International PhD program in Cardiovascular Pathophysiology and Therapeutics

Innovation in interventional cardiology

PhD thesis

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Innovation in cardiovascular medicine

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“If I had asked people what they wanted, they would have said faster horses.”

Henry Ford

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CHAPTER 1

General introduction

Innovation is the engine of sciences progression, improvement and promotion. It represents the finest and the most exciting aspect of knowledge.

Thank to the introduction of new approaches and therapies (i.e. drugs and devices) the treatment of cardiovascular disease has changed dramatically over the past 3 decades, allowing patients to live longer and with a better quality of life. Interventional cardiology, in particular, played a leading role into the innovation arena, witnessing disruptive inventions and revolutionary breakthroughs. Since the introduction of the very first coronary angioplasty (POBA) in September 1977[1] (first revolution in interventional cardiology), performed by means of a hand made balloon catheter to dilate a coronary stenosis using a percutaneous approach, this field has costantly and progressively improved. The main flaw, limiting the widespread diffusion of POBA (acute and late vessel recoil), was resolved ten years later in 1986 when bare metal stents (BMS) were introduced into the interventional cardiology practice[2] (second revolution). A further improvement of stent technology was achieved in 1999 with drug eluting stents DES[3] (third revolution), a stent platform eluting antiprolifertive drug in order to hinder instent restenosis and to garantee long term patency of the stented segment. The results shown by DES were so promising that percutaneous coronary intervention (PCI) slowly started to replace coronary

artery bypass graft (CABG) surgery as gold standard approach for the treatment of coronary artery disease (CAD). Beginning in 2002 the interventional practise escalated leading to approximately 800.000 PCI procedures in the United States alone, compared with some 350.000 CABG surgeries[4]. This explosive growth was fueled by the availability of new devices (guidewires, angioplasty balloons, stents, etc.) coupled with the validation of PCI by clinical data primarily in the form of randomized clinical trials. In the same years, a new concept of bioresorbable vascular scaffold (BRS) (a fully resorbable drug eluting scaffold) for PCI was developed[5]. The initial promising results coming from randomized trials led the bioresorbable scaffold field to flourish with several companies investing in the development of novel BRS. Unfortunately, safety concerns arisen from increased late/very late scaffold thrombosis and myocardial infarction occurring in patients treated with BRS detemined the discontinuation of global sales of BRS in 2017. This disastrous worldwide failure determined the abrupt interruption of investments from most of the companies involved in the frantic race to develop new BRS causing, de facto, the sunset of this technology.

Parallel to the coronary field, lower limb revascularization was implemented with innovation and improvements characterized by a rollercoaster of different approaches alternating over the years. Lower limb POBA was first replaced with peripheral BMS which showed, as previously demonstrated in the coronary setting, low rate long term patency. In order to reproduce the success of DES for the treatment of peripheral artery disease (PAD), dedicated peripheral DES were developed specifically for

lower limb revascularization. Unexpectedly, peripheral DES were a legit failure due to high re-occlusion and stent-thrombosis rate[5]. The effort to overcome stent limitations in the lower limb setting gave birth to paclitaxel eluting balloon (PEB), a balloon catheter loaded with and releasing the antiproliferative drug taxol into the vessel wall during the balloon inflation. Despite the promising outcome showed by this technology, in 2018 a review showing an increased risk of death in patients treated with PEB[7] halted their application into clinical practise. This alert promoted the development of new generation peripheral DES with novel drug release kinetics showing similar results compared to PEB[8]. Nowadays, coronary and peripheral intevention developments and advancements reached a platueau as a consequence of the high performances hard to improve demostrated from of the devices produced over the last 20 years.

In terms of innovation, percutaneous structural heart intervention is the current setting where innovators are striving to make the impossible, possible.

Heart valve repair and/or replacement have always been considered surgical procedures with no chances of development of less invasive approaches due to complex technical and anatomical features.

In 2002 the first percutaneous trans-aortic valve implantantion (TAVI) was performed[9]. Aortic valve has been the first valve treated with a percutaneous approach and since the treatment of the very fist patient with TAVI, the advancements into this field have been enormous and are not even close to a halt. The clinical indication for TAVI have been progressively increasing due to the safety and

efficacy of this tecnique demonstrated by randomized trials. Recently, along with aortic valve percutaneous treatment, mitral percutaneous repair (i.e. Mitraclip intervention) found its way to success despite initial controversial data coming from literature[10] and many company are investing to develop a full percutaneous mitral replacement system (i.e. percutaneous mitral valve).

The examples reported into this introduction define the real essence of the innovation pathway and how the development process of a new decive can take, sometimes, swift and unexpected turns. The journey standing between the conception of an idea and its concrete realization is a minefield characterized by days of sensational excitement and days of deep depression. During the 2 years I attended, as a fellow, the Skirball center for Innovation (SCI)(Cardiovascular Research Foundation, CRF, New York, USA), I had the privilege of taking part to this terrific and unique process working along with engineers, investors and CEO from numerous Startups and companies developing new devices and terapeutics approaches in their preclinical stage. I worked on the development of several animal models. Animal models are the foundation of preclinical research. Those are foundamental to accurately reproduce the human diseases the devices are conceived and designed for. I had the opportunity to work into an incredibly stimulating enviroment and to witness marvellous (and sometimes eccentric) ideas having always the same question in my mind: “why didn’t I think of that?”. Working as a physician is time-and-energy-consuming and lives a small room for the “out-of-the-box-thinking”. With the due exceptions, we spend our time working in a carved lane rather than thinking to how a procedure, a treatment or

a technique may be improved or how an unmet clinical need may be adressed in alternative ways. The period I spent at SCI and the preclinical studies I carried out during my PhD program gave me a hint of how fascinating the world of innovation is and I wish I will be able to keep the alternative approach I learnt with me throughout my all career.

Outiline of the thesis

The thesis is divided into six parts:

Part I. Traslational research and animal model. Translational research is the cornerstone for medical technology advancement. All the new devices, as well as new drug therapies, need to be tested in term of safety and preliminary efficacy on dedicated animal models. The accuracy of the animal model in reproducing specific human diseases is crucial in order to allow reliable results coming from preclinical testing.

We discuss into this section the limitation of the swine model into predicting LVOT obstruction, one of the worst complications following transcatheter mitral valve replacement (TMVR).

We created a swine model reproducing cronic total occlusions (CTO) using human atherosclerotic plaque tissue in order to test CTO dedicated devices.

Part II_1_2 Bioresorbable Scaffold preclinical. Part II is divided into two sections (_1 and _2) regarding the studies we performed on BRS into the preclinical (_1) and clinical (_2) setting.

- Preclinical: We evaluated the performance of BRS (commercially avialable and novel BRS) in terms of radial force, strut thickness impact on mechanical and biological interaction, resorption and scaffold dismanteling, relation between atherosclerosis and scaffold resorption. We evaluated the performance and the safety of a novel peripheral-dedicated BRS in swine femoral arteries on the short and long term (3 years) follow-up.
- Clinical: we evaluated the performance of a novel thin-strut bioresorbable scaffold as part of the first-in-human (FIH) clinical program.

Part III Drug coated balloon. Drug Coated Balloon (DCB) are one of the main therapeutic options available for the treatment of the lower limb atherosclerosis. Several balloons are commercially available differing in the type of coating and in the concentration of drug loaded onto the balloon. The main concerns regarding this technology are the long term sustainability of neointimal proliferation over time and the impact the antiproliferative drug embolized during the balloon inflation may have on the worst clinical scenario in peripheral artery diseased (PAD) patients, i.e. acute limb ischemia (ALI). We evaluated the efficacy in preventing neointimal proliferation of two different DCB (high vs low paclitaxel dose) and the impact on wound healing the paclitaxel embolized has on a ALI swine animal model.

Part IV Innovation. We evaluted several devices in the preclinical/early clinical development stage. Here we report some of the most interesting innovative approaches for the treatment of different human disease.

- *A Novel Approach for Treatment of Aortic Stent Graft Endoleak*
- *A Novel Approach for Left Atrial Appendage Occlusion*
- *An initial experience with a transfemoral TAVR system in patients with severe aortic stenosis and risk for coronary occlusion*

Part V Discussion and conclusions The final part of the thesis summurises the findings derived from the 3 years PhD program and includes the conclusions.

Part I

Traslational research and animal model

CHAPTER 2

Traslational Research: the cornerstone for medical technology advancement

If at first the idea is not absurd, then there will be no hope for it.
Albert Einstein

Significant improvements in quality of life and mortality have occurred over the last century due to the giant advancements in medical innovation. The history of medical innovation is enormous, and it is full of lessons of success and failure. A new revolution in medical innovation started with the introduction of biologic agents able to either prevent or treat infectious diseases. Nineteenth-century giants such as Louis Pasteur revolutionized patient care. A second wave of innovation occurred after the introduction of X-rays. Imaging enabled for the first time the evaluation and understanding of disease states as never seen before. An inflection point in medical device innovation occurred with the introduction of medical device technologies. At this point in history, the use of technologies already used in other industrial fields improved the diagnosis and treatment of complex disease conditions. Clinicians of the premodern era were just as curious and inventive as today's and with rustic techniques and tools, they sometimes influenced the natural history of disease, albeit not always for the better. The same scientific curiosity and brewing creativity can be observed in medicine today, still motivated by improving patient health and quality of life. The successful introduction of medical technologies into the clinical arena follows a complex and not always predictable process, and it requires a coordinated effort involving a multidisciplinary team working in good harmony and collaboratively (i.e., scientist, regulatory experts, engineers, pathologists, imaging

specialists, clinicians). In today's world, bringing a new drug to market may cost in excess of US$1.8 billion while the cost of bringing a low to moderate risk 510(k) product to market can be close to US$100 million (Morgan et al. 2011; Makower, Meer, and Dened 2010). The journey to clinical market is rarely linear, encounters many challenges, and may take anywhere from five to ten years from inception to approval. It is therefore imperative that appropriate testing and efficient clinically oriented decision-making process lead the way to avoid mistakes and waste in resources. Failures occurring early during the experimental process may halt the further development of disruptive technologies. On the other hand, failures occurring late during the developing process (sometimes at a clinical stage) lead to a massive waste of resources. Failure is an inherent risk in innovation, and a calculated failure risk analysis should always be part of the medical innovation process. Unfortunately, due to the large development costs and inherent risks, medical innovation is greatly impacted by financial drivers. In today's environment, technology developers, and investors at large, preferentially support therapeutic areas with greater market size and regulatory predictability and a faster return on investment. In consequence, business, and not technology-related decisions, commonly stifles innovation and impacts the further development of medical innovation. The clinical adoption of medical technologies depends on its regulatory approval, ease of use, and availability of solid biological and clinical data. Then, the development of a solid preclinical and clinical data and strategy is key and is contingent upon the understanding of the human disease process and the use of relevant and established translational models. Computer simulation is becoming an important component in the experimental process of medical technologies. However, in vivo evaluation by the use of animal models continues to play a key role and remains widely used as the best predictors of clinical safety and efficacy. Many factors come to play when selecting an appropriate animal model including anatomical, economical, and ethical considerations. For medical implants, similarities to human anatomy is key. Also, the potential to reproduce potential mechanisms of failure and healing response seen in humans is

particularly important. Results from animal studies enable researchers to optimize biomaterial selection and implant design, and refine and test procedural performance. In addition, preclinical studies may contribute to the development of appropriate procedural flow and optimize implantation technique. As medical innovators, we owe a great deal of debt to our "biosimilars" (i.e., fellow mammals) and must always provide them with the best available care. Good science is rooted in good ethics. Medical innovation is moved forward by technological advances in biomaterial and manufacturing research and development. However, clinical introduction and adoption can only be achieved through a thoughtful step-by-step verification approach. Proof of principle is achieved by the demonstration of a therapeutic effect via in vivo imaging or tissue-level pathology. For technology developers, demonstrating positive tissue-level effects confirms the validation of their technological approach. In vivo imaging and high-quality histopathology have become of paramount importance in the experimental process of medical technologies. It is of utmost importance that the evaluation of these outcomes is rooted in solid scientific basis, standardized analytical techniques, and be reported in a way that reflects the relevance to human disease conditions. The medical innovation landscape is rapidly expanding, and efforts to standardize analytical methods and clarify pathology end points are critically needed. This special edition is a great example of achieving such milestone. Medical innovation continues to move forward, and it is expanding to areas never explored before. In particular, the advancement in big data analytics is now enabling the rapid progress in the understanding of gene influence in human diseases. The progress in medical innovation achieved until today is significant; however, the potential that future technologies have to modify patterns of disease thought to be incurable is mind-boggling. In the present issue of Toxicologic Pathology, a wide variety of devices and evaluation platforms are presented as a clear evidence of the multidisciplinary approach that is necessary for the progress of this field.

Chapter 3

LVOT Obstruction Cannot Be Reliably Predicted by the Swine Model Testing of Transcatheter Mitral Valve Replacement TMVR Technologies

The preclinical evaluation of a new device aims to determine the safety as well as the efficacy in an animal model. Animal models are a reliable benchmark to test the most of the devices used in interventional cardiology. Nevertheless, in the setting of TMVR evaluation, one of the most feared complication coming from a percutaneous mitral valve replacement, i.e. LVOT obstruction, cannot be predicted by the swine model due to several anatomical differences between the swine and the human heart.

BACKGROUND

In development of transcatheter mitral valve replacement therapies, the complexity of mitral valve apparatus requires a remarkable engineering and testing effort to prevent potentially fatal complications resulting from interactions between the native valve and the prosthesis, such as left ventricular outflow tract obstruction. The animal-human anatomy discrepancy is a recognized impediment in the transcatheter mitral valve replacement testing in vivo, but concrete characterization is lacking. This study aimed to systematically quantify the anatomical differences between human and swine mitral apparatus.

METHODS

In 16 Yorkshire pigs, a computed tomography scan (Somatom Flash, Siemens, Germany) was used to measure left heart structures following a systematic step-by-step protocol striving for optimal data reliability. The swine were divided in 2 groups

based on weight (7 were 80 kg) to account for the impact of animal growth on heart dimensions, which affects the long-term device-anatomy interaction.

RESULTS

The results are summarized in the Table. Several anatomical features are different in pigs when compared with humans: 1) the mitral annulus has a D-shape that is particularly pronounced during the systolic phase; 2) anterior and posterior leaflets roughly have the same length; 3) the aortomitral curtain is not as developed as in humans; 4) aortomitral angle is narrower than in humans, resulting in a "more vertical" aorta.

CONCLUSION

Swine are generally an indispensable animal model for testing of cardiovascular devices pre-clinically. However, in the context of transcatheter mitral valve replacement, short anterior leaflet, lack of a developed aortomitral curtain, and narrow aortomitral angle are significant limitations of the porcine model that have to be accounted for when attempting to predict the impact of an investigational transcatheter mitral valve on the left ventricular outflow tract

	<80 kg	**>80 kg**
CC diameter diastole	4.01 ± 0.49	4.78 ± 0.50
AP diameter diastole	3.13 ± 0.27	3.53 ± 0.19
Projected area diastole	10.76 ± 2.04	13.79 ± 1.61
CC diameter systole	4.40 ± 0.63	4.98 ± 0.53
AP diameter systole	2.78 ± 0.23	2.98 ± 0.28
Projected area systole	10.70 ± 2.43	13.20 ± 2.08
Anterior leaflet length	1.67 ± 0.26	1.90 ± 0.32
Posterior leaflet length	1.41 ± 0.23	1.79 ± 0.25
Aortomitral angle	151.42 ± 4.80	145.11 ± 4.04

AP = anteroposterior; CC = commissure-commissure.

Chapter 4

Creation of a Preclinical Coronary Chronic Total Occlusion (CTO) Model Using Human Atherosclerotic

The creation of a CTO animal model reliably reproducing human CTO is crucial to test dedicated devices. One of the most important characteristics this model should have is resembling the resistance a real human CTO would exert when crossed from a guidewire or any other specific device. In order to obtain the appropriate hardness and tactile feedback into an animal model we created a CTO model in the swine coronary arteries using human aterosclerotic tissue.

BACKGROUND

There is a continued need for a reproducible preclinical large animal model of coronary chronic total occlusion (CTO) adequately mimicking human CTO pathology and biomechanics for testing of CTO-targeting therapies.

METHODS

A novel calcific plug model was created using powder calcium, cholesterol esters and fragments of human atherosclerotic plaques and intimal tissue extracted from human aortas, rolled into a bioabsorbable sponge (Figure A). Ca. 20mm long plugs were loaded into the distal catheter tip and pushed into pre-injured (angioplasty balloon or Fogarty catheter) left anterior coronary arteries of 20 swine where they lodged in the mid-segment and were left to fully thrombose and integrate with the native vessel over 2-6 weeks (Figure B).

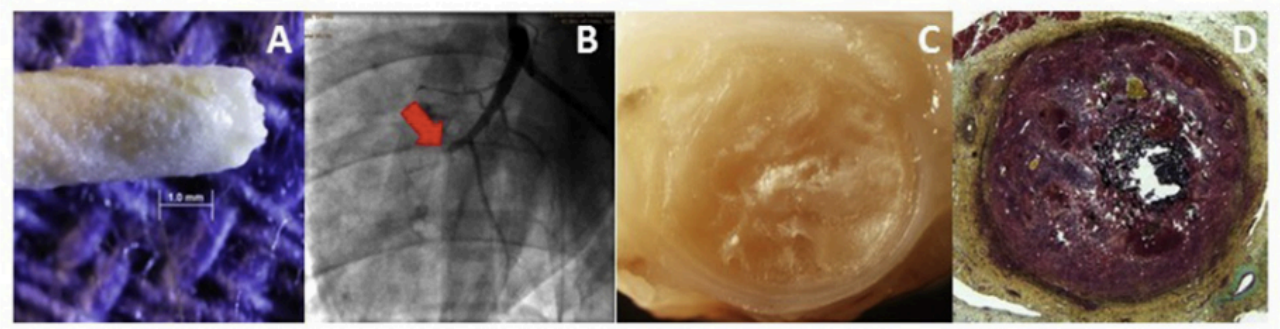
RESULTS

Seventeen of 20 animals survived the model-induced myocardial infarctions. Biomechanically, operator feedback suggested that the hardness and crossing

challenge most resembled human CTO at 3 weeks post model creation; longer incubation resulted in excessive difficulty to penetrate. Histopathology demonstrated time-proportionate resorption of the bioresorbable material between 2 and 6 weeks, gradually replaced by organized thrombus, inflammatory cells and smooth muscle cells migrating into the plug, resulting in effective merging with native injured artery, and proper fibrocellular caps on both ends of the CTO (Figure C/D).

CONCLUSION

Including biological plaque components in an animal CTO model enhances its resemblance to human CTO and results in a useful preclinical testing tool for development of CTO-targeted therapies.



Part II_1

Bioresorbable Scaffold preclinical

Chapter 5

Five-Years Comparison of Vessel Remodeling Between a Thin-Strut Non-Drug Eluting Bioresorbable Stent and Bare Metal Stent in Porcine Coronary Arteries.

The biggest advantage of BRS is the dissolution of the scaffold backbone overtime allowing the native vessel to restore its intrinsic motility features. We evaluated by means of Optical coherence tomography (OCT) how this features translates into vessel remodelling on a long-term follow-up (FU)(5 years) in swine coronary arteries comparing bare BRS to BMS.

BACKGROUND

Degradation of bioresorbable stents (BRS) has been shown to allow restoration of the treated segment's plasticity and reactivity, a desirable feature unattainable with bare-metal stents (BMS). The authors have previously reported the dynamic changes in arterial geometry in response to a novel non–drug-eluting BRS as compared to BMS up to 3 years. This study provides an insight over a 5-year duration.

