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Special feature: Bioresorbable scaffolds

First-in-human evaluation of the novel sirolimus-eluting ultra-high molecular weight APTITUDE bioresorbable scaffold: 9- and 24-month imaging and clinical results of the RENASCENT II trial

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A list of the study collaborators can be found in the Appendix paragraph.

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KEYWORDS

- bioresorbable scaffolds
- optical coherence tomography
- QCA

Abstract

Aims: The novel sirolimus-eluting ultra-high molecular weight APTITUDE bioreabsorbable vascular scaffold (BRS) displays higher mechanical strength, expansion capabilities and resistance to fracture compared to other BRS technologies. RENASCENT II is a prospective, multicentre first-in-human clinical study evaluating the clinical performance of the APTITUDE BRS in the treatment of single *de novo* coronary lesions among patients undergoing percutaneous coronary intervention.

Methods and results: The APTITUDE BRS was tested in a prospective study in two countries (Italy and Colombia). Study objectives were angiographic in-scaffold late lumen loss (IS-LLL) measured by quantitative coronary angiography (QCA) and target vessel failure (TVF) defined as the composite rate of cardiac death, target vessel myocardial infarction (TV-MI) or ischaemia-driven target lesion revascularisation (TLR) at 9 and 24 months. A total of 60 patients were enrolled. All patients underwent lesion predilatation and 46 patients (76.7%) underwent post-dilatation. Clinical device and procedural success were 98.3% (59/60 patients) and 100%, respectively. Angiographic late lumen loss was 0.19±0.26 mm at 9 months and 0.3±0.41 mm at 24 months. At 9 months, TVF occurred in 2/59 patients (3.4%) due to TV-MI but there was no TLR. No further cases of TVF, MACE or stent thrombosis were reported up to 24-month follow-up.

Conclusions: In this multicentre prospective study, the APTITUDE BRS was shown to be safe and effective in the treatment of single coronary lesions at 24-month clinical follow-up.

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Abbreviations

BRS	bioresorbable scaffold
BVS	bioresorbable vascular scaffold
DES	drug-eluting stent
DS	diameter stenosis
EES	everolimus-eluting stent
IS-LLL	in-scaffold late lumen loss
IVUS	intravascular ultrasound
LVEF	left ventricle ejection fraction
MACE	major adverse cardiovascular events
MLD	minimal luminal diameter
OCT	optical coherence tomography
PLLA	poly-l-lactic acid
QCA	quantitative coronary angiography
TIMI	Thrombolysis In Myocardial Infarction
TLR	target lesion revascularisation
TVF	target vessel failure
TV-MI	target vessel myocardial infarction

Introduction

Current drug-eluting stents (DES) are safe and have very low thrombosis rates[1]. However, the potential limitations of DES include the permanent presence of a metallic foreign body within the artery and often a durable polymer, either of which may cause vascular inflammation, neoatherosclerosis and restenosis or perpetuate the risk of very late stent thrombosis[2]. Moreover, metallic stents indefinitely impair the physiological vasomotor function of the vessel and also the potential for future grafting within the stented segment[3,4]. In this context, bioresorbable scaffolds (BRS) represent the latest innovation in the field of percutaneous coronary intervention (PCI). They aim to provide a transient vessel scaffold, preventing acute vessel closure/recoil and subsequently dissolve. In addition, complete bioresorption of the scaffold is associated with plaque regression, late vessel lumen enlargement and restoration of vasomotion within a few years. Thus, BRS hold the potential to achieve the paradigm of vascular restoration therapy, restoring both vessel lumen and vascular function eliminating the risk of late stent-related events.

However, BRS have several limitations including thicker, wider struts, less radial strength and limited expansion capabilities. These limitations require altered implantation techniques to those of standard DES, especially in complex coronary artery disease. To counteract the lower radial strength ascribable to the nature of their manufacturing, some companies have designed their BRS products with struts thicker than most second-generation DES. Furthermore, BRS have been shown to have an increased stent thrombosis risk compared to metallic DES, particularly very late stent thrombosis (VLST)[5,6]. Scaffold dismantling related to scaffold reabsorption was found to be the commonest mechanism of VLST in the INVEST registry[7].

New-generation thinner BRS implanted using an optimal technique might offer early and intermediate-term outcomes comparable to contemporary metallic DES (prior to complete bioresorption), with improved long-term event-free survival.

The reduction of strut thickness from the current 150 µm BRS to the newer-generation scaffolds having 100-120 µm struts may reduce flow disturbances and hence thrombogenicity[8]. There are multiple newer-generation BRS at different stages of development with varying mechanical or bioresorption properties. RENASCENT III is a first-in-man (FIM) clinical safety trial of the newest (98 µm strut thickness) BRS MAGNITUDE® (Amaranth Medical Inc., Mountain View, CA, USA). These new BRS first have to show clinical safety in FIM trials and subsequently be tested further in randomised controlled trials (RCT) with proven metallic DES.

The aim of the RENASCENT II trial is to evaluate the clinical and safety performance of the APTITUDE® (Amaranth Medical Inc.) BRS.

Editorial, see page 103

Methods

STUDY DESIGN AND PATIENT POPULATION

The RENASCENT II study is a prospective, non-randomised, non-inferiority study of the APTITUDE bioresorbable drug-eluting coronary scaffold (NCT02568462) that enrolled 60 patients from Colombia and Italy. The ethics committee at each participating institution approved the protocol and each patient gave written informed consent before inclusion. As required by national regulations, the approval of the relevant national regulatory agency was also obtained.

