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Tese de doutoramento

Effectiveness and security evaluation of bioresorbable vascular scaffolds for percutaneous coronary intervention in a non-selective clinical cohort of patients

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TESE DE DOUTORAMENTO

EFFECTIVENESS AND SECURITY EVALUATION OF BIORESORBABLE VASCULAR SCAFFOLDS FOR PERCUTANEOUS CORONARY INTERVENTION IN A NON-SELECTIVE CLINICAL COHORT OF PATIENTS.

Rosa Alba Abellás Sequeiros

ESCOLA DE DOUTORAMENTO INTERNACIONAL

PROGRAMA DE DOUTORAMENTO EN INVESTIGACIÓN CLÍNICA EN MEDICINA

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Dna Rosa Alba Abellás Sequeiros

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Effectiveness and security evaluation of bioresorbable vascular scaffolds for percutaneous coronary intervention in a non-selective clinical cohort of patients.

D. José Ramón González Juanatey
D. Raymundo Ocaranza Sánchez

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4. INTRODUCTION

Since the first successful percutaneous transluminal coronary angioplasty (PTCA) procedure carried out in 1977 by Andreas Grüntzig (1), interventional cardiology has undergone great advances. As a result, we are now able to offer patients minimally invasive revascularization in increasingly complex coronary arterial disease (CAD) scenarios, with high success and safety rates. Indeed, the current clinical practice guides recognize percutaneous coronary intervention (PCI) as the first choice revascularization technique in chronic ischemic heart conditions involving one- or two-vessel coronary disease. The technique is even clearly recommended in preference to surgical revascularization in the absence of involvement of the proximal segment of the anterior descending artery (2). In more complex scenarios such as triple-vessel coronary disease or left main coronary disease adequate assessment of the anatomical complexity is advised, based on the so-called Syntax score, which has been shown to be an independent long-term predictor of death or major cardiac or cerebrovascular events after PCI in these settings (3, 4). Accordingly, even in this increased risk scenario, if the predicted anatomical complexity is low (Syntax score < 22), percutaneous revascularization is regarded as first-line treatment on a par with surgical revascularization (except in triple-vessel disease in diabetic patients) (2).

Nevertheless, in order to reach the current level of excellence in percutaneous coronary treatment, it has been necessary to go a long way, with much technological development and research. Such development would not have been possible without in-depth knowledge of the physiopathology of coronary atherosclerosis. The coronary artery wall consists of three layers which, from luminal to abluminal, comprise the intimal, medial and adventitial layers (Fig. 1a, 1b). These in turn are respectively separated by two membranes: the internal and the external elastic laminas:

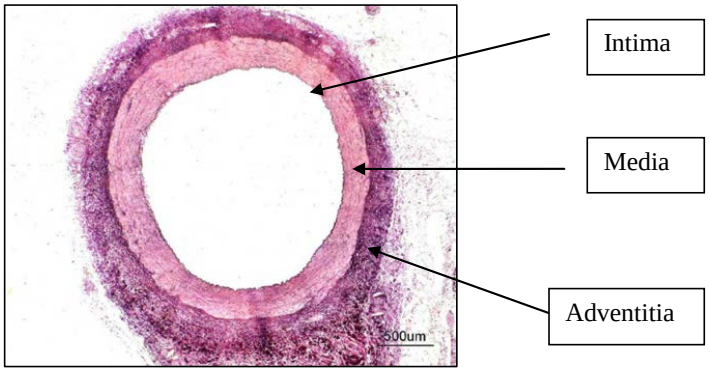
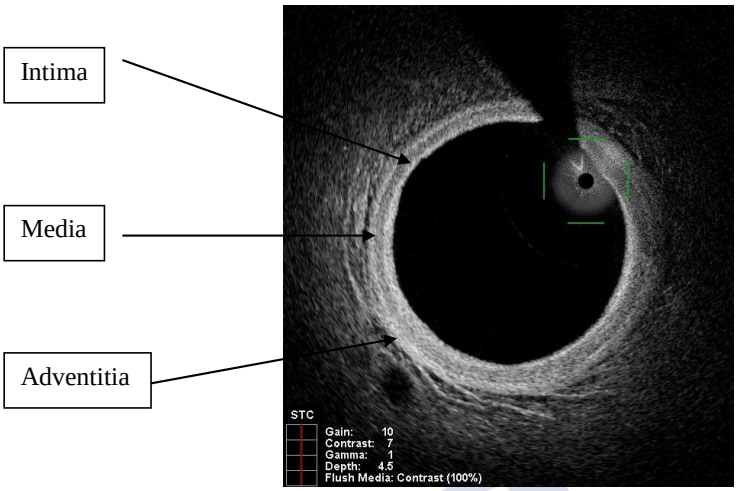


Fig 1a. Histological image of coronary vessel wall.



1b. Coronary vessel wall components: correlation in optical coherence tomography images.

While the adventitial layer (or tunica adventitia) is mainly composed of fibroblasts, the medial layer (or tunica media) mainly contains smooth muscle cells that afford arterial wall contractility. The composition of the intimal layer (or tunica intima) is more complex, with a monocellular lining on the intimal surface called endothelium, that constitutes an organ in itself, thanks to the synthetic capacity of the cells that conform it. One of the main functions of the endothelium is the regulation of vascular tone (and therefore of blood flow) through the release of both vasoconstricting substances such as endothelin-1 or thromboxane AII, and vasodilating substances such as nitric oxide (NO) or prostacyclins (5). The intimal layer also contains slightly thickened zones that have been referred to as “eccentric adaptive thickening zones”, and which are characterized by the presence of smooth muscle cells in the absence of lipids or foam cells. These zones are preferentially located in regions of increased flow or turbulent flow, such as the bifurcations or proximal segment of the anterior descending artery, and are regarded as zones associated to an increased risk of atherosclerosis. In fact, it is common for the first changes in the arterial wall to be detected in these adaptive thickening zones, with the presence of isolated foam cells (6). These changes are observed particularly in childhood, and it is believed that they still be able to undergo regression. However, they can also progress to give rise to what is typically called a “fatty streak”, representing a more advanced degree of intimal alteration characterized by a greater accumulation of foam cells (distributed in rows) together with smooth muscle cells exhibiting a slight lipid content. Thus, in this phase the main lipid deposits are located at intracellular level, and the changes are considered to still be potentially reversible (6). The above described changes are classically referred to as type I and type II lesions, respectively (Fig.2). Although the mechanisms favoring their progression are not well known, type III (or “pre-atheroma”) lesions are considered to be present when small lipid deposits are identified at extracellular level, with very slight displacement of the proteoglycan matrix and smooth muscle cells (6). As the lipid deposits increase, atherosclerosis enters a more advanced phase, with the formation of type IV

(or “atheroma”) lesions. These are characterized by the presence of a well-organized extracellular lipid core that displaces the usual intimal smooth muscle cells and extracellular matrix (7). It is also common to observe the development of capillaries close to the lipid core, with the presence of macrophages, foam cells and lymphocytes. However, in these type IV lesions the separation between the core and the endothelium is essentially at the expense of the layers of proteoglycan matrix of the tunica intima, which are displaced by the lipid material (with no significant increase in the number of smooth muscle cells or collagen). Once the atherosclerotic lesion has developed a thickened layer of fibrotic material (composed mainly of collagen), progression towards a type V lesion is considered to have occurred (7). This collagen is fundamentally produced by the existing smooth muscle cells, and it mostly consists of type I collagen. The type V lesions in turn are subdivided into type Va, Vb and Vc lesions, depending on their characteristics and the presence or absence of a lipid core (see fig. 2 below). Based on this classification proposed by Stary (6, 7), both the type IV and the type V lesions can undergo ulceration, hemorrhage and thrombosis - becoming what are referred to as type VI lesions or complicated plaques (7).

Stary classification of atherosclerotic plaques

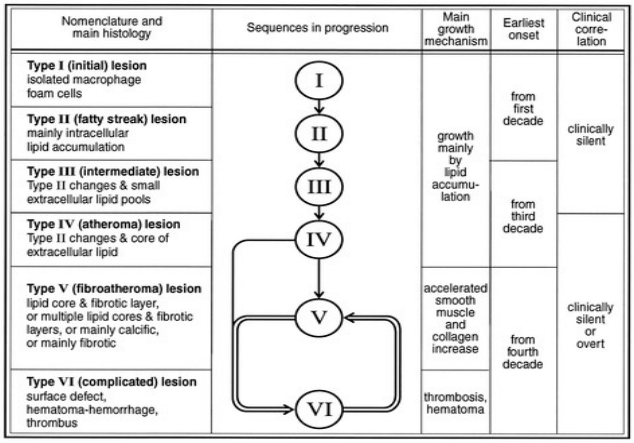


Fig. 2 Permitted by Wolters Kluwer Health.

Stary et al. Arterioscler Thromb Vasc Biol. Sep;15(9):1512-31.(7)

However, in the light of the results obtained from post-mortem studies on coronary disease in the context of sudden death, Virmani et al. in the year 2000 published a modification of the previously described classification of atherosclerotic lesions (8). This post-mortem study showed that arterial thrombosis is not always linked to plaque rupture or inflammation, and that the presence of apparently stable plaques (such as type Va, Vb and Vc lesions)(7) does not rule out the presence of past thrombotic events that have gone undetected due to their non-occlusive nature or because of spontaneous lysis or recanalization. Considering the changes and characteristics of the lipid core, fibrous layer and the different detected plaque

phenomena, Virmani et al. suggested the distinction of 7 categories of atherosclerotic plaques (Fig.3):

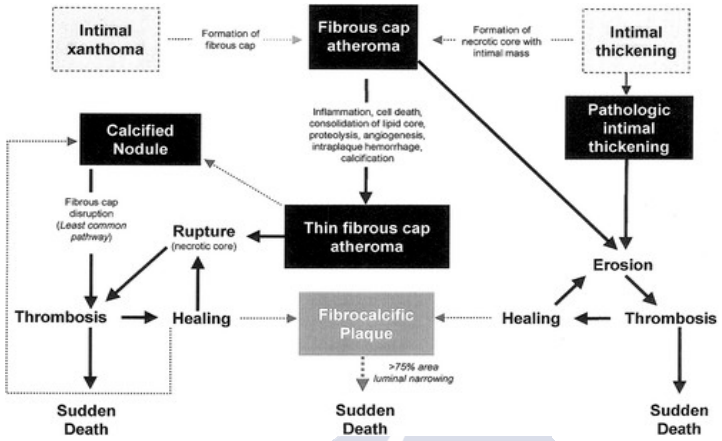


Fig. 3 Permitted by Wolters Kluwer Health.

Virmani et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;20:1262-1275(8)

Although different major risk factors have been identified in the process of atherosclerosis, such as arterial hypertension, diabetes mellitus or smoking, dyslipidemia is regarded as the main precursor element in the progression of the disease. In the presence of excessive circulating LDL-cholesterol, the particles of the latter cross the endothelial barrier in a concentration-mediated process called transcytosis. This process can be facilitated in situations of endothelial activation, mediated by the vascular changes secondary to arterial hypertension, flow alterations, etc. At intimal level, the LDL-cholesterol particles bind to the extracellular proteoglycan molecules through apolipoprotein B, exposing them to molecular oxidation processes. The first oxidized LDL-cholesterol molecules (minimally modified LDL particles or LDLmm) produce endothelial cell activation or damage, triggering a proinflammatory cascade involving the expression (by the activated endothelial cells) of molecular adhesion factors such as VCAM-1 or MCP-1 (9). As a consequence, a significant percentage of circulating monocytes bind to the endothelial cells, becoming internalized within the intimal layer and transforming into macrophages. This monocyte-to-macrophage conversion process is mediated by the LDLmm molecules and by mediators released by T lymphocytes (10). The macrophages capture part of the oxidized LDL-cholesterol molecules present at subintimal level, accumulating them in small “droplets” of cytoplasmic cholesterol. These droplets in turn increase and merge to give rise to the so-called “foam cells”. On establishing a correlation with the classical stratification proposed by Stary, at this point we would have the so-called type I and type II atherosclerotic lesions (6). As mentioned above, these two lesions are potentially reversible, since in these early phases, the foam cells are still able to externalize the excess cholesterol to the endothelial membrane, with capture by the circulating high-density lipoprotein (HDL) molecules. This results in “reverse cholesterol

transport" towards the liver, where it is cleared. However, in the presence of permanently elevated LDL-cholesterol levels, together with conditions such as diabetes mellitus (where hyperglycemia favors oxidative states) (11), an increasing intracellular accumulation of LDL-cholesterol would take place within the foam cells, no longer compensated by this reverse transport phenomenon. Finally, this leads to apoptosis of the mentioned cells and therefore to the extracellular accumulation of cholesterol, giving rise to type III lesions of the classification of Stary. If this process continues, the extracellular accumulation of cholesterol expands and becomes organized, giving rise to so-called atheroma lesions (type IV and V lesions) (7).

Likewise, it has been shown that the interaction of LDLmm with the endothelial cells favors expression by the latter of increased BMP2 and alkaline phosphatase levels - both of these factors playing a key role in vascular calcification (12). Specifically, BMP2 stimulates osteoblast migration and differentiation, and acts as an osteogenic differentiation factor for smooth muscle cells. These cells experience progressive calcification favored by the presence of high alkaline phosphatase levels, with a secondary decrease in the levels of pyrophosphate (the main inhibitor of vascular calcification) (12).

