

Durable Versus Biodegradable Polymer Drug-Eluting Stents

An overview of outcomes and the impact on real-world clinical practice.

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The considerable reduction in repeat revascularization procedures achieved with the first generation of coronary drug-eluting stents (DES), as compared to their bare-metal stent (BMS) predecessors, led to their widespread use worldwide. However, concerns emerged regarding late and very late stent thrombosis events, reported for the first-generation DES, which in turn was associated with a high rate of death and myocardial infarction (MI).^{1,2} Such events have been attributed mainly to the incomplete re-endothelialization caused by drug-induced inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis, and, importantly, polymer-induced prolonged vessel wall inflammation.³ Although some of these factors are also inherent to BMS, polymer-induced vessel wall inflammation and impaired re-endothelialization were strongly related to DES and, therefore, the idea that polymers have a deleterious effect and are better avoided gained appeal.

In an attempt to improve the general performance of first-generation DES and, in particular, their safety profile, new DES devices were developed. Specifically, the polymer coating issues with the first-generation DES were addressed, with two major design concepts being pursued. The first maintained the use of a permanent polymer coating as a drug carrier, but employed (for this purpose) newer types of durable polymers with better biocompatibility and mechanical properties than their predecessors in combination with radical changes in the stent design (mainly the metallic platform), giving rise to the second-generation, durable-polymer DES (DP-DES). The second opted to minimize the use of polymer carriers either by substituting the durable

polymers of the first-generation DES with newer, bioabsorbable polymers, which will fully absorb after the drug-elution process, giving rise to a new line of DES: the bioabsorbable polymer DES (BP-DES), or by eluting the drug directly from the metallic stent platform, avoiding in this way the need for a polymer drug carrier as is the case with the nonpolymeric DES.

Both of these DES categories have recently undergone rapid development, and newer devices with further design improvements have also been introduced.

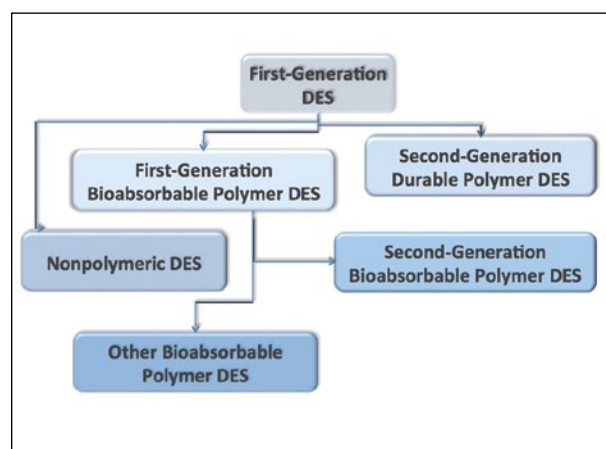


Figure 1. Proposed classification for existing DES. *First-generation* denotes bioabsorbable- or DP-DES with thick struts ($> 100 \mu\text{m}$). *Second-generation* denotes bioabsorbable polymer or durable-polymer DES with thinner struts ($< 100 \mu\text{m}$). *Nonpolymeric* denotes DES that employ no polymeric coatings. *Other* denotes BP-DES that, beyond drug elution from a bioabsorbable polymer, simultaneously employ other therapeutic vehicles.

Meanwhile, a large quantity of data from randomized clinical trials comparing newer DES with each other, or with first-generation DES, has been generated; however, despite these major efforts, the results of these trials are often contradictory, and therefore, the safety and efficacy of these new DES remains a largely debated topic. This article focuses on the clinical outcomes of these newer bioabsorbable and durable polymer DES and their impact on daily clinical practice.

DETAILED DESCRIPTION AND PROPOSED CLASSIFICATION FOR DES DESIGNS

The major determinants of DES performance are the metallic scaffold platform, drug carrier system (often a polymer), and drug type. Based on the combination of these characteristics, DES can be divided into different classes. Figure 1 represents a proposed classification of the currently used metallic DES.

First-Generation DP-DES

The first DES devices introduced in the market were the sirolimus-eluting stent (Cypher, Cordis Corporation, Bridgewater, NJ) and the paclitaxel-eluting stent (Taxus, Boston Scientific Corporation, Natick, MA). Both stents share a thick-strut, stainless steel slotted tube stent platform coated with a thick layer of a permanent, amorphous polymer to carry and control the release of the antiproliferative drugs. The main issues with the permanent polymers of these first-generation DES were the vessel toxicity and inflammatory reactions,^{4,5} as well as mechanical complications (polymer delamination and “webbed” polymer surface),⁶ resulting in impaired drug delivery and delayed vessel healing, which in turn directly affected the efficacy and safety outcomes with these devices.³

Second-Generation DP-DES

The newer-generation DP-DES share three main characteristics: (1) durable but thinner and more biocompatible polymers with improved mechanical properties, (2) thinner stent struts (mainly metallic alloys), and (3) more conformable open-cell stent designs and overall improved stent delivery systems.