Inclusion and exclusion criteria are shown in **Supplementary Table 1**.

STUDY DEVICE

The APTITUDE design is based on the FORTITUDE® scaffold (Amaranth Medical Inc.). The FORTITUDE scaffold has been demonstrated to be biocompatible and to maintain mechanical integrity with controlled drug release in previous trials. The key design difference between the two is a reduction of strut thickness (APTITUDE 115 µm vs FORTITUDE 150 µm). The scaffold material (ultra-high poly-L-lactic acid [PLLA]), manufacturing process and delivery system have not changed.

The APTITUDE BRS is made with a continuous "closed cell" zigzag helical design made of ultra-high PLLA and coated with a polymer-antiproliferative drug matrix (poly-L-lactic acid + sirolimus) mixed in a 1:1 polymer to drug ratio with 90% of the drug being released by 90 days.

In vitro studies have shown that the scaffold degrades over time with the reduction in molecular weight reaching approximately 50% at 8 months and greater than 85% at 18 months. The radial support is maintained for 8 to 10 months[9]. As the scaffold degrades, the polymer is converted into lactic acid, which is metabolised through the Krebs cycle. The degradation process takes approximately two years and is very similar to that of the Abbott BVS bioresorbable scaffold.

The polymer and design of the scaffold provide uniform strength in all directions. This uniform strength also makes the scaffold less likely to fracture or crack in high stress areas.

Supplementary Table 2 shows features of the APTITUDE BRS. **Figure 1** shows optical coherence tomography (OCT) images comparing the Abbott BVS, and the Amaranth FORTITUDE and APTITUDE.

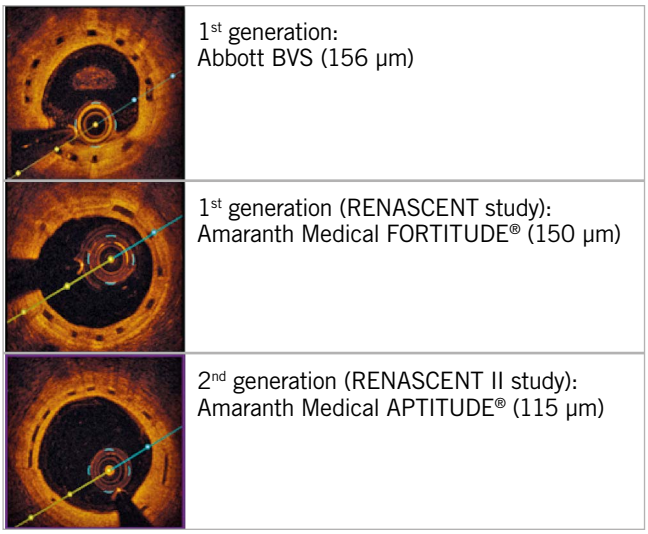

Figure 1. *OCT images showing the APTITUDE BRS with thinner struts (9 months post implantation) in comparison with the Abbott BVS and FORTITUDE BRS.*

STUDY PROCEDURE

Target lesions were treated using standard interventional techniques; successful predilatation of the target lesion was mandatory (1:1). Baseline intravascular ultrasound (IVUS) assessment was performed during the index procedure to evaluate vessel size and degree of calcification, and to determine the appropriate scaffold size. The target lesion had to be treated with a single study device and planned overlapping with another stent was not allowed. Post-dilatation was not mandatory but allowed at the operator's discretion (if the angiographic result was suboptimal) using a non-compliant balloon with diameter ≤0.5 mm larger than the nominal scaffold size. Bail-out stenting with DES for non-flow-limiting edge dissection was recommended and, as per clinical practice, required for flow-limiting dissection. Post-procedural intravascular imaging with OCT was required in all cases.

Treatment with aspirin was started at least 24 hours before the procedure and a ≥75 mg/day dose was required for the duration of the study. A loading dose of ≥300 mg clopidogrel (or 60 mg prasugrel/180 mg ticagrelor) was administered before the procedure, followed by 75 mg clopidogrel daily (or 10 mg prasugrel daily/90 mg ticagrelor twice daily) for a minimum of 12 months. The duration of dual antiplatelet therapy beyond 12 months was left to the discretion of the physician.

The 30-day follow-up was performed via an office visit or by phone call. At nine months, angiographic follow-up with OCT was performed. Coronary computed tomography angiography (CTA) or invasive coronary angiography was carried out at 24 months, depending on centre preference. Colombian centres performed invasive coronary angiography while Italian centres preferred to use coronary CT. All data were collected in dedicated electronic case report forms. The study stopped at the end of 24 months.

STUDY OBJECTIVES

The primary performance endpoint was in-scaffold late lumen loss (IS-LLL), defined as the amount of vessel lumen diameter lost/gained at the time of angiographic follow-up measured by quantitative coronary angiography (QCA) at nine months. The assessment was made within the segment of vessel including the scaffold.

The primary safety endpoint was the incidence of target vessel failure (TVF), defined as cardiac death (Academic Research Consortium [ARC] definition)[4], target vessel myocardial infarction (TV-MI) (using the expert consensus document from the Society for Cardiovascular Angiography and Interventions [SCAI])[10], or clinically indicated target lesion revascularisation (TLR) (ARC definition) at nine months. Although the adjudication of periprocedural MI was performed using the SCAI definition, additional analyses were performed using the third universal definition of MI[6]. Stent thrombosis was defined using the ARC "definite" or "probable" stent thrombosis definitions[4].

