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Biodegradable Polymers and Stents: the Next Generation?

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Abstract

Purpose of Review Stent design continues to evolve with newer generation of stents aimed at improving clinical outcomes. This review compares different generations of stents with a focus on biodegradable polymers and stents and their potential benefits.

Recent Findings Drug-eluting stents (DES) reduce stent thrombosis when compared with bare-metal stents (BMS). However, they are associated with impaired vascular healing/endothelialization and excess very long-term events (beyond 1 year). Much of these events (beyond 1 year) have been attributed to continued inflammation due to the polymer. Biodegradable-polymer drug-eluting stents (BP DES) were designed to overcome this polymer related limitation of first-generation DP DES by combining the benefits of reduced in-stent restenosis seen with DES and the benefits of reduced very-late stent thrombosis and myocardial infarction due to absence of polymer with bare-metal stents (BMS). Earlier generation of BP DES showed superiority over first-generation DP DES but at best non-inferior to second-generation DP DES for clinical outcomes; however, the newer-generation BP DES with ultrathin struts show promise in further reducing clinical outcomes when compared with second-generation DP DES. Whether this is due to the biodegradable polymer or the ultrathin struts continues to be debated.

Summary Biodegradable polymer stents in conjunction with ultrathin struts have shown promise as the next generation of DES; however, additional studies and long-term follow-up are needed to confirm these effects.

Keywords Biodegradable polymer stent · Ultrathin struts · Restenosis

Introduction

As the incidence of ischemic heart disease continues to rise over the past several decades and remains the leading cause of death worldwide [1], percutaneous coronary intervention (PCI) and stent design have evolved to face this global epidemic. Through the years, from Gruentzig's first balloon percutaneous transluminal coronary angioplasty (PTCA) to the development of contemporary coronary stents, the aim to optimally recanalize obstructive atherosclerotic plaque with the intention to not only improve symptoms of angina and quality of life (in those with stable ischemic heart disease) but also reduce hard clinical endpoints of myocardial infarction and death (in those presenting with acute coronary syndromes) remains the ultimate goal. Through the years, stent design has evolved to meet these demands. This review will aim at describing contemporary stent design and technologies with a particular focus on biodegradable polymer (BP) stents.

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Evolution of Stent Technology

Over the past three decades, limitations of existing percutaneous coronary intervention (PCI) technique have led to innovation and design changes with the ultimate intent of improving patient-related outcomes (Figs. 1 and 2). Bare-metal stents (BMS) were first introduced in the late 1980s as a response to limitations of plain old balloon angioplasty (POBA) namely acute recoil, dissections, and need for repeat PTCA [2, 3]. However, with long-term follow-up, rates of restenosis reached up to 15–30%. Etiology of restenosis was shown to revolve around the development of neointimal hyperplasia from vessel inflammation and smooth muscle proliferation. This led to the idea of applying anti-proliferative drugs to

Fig. 1 Progress in PCI from POBA to DES

stents to prevent restenosis creating the first-generation drug-eluting stents (DES). To aid in the slow and controlled release of the antiproliferative drug, the drug was coated on a durable polymer (DP) which released the drug over a 3–4-month period. These stents led to a significant reduction in restenosis when compared with BMS [4, 5]. However, with long-term follow-up, the first-generation DP DES were found to have an increased risk of very-late stent thrombosis and late-acquired stent malapposition, attributed to delayed vascular healing and endothelialization, with the polymer coating implicated for continued inflammation and hypersensitivity reaction [6, 7]. Furthermore, the thick struts in the first-generation DP DES led to greater recirculation and stagnation of blood that resulted in increased stent thrombosis [8]. The solutions to these problems proceeded in three general directions: (1) improvement in biocompatibility and coating technology of durable polymers leading to second-generation DP DES; (2) development of biodegradable polymer (BP) DES where the polymer bioabsorbs after drug elution leaving behind a bare metal or a "bare metal–like" stent with the objective of avoiding late issues resulting from the durable polymer; and (3) development of polymer-free DES where the drug is released without a polymer leaving behind a BMS after drug elution. Moreover, there was parallel refinement in strut thickness leading to thin-strut DES (Fig. 2). The objective of these newer-generation DES is to promote vascular healing thereby reducing the risk of early and late stent-related events.