METHODS

Forty-seven coronaries of 10 swine received thinstrut BRS (115 mm) (Amaranth Medical, Mountain View, California) (n = 18) or BMS (Liberte, Boston Scientific, Natick, Massachusetts) (n = 10). Optical coherence tomography was done at day 0, 1 month (BRS, n = 18; BMS, n = 10), 1 year (BRS, n = 8; BMS, n = 5), 2 years (BRS, n = 8; BMS, n = 5), 3 years (BRS, n = 7; BMS, n = 4), 4 years (BRS, n = 7; BMS, n = 4), and 5 years post implantation (BRS, n = 7; BMS, n = 4).

RESULTS

Between 2 and 5 years, BRS-treated coronary segments continued to positively remodel, with further late lumen area gain paralleling the reference segment

expansion over time. This pattern, uniquely possible due to scaffold degradation and unattainable in the BMS-caged segments, appears to be a reproducible and inherent behavior of non– drug-eluting bioabsorbable stents in the normal porcine coronary model (Figure).

CONCLUSION

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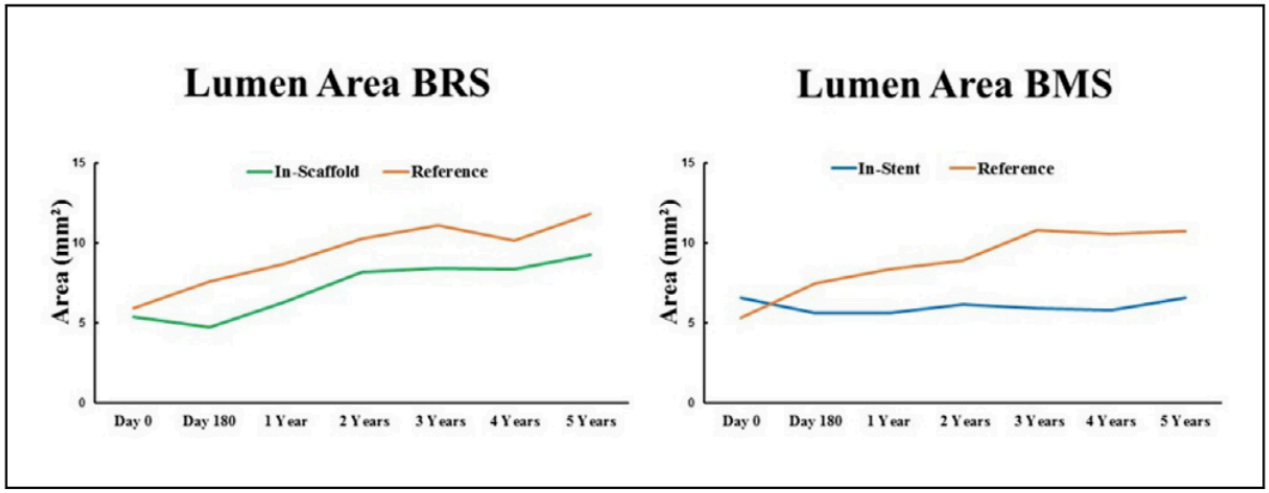


Chapter 6

Early Scaffold Disruption and Late Structural Discontinuity after Implantation of the Aptitude Sirolimus-Eluting Bioresorbable Scaffold in Normal Porcine Coronary Arteries: An OCT Study.

Many studies tried to investigate BRS failure mechanism. Into this study we investigated the percentage of scaffold discontinuity as a possible mechanism of BRS failure evaluating any possibile correlation with the vessel implanted and relating the dismanteling to clinical outcomes and at different time FU.

BACKGROUND

Scaffold discontinuity might be a potential cause of late scaffold thrombosis (ScT). We aimed to describe the frequency and impact of acute, early scaffold disruption (< 6 months) and late scaffold discontinuity (> 6 months) in the Aptitude sirolimus-eluting bioresorbable scaffold (BRS) (strut thickness = 115 mm, Amaranth Medical) by optical coherence tomography (OCT) in normal porcine coronary arteries.

METHODS

A total of 52 Aptitude BRS (2.5 or 2.75 18 mm) were implanted in 52 coronary arteries of 17 swine. OCT analysis was performed at baseline and at 3 (5 pigs), 6, 12, and 24 months (4 pigs for each group) before termination. The presence of acute, early disruption or late discontinuities was defined as the presence of stacked, overhung struts or isolated intraluminal struts disconnected from the expected circularity of the device. Late recoil was calculated as: ([scaffold area day 0 - scaffold area follow-up]/scaffold area day 0) x 100%.

RESULTS

No post-procedural acute scaffold disruption was observed in any implanted vessels. Early scaffold disruption was observed in 3 of 15 vessels (20%, all in left anterior

descending [LAD]) at 3 months and 5 of 13 vessels (38%: LAD = 3, left circumflex [LCX] = 2) at 6 months which was associated with a higher percentage scaffold recoil as compared with the vessels without disruption (11 ± 10% vs. 5 ± 11%; p = 0.03) and area stenosis (41 ± 4% vs. 29 ± 7%; p = 0.003). Late discontinuities were observed in 5 of 12 vessels (42%: LAD = 3, LCX = 2) at 12 months and 5 of 12 vessels (42%: LAD = 2, LCX = 1, and RCA = 2) at 24 months, respectively. Compared with the vessels without late strut discontinuity, there was no difference in the percent late recoil (12 months: 31% vs. 15%; p = 0.15; 24 months: 46% vs. 52%; p = 0.69) or area stenosis at 12 and 24 months. No ScT or other major adverse cardiac events occurred in association with scaffold disruption or late discontinuities.

CONCLUSION

Early scaffold disruption was mostly observed in LAD and was associated with higher percentage scaffold recoil and area stenosis at 6 months, whereas late strut discontinuity at 12 to 24 months was observed in approximately 42% of implanted segments and seems to be part of the normal resorption process, not affecting long-term healing response.

Chapter 7

Impact of Strut Thickness on Radial Force and Late Vascular Recoil of a Novel Thin-Strut Ultra High Molecular Weight PLLA Sirolimus-Eluting Bioresorbable Coronary Scaffold.

Strut thickness has been recognized as one of the most important contributors to scaffold thrombosis. The effort to improve BRS techology are headed towards a reduction in the struts' thickness without increasing the surface area and without compromising the acute radial force and long term scaffolding support provided by the BRS. Into this study we evaluted the performance of three different generations of a novel BRS, manifactured with progressively lower strut thickness tho assess their mechanical performances compared to the commercially available Bioresorbable Vascular Scaffold (BVS).

BACKGROUND

First generation bioresorbable scaffolds (BRS) achieved stent-like mechanical performance by increasing strut thickness and scaffold's surface area. The future of the BRS field depends on the development of devices with mechanical and biological performance comparable to metallic DES but the development of thin-strut BRS has been challenging. In this study, we compared the mechanical performance of 3 generations of a novel ultra-high molecular weight BRS (150-mm, 115-mm, and 98-mm, Amaranth Medical (AMA), Mountain View, CA) to Absorb (BVS, Abbott, Santa Clara, USA) using serial OCT analysis up to 180 days.

METHODS

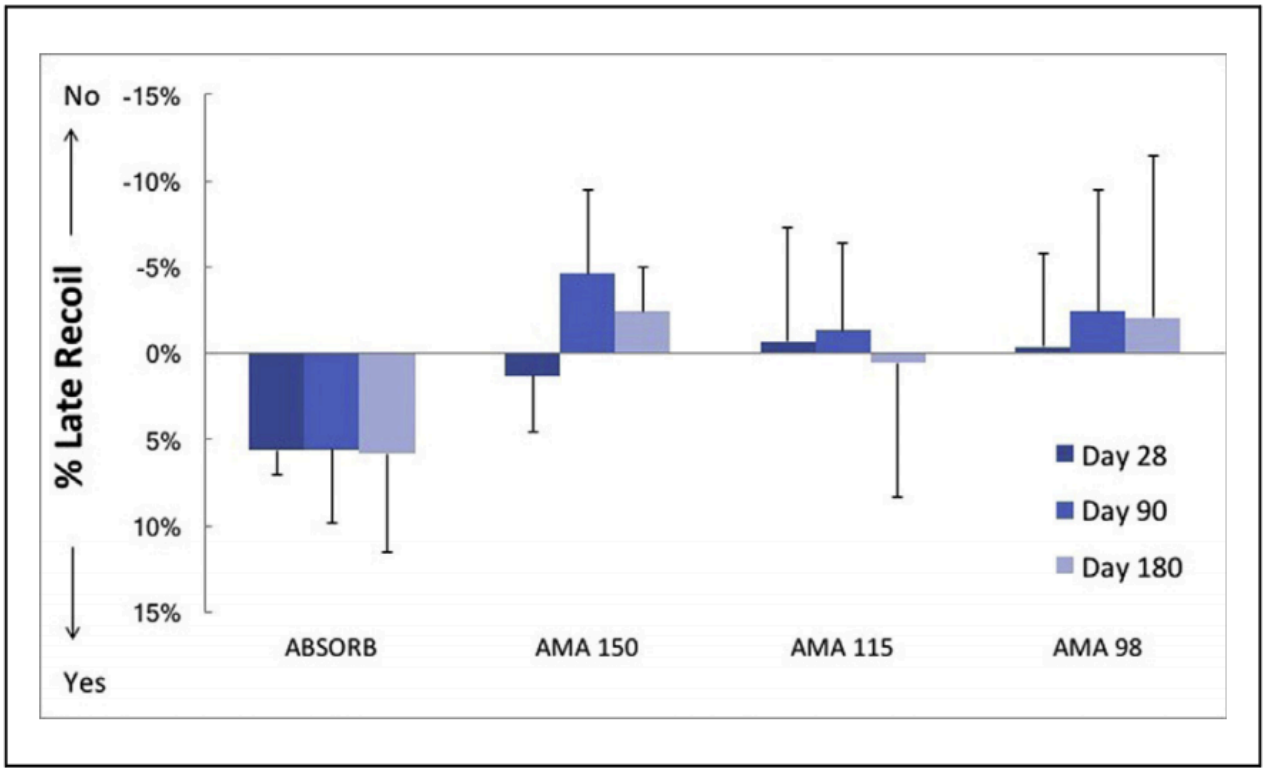
A total of 182 scaffolds (46 AMA-150; 48 AMA-115; 43 AMA-98; and 45 BVS) were implanted at 10% overstretch in healthy porcine coronary arteries. Percent late recoil (%LR) defined as (inner scaffold area at post–procedure – inner scaffold area at follow-up)/inner scaffold area at post-procedure) was derived from OCT at 28, 90 and 180 days.

RESULTS

Late vascular recoil was evident in the BVS group as early as 28 days and remained unchanged over time. None of AMA-BRS groups displayed significant late vascular recoil at 28 days and the scaffold architecture remained stable up to 180 days (Figure). The AMA-98 group displayed a mechanical performance comparable to the AMA150 BRS and superior to BVS ($p<0.03$) (180d %LR: -2.10±9.4 vs. -2.43±2.6 vs. 5.85±5.67).

CONCLUSION

In vivo OCT analysis showed that the mechanical stability of the novel ultra-high molecular weight BRS is maintained below the 100-micron strut thickness level and is superior to Absorb BVS.



Chapter 8

Pre-Clinical Evaluation of a Novel Thin Strut (85 mm) Ultra-High Molecular Weight PLLA Sirolimus-Eluting Bioresorbable Scaffold: A Comparative Multi-Modality Imaging-Based Study

The development of "DES-like" behaviour BRS is foundamental to devolp a reliable BRS technology. The development o thinner struts BRS must be validated investigating whether the reduction in strut thickness guarantees an equally high-mechanical performance scaffold. Into this study we evaluated the mechanical and biological performance of a thin-strut BRS compared to an equivalent strut thickness DES.

BACKGROUND

First generation Bioresorbable Scaffolds (BRS) are more prone to mechanical failure and vascular recoil despite their redundant surface area and wall thickness (≈157-microns). The development of DES-like BRS is key for the future of this field. In this study, we tested the biological performance of a highly durable thin strut (85 mm) ultra-high molecular weight PLLA-based sirolimuseluting BRS (Amaranth Medical, Mountain View, CA) to an equivalent strut thickness sirolimus drug-eluting metal stent (DES) (Ultimaster, Terumo, Tokyo, Japan) in a preclinical swine model.

METHODS

A total of 15 coronary segments (5 healthy swine) were implanted with 10 thin-strut sirolimus-eluting BRS and 5 sirolimus DES at 10% overstretch (day 0). At 0 and 28 days mean balloon diameter (MBD), mean scaffold diameter (MSD), and percent diameter stenosis were assessed by angiography. Acute recoil (AR) was calculated as (MBD – MSD) / MBD x 100%). Strut coverage, neointimal thickness, lumen, and device area were examined by OCT. Late recoil (LR) was calculated from OCT as

(inner scaffold area at post-procedure – inner scaffold area at follow-up)/inner scaffold area at postprocedure).

RESULTS

OCT findings were comparable in both groups showing no statistically significant difference. Likewise, biomechanical features were also statistically equivalent between the BRS and DES groups (Table). Angiographic data such as AR and stenosis at 28 days were comparable in both groups. All devices were embedded and fully covered by neointimal tissue, with no difference in apposition or strut coverage rates.

CONCLUSION

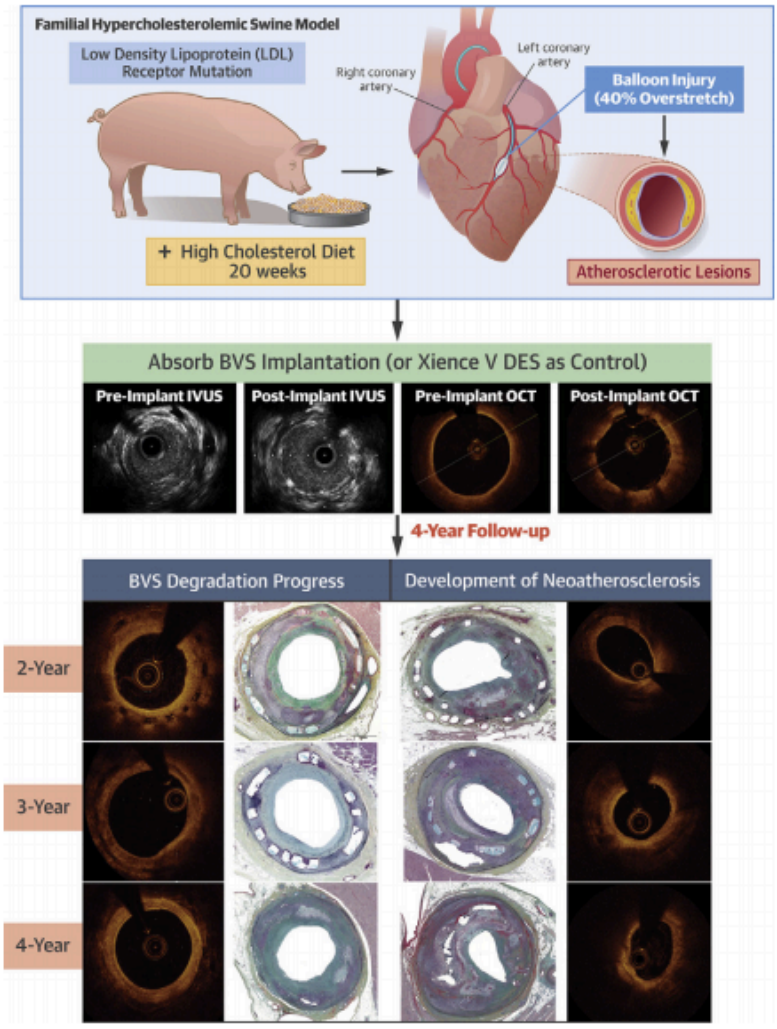
This novel thin strut ultra-high molecular weight sirolimus-eluting BRS demonstrated comparable biological and mechanical behavior to a metallic DES after 28 days in normal porcine coronary arteries.

		BRS (85 microns) n=10	DES (85 microns) n=5	p-value
OCT	Lumen Area (mm2)	4.28 ± 0.92	5.21 ± 1.83	0.20
	Device Area (mm2)	6.19 ± 0.45	6.62 ± 1.47	0.40
	Neointimal Thickness (mm)	0.25 ± 0.12	0.18 ± 0.10	0.28
	Area Stenosis (%)	31.13 ± 12.95	23.34 ± 13.77	0.30
	Late Recoil (%)	7.34 ± 6.82	10.14 ± 1.34	0.39

Chapter 9

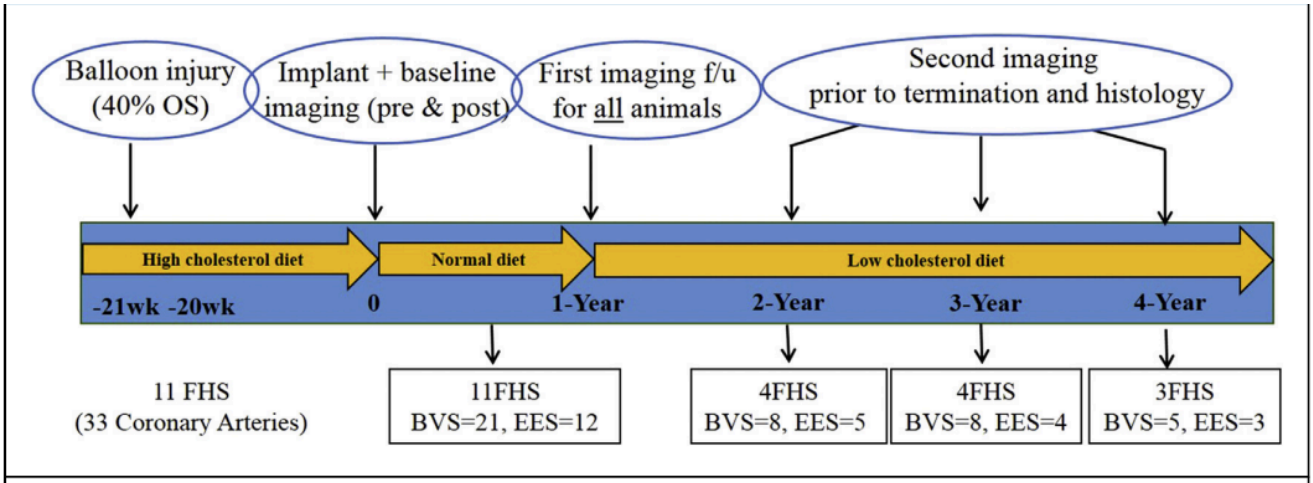
Impact of Coronary Atherosclerosis on Bioresorbable Vascular Scaffold Resorption and Vessel Wall Integration.

The resorption process of BVS is an important feature dealing with mechanical and biological performance of the scaffold. Whether this process is affected by the precence of atherosclerosis is not defined in clinical study. We evaluated the resorption process and the healing response of the BVS compared to a DES in relation to coronaries aterosclerosis in an animal model of Familial Hypercolesterolemic Swine (FHS) through a multimodality imaging and hystological approach up to 4 years.