However, the presence of elevated circulating LDL-cholesterol levels in dyslipidemic individuals not only favors the development of atheroma plaques but has also been seen to cause vascular tone dysregulation, while the oxidized LDL-cholesterol molecules can produce a decrease in the expression of the eNOS enzyme. This implies a decrease in the synthesis of nitric oxide and hence a greater tendency towards vasoconstriction and the proliferation of smooth muscle cells (since it normally avoids binding to the respective growth factors) (10).

At this point, and knowing the physiopathology underlying the development of advanced atherosclerotic lesions, we are able to understand - in accordance with the descriptions of Virmani et al. (8) - that atherosclerotic plaques exhibit different phenotypes. We not only observe fibro-atheromatous plaques but also eminently fibrous or calcified plaques. Likewise, it is clear that atherosclerotic plaques can not only experience rupture but also erosion or complicated calcification (Fig.4). Manifest or frank rupture occurs in atheroma plaques with a very fine fibrous layer (thickness < 65 µm). When this layer ruptures, the lipid core becomes externalized and, on coming into contact with the bloodstream, it activates the coagulation cascade - giving rise to intraluminal thrombus or clot formation. In the case of erosion, the fibrous layer does not rupture; rather, these are atherosclerotic plaques mainly composed of an accumulation of smooth muscle cells with zones characterized by the absence of a covering endothelial layer, where the thrombotic process is triggered. Thrombotic phenomena in relation to calcium nodules are attributable to the "eruption" of calcium through the intimal layer, activating thrombosis on coming into contact with the bloodstream (Fig.4)(8).

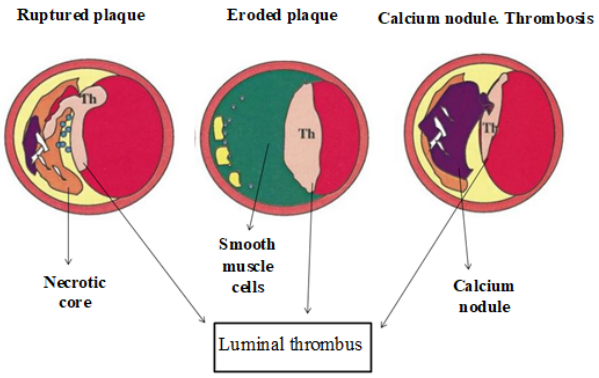


Fig. 4 Permitted by Wolters Kluwer Health.

Virmani et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;20:1262-1275(8)

Likewise, it must be taken into account that apparently stable plaques can cause the death of the patient (8), since lesions that are sufficiently severe (stenosis > 70-75% with respect to the basal coronary diameter) imply a significant decrease in coronary blood flow. This leads to myocardial ischemia that can manifest as exertional or resting angina, but also as the development of heart failure, ventricular dysfunction or proarrhythmogenic conditions of variable severity.

Percutaneous coronary intervention was developed in the late 1970s with the aim of avoiding these complications and of improving the quality of life of patients with ischemic heart disease. As mentioned previously, the first successful percutaneous transluminal coronary angioplasty (PTCA) procedure was carried out in 1977 by Grüntzig (1), in a 38-year-old male with significant single-vessel disease of the anterior descending artery. The scientific community was initially reluctant to expand the technique in view of the uncertain outcomes, high costs and the initial need to have a back-up surgical team available. However, the technique (which became known as POBA or “plain old balloon angioplasty”) gradually became incorporated to the hemodynamics units and underwent optimization thanks to greater knowledge of the procedure and improvements in the materials used. As an example, as the operators gained experience, routine simultaneous right-side catheterization was abandoned - this maneuver initially having been used to measure pulmonary pressure and for right ventricle overstimulation during balloon insufflation. Likewise, improvements in imaging techniques made it possible to obviate the measurement of distal pressure before and after angioplasty, in favor of visual guiding based on fluoroscopic images. The technological development of the materials used was both rapid and crucial for generalization of the technique. In particular, mention must be made of the decrease in caliber of the catheters used (from 9 French [F] initially to 4-6 F at present), the development of preformed catheters with side holes, new guides and balloons with improved crossing profiles, etc. Furthermore, the need for a back-up or standby surgical team was rejected after confirming that its presence did not result in significantly improved patient safety, since in general the delays and complications of surgery itself obscured its purported benefits.

Therefore, this technique, involving the percutaneous dilatation of stenotic coronary lesions through the insufflation of sterile balloons mounted on a positioning catheter (guided by fluoroscopy) quickly became a widespread practice. There were some clear limiting elements, however (13), namely a high risk of acute reocclusion (usually secondary to the presence of residual dissections after balloon-mediated dilatation) and high restenosis rates over follow-up.

Such restenosis over follow-up after POBA is mainly a consequence of two processes:

a) Late recoil phenomenon, due to the viscoelastic properties of the arterial wall (14), whereby following dilatation the external elastic membrane tends to gradually return to its initial diameter.

b) Late negative remodeling of the arterial wall. Following the vascular damage inherent to balloon-mediated dilatation of the arterial wall, a vascular healing response is activated, with local coagulation phenomena, cell proliferation and matrix synthesis at this level (15). Although this process is usually controlled and self-limiting, the mechanisms whereby it may prove more intense or persistent over time (giving rise to greater restenosis rates) are not fully clear. Some of the suggested factors promoting this anomalous response are the existence of flow alterations, greater previous plaque burden, or more aggressive dilatation procedures, for example.

The first revolution within coronary interventionism was the introduction of the so-called conventional or bare-metal stents (BMS). The first coronary stent was implanted in 1986 by Puel and Sigwart, though the use of these devices did not become generalized until introduction of the so-called Palmaz-Schatz stent - the first stent to receive approval from the United States Food and Drug Administration (FDA). The main difference between the two devices was the self-expanding nature of the former versus balloon-controlled expansion of the Palmaz-Schatz stent. Bare-metal stents consist of a metal mesh that is released within the stenotic coronary lesion to open the artery and act as a scaffolding system maintaining adequate architecture of the vascular wall. Classical studies such as the BENESTENT I (16) or STRESS trial (17) showed BMS to overcome the main limitations found up until that time with POBA. In the acute phase, BMS prevented abrupt arterial occlusion secondary to simple post-dilatation dissections, thanks to their scaffolding effect. In turn, over the short-middle term, these stents reduced the high restenosis rates seen after POBA attributable to both late recoil (thanks to the vascular wall scaffolding action of the metal structure of the BMS) and to negative remodeling (since maintenance of an adequate vascular wall architecture, with laminar coronary flow, facilitated adequate vascular healing after initial wall damage inherent to the intervention). As a result, the need for repeat interventions targeted to the treated vessel was significantly reduced.

Nevertheless, the permanent presence of a foreign body on the coronary arterial wall triggered a local intimal hyperplastic reaction which, in a large percentage of cases, produced significant reductions in intrastent luminal area. This was evidenced by a study published in 1996 by Hoffman et al., involving intracoronary intravascular ultrasound (IVUS) follow-up (for an average of 5.4 months post-implantation) of 115 lesions treated with one or two Palmaz-Schatz stents (18). The mentioned study confirmed that the intrastent luminal loss detected after the placement of these devices was attributable to neointimal proliferation clearly visible in the intracoronary imaging studies. Although there were no differences in stent volume over follow-up, a significant decrease in luminal volume was observed, and this

was moreover numerically correlated to an increase in neointimal tissue volume (18). These findings are consistent with those of other studies published during the same period, such as that of Dussaillant, which moreover found the use of smaller diameter stents to constitute a risk factor for restenosis (19).

Histopathological studies have identified this neointimal proliferation as the result of pathological vascular remodeling secondary to the chronic mechanical damage caused by the sustained presence of the stent over the vascular wall. This permanent damage induces a feedback chronic inflammatory response of the vascular wall. The hyperplastic tissue at intimal level mainly consists of an accumulation of smooth muscle cells and fibroblasts within a collagen matrix. The formation of this pathological new tissue starts with the initial damage to the endothelium during the revascularization process. The damaged or "activated" endothelial cells undergo changes that result in:

a) Dysregulation of eNOS activity (20), which leads to a decrease in NO levels, associated to an increase in inflammatory activity with increased concentrations of interleukins such as IL-5 and IL-6, stimulating factors such as GM-CSF or attractants such as MCP-1.

b) Activation of circulating platelets upon coming into contact with the damaged endothelial cells, resulting in the formation of a platelet-rich thrombus over which leukocytes activated by the dysfunctional endothelium are seen to deposit.

c) Activation of the so-called matrix metalloproteinases (MMPs). These zinc-dependent enzymes regulate the fragmentation of extracellular matrix proteins such as collagen or elastin (21). Increased activation of these enzymes therefore implies greater collagen and elastin fragmentation, which in turn constitutes a stimulus for a) the migration of smooth muscle cells from the medial to the intimal layer of the vascular wall, and b) for their proliferation and differentiation into secretory (instead of contractile) cells (21,22). This differentiation contributes to perpetuate the inflammatory cascade, since the cells begin to secrete mainly growth factors, extracellular matrix, etc.

The so-called drug-eluting stents (DES), which release different drugs at local level, were developed in an attempt to avoid the mentioned intimal hyperplastic phenomena. These devices consist of a metal skeleton with a polymeric matrix containing an immunosuppressor and antiproliferation drug substance that undergoes controlled release over the arterial wall. These immunosuppressors avoid the abovementioned smooth muscle cell proliferation (23), thereby impeding excessive intimal proliferation (24).

This strategy results in a significant decrease in the incidence of stent restenosis, though at the expense of an increased thrombotic risk due to the presence of a foreign body in permanent contact with the arterial endothelium - thus making it necessary to subject the patient to prolonged antithrombotic treatment.

The introduction over 10 years ago of the first bioresorbable scaffolds (BRS) led to a change in concept in interventional cardiology, and we now speak of endovascular therapy instead of coronary revascularization. These devices offer the benefits of BMS and DES, with the advantage of absorption of the scaffolding. This in theory would allow recovery of vascular motility and compliance, with an increase in luminal area and the theoretical suppression of thrombotic risk following complete degradation of the scaffold (25).

The technological development of these devices was not simple. At first, any metal material forming part of their structure was discarded because of its permanent nature. Instead, different synthetic polymers were tested, such as polycaprolactone, polyhydroxybutyrate, polyorthoester, etc. However, these materials were discarded once the preclinical (non clinical) studies evidenced a strong inflammatory response with high neointimal proliferation rates after their implantation (26). Nevertheless, one material, poly-L lactic acid (PLLA), exhibited greater blood compatibility with favorable mechanical properties (27), and was thus used for the design of these devices.

Thus, in 2004, Vogt et al. presented the first results following the implantation of resorbable scaffolds in a porcine coronary model. In this study the authors compared the histomorphometric and histopathological responses following the placement of two types of resorbable scaffolds: a) PLLA stent coated with paclitaxel; and b) uncoated PDLLA stent, versus the placement of BMS. The group receiving the polymeric scaffold coated with paclitaxel showed a significant decrease in neointimal area, with lower coronary restenosis rates after three months versus the other groups (coronary stenosis 49% versus 71% in the uncoated PDLLA group and 68% in the BMS group), with disappearance of the arterial scaffold structure (28).

These promising results led to development of the first bioresorbable devices for implantation in humans - the first case series being published by Tamai et al. in the year 2000 (29). The mentioned study evaluated the efficacy and safety of the so-called Igaki-Tamai stent: a bioresorbable stent comprising a polymeric PLLA scaffold with a zig-zag helicoid structure with no drug coating. A total of 25 devices were successfully implanted in 19 coronary lesions, followed by angiographic and intracoronary imaging controls (IVUS) immediately after stent placement and after 24 hours and three and 6 months. Mechanical behavior was assessed in terms of minimum luminal diameter and stent and luminal cross-sectional area, together with the degree of coverage over follow-up. After 6 months, adequate vessel expansion was seen to persist, with a degree of intimal hyperplasia no greater than that previously reported for BMS, together with a good clinical course - with no cases of stent thrombosis, death or acute myocardial infarction (29). This study for the first time evidenced the viability and safety of the use of bioresorbable polymeric scaffolding in coronary interventionism in human patients. Nevertheless, these results received a setback in 2001 with the publication of the data after 12 months of follow-up of over 60 lesions treated with the Igaki-Tamai stent, in which a high restenosis rate of about 19% was reported (30).

In the light of these studies, it was concluded that bioresorbable polymeric stents could be an effective alternative in coronary revascularization, but that further technological development was needed in order to afford not only optimum transient protection against acute recoil and negative remodeling but also against restenosis derived from intimal hyperplasia secondary to placement of the device. Therefore, optimization of the concept of vascular therapy entailed the conversion of these resorbable scaffolds into local drug-eluting devices (as was previously achieved with the metal DES). In this regard, the American company Abbot® developed the first resorbable drug-eluting polymeric scaffold for human use: the so-called Absorb 1.0. This device consisted of a resorbable PLLA scaffold covered with a finer layer of PDLLA from which an antiproliferative drug (everolimus) was eluted in a controlled manner. Both polymers (PLLA and PDLLA) are fully bioresorbable thanks to hydrolysis in which each of the long chains of polymer are broken up into small particles measuring < 2 µm in size, and which are ultimately degraded into carbon dioxide and water

following phagocytosis by the circulating macrophages. The duration of this resorption process was initially estimated to take two years, based on studies in a porcine model. The everolimus eluting period was much shorter, since the greatest percentage of the drug was released in the first three hours after placement of the stent (reaching a mean peak concentration in the luminal arterial wall of 15 ng/mg), though this process was continuously maintained during the first month, with 80% of total drug release being recorded 28 days after placement (31).

