REVIEW

The benefits of drug-eluting stents in the treatment of coronary artery disease

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Abstract: The advent of coronary stents has been a landmark development in the treatment of coronary artery disease with percutaneous coronary intervention. Initial percutaneous treatment using balloon angioplasty alone had limited clinical efficacy due to immediate vascular elastic recoil and dissection, in addition to late negative vascular remodeling and neointimal hyperplasia. With the introduction of coronary stents, initially bare-metal stents (BMS), the problems of dissection and negative remodeling due to injury in addition to vascular elastic recoil were eliminated; however, neointimal hyperplasia remained an ongoing obstacle in the long-term efficacy of stents. Neointimal hyperplasia resulted in in-stent restenosis in 20%–30% of cases after intervention with BMS, which led to high rates of target lesion revascularization. Subsequently, drug-eluting stents (DES) were introduced, which had the added advantage of releasing an anti-proliferative drug from the stent to reduce the neointimal proliferation, thus resulting in the reduction of the rates of in-stent restenosis. Although the first-generation DES had significantly improved outcomes over its predecessor, the BMS, several challenges including stent thrombosis and delayed endothelialization of the stent remained. The second-generation DES have been significantly improved over their first-generation predecessors in regard to efficacy and safety, ie, improved long-term outcomes and significant reductions in stent thrombosis. The duration of dual antiplatelet therapy after DES has also been studied extensively in multiple large trials. A newer generation of stents, including those with bioresorbable polymers, polymer-free, and fully bioresorbable scaffolds is still in the early stages of development. Lastly, the ongoing heated comparison in multiple trials regarding the use of coronary stents vs coronary artery bypass surgery for the treatment of complex/multi-vessel coronary disease continues to evolve.

Keywords: bare-metal stent, everolimus, zotarolimus, sirolimus, paclitaxel, percutaneous coronary intervention

The beginning of percutaneous coronary intervention – conventional balloon angioplasty

Percutaneous coronary intervention (PCI) has evolved tremendously since the first balloon coronary angioplasty was performed by Andreas Gruentzig in 1979.[1] The introduction of balloon coronary angioplasty, also known as percutaneous transluminal coronary angioplasty, which subsequently has also been called 'plain old balloon angioplasty'(POBA), provided a historical breakthrough medical concept of using a non-surgical percutaneous form of revascularization as an alternative strategy to coronary artery bypass graft (CABG)[1] surgery. However, the immediate complications including acute vessel recoil and vascular dissection, in addition to long-term effects such as negative remodeling and intimal hyperplasia due to focal vascular injury, compromised its efficacy and

safety. Angiographically significant restenosis occurred in approximately 40% of patients at 6 months, of whom, 50%–75% had recurrent ischemic symptoms.[2] Therefore, approximately 20%–30% of patients appropriately required repeat revascularization of the index lesion within the first year after balloon angioplasty. Recurrent ischemic symptoms after 1 year were mostly due to new or progressive lesions.[2–4] The pathophysiology of restenosis after balloon angioplasty was due to a combination of the following factors including: a) acute arterial recoil, b) coronary dissection, c) negative remodeling, and d) neointimal hyperplasia. Negative remodeling occurs gradually at the injured segment due to the contraction of the arterial wall during the healing process and is also related to the interaction of the endothelium with the blood flow. Neointimal hyperplasia occurs within weeks to months and is the proliferation and migration of smooth muscle cells (SMCs) from the tunica media into the tunica intima resulting in the encroachment onto the vascular lumen.[5–8] The first three processes and/or their sequelae were essentially completely controlled with the subsequent advent and use of bare-metal stents (BMS). However, the fourth factor, neointimal hyperplasia, continued to be a major challenge in the BMS era.[9] Although neointimal hyperplasia is a major mechanism for restenosis after balloon angioplasty, it is the only mechanism for in-stent restenosis (ISR), excluding under-expansion of the stent. The pathophysiology of neointimal hyperplasia is therefore, very important and will be comprehensively discussed in the section of BMS.

BMS as the next major evolutional technology in percutaneous intervention

BMS was the first device used for coronary stenting and it was specifically developed to prevent acute artery closure due to vascular recoil or dissection following POBA. Subsequently, acute closure was reduced from 2% to 10% with POBA alone down to <1% in the stent era and has resulted in a lower rate of peri-procedural myocardial infarction (MI). Further refinement of the BMS design, implantation techniques, and improved operator experience resulted in the rates of target lesion revascularization (TLR) being reduced to approximately 20% at 1 year after BMS implantation.[10–12] The etiology of the relatively high rates of TLR was secondary to ISR due to the exaggerated neointimal proliferation.[13]

Pathophysiology of neointimal proliferation – the major mechanism of ISR after stenting

The mechanisms of neointimal hyperplasia after balloon angioplasty have been well described in the literature.[13–15] The most commonly accepted model of neointimal hyperplasia is an adaptation of the "response-to-injury" model, which was initially described by Ross and Glomset in 1976. This model explains that the mechanical disruption of the endothelium by the PCI procedure is the initiating step in the neointimal hyperplasia mechanism.[16,17] The initial compromise of a denuded endothelium and injury to the tunica intima and possibly tunica media due to the acute mechanical trauma of the PCI causes an initial inflammatory response in the vascular wall leading to platelet adhesion, activation and aggregation, and subsequent fibrin deposition and thrombus formation within the stent (thrombotic phase: days 0–3). These microthrombi as well as the stretch injury of the vessel wall attract inflammatory cells such as macrophages and lymphocytes, which demarginate from the vascular space and also from the vasa vasorum (recruitment phase: days 3–8). Subsequently, these inflammatory cells stimulate the production of various local growth factors and cytokines, which activate the dormant G0 phase of the mitotic cycle of the SMCs in the intima media (Figure 1). This causes a subsequent remodeling process with significant inward migration of the SMCs to the interior of the implanted stent. Furthermore, the SMCs start to produce and deposit significant amounts of extracellular matrix (ECM) proteins, mostly proteoglycans,[18] which lead to progressive narrowing and development of obstruction of the vessel lumen inside the index stent placement (proliferative phase: day 8 to healing). The hygroscopic quality of the proteoglycan matrix, when hardened, is relatively rigid and only transiently compressible, and may explain the difficulty with recoil in the setting of balloon angioplasty of ISR lesions. The exaggerated re-endothelialization is thought to play a major role in neointimal proliferation, and studies have reported variable patterns after coronary stent implantation.[15,19,20] Furthermore, it is yet unclear whether the new endothelium that covers the stent struts is adequately functional or not.[21] However, given prior experiments performed in porcine animal models, it is fairly clear that the injury to the vascular wall caused by balloon-expandable stent implantation is greater and more sustained than that caused by POBA alone,[22,23] and therefore, stent deployment actually induces more neointimal tissue growth than POBA alone.[22,24–26] However, the magnitude of increase in lumen diameter made possible with a stent is greater than the increased neointimal growth.[22] Therefore, the net increase in lumen diameter with the use of a stent improves the clinical outcomes when compared to POBA alone.