The first and most studied prototype of the second-generation DES (Xience V, Abbott Vascular, Santa Clara, CA) employs a thin layer of a durable polymer coating composed of poly n-butyl methacrylate, a polymer that adheres to the stent and drug coating, and poly-vinylidene fluoride-hexafluoropropylene, a nonerodible, semicrystalline copolymer that is composed of monomers that serve as the drug matrix layer containing everolimus (a sirolimus analog) with a drug

load of 100 µg/cm². The stent platform is composed of a cobalt chromium metallic alloy. The stent strut and polymer thickness are both significantly reduced compared to the first-generation DES (87 µm and 7.8 µm, respectively). Similar stent designs are shared by other DES, with the most used being the zotarolimus-eluting Resolute stent (Medtronic, Inc., Minneapolis, MN), and the everolimus-eluting Promus Element platinum chromium stent (Boston Scientific Corporation). Clinical randomized trials have proven the noninferiority of these devices compared to the Xience V stent.^{7,8} These devices are characterized by improved endothelial healing and reduced vessel wall inflammation after implantation as compared to the first-generation devices.⁹

Bioabsorbable Polymer DES (First and Second Generation)

The term *bioabsorbable polymer DES* refers to a class of DES that share a common characteristic—a bioabsorbable polymer coating employed to carry and release the active principle, that will erode and fully absorb over a period of time (mostly within a year). These devices are designed with the purpose of eliminating the permanent polymer-induced vessel inflammation believed to be one of the main causes of very late safety events (more than 1 year after implantation). However, significant differences in the designs of these stent platforms do exist. The first prototypes of this DES class were the bioabsorbable polymer biolimus-eluting stents, Biomatrix (Biosensors International Group, Ltd., Singapore) and Nobori (Terumo Interventional Systems, Somerset, NJ). Both devices, which are almost identical, employ a biodegradable polymer (polylactic acid [PLA]) applied solely to the abluminal stent platform surface from which biolimus, a sirolimus analog, is eluted at a concentration of 15.6 mg/mm. Both stents share a similar stainless steel platform, with strut thickness comparable to that of the first-generation DP-DES. From this perspective, they can also be considered a first-generation BP-DES. Further improvements in stent design in this class led to the development of newer DES, which despite having a bioabsorbable polymer, differ from their predecessors in that they also employ thinner-strut metallic stent platforms mainly composed of metallic alloys, much like those of second-generation DP-DES, and therefore can be similarly generalized under the name of *second-generation BP-DES*.

The most studied devices in this group are the Yukon stent with bioabsorbable polymer (Translumina, Hechingen, Germany), Supralimus and Supralimus-Core (Sahajanand Medical Technologies Pvt. Ltd., Gujarat, India), and, more recently introduced, Synergy (Boston

Scientific Corporation) and Orsiro (Biotronik, Inc., Lake Oswego, OR).

Nonpolymeric DES

In an effort to eliminate the use of the polymeric drug carriers, new DES were designed in which the drug is eluted directly from the metallic platform without the need for a polymeric drug carrier. The main prototypes that have been or are being investigated in clinical trials are the Yukon Choice (Translumina), which employs a microporous metal stent backbone from which sirolimus and probucol are eluted, and the Biomatrix Freedom stent (Biosensors International Group, Ltd.), which employs microstructured surface holds to carry and elute biolimus A9. Another interesting stent design in this category is the recently announced drug-filled stent (Medtronic, Inc.), which is expected to start a first-in-man trial next year, in which the drug is carried inside the lumen of a tubular stent platform and is eluted from small holes located in the abluminal side of the stent strut.

Other BP-DES

This category comprises a limited group of DES technologies that employ a bioabsorbable polymer to carry and elute the drug in combination with another coating that mostly serves a different purpose than drug carriage. A prototype is the Combo stent (OrbusNeich, Fort Lauderdale, FL), which consists of a metallic 100-mm, stainless steel stent platform with an abluminal coating of a bioabsorbable polymer matrix formulated with sirolimus for sustained release and an anti-CD34 antibody cell-capture coating on the luminal surface that targets CD34+ endothelial progenitor cells in the circulation.