The first results following implantation of this device were published in 2008, corresponding to what was known as the Absorb A cohort (31). This study involved 30 patients with a single native vessel lesion (presenting a diameter of about 3 mm) and treated with a 12 or 18 mm Absorb 1.0 stent, depending on the length of the lesion. During stent placement, plaque predilatation was considered essential, postdilatation was regarded as optional, and the overlapping of bioresorbable devices was considered to be contraindicated. Clinical and angiographic follow-up (including imaging explorations) was carried out after 6 months and two years. Clinically, only one adverse event was recorded over follow-up at 24 months in the form of non-Q wave acute myocardial infarction. From the angiographic perspective, the rates were clearly higher than those of the metal DES in terms of in-stent late loss of up to 0.44 mm at 6 months (31) and 0.48 mm at 24 months (32). Although the neointimal area did not differ significantly from that quantified in studies with metal everolimus devices, a significant decrease in stent area was observed as assessed by IVUS - this implying a significant global reduction of the intrastent luminal area. It therefore was concluded that the antiproliferative drug elution process from the PDLLA coating was as effective as from permanent coatings, though conformational and design modifications of the device would be needed in order to avoid stent recoil (31). The introduction of these modifications resulted in the second generation of polymeric bioresorbable scaffolds in the form of Absorb 1.1. This new device maintained a PLLA scaffold with PDLLA coating, but with two fundamental differences: a zig-zag design with connecting bridges between the PLLA filaments affording greater radial strength without losing conformability (33), and small chemical variations in the nature of the polymer, resulting in slower hydrolysis (25).

The efficacy and safety of Absorb 1.1 were evaluated in what is commonly known as the Absorb Cohort B trial. A total of 101 patients were included and subjected to clinical and multimodal (invasive and noninvasive) imaging follow-up. The reported major adverse cardiovascular events (MACE) rate was 9% (34) (understood as the combination of death due to cardiac causes, any myocardial infarction and target lesion ischemia guided revascularization). There were two main findings from the angiographic perspective:

a) A marked decrease was observed in late lumen loss (LLL) (34) with respect to the data reported for Absorb A, after both 6 and 24 months (0.19 versus 0.44 mm and 0.27 versus 0.48 mm, respectively) (31,32).

b) Intracoronary optical coherence tomography (OCT) confirmed greater persistence over time of the polymeric scaffolding, with slower and more controlled resorption. Accordingly, 24 months after implantation, the number of clearly discernible struts in the Absorb A cohort was 34% lower than at the time of placement (32), versus practically all the struts found to be unaltered in the OCT study after 24 months in the Absorb B cohort (34).

These favorable findings were consolidated after the publication in 2015 of the randomized Absorb III trial (35), in which comparison was made of the results after implantation of two

everolimus-eluting platforms: bioresorbable polymeric stent (Absorb 1.1) versus permanent metal stent (Xience). Absorb was shown not to be inferior in terms of target lesion failure (TLF), and there were no significant differences in terms of target lesion revascularization (TLR) or stent thrombosis (ST) after 12 months (1.5% versus 0.7%; p = 0.13) (35).

On the basis of these findings, it was concluded that the polymeric bioresorbable devices are an effective and safe alternative in the treatment of uncomplicated native vessel lesions - affording sufficient arterial support to maintain arterial permeability, with adequate control of intimal proliferation. In this respect, Absorb 1.1 was the first BRS to obtain CE® and FDA® certification.

Simultaneously, in view of the suboptimal results with low radial strength of the first polymeric BRS, the possibility was raised of developing metal-based resorbable devices capable of affording the same mechanical properties as the traditional chromium-cobalt DES, though in a temporary manner. After obtaining favorable results in the preclinical phase (36), Biotronik® for the first time developed and implanted a metal BRS in humans: AMS-1. This device consisted of a bioresorbable magnesium skeleton without drug coating and exhibiting rapid resorption (in less than 4 months). However, the initial results fell short of the expectations, with high target lesion revascularization rates over follow-up: 24% at four months and 45% at one year after implantation (37). These findings were attributed to a high late lumen loss rate, derived from a lack of intimal proliferation control (as this stent lacked a drug coating) and from the existence of an excessively rapid resorption process (4 months) leading to premature radial strength loss and secondary negative remodeling (37).

In order to correct the weak points of this design, important structural changes were made, resulting in the so-called DREAMS-1 device. This was also a metal device (with a magnesium structure), but with two key modifications: a) a more controlled and prolonged resorption process (about 9 months); and b) the inclusion of a paclitaxel antiproliferative drug coating. These modifications resulted in clear improvement of the outcomes of coronary revascularization in humans, with a very significant decrease in the TLF rate (fundamentally at the expense of TLR), from 45% with the AMS-1 (37) to only 7% TLR after 12 months with the DREAMS-1 (38). However, over 12 months of follow-up, a significant decrease in minimum luminal area was observed, with late luminal loss rates higher than those reported for the coetaneous polymeric BRS: 0.39 mm at 12 months for DREAM-1 (38) versus 0.27 mm at 24 months for Absorb 1.1 (34). New design changes were introduced to overcome these limitations, giving rise to the DREAMS 2G. This bioresorbable metal device (now known as Magmaris®) is fundamentally distinguished from the first-generation DREAMS design in that it possesses a sirolimus antiproliferative component within a PLLA matrix, with a slightly greater strut thickness (about 150 µm). This structural change affords optimum transient radial strength while maintaining a resorption time shorter than that of the polymeric BRS, due to its magnesium component (39). It has been estimated that 95% of the implanted magnesium is degraded within 12 months after stent placement (Fig.5), in the context of a two-phase process: a first step characterized by magnesium conversion to oxidized magnesium, followed by conversion of the oxidized magnesium to magnesium phosphate and final degradation to amorphous calcium phosphate (39).

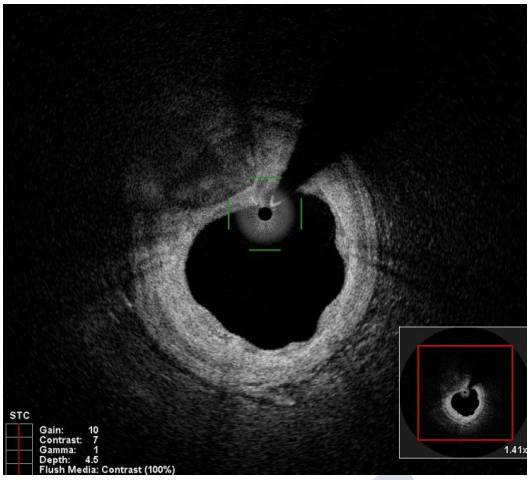


Fig. 5 OCT evaluation of magnesium BRS 12 months after its coronary implantation.

Struts are no longer visible

Thanks to these changes, exceptional outcomes were achieved over 24 months of follow-up, with a TLF rate of 5.9% and an ischemia guided TLR rate of only 3.4% (40) - these rates being lower than those of the coetaneous polymeric Absorb 1.1 device, which presented a TLR rate at 24 months of 6% (41).

Based on the favorable results obtained with both devices, Absorb 1.1 and Magmaris, in the respective pivotal studies (as described above), these designs were considered to constitute a safe and effective alternative in coronary revascularization in humans. In this way (after receiving CE® mark), these stents became common material in many cathlabs. Nevertheless, we consider that there was no solid scientific evidence of their behavior in different clinical scenarios outside the controlled setting of a clinical trial (e.g., coronary revascularization in the context of acute coronary syndrome [ACS], treatment of chronic occlusions, lesions over 20 mm in length, etc.). The studies included in the present Doctoral Thesis were therefore designed to analyze the behavior of these devices in the real life setting from the clinical, angiographic and advanced imaging perspectives.

5. OBJECTIVES

An evaluation was made of the efficacy and safety of bioresorbable devices in coronary angioplasty involving a non-selected cohort of patients in the real life setting, in different clinical scenarios.

Objectives have been divided in two groups:

-From the clinical perspective: the development of angina, myocardial infarction, death, stent thrombosis.

-From a morphological perspective: intracoronary imaging parameters, including neointimal coating, malapposition and strut rupture.

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6. METHODS AND RESULTS

Although the first studies with BRS yielded favorable results in application to coronary interventionism, the generalization of their use and the experience gained with longer follow-up periods have raised concerns about their suitability and possible associated risks. With the publication in 2016 of the three-year follow-up findings referred to Absorb II (42), a higher LLL rate was detected (0.37 mm versus 0.25 mm), together with higher infarction rates secondary to target vessel revascularization (TVR) and definitive or probable stent thrombosis, in the group of patients treated with Absorb versus metal DES. Similar results in terms of an increased stent thrombosis rate associated to Absorb have been obtained in studies involving large patient samples, such as Absorb III (43), or in meta-analyses such as that published by Mahmoud et al. (44), alerting to a globally increased risk of definitive or probable stent thrombosis (relative risk [RR] 3.22) and very late thrombosis with these devices (RR 4.78). However, it should be noted that the pivotal studies of both (Absorb B and BIOSOLVE II) reported no cases of stent thrombosis (34, 40). Because of this, different theories were proposed regarding the possible causes of thrombosis with these devices - the initial studies suggesting defects in the implantation technique. Thus, stent malapposition or under-expansion, together with a lack of atheroma plaque coverage or distal dissections, were identified as causes of subacute thrombosis (45).

With the aim fundamentally of avoiding the first two problems, the advisability of always performing final postdilatation after BRS placement was suggested in order to optimize the results obtained. However, this recommendation came into conflict with the alert raised by the hemodynamics laboratories following publication of the first case of strut rupture after Absorb implantation (46) and of a new case of device rupture after high pressure (20 and 16 atm) postdilatation described by Ormiston et al. (47). The OCT follow-up data on 51 patients of the Absorb B cohort evidenced isolated acute disruption phenomena following placement of the stent, though the incidence was very low (48). Indeed, only two cases were identified, and in both of them high-pressure postdilatation was described during implantation, expanding the device to diameters above the established rupture threshold (> 0.5 mm with respect to nominal) (48). The problem was therefore attributed more to over-expansion of the device than to postdilatation. Nevertheless, the initial concern generated in the scientific community hindered the possibility of postdilatation of these devices, due to an eventual risk of rupture, with uncertain consequences.

At that point it became necessary to clarify the relationship between postdilatation and strut rupture for polymeric BRS. With this purpose, the first study of this research project (49) was designed in the form of a prospective observational trial including all the patients treated with Absorb 1.1 in our laboratory between June and December 2015. On a per protocol basis, predilatation of the lesion and postdilatation of the device was performed in all cases with non-compliant (NC) balloons in 1:1 ratio with the artery and with a minimum pressure of 10-12 atmospheres (atm). In all cases the end result was assessed by intracoronary imaging using

OCT. The primary objective of the study was to quantify the percentage of ruptured struts following postdilatation, while the secondary objective was to evaluate the percentage of malapposed struts. A total of 14 patients were included (with 14 treated lesions). The subjects underwent percutaneous coronary intervention (PCI) in both a stable context (50%) and during acute coronary syndrome (ACS) (21% non-ST-segment elevation [ACS-NSTE] and 29% ST-segment elevation myocardial infarction [STEMI]), with great lesion complexity (mostly type C lesions of the American Heart Association [AHA] classification). Pre- and postdilatation was performed in all cases, with a mean postdilatation pressure of 17 atm and a maximum pressure of 20 atm, with no incidents during the procedure (49). The current consensus was used for analyzing the OCT images (48), defining strut disruption as the presence of two struts in the same angular sector of the lumen, whether one over the other separated by a space ("overhung struts") or in contact ("stacked struts") (Fig.6).

Fig. 6 The letter A shows an example of "stacked struts" disruption

Disruption was also considered to be present when "free" struts were identified within the lumen, with no connection to the circumference generated by the device - a situation known as "isolated struts" (Fig. 7a,7b).

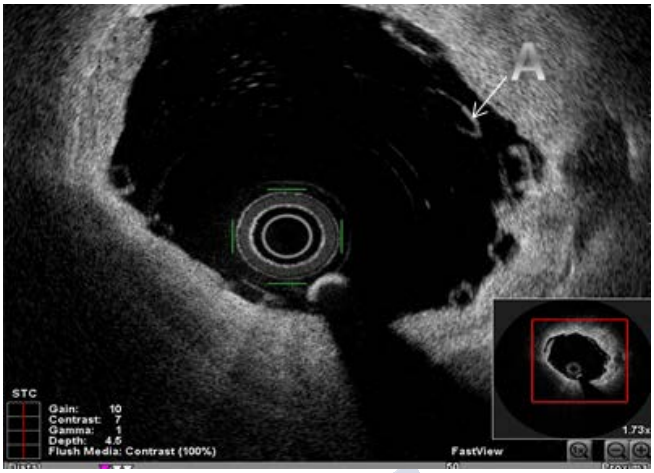

Fig. 7a Example of "isolated struts" disruption in a polymeric BRS

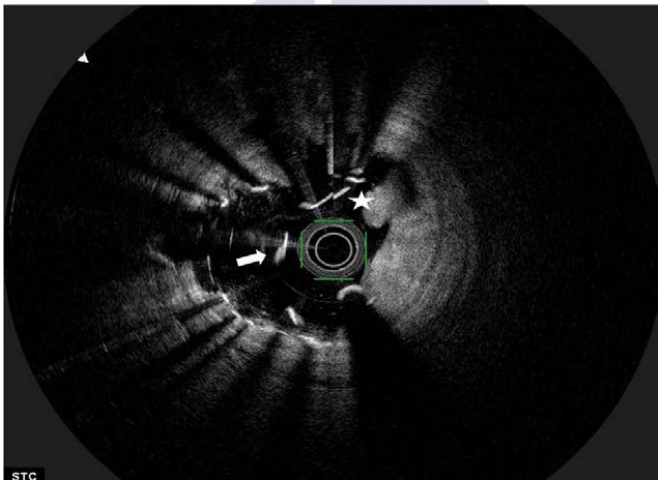

Fig. 7b Example of a disrupted magnesium-BRS with "isolated struts" (arrow) and " overhung struts" (star)

Out of a total of 39,590 struts analyzed, disruption was identified in only 0.22% (89 struts) (49).