As the setting of the main process leading to ISR occurs locally at the site of injury of the vessel, a stent-based drug delivery system that can deliver a high concentration of an
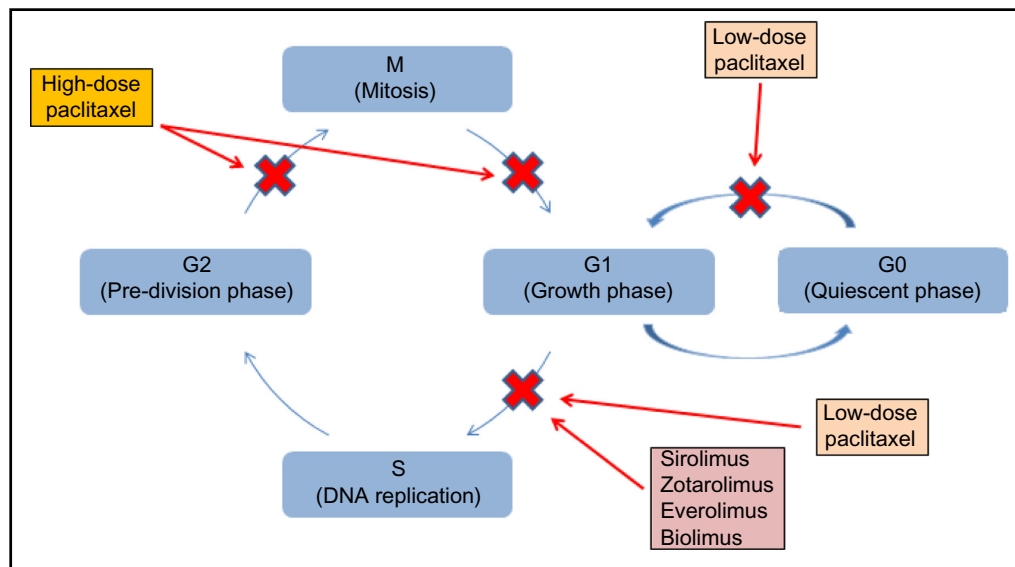
Figure 1 Endothelial cell cycle and inhibitory targets of anti-proliferative drugs.
Abbreviations: M, mitosis; G1, growth-1 phase; S, DNA synthesis phase; G2, growth-2 phase; G0, resting phase.

effective anti-proliferative agent locally to attenuate the neointimal proliferation process without any systemic toxicity, would be the most logical solution to address ISR.

Emergence of the first-generation drug-eluting stent devices as a breakthrough to minimize the restenosis
Drug-releasing mechanisms of DES

The stent-based delivery of the anti-proliferative drug consists of three components: a metallic scaffold backbone, a drug carrying polymer that harbors the drug and allows it to diffuse into the vascular tissue in a controlled manner, and an effective anti-proliferative drug that would reduce the neointimal growth after injury of the vessel wall during stent implantation. The stent design relative to the drug distribution to the vessel wall is also an important factor in the delivery of the drug from the drug-eluting stent (DES). Prior published studies have demonstrated that a symmetric expansion of the stents with homogeneous distribution of struts is important for optimal drug distribution.[27] Furthermore, a study with the use of intravascular ultrasound (IVUS) demonstrated that stents with non-uniform stent strut distributions led to greater gap distance between struts and therefore, resulted in more neointimal hyperplasia after sirolimus-eluting stent (SES) implantation.[28]

A large number of stent designs have been developed to date, although the most commonly used is the multi-cellular design. The multi-cellular design is categorized into "closed-cell" and "open-cell" configurations. The closed-cell stent is

designed to have uniform cell expansion and constant cell spacing when it is deployed in a curved coronary segment, which leads to a more uniform drug distribution. On the other hand, the open-cell stent is designed to have a larger surface coverage between the inner and outer curvatures in the curved coronary segments thus yielding improved conformability to curved surfaces at the expense of less uniform drug-release distribution. In summary, the optimal stent design for drug delivery includes a large stent surface coverage area, a small cell gap, and minimal strut deformation after deployment while maintaining high conformability, radial strength, and flexibility.

The pharmaceutical agent is usually bound to a matrix polymer, which functions as a drug reservoir to ensure that the drug is retained during the stent deployment process and subsequently controls the distribution of the drug. The type, composition, and design of the polymer coated on the stent frame dictate the drug-eluting kinetics of the DES. The release of the drug occurs in a sustained fashion over a period of weeks to months after implantation. The polymer coating can be categorized into organic vs inorganic, bioresorbable vs non-bioresorbable, synthetic vs naturally occurring substances. Usually a non-bioresorbable polymer coating is used in order to prevent triggering inflammatory processes. The most successfully tested DES have been coated with synthetic materials. The sirolimus stent has been coated with poly-*n*-butyl methacrylate and polyethylene-vinyl acetate. The paclitaxel stent was coated with a triblock polymer matrix (poly lactide-*co*-ε-capro-lactone copolymer) (Table 1). All naturally occurring organic materials are both bio- and hemo-compatible and most have been known to elicit inflammatory

responses in the vascular context, therefore have not been usually utilized as polymer material.

Therapeutic agents to limit neointimal growth

Many agents with anti-inflammatory and anti-proliferative properties have been tested as agents for DES. The general mechanism of action of most of the drugs tested is to stop the cell cycle progression of endothelial cells by inhibiting DNA synthesis[29] (Figure 1). Ultimately, the ideal drug to prevent restenosis exerts sufficient anti-proliferative effects while maintaining a wide enough therapeutic index at the site of implantation to allow eventual stent endothelialization and adequate vessel healing. In addition, it should have negligible or no systemic effects and also be compatible with the polymer and stent it is bonded with, in order to deliver an adequate dose uniformly to the target endothelium.[30–32] Currently, several anti-proliferative agents have been proven to be effective in preventing neointimal hyperplasia in human clinical trials (Table 1). Sirolimus (also called rapamycin), used in the SES system, is a fermentation product isolated from the bacterium, *Streptomyces hygroscopicus*. The drug is an immunosuppressant, which has been widely utilized for prevention of rejection solid organ transplantation.[33] It is a lipophilic molecule; therefore, it can readily diffuse across the cell membranes of vascular SMCs and leukocytes when released from the stent surface, and

ultimately blocks the cell cycle progression from G-1(growth) phase to S (DNA synthesis) phase of mitosis (Figure 1), and, thereby, limits SMC replication and proliferation.[34–36] The first experience with the SES was published in 2001 demonstrating promising results with significant reduction in neointimal proliferation,[37] which led to the development of the commercial Cypher stent.[38] Paclitaxel, used in the paclitaxel-eluting stent (PES) system, is an antineoplastic agent originally isolated in the 1960s from the bark of the Pacific Yew Tree, *Taxus brevifolia*, which is found in the northwestern areas of the USA and Canada. It was approved by the US Food and Drug Administration (FDA) in the 1990s as a therapeutic agent for solid tumor cancers such as breast and ovarian cancer.[39] It is also a lipophilic molecule, which can readily diffuse across cell membranes and has a potent stabilizing effect on microtubules by polymerizing the alpha units and subunits of tubulin and thereby enhancing microtubule assembly. This mechanism halts the progression of the cell cycle from growth-2 phase to G2 phase to M (mitosis) phase (Figure 1).[40,41]

