline angiographic indexes and the post-implantation angiographic results of the group with serial long-term follow-up were similar to the entire cohort (Table 2). The follow-up angiographic analysis of the group with serial angiographic studies is displayed in Table 3. Overall 8 subjects underwent repeat angiography between 12 and 28 months after implantation, with available QCA analyzable films. The median difference between in-stent late loss at 4 months and the late follow-up was −0.23 mm (range −0.93 to 0.05), with a median reduction of 8% in DS. A similar observation was made for in-segment difference in late loss with a median of −0.32 mm (range −0.92 to 1.29) and reduction median in-segment DS from 21.5% to 12% at 4 months and the late follow-up, respectively. Furthermore, the in-stent MLD was stable or increased from that at 4 months to the long-term follow-up with the median long-term follow-up MLD of 2.17 mm and a difference between follow-ups of 0.22 mm. All but 1 patient increased a minimum of 0.1 mm between follow ups; this patient had a stagnant MLD of 2.3 at both 4-month and long-term follow-ups.

Table 1. Baseline Clinical Characteristics of the Study Population and of IVUS Subset Population

	Overall Study Population (n = 63)	Long-Term Follow-Up Subset (n = 8)*
Age (yrs), mean ± SD	61.3 ± 9.5	62.8 ± 7.1
Male	44 (70)	7 (78)
Stable angina	52 (83)	8 (89)
Unstable angina	6 (10)	1 (11)
Prior CABG	3 (5)	0 (0)
Prior myocardial infarction	26 (41)	6 (67)
Prior PCI	15 (24)	2 (22)
Prior PCI of the target vessel	14 (22)	2 (22)
History of CVA or TIA	1 (2)	0 (0)
History of PVD	4 (6)	1 (11)
History of diabetes	11 (18)	0 (0)
Insulin dependent diabetes	3 (5)	0 (0)
Any smoking history	30 (48)	6 (67)
Hypertension	41 (65)	8 (89)
Hyperlipidemia	39 (62)	5 (56)
Lesions treated		
RCA	23 (37)	3 (33)
LAD	22 (35)	2 (22)
LCX	18 (29)	4 (44)
ACC/AHA lesion type A	31 (49)	4 (44)
ACC/AHA lesion type B1/B2	32 (51)	5 (56)
ACC/AHA lesion type C	0 (0)	0 (0)

Values are n(%), unless otherwise indicated. *There are no statistical differences between the patients who underwent serial follow-up and those who did not (Fisher exact test).

ACC/AHA = American College of Cardiology/American Heart Association; CABG = coronary artery bypass graft surgery; CVA = cerebrovascular accident; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack.

IVUS results. The overall analysis included 32 subjects who had IVUS images acquired before the AMS implantation, 57 studies immediately after implantation, and 48 studies at 4 months, and overall 35 pair analysis after AMS implantation IVUS examination detected thick stent struts, which were well apposed to the vessel wall (Fig. 1). The overall final minimum stent CSA was 6.2 ± 1.5 mm^2.

Changes up to 4 months. At 4 months' follow-up, the strut echoreflectivity was drastically diminished, yet it was still possible to identify their original position as

Table 2. Baseline Angiographic Characteristics of the Study Population and of the Long-Term Follow-Up Subset Population