An analysis was subsequently made of the presence of incomplete strut appositioning (ISA) (Fig.8a, 8b), defined as the presence of a separation between the abluminal surface of the device and the endoluminal surface of the vessel, greater than the thickness of the strut of the device (50). Out of a total of 39,590 struts analyzed, 564 presented malapposition - this representing a low percentage ISA of 1.42% (49).

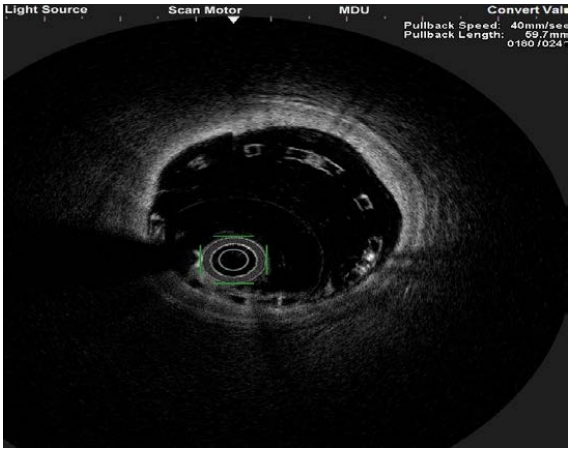

Fig. 8a Example of acute malapposition after implantation of a polymeric BRS

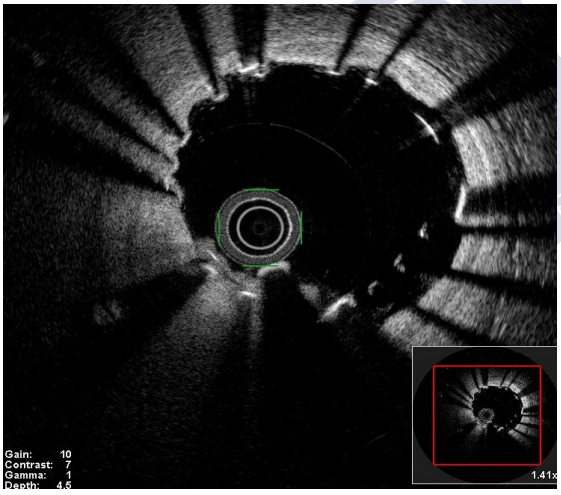

Fig. 8b OCT image of acute malapposition after implantation of a magnesium BRS

These results strengthen the findings published practically at the same time by Fabris et al. (51), who reported a low percentage of malappositioned struts (1.84%) after high-pressure (maximum 30 atm) postdilatation in Absorb 1.1, with no detection of fractured struts. However, it should be noted that only 41% of the devices included in the study of Fabris et al. were subjected to postdilatation - in contrast to the situation in our laboratory, where postdilatation was performed in 100% of the cases, thereby avoiding any selection bias.

Therefore, our results evidence the scant impact of high-pressure postdilatation of the Absorb 1.1 in terms of strut disruption, provided such postdilatation is produced at high pressure, but with non-compliant balloons and in 1:1 ratio with the artery, in order to avoid any possible over-expansion of the device. This is because although the radial strength of

these polymeric BRS is similar to that of BMS, the percentage elongation to rupture is smaller (2-10% versus 40% for chromium-cobalt devices)(25,48). Safe postdilatation affords highly optimized outcomes after placement, with low final malapposition rates (percentage ISA 1.42%) - this being essential in order to reduce the risk of thrombosis of the device.

Likewise, it should be underscored that our results are referred to a real population, not previously selected as in the pivotal studies in terms of the indication of revascularization (including patients with ACS) and lesion complexity (with a majority of lesions corresponding to type C of the AHA classification). Of the lesions included in our study, 28% presented thrombus, 21% were defined as lesions at bifurcations, and another 21% corresponded to chronic total occlusions (CTOs) (49) - all these being scenarios where the possibility of malapposition and under-expansion of the device are greater.

It is precisely in this scenario of CTO revascularization where these BRS devices were postulated to offer greater benefit by avoiding permanent “full metal jacket” situations. However, this was also regarded as the field where BRS could pose greater technical limitations due to their lesser radial strength (25) in resisting negative remodeling and recoil phenomena. In order to gain more in-depth knowledge of the behavior of BRS in this context, a second study was designed, involving clinical and OCT follow-up over 6 months of 9 chronic lesions treated with Absorb 1.1 in our laboratory (52). Exhaustive plaque preparation was made in all cases, and the outcome was optimized with high pressure (mean 16 atm and maximum 20 atm) postdilatation in 89% of the cases, achieving a procedure success rate of 100%. In the OCT follow-up study, a total of 44,723 struts were analyzed, of which only 134 were identified as being fractured - this representing a disruption rate of 0.29%. In this case, no struts were found to be malappositioned (52). These findings, which are consistent with those previously described (49), warrant the safety of high-pressure postdilatation of these devices, making it possible to obtain optimized outcomes even in scenarios as complex as chronic occlusions.

Another key factor in the etiopathogenesis of stent thrombosis is the absence of strut coating. In 2007, Finn et al. presented a post-mortem study in patients carrying first generation DES, divided into two groups: stent-related death (when occlusive or non-occlusive thrombus with distal embolization was observed) and non-stent related death (when the implanted DES showed no evidence of thrombosis or restenosis). The comparative analysis showed the cases of stent thrombosis to be associated to lesser neointimal coating in terms of both neointimal thickness and the length of uncoated stent (53). Later studies involving in vivo analysis based on intracoronary imaging techniques reinforce this idea. An analysis seeking to identify the causes of stent thrombosis in 217 cases found that the earlier stent thrombosis, the greater the presence of uncoated struts. In this regard, among the identifiable causes of stent thrombosis, in situations of acute and subacute thrombosis the main underlying cause was the absence of strut coating (66% and 61%, respectively) - the prevalence decreasing in the case of late thrombosis to 33% and particularly in very late thrombosis, where the presence of neoatherosclerosis was seen to predominate (54).

Based on the type of lesion, observational studies such as the RESTART registry have established a special association between: a) PCI targeted to the culprit artery in infarction and a greater incidence of acute thrombosis (probably related to inadequate antiplatelet therapy, acute malapposition, the presence of thrombus or residual dissections); and b) PCI targeted to chronic occlusions and greater late / very late stent thrombosis rates (55). A priori, and in accordance with earlier studies, it could be postulated that this excess of late

thrombosis in CTO is related to the presence of neoatherosclerosis combined with persistent under-expansion. However, following publication of the results of the ALSTER-OCT-CTO registry, it was suggested that the absence of strut coating could be the key factor also in the development of stent thrombosis over CTO subjected to PCI (56). This registry included 20 chronic lesions and 28 non-CTOs subjected to intracoronary imaging study after 6 months. Out of a total of 9219 struts analyzed in the CTO group and 10,724 struts in the non-CTO group, the uncoated strut rate was found to be 31% in the CTO group versus 10% in the non-CTO group - this representing a significantly greater percentage of absence of strut coating in the former group ($p < 0.001$). However, not only was the coating rate lower but the neointimal thickness of the coated zones was also smaller (after a similar duration of follow-up) in the case of the struts of treated chronic lesions versus the non-CTOs (92 µm versus 109 µm; $p = 0.03$) (56).

Nevertheless, the evidence of a possible late or inadequate coating process in revascularization over CTOs was scarce, and since no data were available on the coating process of polymeric BRS devices in this context, we designed the previously described follow-up study after the revascularization of chronic lesions with Absorb 1.1 (52). Although other parameters such as strut malapposition or disruption were also evaluated, the primary objective of this study was to know the percentage of coated polymeric struts at 6 months post-implantation, together with the mean thickness of that coating. For this purpose intracoronary imaging studies were made using OCT and, in accordance with the literature, coated struts were defined as those with a coating measuring ≥ 30 µm as established from the abluminal margin of the strut to its core (57). A total of 44,723 struts were analyzed over a total stented length of 636 mm, with the identification of only 2051 uncoated struts - this representing 4.59% of the total. These data are consistent with those published practically at the same time by Vaquerizo et al. in their OCT follow-up study at 12 months post-BRS implantation in 24 chronic occlusions, where 5% of the struts were seen to lack coating (58). In addition, our study for the first time quantified mean strut coating thickness in CTOs, with a value of 0.13 ± 0.05 mm.

These values were consistent with those previously described in studies of the coating of metal DES positioned in chronic occlusions (with an uncoated strut rate of about 3% and a mean neointimal thickness of 0.126 mm) (59), and with those reported for DES outside the context of CTO, with mean coating values of about 0.12 mm (60).

Therefore, on the basis of these findings, it was concluded that drug-eluting BRS are as effective as permanent metal devices in controlling arterial healing, and that this process evolves similarly in both PCI targeted to chronic occlusion and in non-CTO of native vessels.

Accordingly, it was considered that the greater stent thrombosis rates detected after PCI with polymeric BRS was related to a suboptimal revascularization technique. The so-called PSP technique (P - optimal Predilatation, S - vessel and device Sizing, and P - Postdilatation) was developed in an attempt to minimize these effects. In this respect, an adequate implantation technique was considered to comprise three steps (61):

1. - Adequate assessment of the vessel reference diameter.

Diameters suitable for placement of a polymeric BRS were considered to be ≥ 2.25 mm to ≤ 3.75 mm according to quantitative coronary analysis (QCA) or between 2.5-4 mm according to visual assessment.

2.- Optimum predilatation, performed with balloons of a nominal diameter

in 1:1 ratio with the vessel diameter according to QCA or visual assessment.

3. - Final postdilatation, performed with non-compliant balloons with a diameter in no case > 0.5 mm with respect to the scaffold, and at high pressure (≥ 18 atm).

Retrospectively, an evaluation was made of the impact which this optimized implantation technique could have upon the middle- to long-term clinical outcomes after PCI with polymeric BRS. To this effect, a review was made of all the cases of PCI with Absorb 1.1 included to date in four large trials: Absorb II, Absorb Japan, Absorb III and Absorb China, plus those included in the Absorb Extend registry. It should be noted that out of a total of 3149 lesions, 60% were considered to be adequately pre-dilated, while only 12.7% were considered to be adequately post-dilated. The stent thrombosis and target lesion failure (TLF) rates were recorded at one and three years, and those lesions treated with an optimized implantation technique were seen to show a significant decrease in the presence of these events (61). Subsequent real-life studies such as the GHOST-EU registry confirmed this significant decrease in events after the application of optimized implantation techniques, with a reduction of close to 30% (62).

In view of these results, the decision was made to extend the recommendation to use a PSP optimization technique for the placement not only of polymeric BRS but also metal BRS (63). Nevertheless, this recommendation is not based on solid evidence, since in the pivotal study of the magnesium BRS (BIOSOLVE II) (39), only dilatation of the lesion prior to placement was considered mandatory - leaving postdilatation of the device to the discretion of the operator (69% of the cases) (40). In an attempt to clarify the relevance of an optimized implantation technique in the case of PCI with metal BRS, we designed a new prospective follow-up registry including all those patients treated with magnesium BRS in our center between June 2016 and April 2017 (64). In accordance with the above descriptions, and on a per protocol basis, exhaustive predilatation of the lesion and post-implantation high-pressure postdilatation of the device was performed with non-compliant (NC) balloons of a diameter in 1:1 ratio with the scaffold (or no more than 0.5 mm greater). For adequate characterization of the size of the vessel (and thus of the scaffold to be used), we not only used visual angiographic assessment as reference but also performed a baseline intravascular OCT imaging study. Likewise, correct selection of the patients and target lesions was considered to be crucial. Accordingly, we mainly selected: a) young patients, where the benefits of a transient scaffold with eventual functional recovery of the vessel would afford benefits over follow-up; and b) native vessel lesions with no major calcium component and excluding complex scenarios such as the presence of left main disease or intrastent restenosis (64). It should be mentioned that this modified OCT guided implantation technique is known as the “4P” procedure.

A total of 42 patients were included (with 42 treated lesions), using magnesium BRS, with a procedure success rate of 100% (defined as successful placement of the BRS device with final residual stenosis < 20% in the absence of complications such as death, acute myocardial infarction or TLR during hospital stay) (64). This evidences the importance of adequate characterization and preparation of the lesion to be treated with metal BRS, allowing our registry to reach an implantation success rate of 100% versus a lower rate (93% of device success) in the BIOSOLVE II trial, where the absence of adequate predilatation was identified as the main cause of such failure (39).

From the clinical perspective, the existing evidence in relation to the results obtained after PCI with magnesium BRS was favorable but limited, being almost entirely based on the results of the pivotal studies: BIOSOLVE II and III (39,40,63). For this reason, the decision was made to define a primary clinical follow-up endpoint as the primary objective of our registry, in order to assess the results of the magnesium device in a real-life patient cohort.