METHODS

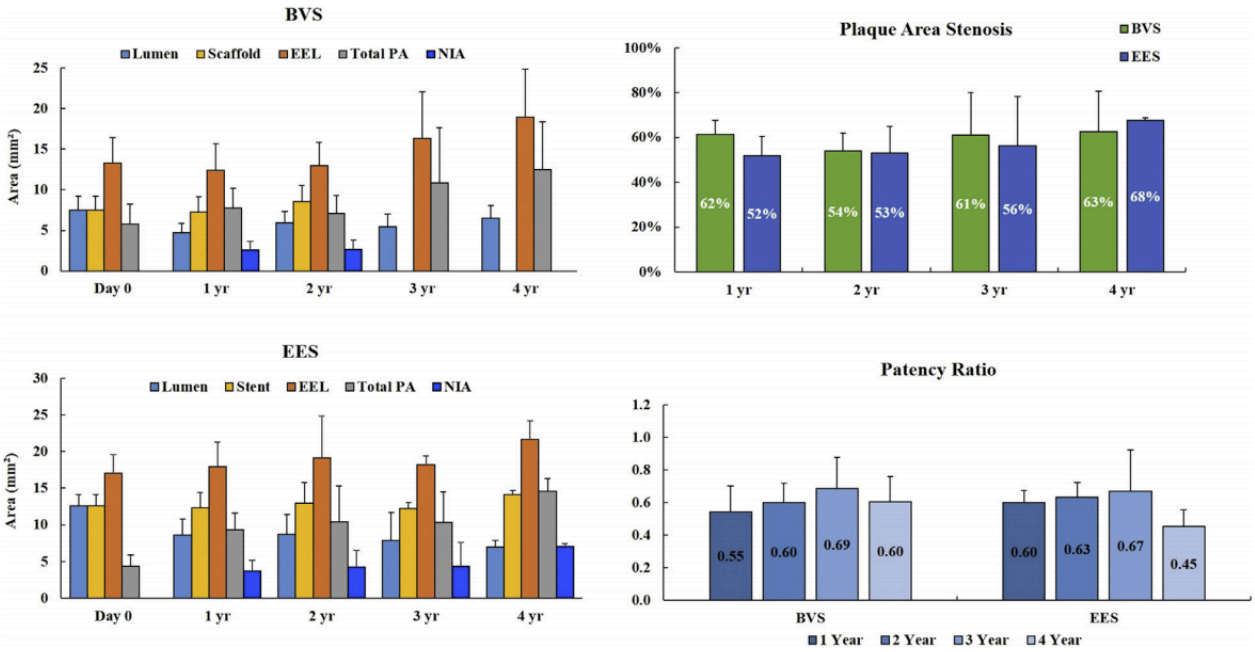
Eleven FHS (10 ± 0.07 months of age; weight: 70.8 ± 7.1 kg) were used in this study. Mean cholesterol levels at baseline was 709 ± 90 mg/dl (range 612 to 956 mg/dl). Animals were maintained on a low-grade high-cholesterol diet (0.6% cholesterol) for the first 21 weeks to accelerate lesion development. At device implantation, the mean cholesterol level was 654 ± 65 mg/dl, and the animals were switched to a standard porcine diet, yet cholesterol level remained markedly elevated at the end of the study at 361 ± 64 mg/dl. Proximal coronary segments were balloon-injured, targeting at least approximately 40% overstretch (day 0). Twenty weeks after initial injury, either BVS (n = 21; 3.0 x 18 mm or 3.5 x 18 mm) or EES (n = 12; 3.5 x 18 mm or 4.0 x 18 mm) were implanted in the previously injured segments, targeting a device-to-artery ratio of 1.1:1, under angiographic guidance. Quantitative coronary angiography analysis was performed with QAngio XA Software. IVUS pullback images were generated and analyzed with commercially available software. Luminal, device, and vessel areas were measured, and the neointimal and total plaque areas were calculated. OCT images were obtained. Qualitative analyses were performed at 1-mm intervals with commercial software. Cross-section lumen, device areas, and percent area stenosis were measured. Alterations of the BVS struts in their optical appearance at follow-up were categorized into 4 subgroups that have been applied in the preclinical study: preserved box, open box, dissolved bright box, and dissolved black box. An independent pathology laboratory conducted the histological analysis. Vessel injury (range 0 to 3), neointimal inflammation (range 0 to 4), adventitial inflammation (range 0 to 3), and fibrin (range 0 to 3) were semiquantitatively scored for each section. All sections were also evaluated for the presence of neoatherosclerosis, which is defined as the presence of foam cells, cholesterol clefts, and/or calcification in the neointima, and assigned a score from 0 to 3.



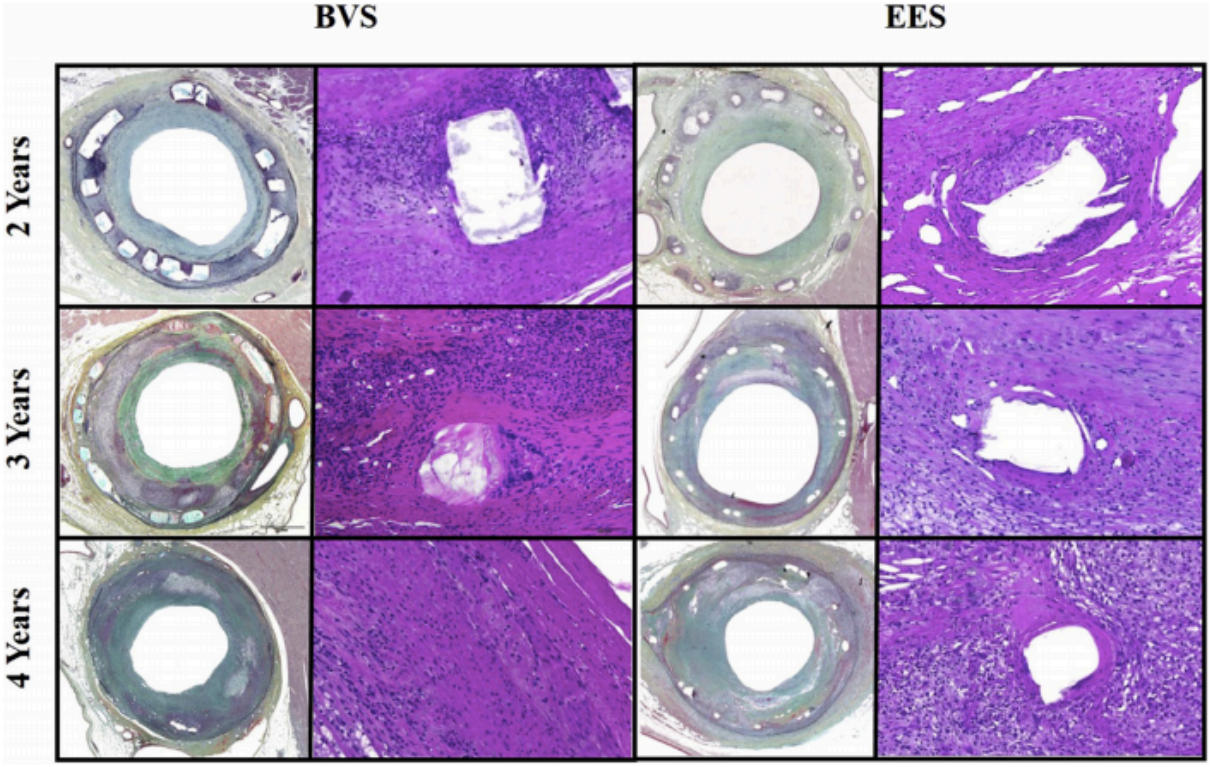
BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; FHS = familial hypercholesterolemic swine; f/u = follow-up; OS = overstretch.

RESULTS

Angiographic late lumen loss and %DS were not significantly different between BVS and EES at 1, 2, and 3-year follow-up time points. At 4 years, despite the difference in device size used in this study favoring EES, BVS showed lower late lumen loss than EES (BVS: 1.14 ± 0.37 vs. EES: 2.09 ± 0.12; p = 0.0056), whereas the difference in %DS between the 2 devices was not significant at this time point. Twenty weeks after injury, a comparable degree of plaque burden at IVUS evaluation (% area stenosis) before device implantation was found in both groups (BVS: 25.5 ±10.3% vs. EES: 22.1 ± 4.6%; p = 0.207). The implanted scaffolds were no longer discernible by IVUS by 3 years. Average total plaque areas were also higher in both groups at later time points than at baseline because of atherosclerosis progression. Compared to 1-year values, the lumen area remained stable in BVS at 4 years but significantly decreased in EES. The patency ratio of BVS-treated vessels appeared stable between 2 and 4 years but dropped in the EES-treated vessels at 4 years. In all animals, the scaffold struts were no longer discernible along the length of the implanted segments by OCT at 4 years. The strut count and its optical appearance changed over time: the recognizable struts were decreased over time, with 95% of preserved box appearance at 1 year, 17% at 2 years, and 7% at 3 years; at 4 years, the struts were not discernible in any implanted segments.



Compared to 1 year, the scaffold area was higher by 15% at 2 years, and the mean lumen area was larger by 25% between 1 and 2 years and 37% between 1 and 3 years. Consistent with IVUS findings, the lumen area was significantly decreased by 34% in the EES group between 1 and 4 years, whereas no further lumen area changes were observed in the BVS group. In all evaluated arteries, all lumens were widely patent, and struts were completely incorporated within neointimal growth (Figure 6). BVS struts at 2 years were readily visible as unstained rhombi sequestered within the neointima, whereas at 3 years, struts stained blue-green (Movat's pentachrome) and were faintly eosinophilic (hematoxylin and eosin) (Figures 6 and 7). Evidence of BVS dismantling, defined as stacking or misaligned struts, was observed infrequently at 2 and 3 years. At 4 years, BVS struts were difficult to discern and were mainly recognized as discrete foci of fibrous tissue, although blue-green–tinted irregular to rhomboid-shaped regions were rarely observed. Neointimal inflammation was moderate to severe in both BVS and EES at 2, 3 and 4 years. Fibrin deposition and red blood cell extravasation were absent to minimal in both groups at each time point. Evidence of neoatherosclerosis was observed in both BVS and EES and included focal to focally extensive foam cells, calcification, cholesterol clefts, and necrotic cores starting at 2 years.



CONCLUSION

In the presence of untreated hyperlipidemia and atherosclerosis, by using multimodality imaging and histology, BVS demonstrates comparable long-term vascular healing and anti-restenosis efficacy compared with EES, with lower late lumen loss at 4 years attributable to favorable remodeling not attainable in the EES-caged segments. In addition, the integration process is complete at 4 years based on OCT and histological findings, indicating that the scaffold bioresorption/integration timeline defined in normal animals is not significantly altered by atherosclerotic disease.

Chapter 10

Long-term performance and biocompatibility of a novel bioresorbable scaffold for peripheral arteries: A three-year pilot study in Yucatan miniswine

Femoral arteries are the most demanding enviroment for the stent implantation. Several mechanical stresses e.g. stretching, compression, twisting, contribute to the failure of this technology into this anatomical setting, We evaluated the performance of a novel dedicated peripheral BRS in the femoral arteries of Yucatan miniswine up to three years FU.

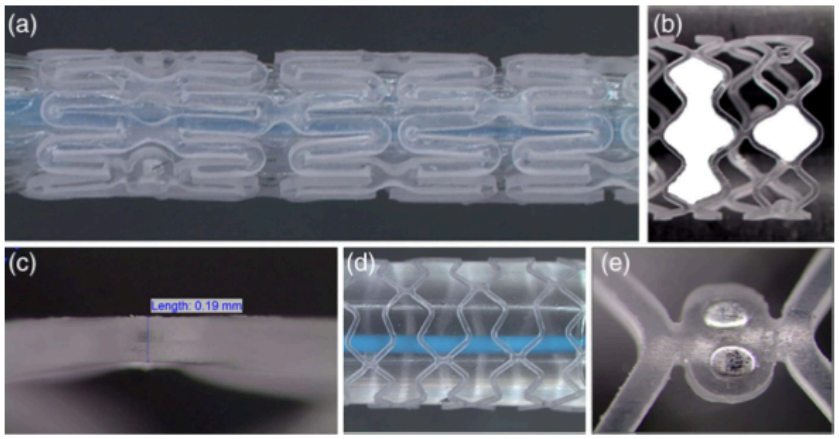


FIGURE 1 Credence BRS design and features. (a) Crimped scaffold. (b) Hybrid design combining closed cells at the edges and open cells throughout the body. (c) Strut profile with thickness measurement. (d) Fully expanded scaffold with open cells facilitating side branch access. (e) Dual platinum–iridium markers placed tri-axially around the scaffold edges' circumference [Color figure can be viewed at wileyonlinelibrary.com]

INVESTIGATED DEVICE

Specifically developed for PAD treatment, Credence BRS is balloon- expandable scaffold consisting of a poly-L-lactic acid (PLLA) backbone coated with a polymer-antiproliferative drug matrix (poly D, L-lactide + sirolimus) mixed in a 1:1 polymer to drug ratio, resulting in a surface drug concentration of 1.25 μg/mm^2. The strut thickness is higher than a coronary BRS (200 ± 20 μm) in order to achieve radial force adequate for peripheral vessels. Credence BRS features a hybrid cell design consisting of repeated, uniformly oriented zigzag crowns con- nected by longitudinal links with closed cells at the edges (proximal and distal) and open cells along its body for optimal side branch access (Figure 1). The device sizes used in the study were 5.0 × 15 mm, 5.0 × 17 mm, 6.0 × 15 mm, and 6.0 × 17 mm.

METHODS

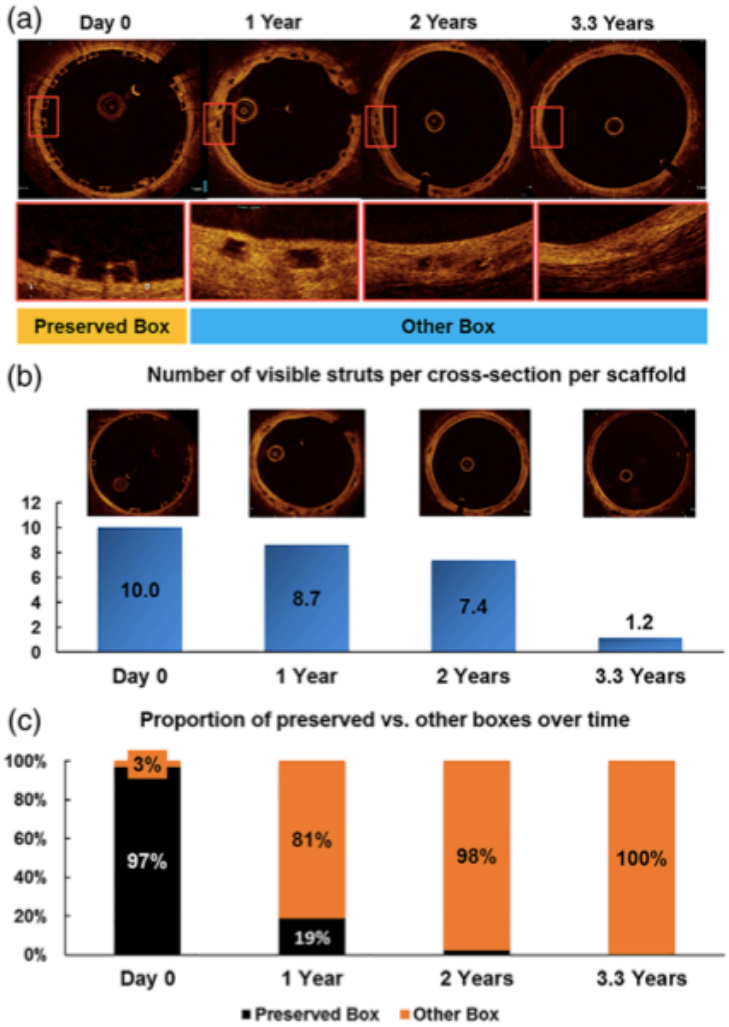
Fourteen sirolimus-eluting balloon-expandable Credence BRS were deployed in iliofemoral arteries of seven healthy Yucatan miniswine. Two animals each were sacrificed at 90 days and 180 days rendering two and two scaffolds, respectively, for histologic and sirolimus evaluation, one at 2 years for histology only (two scaffolds) and two at 3.3 years for histology (two scaffolds) and polymer degra- dation analysis (two scaffolds). Online quantitative vascular angiography (QVA) was used for scaffold sizing. Deployment of the BRS was done by balloon inflation with 1 atm increments every 2–3 s until obtaining complete scaffold expansion up to the target diameter (20% stent-to-artery overstretch ratio). Post-dilatation was not performed, as it is generally avoided in preclinical studies of stents and scaffolds implanted in normal vessels seeking consistent stent-to-artery oversizing ratio that minimizes vari- ability in arterial injury between implanted devices and helps interpretation of histopathology data. The pharmacokinetic profile of the sirolimus release from Credence BRS(n=4)was evaluated at 90(n=2) and 180days (n=2) using the liquid chromatography mass spectrometry. The sirolimus concentration in whole blood was evaluated in three pigs bearing six Credence BRS. Blood samples were collected pre-procedure and at 30 min, 1, 2, 4, 8, 24 hr, and 7, 14, 28, 60, 90 days post implant, using protein precipitation followed by a solid phase extraction procedure and analysis by LC–MS/MS. With the lower limit of quantitation was 0.5 ng/ml. QVA analysis was performed. OCT images were recorded. Percent area stenosis (%AS) was calculated as [1−(lumen area/inner scaffold area)] × 100. Neointimal thickness (NIT) was measured as the distance from the inner surface of the scaffold struts to the luminal borders. As established for ABSORB BVS (Abbott Vascular), changes in appearance of BRS struts in serial OCT are reflective of scaffold degradation and integration. Scaffold cross-sections were evaluated every 2 mm and the number of "preserved boxes" and "other boxes" were counted for every scaffold. An independent laboratory conducted the histopathologic analysis. ross-sectional areas, including external elastic lamina (EEL), internal elastic lamina (IEL), and lumen area

of each section were measured. %AS was calculated as [1 −(lumen area/IEL area)] × 100. Qualitative histological assessment of healing was performed using standardized score system. Peristrut inflammation was evaluated for each individual strut. The average inflammatory score for each cross section was calculated by dividing the sum of inflammatory scores by the total number of struts at the examined section. Furthermore, qualitative histological assessment included analysis of the uniformity and maturity of neointimal coverage, fibrin deposition neointimal and adventitial inflammation, and acquired malapposition. The in vivo degradation characteristics including molecular weight dis- tribution, scaffold mass loss, and molecular weight loss of the investi- gational PLLA scaffolds were assessed at the 3.3 years follow-up by size exclusion/gel permeation chromatography. Subsequently to the extraction procedure of PLLA scaffold from the explanted stented artery, the GPC was performed on each sample.

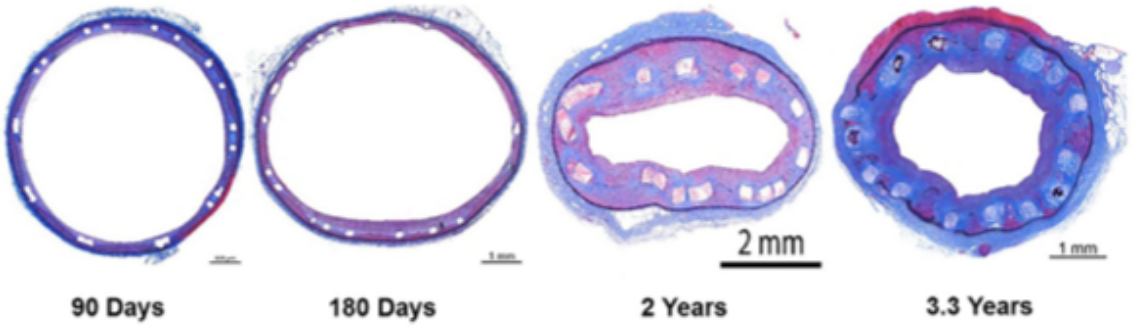
RESULTS

The sirolimus arterial tissue concentration gradually declined over time. At 180 days, it was about 50% lower than at 90 days but still present in the arterial wall. Peak drug concentration in blood was observed at 1–4 hr post implant, with an average peak concentration of sirolimus of 63.5 ± 5.67 ng/ml. The blood levels of sirolimus quickly declined to below the limit of quantification after 14days. Baseline average vessel diameters were comparable among all animals (mean baseline MLD: 4.40 ± 0.76 mm, $p = .099$), and so was the extent of balloon injury achieved in all animals (mean balloon to artery ratio: 1.11 ± 0.16, $p = .381$), and there were no differences in the post-implant MLD between the scaffolds (mean post-implant MLD: 4.64 ± 0.60 mm, $p = .124$). There was a significant lumen gain during the analyzed time interval, eventually manifested at a lumen patency equivalent to those in the adjacent reference segment (%DS at 3.3 years: −1.04 ± 10.57%, $p < .01$). At the early time points (30–- 180 days), PCT showed a significant decrease in the lumen area, resulting both from reduction of the scaffold area and from neointimal proliferation.