Clinical efficacy of first-generation DES

DES were developed not only to act as vascular scaffolds in the diseased coronary artery but also to reduce the relatively high rates of ISR and subsequent TLR compared to its predecessor BMS, by becoming a drug delivery system. This led to the development of the modern day DES. Subsequent

Table I Drug-eluting coronary stents

Stent type	Brand name	Drug	Manufacturer	Scaffold material	Strut thickness (μm)	Polymer material	Polymer thickness (μm)	Drug elution kinetics
First-generation	Cypher	Sirolimus	Cordis/J&J	Stainless steel	140	PEVA, PBMA	12.6	80% within the first 4 weeks
	Taxus Express	Paclitaxel	Boston Scientific	Stainless steel	132	SIBBS	16	10% within the first 2 weeks
	Taxus Liberte	Paclitaxel	Boston Scientific	Stainless steel	97	SIBBS	14	10% within the first 2 weeks
	Taxus Ion	Paclitaxel	Boston Scientific	Platinum-chromium	97	SIBBS	16	10% within the first 2 weeks
Second-generation	Endeavor	Zotarolimus	Medtronic	Cobalt-chromium	91	MPC, LMA, HPMA, 3-MPMA	5.3	95% within the first 2 weeks
	Resolute	Zotarolimus	Medtronic	Cobalt-chromium	91	PBMA, PHMA, PVP, PVA (Biolynx)	5.6	85% within the first 8 weeks
	Xience (V, Prime, Xpedition, Alpine)	Everolimus	Abbott Vascular	Cobalt-chromium	81	PBMA, PVDF-HFP	7.6	80% within the first 4 weeks
	Promus	Everolimus	Boston Scientific	Cobalt-chromium	81	PBMA, PVDF-HFP	7.6	80% within the first 4 weeks
	Promus (Element, Premier)	Everolimus	Boston Scientific	Platinum-chromium	81	PBMA, PVDF-HFP	7.6	80% within the first 4 weeks

Abbreviations: PBMA, poly-*n*-butyl methacrylate; PEVA, poly-ethylene-*co*-vinyl acetate; SIBBS, styrene-*b*-isobutylene-*b*-styrene; MPC, methacryloyloxyethyl phosphorylcholine; LMA, lauryl methacrylate; HPMA, hydroxypropyl methacrylate; 3-MPMA, 3-trimethoxysilyl-propyl methacrylate; PHMA, poly-hexyl methacrylate; PVP, polyvinylpyrrolidone; PVA, polyvinyl acetate; PVDF-HFP, copolymer of vinylidene fluoride and hexafluoro-propylene.

clinical trials have confirmed a reduction of as much as 50%–70% in TLR by DES compared to BMS with levels of ISR markedly reduced to 5%–8% range with the early first-generation DES trials.[42,43]

In clinical trials, DES outperforms BMS with regard to the efficacy endpoint of the need for repeat revascularization. The studies do not demonstrate a difference in long-term mortality. The different types of stents are presented in a table format (Table 1). Restenosis and the need for TLR usually occur within the first year after stent placement. It is within the first year that DES are superior to BMS. Very-late ISR (after 1 year) has been documented with all types of coronary stents. The rate is approximately 1%–2% per year and is similar between first- and second-generation DES and BMS.[44–47]

Several landmark clinical trials demonstrated the efficacy of SES in the reduction of ISR compared to BMS. The RAVEL Trial[38] and the SIRIUS Trial[48,49] both demonstrated that the SES was significantly superior to BMS in reducing ISR and TLR. Furthermore, subsequent studies demonstrated that SES reduced ISR and TLR specifically in patients with diabetes and MI.[50,51] The long-term 5-year follow-up of the SIRIUS trial[44] demonstrated the sustained benefit of the SES over the BMS with target vessel revascularization (TVR) at 9.4% vs 24.2%, $P<0.001$, respectively. However, overall there were no significant reductions of the clinical endpoints of death or MI.

The PES was largely evaluated with the multiple TAXUS trials,[43,45,52–54] which demonstrated significant reductions of ISR and TVR in the PES vs BMS. Long-term 5-year data of the TAXUS-IV trial also confirmed the efficacy and safety of the PES over BMS, in non-complex lesions, with sustained long-term results, including improved TVR (16.9% vs 27.4%; $P<0.0001$), and improved major adverse cardiac events (MACE) (composite of cardiac death, myocardial infarction, or TLR) (24.0% vs 32.8%, $P=0.0001$) of PES vs BMS, respectively.[45] The TAXUS V and VI trials also demonstrated safety of the PES in high-risk, long and complex coronary lesions, confirming its safety and efficacy for real-world practice.[55,56]

After the establishment of the superiority of the first-generation DES over their BMS predecessors, preliminary head-to-head data published in 2005 demonstrated that SES may be superior to PES based on reductions in MACE, which were predominantly driven by decreases in TLR at a 9-month follow-up period.[57] On the other hand, late outcomes at 5-year follow-up demonstrated that SES and PES had similar outcomes in regards to cardiac events, MI, TLR, ISR profiles and

very-late stent thrombosis (ST) rates.[58] The largest and most comprehensive meta-analysis was published by Stettler et al[59] in 2007, which included 38 randomized trials and over 18,000 patients who had undergone PCI with a first-generation DES or BMS, excluding left main disease, chronic total occlusions, and bifurcation lesions. It demonstrated an overall reduction in TLR, increased late-ST (30 days to 1 year), and no difference in mortality at up to 4 years of follow-up in the first-generation DES vs BMS, respectively.

The shortcomings of first-generation DES: late and very-late ST as well as a late catch-up phenomenon

The initial reported randomized controlled trials of first-generation DES as described earlier did not result in any safety concerns;[42,43] however, later reports of four cases of angiographically confirmed late ST after SES and PES caused concerns about the possibility of late and very-late ST associated with first-generation DES.[60,61] Subsequently, a report which included pooled data from two high-volume European centers with a total N=8,146 patients demonstrated a cumulative incidence of definite and probable ST of 5.7% after 4 years without signs of a plateau and in a setting of a steady accrual of late definite ST at a rate of 0.44%–0.63% per year without plateau after 4 years of follow-up.[62] A later, very concerning, meta-analysis comparing first-generation DES vs BMS suggested a higher risk of death and MI with first-generation DES vs BMS.[63] Other reports from real-world studies demonstrated an elevated risk of very-late ST and MI in patients treated with first-generation DES after stopping dual antiplatelet therapy (DAPT).[62,64] Animal and human autopsy data indicated that the first-generation DES, when compared to BMS, significantly compromised the healing process of the injured arterial wall with evidence of chronic incomplete re-endothelialization and persistence of fibrin deposition, and therefore, concluded that this was the principal etiology of late and very-late ST.[65] Other meta-analyses demonstrated no significant differences in the risk of mortality or MI, but did show a significantly increased risk of very-late ST with both SES and PES compared to BMS.[66–69] These reports prompted cardiac societies and the FDA to recommend lengthening the guideline requirement of DAPT after DES from the previous 3–6 months (per study in the pivotal FDA approval trials of first-generation DES) to an arbitrary minimum of 1 year post-stent implantation.[64,70–73]

Furthermore, the SIRTAX-LATE trial[58] suggested that there may be a "catch-up" occurrence (late lumen loss) with both SES and PES after long-term follow-up. Among patients

undergoing paired angiography at 8 months and 5 years, delayed lumen loss amounted to 0.37±0.73 mm for SES and 0.29±0.59 mm for PES (P=0.32). The overall rate of definite ST was 4.6% for SES and 4.1% for PES (P=0.74), and very-late definite ST occurred at an annual rate of 0.65%. The ongoing increase in late lumen loss in addition to the continuous risk of very-late ST suggested that vascular healing remained incomplete at up to 5 years after implantation of a first-generation DES.