CLINICAL EVIDENCE ON BP- AND DP-DES

The LEADERS trial¹⁰ was the first randomized trial that compared in large scale a first-generation biolimus-eluting BP-DES (Biomatrix) with a first-generation DP-DES (Cypher) in all-comer patients. The trial met its primary endpoint: cardiac death, MI, and target vessel revascularization (TVR) at 9 months. Statistically nondifferent and numerically similar event rates also were observed for the safety endpoint of cardiac death and MI at 9- and 12-month follow-up. At 5 years, the primary endpoint was not significantly different between the two stents (22.3% and 26.1%, respectively; $P = .07$); however, a clear trend in favor of Biomatrix was evident.¹¹ The safety endpoints of cardiac death and MI were also almost identical for both stents, with curves overlapping each other at up to 5-year follow-up (cardiac

death, 8% vs 8.4%; $P = .72$; MI, 9.9% vs 10.5%; $P = .79$). However, definite stent thrombosis rates at 5 years showed a trend in benefit for the Biomatrix stent (2.6% vs 4.5%; $P = .06$) and a significant advantage beyond 1 year (0.7% vs 2.5%; $P = .003$).

Another large trial, the SORT-OUT V, which compared the Nobori stent to the first-generation Cypher stent showed similar event rates for both stents but failed to prove noninferiority for a composite of safety and efficacy primary endpoint (cardiac death, MI, definite stent thrombosis, and clinically driven TVR; 4.1% vs 3.1%, respectively; $P = .22$; P noninferiority = .06).¹² Interestingly, the rates of definite stent thrombosis at 1 year were significantly higher in the Nobori arm (0.7% vs 0.2%; $P = .034$).

Differently from the BP-DES, the clinical programs with the second-generation DP-DES, and in particular the everolimus-eluting Xience V stent, engaged in superiority trials as compared to the first-generation DP-DES. Indeed, two large prospective randomized trials, the SPIRIT IV¹³ and COMPARE trials,¹⁴ both showed superiority of the Xience V stent compared to the first-generation paclitaxel-eluting Taxus stent in moderate-risk and all-comer patients for the respective primary endpoints, as well as separate safety and efficacy endpoints. Both trials showed a reduced rate of stent thrombosis already at 30 days, which was maintained at 1 year. The superiority for the safety and efficacy endpoints, as well as for stent thrombosis, was maintained up to the latest available follow-up (3 years for the SPIRIT IV trial¹⁵ and up to 5 years for the COMPARE trial¹⁶).

Furthermore, two recent network meta-analyses have also shown that the Xience V stent is associated with significant reductions in TVR, MI, and definite stent thrombosis rates when compared to the first-generation DP-DES and, importantly, BMS.^{17,18} These results have led to a paradigm shift in that second-generation DP-DES are not only more efficient than the BMS, but their utilization might also be associated with incremental safety advantages.

Large-scale comparisons between the first-generation BP and second-generation DP-DES are limited. Only two trials, COMPARE II¹⁹ and NEXT,²⁰ have completed 1-year follow-up to date, both comparing the everolimus-eluting Xience stent with the biolimus-eluting Nobori stent. However, neither of these trials was adequately powered to study safety endpoints. In the COMPARE II trial, the Nobori stent showed numerically higher event rates for the primary endpoint (death, MI, and TVR) than Xience (5.2% vs 4.8%, respectively); however, by using a noninferiority margin of 4% (> 80%

of the observed 4.8% event rate in the control arm), the authors claimed noninferiority (P noninferiority = .0001). The NEXT trial also proved noninferiority of the Nobori stent compared to Xience; however, the trial was powered for target lesion revascularization, and therefore, further conclusions on safety outcomes cannot be drawn.

In light of the conflicting results from these trials, two large-network meta-analyses were conducted to study the first-generation biolimus-eluting BP-DES compared to other first- and second-generation DP-DES.^{21,22} Both analyses found improved safety endpoints (reduced rates of MI and definite stent thrombosis, respectively) with the second-generation everolimus-eluting DES stent compared to the first-generation BP-DES. Furthermore, in the first meta-analysis,²¹ posterior probability curves generated by means of Bayesian statistics for available FDA-approved DES and biolimus-eluting BP-DES, with Cypher as the common comparator, showed that the second-generation DP-DES (Xience and Resolute) are associated with a more favorable profile than the other DES, including biolimus-eluting DES, for the safety endpoints of mortality, MI, and definite or probable stent thrombosis and therefore can be considered the safest DES to date (Figure 2).

