Although coronary artery disease (CAD) mortality rates have declined, CAD remains the leading cause of death worldwide, contributing to over 7.2 million deaths annually (1). Percutaneous coronary intervention (PCI) has made significant progress in the management of obstructive CAD over the past three decades. Since the introduction of percutaneous balloon angioplasty by Gruntzig in 1977, PCI techniques have evolved dramatically. In 1986, Puel and Sigwart deployed the first coronary stent to act as a scaffold, thus preventing vessel closure during PCI, and reducing the incidence of restenosis, which was occurring in up to 40% of cases (2). Bare metal stents (BMS), however, were still associated with intra-stent restenosis rates of 20-30% requiring re-intervention (3). Such restenosis occurred as a result of neointimal hyperplasia within the stent, caused by the migration and proliferation of vascular smooth muscle cells. In 2002, drug-eluting stents (DES), which inhibit the development of neointimal hyperplasia by releasing anti-proliferative and anti-inflammatory drugs directly into the vessel wall, were introduced as a strategy to minimize restenosis and hence the necessity for re-intervention.

Initial animal studies (3) demonstrated a definite benefit of DES over BMS (4-6% restenosis rate versus 20-30%), and a meta-analysis of early randomized trials suggested the use of DES conveyed a 74% reduction in the risk of target lesion revascularization (TLR) at 1 year after stent implantation, when compared to the use of BMS (4).

Despite the initial enthusiasm generated by DES, incomplete endothelialization and stent thrombosis continued to plague these devices. Animal studies demonstrated complete endothelialization with BMS at 28 days, whereas DES uniformly showed incomplete healing at 180 days (5). It was therefore recommended that patients with DES receive dual anti-platelet therapy with aspirin and clopidogrel for at least 6 months, followed by life-long aspirin therapy, depending on the stent type placed and the pre-existing comorbidities which may further increase the risk of stent thrombosis (6). Despite this regimen, late stent thrombosis (LST), defined as stent thrombosis occurring >30 days post-stent implantation, remained a significant complication in patients with DES. The potentially catastrophic clinical consequences of stent thrombosis, i.e., myocardial infarction and death, subsequently focused stent research and development on enhanced safety and efficacy by optimally combining stent platform, drug and drug release kinetics.

Important developments in stent platform, including design, structure and composition, resulted in significant technical advances and clinical benefits. For many years, stents utilized 316L stainless steel (SS), owing to its excellent combination of mechanical properties, corrosion resistance and biocompatibility. A reduction of strut thickness (to approximately 130 µm) further improved the flexibility and trackability, however, at a cost of reduced stent visibility. This loss in radiopacity was addressed by developing newer alloys, balancing ideal mechanical properties with stent radiopacity. Cobalt chrome and platinum chrome represented appealing alloy compounds given their known biocompatibility, chemical stability, corrosion resistance and strength. These alloys provide improved radial strength and increased radiopacity, as compared with SS, allowing for engineering of thinner struts (80-90 µm) with greater deliverability. Platforms made with thinner struts result in less arterial injury and reduce further the risk of restenosis (7) whilst exhibiting lower thrombogenicity (8). The ideal stent platform therefore comprises a highly deliverable, thin-strut, low-profile flexible design with high radiopacity, high radial strength and minimal recoil (9).

Anti-proliferative agents that are used for the platforms of drug-eluting stents are highly lipophilic molecules...
that are distributed into the arterial wall and exert either immunosuppressive effects or anti-proliferative effects on smooth muscle cells, thereby inhibiting neointimal hyperplasia. First generation DES used sirolimus or paclitaxel as anti-proliferative agents. Both sirolimus- and paclitaxel-eluting stents significantly reduced the rate of repeat revascularization as compared with BMS, however several studies reported an increased risk of late and very late stent thrombosis with these DES (10). In an effort to overcome these important clinical complications and to enhance the safety and efficacy of DES, newer generation stents eluting almost invariably limus analogues were developed. In large randomized trials these everolimus-, zotarolimus- and biolimus-eluting stents showed improved clinical outcomes as compared to first generation DES, in respect to the risk for death, MI or repeat revascularization, and/or with regards to stent thrombosis (11-17).