Second-generation DES as current standard therapy in PCI
Development of the second-generation DES

The ongoing safety concerns about late and very-late ST with first-generation DES[64] sparked the development of newer stents with more biocompatible polymers, advanced stent platforms, and use of different drugs, with the resultant development of second-generation DES. In the setting of incomplete re-endothelialization and persistent fibrin deposition being the major causes of late ST,[65] the objective was to develop a stent device that would promote early re-endothelialization.

Incomplete re-endothelialization can be secondary to two causes: 1) the anti-proliferative effects of the drug released from the polymer of the stent, which attenuates the endothelial healing response and 2) the intrinsic deficiency of the vascular endothelial progenitor cells, which is associated with poor outcomes.[74,75] It is important to note that BMS can achieve complete re-endothelialization by 6–7 months post-PCI, on the other hand, first-generation DES may not be fully re-endothelialized at up to 40 months post-PCI.[76] In addition, the polymer matrix itself has been shown to induce local inflammation, which leads to negative remodeling and compromised vascular healing and re-endothelialization.[76,77] The second-generation DES with their thinner and more biocompatible polymers (Table 1) have been shown to have reduced ST rates and better re-endothelialization than the first-generation DES.[78,79] Moreover, stent construction and design has also been shown to play an important role in the re-endothelialization of the stent struts as studies have demonstrated that thinner struts reduce the late-luminal loss.[80] Therefore, the second-generation DES are constructed with thinner stent struts (Table 1). In fact, optical coherence tomography studies of the second-generation stent – zotarolimus-eluting stent (ZES) demonstrated that thinner stent struts reduces malapposition and improves re-endothelialization, thus reducing the risk of subsequent ST.[81,82] Second-generation DES were developed with advanced designs and features, including thinner strut design, improved flexibility and deliverability, and a platform using either a cobalt-chromium (CoCr) or a platinum-chromium (PtCr) metal, more biocompatible polymers, thinner polymer layers, and accelerated kinetics of drug elution to promote faster re-endothelialization (Table 1). Everolimus, similar to sirolimus, is an anti-proliferative agent demonstrated to inhibit SMC proliferation in vitro and inhibit vascular neointimal hyperplasia in animal transplant models[83] (Figure 1). Given its effective cytotoxic properties, it was deemed to be of benefit in the pursuit against ISR, subsequently prompting the development of the Xience-V CoCR-everolimus-eluting stent (EES) and the Promus CoCr-EES as initial second-generation DES.

The mechanisms of the CoCr-EES that lead to better outcomes is likely multifactorial and include (Table 1): the more rapid and complete endothelialization of the struts, the different scaffold alloy, architecture, and thinner (81 or 91 μm) malleable struts, low polymer load and drug type, and the drug-release kinetics in addition to the thromboresistant fluoro-copolymer, all contributing to the reduced rates of ST.[68,84] The utilization of fluoro-copolymer coated stents has been demonstrated to be safer than BMS counterparts with lower rates of ST and platelet deposition.[68,84] Two versions of the EES are currently commercially available in the USA: the CoCr-EES and PtCr-EES frame materials. Zotarolimus is a derivative drug of sirolimus with a similar anti-proliferative mechanism of action in the cell cycle although with enhanced lipophilic properties (Figure 1). The ZES is made by Medtronic, Inc. and is produced in two models, the older Endeavor (E-ZES) and the newer Resolute (R-ZES). Both stents are built on a CoCr platform. At the 9-month follow-up period, in-stent late lumen loss was 0.22 mm with the newer R-ZES, which was significantly lower than that previously observed in the older version E-ZES.[85]

Superiority of second-generation DES over first-generation DES

SPIRIT III randomly assigned 1,002 patients with de novo coronary artery lesions to either EES or PES in a 2:1 fashion.[86] The EES was superior to PES regarding the primary endpoint of angiographic in-segment late loss at 8 months (0.14 vs 0.28 mm, P≤0.004). At the 2-year follow-up, the endpoint of target vessel failure (composite of cardiac death, target vessel MI, or ischemia-driven TVR) demonstrated significantly lower rates with the EES vs PES (10.7% vs 14.4%, P=0.04), and the endpoint of MACE was significantly lower with EES vs PES (7.3% vs 12.8%, P=0.004).[87] The SPIRIT IV trial randomly

assigned 3,687 patients with more complex coronary disease in a 2:1 fashion to EES or PES.[88] The primary endpoint of target lesion failure (TLF) (composite of cardiac death, target vessel MI, ischemia-driven TLR) at 2 years was significantly lower in the EES vs the PES group (6.9% vs 9.9%, P=0.003).[89] The COMPARE trial randomly assigned 1,800 all-comer, real-world patients to EES or PES. The rate of the primary endpoint (composite of death, MI, and TVR) was significantly less with EES vs PES at 12 months (6% vs 9%)[90] and at 2 years follow-up (9.0% vs 13.7%),[91] thus providing additional support for the superior performance of the EES over its first-generation predecessor PES (Table 2).

Comparable clinical trials among the three current second-generation DES available

The RESOLUTE All Comers Trial randomly assigned 2,292 patients undergoing PCI with either R-ZES or Xience-V EES including a primary endpoint of TLF within 12 months, which demonstrated similar results with R-ZES vs Xience-V EES (8.2% vs 8.3%, P<0.001) for non-inferiority.[92–94] At 2 and 4 years follow-up, there was no significant difference between the R-ZES and EES groups in either the composite patient-related outcome or the stent-related outcome. The rate of definite or probable ST was not significantly different between R-ZES and EES at 1 year (2.3% vs 1.5%, respectively, P=0.17) or 4 years (2.3% vs 1.6%, respectively, P=0.23).[92–94] Furthermore, the DUTCH PEERS trial randomized 1,811 all-comer patients with a total of 2,371, both stable and unstable target lesions, to the newly designed, more flexible, Resolute Integrity-ZES vs the PtCr-EES.[95] The primary combined endpoint of target vessel failure at 1 year occurred with similar rates in the R-ZES vs PtCr-EES groups (6% and 5%, respectively)[95] (Table 3).