It appears that both stent categories, the first-generation BP-DES and the second-generation DP-DES, have achieved the goal for which they were designed (ie, reduction of the very late [beyond 1 year] stent thrombosis events). However, the overall results still favor second-generation DP-DES, as these favorably affect safety outcomes already within the first year, with such effect maintained beyond 1 year, whereas the impact on safety with the first-generation BP-DES is observed only beyond 1 year. The observed reduction in 30-day and 1-year stent thrombosis event rates points to the importance of these events in the overall performance of any DES device on longer follow-up, as the majority of the stent thrombosis events with DES occur within the first year.^{2,23}

From this perspective, the favorable outcomes with the second-generation DP-DES might be due not only to improvements in the polymer coating but also to other differences between these devices—mainly the thinner-strut stent design. Thinner stent struts have been associated with less mechanical trauma and inflammation of the vessel wall and faster re-endothelialization in preclinical⁹ and clinical²⁴ studies. Therefore, these stent platform changes, which are incorporated in the design of the second-generation BP-DES, might be associated with improved safety outcomes not only

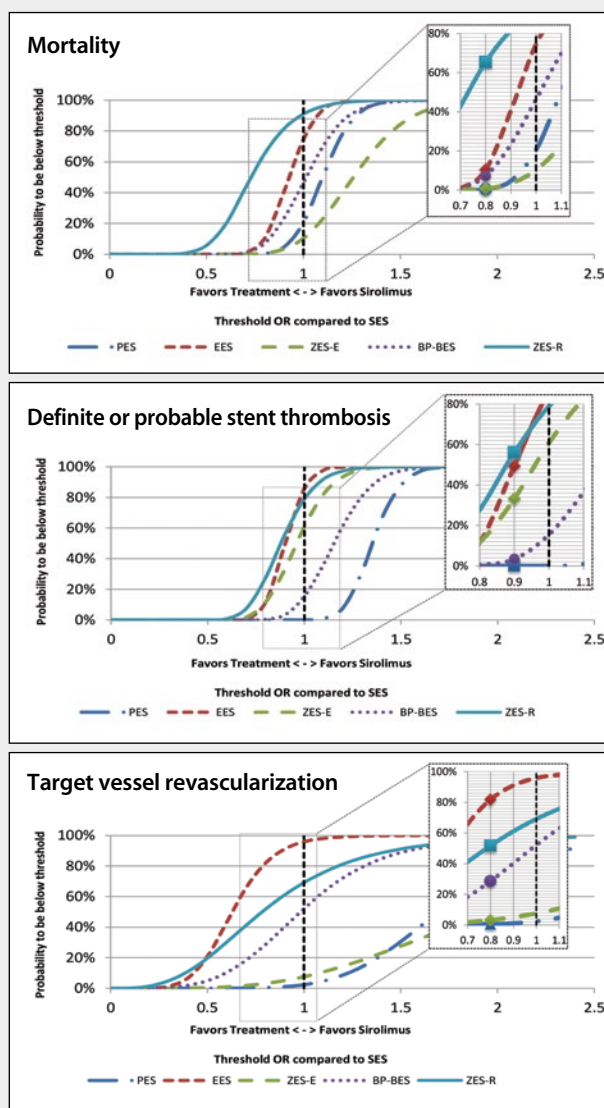
beyond 1 year, as is the case with the first-generation BP-DES, but also during the first year, as is the case with the second-generation DP-DES. The currently available data from randomized controlled trials are limited but do point in this direction.

The results of the ISAR-TEST 4 trial comparing the bioabsorbable polymer Yukon SS stent (strut thickness, 87 μ m) with DP-DES (a mix of Xience and Cypher) showed numerically very similar safety and efficacy outcomes at 1 and 3 years between this stent and the Xience arm.^{25,26} Similarly, the results of BIOFLOW II,²⁷ which compared the sirolimus-eluting, ultra-thin-strut (60 μ m), bioabsorbable-polymer Orsiro stent with Xience Prime are very promising, with both stents having a very low rate of events (4.8% and 5.2%, respectively; P = NS). Importantly, the optical coherence tomography-detected mean neointimal area was significantly lower with the newer stent at 9 months (when the polymer is still present), whereas the percentage of covered struts was 98.3% for Orsiro and 97.5% for Xience Prime (P = .042). This further corroborates the hypothesis that thinner stent struts may foster a very thin but uniform stent coverage.