Between 180 days and 2 years, the average lumen area increased over time, at a rate matching the increments in scaffold area and also in the reference area (due to artery growth typical for the model), after which the increase plateaued between 2 and 3.3 years. The OCT hallmarks of scaffold integration into the arterial wall started to be evident at 1 year and very advanced at 3.3 years. Immediately after implantation, all struts had a preserved box appearance and were well apposed to the vessel wall; the strut footprints were increasingly less distinct over time. The numbers of recognizable struts per cross section per scaffold has dropped radically by the study's end. At day 0, 97% of struts presented a preserved box appearance, while only 3% had “other” pre- sentation. At 1 year, on average, the proportion was 81–19%. At 3.3 years, no preserved boxes were present in any of the scaffolds.



At the histological all struts were covered at all time-points with minimal asymmetry. There was no evidence of luminal thrombosis in either the main or the side branches. The vascular healing response appeared adequate in all implanted Credence BRS based on coverage of the struts by fully mature, fibro-muscular, and endothelialized neointima with no residual fibrin and no thrombosis. The neointimal and adventitial inflammation was benign up to 2 years and completely absent at 3.3 years. There was no evidence of acquired scaffold malapposition or any uncovered struts. In regard to resorption, there was no substantial evidence of it by 180 days. The process started being discernible at 1 year and at 2 years the strut degradation was appreciable by hyaline hydrolysis of the poly- mer and partial hyaline substitution of the scaffold struts. Scaffolds harvested at 3.3 years demonstrated advanced biodegradation as illus- trated by strut erosion, prominent hyaline hydrolysis of the polymer, and evident fragmentation and phagocytosis. Overall, the healing fea- tures and patency characteristics recorded at 3.3 years were very consistent with data recorded at earlier time periods.



CONCLUSION AND LIMITATIONS

This long-term small experimental feasibility and proof of principle study provided preliminary evidence of acceptable durability and sat- isfactory biocompatibility of peripheral Credence BRS over 3.3 years after implantation in iliofemoral arteries of Yucatan miniswine. Two main limitations of this study are worth highlighting. One, the sample size was small, although owing to multiple techniques employed, it was

sufficient to provide a fairly complete initial insight throughout nearly entire lifetime of the device. Also, past experience with BRS failures indicates that long-term follow-up is of utmost importance, and this was made the study's top priority within the available resources. Second, the study lacks a comparator device, but it has to be acknowledged that no suitable comparator (peripheral balloon-expandable BRS) has been available to date, while compari- sons to metallic DES are of limited value biologically due to funda- mentally different nature of total body degradation of BRS. Third, lack of atherosclerosis and challenging biomechanical environment in the arterial segments available for the study in the animal model limits the clinical applicability of the findings, although the normal model was entirely appropriate for the first-ever in-vivo evaluation's comparative purpose.

Part II_2

Bioresorbable Scaffold clinical

CHAPTER 11

First in human evaluation of a novel Sirolimus-eluting ultra-high molecular weight bioresorbable scaffold: 9-, 24-and 36-months imaging and clinical results from the multi-center RENASCENT study

RENASCENT study is part of the clinical FIH program from the Amaranth (Santa Clara, California) company evaluating the safety and efficacy of a novel BRS manufactured through an innovative process different from the BVS in order to obtain higher mechanical performances. Into this study we evaluated the first generation Amaranth BRS FORTITUDE (150 μm) in a clinical setting.

STUDY DEVICE

The FORTITUDE® balloon expandable BRS displays a zigzag helical design and is manufactured using an ultra-high molecular weight PLLA scaffold coated with a sirolimus:polymer matrix (1:1) releasing 90% of the drug by 90 days. In vitro studies have shown reduction in molecular weight by ~50% at 8 months and greater than 85% at 18 months. Radial vessel support is maintained for ~ 8 to 10 months. The core polymer technology involves a proprietary polymer synthesis and processing technology designed to achieve a balance between strength, flexibility and high resistance to fracture. The scaffold structure reacts in a highly balanced way to balloon expansion, virtually eliminating strut distortions associated with crimping and dilatation of the scaffold. This minimizes stress concentrations and susceptibility to fractures. The high radial strength of the FORTITUDE® scaffold is maintained for an extended period of time (up to 10 months), fully supporting the treated vessel during the healing period and then gradually ceasing to provide luminal support when it is no longer needed.

METHODS

The RENASCENT was a prospective, non-randomized, multicenter trial of 63 patients treated with the FORTITUDE® BRS in Colombia and Italy. The study included patients between 18 and 85 years old with single de novo lesions in native coronary vessels with TIMI flow≥1. The vessel needed to be between 2.5-3.75 mm in diameter with lesion length < 14mm. Patients with acute ST elevation MI, restenotic or severely calcified lesions were excluded. Target lesions were treated using standard interventional techniques. Adequate pre-dilatation of the target lesion was mandatory (1:1). Baseline IVUS assessment was performed during the index procedure to evaluate vessel size, degree of calcification and to determine the appropriate scaffold size. The target lesion had to be treated with a single study device and planned scaffold overlapping was not allowed. Post-dilatation was allowed at the operator's discretion. Bailout stenting with DES for non-flow limiting edge dissection was recommended if required. Post-procedural OCT was required in all cases. The 30-day follow-up was performed via an office visit if possible or otherwise by phone call. At 9-months, angiographic follow-up with OCT was performed. Coronary computed tomography angiography or invasive coronary angiography was performed at 24-months follow-up. The patients underwent clinical follow-up at 36-months with further phone follow-up at 4 and 5 years planned. Primary performance endpoint was in-scaffold late lumen loss (IS-LLL) defined as the amount of vessel lumen diameter lost/gained measured by quantitative coronary angiography (QCA) at 9- months angiography. The assessment was made within the segment of vessel including the scaffold. Primary safety endpoint was the incidence of target vessel failure (TVF), defined as cardiac death (using the Academic Research Consortium [ARC] definition), target vessel myocardial infarction (TV-MI) (using the Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions [SCAI]), or clinically indicated target lesion revascularization (TLR) (using the ARC definition) at 9-months. 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 the occurrence of major adverse clinical events related to ischemia up to day of discharge were assessed. QCA was performed at baseline. The OCT assessment was performed during the index procedure (after scaffold implantation) and at 9-months follow-up. The following parameters were analyzed at: mean lumen area, mean outer and inner scaffold area, post-implantation scaffold fracture and strut malapposition. Furthermore on follow-up, intra-scaffold neointimal hyperplasia, presence of scaffold dismantling, percentage of strut coverage / malapposition were analyzed.

RESULTS

A total of 63 patients were enrolled: 42 in Colombia and 21 in Italy. Clinical device success was 98.4% (n=62); 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 96.8% (n=61). 2 cases (3.2%) were reported as non-Q-wave peri-procedural MI because of troponin rise without EKG changes or clinical symptoms. At 9-months, 61 (97%) patients completed clinical and mandatory angiographic follow up. 1 patient died of non cardiac causes. 1 patient did not receive the study device and as per protocol exited the study at 30 days. There was one TLR at 9-months follow-up in an asymptomatic patient which was successfully treated with a DES. This was related to proximal disease progression due to inadequate lesion coverage. The cumulative 9-months TVF was 4.9%. Between 9- to 24-months, additional TVF was 4.9% (n=3), all driven by TLR due to restenosis. One patient had clinical symptoms and the other found on follow-up. Third patient had very late scaffold thrombosis following stopping all his medications. All patients underwent uneventful successful revascularization. Between 24- and 36-months follow-up, there were no further TVF cases reported. There was one further non-cardiac death during this period. IS-LLL was reported as

0.29 ± 0.43 at 9-months. At 24-months angiographic follow up was performed in 49 patients; 31 patients with coronary angiography (31 analysed) and 18 patients with CTCA scan. Binary stenosis was reported in one case at 9-months (1/61, 1.6%) and two (2/30, 6.7%) at 24-months. OCT pullbacks were performed at index and 9-months. The total percentage of covered struts at 9-months was 95.6 ± 6.0%, of which 94.3 ± 7.1% were apposed to the vessel wall. 0.6 ± 1.8% of struts were malapposed and covered. The total percentage of uncovered struts at 9-months was 4.4 ± 6.0%. Only 0.2 ± 0.7% were uncovered malapposed struts. Only one case showed evidence of strut scaffold dismantling at 9-months. Supplemental Figures 6 shows matched Mean outer surface area at 9-months. OCT differences at 9-months shows females having larger MLA post BRS implantation and at 9-months follow-up.

CONCLUSION

The early clinical experience with the FORTITUDE® BRS demonstrated that the polymer is biocompatible, safe and effective in improving coronary luminal diameter in patients undergoing elective percutaneous coronary intervention on follow-up to 36-months.

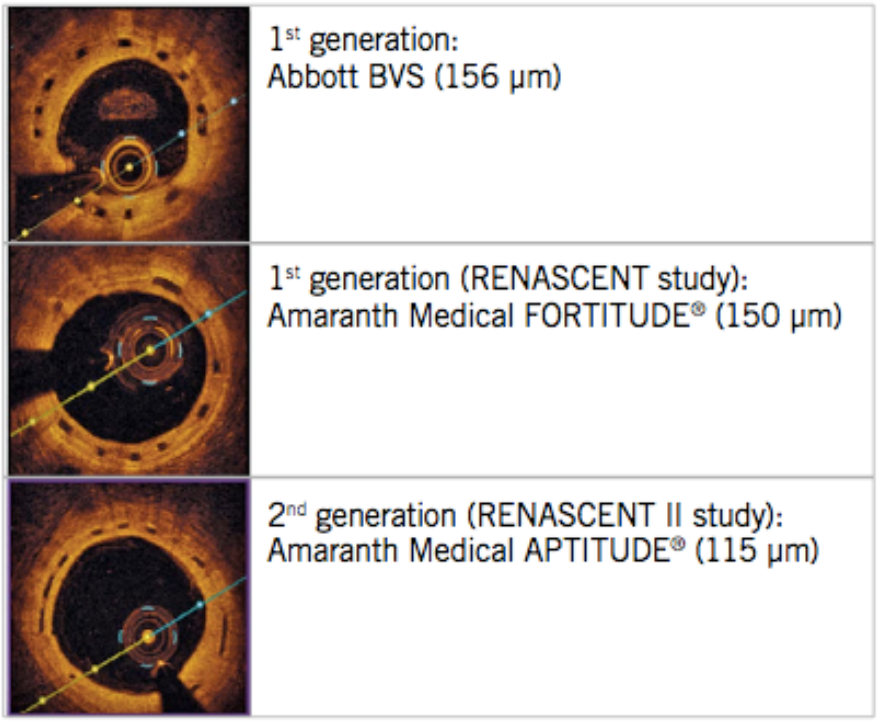
CHAPTER 12

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

RENASCENT II study is part of the clinical FIH program from the Amaranth (Santa Clara, Californina) company evaluating the safety and efficacy of the next generation thinner BRS APTITUDE (115 μm) in a clinical setting.

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 thick-ness (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



METHODS

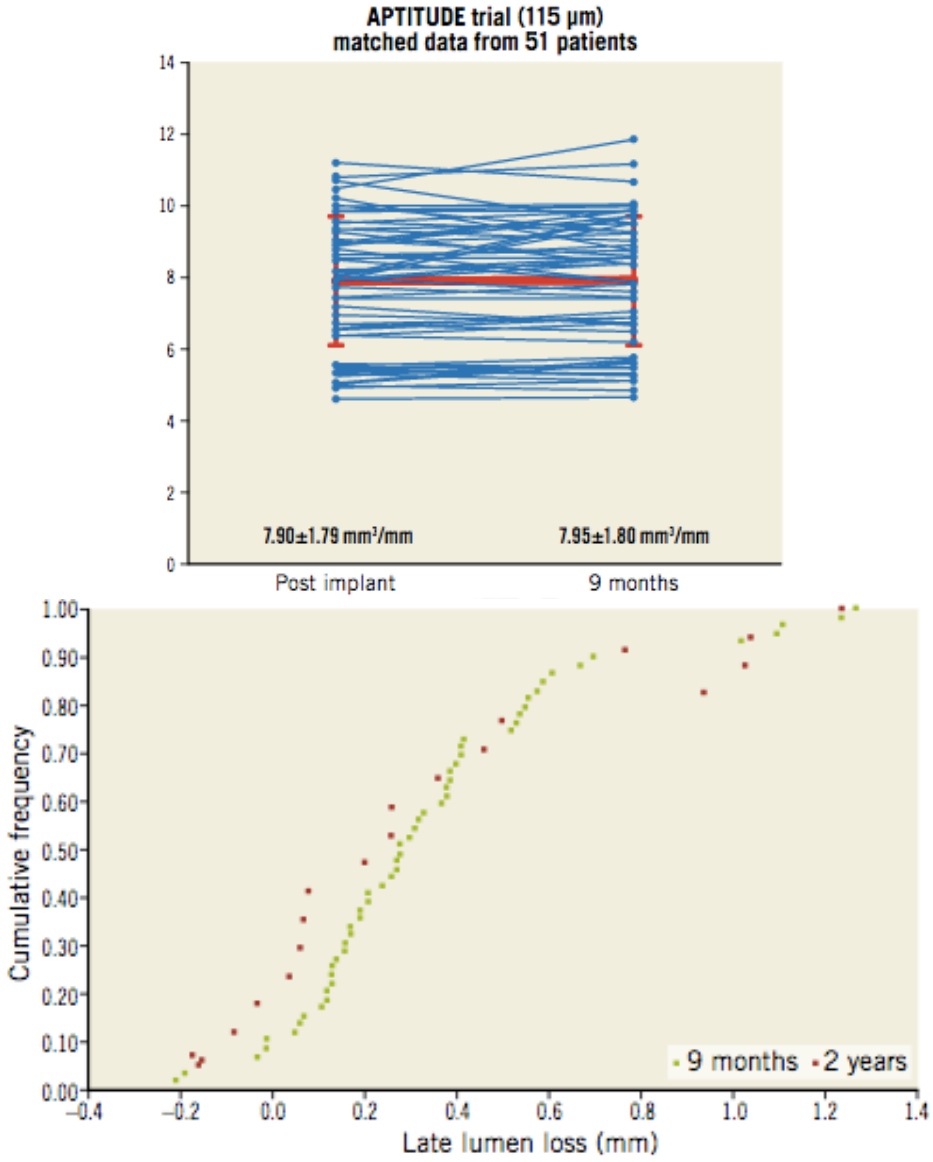
Target lesions were treated using standard interventional tech-niques; successful predilatation of the target lesion was manda-tory (1:1). Baseline intravascular ultrasound (IVUS) assessment was performed during the index procedure to evaluate vessel size and degree of calcification, and to determine the appropriate scaffold size. The target lesion had to be treated with a sin-gle 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 subop-timal) 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. 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. 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 quantita-tive 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 ves-sel failure (TVF), defined as cardiac death (Academic Research Consortium [ARC] definition), target vessel myocardial infarction (TV-MI) (using the expert consensus document from the Society for Cardiovascular Angiography and Interventions [SCAI]), or clinically indicated target lesion revascularisation (TLR) (ARC definition) at nine months. Although the adjudication of periproce-dural MI was performed using the SCAI definition, additional ana-lyses were performed using the third universal

definition of MI. Stent thrombosis was defined using the ARC “definite” or “probable” stent thrombosis definitions. Furthermore, both “clinical device success”, defined as success-ful 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.

RESULTS

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 months, TVF was 3.4% (n=2) due to two non-Q-wave MIs (target vessel MIs) but there was no TLR. 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. However, these patients were asymp-tomatic 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. Based on 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. Other significant QCA measurements were in-segment minimal luminal diameter (MLD) 1.0±0.3 mm at baseline, and 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 pullbacks were analysed in 53 lesions during the index pro-cedure (post scaffold implantation) and 58 lesions at 9-month angiographic follow-up. 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%).



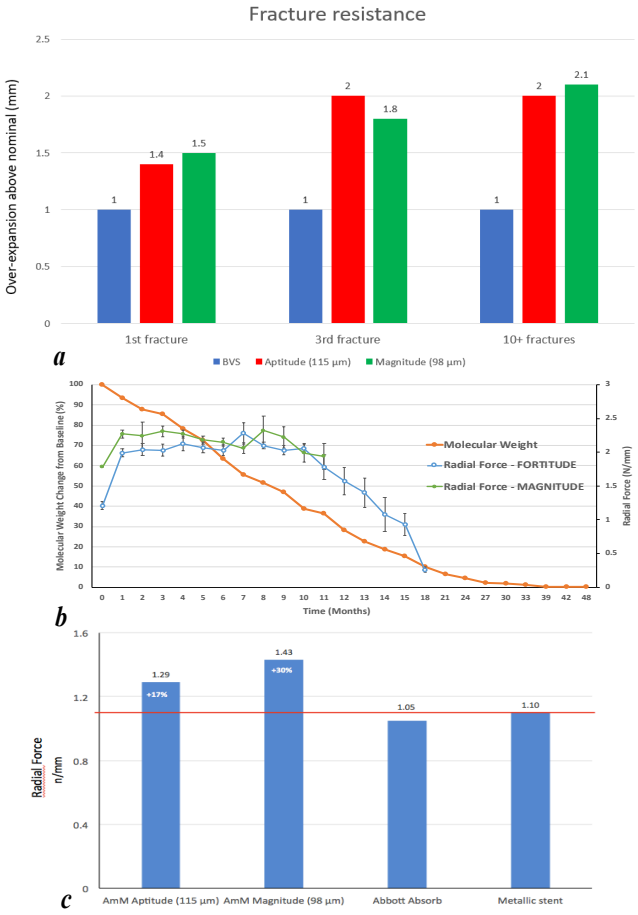
CONCLUSION

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 elec-tive PCI. The APTITUDE BRS has shown that, despite reduction in struct thickness, it matches previous safety clinical endpoints seen with the FORTITUDE BRS.

CHAPTER 13

RENASCENT III: First in Human Evaluation of the Novel Thin Strut MAGNITUDE Sirolimus-Eluting Ultra-High Molecular Weight MAGNITUDE Bioresorbable Scaffold: 9-months Imaging and 2-Year Clinical Results

RENASCENT III study is the last part of the clinical FIH program from the Amaranth (Santa Clara, Californina) company evaluating the safety and efficacy of the last generation thinner-strut below 100 μm BRS MAGNITUDE (98 μm) in a clinical setting.