	Overall Study Population	Long-Term Follow-Up Subset
Angiographic characteristic before stenting		
Reference diameter (mm)	2.75 (0.47), 63	2.97 (0.43), 7
Minimal luminal diameter (mm)	1.05 (0.38), 62	0.95 (0.44), 7
Diameter stenosis (%)	61.48 (13.10), 62	68.07 (15.42), 7
Lesion length (mm)	9.84 (3.97), 59	9.90 (6.30), 6
Angiographic characteristic after stenting		
Reference diameter (mm)	2.68 (0.46), 60	2.78 (0.56), 8
Stented length (mm)	12.79 (3.73), 60	12.42 (3.25), 8
In-segment minimal luminal diameter (mm)	2.17 (0.38), 60	2.09 (0.52), 8
In-segment diameter stenosis (%)	20.50 (7.50), 60	24.88 (7.38), 8
In-segment acute gain (mm)	1.11 (0.42), 59	1.14 (0.56), 8
Proximal margin minimal luminal diameter (mm)	2.60 (0.47), 60	2.57 (0.45), 7
In-stent minimal luminal diameter (mm)	2.46 (0.37), 60	2.56 (0.41), 8
Distal margin minimal luminal diameter (mm)	2.28 (0.44), 60	2.16 (0.54), 7
Proximal margin diameter stenosis (%)	11.87 (8.47), 60	13.29 (12.89), 7
In-stent diameter stenosis (%)	12.43 (5.64), 60	13.29 (9.46), 7
Distal margin diameter stenosis (%)	16.66 (9.11), 60	21.93 (9.16), 7
In-stent acute gain (mm)	1.41 (0.45), 59	1.60 (0.45), 8

Values are mean (SD), n. There are no statistical differences between the patients who underwent serial follow-up and those who did not.

small circular areas with higher echo reflection than the surrounding tissue but without shadowing (Fig. 1). With these areas as markers indicating the border zone between the original plaque and the neointima, the mechanism of the structural changes leading to lumen loss at follow-up after implantation of an AMS stent could be quantitatively analyzed. The overall IVUS indexes analysis is displayed in Table 4. The LLL was the combined effect of a decrease in EEM area and of the area originally encircled by the stent (42%, -18.9 ± 45.4 mm^3, and 18%, -23.9 ± 32.9 mm^3) and neointima formation (40% of the entire LLL, -20.1 ± 14.7 mm^3), with no significant changes in the original plaque (Fig. 2).

Changes from 4 months to 12 to 28 months. At later follow-up, the location of the stents was assisted by side branches, because there was no evidence of the presence of struts (Fig. 3). Furthermore, there was neither calcification nor any adverse vascular changes seen by IVUS. The IVUS indexes at follow-up after 4 months remained stable over the course of the long-term follow-up and are displayed in Table 5. Overall there was not a significant change from 4 months to the later follow-up time points for all IVUS indexes as shown in Figure 4. Furthermore, at long-term follow-up there was no evidence of aneurysm formation or calcifications at the site of the previously stented segment and at the edges.

Discussion

This paper presents the first long-term (up to 28 months) serial angiographic and IVUS analyses after deployment of an AMS. The analysis detected the main features of the AMS in patients who underwent coronary implantation: 1)

Table 3. Angiographic Characteristics for the 8 Patients Undergoing Serial Follow-Up

	Baseline, After Stenting	4 Months Follow-Up	>12 Months Follow-Up
Reference vessel diameter, mm	2.8 (1.9 to 3.5)	2.9 (2.3 to 3.3)	3.3 (2.3 to 3.6)
In-stent diameter stenosis, %	12 (4 to 27)	35.5 (14 to 57)	24.5 (11 to 44)
In-stent minimal luminal diameter, mm	2.6 (2.0 to 3.1)	1.8 (1.1 to 2.6)	2.2 (1.6 to 2.9)
In-stent late loss, mm	—	0.66 (−0.1 to 1.66)	0.44 (−0.09 to 0.73)
In-segment diameter stenosis, %	25.5 (16 to 34)	37 (14 to 57)	30.5 (11 to 61)
In-segment minimal luminal diameter, mm	2.0 (1.3 to 3.0)	1.7 (1.1 to 2.6)	2.0 (1.4 to 2.4)
In-segment late loss, mm	—	0.2 (−0.4 to 1.5)	0.1 (−0.4 to 0.9)
Change between follow-up, mm			
Delta in-stent late loss	—	—	−0.2 (0.9 to 0.1)
Delta in-segment late loss	—	—	−0.3 (−0.9 to 1.3)

Values are median (range).