In this regard, the primary objective was established as the TLF rate at 12 months post-implantation, defined as the combination of cardiac death, myocardial infarction related to the target vessel, and ischemia guided TLR.

In a total of 42 lesions treated in our center (42 patients), the TLF rate at 12 months was 4.7%, in relation to two cases of TLR due to restenosis of the previously implanted devices (64). These findings coincide with those published almost at the same time in January 2019 corresponding to the BIOSOLVE IV study (65), a prospective multicenter registry developed in parallel to our own, with the start of patient recruitment in September 2016. In that study, out of a total of 400 patients with 425 treated lesions, Verheye et al. reported a TLF rate of 4.3%, at the expense of TLR in all cases (65). It is important to point out that these results in the real life setting show continuity with those previously obtained in the BIOSOLVE II trial (with a TLF rate of 3.4%) (63), even though our registry includes patients and lesions with a greater risk profile (e.g., 54.7% of PCI in the context of ACS, 28.6% of patients with diabetes mellitus, and a longer stented vessel length of 21.6 mm versus 12.6 mm in the BIOSOLVE II trial) (39). All these results are not only encouraging in themselves but are moreover also comparable to those previously described for PCI with permanent DES (66).

On the other hand, given the concern within the scientific community regarding the description of slightly higher late thrombosis rates after the placement of polymeric scaffolds, the results obtained in our series are encouraging, with a stent thrombosis rate of 0% at 12 months post-implantation of magnesium BRS (64). These results are consistent with those obtained by the real-life BIOSOLVE IV registry, where no late stent thromboses were recorded after 12 months, and with a single episode of acute stent thrombosis (10 days after placement) in relation to very early suspension of the antiplatelet medication (65). Thus, solid evidence is produced that warrants the safety of metal BRS outside a controlled setting such as a clinical trial, where a 0% stent thrombosis rate at 24 months had already been reported (40).

However, on the basis of these results, it is clear that the clinical behavior of metal BRS is not fully comparable to that of the polymeric devices, despite their common bioresorbable nature. Although the introduction of an optimized implantation technique resulted in a decreased risk of events after PCI involving polymeric BRS (62), follow-up studies have shown that the event rates for these devices - while decreased and considered to be acceptable - remain higher (about 5.5-7.1% at 24 months) (67,68) than in the case of magnesium BRS (40).

In an attempt to clarify the mechanism underlying this disparity of results, we analyzed the data obtained in our comparative study between polymeric and magnesium BRS, the primary objective of which was the assessment (using intracoronary OCT) of the strut malapposition and disruption rates, together with the diameters corresponding to the lumen, scaffold and vessel in the immediate post-implantation period (69). A total of 10 lesions treated with PLLA BRS and 10 lesions treated with magnesium BRS were included, using a 4P optimized placement technique in all cases. No significant differences were found from the

clinical-demographic perspective or in terms of the type of lesion - most cases corresponding to type B-C lesions of the AHA classification, with a mean vessel diameter of about 3.50 mm in both groups. Likewise, no significant differences were recorded in terms of the implantation technique, with the exception of the application of slightly higher postdilatation pressures in the metal BRS group (18.01±2.15 versus 17.20±3.80 atm; p=0.05). The analysis of the studies involving post-implantation OCT showed the magnesium BRS group to reach greater vessel and scaffold diameters (4.12±0.51 versus 4.04±0.46 mm; p=0.04 and 3.11±0.38 versus 3.07±0.36 mm; p=0.03, respectively) (69). Taking into account that these were two well balanced groups of lesions in which the implantation technique did not differ significantly, these results were considered to support the idea of greater radial strength and expansion capacity of the metal BRS (63). Furthermore, no structural damage was detected, since the percentage of ruptured struts barely reached 0.15% - this figure in turn being significantly lower than the likewise low percentage recorded in the polymeric BRS group (0.15% versus 0.27%; p=0.03). This reaffirms the previous hypotheses that suggested a greater percentage elongation to rupture for these devices, based on the mechanical properties of magnesium (70). Likewise, the detection of lesser post-implantation eccentricity indices in the metal BRS group supports the data obtained in "in vitro" studies, where lesser rigidity and greater conformability of these devices was suggested (71).

Thus, on the basis of described results, we consider polymeric and metal BRS to exhibit different mechanical properties, which rejects the idea of the existence of a "class phenomenon" attributable to their common resorbable nature. This mechanical behavior could explain the different behaviors over time of these devices after implantation.

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7. CONCLUSIONS

I/ BRS implantation is safe, with high procedural success rates and no peri-procedural major adverse cardiac events.

II/ An optimized implantation technique must be performed to achieve those excellent angiographic and clinical outcomes, including an adequate assessment of the vessel reference diameter, as well as an exhaustive lesion predilatation and postdilatation of the scaffold deployed.

III/ A complete evaluation with intracoronary imaging techniques, in particular OCT images; is mandatory in order to warrant an optimal vessel and lesion characterization and to evaluate immediate stent results after deployment.

IV/ BRS postdilatation is safe, with very low rates of acute scaffold disruption; and it allows the operator to significantly reduce incomplete struts apposition.

V/ Optimal post-implantation results are achieved after BRS PCI even in such complex scenarios as bifurcation lesions, long lesions or CTOs, as long as an optimized implantation technique is performed.

VI/ Differences in acute mechanical performance between polymeric and metallic BRS have been detected, demonstrating greater percentage of elongation-at-break for magnesium devices.

VII/ Mid-term vascular healing response in terms of struts coverage, after PLLA BRS deployment is comparable to vascular response after DES implantation, even in CTOs PCI

VIII/ Long-term clinical outcomes after magnesium BRS PCI are excellent, with low TLR rates and no cardiovascular death or myocardial infarction; and consistent with those reported in its pivotal trial.

IX/ Neither acute nor subacute stent thrombosis were detected after magnesium BRS PCI in a twelve-months follow-up after an optimized implantation technique.

X/ Outside the controlled setting of randomized trials, the clinical and angiographic results obtained after resorbable platform implantation are largely dependent upon the use of optimized placement techniques. Under this premise, it is considered that such devices may constitute an effective alternative in percutaneous coronary revascularization treatments in humans.

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8. SPANISH ABSTRACT

ESTUDIO DE EFICACIA Y SEGURIDAD DEL USO DE PLATAFORMAS DE ANDAMIAJE (STENTS) BIORESORBIBLES EN EL TRATAMIENTO DE LAS LESIONES CORONARIAS TRATADAS MEDIANTE ANGIOPLASTIA EN DIFERENTES ESCENARIOS CLÍNICOS.

8.1 INTRODUCCIÓN

Desde que Andreas Grüntzig realizara en 1977 con éxito la primera angioplastia coronaria transluminal percutánea (ACTP) (1), la cardiología intervencionista ha experimentado un gran desarrollo. Esto nos permite hoy en día ofertar a nuestros pacientes una revascularización mínimamente invasiva, en escenarios de enfermedad arterial coronaria cada vez más complejos, con altas tasas de éxito y seguridad.

La primera revolución dentro del intervencionismo coronario se produjo con la introducción de los llamados stent metálicos o convencionales (BMS). Se trataba de dispositivos conformados por una malla metálica que se liberaba sobre la lesión coronaria estenosante consiguiendo la apertura arterial. Estudios clásicos como BENESTENT I (16) o STRESS trial (17) demostraron cómo los BMS superaban los principales limitantes hasta el momento en la angioplastia simple: la reestenosis a corto-medio plazo por mecanismo de recoil así como el desarrollo de remodelado negativo. Además, el implante de BMS prevenía la oclusión arterial abrupta secundaria a disecciones post-dilatación simple con balón de angioplastia.

No obstante, la presencia permanente de un cuerpo extraño sobre la pared arterial coronaria desencadena una reacción local de hiperplasia intimal que, en un porcentaje elevado de casos, produce reducciones significativas del area luminal intrastent. Para evitar esto, se desarrollaron los llamados stent farmacoactivos (DES). Estos se componen de un esqueleto metálico sobre el cual se deposita un fármaco con propiedades inmunosupresoras antiproliferativas, el cual se libera de forma controlada sobre la pared arterial evitando la proliferación intimal excesiva (24). Gracias a esto, se reduce de forma significativa el porcentaje de reestenosis de stent, pero a expensas de un aumento del riesgo trombótico derivado de la presencia de un cuerpo extraño en contacto permanente con el endotelio arterial (lo cual obliga a mantener al paciente bajo pautas prolongadas de tratamiento antitrombótico).

Unificando los beneficios de BMS y DES pero con una diferencia fundamental: el proceso de resorción de su armazón; nacen los denominados dispositivos bioresorbibles (BRS). Los cuales permitirían teóricamente una recuperación de la vasomotilidad y compliance del vaso, con incremento del área luminal y la teórica desaparición del riesgo trombótico una vez degradado por completo su andamiaje (25).

En su diseño inicial se evitó el uso de materiales de naturaleza metálica como parte de su estructura debido a su carácter permanente. En su lugar, se testaron diferentes polímeros sintéticos como: polycaprolactone, polyhidroxibutirato, polyorthoester, ácido poliglicólico…los cuales fueron desechados tras detectarse en estudios preclínicos una fuerte respuesta inflamatoria con altas tasas de proliferación neointimal tras su implante (26). Sin embargo, se observó que uno de ellos: el ácido poli-L-láctico PLLA, presentaba mejor compatibilidad sanguínea con propiedades mecánicas favorables (27), por lo que se adoptó su uso para el diseño de estos dispositivos.

En esta línea Vogt y colaboradores presentaron los resultados tras el implante de andamiajes resorbibles en un modelo coronario porcino. En este estudio se compararon las respuestas histomorfométricas e histopatológicas tras el implante de dos tipos de andamiajes resorbibles: a) stent de PLLA con recubrimiento de paclitaxel y b) stent de PDLLA no recubierto; frente al implante de BMS. Se demostró que el grupo de BRS polimérico recubierto de paclitaxel presentaba una reducción significativa del área neointimal con tasas menores de reestenosis coronaria a 3 meses, con la desaparición del andamiaje permanente de la arteria (28).

De forma casi paralela se publica la primera serie de casos de BRS en humanos por Tamai y colaboradores (29). En este estudio se testó la eficacia y seguridad del denominado stent de Igaki-Tamai: un stent bioresorbible conformado por un armazón polimérico de PLLA con estructura helicoidal en zig-zag, sin recubrimiento farmacológico. Se valoró el comportamiento mecánico en términos de diámetro mínimo luminal y área seccional luminal y de stent, así como grado de recubrimiento en el seguimiento. A 6 meses persistía una adecuada expansión del vaso, con un grado de hiperplasia intimal no superior a la previamente reportada para BMS, y con adecuado curso clínico evolutivo: sin casos detectados de trombosis de stent, muerte o infarto agudo de miocardio (29). No obstante, los resultados de seguimiento prolongado tras el implante de este dispositivo en series mayores de casos no fueron favorables; reportando elevadas tasas de reestenosis: 19% a 12 meses (30).

A la luz de estos estudios, se concluyó que los dispositivos BRS debían aportar no sólo protección transitoria óptima frente al recoil agudo y remodelado negativo, sino también, frente a la reestenosis derivada de la hiperplasia intimal secundaria a su implante. Por tanto, debían convertirse en dispositivos liberadores de droga a nivel local. Así se desarrolló el primer andamiaje resorbible polimérico liberador de fármaco para uso en humanos: el llamado Absorb 1.0 Este dispositivo se componía de un armazón resorbible de PLLA, recubierto de una capa más fina de PDLLA desde donde se libera el fármaco antiproliferativo everolimus, en un proceso controlado donde el mayor porcentaje de fármaco se desprende en las primeras 3 horas tras el implante, completando un 80% de liberación a los 28 días post-implante (31). Por su parte, ambos polímeros (PLLA y PDLLA) son completamente bioresorbibles gracias a un proceso de hidrólisis donde acabarán por degradarse en dióxido de carbono y agua. Este proceso de resorción se estimó inicialmente en unos 2 años de acuerdo con estudios en modelo porcino.

Los primeros resultados tras implante de este dispositivo se publicaron en la denominada cohorte Absorb A (31), donde se incluyeron 30 pacientes con lesión única tratados con un dispositivo Absorb 1.0 Clínicamente se detectó un único evento adverso en seguimiento a 24 meses en forma de infarto agudo de miocardio no-Q y, desde el punto de vista angiográfico, se observaron tasas claramente superiores a las de los DES metálicos en términos de "in–stent late loss" de hasta 0.44 mm a 6 meses (31) y 0.48 mm a 24 meses (32). Si bien el área

neointimal no difería de forma significativa con la cuantificada en estudios con dispositivos de everolimus metálicos, sí se observaba una reducción significativa del área de stent valorada por IVUS. Por tanto, se concluyó que el proceso de liberación de fármaco antiproliferativo desde un recubrimiento de PDLLA era eficaz, pero que debían realizarse cambios en el diseño del dispositivo para evitar fenómeno de recoil del stent (31). Como resultado, nace la segunda generación de BRS poliméricos Absorb 1.1 Este nuevo dispositivo mantenía un armazón de PLLA con recubrimiento de PDLLA, pero con dos diferencias fundamentales: un diseño en zig-zag con puentes de conexión entre los filamentos de PLLA que le confería una mayor fuerza radial sin perder conformabilidad (33), junto con pequeñas variaciones químicas en la propia naturaleza del polímero, que conllevaba un proceso de hidrólisis más lento (25).

