Bioactive Polymers and Cardiovascular Therapy

Subjects: Polymer Science

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Coronary heart disease remains one of the leading causes of death in most countries. Healthcare improvements have seen a shift in the presentation of disease with a reducing number of ST-segment elevation myocardial infarctions (STEMIs), largely due to earlier reperfusion strategies such as percutaneous coronary intervention (PCI). Stents have revolutionized the care of these patients, but the long-term effects of these devices have been brought to the fore. The conceptual and technologic evolution of these devices from bare-metal stents led to the creation and wide application of drug-eluting stents; further research introduced the idea of polymer-based resorbable stents.

drug-eluting stent polymers bioresorbable scaffolds coronary cardiovascular

1. The Clinical Problem

Coronary heart disease (CHD) is one of the leading causes of death in many countries, as it is estimated that each minute, a myocardial infarction (MI)-related death occurs [1]. Other than first or recurrent symptomatic CHD registered as hospitalized MI or cardiac-related deaths, about 20% of events still remain silent [2][3]. Each year, scientifical societies estimate 515,000 new attacks and 205,000 recurrent attacks, with an average first presentation age of 64.9 years for men and 72.3 years for women [2][4][5][6]. Data from the Framingham Heart Study (FH) revealed that CHD constitutes more than half of all cardiovascular events in the aged population [2][3]. Fortunately, early reperfusion strategies (percutaneous coronary intervention, PCI) and the decline in ST-elevation myocardial infarction (STEMI) presentation (from 133 to 50 cases per 100,000 person/years) have reduced CHD-associated mortality rates. In this setting, nearly two million stents are used annually (Interventional Cardiology Devices Market Report Suite for US, 2018–2024, available at https://idataresearch.com/product/interventional-cardiology-market/) for CHD [5]. However, stent thrombosis remains a significant complication and is generally associated with adverse clinical events [4][7]. The targeted delivery of drugs in coronary atherosclerotic disease was an inviting avenue, with early bare-metal stents (BMSs) gradually replaced by drug-eluting stents (DESs) [4]. The advantages of localized drug delivery, affecting, through a paracrine mechanism, the sites of disease, were established as the ideal strategy for handling coronary artery disease (CAD) in patients with lipid dysmetabolic disease and restenosis [2][4][5]. However, some patients have more complex vascular lesions, and the use of targeted delivery of drugs may be ineffective with potentially harmful side effects [8]. Neo-atherosclerosis is not an infrequent event in patients who received a DES [7]. Unstable features of neo-atherosclerosis, even though identified in both BMSs and DESs, appear to be related to shorter durability only for DESs [8][9][10][11]. The

development of neo-atherosclerosis may represent another rare factor contributing to the onset of late thrombotic events [7].

2. New Frontiers of Stenting

Despite the strong increase in the PCI and stenting procedure using the second generation of DES, thrombosis, and restenosis of stents remain the Achilles heel of the procedure. For this reason, research has shifted to other design approaches for the development of new stents. The use of heparin incorporated in the device, negating the prothrombotic components on the stent, has been a new direction for the prevention of thrombosis. The use of heparin impregnated on the surface of the stent can be a valid option to prevent restenosis of the device due to the reactive formation of thrombi on the metallic core. The percutaneous procedures can use a commercially available heparin releasing stent. This device known as Viabahn is made by assembling a nitinol core which is coated with ePTFE and non-mobilizable heparin. The Viabahn stent has been proven to have better patency rates in clinical trials than the bare-metal stent [12][13].

Patients who have a sensitivity to polymers can benefit from polymer-free drug-eluting stents. A number of devices have been used in which even the loading of drugs onto the metal surface can be challenging, with results that are effective after stent implantation. Carrie et al. [14] investigated the effectiveness of the Cre8 stent, in which amphilimus is integrated into reservoirs of nanoparticles arranged on the abluminal side of the stent. Urban et al. [15] created a BioFreedom stent in which biolimus adheres to a microstructured metal surface. Another innovative stent is in VESTA sync, which is combined with a microporous coating of hydroxyapatite [16][17].

In particular, three different large-scale RCTs (SORT OUT V, COMPARE II, and LEADERS) showed that stents eluting biolimus from a biodegradable polymer are a safe and effective alternative to sirolimus [18][19] or everolimus [20]. As for the stent that integrates the biodegradable polymer biolimus, it is evident that the optimal clinical results obtained by these more complex stent models are due to better optimization of the drug release kinetics, in addition to the material and mechanical properties. The advantage of these stents is that they have reservoirs that can be filled with drugs. They are progressively released through small perforations on the luminal side of the stent, allowing a more sustained and targeted drug administration [21]. In particular, cobalt-chromium stents have been combined with polymerized paclitaxel or everolimus [20][22].