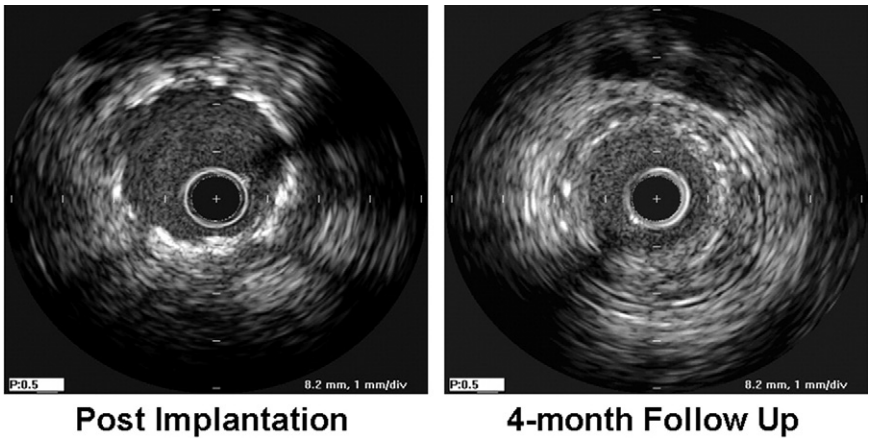

Figure 1. Absorbable Metal Stent After Implantation and at 4 Months' Follow-Up

Intravascular ultrasound imaging after implantation and at 4 months' follow-up, demonstrating adequate expansion and apposition of the stents to the vessel wall and degradation of the thick struts seen immediately after implantation over the 4 months of the follow-up.

Table 4. IVUS Characteristics for all Patients at 4 Months Follow-Up

	Overall	n
Before		
Minimum stent CSA (mm^2)	5.4 ± 1.5	32
Minimum vessel CSA (mm^2)	15.4 ± 4.8	30
After		
Stent length index (mm)	15.9 ± 4.1	50
Minimum stent CSA (mm^2)	6.2 ± 1.5	57
Minimum vessel CSA (mm^2)	14.6 ± 4.2	56
Stent volume index (mm^3)	116.5 ± 40.2	50
Lumen volume index (mm^3)	116.9 ± 40.0	50
EEM volume index (mm^3)	254.4 ± 84.4	45
4 months follow-up		
Stent length follow-up (mm)	16.2 ± 4.1	42
Minimum stent CSA, follow-up (mm^2)	4.2 ± 1.6	48
Minimum vessel CSA, follow-up (mm^2)	12.6 ± 4.4	48
Stent volume follow-up (mm^3)	95.0 ± 38.9	42
Lumen volume follow-up (mm^3)	74.9 ± 32.8	42
EEM volume follow-up (mm^3)	242.8 ± 87.4	40
Intimal hyperplasia follow-up (mm^3)	20.4 ± 14.4	42
Extra-stent neointima follow-up (mm^3) (defined as EEM volume − stent volume)	148.4 ± 53.9	42
Net volume obstruction (%)	21.8 ± 11.0	42
Change from baseline to 4 months follow-up		
Minimum stent CSA change (mm^2)	−2.0 ± 1.3	43
Minimum vessel CSA change (mm^2)	−1.8 ± 1.9	42
Stent volume change (mm^3)	−23.9 ± 32.9	35
Lumen volume change (mm^3)	−45.2 ± 40.5	35
EEM volume change (mm^3)	−18.9 ± 45.4	29

CSA = cross sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound.

immediate after deployment of the AMS with some additional use of post-balloon dilation, the stent is well-expanded with adequate apposition to the vessel wall; however, the final CSA of the AMS seems to be smaller when compared with the 1 obtained with nonabsorbable metallic stents; 2) the main mechanisms for restenosis with the AMS are early recoil (negative remodeling of the vessel area) and modest neointima formation; 3) as seen in the current study the stents are degraded fast and undergo nearly complete degradation at 4 months; 4) after complete degradation there is stability and durability of the vessel indexes (up to 28 months); and 5) there are no adverse effects to the vessel wall at the site and the edges of where the AMS was implanted.