Thin-Strut Second-generation DP DES

The use of metals such as cobalt chromium and platinum chromium allowed for thinner struts while maintaining adequate radial strength and radio-opacity (Table 1). Ex vivo flow loop models have shown that thinner struts have lower recirculation and stagnation of blood pool when compared with otherwise identical thick-strut stent thereby promising to be an important development to reduce the risk of stent thrombosis. Moreover, the use of biocompatible polymer and improvement in coating technology with more uniform coating, less webbing, and bonding of polymer surface, and less propensity for polymer delamination led to less surface irregularities on the stent, with lower inflammation and therefore faster endothelialization. As such, a second-generation DP DES on this platform of a thin strut with a biocompatible polymer has the potential to further improve patient outcomes. In fact, data from the last decade shows a clear improvement in outcomes with a further reduction in restenosis, reduction in stent thrombosis, and reduction in death and MI when compared with 1st-generation DP DES [9]. Furthermore, the complication of very-late ST seen with first-generation DES was reduced by up to 59% with the 2nd-generation DES in 4-year follow-up [10]. Thus, second-generation DP DES became the stent of choice for PCI and became the benchmark for both efficacy and safety. However, despite the significant improvements in outcomes, late events accrue even after second-generation DP DES [11•], emphasizing the further need to refine stent design.

Biodegradable Polymer DES

BP DES were designed using a framework from a decade ago that the most efficacious stents (at preventing restenosis) were DES whereas the best benchmark for safety (reduced MI, stent thrombosis, or death) was BMS. BP DES were considered the

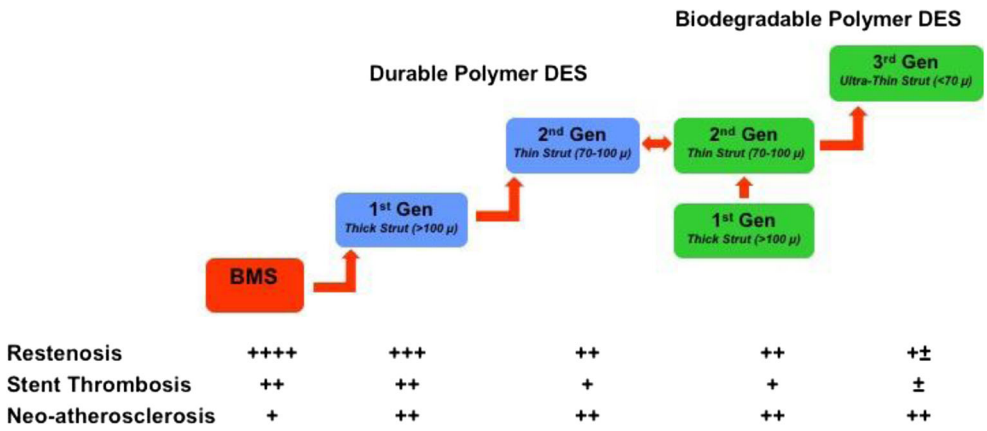

Fig. 2 Stent design progression and effects on clinical outcomes

Table 1 FDA-approved drug-eluting stents; *DES*, drug-eluting stent; *BMS*, bare-metal stent; *DP DES*, durable-polymer drug-eluting stent; *BP DES*, biodegradable-polymer drug-eluting stent; *CoCr*, cobalt-chromium; *Pl-Cr*, platinum-chromium; *PBMA*, polyn-butyl methacrylate; *PDLLA*, poly(D,L)-lactic acid; *PEVA*, polyethylene-co-vinyl acetate; *PlCr*, platinum-chromium; *PLGA*, poly(D,L-lactide-co-glycolide); *PLLA*, poly-L-lactic acid; *PVDF-HFP*, poly(vinylidene fluoride-co-hexafluoropropylene); *SIBS*, poly(styrene-block-isobutylene-block-styrene); *PC*, phophorylcholine

Stent	DES generation	BMS material	Drug eluted	Polymer	Polymer thickness (μm)	Strut thickness (μm)
Cypher	1st-gen DP DES	316 L SS	Sirolimus	Parylene, PEVA. PBMA	13.0	140
Taxus	1st-gen OP-DES	326 L SS	Paclitaxel	SIBS	22.0	132
Endeavor	2nd-gen OP-DES	CoCr	Zotarolimus	PC	5.3	91
Resolute	2nd-gen DP DES	CoCr	Zotarolimus	BioLinks	5.6	91
Xience	2nd-Gen DP DES	CoCr	Everolimus	PBMA, PVDF-HFP	7.6	81
Promus	2nd-gen DP DES	CoCr	Everolimus	PBMA, PVDF-HFP	7.6	81
EluNir	2nd-gen DP DES	CoCr	Ridatorolimus	CarboSil, PBMA	7.0	72
Synergy	2nd-gen BP DES	PICr	Everolimus	PULA	4.0	74
Orsiro	3rd-gen BP DES	CoCr	Sirolimus	PDLLA	7.0	60