Similarly, in the EVOLVE trial,²⁸ the other novel second-generation BP-DES, Synergy, as compared with the second-generation DP-DES Promus Element, resulted in similar outcomes of clinical and angiographic endpoints. Although these trials were not powered for clinical endpoints, the emerging results for the second-generation BP-DES are promising and have prompted further research on these devices. Indeed, larger and adequately powered randomized trials, such as the ongoing BIO-RESORT (comparing Orsiro, Synergy, and Resolute stents; NCT01674803) and EVOLVE II (comparing Synergy with the Promus Element stent; NCT01787799) trials, will shed further light on the potential of the newer devices to further improve safety and efficacy outcomes compared to the current gold standard, the second-generation DP-DES. Furthermore, BIO-RESORT might also give further insights on the impact of the polymer absorption velocity (3 months for the Synergy stent and up to 1 year for the Orsiro stent) on the polymer absorption-induced vessel wall inflammatory reactions.

The evidence for the polymer-free DES to date is limited. The advantages these stents offer compared to other DP- or BP-DES is the absence of a polymer, which basically confers BMS properties to these stents once the drug is eluted. Although this is perceived as a potential safety benefit, it should not be forgotten that, similarly to the other DES, these stents also elute an antiproliferative drug, which beyond the inhibition of

Figure 2. Posterior probabilities of different risk thresholds (odds ratios) for each stent compared with a sirolimus-eluting stent (SES, reference treatment). Their curves can be used to examine the overall safety and efficacy profile of specific DES compared with reference treatment SES (identity line = unit value); improved safety profiles indicated by the highest leftward shift of curve, as shown with the Resolute zotarolimus-eluting stent (ZES-R) and everolimus-eluting stent (EES) with regard to mortality and myocardial infarction; curves allow inferences to extract probabilities of specific risk thresholds corresponding to minimal odds ratio compared with SES as reference treatment. For example, compared with SES, there is a probability of 65% that the ZES-R reduces odds of mortality by at least 20% corresponding to odds ratio of 0.8; conversely, this probability is estimated to be close to 0% with a biodegradable polymer biolimus-eluting stent (BP-BES), meaning no additional mortality benefit provided by BP-BES compared with SES. There is a probability of 56% and 49%, respectively, that ZES-R and EES reduced odds of MI by at least 10%, corresponding to an odds ratio of 0.9, but this probability is estimated close to 0% with BP-BES, meaning there are no additional MI benefits provided by BP-BES compared with SES (reference treatment). PES, paclitaxel-eluting stent; ZES-E, Endeavor zotarolimus-eluting stent (Medtronic, Inc.). Reproduced with permission from Navarese EP et al. *Br Med J*. 2013;347:f6530.²¹



smooth muscle cells also delays neoendothelialization at least for as long as the drug is eluted.

The only clinical evidence worth mentioning for this group of devices comes from the ISAR-TEST 5 trial,²⁹ which compared the Yukon Choice stent with the second-generation Resolute DP-DES. The 1-year results were almost identical for both stents, with time-to-event curves fully overlapping. Although noninferiority was uncontestedly proven, any potential benefits with the Yukon Choice device remain to be adjudicated on long-term follow-up. Likewise, potential benefits in terms of shorter dual-antiplatelet therapy regimens, for this as for other devices in this category, remain to be proven. Indeed, the safety of these devices with

shorter dual-antiplatelet therapy regimens is being tested in the LEADERS FREE trial,³⁰ which compares the BioFreedom DES (Biosensors International Group, Ltd.) with an identical-platform BMS. The LEADERS FREE trial assesses the potential of the BioFreedom DES to deliver the antirestenotic benefit of a DES (designed for superiority vs BMS for clinically driven TLR) while maintaining the safety of a BMS (noninferiority of BioFreedom compared with BMS in terms of cardiac death, MI, and definite/probable ST) in patients with a high risk of bleeding receiving a short course (30 days) of dual-antiplatelet therapy. Although BMS are not the gold standard nowadays, they are still used, particularly in this not-small category of patients in whom

the polymer-free DES might be more appropriate than other DES.

CONCLUSION

Clinical outcomes with the current-generation bioabsorbable- or durable-polymer DES have dismantled the safety concerns related to the first-generation DP-DES. However, differences between the novel DES devices exist, with the second-generation DP-DES being associated with significantly improved safety outcomes emerging already in early and maintained until very late follow-up as compared to its predecessors (the first-generation DP-DES and BMS), whereas the safety impact of the biolimus-eluting, first-generation BP-DES appears to be limited only to very late thrombotic events. Direct comparisons between first-generation BP-DES and second-generation DP-DES are underpowered for safety endpoints; however, large-network meta-analyses show a favorable safety profile for the second-generation DP-DES, which can be considered the gold standard DES to date.

Second-generation BP-DES or polymer-free DES might carry the potential to further improve safety and efficacy outcomes compared to other first-generation BP-DES, as well as second-generation DP-DES; however, very large trials would be needed to prove any clinically meaningful differences between these devices. ■

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