These two versions of the EES were found to have similar efficacy and safety endpoints in the PLATINUM trial, which randomly assigned 1,530 patients with one or two de novo native coronary lesions to CoCr-EES or PtCr-EES.[96] The novel PtCr-EES was found to be non-inferior to the CoCr-EES with 12-month rates of TLF (a composite of target vessel-related cardiac death, target vessel-related MI, or ischemia-driven TLR) at 2.9% vs 3.4% for the CoCr-EES vs PtCr-EES, respectively.[96] Subsequently, again at the 4-year follow-up, no significant differences were found.[97]

Network meta-analyses of clinical trials comparing first- and second-generation DES and BMS

Bangalore et al[98] published the largest network meta-analysis comparing the various types of stent designs among approximately 118,000 patients at ≤1 year and long-term endpoints with a mixed-treatment comparison. TLR for SES, EES, and R-ZES were similar and had lower rates than PES or E-ZES. With regard to the risk of MI, there was a reduction in all DES except PES vs BMS. With regard to the risk of definite or probable ST, EES had the lowest risk of any DES, and therefore appeared to be the safest stent. In another network meta-analysis, Palmerini et al included 50,844 patients in 49 trials.[99] The ST rate is the lowest with the CoCr-EES compared to all the other first-generation DES and BMS both at 1 and 2 years follow-up. PtCr-EES also had a lower rate of ST compared to first-generation DES or BMS. In a similar, more recent meta-analysis, which included a total of 52,158 randomized patients,[100] it was demonstrated that after a median follow-up of 3.8 years, all DES demonstrated superior efficacy compared with BMS in terms of revascularization and MI. In addition, among DES, the currently utilized second-generation devices have largely equivalent

Table 2 Clinical trials demonstrating superiority of second-generation DES over first-generation DES

Clinical trials	Stent compared	Efficacy endpoint*	Safety endpoint stent thrombosis*	Follow-up duration	Patient number
SPIRIT III[87]	Xience V vs Taxus Express 2	TVF: 10.7% vs 15.4% MACE: 7.3% vs 12.8%	1.0% vs 1.7%	2 years	1,002
SPIRIT IV[89]	Xience V vs Taxus Express 2	TLF: 6.9% vs 9.9% MACE: 7.1% vs 10.1%	0.4% vs 1.2%	2 years	3,687
COMPARE[91]	Xience V vs Taxus Liberte	TVR: 3.2% vs 8.0% MACE: 7.4% vs 11.3%	0.9% vs 3.9%	2 years	1,795
SCAAR Registry[47]	Second-gen vs first-gen DES	TLR: 3.1% vs 4.9% Death: 1.9% vs 3.4%	0.6% vs 1.3%	2 years	29,753 (excluding BMS patients)

Notes: Second-generation DES include Endeavor Resolute, Xience V, Xience Prime, Promus, Promus Element. First-generation DES include Cypher, Cypher Select, Taxus Express and Taxus Liberte. *All comparisons in efficacy and safety endpoints were clinically significant.
Abbreviations: DES, drug-eluting stents; gen, generation; TLR, target lesion revascularization; MACE, major adverse cardiac events (composite of cardiac death, myocardial infarction, or TLR); TLF, target lesion failure (composite of cardiac death, target vessel myocardial infarction, or ischemia-driven TLR); TVR, target vessel revascularization; TVF, target vessel failure (composite of cardiac death, target vessel myocardial infarction, or ischemia-driven TVR); BMS, bare-metal stents.

Table 3 Equivalency of outcomes in clinical trials among the current three second-generation DES

Trial name	Stent compared	Efficacy endpoint*	Safety endpoint stent thrombosis*	Follow-up	Patient number
PLATINUM[96]	Promus Element vs Xience V	TLF: 3.4% vs 2.9% Cardiac death/MI: 2.0% vs 2.5%	0.4% vs 0.4%	1 year	1,530
PLATINUM[97]	Promus Element vs Xience V	TLF: 7.4% vs 8.5% All-cause death: 5.0% vs 6.0% MI: 2.6% vs 2.8%	0.7% vs 0.7%	4 years	1,530
RESOLUTE All Comers[93]	Resolute vs Xience V	TVR: 10.0% vs 9.1% MACE: 12.5% vs 12.9%	1.9% vs 1.0%	2 years	2,292
DUTCH PEERS[95]	Resolute Integrity vs Promus Element	TLR: 3% vs 3% TVF: 6% vs 5%	1% vs 2%	1 year	1,811

Notes: Promus Element = PtCr-EES (platinum-chromium everolimus-eluting stent); Xience V = CoCr-EES (cobalt-chromium everolimus-eluting stent); Resolute +/− Integrity = zotarolimus-eluting stent. *All comparisons in efficacy and safety endpoints were clinically non-significant.

Abbreviations: DES, drug-eluting stents; TLR, target lesion revascularization; MACE, major adverse cardiac events (composite of cardiac death, myocardial infarction, or TLR); TLF, target lesion failure (composite of cardiac death, target vessel myocardial infarction, or ischemia-driven TLR); TVR, target vessel revascularization; TVF, target vessel failure (composite of cardiac death, target vessel MI, or ischemia-driven TVR); MI, myocardial infarction.

outcomes and have substantially improved long-term safety of lower ST and efficacy of lower TVR and MI compared with the first-generation DES and BMS.

The dilemma of optimal duration of DAPT: a balance of reducing ischemia vs increased risk of bleeding

The current standard duration of DAPT after DES implantation recommendation

The American College of Cardiology/American Heart Association guidelines 2011 recommend a 12-month duration of DAPT in patients undergoing PCI with DES for stable coronary artery disease at low bleeding risk.[70] The 2013 European Society of Cardiology guidelines on stable coronary artery disease[101] recommend a duration of 6 to 12 months of DAPT in patients undergoing PCI with DES, but more recently recommended a DAPT duration of 6 months after DES implantation in patients with stable coronary artery disease (Class I, Level B)[102] and call for individualized treatment according to bleeding and thrombotic risk. The recent DAPT trial randomly[103] assigned 9,961 patients who had undergone PCI with a first or second-generation DES, and who had subsequently undergone successful treatment with 12 months of aspirin and a $P2Y_{12}$ receptor blocker (either clopidogrel or prasugrel), to either continue receiving the $P2Y_{12}$ receptor blocker or a placebo for an additional 18 months with all patients continuing aspirin therapy.[103] The rates for each of the co-primary efficacy endpoints of ST and MACE (a composite of death, MI, or stroke) during the period from 12 to 30 months were lower with continued $P2Y_{12}$ therapy (0.4% vs 1.4%, $P<0.001$ for ST and 4.3% vs 5.9%, $P<0.001$ for MACE). However,

the rate of the primary safety endpoint ie, moderate or severe bleeding was increased (2.5% vs 1.6%, $P=0.001$) with the continued $P2Y_{12}$ therapy group.