Furthermore, both "clinical device success", defined as successful delivery and deployment of the clinical investigation scaffold with a final residual stenosis of <50% by QCA after the index procedure, and "clinical procedure success", defined as clinical device success using any adjunctive device without occurrence of major adverse clinical events related to ischaemia up to day of discharge, were assessed.

Meditrial Europe Ltd (Zürich, Switzerland) was responsible for the submission of the protocol to the relevant ethics committees and authorities, monitoring of the patients' data and the reporting of serious adverse events to the respective authorities for the RENASCENT II trial. Adverse events were adjudicated by an independent clinical events committee. An independent core lab (Cardiovascular Research Foundation, New York, NY, USA) performed angiographic (QCA), OCT and CTA data analysis.

Angiographic, QCA, OCT image acquisition and data analysis are described in **Supplementary Appendix 1-Supplementary Appendix 4**, **Supplementary Figure 1** and **Supplementary Figure 2**.

STATISTICAL ANALYSIS

Angiographic IS-LLL at nine months was analysed using a one-sample t-test for non-inferiority. If the assumptions for normality were not met, then a Wilcoxon signed-rank test was used. When provided, the 95% confidence intervals were computed with the Gaussian approximation, taking into account the paired analysis. Paired comparisons between post-procedural and follow-up results were performed using a Wilcoxon signed-rank test. The results for the endpoints are presented using summary statistics and 95% confidence intervals. For discrete outcomes, the total number and percentage are presented.

Results

BASELINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS

The baseline clinical and angiographic characteristics of the study population are shown in **Table 1**. A total of 60 patients were enrolled, 23 in Colombia and 37 in Italy. The mean reference vessel diameter was 2.8±0.4 mm and lesion length 12.4±3.6 mm. Most of the lesions were type ACC/AHA B1-C (83.3%, n=50). There was moderate-severe calcification in six cases (10%). **Figure 2** shows the RENASCENT II study flow chart.

PROCEDURAL CHARACTERISTICS

Table 2 shows the procedural characteristics of the study population. Baseline IVUS assessment was performed during the index procedure in all patients to evaluate vessel size and grading of calcification, and to select the appropriate scaffold size. Appropriate predilatation was performed in 100% of the lesions. In 76.7% (n=46) of cases, post-dilatation was performed. There were no dissections requiring a bail-out DES.

Clinical device success was 98.3% (n=59); in one case the scaffold was not implanted due to inability to track through a calcified and tortuous vessel proximal to the target lesion. The resulting clinical procedure success rate was 100% (n=60).

STUDY OBJECTIVES

Table 3 shows results of major adverse cardiovascular events (MACE) during the trial up to 24-month follow-up. There were no major cardiovascular events in hospital or up to 30-day follow-up.

At nine months, 59 (98%) patients had completed clinical and mandatory angiographic follow-up. One patient did not receive the study device and, per protocol, exited the study at 30 days. At nine

Table 1. Baseline clinical and angiographic characteristics of the study population.

Baseline clinical characteristics		APTITUDE BRS (n=60) Mean±SD or % (n)
Male		78.3% (47)
Age, years		65.2±8.0
History of smoking		60.0% (36)
Medically treated diabetes		18.3% (11)
Medically treated hypertension		73.3% (44)
Clinical presentation	Stable angina	50.0% (30)
	Acute coronary syndrome	33.3% (20)
	Silent ischaemia	16.7% (10)
Previous MI		51.7% (31)
History of PCI		63.3% (38)
History of CABG		0%
LVEF		54.9±8.1%
Target artery	LAD	40.0% (24)
	LCX	30.0% (18)
	RCA	30.0% (18)
Lesion location		
Proximal-mid		81.7% (49)
Reference vessel diameter, mm		2.8±0.4
QCA diameter stenosis		63.2±10.8%
QCA length, mm		12.4±3.6
ACC/AHA lesion classification		
Type B1-C		83.3% (50)
Any bifurcation/side branch calcification		5.0% (3)
Moderate-severe		10.0% (6)
Pre-procedure TIMI 3 flow		100% (60)

CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention: QCA: quantitative coronary analysis; TIMI: Thrombolysis In Myocardial Infarction

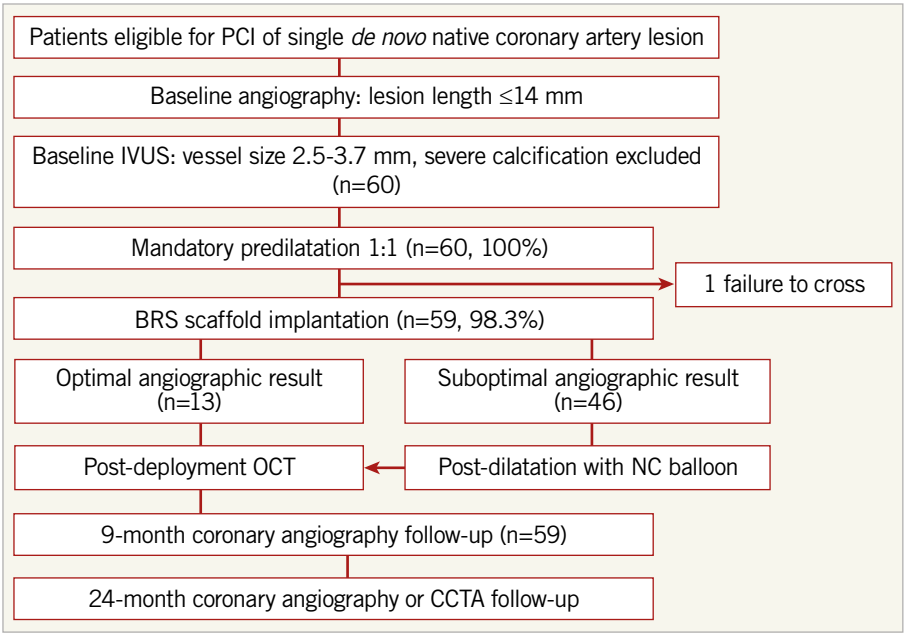

Figure 2. *A flow chart of the APTITUDE study design.*

Table 2. Procedural characteristics of the study population.