La seguridad y eficacia de Absorb 1.1 se testó en lo que se conoce como estudio Absorb Cohorte B, donde se incluyeron un total de 101 pacientes. La tasa de eventos adversos cardiovasculares mayores a 2 años reportada fue de 9% (34) (entendida como combinado de muerte de causa cardiaca, cualquier infarto de miocardio y revascularización guiada por isquemia de la lesión diana).

Desde el punto de vista angiográfico, dos fueron los hallazgos principales:

a) Se observó una reducción marcada de los niveles de late luminal loss (LLL) (34) respecto a los reportados en Absorb A, tanto a 6 como a 24 meses (0.19 Vs 0.44 mm y 0.27 Vs 0.48 mm respectivamente (31, 32).

b) Se confirmó una mayor persistencia en el tiempo del andamiaje polimérico con un fenómeno de resorción más lento y controlado. A 24 meses tras el implante, el número de struts claramente discernibles en la cohorte Absorb A era un 34% menor que al implante (32) frente a la práctica totalidad de struts inalterados en OCT a 24 meses en la cohorte Absorb B (34).

Estos resultados se vieron consolidados tras la publicación del estudio Absorb III (35) donde se comparaban los resultados tras el implante de sendas plataformas liberadoras de everolimus: bioresorbible polimérica (Absorb 1.1) y permanente metálica (Xience). Se demostró que Absorb no era inferior en términos de fallo de lesión diana (TLF) y que no existían diferencias significativas en términos de revascularización de lesión diana (TLR) o trombosis de stent (TS) a 12 meses (1.5% Vs 0.7%, p 0.13) (35).

Ante estos hallazgos, se consideró que los BRS poliméricos constituían una alternativa eficaz y segura en el tratamiento de lesiones no complejas en vaso nativo por lo que Absorb 1.1 fue el primer BRS en alcanzar la marca CE ® y FDA®.

De forma simultánea, ante los resultados subóptimos con baja fuerza radial de los primeros BRS poliméricos, se planteó la posibilidad de desarrollar BRS de naturaleza metálica que pudieran aportar las mismas propiedades mecánicas que los DES de cromo-cobalto, pero de forma transitoria. Tras obtener resultados favorables en fase preclínica (36), se desarrolla e implanta el primer BRS metálico en humanos: AMS- 1; conformado por un esqueleto de magnesio biodegradable, sin recubrimiento farmacológico y con tiempo de resorción inferior a 4 meses. No obstante, los resultados tras implante fueron negativos con altas tasas de TLR: 24 % a 4 meses y 45% acumulada a 1 año (37). Estos hallazgos se pusieron en relación con una alta tasa de LLL derivada: de un aparte de la ausencia de control de proliferación neointimal (al no presentar recubrimiento farmacológico) y de otra parte, por

la presencia de un proceso de resorción demasiado rápido que conllevaba una pérdida prematura de fuerza radial y remodelado negativo secundario (37).

Con el fin de superar las debilidades de su predecesor se presenta el denominado: DREAMS-1. Un dispositivo que mantiene su naturaleza de magnesio pero con dos cambios fundamentales: a) un proceso de resorción más controlado y prolongado en el tiempo: en torno a 9 meses; y b) con presencia de recubrimiento farmacológico antiproliferativo de paclitaxel. Modificaciones que conllevan una optimización clara de resultados con una reducción muy significativa de las tasas de TLF (a expensas fundamentalmente de TLR) que pasaron de un 45% para el AMS-1 (37) a 7% de TLR a 12 meses en DREAMS-1 (38). Sin embargo se detectó, en el seguimiento a 12 meses, una reducción significativa del área mínima luminal, con tasas de LLL superiores a las reportadas por su BRS polimérico coetáneo (0.39mm a 12 meses para DREAMS 1 (38) Vs 0.27 mm a 24 meses para Absorb 1.1) (34). Para superar estas limitaciones, se realizaron nuevas modificaciones que culminan con la presentación del DREAMS 2G. Este BRS metálico (actualmente denominado Magmaris ®) se diferencia fundamentalmente con el DREAMS-1 en que presenta un recubrimiento antiproliferativo de sirolimus, embebido en una matriz de PLLA, con un ligero mayor grosor de struts (en torno a 150µ). Esto le permite mantener una fuerza radial transitoria óptima, con un tiempo de resorción menor que el de los BRS poliméricos debido a su naturaleza de magnesio (39). Gracias a esto, se consiguieron resultados excepcionales en seguimiento a 24 meses, con tasas de TLF de 5.9% y de TLR guiada por isquemia de 3.4 % (40) (lo que representa tasas menores a las de su coetáneo polimérico Absorb 1.1, el cual presentaba una tasa de TLR a 24 meses superior del 6% (41).

A la luz de los resultados favorables obtenidos por ambos dispositivos: Absorb 1.1 y Magmaris en sus estudios pivotales, se consideró que representaban una alternativa segura y eficaz en el tratamiento de revascularización coronaria en humanos. No obstante, consideramos que no existía evidencia científica sólida acerca de su comportamiento en diferentes escenarios clínicos fuera del ambiente controlado de un ensayo como por ejemplo, en revascularización en el contexto de un síndrome coronario agudo, tratamiento de oclusiones crónicas, lesiones de longitud > 20 mm…Por esto motivo se diseñan los estudios incluidos en la presente tesis doctoral, con el fin de analizar el comportamiento de estos dispositivos en vida real: tanto desde un punto de vista clínico, como angiográfico y con técnicas de imagen avanzada.

8.2 OBJETIVOS

Evaluación de la seguridad y eficacia del uso de dispositivos bioresorbibles en angioplastia coronaria en una cohorte no seleccionada de pacientes en vida real, en distintos escenarios clínicos.

Los objetivos se han dividido en dos grupos:

- Desde un punto de vista clínico: desarrollo de angina, infarto de miocardio, muerte, trombosis de stent.

- Desde un punto de vista morfológico: parámetros de imagen intracoronaria: endotelización, malaposición y disrupción de struts.

8.3 MÉTODOS Y RESULTADOS

Si bien los primeros estudios con BRS presentaban resultados favorables para su empleo en intervencionismo coronario, con la generalización de su uso y ante periodos de seguimiento más prolongados, surgen las primeras alarmas acerca de su idoneidad y posibles riesgos asociados. Con la publicación de los resultados de seguimiento a 3 años de Absorb II (42) se detecta una mayor tasa de LLL (0.37mm Vs 0.25 mm), junto con mayores tasas de infarto secundario a revascularización de vaso diana (TVR) y trombosis definitiva o probable de stent en el grupo de pacientes tratados con Absorb Vs DES metálico. Resultados similares, en relación con mayores tasas de trombosis de stent para Absorb, se detectan en estudios de gran volumen de pacientes como Absorb III (43) o en metaanálisis como el publicado por Mahmoud y colab. (44), donde se alertaba de un mayor riesgo global de trombosis de stent definitiva o probable (RR 3.22) así como de trombosis muy tardía para estos dispositivos (RR 4.78). Sin embargo, cabe destacar que en los estudios pivotales de ambos dispositivos (Absorb B y BIOSOLVE II) no se reportó ningún caso de trombosis de stent (34, 40). Es por esto, que comienzan a desarrollarse distintas teorías acerca de las posibles causas de trombosis en estos dispositivos, apuntándose inicialmente a defectos en la propia técnica de implante. Así, se relacionó la presencia de malaposición o infraexpansión de stent, junto con la ausencia de recubrimiento de placa o disecciones distales como causa de trombosis subaguda (45).

Para evitar fundamentalmente los dos primeros, se planteó la conveniencia de optimizar siempre el resultado tras implante de BRS mediante postdilatación final. Sin embargo, esta recomendación chocaba con la alerta surgida tras la publicación del primer caso de disrupción de struts tras el implante de Absorb (46) y de un nuevo caso de disrupción de dispositivo tras postdilatación a alta presión (20 y 16 atmósferas) por Ormiston y colab. (47). Los resultados de seguimiento por OCT en 51 pacientes de la cohorte B de Absorb evidenciaron aislados fenómenos de disrupción aguda tras el implante; no obstante, con muy baja incidencia (48). Apenas dos casos fueron detectados, y en ambos, se describía la postdilatación a alta presión durante el implante, hasta llevar al dispositivo a diámetros por encima del establecido como rotura (> 0.5mm respecto al nominal) (48). Por tanto, se planteó que no era tanto un problema de postdilatación sino más bien de sobreexpansión del dispositivo. No obstante, la inquietud generada entre la comunidad científica supuso un freno a la posibilidad de postdilatación de estos dispositivos ante un eventual riesgo de rotura, cuyas consecuencias eran desconocidas.

En ese momento, surge la necesidad de esclarecer la relación entre postdilatación y disrupción de struts para BRS poliméricos. Con este fin se diseña el primer estudio de este proyecto de investigación (49): un estudio observacional prospectivo donde se incluyeron todos los pacientes tratados con Absorb 1.1 en nuestro laboratorio entre junio y diciembre de 2015. Por protocolo, en todos los casos se realizaba predilatación de la lesión y postdilatación del dispositivo con balones no compliantes (NC), en una relación 1:1 con la arteria y con una presión mínima de 10-12 atmósferas (atm). El resultado final se corroboraba por estudio de imagen intracoronaria mediante tomografía de coherencia óptica (OCT). El objetivo de estudio principal era la cuantificación del porcentaje de struts rotos tras postdilatación, valorando también como objetivo secundario el porcentaje de struts malapuestos. Se incluyeron un total de 14 pacientes, (14 lesiones tratadas) sometidos a intervencionismo coronario percutáneo (ICP) tanto en contexto estable (50%), como durante síndrome coronario agudo (SCA) (21% sin elevación persistente del ST [SCASEST] y 29% con elevación persistente del ST [STEMI]) con una complejidad de lesión elevada (en su mayoría

lesiones tipo C de AHA). Se realizó pre y postdilatación en el 100% de los casos, con una presión de postdilatación media de 17 y máxima de 20 atm, sin incidencias durante el procedimiento (49). Para el análisis sobre las imágenes de OCT, se siguió el consenso vigente (48) donde se definía la disrupción de struts como la presencia de dos struts en el mismo sector angular del lumen: tanto si están uno sobre el otro separados por un espacio "overhung struts" como si aparecen en contacto "stacked strus". Se consideraba también la presencia de disrupción cuando se detectaba la presencia de struts "libres" en el lumen, sin conexión con la circunferencia que genera el propio dispositivo, lo cual se conoce como "isolated struts". De un total de 39590 struts analizados, se identificó disrupción en únicamente el 0.22% del total (89 struts) (49).

Tras esto, se analizó la presencia de malaposición (ISA) definida como la presencia de una separación entra la cara abluminal del dispositivo y la endoluminal del vaso superior al grosor de strut del dispositivo (50). Del total de 39590 struts analizados se identificaron 564 como malapuestos, lo que supone un bajo porcentaje de ISA de 1.42% (49).

Estos resultados aportan solidez a los publicados de forma prácticamente coetánea por Fabris y colab. (51), donde se reportaba un bajo porcentaje de struts malapuestos (1.84%) tras postdilatacion a alta presión (máxima 30 atm) en Absorb 1.1, sin detección de struts fracturados. No obstante, cabe destacar que únicamente el 41% de dispositivos incluidos en el estudio de Fabris y colab. se sometió a postdilatacion; a diferencia del estudio realizado en nuestro laboratorio, donde se practicó postdilatación en el 100% casos evitando así cualquier sesgo de selección.

Por tanto, nuestros resultados evidencian la escasa repercusión que presenta el aplicar postdilatación a alta presión sobre Absorb 1.1 en términos de disrupción de struts, siempre y cuando dicha postdilatación se realice a alta presión pero, con balones no compliantes y en una relación 1:1 con la arteria, de forma que se evite cualquier fenómeno de sobreexpansión del dispositivo. Esto se debe a que, si bien la fuerza radial de estos BRS poliméricos es similar a la de BMS, no así su porcentaje de elongación a rotura que es menor (2-10% vs 40% para dispositivos de cromo-cobalto) (25, 48). Una postdilatación segura nos permite obtener tras el implante resultados muy optimizados con bajas tasas de malaposición final (porcentaje de ISA 1.42%), primordial para reducir el riesgo de trombosis de dispositivo.

Asimismo cabe destacar que nuestros resultados aplican a una población real, no previamente seleccionada, en términos de indicación de revascularización (incluyendo pacientes con SCA) y de complejidad de lesión (con una mayoría de lesiones clasificadas como tipo C AHA). De entre las lesiones incluidas en nuestro estudio, un 28% presentaba trombo, un 21% se definían como lesiones en bifurcaciones y otro 21% se correspondían con oclusiones crónicas totales (OCT) (49), todos ellos escenarios donde la posibilidad de malaposición e infraexpansión del dispositivo son mayores.