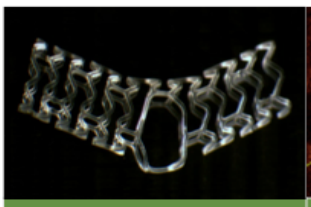


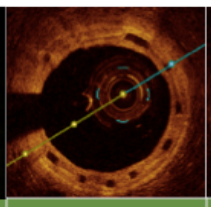
STUDY DEVICE

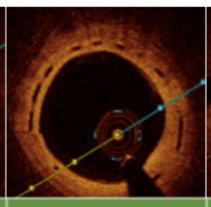
MAGNITUDE® is a novel sirolimus-eluting ultra-high molecular weight (UHMW) amorphous PLLA BRS. PLA is a versatile material and the properties of the resin

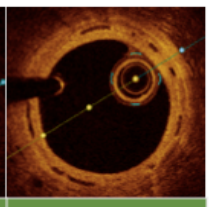
polymer can be different depending on the manufacturing process unlike DESs metallic alloys that have group specific features. The Amaranth manufacturing process is different form the other BRS allowing this polymer (UHMW PLLLA) to keep high mechanical performances regardless of a thinner structure. Indeed, MAGNITUDE® BRS, despite having a strut thickness of 98 µm, shows higher radial force and higher resistance to fracture compared to the BVS.

Design features	MAGNITUDE BRS
Polymer	Ultra high MW-Poly-L-Lactide (PLLA)
Diameters	2.5, 3.0, 3.5 mm
Lengths	13, 18 mm
Wall thickness	98 µm
Surface coverage area (at RBP)	22%
Drug coating	1:1 Poly D L-Lactide:Sirolimus
Drug content (depending on scaffold size)	97 to 144 µg
Drug density	96 µg/cm^2
Inflation pressures	Nominal: 6 to 9 ATM RBP: 16 ATM
Guide catheter size	6 Fr compatible
Bio-resorption time	Scaffolding effect diminishes ~ 10 months 95% MW reduction ~ 18 months









	FORTITUDE® 150 µm	APTITUDE® 115 µm	MAGNITUDE® 98 µm
Vessel Coverage at RBP (%)	20	22	22
Eluted Drug	Sirolimus		
Expansion Above Nominal to First Fracture (mm)	2.0	1.4	1.5
Available Sizes (mm)	2.5 – 3.7	2.5 – 3.7	2.5 – 3.5

The main improvements of MAGNITUDE BRS compared to its predecessors (FORTITUDE, APTITUDE) are:

- Thinner struts (98 µm vs 150 µm and 110 µm respectively)

- Maintained low scaffold SA 22% (similar to metal stents and less than some other commercially available bioresorbable scaffolds)
- Oversizing is allowed up to 1.5 mm above the nominal diameter (DES like behavior despite the thinner struts).

METHODS

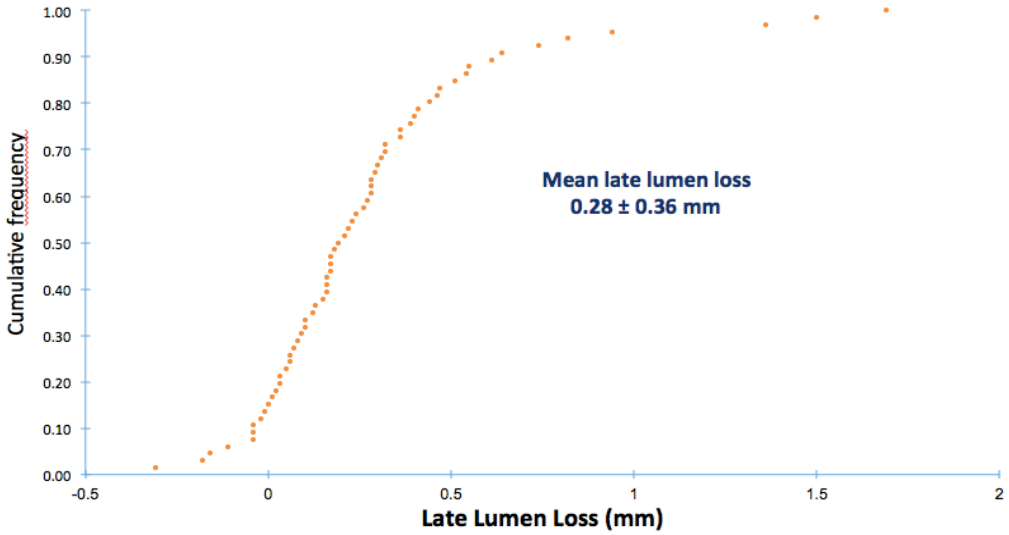
The RENASCENT III study is a prospective, non-randomized, non-inferiority study of the MAGNITUDE® Bioresorbable Drug-Eluting Coronary Scaffold. A total of 70 patients from 4 centers in Colombia and 4 in Italy were enrolled. Inclusion criteria were: patients >18 and <85 years of age presenting with either stable or unstable angina pectoris, silent ischemia, low or intermediate risk NSTEMI, evidence of myocardial ischemia in a coronary territory previously affected by STEMI as long as the intervention performed ≥ 3 months following the STEMI and de novo lesions in a native coronary artery with a diameter between 2.5 and 3.7 mm by IVUS, lesion length of <14 mm by QCA, a percentage visually estimated diameter stenosis (DS) ≥50% and <100% and a Thrombolysis in Myocardial Infarction (TIMI) flow grade of ≥1. Up to two de novo lesions were allowed to be treated. Exclusion criteria were: acute ST segment elevation myocardial infarction, unstable arrhythmias, left ventricular ejection fraction <30%, renal insufficiency with eGFR < 60 ml/kg/m2 or serum creatinine level of > 2.5 mg/dL, restenotic or severely calcified lesions, lesions located in the left main coronary artery or located within ≤3 mm of the aorta junction or within ≤3 mm the origin of the left anterior descending or circumflex, lesions involving an epicardial side branch >2 mm in diameter by visual assessment and thrombus or another clinically significant stenosis in the target vessel. 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 9-months. The assessment was made within the segment of vessel including the scaffold. Primary safety endpoint was the incidence of target vessel failure, defined as cardiac death (using the

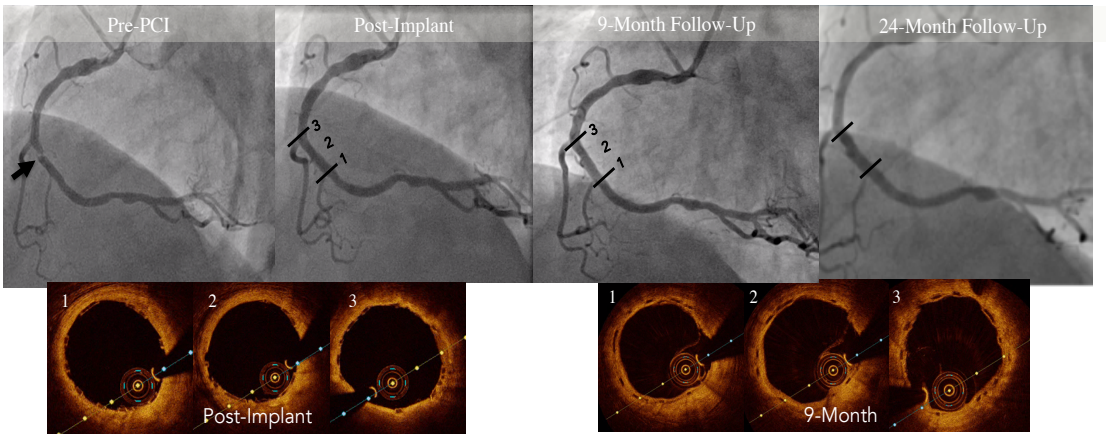
Academic Research Consortium [ARC] definition), target vessel myocardial infarction (TV-MI) or clinically indicated target lesion revascularization (TLR) at 9-months. Although the adjudication of periprocedural MI was performed using the SCAI definition, additional analysis were performed using the Third Universal Definition of MI. Stent thrombosis was defined using the ARC "definite" or "probable" stent thrombosis definitions. 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 the occurrence of major adverse clinical events related to ischemia up to day of discharge were assessed.

RESULTS

The 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). At 9 months, 59 (98%) patients completed clinical and mandatory angiographic follow up. 1 patient did not receive the study device and per protocol exited the study at 30 days. At 9-months TVF was 3.4% (n=2) due to 2 non- Q wave MIs (target vessel MIs) but no target lesion revascularization (TLR). No ischemia driven TLR and scaffold thrombosis have been reported up to 24-months follow-up. There were 2 cases of binary stenosis on CT angiography at 24-months follow-up. However, these patients were asymptomatic and no further intervention was carried out (TLR) as not clinically indicated. In-scaffold late lumen loss (IS-LLL), was 0.33 ± 0.36 mm at 9 months. Other significant QCA measurements were: MLD 1.0 ± 0.3 at baseline, 2.5 ± 0.4 mm post-BRS implantation and 2.3 ± 0.4 mm at 9 months. There was an acute gain of 1.8 ± 0.4mm post BRS insertion. OCT pullbacks were analyzed in 53 lesions during the index procedure (post-scaffold implantation) and 58 lesions at 9-months angiographic follow-up. The percentage of intra-scaffold 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 (0.037% ± 0.161% were malapposed). The total percentage of uncovered struts at 9 months was very low (2.97%).





CONCLUSIONS

24-months clinical experience with the PLLA BRS APTITUDE® (Amaranth Medical Inc., Mountain View, CA) has demonstrated that the polymer is safe and effective in improving coronary luminal diameter in patients undergoing elective percutaneous coronary intervention. The APTITUDE® BRS has shown that despite reduction in struct thickness, it matches previous safety clinical endpoints seen with FORTITUDE® BRS.

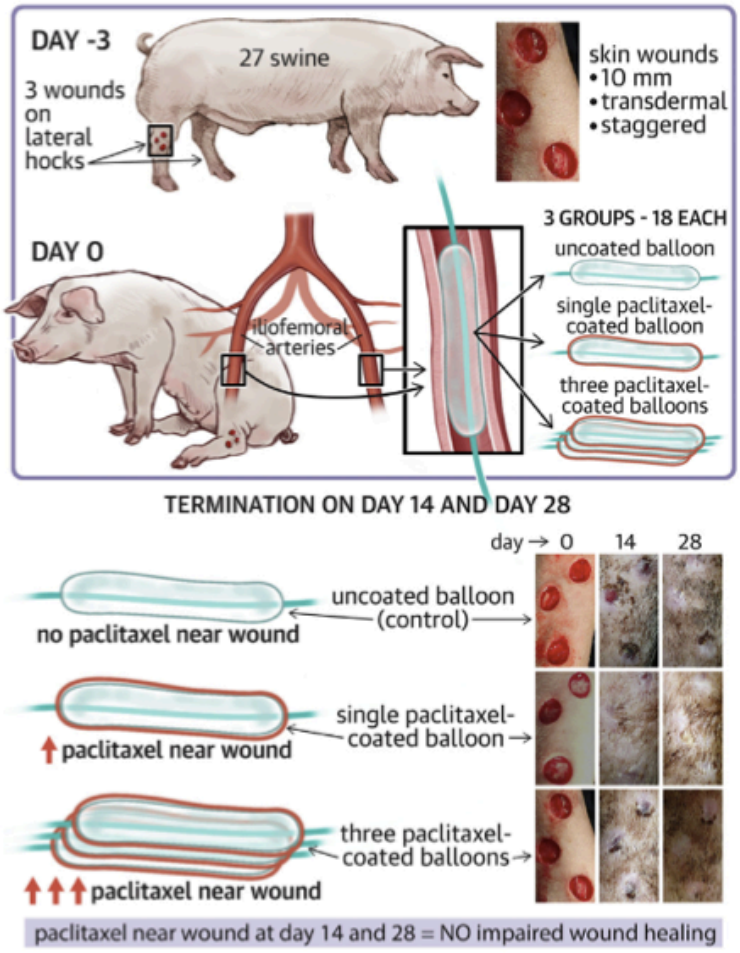
Part III

Drug coated balloon

CHAPTER 14

Downstream Paclitaxel Released Following Drug-Coated Balloon Inflation and Distal Limb Wound Healing in Swine.

Paclitaxel embolization following DCB inflation is one of the biggest concerns regarding this technology. ALI, is a critical and delicate condition putting the patient at risk of lower limb amputation. The paclitaxel embolized during the lower limb revascularization with DCB may slow down the wound healing process as a consequence of its antiproliferative action worsening the clinical scenario into these patients. This study tries to evaluate the effect on induced distal leg wounds healing of the inflation in the ileo-femoral artery of PCB, single inflation and triple inflation of DCB. In order to assess this effect we decided to use the DCB mostly associated to coating embolization (crystalline isoform).



METHODS

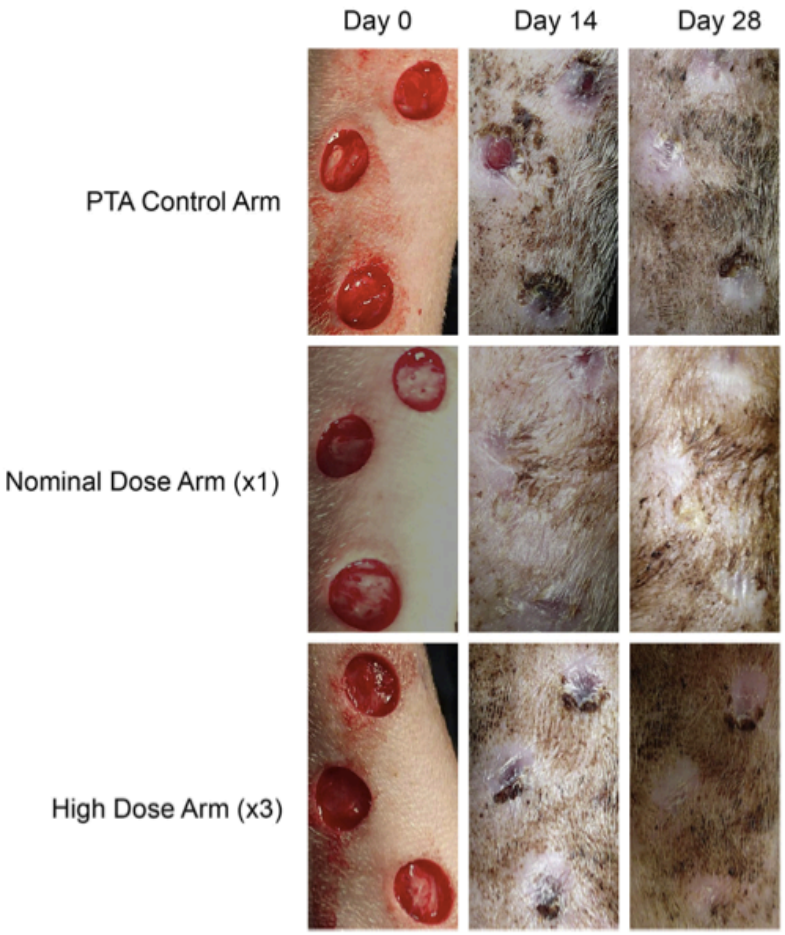
A total of 27 female juvenile Yorkshire domestic swine weighing between 17.3 and 24.8 kg were used in this study. Two to 3 days before PCB treatment, uniform full-thickness wounds were created under sedation using 10-mm biopsy punches. The wounds were placed in a staggered vertical pattern below the hock joint on the anterolateral aspect of each distal hind limb with approximately 10 to 20 mm between each wound. The wounds were bandaged with Tegaderm. The bandaging was replaced on awake animals 3 times per week after wounding throughout the in-life duration of the study. Each animal received prophylactic antimicrobial and anti-biotic medications daily from day -4/-3 to day 7. Antiplatelet therapy was administered daily; 325 mg aspirin and 75 mg of clopidogrel from day -3 to -1 then 81 mg of aspirin and 75 mg of clopidogrel from day 0 for the remainder of the study. Animals were randomly allocated to 3 study arms and sacrificed at 14 days(n = 49) and 28 days (n =18). The 3 study arms were: 1) single PCB treatment (PCB 1, 3.5 mg/mm2, IN.PACT Admiral balloon catheters, 5.0/ 6.0 80 mm; Medtronic, Santa Rosa, California), 2) 3 overlapping PCB treatments (PCB 3, 10.5 mg/mm2, IN.PACT Admiral balloon catheters, 5.0/6.0 80 mm; Medtronic), and 3) a percutaneous transluminal angioplasty (PTA) control (no drug coating, Admiral Extreme PTA catheter, 4.0/5.0/6.0 80 mm; Med- tronic). Three animals from each arm were evaluated at the first time point (14 days), 6 animals from each arm were evaluated at the second time point (28 days). In the PCB 3 arm, 3 sequential/different balloons were used consecutively and aligned to overlap an ≈100% margin of coverage by means of angiographic visualization using a digital fluoroscope and software. Two iliofemoral treatment sites were selected per animal; animals were limited to 1 study arm with bilateral treatment. Balloon inflations were performed for 1 min to reach a target vessel over- stretch of 20% to 30% based on pretreatment qualitative vascular angiography of the target region using standard interventional techniques via carotid access. As such, there were 6 arteries treated in each study arm survived to 14 days (total of 18 sites in 9 animals) and 12 arteries in each study arm survived to 28 days

(total of 36 sites in 18 animals). Wound healing was assessed over time by: 1) visual observation with sequential photography at time of creation and at each bandage change; and 2) histologic evaluation of re-epithelialization, granulation, inflammation, and collagen formation. Each bandage was changed a minimum of 3 times per week throughout the in-life study duration on awake ani- mals while in a sling. The wound sites were photographed with a measuring device in view. Each wound was quantitatively scored in a blinded manner using a modified system of objective inflammation and cosmesis scoring parameters modified from published methods. At time of termination, while under general anesthesia, 3 full- thickness skin biopsy specimens per hind limb, 10 mm in diameter, were collected immediately adjacent to the healing wounds for a total of 6 biopsy specimens per animal and flash-frozen in liquid nitrogen for drug content analysis. Only local peri-wound tissue was analyzed for drug content. The animal was euthanized while still under general anesthesia using a pentobarbital-based solution of (88 mg/kg intravenously). The entire wounded area of each distal limb including approximately 2.5 cm of surrounding tissue was collected as 1 specimen with proximal end marked with suture. Tissue samples for histology traversed deep in the fascial plane and muscle so as not to disturb the wound or fibrosis below the wound. Frozen tissue samples were homogenized, and paclitaxel was quantified using liquid chromatography/tandem mass spectroscopy. Each individual wound was bisected and embedded in paraffin and sectioned at approximately 5-mm thick- ness to produce 2 serial histological sections, 1 stained with hematoxylin and eosin and the second with Masson's trichrome. The individual wounds were independently scored in a semiquantitative manner for re-epithelialization, fibroplasia, neo-vascularization, and inflammation.