Index procedure characteristics	APTITUDE BRS (n=60) Mean±SD or % (n)
Pre-procedure diameter stenosis	63.2±10.8%
Predilatation prior to implant	100% (60)
Single post-dilatation using NC balloon	76.7% (46)
Max. scaffold deployment inflation pressure, atm	11.8±2.4
Final in-segment diameter stenosis	7.1±6.8%
Failure to cross due to severe calcification/tortuosity	1.7% (1)
Distal dissection treated with drug-eluting stent	0%
Clinical device success	98.3% (59)
Clinical procedure success	100%
atm: atmospheres; NC: non-compliant	

months, TVF was 3.4% (n=2) due to two non-Q-wave MIs (target vessel MIs) but there was no TLR. Details of these two cases are provided in **Supplementary Table 3**. No ischaemia-driven TLR or scaffold thrombosis was reported up to 24-month follow-up. There were two cases of binary stenosis at 24-month follow-up **(Supplementary Table 4)**. However, these patients were asymptomatic and no intervention was required as it was not clinically indicated. At 24-month follow-up, 24 out of 55 patients (43.6%) were still on dual antiplatelet therapy.

ANGIOGRAPHIC AND QCA ANALYSIS

Table 4 shows QCA measurements at baseline, post scaffold implantation, and at 9- and 24-month follow-up. IS-LLL was 0.35±0.33 mm at 9 months and 0.37±0.44 mm at 24 months **(Figure 3)**. Other significant QCA measurements were in-segment minimal luminal diameter (MLD) 1.0±0.3 mm at baseline, and

Table 4. Baseline, post-BRS implantation, 9- and 24-month coronary angiography and QCA measurements.

QCA measurements Mean±SD (n)	Baseline procedure (n=60)	Post-BRS implantation (n=59)	9-month follow-up (n=59)	24-month follow-up (n=17)
In-segment QCA analysis				
Interpolated RVD, mm	2.8±0.4	2.9±0.4	2.9±0.4	2.7±0.4
MLD, mm	1.0±0.3	2.5±0.4	2.3±0.4	2.1±0.5
Late lumen loss, mm	–	–	0.18±0.26	0.24±0.36
Diameter stenosis, %	63.2±10.8	13.7±6.2	17.7±9.1	19.6±13.8
In-scaffold QCA analysis				
Interpolated RVD, mm	–	3.1±0.4	2.9±0.4	2.7±0.4
MLD, mm	–	2.9±0.4	2.5±0.4	2.3±0.6
Acute gain, mm	–	1.9±0.4	–	–
Late lumen loss, mm	–	–	0.35±0.33	0.37±0.44
Diameter stenosis, %	–	6.5±5.5	13.4±9.4	15.3±16.6
MLD: minimal lumen diameter; RVD: reference vessel diameter				

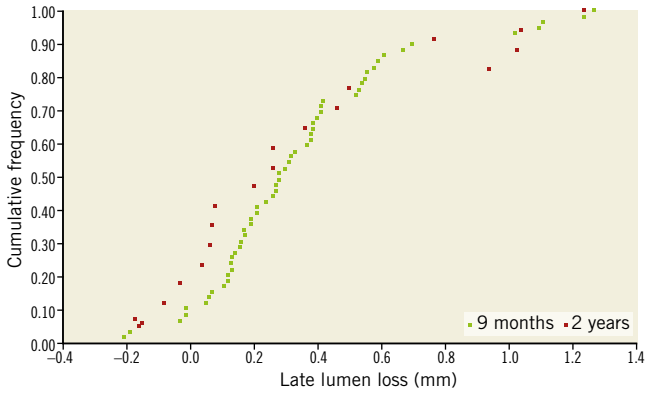

Figure 3. *Cumulative frequency of in-scaffold late lumen loss at 9 and 24 months.*

Table 3. Major adverse cardiac events - safety endpoints in hospital, at 30 days, and at 9- and 24-month clinical follow-up.

Safety endpoints, % (n)		In hospital (n=60)	Discharge to 30 days (n=60)	1 to 9 months (n=59)	9 to 24 months (n=56)	0 to 24 months (n=56)
TVF (cardiac death, TV-MI, or ID-TLR)		0%	0%	3.4% (2)	0%	3.4% (2)
All death		0%	0%	0%	0%	0%
Cardiac death		0%	0%	0%	0%	0%
Non-cardiac death		0%	0%	0%	0%	0%
Target vessel MI		0%	0%	3.4% (2)	0%	3.4% (2)
Q-wave MI		0%	0%	0%	0%	0%
Non-Q-wave MI		0%	0%	3.4% (2)	0%	3.4% (2)
Ischaemia-driven TLR		0%	0%	0%	0%	0%
PCI		0%	0%	0%	0%	0%
CABG		0%	0%	0%	0%	0%
ARC stent thrombosis	Definite or probable	0%	0%	0%	0%	0%
	Possible	0%	0%	0%	0%	0%
ARC: Academic Research Consortium; ID-TLR: ischaemia-driven target lesion revascularisation; TV-MI: target vessel myocardial infarction						

in-scaffold MLD 2.9±0.4 mm post BRS implantation, 2.5±0.4 mm at 9 months and 2.3±0.6 mm at 24 months. There was an acute gain of 1.9±0.4 mm post BRS insertion.