Es precisamente en el escenario de revascularización de OCT donde se planteó un posible mayor beneficio de estos dispositivos BRS al evitar situaciones de "full metal jacket" permanente. Sin embargo, también se consideró que suponía el campo donde los BRS podrían presentar una mayor limitación técnica derivada de su menor fuerza radial (25) a la hora de soportar fenómenos de remodelado negativo y recoil. Con el fin de profundizar en el conocimiento sobre el comportamiento de BRS en este contexto, se diseña un segundo estudio en el que se completa seguimiento clínico y mediante OCT a 6 meses de 9 lesiones crónicas tratadas con 29 Absorb 1.1 en nuestro laboratorio (52). Se realizó una preparación exhaustiva

de placa en el 100% de casos y se optimizó el resultado con postdilatación a alta presión (media 16 atm. y máxima de 20 atm.) en un 89% de casos, consiguiendo una tasa de éxito del procedimiento 100%. En el estudio de seguimiento por OCT se analizaron 44723 struts, de los cuales únicamente 134 se identificaron como fracturados, lo que supone un porcentaje de disrupción del 0.29%. En este caso, no se detectó la presencia de struts malapuestos (52). Estos resultados, en línea con los previamente reportados (49), apoyan la seguridad de la postdilatación a alta presión de estos dispositivos, permitiendo la obtención de resultados optimizados incluso en escenarios tan complejos como el de las oclusiones crónicas.

Otro de los factores clave identificados en la etiopatogenia de la trombosis de stent es la ausencia de recubrimiento de struts. Finn y colab. presentaron en 2007 un estudio post-morten en pacientes portadores de DES de primera generación divididos en dos grupos: muerte relacionada con stent (cuando se evidenciaba presencia de trombo oclusivo o no-oclusivo con embolización distal) y no-relacionada con stent (cuando el DES implantado no presentaba datos de trombosis ni reestenosis) (53). En el estudio comparativo se observó que los casos de trombosis de stent se relacionaban con menor grado de recubrimiento neointimal: tanto en términos de grosor neointimal como de longitud de stent no cubierta (53). Estudios posteriores con análisis in vivo mediante técnicas de imagen intracoronaria refuerzan esta idea. En un análisis dirigido a identificar las causas de trombosis de stent en 217 casos se observó que, cuanto más precoz era la trombosis stent, mayor la presencia de struts no recubiertos. Así, de entre las causas identificables de trombosis de stent, se observó que en trombosis aguda y subaguda la principal causa subyacente era la ausencia de recubrimiento de struts (66% y 61% respectivamente), bajando su prevalencia en los casos de trombosis tardía a un 33% y sobre todo, en los casos muy tardíos, donde predominaba la presencia de neoateroesclerosis (54).

Atendiendo al tipo de lesión, estudios observacionales como el registro RESTART observaron que existía una especial relación entre: a) ICP a arteria responsable de infarto con mayor tasa de trombosis aguda (en probable relación con antiagregación inadecuada, malaposicion aguda, presencia de trombo o disecciones residuales) e b) ICP a oclusiones crónicas con mayores tasas de TS tardía/muy tardía (55). A priori y, de acuerdo con estudios previos, cabría pensar que este exceso de trombosis tardía en OCT se relacionaría con la presencia de neoateroesclerosis combinada con infraexpansion persistente. Sin embargo, tras la publicación de los resultados del registro ALSTER-OCT-CTO se sugirió que la ausencia de recubrimiento de struts podría ser un factor clave también en el desarrollo de TS sobre OCT sometidas a ICP (56). En este registro se incluyeron 20 lesiones crónicas y 28 no-OCT sobre las que se había realizado valoración con imagen intracoronaria a 6 meses. En un total de 9219 struts analizados en el grupo OCT y 10724 struts en el grupo no-OCT, se identificó como struts no recubiertos un 31% en grupo OCT Vs 10% en el grupo no OCT, lo cual representa un porcentaje significativamente mayor ($p<0.001$) de ausencia de recubrimiento de struts en el grupo de OCT. Pero no sólo existían tasas menores de recubrimiento, sino que el grosor neointimal de las zonas recubiertas era menor (en un tiempo evolutivo similar) sobre los struts de lesiones crónicas tratadas frente a lesiones no OCT (92 µ Vs 109 µm, p 0.03 (56).

Sin embargo, la evidencia disponible acerca de un posible proceso de recubrimiento tardío o inadecuado en revascularización sobre OCT era escasa y, dado que no existían datos acerca del proceso de recubrimiento de dispositivos BRS poliméricos en este contexto, diseñamos el previamente descrito estudio de seguimiento tras revascularización de lesiones

crónicas con Absorb 1.1 (52) Si bien se evaluaron también otros parámetros como disrupción o malaposición de struts, el objetivo primario de este estudio era conocer el porcentaje de struts poliméricos recubiertos a 6 meses post-implante junto con el grosor medio de dicho recubrimiento. Para ello se realizaron estudios de imagen intracoronaria mediante OCT y, de acuerdo a la literatura previa, se definieron como struts recubiertos aquellos que presentaban un recubrimiento ≥ 30 µm medido desde el borde abluminal del strut hasta su core (57). Se analizaron un total de 44723 struts a lo largo de los 636 mm de longitud total stentada y se identificaron únicamente 2051 struts como no recubiertos, lo que supone un 4.59% del total. Estos resultados se mantenían en línea con los publicados de forma prácticamente simultánea por Vaquerizo y colab. en su estudio de seguimiento con OCT a 12 meses tras el implante de BRS en 24 oclusiones crónicas, donde reportaban un 5% de struts no recubiertos (58). De forma añadida, nuestro estudio cuantificó por primera vez el grosor medio de recubrimiento de struts poliméricos en OCT, siendo de 0.13± 0.05 mm.

Estos valores se correlacionaban favorablemente con los previamente descritos en estudios de recubrimiento de DES metálicos sobre OCT (donde la tasa de struts no cubiertos rondaba el 3%, con un grosor neointimal medio de 0.126 mm) (59) así como en los reportados para DES fuera del contexto de OCT, con valores medios de recubrimiento en torno a 0.12 mm (60).

Por tanto, a la vista de estos resultados, se consideró que los BRS liberadores de fármaco eran tan eficaces como los metálicos permanentes a la hora de controlar los procesos de healing arterial y que, este proceso transcurría de forma similar tanto en ICP a oclusión crónica como en lesiones de vaso nativo no OCT.

De acuerdo con esto, se consideró que las mayores tasas de trombosis de stent detectadas tras ICP con BRS poliméricos debían estar en relación con una técnica de revascularización subóptima. Para tratar de minimizar estos efectos se desarrolló la denominada técnica PSP, acrónimo en inglés de: "P- optimal Predilatation, S- vessel and device Sizing y P- postdilatation". Así, se consideraba que una adecuada técnica de implantación requería de tres pasos (61):

1/ Adecuada valoración del diámetro referencia del vaso.

Se consideraban diámetros aptos para implante de un BRS polimérico si ≥2.25 hasta ≤3.75 mm por "quantitative coronary analysis" (QCA) o entre 2.5 a 4 mm por valoración visual.

2/ Predilatación óptima: realizada con balones con un diámetro nominal en relación 1.1 con el diámetro del vaso por QCA/ visual.

3/ Postdilatación final: realizada con balones NC con diámetro nunca >0.5mm respecto al del scaffold, y a alta presión (≥ 18 atm).

De forma retrospectiva, se valoró el efecto que esta técnica de implante optimizada podía tener en los resultados clínicos a medio-largo plazo tras ICP con BRS poliméricos. Para esto se revisaron todos los casos de ICP con Absorb 1.1 incluidos hasta la fecha en 4 grandes ensayos: Absorb II, Absorb Japan, Absorb III y Absorb China; más los incluidos en el registro Absorb Extend. Cabe destacar que, en un total de 3149 lesiones, se consideraron como adecuadamente predilatadas el 60% de lesiones incluidas y, sólo un 12,7% como adecuadamente postdilatadas. Se identificaron las tasas de TS y TLF a 1 y 3 años y se observó que, aquellas lesiones sometidas a una técnica de implante optimizada, presentaban una

reducción de estos eventos de forma significativa (61). Estudios posteriores en vida real como el registro GHOST-EU confirmaron esta reducción significativa de eventos tras la aplicación de técnicas de optimización al implante, llegando a cuantificarse como una reducción próxima al 30% (62).

A la luz de estos resultados se decidió extender la recomendación del empleo de una técnica PSP de optimización al implante no sólo para BRS poliméricos, sino también para BRS de naturaleza metálica (63). No obstante, dicha recomendación no se basa en la existencia de evidencia sólida al respecto dado que, en el estudio pivotal del BRS de magnesio (BIOSOLVE II) (39) únicamente se consideraba obligatoria la dilatación de la lesión previa al implante, dejando la postdilatación del dispositivo a discreción del operador (69% de casos) (40). Para tratar de esclarecer la relevancia de una técnica de implante optimizada en el caso de ICP con BRS metálicos, diseñamos un nuevo registro prospectivo de seguimiento donde se incluyeron todos aquellos pacientes tratados con BRS de magnesio en nuestro centro entre junio de 2016 y abril de 2017 (64). De acuerdo con lo previamente descrito, se realizaba por protocolo predilatación exhaustiva de la lesión y, tras el implante, postdilatación a alta presión con balones NC de diámetro en relación 1:1 con el scaffold (o como máximo 0.5mm superiores). Para la adecuada caracterización del tamaño del vaso (y por ende, del scaffold a emplear) se decidió no sólo tomar como referencia una valoración angiográfica visual, sino completar el análisis con estudio por imagen intravascular con OCT basal. Asimismo, se consideró de vital relevancia el hacer una correcta selección de los pacientes y lesiones a tratar. Así se incluyeron principalmente a) pacientes jóvenes, donde los beneficios de un andamiaje transitorio con eventual recuperación funcional del vaso aportaría beneficios en el seguimiento y b) con lesiones en vaso nativo, sin un componente cálcico importante y excluyendo escenarios complejos como la presencia de enfermedad de tronco coronario o restenosis intrastent (64). Esta técnica modificada de implante guiada por OCT se denominó técnica “4P”.

Se incluyeron un total de 42 pacientes con 42 lesiones tratadas con BRS de magnesio con una tasa de éxito de procedimiento del 100% (definido como implante exitoso del dispositivo BRS con estenosis residual final < 20% en ausencia de complicaciones tales como muerte, infarto de miocardio o TLR durante la estancia hospitalaria) (64). Esto pone de relevancia la importancia de la adecuada caracterización y preparación de la lesión a tratar con BRS metálicos, permitiéndonos alcanzar en nuestro registro una tasa de éxito al implante del 100% frente a una tasa más reducida (93 % de éxito del dispositivo) en el estudio BIOSOLVE II, donde se identificó la ausencia de una adecuada predilatación como causa principal de dicho fracaso (39).

Desde el punto de vista clínico, la evidencia existente en resultados tras ICP con BRS de magnesio era favorable pero escasa, basada prácticamente en exclusiva, en los resultados de los estudios pivotales: BIOSOLVE II y III (39, 40, 63). Por este motivo, se decide definir un objetivo primario de seguimiento clínico como objetivo principal de nuestro registro, con el fin de valorar los resultados del dispositivo de magnesio en una cohorte de pacientes en vida real.

Se establece como objetivo primario la tasa de TLF a 12 meses tras implante, definida como el combinado de muerte cardiaca, infarto de miocardio relacionado con vaso diana y TLR guiada por isquemia.

En el total de 42 lesiones tratadas en nuestro centro (42 pacientes) se reportó una tasa de TLF a 12 meses del 4.7% en relación con dos casos de TLR por restenosis de los dispositivos previamente implantados (64). Estos resultados son consistentes con los reportados de forma casi simultánea en enero 2019 en el registro BIOSOLVE IV (65), un registro multicéntrico prospectivo desarrollado de forma paralela al nuestro, con inicio de reclutamiento en septiembre de 2016. Donde, en un total de 400 pacientes con 425 lesiones tratadas, Verheye y colab. reportaron una tasa de TLF del 4.3% a expensas de TLR en todos los casos (65). Es importante destacar que estos resultados en vida real muestran una línea de continuidad con los previamente descritos en el estudio BIOSOLVE II (con tasas de TLF del 3.4%) (63), incluso cuando en nuestro registro se incluyen pacientes y lesiones con un mayor perfil de riesgo: ej. 54,7% de ICP en contexto de SCA, 28.6% de pacientes con Diabetes Mellitus y mayor longitud de vaso stentado (21,6 mm frente 12.6mm en BIOSOLVE II (39). Resultados todos ellos que no sólo son favorables en sí mismos, sino que además son comparables con los previamente descritos con ICP con dispositivos liberadores de fármaco permanentes (66).

Por otro lado, dada la preocupación entre la comunidad científica a tenor de la descripción de tasas ligeramente superiores de trombosis tardía tras el implante de scaffold poliméricos, resultan alentadores los resultados obtenidos en nuestra serie con tasas de trombosis de stent del 0% a 12 meses tras el implante de dispositivos BRS de magnesio (64). Resultados consistentes con los publicados en el registro en vida real BIOSOLVE IV donde no se detectaron casos de trombosis tardía de stent a 12 meses, con un único episodio de trombosis de stent aguda (a 10 días post implante) en relación con retirada muy precoz de tratamiento antiagregante (65). Por tanto, se genera evidencia sólida que refuerza la seguridad de los dispositivos BRS metálicos fuera de un ambiente controlado como es el del ensayo clínico, donde ya previamente habían demostrado una tasa 0% de trombosis de stent a 24 meses (40).

Sin embargo a la vista de estos resultados, queda patente que el comportamiento clínico de los BRS metálicos no se compara de forma total con el de los dispositivos poliméricos, pese a su naturaleza común bioresorbible. Aunque la introducción de una técnica de implante optimizada permitía reducir el riesgo de eventos tras ICP con BRS poliméricos (62), en estudios de seguimiento se ha observado que las tasas de eventos para estos dispositivos, si bien se reducen y se consideran aceptables, se mantienen superiores (en torno al 5.5-7.1% a 24 meses) (67, 68) frente a sus homólogas reportadas para BRS de magnesio (40).