Early IVUS findings after AMS implantation. The IVUS imaging immediately after AMS implantation detected thick struts with adequate expansion and apposition of the stent to the vessel wall. Post-balloon dilation to optimize the deployment results was required in 42 patients (66.7%), which is an acceptable rate for stent technology. Despite this fact, the mean stent CSA of the AMS after implantation was 6.2 ± 1.5 mm^2, which is lower than the minimum CSA of nondegradable metallic stents reported previously with bare metal stents (BMS) for similar vessel sizes (3.0 to 3.5 mm). In the Taxus II (Boston Scientific, Natick, Massachusetts) study, the BMS minimum CSA was 8.1 ± 2.5 mm^2 (23). The AMS stent volume after implantation was 116.5 ± 40.2 mm^3, which is lower when compared with the stent volume of the BMS in the Taxus IV study (151 ± 56 mm^3). Thus, the initial implantation of the AMS has less expansion and less stent volume when compared with stainless steel metallic stents (24). These differences might result from differences in the radial force, which is lower in the magnesium when compared with the stainless steel

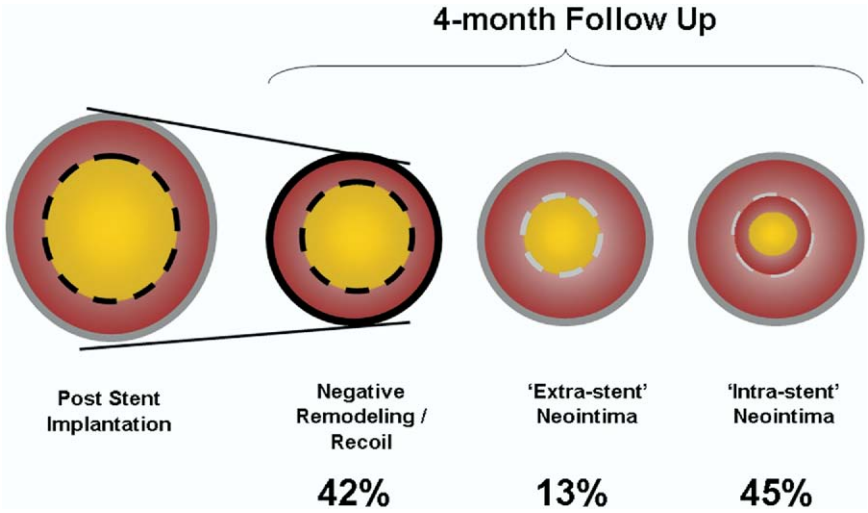

Figure 2. Mechanism of Absorbable Metal Stent Restenosis

Mechanism of absorbable metal stent restenosis, demonstrating the relative contribution of the components of restenosis: stent recoil and neointima within the stent (intra-stent) and outside of the stent (extra-stent).

alloy, by immediate recoil after implantation as seen at post-balloon angioplasty or by a combination of the two. These IVUS results are concordant with the angiographic QCA results, which measured in-stent MLD immediately after stenting as 2.47 ± 0.37 mm, whereas the reference vessel was measured at 2.74 ± 0.42 mm. Because the angiographic elastic recoil after implantation was calculated only as 7 ± 15%, it is probable that differences between the historical reported lumen volume and the AMS lumen volume are mainly due to differences in stent expansion due to the weakness of the magnesium alloy when compared with stainless steel or cobalt chromium. This suggests that,