Polymer coatings that are applied to the stent surface serve as drug carriers and permit controlled drug release. Progress in polymer technology has been aimed at decreasing local inflammatory reactions and thrombosis by improving the biocompatibility of polymers. The types, compositions and designs of the polymers coated on the stent dictate the kinetics of drug-release over a period of weeks to months following implantation. However, hypersensitivity reactions to polymer carriers can produce various kinds of inflammation, which can induce a delay and sometimes a failure of stent strut re-endothelization that may contribute to an increased risk of late and very late stent thrombosis, when compared to BMS (18).

As a consequence, research targeted the development of biodegradable polymer coatings that offer the attractive prospect of controlled drug-release without the potential for late polymer-associated adverse effects. Although there have been conflicting results (19-21), recent pooled analyses suggest a significant reduction of thrombosis risk at 4 years post stent implantation (22) and a significant reduction in TLR (23) in patients treated with biodegradable polymer DES. Another novel approach to remove the limitations associated with permanent polymers is the development of polymer free DES, such as the Cre8 polymer-free DES (CID, Saluggia, Italy) which employs an abluminal reservoir technology with specially formulated sirolimus loaded into the reservoirs. The results of early preclinical and clinical trials of the Cre8 are promising although results from larger clinical trials are awaited (24). The development of the polymer-free drug-filled stent (Medtronic, Minneapolis, US; data on file) is another alternative technology currently under investigation in early clinical trials.

The next milestone in coronary intervention appears to be the development of fully bioabsorbable vascular scaffolds (BVS), which could provide an alternative treatment modality to metallic stents. Recent evidence suggests that the current metallic coronary stents may alter flow dynamics, abolish vascular reactivity and limit the potential for maximal vasodilation (25). Furthermore, data suggests that coronary stenting results in persistent inflammation and abnormalities of endothelial function, which may have deleterious effects (26). The concept of a bioabsorbable scaffold is to provide equivalent performance to existing metallic DES but deliver complete reabsorption of the scaffold within 6 to 12 months, facilitating complete vessel healing with restoration of normal vascular function. An additional benefit of BVS is that future percutaneous and surgical revascularization strategies can be performed without the hindrance of previous permanent metal prostheses.

Although the concept of bioabsorbable scaffolds has created interest for over 20 years, there are challenges in making a scaffold that has sufficient radial strength for an appropriate duration, that does not have unduly thick struts, that can be a drug delivery vehicle, and where degradation does not generate an unacceptable inflammatory response (27). Currently over 16 different scaffolds are being developed and investigated by device manufacturers. Four materials are presently used in BVS, of which lactide polymers, particularly poly-levo-lactic acid (PLLA), form the basis of several devices and are the most extensively investigated. Other materials include magnesium, polyanhydrides and polycarbonates. The most widely investigated is the Absorb everolimus-eluting bioresorbable vascular scaffold (Absorb BVS, Abbott Vascular, Santa Clara, California). It is the first bioabsorbable scaffold, with a strut thickness of 150 µm, to have clinical and imaging outcomes similar to those following DES implantation for 2 years but with the potential advantage of full-stent absorption (28). Following several design modification as a result of the ABSORB cohort A Trial, the second generation Absorb BVS was investigated in the ABSORB Cohort B clinical trial which reported excellent clinical results up to 2-year follow-up (29). The Absorb BVS obtained CE mark and became commercially available in Europe in early 2012. The Absorb BVS is currently under investigation in the ABSORB II trial, a randomized controlled trial to compare the safety, efficacy and performance of the device with the Everolimus-eluting Xience V (Abbott Vascular, Santa Clara, California), a conventional new generation metallic DES, in the treatment of de novo native coronary artery lesion.

There remain significant challenges of fine tuning these bioabsorbable scaffolds to match the initial performance and handling characteristics of conventional metallic stents, with scaffold deliverability in tortuous and calcified vessels potentially presenting a major concern. Furthermore, it remains to be demonstrated whether bioabsorbable scaffolds can truly restore vascular integrity and function and the results of ongoing trials are eagerly awaited.

In summary, the treatment of obstructive CAD using minimally invasive PCI has evolved dramatically in the last
30 years. However, the enthusiasm for each advance has been fraught with unforeseen complications. Drug-eluting stents mitigate the risk of stent restenosis and thus represent an important advance in the percutaneous treatment of CAD. New generation DES with thin struts releasing limus-family analogues from durable polymers have further improved clinical outcomes and patient safety. The next major advance in the evolving field of PCI may be the incorporation of biodegradable polymer stents and fully bioresorbable vascular scaffolds into routine clinical practice, although their efficacy, safety and ultimately their place in therapy remain to be determined.

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**References**