The results of current trials comparing short duration, standard duration, and long duration of DAPT

Up to date, there have been ten randomized trials with five trials comparing shorter duration (3–6 months) vs standard duration (12 months),[104–108] and the other five trials comparing shorter duration (6–12 months) vs long duration (>24 months).[103,109–112] However, except for one trial (ITALIC), which used only second-generation DES,[109] the other nine trials used a combination of first and second-generation DES with or without BMS. In all but one trial, the results demonstrated that prolonged (>24 months) DAPT is associated with reduced ischemic events. Most of the trials demonstrated that a shortened duration vs standard duration or that a standard duration vs long duration were equivalent in clinical outcomes. However, a recent meta-analysis based on these ten randomized controlled trials[113] concluded that the rate of ST is higher and statistically significant with shorter duration than longer duration (0.9% vs 0.5%, $P=0.001$); major bleeding events are less with shorter duration than long duration (1.2% vs 1.9%, $P<0.001$), (Table 4). Nonetheless, these conclusions should be interpreted with great caution. As discussed earlier, first-generation DES are associated with higher rates of ST and lower efficacy compared with second-generation DES. A total of nine out of these ten clinical trials have utilized a mixture of first-generation DES, second-generation DES, and BMS. ST is a very rare event and the vast majority of the trials to date have not been powered enough to reveal an accurate difference. Therefore, the endpoint of these trials usually

Table 4 Randomized trials of DAPT comparing different durations of therapy after stenting

Trial name	Stent types	Patient number	Duration compared (months)	Ischemia[a]	Bleeding[b]	Equivalency[c]	Follow-up duration
Short duration DAPT							
ISAR-SAFE[104]	EES and R-ZES 60%	4,000	6 vs 12	Death/MI/Stroke/ST/Bleeding: 1.5% vs 1.6% ST: 0.3% vs 0.2%	0.2% vs 0.3%	Yes	9 months
EXCELLENT[105]	CoCr EES 75%	1,443	6 vs 12	Death/MI: 2.4% vs 1.9% TLR: 2.4% vs 2.6% ST: 0.9% vs 0.1%	0.3% vs 0.6%	Yes	1 year
OPTIMIZE[106]	E-ZES 100%	3,119	3 vs 12	Death/MI/ST: 4.7% vs 4.2% TLR: 3.2% vs 3.5% ST: 0.8% vs 0.8%	0.6% vs 0.9%	Yes	1 year
RESET[107]	E-ZES 50%, R-ZES 20%, EES 15%, SES 15%	2,117	3 vs 12	Death/MI/ST: 0.8% vs 1.3% ST: 0.2% vs 0.3% TLR: 3.9% vs 3.7%	0.2% vs 0.6%	Yes	1 year
SECURITY[108]	Second-generation DES 70%	1,399	6 vs 12	Death/MI/ST/Bleeding: 4.5% vs 3.7% ST: 0.4% vs 0.4%	0.2% vs 0.3%	Yes	1 year
Long duration DAPT							
ITALIC[109]	Xience only	2,031	6 vs 24	Death/MI/Stroke/Bleeding: 1.6% vs 1.5% ST: 0.3% vs 0%	0% vs 0.3%	Yes	1 year
PRODIGY[110]	BMS 25%, Cypher 25%, Taxus 25%, Endeavor 25%	2,013	6 vs 24	Death/MI/Stroke: 10.0% vs 10.1% ST: 1.5% vs 1.3%	3.5% vs 7.4%	Increased bleeding	2 years
DAPT[103]	Xience 47%, Taxus 27%, Endeavor 13%, Cypher 11%	9,961*	12 vs 30	Death/MI/Stroke: 5.9% vs 4.3% ST: 1.4% vs 0.4%	1.6% vs 2.5%	Increased bleeding reduced ischemia	1 year
ARCTIC-Interruption[111]	First-generation DES 40%, Second-generation DES 60%	1,259	12 vs 18–30	Death/MI/Stroke /Urgent PCI: 4.0% vs 4.0% ST: 1% vs 0%	<0.5% vs 1%	Yes	1 year
DES-LATE[112]	Cypher 40%, Taxus 20%, Endeavor 20%	5,045	12 vs 24	Death/MI/Stroke: 2.4% vs 2.6% TLR: 2.8% vs 3.5% ST: 0.5% vs 0.3%	1.1% vs 1.4%	Yes	2 years

Notes: [a]Ischemic: endpoint of studies (some studies included bleeding events); [b]bleeding: major bleeding events (definitions vary among studies); [c]conclusion of studies whether the two strategies achieved similar outcomes; *35% of patients in DAPT trial were on prasugrel.
Abbreviations: DAPT, dual antiplatelet therapy; DES, drug-eluting stents; TLR, target lesion revascularization; MI, myocardial infarction; ST, stent thrombosis; EES, everolimus-eluting stent; CoCr, cobalt-chromium; E-ZES, Endeavor zotarolimus-eluting stent; R-ZES, Resolute zotarolimus-eluting stent; SES, sirolimus-eluting stent; BMS, bare-metal stents; PCI, percutaneous coronary intervention.

includes other adverse events, for example, death and MI. Furthermore, prasugrel and ticagrelor are gradually replacing the use of clopidogrel due to better clinical outcomes. This may also influence the outcomes in detecting differences in ST. In addition to the stent types, other factors such as lesion characteristics including: long lesions, bifurcation lesions, and acute coronary syndrome vs stable coronary disease all have a major influence on the ischemic event rates. Patients who have preexisting bleeding-prone conditions such as gastritis or gastrointestinal ulcer disease have a higher risk for bleeding and are likely to develop major bleeding with prolonged DAPT. It is difficult to extrapolate the conclusions of these studies to our current practice using the state-of-the-art second-generation DES with improved antiplatelet agents.

Current postulated duration of DAPT – individualized therapy

Therefore, before more clinical trials are conducted using a larger population, more unified stent types, and lesion characteristics, it may be postulated that second-generation DES may be safe for a shorter duration of DAPT if there is a clinical indication to shorten the duration of treatment, such as increased risk of gastrointestinal bleeding or need for surgical intervention. Longer duration of DAPT with second-generation DES may be used if lesion types and characteristics are highly complex and the patient is at a higher risk, such as acute coronary syndrome with multi-vessel disease. Therefore, an individualized, case-by-case approach in regard to the use of second-generation DES and DAPT, in the setting of a

judicious and comprehensive consideration of the bleeding and thrombotic risks of each patient, should be exercised.

Bioresorbable polymer stents, polymer-free stents, and fully bioresorbable scaffolds with vascular restoration

The coronary stents currently available in the US are permanent implants composed of a metallic alloy scaffold, and all have a durable polymer, which remains permanently on the stent after the drug is eluted. While DES have improved outcomes for patients compared to BMS, they have several limitations. The development of ST and residual rates of ISR after DES are the main reasons for the development of newer coronary artery stents in the hope of further improving outcomes.

The durable polymer, which coats the metallic scaffold, itself may result in vascular inflammation or delayed endothelialization and healing therefore, contributing to the risk of ST.[114] Henceforth, two very large network meta-analyses reflect the current evidence regarding bioresorbable polymer stents. They included all coronary stents, including BMS, first- and second-generation DES, and bioresorbable polymer stents and demonstrated that the rates of TLR were comparable between bioresorbable polymer DES and the standard EES.[115] Bioresorbable polymer stents were inferior to EES with regard to definite ST and were associated with increased mortality.[115] In addition, compared with EES, bioresorbable polymer biolimus-eluting stents were associated with an increased risk of MI.[116] In conclusion, the bioresorbable polymer stents have not shown excellent clinical outcomes in comparison to the state-of-the-art second-generation durable polymer DES.