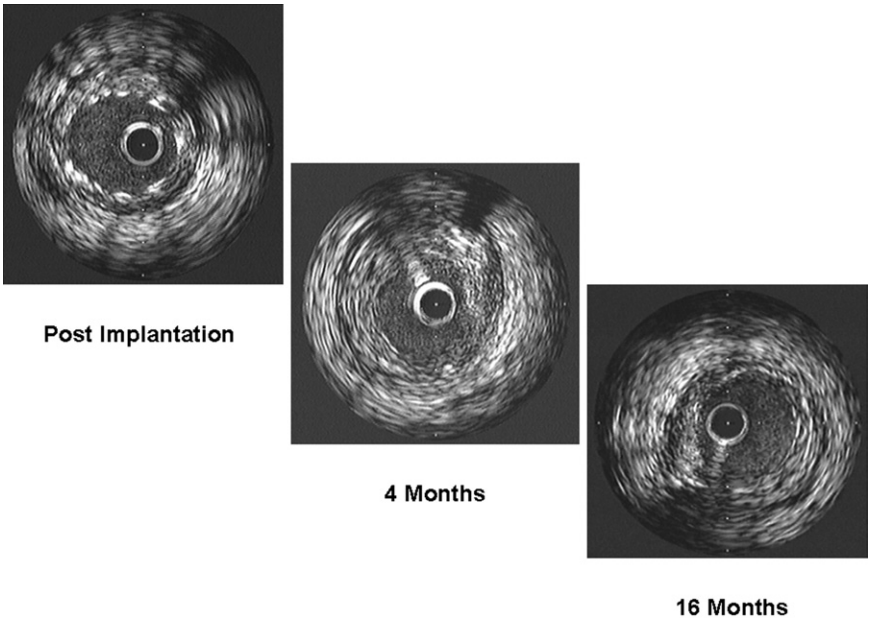

Figure 3. Complete Degradation of Absorbable Metal Stent at 4 and 16 Months

Serial intravascular ultrasound imaging after implantation, at 4 and 16 months, demonstrating degradation of the struts with preservation of the lumen.

Table 5. IVUS Data >12 Months (Average Time to IVUS 20.3 ± 6.4 Months)

	Baseline, After Stenting	4 Months Follow-Up	>12 Months Follow-Up
Minimum stent CSA (mm^2)	5.7 (4.2 to 7.8), 7	3.6 (2.5 to 7.2), 7	4.0 (1.9 to 8.3), 8
Minimum vessel CSA (mm^2)	13.9 (8.1 to 19.9), 7	14.0 (7.3 to 19.8), 7	9.9 (5.8 to 20.8), 8
Stent volume (mm^3)	124.5 (82.9 to 136.8), 5	106.0 (69.3 to 158.8), 7	94.2 (46.7 to 171.2), 7
Lumen volume (mm^3)	124.5 (82.9 to 136.8), 5	100.9 (50.7 to 129.1), 7	93.0 (40.6 to 140.0), 7
EEM volume (mm^3)	234.5 (156.7 to 303.9), 3	259.9 (142.7 to 345.5), 6	203.8 (122.1 to 324.7), 6
Intimal hyperplasia (mm^3)	—	14.6 (2.9 to 29.7), 7	6.3 (1.2 to 31.1), 7
Extra-stent neointima (mm^3) (defined as EEM volume − stent volume)	—	137.3 (73.4 to 186.8), 6	106.2 (68.0 to 153.5), 6
Net volume obstruction (%)	—	10.2 (4.2 to 27.5), 7	11.0 (1.3 to 18.2), 7
Change between follow-up			
Minimum stent CSA change (mm^2)	—	—	0.6 (−1.4 to 1.6), 7
Minimum vessel CSA change (mm^2)	—	—	0 (−2.5 to 2.2), 7
Stent volume change (mm^3)	—	—	4.5 (−4.4 to 16.1), 6
Lumen volume change (mm^3)	—	—	7.6 (−8.0 to 22.4), 6
EEM volume change (mm^3)	—	—	−1.2 (−38.4 to 6.7), 5

Values are median (range), n. No statistical significance at the 0.05 level (signed rank test).
Abbreviations as in Table 4.

when implanting AMS, the "bigger the better" lumen theory on implantation is applicable and the focus should be on obtaining larger lumen perhaps by post-dilation with semi-compliant balloons.