OCT ANALYSIS

OCT pullbacks were analysed in 53 lesions during the index procedure (post scaffold implantation) and 58 lesions at 9-month angiographic follow-up. **Supplementary Table 5** shows the in-scaffold OCT measurements. The percentage of intra-scaffold neointimal hyperplasia (NIH) volume at 9 months was very low (13.3±6.1%). The total percentage of covered struts at 9 months was 97.0%, of which 96.52±5.02% were apposed to the vessel wall. The total percentage of uncovered struts at 9 months was very low (2.97%). **Figure 4** shows the mean outer scaffold area in 51 matched patients at post implant and at nine months (for each patient).

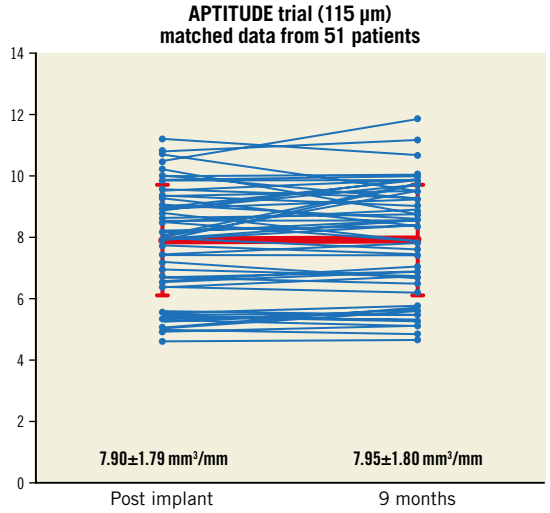

Figure 4. *Scaffold integrity at 9 months: mean outer scaffold area by OCT for 51 patients post implant and at 9 months.*

Discussion

The major findings of the international, multicentre study of the novel thin-walled 115 µm APTITUDE bioresorbable scaffold are the following: a) high clinical device success rate; b) low MACE rate up to 24-month follow-up (3.4%; both non-Q-wave MIs related to non-TLR) as expected in this population, c) no scaffold thrombosis, d) scaffold stability maintained up to 24 months, e) high level of strut coverage (97.0%) and low rate of malapposition (0.037%, all covered) as evidenced by OCT.

One of the major challenges in the BRS field has been the development of scaffolds displaying stent-like mechanical strength and resistance to the compressive load imposed by vessel recoil following deployment in challenging anatomical conditions[9]. In first-generation BRS, crystalline polymeric structures provided mechanical strength to the scaffold. However, the highly crystalline polymer structure limited the scaffold's expansion capabilities and its resistance to fracture. As a result, current-generation BRS display limited expansion capabilities beyond pre-determined limits and are prone to fracture if not deployed properly.

The ultra-high molecular weight PLLA-based BRS have already displayed higher expansion capabilities and resistance to fracture under static and dynamic loading conditions[9]. At EuroPCR 2018, the RENASCENT trial showed good safety performance of the FORTITUDE BRS with lumen patency and vessel wall stability up to 24 months. This is once again reproduced in this trial with the low angiographic LLL rate (0.35 mm at 9 months and 0.37 mm at 24 months). Furthermore, OCT analysis showed high strut apposition and coverage rates at nine months.

ACUTE GAIN AND LATE LUMEN LOSS

In our analysis, the APTITUDE BRS showed an acute gain of 1.9±0.4 mm, the same as that reported for the FORTITUDE BRS. Ormiston et al reported an acute gain of 1.22±0.38 mm for the second generation of the Absorb™ BVS (Abbott Vascular, Santa Clara, CA, USA) in the ABSORB cohort B trial which was numerically lower compared to the EES (1.32±1.26 mm)[6] . The numerically higher EES acute gain could be secondary to higher recoil rates or more conservative post-dilatation techniques used during BVS deployment aiming to avoid strut fractures[5]. The *in vivo* acute gain of the FORTITUDE BRS has been reported to be higher compared to the BVS. Cheng et al reported *in vitro* analysis that compared the capability of the Amaranth Medical BRS to resist fracturing under high load conditions[9]. They reported that the number of fractures was higher in BVS versus the FORTITUDE BRS with lower percentages of late scaffold recoil at three months.

Numerous studies have shown that LLL is a predictor of MACE. LLL provides an indirect angiographic evaluation of the vessel wall response to the metallic stent related to neointimal proliferation in metallic stents[5]. In BVS, LLL also depends on the late scaffold expansion[11]. Current BVS data show an LLL of 0.16±0.18 mm at 6 months and 0.27±0.20 mm at 2-year follow-up for the second generation of BVS[6], while an LLL of 0.21±0.34 mm at 6 months was reported for the DESolve® scaffold (Elixir Medical Corporation, Milpitas, CA, USA)[12]. Recent analyses have shown that the LLL for the FORTITUDE scaffold is 0.29±0.43 mm at nine months of follow-up, which is comparable with the current BVS previously reported. In our analysis, in-scaffold LLL for the APTITUDE BRS is comparable with the Absorb and FORTITUDE at 9 months (0.35±0.33 mm) and at 24 months (0.37±0.44 mm).