best of both worlds being a DES early on (during drug elution) and being converted to a BMS after the polymer bioabsorbs, potentially affording long-term safety. A series of randomized trials proved the improved efficacy and safety of BP DES when compared with first-generation DP DES. The stents were considered the next paradigm shift in DES technology [12]. Many trials, which were designed to assess short-term outcomes, left with a promissory note of continued longer-term benefit after the polymer bioabsorbs. On this note, it is important to recognize that not all bioabsorbable polymers are created the same. Some polymers bioabsorb within months, others within a few months to few years, and yet, others much longer and take a few years for full bioabsorption. Moreover, not all BP DES convert to a BMS. Some stents are left with a passive polymer coating and thus become a "BMS-like stent" after active polymer coating bioresorption. In addition, the early BP DES were on a thicker-strut platform (1st-generation BP DES), the others are on a thinner-strut platform (2nd-generation BP DES), and more recently, BP DES are on an ultra-thin platform (3rd-generation BP DES).

First-generation BP DES (Strut Thickness > 100 μm)

First-generation BP DES included stents such as the Nobori (125 μm) and the BioMatrix (120 μm) stents. There are currently no FDA-approved first-generation BP DES, although these stents are used outside the USA. The NOBORI 1 trial compared the Nobori stent with first-generation DP DES (Cypher) in 243 patients showing superiority in terms of in-stent late loss and binary restenosis [13]. Major adverse cardiac events (MACE) were also lower with the first-generation BP DES compared with the first-generation DP DES (4.6% vs 5.6%); however, the trial was not powered to detect statistical significance for MACE. However, longer-term follow-up with the SORT OUT V trial comparing the Nobori stent with the Cypher stent up to 1 year showed no difference in the primary composite outcome of cardiac death, myocardial infarction, definite stent thrombosis, and target vessel revascularization. Additionally, there was a statistically significant increase in definite stent thrombosis with the Nobori stent compared with the Cypher stent (0.7% vs 0.2%) [14]. The LEADERS trial was another trial that compared a first-generation BP DES (BioMatrix) with a first-generation DP DES (Cypher). At 5-year follow-up, the BioMatrix stent was non-inferior to Cypher stent with regard to the primary composite endpoint of cardiac death, MI, or clinically indicated TVR. When looking at the patient-oriented composite endpoint of all-cause death, MI, and all-cause revascularization, the BioMatrix stent was found to be superior at 5-year follow-up, with 16% decrease in this patient-oriented composite outcome. Furthermore, there was a significant reduction in very-late definite ST over the 5-year follow-up with a reduction in ST-associated clinical events [15].

When these first-generation BP DES were compared with the second-generation DP DES (Xience) in the COMPARE II trial, the Nobori stent showed non-inferiority with regard to the primary composite safety and efficacy endpoint (5.2% vs 4.8%) [16]. Despite non-inferiority, these stents still had concerns for stent thrombosis, likely related to their greater strut thickness.

Second-generation BP DES (Strut Thickness > 70 to < 100 μm)

Second-generation BP DES include stents such as the Synergy stent (74 μm) which is the first FDA-approved BP DES used in the USA. This stent is a thin-strut platinum-chromium metal alloy platform with a bioresorbable polymer that fully absorbs early after everolimus-drug elution (around 3–4 months). The EVOLVE II trial compared the Synergy stent with a second-generation DP DES (Promus Element Plus). At 1-year follow-up, the Synergy stent was found to be non-inferior to Promus Element Plus with regard to the composite primary endpoint of target lesion failure, target vessel MI, or cardiac death with clinical outcomes of cardiac death, MI, and revascularization similar in both arms [17].

Many other second-generation BP DES are in use outside of the USA. The ISAR TEST 4 trial compared a second-generation BP DES (Yukon PC) with a first-generation DP DES (Cypher) and a second-generation DP DES (Xience) [11•]. At 10-year follow-up, second-generation BP DES was superior to first-generation DP DES with regard to the primary outcome of MACE (18% reduction), all-cause death, and definite stent thrombosis. However, when the second-generation BP DES was compared with second-generation DP DES, there was no difference in MACE, all-cause death, MI, TLR, and definite stent thrombosis, overall, showing non-inferiority.