The innovative design with dynamic and mechanical features of the layer-by-layer assembly system to coat the stents proved effective. Chitosan and hyaluronic acid are generally chosen as materials and enhanced with growth factors or heparin to customize drug release kinetics [23][24][25][26][27][28]. For example, released coatings with a combination of sirolimus and heparin have been shown to have a favorable action in preventing restenosis and thrombosis, respectively [25].

The action of heparin is also manifested on growth factors due to their high affinity, which are sequestered on the heparin surface. Liu et al. [28] showed that heparin was rendered inactive on the stent surface using an avidin-biotin system, and thus, CD34 and VEGF are embedded to heparin to accelerate endothelialization. Our group achieved

the same effect with poly-L-lactide (PLLA) [23][29][30], and these studies showed promising results in vitro and in vivo.

3. Bioresorbable Vascular Scaffolds

The use of a bioresorbable vascular stent (BDES or BVS) in clinical practice has been suggested to overcome DES limitations such as in-stent restenosis. Bioresorbable DESs or vascular scaffolds (BVSs) were initially designed from metallic or polymeric compounds (Table 3).

Table 3. Summary of the polymers currently used in stents and balloons.

Commercial Name	Compound
PES	Paclitaxel
BES	Biolimus
BP-BES	Biodegradable polymer biolimus
SES	Sirolimus
C-SES	Cypher sirolimus
EES	Everolimus
CoCr-EES	Cobalt-chromium everolimus
PtCr-EES	Platinum-chromium everolimus
Re-ZES	Resolute zotarolimus
E-ZES	Endeavor zotarolimus
PC-ZES	Phosphorylcholine zotarolimus
SPC-ZES	Phosphorylcholine polymer-based zotarolimus

Recently, many companies have been researching new stent designs in response to concerns about thrombosis caused by the long-term implantation of second-generation DESs. In January 2011, Abbott announced the European approval of ABSORB, the world's first bioresorbable vascular stent (BDES) for coronary artery disease. Absorb™ was approved by the FDA in 2016 but was later removed from the global market. Nevertheless, there has been continual development in this market, with several new innovations awaiting approval or in clinical trials. The BDES consists of the combination poly-D, L-lactide (PDLLA), more commonly known as PLLA, with everolimus or novolimus. The most widely commercially used BDESs are the ABSORB stent and the DESolve stent, which are a combination of a dimeric shape of PLLA and everolimus (ABSORB) or novolimus (DESolve). Recently, another BDES, magnesium-based scaffolds (DREAMS 2G), functioning as degradable metals, was approved for clinical use. The only commercially available DREAMS 2G BDES consists of a magnesium alloy with a sirolimus-loaded PLA coating, approximately 95% of which resorbs within one year of implantation. During the year of bio-

reabsorption, the magnesium compound degrades. The last stage of the transformation is amorphous calcium phosphate, which remains within the tissue. Haude et al. [31], in a randomized clinical trial, showed that the DREAMS 2G BDES demonstrated similar results to the use of other commercially available polymeric bioresorbable vascular scaffolds, but tailored studies with direct comparisons are awaited.

Reabsorption time varies between 1 (DESolve) and 3 (Absorb) years, but after the external material is reabsorbed, the coronary artery does not contain persistent structures, which can be daunting if subsequent coronary surgery is required. In fact, the surgeon performing the CABG surgery can intervene on small vessels that are free from the free presence of the metal component of the stent because the BDES is completely degrading. Hence, surgeons can operate more comfortably and can alleviate many of the negative effects seen with metal–polymer coatings. Another concern is related to the fact that the stents are often inserted in the part of the coronary artery that has the best caliber, thus forcing the surgeon to perform the bypass in the most distal part of the vessel that has a smaller caliber.

From a pathophysiological point of view, Serruys et al. [32] noted that the use of a BDES determines the return of the physiological function of the vessel. Non-degradable stents favor a permanent focal decrease in vascular compliance, leading to a mismatch of regional compliance which is a contributing factor to restenosis [33][34]. While awaiting the outcome of the ABSORB trial at 5 years, there has been a substantial body of circumstantial evidence to support the use of BDESs, which offer an additional benefit on restenosis of the stent, with a similar risk of death when compared to the second generation of DESs [32][35][36][37][38].

The randomized clinical trial ABSORB III, which enrolled 2084 patients, compared the use of the BDES Absorb (n = 1322) versus the everolimus-eluting Xience DES (n = 686) and was the pilot study. The results of the ABSORB trials showed good performance compared to everolimus DESs. However, slightly poorer outcomes impairing any long-term benefits were recognized.