OCT ANALYSIS

The OCT analysis conducted at 9 months showed no statistically significant difference in mean scaffold area (7.82±1.81 mm^2 at baseline to 7.84±1.79 mm^2 at 9 months). Almost all struts were covered by neointimal tissue (97%) and completely apposed to the vessel wall (96.5±5.02%). A total of 3% of all struts were uncovered but fully apposed. A very low percentage of all struts

analysed were covered but malapposed (0.037±0.16%). No uncovered, malapposed struts were detected. Strut apposition and coverage have been important predictors of late stent thrombosis in DES trials. In our study, the high percentage of strut apposition (~99%) and very low percentage of uncovered malapposed struts may result in an improvement in long-term clinical outcomes. However, these OCT findings indicate stent struts still present at nine months, indicating the active resorption process still ongoing. These OCT findings observed during the active process of resorption need to be confirmed in the long term with the use of serial imaging.

CLINICAL OUTCOMES

Serruys et al[6] reported a MACE rate at one year of 7.1% for the second generation of BRS in the ABSORB cohort B trial. In the FIM DESolve scaffold study, the overall MACE rate was 20% at one-year follow-up[12]. RENASCENT II showed very high clinical device and procedural success rates with no MACE reported at hospital discharge. Two non-Q-wave MIs (TV-MIs) were reported because of troponin rise but without ECG changes or clinical symptoms at 9-month follow-up without any TLR. No cardiac death or stent thrombosis was seen at 9-month follow-up. Our analysis demonstrated that the APTITUDE BRS is safe and effective for use in the treatment of *de novo* stenotic native coronary artery lesions in patients undergoing elective PCI.

Furthermore, there are other new BRS at various stages of testing. These all need to undergo FIM trials and then eventual RCTs with current DES to evaluate their safety and clinical performance[13].

Limitations

This study is limited by the number of patients and also the follow-up period. It would also be worth noting that BRS implantation during RENASCENT II was guided by IVUS and OCT assistance. Further studies are required to analyse the results of the APTITUDE BRS using routine implantation techniques as well as assessing clinical outcomes in longer follow-up.

Conclusions

The 24-month clinical experience with the PLLA APTITUDE BRS has demonstrated that the polymer is safe and effective in improving coronary luminal diameter in patients undergoing elective PCI. The APTITUDE BRS has shown that, despite reduction in struct thickness, it matches previous safety clinical endpoints seen with the FORTITUDE BRS.

Impact on daily practice

RENASCENT II was a first-in-human study to analyse the APTITUDE BRS which was found to be safe and effective up to 24 months. It had low levels of target vessel failure and late lumen loss, warranting further BRS studies with longer follow-up and implantation using standard implantation techniques.

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Conflict of interest statement

A. Chieffo reports proctorship fees from Amaranth Medical Inc. J.F. Granada reports being a scientific advisor for and equity shareholder in Amaranth Medical Inc. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Definitions.

Supplementary Appendix 2. OCT analysis.

Supplementary Appendix 3. CT analysis.

Supplementary Appendix 4. Supplementary background information.

Supplementary Figure 1. OCT imaging used to measure neointimal hyperplasia.

Supplementary Figure 2. Nine-month OCT imaging measurement used to calculate "strut coverage" if thickness was ≥0.03 mm.

Supplementary Table 1. Inclusion and exclusion criteria for the RENASCENT II study.

Supplementary Table 2. APTITUDE scaffold's design features and description.

Supplementary Table 3. Details of patient events.

Supplementary Table 4. Binary stenosis.

Supplementary Table 5. In-scaffold OCT measurements.

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Supplementary data

Supplementary Appendix 1. Definitions

Scaffold struts were classified as covered if the total thickness of the hyperintensity region (presumably including scaffold rim and neointima) was ≥0.03 mm.

Follow-up scaffold dismantling was defined as isolated struts that could not be integrated into the expected circularity of the device without embedding it into neointima.

Supplementary Appendix 2. OCT analysis

The outer (abluminal) and inner (endoluminal) scaffold area and lumen area were analysed every 1 mm. Outer scaffold area was contoured as the abluminal leading edge of black strut core and inner scaffold area was contoured as the endoluminal leading edge of black strut core **(Supplementary Figure 1)**. Lumen area was contoured as the interface between blood and the surface of plaque or neointima. Intra-scaffold neointimal area was calculated as inner scaffold area minus lumen area. Volume was calculated using Simpson's rule and shown as mean value (volume divided by analysed length).

The strut-level analysis was also performed every 1 mm. As shown in **Supplementary Figure 2**, to determine scaffold coverage, we previously measured the thickness of the endoluminal hyperintensity border for 150 randomly chosen APTITUDE scaffold "struts" immediately after scaffold implantation; the mean was 0.0211 (confidence interval 0.0206, 0.0216) mm. Therefore, if the total thickness of the hyperintensity region (presumably including scaffold rim and neointima) was ≥0.03 mm, it was considered to be "covered." A malapposed strut required visible blood between the outer scaffold border and the surface of the plaque.