IVUS findings of the AMS from implantation up to 4 months. The main findings at this time frame suggest that early recoil with 42% reduction in EEM is a major contributor for the LLL and restenosis. This reduction in EEM, which is not seen in nondegradable metallic stents, can be attributed to early and fast degradation and loss of the radial force, perhaps even few weeks after AMS implantation. An IVUS study in 1 patient who was brought to an earlier study at 3 weeks after implantation due to atypical chest pain indicated that the nearly 50% of the stent struts were degraded, thus suggesting a degradation rate immediately after AMS implantation faster than initially expected. Although the patient did not experience compromised lumen or stent malapposition at that early time point, restenosis was detected at 4 months—mainly due to recoil. Thus, it is conceivable that the early and fast degradation of the stent mass significantly weakened the radial force of the stent and could be the main cause for the early vessel recoil that does not have enough stent support to prevent early and late vessel contraction as part of the vessel's healing process.

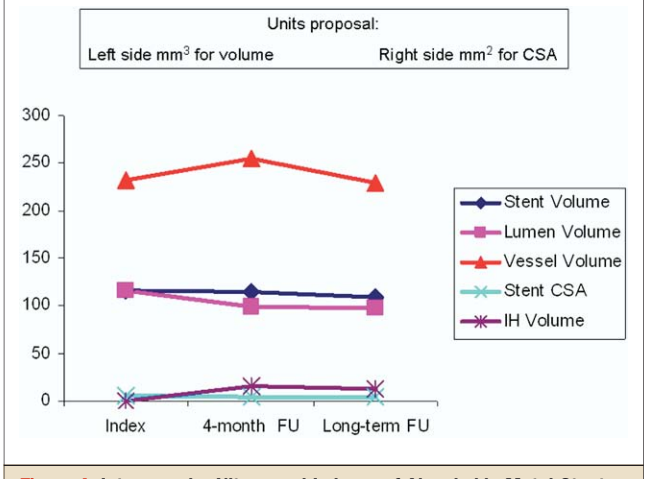

Figure 4. Intravascular Ultrasound Indexes of Absorbable Metal Stent From Index Through Long-Term Follow-Up

Intravascular ultrasound indexes at 4 months through long-term follow-up (FU) demonstrating durability of the results from 4 months to late follow-up. CSA = cross sectional area; IH = intimal hyperplasia.

The question of how long we need the stent to support the vessel wall after deployment has never been convincingly answered. With BMS, endothelialization is nearly complete at 1 month, but does that mean that stent scaffolding is not needed beyond this time point? In the present study the stent was nearly completely degraded at 4 months, but the question is how much of the stent was degraded at 1 month and whether there was enough radial support at 1 month to prevent recoil. Thus the question with bioabsorbable stents should not focus only on the overall degradation time but on the rate of degradation or the degradation kinetics. Very early and fast degradation will result in loss of radial force within weeks or days and could lead to early recoil. Because we did not observe further recoil from 4 months up to 28 months we can assume that there is no need for further scaffolding beyond 4 months and, hence, degradation times beyond this point. To address the recoil phenomenon seen with the AMS, several approaches can be taken to modify the overall degradation and the degradation rate; among them are change in the alloy composition, change in stent design and strut thickness, and passivation technology, and

the like. The neointima formation component of the restenosis seen with AMS was modest when compared with previous studies with BMS. The intimal volume of the AMS at 4 months (20.4 ± 14.4 mm^3) was less than that reported for the Express stent at 9 months (41 ± 23 mm^3) but still higher when compared with the Taxus stent at 9 months (18 ± 18 mm^3) (24). The relatively lower neointima in the AMS compared with BMS technology could be explained by the fact that the stent is degraded with a decrease in strut thickness and elimination of the stent, therefore, the trigger for neointima formation is gone. These lower indexes on neointima rule out a massive inflammatory process during the degradation process. Although the time frame is different, given the fact that there was no more neointima formation reported in the AMS group after 4 months, it is possible that if the recoil phenomenon was eliminated from the equation, the AMS could compete with the Taxus stent in terms of restenosis. The question remains as to whether the recoil can be eliminated and, if so, at what price.