As for bioresorbable stents, their expected benefits would be noted when the stent dissolves, generally after three years [39]. However, these benefits were not shown in the ABSORB III trial, and the device carried several disadvantages, including demonstrable poorer outcomes compared to DESs [39] in terms of target lesion failure. In addition, the results showed that stent thrombosis of the target lesion and MI were higher with this device [39][40].

These results were confirmed in a recent meta-analysis involving 3384 patients. In a 5-year follow-up period, patients who received BVSs compared to those who underwent the use of EESs were associated with higher rates of target lesion failure (TLF) (14.9% vs. 11.6%; HR, 1.26; 95% CI, 1.03–1.54; p = 0.03) and device thrombosis (2.5% vs. 0.8%; HR, 2.87; 95% CI, 1.46–5.65; p = 0.002). Target lesion failure occurred in 11.6% of BDES patients vs. 7.9% of EES patients who received an EES between 0 and 3 years (HR, 1.42; 95% CI, 1.12–1.80), and 4.3% of BDES-treated patients vs. 4.5% of EES-treated patients between 3 and 5 years (HR, 0.92; 95% CI, 0.64–1.31) (p for interaction = 0.046). Device thrombosis was observed in 2.4% of recipients of a BDES vs. 0.6% of patients who had EESs between 0 and 3 years (HR, 3.86; 95% CI, 1.75–8.50) and 0.1% of BDES-treated patients vs. 0.3% of patients who underwent the procedure with the use of EESs between 3 and 5 years (HR, 0.44;

95% CI, 0.07–2.70) (p = 0.03) [40]. The major concern with Absorb/BDES is that the risk/benefit ratio is optimal at 3 years, with an increased risk of complications after this period.

Further investigations are required to clarify the concerns related to very late scaffold thrombosis that may occur at advanced stages of scaffold resorption. Potential mechanisms specific for very late scaffold thrombosis include scaffold discontinuity and restenosis during the resorption process, which may be delayed in humans; this suggests an extended period of vulnerability for thrombotic events [41][42]. Although the remodeling capacity of the endothelium of vessel walls using two types of resorbable material is enhanced, BVSs demonstrate very intense cell proliferative activity both at the level of CD31 cells that differentiate towards endothelial-like morphology and towards cells that produce fibronectin with the use of a BVS [23][43][44]. The BVS showed higher production of new extracellular matrix that was mainly characterized by a higher content of elastin fibers in the vessel wall and a more compact organization of collagen fibers in the elastic zone of the vessel [23][43][44]. Interestingly, we demonstrated overexpression of the metalloprotease MMP-9, which indicates an ongoing matrix remodeling process [45][43][44]. In parallel, cell proliferation was found to be increased in recipients of BVS as testified by the significantly higher percentage of ki67-positive cells (26.89% 68.4% in BVS vs. 51.55% 69.7% in non-BVS $p < 0.05$). These findings were coupled with a significant reduction in apoptosis in BVS recipients, supporting the idea of an active remodeling process in these recipients (47.8% +/− 7.2% in non-BVS vs. 17.5% +/− 5.1% in BVS, $p < 0.05$) [46][47].

A recent paper compared polymer-free vs. polymer-coated DESs in a meta-analysis of 16 RCTs [48]. After a median follow up of 2 years, polymer-free DESs might be associated to reduced mortality compared to polymer-coated DESs (HR 0.82, 95% CI 0.68–0.99, p = 0.03), but no differences were observed in other significant endpoints (major ischemic events, cardiovascular death, myocardial infarction, or TLR). However, the authors point out that particular categories of risk (increased risk of bleeding events or recent MI) should be adequately investigated in future clinical trials and in future stent design [48].

Considering secondary evidence about the comparison between a drug-coated balloon and a DES, two recent meta-analyses focused on small coronary arteries [49] and large vessels [50]. In patients with narrowed arteries [49], balloons reduced the risk of coronary thrombosis (OR 0.12; 95% CI 0.01–0.94; p = 0.04) at the expense of a poorer angiographic result in terms of luminal diameter and percentage diameter stenosis, while TVR and restenosis rates were comparable. In patients with large vessels [50], the balloons seem non-inferior to DESs after 6–9 months after PCI, with no differences in late lumen loss (SMD, −0.07; p = 0.548) and TLR (RR, 1.17; p = 0.746). Those results highlight the impact of the diameter of native coronary arteries in the results of percutaneous procedures and might suggest a tailored approach for current clinical use and future studies.

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