Acute scaffold fracture was defined if 1) two struts overlapped each other, or 2) there was an isolated strut(s) that could not be integrated into the expected circularity of the device. Follow-up (late) scaffold dismantling was defined as isolated struts that could not be integrated into the expected circularity of the device without embedding it into neointima.

All quantitative analyses were performed at a 1 mm sampling interval and total percentage of covered struts was calculated as the number of covered struts divided by the total number of analysed struts. Therefore, each lesion has one value (%), which was summarised as mean± standard deviation (of percentage of covered struts).

Supplementary Appendix 3. CT analysis

CT stenosis was categorised visually as 1 =normal, 2 ≤25% diameter stenosis, 3 =mild 25-49% diameter stenosis, 4 =moderate 50-69% diameter stenosis, 5 =severe 70-99% diameter stenosis, 6 =occluded. Binary restenosis was defined as ≥50% diameter stenosis.

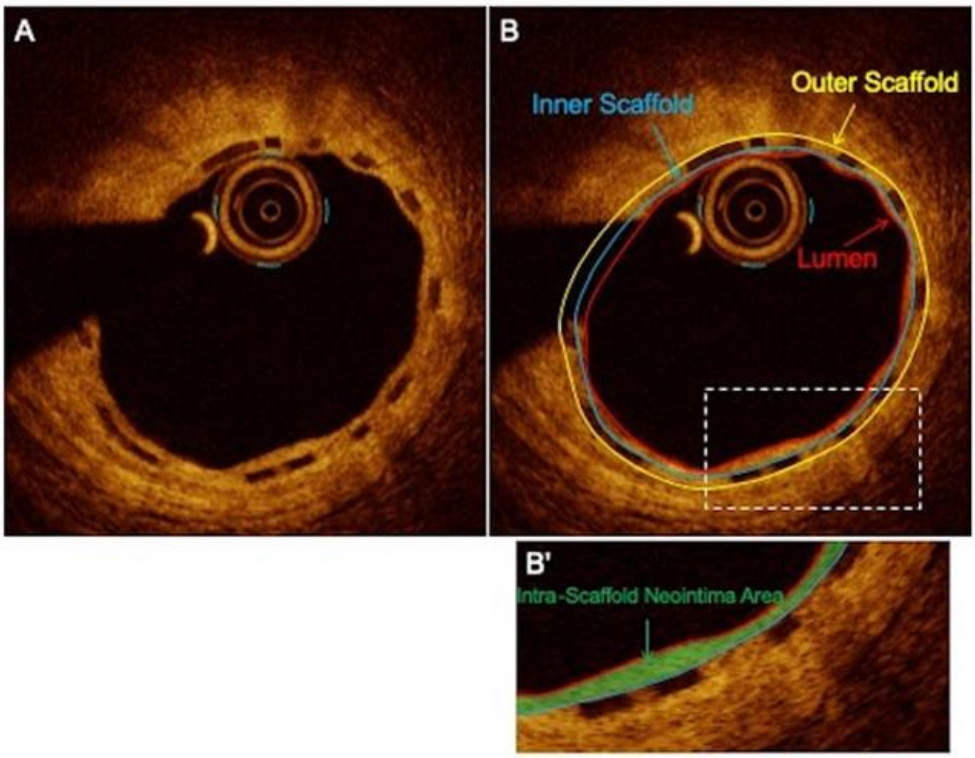
Supplementary Appendix 4. Supplementary background information

As with BMS and DES, the impact of scaffold design, including strut thickness, is an important factor in the clinical outcome of BRS [8,14]. With thicker struts come increased foreign material and flow disturbances, including stagnation, hence increasing the risk of thrombosis [8].

The Absorb® (Abbott Vascular, Santa Clara, CA, USA), with a strut thickness of 157 μm, was withdrawn from the market due to safety concerns [15].

The Amaranth bioresorbable scaffold technology has been shown to be biocompatible, maintain mechanical integrity, and deliver controlled drug release and eventual scaffold resorption in preclinical and clinical studies of the FORTITUDE, a novel sirolimus-eluting ultra-high molecular weight amorphous PLLA BRS. The FORTITUDE scaffold is designed with a strut thickness of 150 μm and was clinically evaluated in the RENASCENT I study. The clinical results of RENASCENT I were presented at EuroPCR 2018 and demonstrated favourable safety and clinical performance outcomes [Esposito G. Fortitude 150μm BRS 2- and 3- year clinical update. Presented at EuroPCR 2018, 21-24 May 2018; Paris, France].

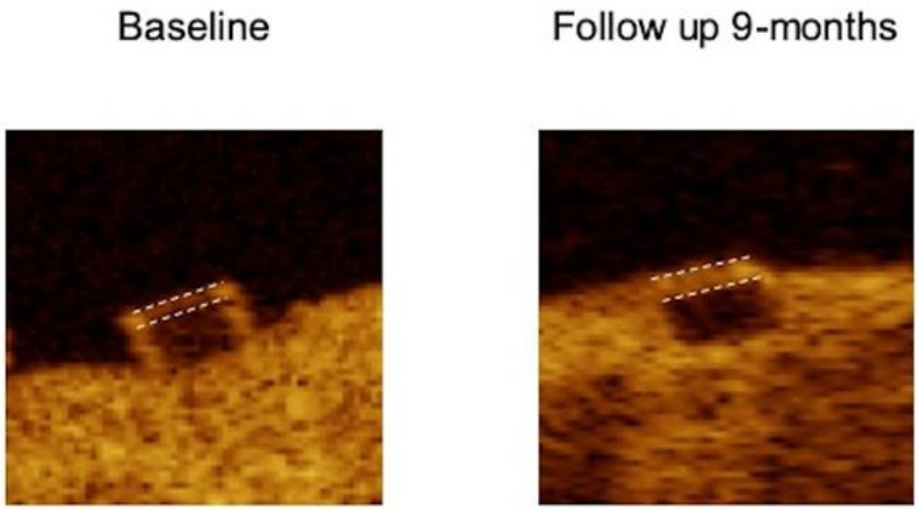
As a consequence of the positive initial results from FORTITUDE, Amaranth Medical developed a thinner scaffold with the same strength, flexibility and versatility seen in the previous product, but with a wall thickness of 115 μm.