Para tratar de dilucidar el mecanismo que lleva a esta disparidad de resultados, analizamos los resultados obtenidos en nuestro estudio comparativo entre BRS polimérico y de magnesio, cuyo objetivo primario consistía en la valoración (mediante imagen intracoronaria OCT) de los porcentajes de disrupción y malaposición de struts junto con los diámetros luminal, del scaffold y del vaso en el post-implante inmediato (69). Se incluyeron 10 lesiones tratadas con BRS de PLLA y 10 con BRS de magnesio, todas ellas bajo una técnica de implante optimizada 4P. No se identificaron diferencias significativas desde punto de vista clínico-demográfico ni en cuanto al tipo de lesión, siendo en su mayoría lesiones de tipo B-C AHA, con un diámetro medio del vaso en torno a 3.50 mm en ambos grupos. Tampoco se detectaron diferencias significativas en cuanto a la técnica de implante, a excepción de la aplicación de presiones de postdilatación ligeramente superiores en el grupo de BRS metálico (18.01±2.15 vs 17.20±3.80 atm, p=0.05). El análisis de los estudios con OCT post-implante demostró que, en el grupo de tratamiento con BRS de magnesio, se alcanzaron mayores diámetros de vaso y de scaffold (4.12±0.51 vs 4.04±0.46 mm, p=0.04 y

3.11±0.38 vs 3.07±0.36 mm, p=0.03, respectivamente) (69) Teniendo en cuenta que se trataba de dos grupos de lesiones bien balanceadas, donde la técnica de implante no difería de forma significativa, se consideró que dichos resultados apoyaban la idea de una mayor fuerza radial y capacidad de expansión del BRS metálico (63). Todo ello, sin detectarse daños estructurales, dado que el porcentaje de struts identificados como rotos apenas alcanzaba un 0.15%; el cual además, resultó significativamente inferior a la también baja tasa identificada en el grupo de BRS polimérico (0.15% vs 0.27%, p=0.03). Por tanto, se reafirman las hipótesis previas que sugerían un mayor porcentaje de elongación a rotura para estos dispositivos basándose en las propiedades mecánicas del magnesio (70). Asimismo, la detección de menores índices de excentricidad post-implante en el grupo de BRS metálico, apoya los datos presentados en estudios in vitro donde se sugería una menor rigidez y mayor conformabilidad de estos dispositivos (71). De acuerdo con los resultados descritos, consideramos que dispositivos BRS poliméricos y metálicos presentan diferentes propiedades mecánicas, lo cual rechaza la idea de la existencia de un "fenómeno de clase" derivado de su naturaleza resorbible común. Comportamiento mecánico éste que podría subyacer en el distinto comportamiento evolutivo de estos dispositivos tras su implante.

8.4 CONCLUSIONES

I/ El implante de BRS es seguro, con altas tasas de éxito de procedimiento y sin eventos cardíacos mayores adversos periprocedimiento.

II/ Con el fin de alcanzar la excelencia desde el punto de vista clínico y angiográfico, el implante se debe realizar bajo una técnica optimizada que incluya una adecuada valoración del diámetro de referencia del vaso, junto con una predilatación exhaustiva de la lesión a tratar y postdilatación del stent implantado.

III/ Se considera obligada la realización de un estudio completo mediante técnicas de imagen intracoronaria, en particular estudio mediante OCT; con el fin de garantizar la adecuada caracterización del vaso y lesión diana así como la valoración de resultados en el post-implante inmediato.

IV/ La postdilatación de BRS se considera segura (con muy bajas tasas de disrupción aguda de strut); al tiempo que permite al operador reducir de forma significativa la tasa de aposición incompleta de strus.

V/ Incluso en escenarios complejos para ICP con dispositivos BRS como son lesiones largas, en bifurcaciones u OCTs; se han conseguido resultados óptimos post-procedimiento gracias a la aplicación de una técnica optimizada de implante.

VI/ Existen diferencias en el comportamiento mecánico agudo de BRS poliméricos y metálicos, con mayor porcentaje de elongación a rotura para los dipositivos de magnesio.

VII/ La respuesta vascular a medio plazo tras implante de BRS de PLLA en términos de recubrimiento de struts es comparable a la respuesta tras implante de DES, tanto en un contexto CTO como no-CTO.

VIII/ Los resultados a largo plazo tras ICP con BRS de magnesio han sido excelentes, con bajas tasas de TLR y ausencia de muerte de causa cardiovascular o infarto de miocardio. ; al

tiempo que consistentes con los previamente reportados en el estudio pivotal de este dispositivo.

IX/ No se ha detectado ningún caso de trombosis de stent aguda o subaguda tras ICP con BRS de magnesio en un seguimiento a doce meses tras implante mediante técnica optimizada.

X/ Fuera del ámbito controlado de los ensayos randomizados, los resultados tanto clínicos como angiográficos tras el implante de plataformas bioresorbibles dependen, en gran medida, de la aplicación de técnicas de implante optimizadas. Bajo esta premisa, se considera que estos dispositivos pueden suponer una alternativa eficaz en el tratamiento de revascularización coronaria percutánea.

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10. ETHICAL ASPECTS

The doctoral candidate declares no conflicts of interest related to her thesis.

The present study has been developed in accordance with the Declaration of Helsinki.

Patients´ confidentiality has been strictly protected.

Patient´s consent has been asked for to be included in the study´s registry.

The present study has an observational nature, with the analysis of existing information. Therefore the study does not need the prior evaluation and report from the ethic research committee

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11. QUALITY CRITERIA FOR DOCTORAL THESIS

As this is a thesis presented as a compendium of articles, the contribution of the doctoral student to each of the articles should be specified. So, this is my contribution declaration:

For the article titled: "Assessment of effectiveness and security in high pressure postdilatation of bioresorbable vascular scaffolds during percutaneous coronary intervention. Study in a contemporary, non-selected cohort of Spanish patients"→ contribution to the design of the work; acquisition, analysis and interpretation of data and drafting and final approval of the work. I am also accountable for all aspects of the work.

For the article titled: "Bioresorbable vascular scaffolds in coronary chronic total occlusions revascularization: safety assessment related to struts coverage and apposition in 6-month OCT follow-up"→ contribution to the conception of the work; acquisition, analysis and interpretation of data as well as drafting and final approval of the work. I am also accountable for all aspects of the work.

For the article titled: "12-months clinical outcomes after Magmaris PCI in a real world cohort of patients: results from CardioHULA registry"→ contribution to the conception and design of the work; analysis and interpretation of data and drafting and final approval of the work. I am also accountable for all aspects of the work.

For the article titled: "Magnesium vs PLLA bioresorbable scaffolds: in vivo OCT comparison of mechanical performance"→ contribution to the conception and design of the work; analysis and interpretation of data and drafting and final approval of the work. I am also accountable for all aspects of the work.

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12. STROBE CHECKLIST

Yes/No/NA		Page
Title and abstract		
Yes	Indicate the study's design with a commonly used term in the title or the abstract	Articles 32,36,37
Yes	Provide in the abstract an informative and balanced summary of what was done and what was found	Articles 32 to 38
Introduction		
Yes	Explain the scientific background and rationale for the investigation being reported	Articles 5-16
Objectives		
Yes	State specific objectives, including any prespecified hypotheses	17 Articles
Methods		
Study design		
Yes	Present key elements of study design	Articles 18-20 23, 24
Setting		
Yes	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Articles 18-20 24
Participants		
Yes	*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Articles 18, 23, 24
N/A	*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
N/A	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
N/A	*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	
N/A	*Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables		
Yes	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Articles
Data source/Measurements		
Yes	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Articles
Yes	Describe comparability of assessment methods if there is more than one group	Articles
Bias		

Yes	Describe any efforts to address potential sources of bias	Articles
Study size		
Yes	Explain how the study size was arrived at	Articles
Quantitative variables		
Yes	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Articles
Statistical methods		
Yes	Describe all statistical methods, including those used to control for confounding	Articles
N/A	Describe any methods used to examine subgroups and interactions	
N/A	Explain how missing data were addressed	
N/A	*Cohort study*—If applicable, explain how loss to follow-up was addressed	
N/A	*Case-control study*—If applicable, explain how matching of cases and controls was addressed	
N/A	*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
N/A	Describe any sensitivity analyses	
Results		
Participants		
Yes	Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Articles
N/A	Give reasons for non-participation at each stage	
N/A	Consider use of a flow diagram	
Descriptive data		
Yes	Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Articles
Yes	Indicate number of participants with missing data for each variable of interest	Articles
Yes	*Cohort study*—Summarize follow-up time (e.g., average and total amount)	Articles
Outcome data		
Yes	*Cohort study*—Report numbers of outcome events or summary measures over time	Articles 20, 22, 23-25 and 26
N/A	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure	
N/A	*Cross-sectional study*—Report numbers of outcome events or summary measures	
Main results		
N/A	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
N/A	Report category boundaries when continuous variables were categorized	
N/A	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analysis		
N/A	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	
Discussion		
Key results		
Yes	Summarize key results with reference to study objectives	Articles 20, 22, 23-25 and 26
Limitations		
Yes	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Articles
Interpretation		

Yes	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Articles 18 to 26
Generalizability		
Yes	Discuss the generalizability (external validity) of the study results	Articles
Funding		
Yes	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	45 Articles

Based on the STROBE declaration. Essential points that should be described in observational studies.

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13. GENERAL CHECKLIST

Yes-No-N/A		Page
For all Thesis		
Yes	Declaration of potential conflicts of interests	45
Yes	Declaration on the origin and copyright status of non original figures, with permisión if necessary. Include them in the text of each figure	7,8,10
N/A	Checklist of statistics adequacy if no other checklists apply.	
For Thesis involving human experimentation, human samples, or personal data.		
N/A	Declaration on approval by the research ethics committee.	
N/A	Code number of the study.	
Yes	Copy of ethics report	45
N/A	Declaration that data are based on anonymous information, and no approval of the ethics committee is needed.	
Yes	If it is an observational study, STROBE checklist.	47
For Thesis that include a clinical assay		
N/A	Declaration of itsauthorizationbytheAgencia Española de Medicamentos y productos sanitarios.	
N/A	Copy of the authorization	
N/A	CONSORT Checklist	
For Thesis that use embryonic or induced human stem cells		
N/A	Declaration on its authorization	
N/A	Reference of the authorization	
N/A	Copy of the authorization	
For Thesis that include animal experimentation		
N/A	Declaration of its authorization	
N/A	Code number of the authorizaton of the animal experimentation Project.	
N/A	Register number of the centro de usuarioautorizadoif experiments were made in Spain	
N/A	Copy of the capacitation certificate if the experiments were made by the Thesis autor.	
N/A	Person, company or service that performed the experiments if applicable.	
N/A	ARRIVE Checklist	

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14. ACKNOWLEDGEMENTS

A mis padres, por su paciencia y cariño infinitos. Porque siempre me han apoyado, tanto en mis aciertos como en mis muchos errores.

A María y Lucía, porque algo me faltaría sin ellas.

A Raymundo, por su confianza y cercanía, por haber creído en mí cuando ni yo lo hacía, y ayudarme a crecer como médico y persona.

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15. ARTICLES

1/Assessment of effectiveness and security in high pressure postdilatation of bioresorbable vascular scaffolds during percutaneous coronary intervention. Study in a contemporary, non-selected cohort of Spanish patients.

Rosa A. Abellas-Sequeiros, Raymundo Ocaranza-Sanchez, Carlos Galvão-Braga, Sergio Raposeiras-Roubin, Diego Lopez-Otero, Belen Cid-Alvarez, Pablo Souto-Castro, Ramiro Trillo-Nouche, Jose R. Gonzalez-Juanatey.

Int J Cardiol. 2016;219:264-70. IF 2016: 6.189

2/ Bioresorbable vascular scaffolds in coronary chronic total occlusions revascularization: safety assessment related to struts coverage and apposition in 6-month OCT follow-up.

Rosa A. Abellas-Sequeiros, Raymundo Ocaranza-Sanchez , Ramiro Trillo-Nouche , Carlos Gonzalez-Juanatey, Jose R. Gonzalez-Juanatey JR.

Heart Vessels. 2017;32(9):1077-84 IF 2017: 2.185

3/.12-months clinical outcomes after Magmaris PCI in a real world cohort of patients: results from CardioHULA registry.

Rosa A. Abellas-Sequeiros, Raymundo Ocaranza-Sanchez, Jeremías Bayon-Lorenzo, Melisa Santas-Alvarez, Carlos Gonzalez-Juanatey.

REPC. 2019;In press. IF 2018: 0.785

4/ Magnesium vs PLLA bioresorbable scaffolds: in vivo OCT comparison of mechanical performance.

Rosa A. Abellas-Sequeiros, Raymundo Ocaranza-Sanchez, Carlos Galvao-Braga, Jorge Marques, Carlos Gonzalez-Juanatey.

Arch.Cardiol.Mex. 2020;90(1):8-15. IF SCOPUS: 0,142

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Polymeric and metallic bioresorbable vascular scaffolds were considered to constitute a safe and effective alternative in coronary revascularization in humans after clinical and angiographical favorable outcomes obtained in their respective pivotal trials. Nevertheless, we consider that there was no solid scientific evidence of their behavior in different clinical scenarios outside the controlled setting of a clinical trial. The prospective studies included in the present Doctoral Thesis were therefore designed to evaluate the efficacy and safety of bioresorbable devices analyzing their behavior from the clinical, angiographic and advanced imaging perspectives.