RESULTS

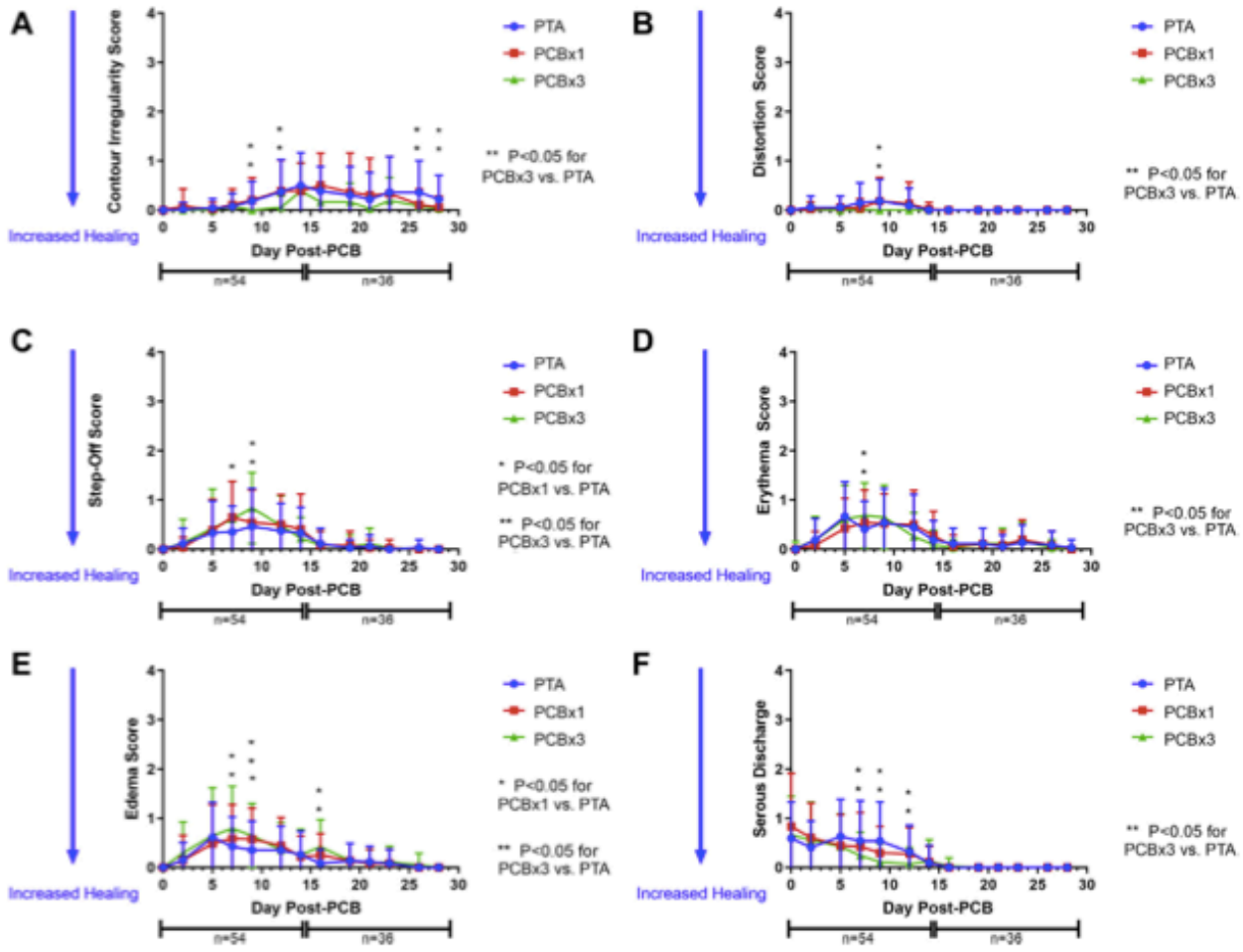
All animals survived to scheduled termination of either 14 or 28 days. At the 28-day time point, all wounds in all 3 study arms epithelialized as assessed by visual examination. The ranges of inflammation and cosmesis scores indicated similar trends in healing parameters between both PCB and PTA control treatments. The

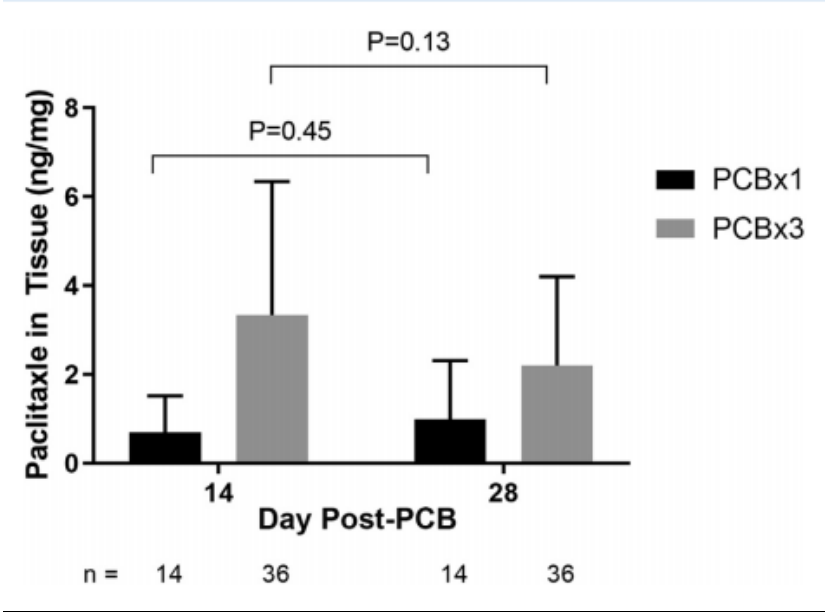
most pronounced changes with evolution of the healing responses were observed in margin separation and purulent exudate scores with lesser magnitude changes observed with the other inflammation and cosmesis parameters. Margin separation scores indicated closely similar progression of wound resolution between all study arms with no discernable inhibition of healing by PCB treatment, relative to the PTA control. Purulent exudate scores indicated an initial increase of inflammation during the first 2 weeks and resolving to 0 in all study arms by day 16 with a consistent trend for lower scores observed in the PCB 3 arm. Furthermore, margin separation scores and exudate scores of individual animals were examined over time to look for temporal variability across groups and consistency in distribution around the group means for any timepoint. Mean score on a per-animal basis were plotted at each time point as well as well as the individual animal scores at each time point (showing distribution around the mean score, represented by a line). Distribution of scores around the mean with greatest variability occurring in the 7- to 14-day period, reflecting, as anticipated, normal variation in the healing response of wounds within individual animals. Lastly, to determine if position of the wounds impacted the resulting margin separation and puru- lent exudate scores, mean scores for each time point were plotted by position for each group (i.e., top, middle, or bottom wounds). The resulting plots show no consistent and obvious differences in healing rate based upon location of the wound in the leg.



The main histopathologic features were similar across all 3 study arms with no microscopic findings attributed to paclitaxel. oxicity. At 14 days, 78% of wounds in the control arm, 50% of wounds in the nominal-dose (PCB 1) arm, and 100% of wounds in the high-dose (PCB 3) arm exhibited grade 3 or 4 re-epithelialization. In the underlying dermis, most wounds across all arms exhibited mild fibroplasia, scores being similar across all study arms. Production and orientation of dermal collagen was within expected limits. Mild neo- vascularization was observed throughout the wound defect. At 28 days, 89% of wounds in the PTA control arm and 100% of wounds in the nominal- (PCB 1) and high-dose (PCB 3) arms exhibited grade 4 or com- plete re-epithelialization. The underlying dermis showed moderate fibroplasia, scores being similar across all study arms, with expected production of dermal collagen and minimal neovascularization. The amount and density of new collagen was less to that observed in the adjacent normal dermis; however, it was still more than the collagen observed at 14 days. Neovascularization was evident mostly in the

superficial dermis indicating ongoing maturation of the collagen architecture and progression of wound healing compared to that at 14 days. Dermal inflammation was scored as mild to minimal in most wounds across all treatment arms. All biopsy samples obtained immediately adjacent to the wound in the nominal-dose (PCB 1) and high-dose (PCB 3) arms contained paclitaxel. The PCB 3 arm had consistently higher concentrations of pacli- taxel to that of the PCB 1 arm at both time points. Drug concentrations in tissue showed no significant change from 14 to 28 days post treatment at either paclitaxel dose; 0.69 ng/mg and 0.98 ng/mg in the nominal-dose (PCB 1) arm ($p = 0.45$) and 3.3 ng/mg and 2.2 ng/mg in the high-dose (PCB 3) arm ($p = 0.13$) at 14 and 28 days, respectively.





CONCLUSION

This study shows that significant tissue drug content post-PCB use in the proximal arterial flow does not preclude the possibility of wound healing in down-Stream tissues. Therefore, the biological effect of particulate paclitaxel embolization on wound healing dynamics in vascular territories with small distribution volume and poor distal runoff merits further investigation to properly balance the relative risks and benefits.

CHAPTER 15

Technical insight on drug-coated balloons. - Current technical challenges and the future of drug-coated balloons

Into these two paragraphs we wrote for the book “Drug-coated balloon” we describe the technical limitation and the flaws of DCB based on a clinical and technical perspective and possible directions this technology may have in teh future.

Technical insight on drug-coated balloons

Interventional cardiology has witnessed several revolutionary developments over the last two decades leading to progressive changes in daily practice. The most striking revolution in the percutaneous treatment of coronary artery disease has undoubtedly been the introduction of the Drug Eluting Stent (DES). Drug Eluting Stents made a revolution in interventional cardiology, not only improving the mechanical limitations of balloon angioplasty but also by radically decreasing restenosis rates. Last generation DES have shown to decrease 12-month restenosis rates to single digits, however, concerns still exist regarding the rare but unpredictable occurrence of late or very late stent thrombosis, a catastrophic event resulting from delayed vessel healing. Current guidelines recommend the use of prolonged double antiplatelet therapy (DAPT) following DES implantation which make become problematic in specific clinical settings where a shorter DAPT period is desired (i.e. high bleeding risk patients). Drug Coated Balloons (DCB) have emerged as a therapeutic alternative to DES in situations in which the use of permanent implantable stents is less desirable. The concept of delivering antiproliferative drugs via balloon angioplasty has been around for several decades. One of the first reports back to 1986 when Goldman et al. demonstrated the effective delivery of horseradish peroxidase to dogs and human arteries using a multiple lumen polyurethane catheter. Since there, several technologies and drugs have been tested aiming to prevent restenosis. (Table 1).

Technical and biological DCB features			
Drug	Immediate transfer into the vessel wall	Prolonged retention into the vessel wall (Lipophilic properties)	No systemic toxic effect
Coating	Homogeneous coating thickness and drug concentration along the balloon surface	Quick drug release	Coating fragmentation into submicron particles to allow drug delivery after balloon inflation
Balloon Catheter	Minimal drug loss during tracking	Minimal drug loss on inflation	Optimal vessel wall contact on inflation

Table 1

Technical Features of DCB Architecture

The concept of developing a balloon-based drug delivery system to prevent arterial restenosis was founded on the hypothesis that a durable effect on neointimal proliferation could be achieved following a single-drug delivery. Drug delivery and retention are key for the long-term prevention of restenosis. Last generation DES release –Limus family drugs, which have proven to be the most effective class of antiproliferative drugs when delivered in a controlled fashion from a permanent implantable stent. On the contrary, drug release from DCB follows a different release pattern and its success relies on the rapid transfer of a single dose of antiproliferative agent that is expected to be retained into the vessel wall over-time.

Heparin was one of the first drugs tested for local delivery by Edelman et al. in 1990, showing that due to its solubility profile the drug was not retained over-time into the vessel wall once released. In 1992 Muller et al. experimented Metotrexate and in 1995 Colchicine was tested as well. All these studies, showed a rapid wash-out of the delivered drugs thus tempering the enthusiasm toward this approach. The first agent showing promising results was published in 2001 by Professor Bruno Scheller who described that Paclitaxel solubility was significantly increased when mixed with contrast agents and allowed its delivery by intracoronary bolus injection resulting in significant reduction of neointimal proliferation in the porcine model of restenosis. The idea of combining paclitaxel with contrast medium was then applied to the

surface of a balloon to create the first DCB prototype. Early clinical data sparked the interest in this field and several DCB programs were created aiming to reproduce this technological approach by the use of hydrophilic carriers as a method to transport paclitaxel into the vessel wall following balloon dilatation.

All commercially available DCB use Paclitaxel due to its lipophilic profile, potent antiproliferative effect and chemical stability following tissue delivery. Paclitaxel has shown to inhibit cell proliferation and migration due to an irreversible stabilization of intracellular microtubules, resulting in inhibition of cell replication during metaphase and anaphase of mitosis. Despite using the same base drug, all DCB technologies differ on multiple aspects due to differences in the use of excipients, dose, manufacturing process and balloon surface technologies (Fig.1).

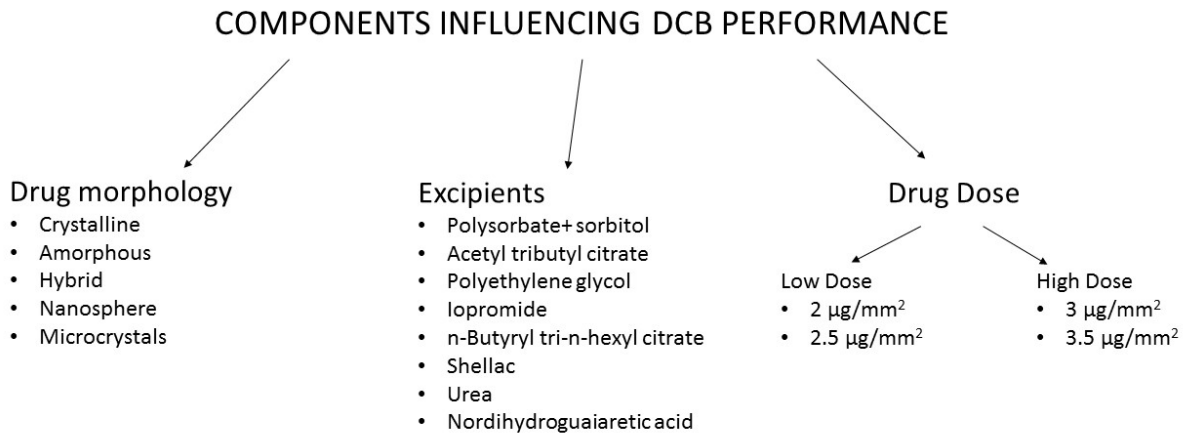


Fig. 1

Coating Morphology and Pharmacokinetics

Different coating Paclitaxel morphologies are found in each DCB technology due to differences in the excipients and manufacturing process. These Paclitaxel isoforms range from highly soluble forms (amorphous) to more insoluble forms (crystalline). Experimental studies have demonstrated the impact of coating Paclitaxel morphology in DCB pharmacokinetics. Crystalline Paclitaxel results in a more brittle coating but yields a more prolonged retention of the drug into the vessel wall at the cost of a higher downstream particle loss during balloon inflation (~ 20-25% of the total dose), as demonstrated from Kelsch et al. for a urea- or iopromide-based DCB in an in vivo

model, or ~42%, as showed from Berg et al. for a iopromide-based formulation during in vitro passage through a hemostatic valve and a guiding catheter. The amorphous Paclitaxel morphology on the other side, results in a more homogeneous and reproducible coating but yields shorter drug retention profiles following Paclitaxel delivery. Experimental models have shown that Paclitaxel morphology does not greatly affect acute post-delivery tissue uptake, but significant differences in tissue levels start to occur one hour following delivery that are maintained all the way through 90-days. At one week both formulations display a significant vessel washout (crystalline 88.6%, amorphous 99.9%) even if the drug remains detectable until 28 days in both groups (tissue half-life for paclitaxel delivered by the crystalline and the amorphous was 7.5 and 3.4 days, respectively). Furthermore, a comparative analysis of the vessel surface Paclitaxel concentration in respect of arterial wall concentration showed a much higher presence of the drug on the surface at 24 h, 7 and 28 days in the crystalline group. Conversely, in the amorphous group the vessel surface and the arterial wall concentrations were similar at 1 and 24 h. After 24 h, the vessel surface concentration declined further in comparison with the arterial wall levels. The most interesting finding about Paclitaxel delivery via DCB is that the large amount of drug eluted onto the vessel surface (≈20 orders of magnitude higher compared with the drug eluted from a paclitaxel eluting stent) does not result in obvious vascular toxicity at any time-point. Intra-luminal drug washout, occurring within 7-days following initial drug delivery, plays a major role in avoiding vascular toxicity and despite the apparent supra-therapeutic tissue levels found immediately after PCB use, drug levels are within the therapeutic tissue levels 30-days following initial drug delivery, maintaining a concentration within the therapeutic range for inhibition of smooth muscle proliferation but below cytotoxic limit.

Role of Excipients in Coating Features

Paclitaxel lipophilicity facilitates intra-mural drug retention and at the same time it presents a challenge for its acute delivery when an excipient is not used. Cremers et

al. demonstrated the value of adding an excipient as an adjuvant to Paclitaxel delivery. Due to its solubility profile, Paclitaxel is difficult to deliver into the vessel unless it is bound to substances increasing its solubility in water. Excipients play an essential role in this setting and directly impact Paclitaxel tissue pharmacokinetics. For this reason, multiple technological approaches are under development using several different excipients and manufacturing processes (Fig.1). At the present time, it is difficult to define which the "ideal formulation" is; some excipients are added with the purpose to modify the pharmacokinetic profile (i.e., Urea, PEG etc.), while others are added with additional therapeutic purposes (i.e., Resveratrol as antioxidant). Regardless, excipient search and manufacturing process refinement are not straightforward processes as they aim to balance coating adhesion on the balloon surface and tissue pharmacokinetic profiles. Kempin et al. tested the impact of excipient selection in pharmacokinetic behavior. In this study, 5 different Paclitaxel and excipient formulations (ethanol, ethanol +PVP, ethyl acetate, acetone) were compared to the SeQuent Please (B. Braun, Melsugen AG, Germay) DCB. This study showed how each coating formulation results in different drug morphology, percentage of drug loss and transfer using an in vitro model (Fig 2).

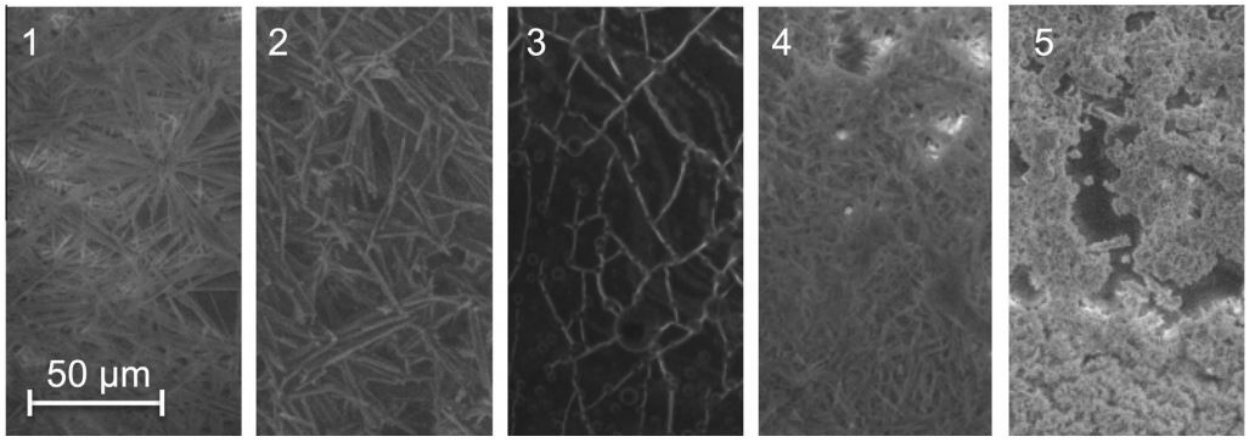


Fig. 2

Balloon Drug Dose

One important consideration about DCB performance is drug dose. Paclitaxel affects cell replication on a dose and time dependent manner. At the present time, there is no

direct head to head clinical comparison study that has tested the impact of total Paclitaxel dose in long term patency. There is some discrepancy in the literature describing the real value of a high-dose DCB in the prevention of restenosis and improvement of clinical outcomes or substantial equivalence between lower dose and standard-dose balloons in other experimental models. Randomized clinical trials have only compared DCB to PTA controls but have showed some differences in primary patency rates at 1 and 2 years. Although the real impact of total dosing in biological efficacy is still unclear, differences in paclitaxel concentration may be important in the setting of comparable solubility profiles. An experimental study showed that in a DCB using a crystalline coating the reduction of neointimal proliferation decreased by ~50% when the total DCB dose was reduced from 3 to 1-mcg per mm square.