Supplementary Figure 1. OCT imaging used to measure neointimal hyperplasia.

A) OCT image without contours.
B) Same OCT image with measuring contours. The outer scaffold (yellow line) was contoured as the abluminal leading edge of black strut core. The inner scaffold (blue line) was contoured as the endoluminal leading edge of black strut core. Lumen area (red line) was contoured as the interface between blood and the surface of plaque or neointima.

B') Magnified image of B (white dotted rectangle). Intra-scaffold neointimal area (green area) was calculated as inner scaffold area (blue line) minus lumen area (red line).



Supplementary Figure 2. Nine-month OCT imaging measurement used to calculate “strut coverage” if thickness was ≥0.03 mm.

Supplementary Table 1. Inclusion and exclusion criteria for the RENASCENT II study.

Inclusion criteria
Patients >18 and <85 years of age
Stable, unstable angina **pectoris or silent ischaemia**
Low- or intermediate-risk NSTEMI
De novo lesions in a native coronary artery with a diameter between 2.5 and 3.7 mm (by IVUS) **and lesion length of <14 mm** (by QCA)
A percentage diameter stenosis (DS) ≥50% and <100%
Thrombolysis In Myocardial Infarction flow grade **of ≥1.**
Exclusion criteria
Acute ST-segment elevation myocardial infarction, unstable arrhythmias
Left ventricular ejection fraction <30%
Restenotic or severely calcified lesions
Renal insufficiency with eGFR <**60 ml/kg/m² or serum creatinine level of >2.5 mg/dL**
Thrombus or another clinically significant stenosis in the target vessel
Lesions located in the left main coronary artery or located within ≤3 mm of the aorta junction or within ≤3 mm of the origin of the left anterior descending or left **coronary circumflex, lesions involving an epicardial side branch >2 mm in diameter by visual assessment**
Another clinically significant stenosis in the target vessel.

Supplementary Table 2. APTITUDE scaffold's design features and description.

Design feature	Description
Polymer	Ultra-high molecular weight poly-L-lactide (PLLA)
Diameters	2.5, 2.75, 3.25, and 3.5 mm
Lengths	13 and 18 mm
Wall thickness	115 µm all scaffold sizes
Surface coverage area	28 to 49%*
Drug coating	1:1 poly D L-lactide: sirolimus
Drug content	95 to 160 µg*
Drug density	96 µg/cm^2
Inflation pressures	Nominal: 8 to 10 atm RBP: 13 to 16 atm
Guide catheter size	6 Fr compatible

*Depending on scaffold size.

Supplementary Table 3. **Details of patient events.**

2 TVF due to TV-MI between 1 and 9 months (no TLR)
Patient 1. Patient had distal LAD PCI with APTITUDE. The patient then presented with chest pain on day 144 post baseline procedure. The patient was diagnosed with MI and on angiography was found to have a patent study stent but disease progression in the target vessel requiring PCI. The patient was adjudicated as having TV-MI but there was no TLR.
Patient 2. Patient had LAD PCI with APTITUDE. On day 273 post baseline procedure, patient had chest pain and subsequent angiography showed LAD disease progression, not related to previous treated lesion. Patient had LAD PCI and was judged to have TV-MI but there was no TLR.

Supplementary Table 4. Binary stenosis.

	9-month follow-up	24-month follow-up
Coronary angiography restenosis (%)	0% (0/59)	10% (1/10)
CT angiography restenosis >50% (%)	n/a	6.7% (1/15)
Cumulative binary stenosis rate (%)	0%	8.0% (2/25)

Supplementary Table 5. In-scaffold optimal coherence tomography measurements.

OCT measurements Mean±SD (n)	Post BRS implantation (n=53)	9-month follow-up (n=58)	Difference (post vs 9-month)
Mean lumen area (mm^2/mm)	7.02±1.69	5.98±1.70	-1.03 (-14.7%)
Mean outer scaffold area (mm^2/mm)	7.82±1.81	7.84±1.79	0.02 (0.3%)
Mean inner scaffold area (mm^2/mm)	6.63±1.60	6.79±1.65	0.19 (2.9%)
Percent intra-scaffold NIH volume (%)	--	13.3±6.1	--
Post-implantation scaffold fracture (%)	--	--	--
OCT strut measurements Mean±SD (n)	Percent covered struts (at 9 months)	Percent uncovered struts (at 9 months)	Total (%)
Apposed of total struts (%)	96.522±5.017	2.971±4.757	99.493±0.856
"Malapposed" of total struts (%)	0.037±0.160	0.00±0.00	0.037±0.160
"Orifice of branch" of total struts (%)	0.438±0.844	0.032±0.139	0.470±0.839
Total (%)	96.996±4.804	3.004±4.804	100

NIH: neointimal hyperplasia