Third-generation BP DES (Strut Thickness < 70 μm)

Third-generation BP DES include BP DES on an ultrathin-strut platform. Recently, the Orsiro stent (60 μm) received FDA approval. The BIOFLOW-V study compared ultrathin third-generation BP DES (Orsiro) with second-generation DP DES (Xience), showing that target lesion failure was significantly reduced at 2-year follow-up with BP DES compared with DP DES (7.5% vs 11.9%), driven by the reduction in target vessel MI and ischemia-driven TLR. Rates of cardiac death or MI were also statistically significantly reduced with third-generation BP DES [18••]. Furthermore, in the ACS subgroup of the BIOFLOW V study, Orsiro significantly lowered rates of target lesion failure (5.6% vs 11%) at 12-month follow-up, driven mainly by both significantly lower periprocedural MI and spontaneous MI [19]. A meta-analysis of 10 randomized-control trials of almost 12,000 patients comparing second-generation DP DES to third-generation ultrathin BP DES showed that ultrathin BP DES were associated with a 16% reduction in target lesion failure driven mainly by lower rates of MI (20%) and a trend towards lower rates of stent thrombosis compared with second-generation DP DES after 1-year follow-up [20••]. These outcomes occurred before the biodegradable polymer degrades, suggesting that these superior findings are related to strut size as opposed to the biodegradable polymer.

Conclusion

Stent design has continued to evolve with changes in polymer design, biocompatibility, and strut thickness. However, despite these advances in stent design, there continues to be continued accrual of MACE (even though the event rates are low) with long-term follow-up even with the widely used second-generation DP DES [11•] (Fig. 3). These events were ascribed to the pro-inflammatory polymer that led to long-term inflammation. To overcome this, biodegradable polymers were designed and, based on the several of the trials described above, have been superior compared with first-generation DP DES and non-inferior to second-generation DP DES. Concomitant reduction in strut thickness with biodegradable polymers has shown promising results, with further improvement in outcomes with ultrathin BP DES. Whether thinner struts that enhance faster endothelialization and vascular healing in addition to lowering the risk of uncovered struts and malapposition [21]

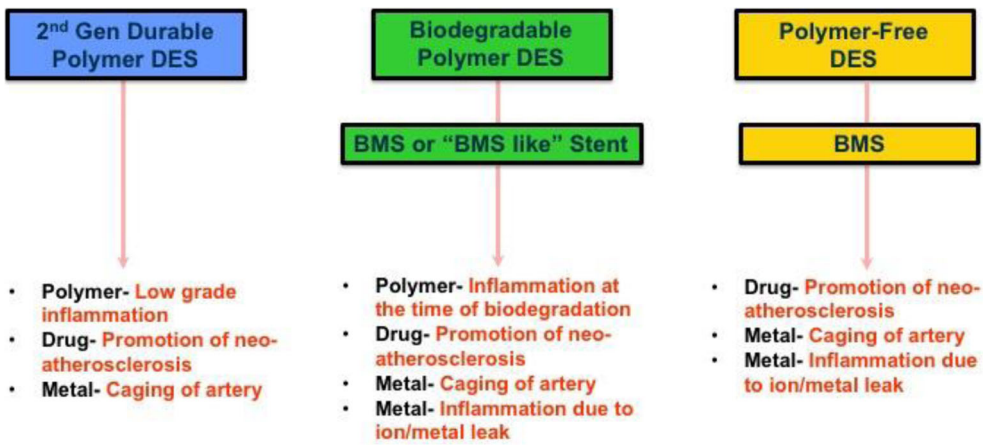

Fig. 3 Persistent problems with contemporary stents

lead to improved clinical outcomes or if biodegradable polymers that decrease long-term inflammation and development of neotherosclerosis remains up for debate. Given the many permutations of polymer composition, strut thickness, stent configuration, and biodegradability, directly isolating and comparing these various stent characteristics to ascertain which elements garner superiority remains a challenge.

In summary, stent design has radically evolved over time. Each iteration of stent design continues to improve upon prior versions. Biodegradable polymers in conjunction with ultrathin struts have shown promise as the next generation of DES; however, additional studies and long-term follow-up are needed to confirm these findings.

Compliance with Ethical Standards

Conflict of Interest Dr. Rebagay: None; Dr. Bangalore: Advisory board/Honoraria: Abbott Vascular, Biotronix, Amgen, Pfizer, AstraZeneca, Menarini, Reata; Research grants: Abbott Vascular, NHLBI.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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