Particulate and DCB Safety

The early enthusiasm gained by the introduction of DCB technologies was tampered theoretical concerns about safety. Drug loss is a real effect occurring following balloon delivery and it has been reported by several experimental bench and in vivo tests. The percentage of drug lost into the bloodstream varies according to each balloon studied and the quantity of particulate loss downstream depends on the type of Paclitaxel coating. Crystalline formulations are much prone to embolize distally than amorphous formulations. In experimental studies, particulate loss is a rare finding seen in histological sections in distal vascular beds and consist of fibrinoid changes seen in small arterioles with or without adjacent skeletal muscle necrosis. However, the real impact of micro-embolization in humans has not been well established. As a matter of fact, in large randomized controlled SFA studies, the incidence of amputation or limb loss in the DCB groups is comparable to the PTA controls. Although particulate embolization may not be a clinical issue in larger vascular territories, concern still exist in regards to the use of these devices in critical vascular territories involving small vessels of poor distal vascular run offs such as in BTK interventions. Vessel toxicity and healing is another safety concern in the DCB

field. One of the major problems of the first generation Paclitaxel eluting DES was the high drug concentration achieved in tissue resulting in local toxicity with the development of aneurysm and thrombosis. The drug concentration released at day 0 from DCBs is much more higher compared to polymer based-DES. However, following initial drug distribution and intra-luminal wash out, paclitaxel tissue levels decrease and remain comparable to metallic DES delivery systems. Randomized studies have shown lack of aneurysm formation or evidence of vascular toxicity by angiography in the SFA territory. In summary, DCBs continue to evolve towards the development of more precise dosing and mechanisms of delivery. A clinical proof of concept has been already achieved, especially in the peripheral vascular territory, however, important technical and clinical challenges still exist for the broader adoption of these technologies as first line of therapy.

Current technical challenges and the future of drug-coated balloons

Technological innovations are introduced to solve the limitations of an existing technology or approach. Bare-metal stents were designed to overcome the elastic recoil and restenosis limiting the effectiveness of plain balloon angioplasty; antiplatelet therapy was introduced to minimize the risk of stent thrombosis after stenting; and drug-eluting stents (DES) were developed to prevent neointimal hyperplasia, responsible for high restenosis rates following bare-metal stent implantation. Nowadays, in the coronary territory, balloon angioplasty is considered as an ancillary tool to coronary stenting and it is frequently used to prepare atherosclerotic lesions for stent deployment or to optimize the angiographic result. Also, plain balloon angioplasty has several limitations, mainly acute vessel closure which may occur in up to 5% of patients as a result of an occlusive dissection with or without thrombus, and restenosis which occurs between 30% and 60% in the first month. Drug Eluting Stents are, for these reasons, the interventional therapy of choice in the treatment of coronary atherosclerotic disease. These devices have

undergone multiple improvements over the years resulting in very low long-term restenosis and thrombosis rates.

Drug-coated balloons (DCB) have been developed as an alternative to address some of the limitations of existing technologies. One major appeal of these devices is the concept to deliver anti-proliferative drugs into the vessel wall "leaving-nothing-behind". Compared with DES and other existing therapeutic approaches, DCBs offer several potential advantages, including drug delivery without the use of a permanent polymer, a potential for delivery in a larger surface area covered by the balloon and a shortened duration of dual antiplatelet therapy. In addition, DCBs have the potential to treat vascular lesions that are not well served by the use of stents, such as high mechanically stressed sites (tortuous vessels), small vessels, diffuse lesions, and bifurcation lesions. Nevertheless, DCBs display the intrinsic mechanical limitations of balloon angioplasty, mainly their lack of scaffolding and mechanical support limiting their standalone application. As a consequence, if the result after the initial DCB use is sub-optimal (i.e. dissection, recoil, inefficacious dilatation), bailout stenting is always needed, thus defeating the purpose of its initial indication. Another potential limitation relates to the fact that vessel injury is required to achieve proper drug delivery. Balloon angioplasty produces a barotrauma with deep vessel injury. Plaque compression is not a significant mechanism of lumen dilation and the main mechanisms of lumen enlargement include plaque rupture with vessel dissection and overstretching of the entire vessel wall. Furthermore, vessel microdissection itself is thought to facilitate drug transfer and to achieve adequate drug bioavailability in the tissue, so that a careful balance between proper balloon sizing and degree of vessel injury must always be taken into consideration.

Currently DCB technology is limited to two main clinical applications: coronary and peripheral artery interventions.

Coronary indications for DCB use include in-stent restenosis (ISR) (class of recommendation Ia in ESC guidelines), small vessel branches and bifurcation lesions. Several studies have been performed testing the efficacy of DCB in the treatment of

small vessels (DCB vs. BMS or DCB vs BMS+DCB) as DES have always shown high rate of restenosis in this setting. The original concept of using DCB+BMS in coronary de novo lesions was to potentially create a "polymer-free" paclitaxel DES. However, the studies comparing this approach have shown inferior results of the combination approach (BMS+DCB) compared to DCB alone or to DES in de novo lesions. As a consequence of these findings, this hybrid strategy has been abandoned in favor of the so-called "DCB-only" strategy, which includes careful lesion preparation, and depending upon the angiographic result, the operator decides whether to proceed with DCB only or use a stent or scaffold in case of major dissection (type C or higher), significant residual stenosis, or reduced flow. Nevertheless, even the use of this approach has shown controversial results is multiple small randomized controlled trials when compared to DES.

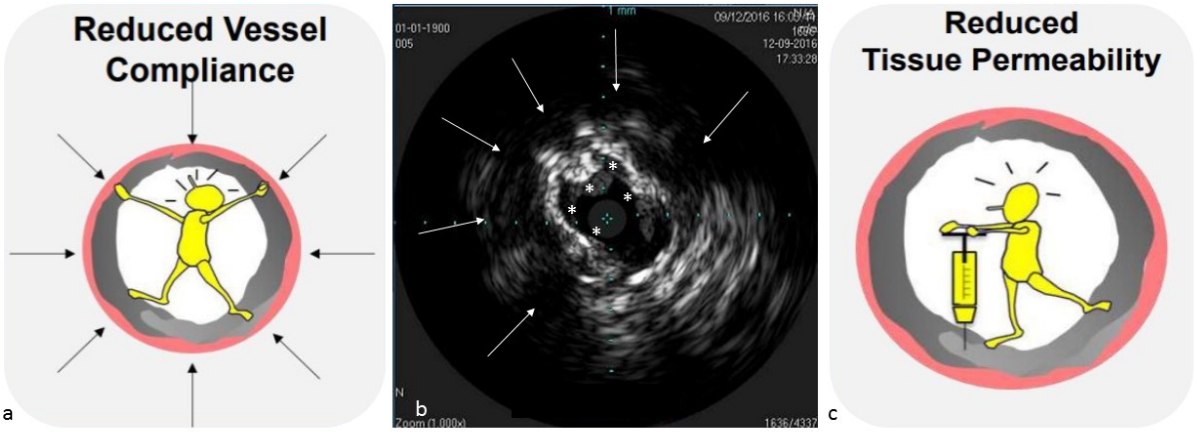
Likewise, the use of DCB in bifurcation lesions is also controversial. Two randomized trials showed the combination of DCB+BMS to be inferior compared to DES, while one randomized study demonstrated superiority of the DCB approach compared to POBA. Despite the promising results in ISR lesions, further trials are needed to determine the real benefit of this technology applied to coronary lesions.

On the other hand, peripheral artery disease is an area in which DCBs have shown to be very effective. Both Superficial Femoral (SFA) and Below the Knee arteries have unique features as the vessels are exposed to biomechanical forces coming from leg motion (torsion, compression, flexion, and extension) and are known to be more susceptible to atherosclerosis because of low shear stress or spiral flow. In this scenario a permanent BMS, constantly undergoing mechanical stress, results in sustained inflammation and worse outcome. Nevertheless, dedicated peripheral DES have improved the outcomes of plain balloon angioplasty and have shown increased patency compared to bare metal stents at 36 months. Despite these promising results, the use of long and more permanent implants limits future options in case re-intervention is needed. As a result, technologies that reduce the need for bailout stenting are highly desirable in patients with femoro-popliteal disease. In the setting

of PVD intervention, DCB are the most suitable alternative to “conventional” stenting showing high patency rates up to 3-years.

Vessel Calcification and Drug Uptake

Both tissue uptake and long-term drug retention into the vessel wall are needed for the prevention of restenosis following initial DCB use. The presence of vascular calcification, an innocuous finding in human atherosclerosis, presents a potential barrier to the delivery and retention of paclitaxel following DCB use. Dense layered intimal calcification may become an initial barrier for early tissue uptake as while medial calcinosis may prevent adequate drug penetration and distribution into the vessel wall. The effect of severe coronary calcification in DES outcomes has been widely described in the literatur. This is particularly relevant in peripheral arteries where vessel calcification becomes more severe in SFA and below-the-knee disease. Several clinical studies have shown that highly calcific vascular segments (in particular circumferential extent of calcification over its length) have a worse primary patency than non-calcific plaques. Severe calcification have demonstrated to be independent predictor of late lumen loss (LLL) and TLR, and is associated with a heightened risk of



procedural complications such as dissection and acute recoil . Calcium remains a challenge, especially in the setting of long and complex lesions making debulking and lesion preparation techniques highly desirable in the peripheral DCB field. A

wide variety of atherectomy and lesion preparation technologies are under development aiming to improve the outcomes and reduce the potential use of additional stents following DCB use.

The use of Orbital Atherectomy (OA) preceding DCB use has been recently investigated. The combined use of OA + DCB resulted in less bailout stenting compared to DCB alone. Likewise, several single-center studies have studied the clinical performance of Directional Atherectomy (DA) plus DCB in patients with lower limb arterial disease. These small clinical studies have shown lower use of cross-over stent and improved lumen gain compared to the DCB-only approach. In one study, the combination of DA + DCB (n = 60) was compared with DA with non-DCB angioplasty (n = 29). The primary patency was 84.7% in the DCB group compared with 43.8% in the non- DCB group. Another single center experience showed that the combination of DCB and DA provided a 90% freedom from clinically driven TLR in 30 patients with heavily calcified lesions. The only randomized, multicenter, study in this setting is the DEFINITIVE AR study. This study was designed to assess the effect of treating vessels with DA prior to a DCB randomizing 1:1 claudicant patients with 7- to 15-cm SFA and/or popliteal lesions to either DA + DCB or to DCB alone. Subjects with severely calcified lesions were assigned to a nonrandomized registry arm and were treated with DA + DCB. One hundred twenty-one subjects were enrolled, 48 in the DA + DCB arm, 54 in the DCB arm, and 19 in the severely calcified lesion DA + DCB registry group. Mean lesion length ranged from 9.7 to 11.9 cm. In the randomized groups, the primary end point, percent stenosis at 12 months, was similar in both cohorts. Angiographic patency (≤50% stenosis and without TLR) was 82.4% in the DA + DCB arm and 71.8% in the DCB arm. The major adverse event rate, defined as a composite of clinically driven TLR, death, and major amputation, was 11.6% for the randomized DA+DCB arm, 9.8% for the randomized DCB arm, and 5.9% for the severely calcified lesion registry arm. This pilot study suggests an added benefit for combination therapy (DA+DCB) in long and calcified lesions that was not observed in the DCB-alone

subgroup. Further investigation in larger, prospective, statistically powered randomized trials is warranted. Thus, this combination approach seems to be feasible and safe in patients with significant arterial obstructive disease. Clearly, the scientific data is still scarce, and the cost-benefit analysis of this approach requires further evaluation.

Future Perspectives

DCB have already proven to be clinically useful tools in certain coronary and peripheral applications. At the present time, several DCB technologies are commercially available including different coating approaches, dosages and formulations. Head to head comparison trials are critically needed to evaluate the real clinical differences between technologies in the real world. Clinical applications involving broader applications depend on the evolution of the clinical data and of these technologies toward safer and more predictable local drug delivery devices. In this sense, technologic improvements are under development including lower-dose, lower-particulate coating technologies and limus-based local drug delivery devices. In addition, dedicated lesion preparation technologies (i.e., scoring) aim to improve the outcomes of DCB technologies. An interesting approach combining drug coated technology with the scoring balloon has been already tested (i.e. scoring coated balloon SCB). Kufner et al. reported the results of the ISAR DESIRE 4 randomized trial in which investigators compared standard treatment with DCB versus the use of SCB followed by DCB in 252 patients with limus-DES ISR. The primary endpoint was the in-segment percent diameter stenosis at 6 to 8 months. SCB pre-dilatation significantly reduced percent diameter stenosis and binary restenosis rates at angiographic follow-up. Late lumen loss and rates of target lesion revascularization (TLR) at 1 year were numerically, but not significantly, lower in the SCB group. In the PATENT C (Paclitaxel-coated or Uncoated AngioSculpt Scoring Balloon Catheter) trial a scoring DCB “all-in-one” device was tested. A total of 61 patients with bare-metal stent ISR were randomized to paclitaxel-coated or uncoated SCB, the

former being associated with superior angiographic and clinical outcomes. In summary, the DCB field continues to evolve toward the development of more precise delivery methods and alternative drugs that permit the expansion to other vascular territories and clinical applications. Lesion preparation technologies promise to improve the outcomes of DCB and hopefully will increase the potential to use them as a "stand-alone-technology". Several local drug delivery approaches including pressure perfusion technologies continue to make progress and expand the interventional options for the future.

PART IV

Innovation

CHAPTER 16

Novel Approach for Left Atrial Appendage Occlusion: A Feasibility Study of Catheter-Delivered Expandable Foam.

LAA occlusion is a safe and effective procedure for the prevention of ischemic stroke in patient unsuitable to receive oral anticoagulation due to high bleeding risk. LAA as often irregular shape making the stiff and preformed available device invasive or causing residual leak. We tested an innovative "foam-constituted" LAA occlusion device in the swine to assess the safety and efficacy of this technology,

BACKGROUND

Left atrial appendage (LAA) exclusion has been employed to reduce thromboembolic risk from atrial fibrillation, especially in patients unable to receive oral anticoagulation due to high bleeding risk or other reasons. However, existing technologies need to be optimized for risk of leak, perforation and thrombosis on the atrial device surface.

METHODS

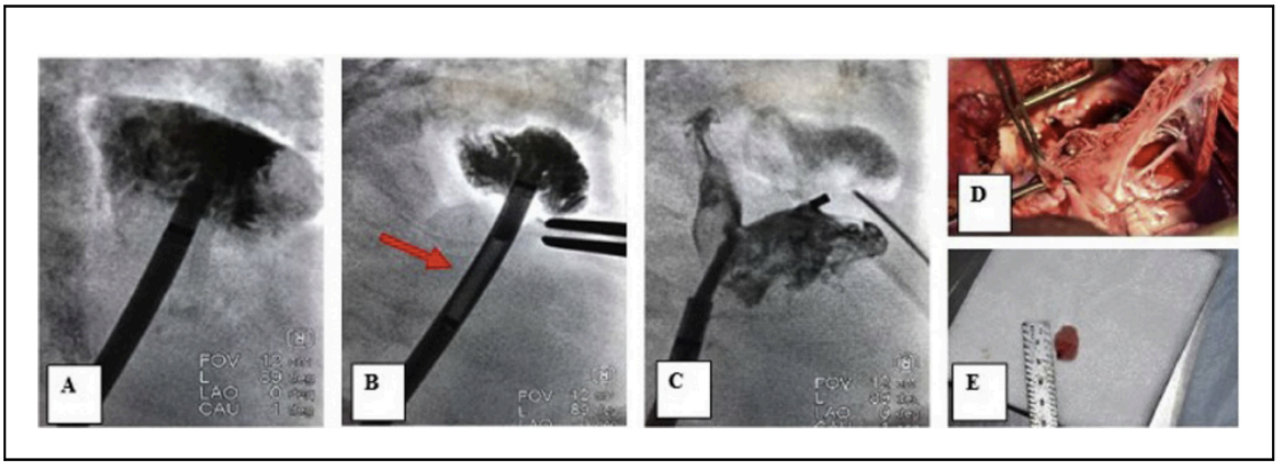
Right atrial appendage (RAA) was targeted in this first-in-animal swine feasibility study due to its closer anatomical resemblance to human LAA shape than the porcine LAA (Figure 1A). Using fluoroscopy, a crimped (Figure 1B – arrow) low density polyurethane foam (LDPF, Shape Memory Medical, Santa Clara, CA) was delivered into the RAA (Figure 1B) from an 8F guide catheter. Thoracotomy was also performed to monitor deployment directly and place a surgical snare to narrow down on overly wide atrial appendage neck to prevent early dislodgment. Sequential angiography was performed during the next hour and the surgical snare was eventually released.

RESULTS

The crimped LDPF expanded over time filling the atrial appendage (Figure 1C) and blood thrombosed on contact with the foam abrogating the blood flow, resulting in complete RAA closure (Figure 1C). Necropsy demonstrated sufficient retention of the expanded LDPF inside the RAA (Figure 1D in situ, retrieved expanded foam shown in Figure 1E).

CONCLUSION

This first preclinical attempt to perform atrial appendage closure with catheter-delivered LDPF demonstrated satisfactory angiographic and post-mortem results. Further development of a dedicated device using LDPF is warranted for proof-of-concept studies.



CHAPTER 17

Novel Approach for Treatment of Aortic Stent Graft Endoleak: A Preclinical Feasibility Study of Catheter-Delivered Expandable Foam.

Endoleak represent a partial failure of abdominal aortic aneurism (AAA) percutaneous treatment. The lack of dedicated devices make the riparative intervention often convoluted with sub-optimal outcome. We tested a "foam-constitued" fully conformable in a swine model of AAA.

BACKGROUND

Endoleak is defined as persistent flow of blood into the abdominal aortic aneurysm (AAA) sac after endograft placement and signifies a failure to completely exclude the aneurysm. It is present in 20-50% of patients treated with endograft implantation and is associated with continued risk for aneurysm expansion or rupture. Treatment of AAA graft endoleak remains a challenge. This abstract aims to describe a new endovascular approach to endoleak treatment.