One of the questions with bioabsorbable stents is related to their degradation products and what is left on the arterial wall. Prior animal studies with the AMS demonstrated a compound including phosphate and calcium in the vessel wall (15), leading to reflections seen by IVUS, but unlike the metallic struts, they are seen without shadows, which help to differentiate this material from metal. Overall, there was some variability in degradation, because it was completed 4 times in all patients, but no documented distal embolization was seen in any of the patients. Furthermore, at longer follow-up, the reflections were not detected, which ruled out late calcifications after degradation of the AMS.

IVUS findings of the AMS after 4 months. The long-term angiogram and IVUS observations up to 28 months in 8 patients who did not experience an event at 4 months reassured us that there is no late development of neointima formation or late recoil beyond the 4 months' time point. On the contrary, in some patients there was evidence of regression in the neointima, and in some patients we observed an increase in vessel and lumen volume by IVUS. This was supported by the QCA analysis that demonstrated overall negative late loss at the previously stented segment. Finally there was no other IVUS or angiographic adverse findings, including evidence of calcifications or aneurysms, at the previously stented segments, including the edges.

The stability and durability of the results after 4 months when the AMS reached complete degradation suggests that with AMS perhaps 4-month results can predict the long-term outcome of the vessel and its edges. If this is true, it is different from the BMS or DES that require much longer time for follow-up until stability is obtained. This difference can be explained by the nearly complete degradation of the AMS at 4 months.

The present study used the AMS without drug elution from the stent and resulted in higher restenosis, which was anticipated due to unexpected recoil phenomenon, most likely resulting from an early loss of radial support. An animal study using vascular brachytherapy with beta radiation as adjunct therapy to AMS implantation in porcine coronary arteries demonstrated a reduction in the neointima formation but did not have an impact on the recoil after 30 days of stent implantation (25). Therefore, it is likely that a drug-eluting AMS with the current alloy and stent design would probably not have impacted the recoil phenomenon but would have reduced the neointima formation as reported in the bioabsorbable everolimus-eluting stent, which demonstrated LLL (0.44 mm) (26) compared with the BMS (0.87 mm) but higher late loss when compared with the Xience (Abbott Laboratories, Abbott Park, Illinois) stent (0.10 mm) with the same drug (27). Therefore, to reduce the recurrence rate with the AMS, efforts should be directed first to improve its mechanical integrity. This can be done by changing the alloy composition and the stent design and perhaps by means of passivation that will slow the initial degradation kinetics. Drug elution might further contribute to a reduction of the neointima and to acceptable late loss and restenosis rates. The comforting results of the present study are that once this goal is obtained there will be durability and stability of the results over the first months after implantation.

Study limitations. The current observation is limited to a small cohort of patients who were enrolled in the first feasibility study with AMS. An even smaller number of patients were available for the later angiographic and IVUS follow-up time points. In addition, the late follow-up was not consistent and ranged from 12 to 28 months. Nevertheless, the IVUS findings available after implantation and at follow-up and the late angiographic and IVUS availability at later time points enabled us to understand the current behavior, benefits, and limitations of this technology and assist in the planning of an improved version of the AMS to be tested in the future.

Conclusions

IVUS imaging of the AMS in human coronaries identified early recoil as a main contributor for restenosis at 4 months. Late IVUS imaging supports the safety profile of AMS—with nearly complete degradation at 4 months and durability of the results without any early or late adverse findings. Efforts to improve the radial force of the stent and the degradation kinetics are warranted to eliminate early recoil and improved patency rates of the AMS when absorption is complete. Drug elution of the AMS might be mandatory to minimize the neointima formation and to maintain sufficient lumen, if the recoil component remains despite the planned iterations in the AMS technology.

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Key Words: bioabsorbable magnesium stent ■ intravascular ultrasound ■ neointima ■ recoil.