A polymer-free stent, similar to a bioresorbable polymer stent, may be associated with less chronic inflammation and improved vascular healing, therefore, improved clinical outcomes. The challenge in designing a polymer-free stent is the difficulty in achieving adequate levels of the anti-proliferative drug over time to effectively inhibit neointimal proliferation and hence, ISR. In addition, the polymer-free stents have a BMS scaffold which is filled with the anti-proliferative drug. This technology uses laser cut, microscopic holes in the metal scaffold to allow for drug storage and elution. Clinical experience with polymer-free stents is still in the early stages and limited, and all polymer-free stents are currently purely investigational. In the ISAR-TEST trial, 450 patients with de novo native coronary artery lesions, excluding left main coronary artery disease, were randomly assigned to a rapamycin-coated Yukon DES (rapamycin stent) or the polymer-based, paclitaxel-eluting Taxus stent (paclitaxel stent). There were no significant differences between the groups in terms of late lumen loss, angiographic restenosis, or TLR due to restenosis.[117] In another ISAR trial,[118] which was a prospective, observational, systematic angiographic follow-up study conducted at two German centers, 2,588 patients underwent stenting with either a durable polymer rapamycin-eluting stent (RES), polymer-free RES, or a permanent-polymer PES, and the primary endpoint of late lumen loss at 2 years follow-up was significantly less for the polymer-free RES vs the other two groups. In conclusion, further studies are needed to establish excellent clinical outcomes of the polymer-free stents in comparison to the state-of-the-art durable polymer second-generation DES in current use today.

Fully bioresorbable scaffold devices, also known as BRS, have been designed in an attempt to overcome some of the disadvantages of DES. In these devices, the scaffold is in place only long enough to protect against subacute closure, wall recoil, and ISR. These stents have the potential to reduce the problems of very-late ST and the requirement for prolonged DAPT. In addition to reducing long-term adverse events associated with metallic stent struts, including stent fracture, vascular endothelial dysfunction, and neoatherosclerosis, BRS have the advantages of restoring vascular functions, ie, endothelial function and SMC phenotype, shielding and recapping of the plaque, late lumen enlargement, and remodeling function. Currently, there are four major categories of materials used for BRS. These are poly-L-lactic acid (PLLA) and co-polymers, tyrosine polycarbonate, magnesium alloys, and nitride iron (Table 5). There are at least two types of BRS approved in Europe and another 20 types of BRS in current clinical trials or under development.

The first-in-human fully BRS, the Igaki-Tamai stent, was constructed of a thick, PLLA polymer scaffold and this initial bioresorbable stent was not drug-eluting. In a long-term safety report of the 10-year outcomes of the first 50 patients treated with 84 stents, survival rates free of all-cause death, cardiac death, and MACE were 87%, 98%, and 50%, respectively.[119] The cumulative rates of TVR were 16%, 18%, and 28% at 1, 5, and 10 years, respectively. Two cases of definite ST were noted. Most stent struts were noted to have been absorbed by 3 years using IVUS.

The safety and efficacy of the first-generation fully bioresorbable EES (BVS-EES) (Abbott Vascular, Abbott

Table 5 Bioabsorbable stents and stages of production

Category of material	Example of manufacturer	Stent name	Status of approval
PLLA and co-polymers	Abbott Vascular	Absorb	CE mark
Magnesium alloys	Biotronik	DREAMS	In clinical trial
Tyrosine polycarbonate	Reva	Fantom	Under preclinical study
Nitride iron	Lifetech	Lifetech Nitride Iron Stent	Under preclinical study

Abbreviation: PLLA, poly-L-lactic acid.

Laboratories, Abbott Park, IL, USA) were evaluated in the open-label, prospective ABSORB study, which enrolled 30 selected patients with single de novo coronary lesions.[120,121] This stent was also made of a backbone of PLLA with a coating of poly-D-L-lactic acid that contained and released the anti-proliferative agent. Although the 2-year results demonstrated its safety and efficacy with a sustained low MACE rate and no cases of ST up to 4 years,[122] subsequent reports suggested less than optimal radial integrity and demonstrated shrinkage of the device at 6 months, which caused significant late lumen loss.[123] Therefore, the stent design and manufacturing protocol of the polymer were modified to provide better vascular support and a slower release of everolimus. The BVS-EES scaffold received a CE mark approval in 2011 and has been in clinical use in Europe and parts of Asia.

The newer second-generation BVS-EES design with intended improved radial strength has been evaluated in the ABSORB BVS 1.1 study in which 101 patients received a single stent. Follow-up for clinical and imaging outcomes at different time intervals was intended for two separate cohorts: 45 patients (cohort 1), and 56 patients (cohort 2).[123,124] At 2 years follow-up, the newer BVS-EES revised scaffold had enhanced radial strength with sustained outcomes, without any ST; however, stent struts were still present.[125]

In the largest trial of the fully bioresorbable BVS-EES scaffold to date, the ABSORB-II trial, 501 patients with evidence of myocardial ischemia and one or two de novo native lesions were randomly assigned in a 2:1 ratio to receive either a BVS-EES or a durable metallic EES.[126] The co-primary endpoints were vasomotion and lumen diameter at 3 years. The secondary endpoints were composite clinical endpoints, including death, TVR, device and procedural success, and angina status at 6 and 12 months. The interim 1-year follow-up results were published in September 2014 and it was demonstrated that the acute lumen gain is significantly

lower for the BVS-EES by coronary angiography and IVUS.[127] However, the cumulative rates of new-onset or worsening angina were lower in the BVS-EES group, although performance during maximal exercise and angina status was similar. The 1-year composite device-oriented endpoint was similar between the two groups. However, three patients in the BVS-EES group had ST vs none in the metallic EES group.[127] Although the theoretical advantages of the fully BRS are appealing, the scientific community needs to await the final results of this and the larger ongoing ABSORB III and IV trials to evaluate the specific advantages and disadvantages of this device's technology, in addition to safety profiles in comparison to the state-of-the-art second-generation durable metallic DES.

DES in advancing the treatment of complex/multi-vessel coronary artery disease

Multiple clinical trials have been performed comparing PCI with CABG surgery starting in the era of POBA, and subsequently in the era of BMS, and then in the eras of first- and second-generation DES.

Robust clinical outcomes comparing POBA or BMS with CABG in treating complex/multi-vessel coronary disease

There have been seven randomized published trials comparing POBA vs CABG in treating symptomatic patients with multi-vessel disease.[128–134] All of these seven trials demonstrated no significant mortality difference between the POBA and CABG treatment groups. Among these trials, only the BARI trial[134] reported the 10-year survival for the complete cohort with 71.0% for POBA and 73.5% for CABG (P=0.18). At 10 years, the POBA group had significantly higher subsequent revascularization rates than the CABG group (76.8% vs 20.3%, P<0.001); however, angina rates for the two groups were similar.[134] In regard to comparing BMS with CABG in treating multi-vessel disease, there were four clinical trials completed: ARTS-I,[135] ERACI-II,[136] SOS,[137] and AWESOME.[138] Again, these clinical trials demonstrated no difference in the mortality rates except for higher rates of revascularization within the PCI cohorts. Furthermore, there was a total of four important clinical trials comparing the first-generation DES and CABG including: ARTS-II,[139] ERACI-III,[140] SYNTAX,[141] and recently FREEDOM.[142]

The performance of first-generation DES compared with CABG in the treatment of CAD in non-randomized studies