METHODS

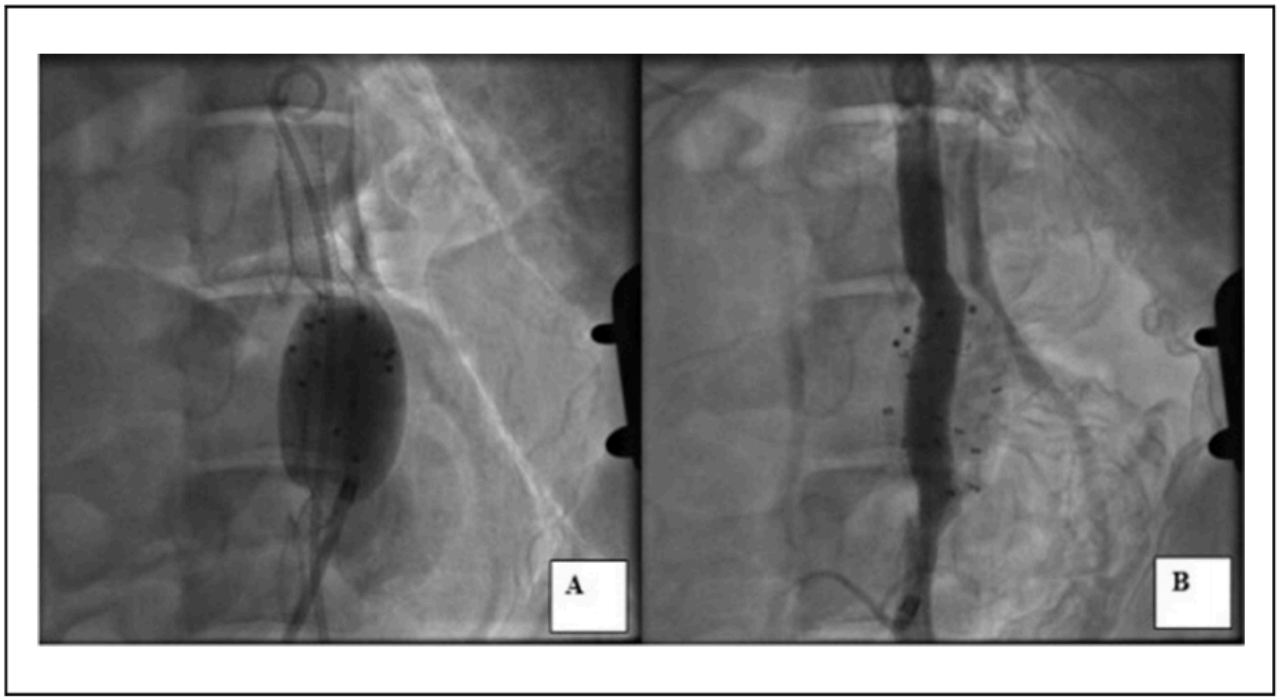
A preclinical AAA model was created by means of laparotomy, dissection of infra-renal aorta and an end-to-end implantation of a PTFE graft regionally dilated with a balloon to simulate an aneurysm sac. An endograft (Gore VIABAHN, 11x5 cm) was then implanted to exclude this simulated aneurysm through the right femoral artery. An 8F multipurpose catheter was left jailed between the endograft and the aneurysm sac wall, through which crimped low density polyurethane foam (LDPF) pieces featuring single pair of radiopaque markers (n =14, Shape Memory Medical, Santa Clara, CA) were deployed into the aneurysm sac (Figure 1A). Sequential angiography over ca. 1 hour documented the expansion of the LDPF and progressive containment of the endoleak via space filling and thrombosis.

RESULTS

Angiography showed complete resolution of endoleak approximately 1 hour after deployment of LDPF into the simulated aneurysm sac (Figure 1B).

CONCLUSION

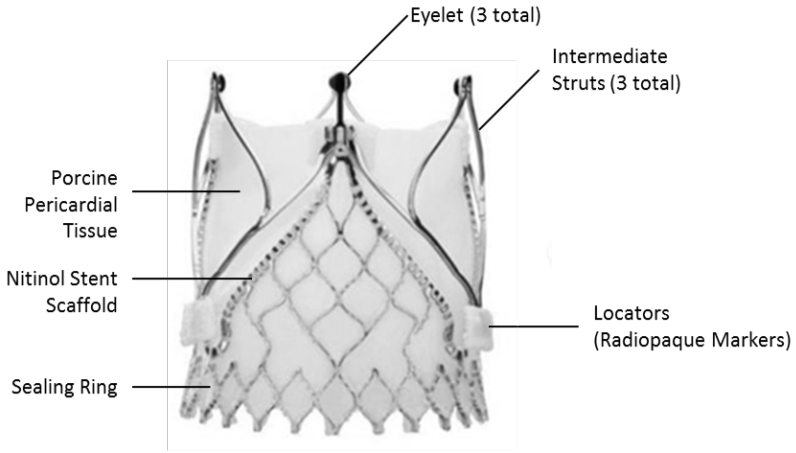
This first attempt to contain an AAA endoleak with shape memory foam delivered through a standard guide catheter showed feasibility and satisfactory angiographic results



CHAPTER 18

Initial experience with the JenaValve transfemoral TAVR system in patients with severe aortic stenosis and risk for coronary occlusion.

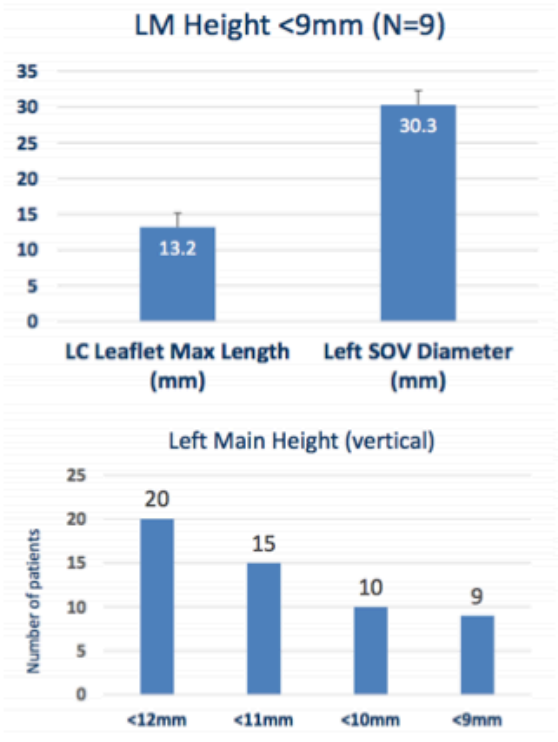
TAVI is a worldwide established procedure to treat patient with aortic stenosis. Only a few condition controindicate this intervention (e.g. unsuitable vascular access, advanced renal impairment). Coronary arteries high is an important parameter to evalute in order to prevent the catastrofic acute coronary artery occlusion due to the overturning of antive aortic leaflet occluding the coronaries ostia. Some parameter have establishe to predict this risk (LCA height < 12 mm and, sinus of Valsalva SOV width < 30 mm). Into this study we evaluated the performance of a TAVI system in preventing coronaries occlusion in patients at high risk for this complication.

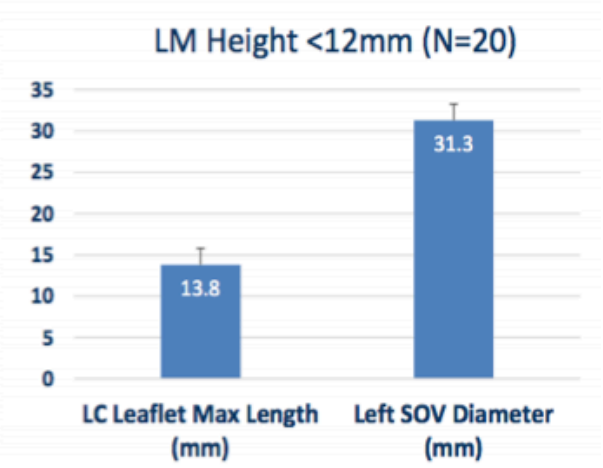


METHODS

This is a substudy from the broader JenaValve global clinical program; a prospective, multi-center, single-arm safety and performance tria. Enrollign up to130 patients at up to 28 centers globally. Key inclusion criteria are Severe aortic stenosis; STS Score of ≥8% or <8% if heart team agrees the patient is at high risk for SAVR. Primary endpoint is 30 days-all-cause-mortality. Secondary endpoint is safety according to VARC-2 definition, valve performance (valve function and haemodinamics, NYHA

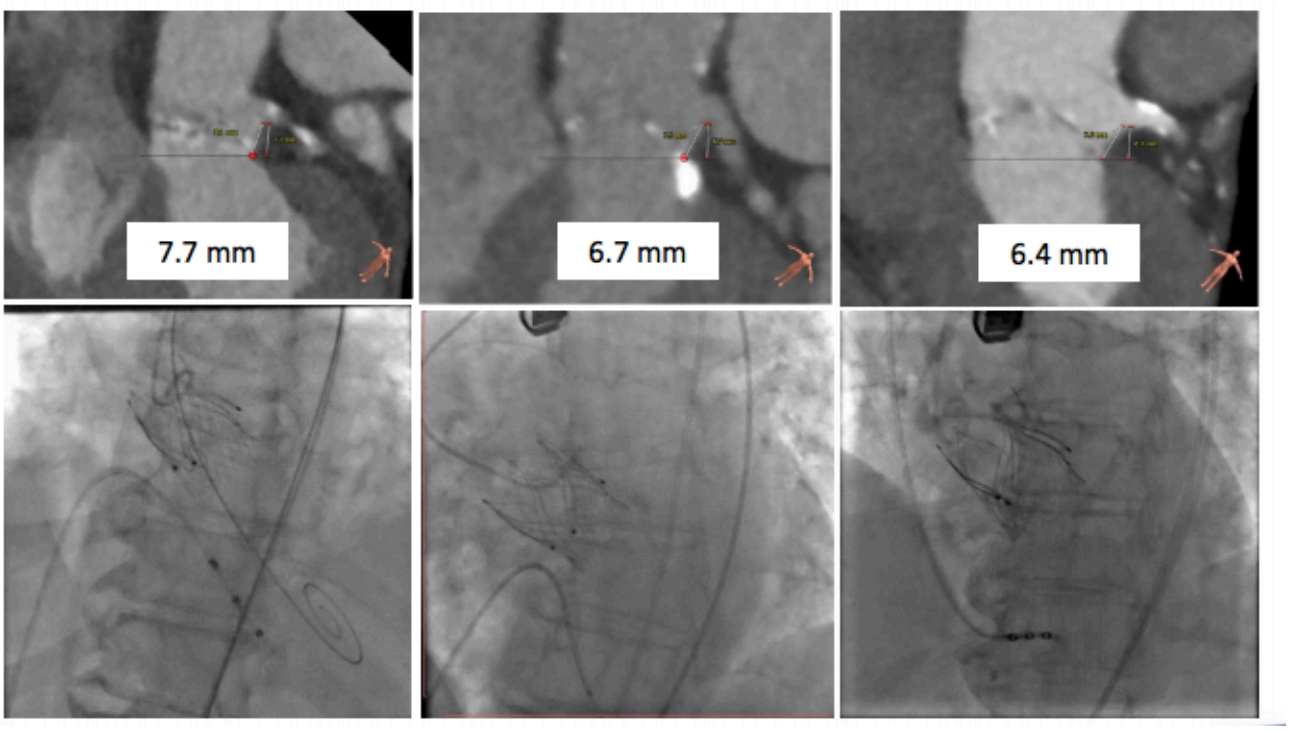
class, 6 MWT, KCCQ. Success endpoint is techinacal, procedural success according to VARC-2 definition. Among 68 patients enrolled, 20 had a LCA height <12 mm. Jenavalve differs from the other available TAVI system because of the precence of three locators pinching the native valve leaflets and allowing a better allignment to the native valve and less risk of embolization. Pinching the native leaflets, locators prevent coronary occlusion making this valve suitable for the the unsuitable valve anatomy. This valve is deployed under fluoroscopic and transesophageal echo (TEE) guidance (in order to place locators properly in the three native sinuses). Following the deployment fluoroscopic imaging and transoesophageal echocardiography were used to assess haemodynamic function and positioning of the valve in relation to the anatomic landmarks. Angiography was used to assess the patency of left and right coronary artery. An invasive transaortic pressure gradient was measured. In case of a high aortic peak gradient or a moderate to severe PVL, post-dilatation was performed.





RESULTS

The procedure was successfull in 100% of patient 20/20. There was no coronay o AS patients had LM < 12 mm and we had no cases of coronary obstruction. In this study patients with coronary heights as low as 6 mm have been treated.



CONCLUSION

JenaValve is currently the only transfemoral TAVR system with integrated coronary protection due to the valve design.

PART V

Discussion and conclusion

Discussion

Translational research and animal model

Translational research is the one of the most important steps during the development of new devices and new treatments. The importance of this stage is related to two main reasons. Startups reaching the animal testing have usually performed previous benchmark evaluations allowing to test mechanical properties and behaviour of a new device. These tests are relatively reliable based on matematical models and computer simulations. Animal testing is the very first "physiological" proof of concept involving a number of variable which can turn a simple and straightforward experiment into a disastrous failure. In addition most of the startups at the preclinical stage have limited funds and the advancement of the project often depends on the results of the animal experiments. Setbacks during this embryonic phase frequently translate into the aborption of the project. For this reason a thorough planning and an accurate selection of the animal model is crucial for the advancement of the research and development (R&D) and to obtain incouraging data to present to investors. Facilities running preclinical research as a service for external companies have a huge responsability in suggesting the most appropriate strategy and in running the experiments without critical flaws. This can make the difference between the progression or the interruption of valid devices/ideas/new concepts. The hard work behind the development of more and more reliable animal model is worth the effort as the most accurate the model is, the most informations this stage can provide in predicting limitation or essential imporvements the devices may need before reaching the human application. The most appropriate animal (e.g. swine, cows, rabbits, sheeps), the breed (e.g. Yorkshire, Yucatan), the anatomical setting (e.g. coronary, carotid, lower limbs), the need of specific animal strains (Rapacz FH swine) are crucial for the planning of an experiment and the experience of the preclinical facility highly impact the final outcome.

Bioresorbable scaffold

Bioresorbabel scaffold were heralded as the fourth revolution in interventional cardiology. The diffusion and the incouraging outcomes coming from the initial randomized trial boosted the field with billions of dollars invested by numerous companies in the effort of developing novel BRS. We carried out studied trying to determine the phisiopatological failure of BRS (relation between resorbtion profile and atherosclerosis, relation between fractures and LLL). Fracture was evaluated to be an important predictor of subsequent LLL, while atherosclerosis didn't seem to impact the resorption process validating the role of BVS for the treatment of coronary artery disease. One of the most important concepts regarding BVS is the "less forgiveness" of this technology. Several studies confirmed how lesion preparation impacted on outcome either in term of lesion failure or thrombosis/myocardial infarction[10-14]. The "boomerang effect" of the eccess of confidence based on the good initial results led many operators to consider the BVS a resorbable DES causing the increase in the adverse event. The consequence of the adverse events (worsened by the precence of the valid alternative DES) created a worldwide alarm with the final discontinuation of BVS sales.

Along with BVS we evaluated three different generation of a novel BRS in the preclinical and clinical setting. This BRS was developed addressing the BVS well-known flaws (low radial force, low resistance to fracture). The data we collected shows best of class clinical outcome and promising better mechanical properties compared to BVS. Amaranth BRS succedeed in reducing strut thickness below 100 micron with increasing the surface coverage area or reducing the radial force creating the awaited DES-like BRS. Nevertheless, a good idea need a good enviroment, and the BVS fall determined a chain reaction psychosis affecting the whole segment and leading to a global relocation of investement from BRS to other fields of innovation.

Drug coated balloon

Drug coated balloon are the first line percutaneous treatment for lower limb atherosclerosis. Despite the incouraging outcomes in terms of efficacy, concerns have been raised regarding the safety profile of these devices. With our study we tried to reproduce the worst PAD critical scenario of ALI investigating whether paclitaxel may impact the healing of wounds distal to the balloon inflation site. Our study showes no interference between paclitaxel and wound healing despite confirming a significant presence of embolized drug at the wounds site. Our study has intrinsic limitations coming from the absence of poor blood run-off typical of patients affected from ALI and, as a consequence, can't be directly applied to clinical practice. At the moment DCB have not showed any confirmed side effect neither impacting wound healing nor impacting the mortality at any timepoint.

Innovation

The best aspect of innovation is that the easiest it is the better it works. During my fellowship at SCI I had the opportunity of working with numerous start up testing ingegnous solutions for the treatment of several disease most of which can't be published due to disclosure obligation. Among those, we published two experiments from the company Shape Memory Medical, Santa Clara, CA conceiving a very elegant way to treat LAA occlusion and paravalvular/paraprostheis endoleak using a polyuretane foam capable of fitting all the anatomies due to the high conformability of the material with successful acute results.

Moreover we performed a sub-analysis from a broader registry (Jenavalve global program) evalutaing the performance of a self-expandable TAVI system for the treatment of high risk coronary occlusion patients. The sub-analysis demonstrated optimal perfomances of this valve due to the particular leaflet gripping technology wiht no coronary occlusion event even in patients with very low coronary ostia.

Conclusion

During my PhD program we investigated:

- The importance of animal model creating a new animal model of human tissue CTO and investigating the anatomical limitation of the swine heart during the preclinical testing of TMVR.

- We investigated several aspects of the BVS confirming vessel positive remodelling following BVS implantation on an experimental level; the contribution of scaffold fracture to LLL and potentially target lesion failure; the relation between atherosclerosis and scaffold structure resorption; the performances in the preclinical and clinical setting of a novel thin-strut BRS.

- We showed the absence of interference between paclitaxel and wound healing in an animal model of ALI.

- We tested numerous devices and innovative solution for the treatment of cardiovascular diseases reporting a few experiments from the cathlab and from the clinical FIH experience.

List of abbreviations

AAA: Abdominal Aortic Aneurism;

AL: Acute Recoil;

ALI: Acute Limb Ischemia;

BMS: Bare Metal Stent;

BRS: Bioresorbable Scaffold;

BVS: Bioresorbable Vascular Scaffold;

CTO: Chronic Total Occlusion;

DCB: Drug Coated Balloon;

DEB: Drug Eluting Balloon;

DES: Drug Eluting Stent;

DS: Dimater Stenosis;

EEL: External Elastic Lamina;

IEL: Internal Elastic Lamina;

FHS: Familial Hypercolesterolemic Swine;

FIH: First In Human;

FU: Follow up;

IS-LLL: In-Stent Late Lumen Loss;

LLL: Late Lumen Loss;

LR: Later Recoil;

MBD: Mean Balloon Diameter;

MLA: Minimal Lumen Area;

MSD: Mean Scaffold Diameter;

NIT: Neointimal Thickness;

OCT: Optical coherence tomography;

PAD: peripheral artery disease;

PLLA: Poly-L-Lactic Acid;

QCA: Quantitative Coronary Angiography;

R&D: Research and Development;

SCI: Skirball Center for Innovation;

SOV: Sinus Of Valsalva;

ScT: Scaffold Thrombosis;

TAVI: Transcatheter Aortic Valve Implantation;

TMVR: Transcatheter Mitral Valve Replacement;

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Curriculum Vitae

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• **EDUCATION:**

- 2006 - 2012 Student at School of Medicine, Federico II University, Naples, Italy.
- 2010 - 2013 Internship at Cardiology Basic Research Laboratories, Biomedical Advanced Sciences Departments, Federico II University, Naples, Italy.
- 2012. MD degree, Federico II University, Naples, Italy;
- 2013. Medical License, Federico II University, Naples, Italy.
- 2018. Board in Cardiology, Federico II University, Naples, Italy.

• **CURRENT APPOINTMENTS:**

- 2018- PhD student at: "International PhD programme in cardiovascular pathophysiology and therapeutic". Federico II University Campus, Naples, Italy.
- 2019- Attending physician at interventional cardiology and ICU, Montevergine Clinic, Mercogliano, Italy.

• **PREVIOUS APPOINTMENTS:**

- 2013 - 2018 Fellow in Cardiology, Biomedical Advanced Sciences Department, Federico II University, Naples, Italy.

- 2014 - 2017 Fellow at Catheterization Laboratory, Federico II University, Naples, Italy.
- 2017-2019 Research Fellow at Cardiovascular Research Foundation – Skirball Center for Innovation. New York, USA.

• MEMBERSHIPS OF SCIENTIFIC SOCIETIES

- 2013 – Member, Italian Society of Cardiology, (SIC).
- 2016 – Member, European Association of Percutaneous Cardiovascular Intervention (EAPCI)
- 2016 – Member, European Association of Cardiovascular Imaging (EAVCI)

• EDITORIAL BOARD

- 2015 – 2017 Member of Scientific Board of "Italian Journal of Invasive Cardiology".

• INSTITUTIONAL RESPONSABILITIES:

- 2014-2017 Study Coordinator for interventional cardiology international trials (CONTRAST, COMPARE-ABSORB, RENASCENT I, RENASCENT II, RENASCENT III).

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