The ARTS II study[139] was a non-randomized trial with the Cypher SES, which applied the same inclusion and exclusion criteria, endpoints, and protocol definitions as the ARTS-I study,[135] and its aim was to determine the safety and efficacy of the Cypher stent in patients with multi-vessel disease, in addition to comparing the outcomes to the historical outcomes of the ARTS-I trial. At 5 years follow-up of the ARTS-II trial,[143] the death/stroke/MI event-free survival rate was 87.1% in ARTS-II SES vs 86.0% ($P=0.1$) and 81.9% ($P=0.007$) in ARTS-I CABG and BMS cohorts, respectively. Thus, the ARTS-II trial demonstrated that the SES had a safety record comparable to CABG and superior to BMS. Patients with multi-vessel CAD who met the ERACI-II trial[136] clinical and angiographic inclusion criteria were treated with DES and enrolled in the ERACI-III registry.[140] The primary endpoint of 3 years MACE was lower in ERACI-III DES (22.7%) than in ERACI-II BMS (29.8%, $P=0.015$), mainly reflecting less TVR (14.2 vs 24.4%, $P=0.009$) in the DES vs BMS groups, respectively. MACE rates at 3 years were the same in DES and CABG-treated patients (22.7 vs 22.7%, risk ratio [RR] =1, 95% confidence interval =0.710–1.406). Thus, the ERACI-III registry demonstrated superior efficacy of the DES compared to BMS and similar outcomes with DES and CABG.

The failure of first generation DES compared with CABG in treating multi-vessel CAD in randomized studies

The SYNTAX trial is a landmark randomized study which compared CABG with first-generation DES for the treatment of patients with left main coronary disease and/or three-vessel disease with approximately 900 patients in either group.[141] At 5 years follow-up, estimates of MI (3.8% in the CABG group vs 9.7% in the PCI group, $P<0.0001$) and repeat revascularization (13.7% vs 25.9%, $P<0.0001$) were significantly increased with PCI compared to CABG. All-cause mortality (11.4% in the CABG group vs 13.9% in the PCI group, $P=0.10$) and stroke (3.7% vs 2.4%, $P=0.09$) were not significantly different between the two groups.[144] Patients with a low SYNTAX score (≤22) had a similar rate of MACE in the PCI group compared to the CABG group. However, patients with intermediate (23–32) or high (≥33) SYNTAX scores had an increased rate of MACE in the PCI group compared to the CABG group. Based on the use of first-generation DES in PCI vs CABG, the SYNTAX trial concluded that CABG should be the standard of care in treating multi-vessel/left main disease with intermediate or high SYNTAX scores.[144] The FREEDOM trial[142] is another major landmark randomized trial assigning patients with diabetes and multi-vessel coronary artery disease to undergo either PCI with first-generation DES (using PES or SES) vs CABG with approximately 950 patients in either group. At 5 years follow-up, the primary composite endpoint of death/infarction/stroke rate was 26.6% in first-generation DES group and 18.7% in CABG group ($P=0.005$). The study concluded that for patients with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of all-cause mortality and MI but with a higher rate of stroke.[142]

The dilemma of comparing DES with CABG
DES treatment as an evolving device-based modality, compared to a solid but static treatment – CABG

As mentioned earlier, various stent comparison trials and meta-analyses have demonstrated that second-generation DES have much less ST and less need for revascularization. Current trials, including SYNTAX, FREEDOM, and ARTS-II only used first-generation DES. The ST was reported at up to 6% to 10% at the end of 5 years follow-up for these three landmark studies. ST is associated with a very high mortality rate which obviously contributed to the worse outcomes in the group of patients treated with first-generation DES compared with CABG in these landmark trials. In a recent meta-analysis comparing DES vs CABG in treating diabetic patients with multi-vessel disease,[145] it was demonstrated that the revascularization rates with PCI have steadily decreased from POBA to first-generation DES, and then to second-generation DES. The need for revascularization in the patients treated with second-generation DES was not significantly higher than patients treated with CABG. Along these lines, there are two randomized, currently ongoing clinical trials,[146] that is, EXCEL and NOBLE using newer generation DES vs CABG in treating patients with unprotected left-main disease and complex coronary disease with low-to-intermediate SYNTAX scores, both of which should further elucidate a more contemporary comparison of PCI with newer generation DES vs CABG surgery. The initial reports may be available in 2016.

Completeness of revascularization

Patients with multi-vessel CAD are often treated with incomplete revascularization in either the PCI or CABG group. However, the rates of incomplete revascularization are

usually higher in the stent group, most likely due to chronic total occlusions or severe tortuous or calcified untreatable lesions. In the SYNTAX trial, incomplete revascularization rates were 43.3% vs 36.8% in the PCI vs CABG groups, respectively; in ARTS-II the rates were 39% vs 16%, respectively. A recent meta-analysis demonstrated that the completeness of revascularization in treatment of multi-vessel disease is associated with a 30% lower long-term mortality rate relative to incomplete revascularization regardless of treatment strategies utilized, that is, PCI or CABG.[147] Furthermore, in the PCI group, complete revascularization was associated with a 22% reduction in MI and a 26% reduction in repeat revascularization.[147] Furthermore, the ongoing improvement in treating chronic total occlusions and highly complex lesions such as tortuous and/or calcified lesions may further decrease the gap in the difference in outcomes between PCI with second-generation DES vs CABG.

Inclusion of clinically non-significant lesions as a part of multi-vessel disease

Less than clinically significant stenoses in patients with multi-vessel disease could potentially have been included as an index lesion in multiple clinical trials. Treatment of less than clinically significant lesions may inadvertently increase the risk of the procedure and worsen the prognosis such as restenosis or ST. Therefore, the current utilization of fractional flow reserve in a physiologic assessment of disease will likely optimize the strategy of PCI and, therefore, treatment of only the hemodynamically significant lesions may translate into improved outcomes.

Conclusion

The first-generation DES delivered major advances in the percutaneous treatment of obstructive CAD over their predecessor BMS in regards to significant improvements in ISR. The second-generation DES have been established as safe and efficacious in addition to providing improvements in outcomes compared to their first-generation predecessors. The significant differences in outcomes were emphasized in multiple randomized trials, large meta-analyses, and registry data, as previously described. Therefore, the second-generation DES represent the state-of-the-art and the current standard in PCI care of obstructive coronary disease, and the three currently available second-generation DES have been demonstrated to have similar efficacy and safety outcomes. Furthermore, the dilemma of optimal duration of DAPT continues to be a passionate topic for discussion in the interventional realm and given the current available data, we currently propose a fine balance of

reducing thrombotic risk and reducing the risk of bleeding on a patient-specific level of management. In regard to the theoretical advantages of the BRS, which may be appealing, we need to await the results of large ongoing trials to evaluate their specific advantages and disadvantages, in addition to safety profiles in comparison to the state-of-the-art second-generation durable metallic EES. In regard to the quickly changing realm of percutaneous vs surgical revascularization, CABG remains the standard of care for patients with advanced coronary disease and diabetes, and for patients with complex three-vessel/left-main disease with intermediate-to-high SYNTAX scores. However, this paradigm may be slowly changing with the advent and further improvement of the second-generation DES devices in addition to the overall improvement of the various aspects in the percutaneous management of coronary disease.

Disclosure

The authors have no conflict of interest to disclose.

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