Second- versus First-generation Drug-eluting Stents

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Abstract

Drug-eluting stents (DES) have demonstrated their superiority over bare-metal stents (BMS) with respect to in-stent restenosis and the need for repeat revascularisation. BMS and first-generation DES, such as sirolimus-eluting (Cypher®) and paclitaxel-eluting stents (Taxus®), have further improved the results of percutaneous coronary intervention (PCI) by improving early results and reducing the risk of restenosis. However, there is currently a debate as to the safety of these first-generation DES given the potential for late stent thrombosis, especially after discontinuation of dual-antiplatelet therapy. Second-generation DES, such as zotarolimus-eluting (Endeavor®) and everolimus-eluting stents (Xience V®), have recently become available in the US and Europe. The available data already suggest the superiority of the Xience V stent in comparison with the Taxus stent in terms of prevention of restenosis, without significant untoward events. Nonetheless, the number of patients studied and the follow-up duration are still too limited to enable definitive conclusions. This systematic review aims to provide a concise and critical appraisal of the available data to compare first- and second-generation stents.

Keywords

Coronary disease, angioplasty, thrombosis, restenosis, stents

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First-generation Stents

Since drug-eluting stents (DES) received the CE mark in 2002 and the US Food and Drug Administration (FDA) approved the first DES in 2003, there has been a significant increase in the use of these devices. The advent of DES has revolutionised the field of interventional cardiology by having a major impact on patient care through their efficacy in reducing the need for repeat revascularisation. The first of the -olimus family drugs used on endovascular prostheses was sirolimus, a natural macrocyclic lactone able to inhibit mammalian target of rapamycin (mTOR) and thereby block the cell cycle mainly of the smooth-muscle cell from the G1 to S phase.[1,2] Sirolimus proved to have potent antiproliferative and immunosuppressive effects. Several successive studies proved the efficacy of the sirolimus-eluting stent (SES) Cypher® (Cordis): RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with *de novo* native coronary artery Lesions (RAVEL), SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with *de novo* coronary artery lesions (SIRIUS), Canadian SIRIUS (C-SIRIUS) and European SIRIUS (E-SIRIUS).[3–9] Due to the polymer, 75% of the drug is released over the first 10 days. Nevertheless, the antirestenotic properties of the SES proved to persist for much longer.[10] The five-year clinical outcome from a pooled analysis of four randomised controlled trials (RCTs) has recently been published and continues to demonstrate superior efficacy of SES over bare-metal stents (BMS), with a significant reduction in target vessel revascularisation (TVR) rate (15.2 versus 30.1%; p<0.0001).[11]

Although not a member of the -olimus family, the paclitaxel-eluting stent (PES) Taxus® (Boston Scientific) was the second DES to receive FDA approval, one year after the SES. Paclitaxel was first discovered by the National Cancer Institute (NCI), who, in a search for naturally occurring agents with strong antiproliferative qualities, isolated it from the bark of the Pacific yew tree, *Taxus brevifolia*. Paclitaxel stabilises microtubules and thereby inhibits cell division in the G0/G1 and G2/M phases. The randomised TAXUS-I trial (2003) was designed as a first-in-man (FIM) phase I feasibility study and proved that a polymer-coated PES was superior to BMS at six- and 12-month follow-up.[12] Thereafter, the TAXUS family trials expanded with the II, IV, V, and VI trials and confirmed the superiority of PES compared with BMS in more complex patients and lesions.[13–16]

Both of these first-generation stents – the SES and PES – were based on a combination of a metallic platform, a durable biocompatible polymer and an antiproliferative drug. There are well-known caveats on the performance of their respective metallic stent platforms, delivery and dilation systems and polymer coatings. While these first-generation DES are a major step forward in that they halve the need for repeat revascularisation without an increase in death or myocardial infarction (MI), there is an increased risk of late stent thrombosis (LST), which is of particular concern after discontinuation of dual antiplatelet therapy.[17]

Data from the BAsel Stent Kosten Effektivitäts Trial – LAte Thrombotic Events (BASKETLATE) study highlighted that this phenomenon is not

trivial.[18] In this randomised clinical trial, a total of 826 patients were randomised to treatment with a DES or BMS. After discontinuation of dual-antiplatelet therapy at six months, the clinical event rate in the subsequent months was worryingly high: 4.9% of the patients with DES experienced cardiac death or MI in the subsequent year compared with 1.3% of the patients with BMS (p=0.01). This was further confirmed by a meta-analysis of 14 clinical trials that randomised 6,675 patients to PES or SES versus BMS: there was a low rate of very LST (>1 year following the index procedure), but it was significantly higher among DES patients (five events/1,000 DES).[19] Although there was significantly more late thrombosis (occurring >30 days post-PCI) associated with PES, the authors acknowledged that SES may similarly increase the risk of late thrombosis compared with BMS.[20] There are plausible biological mechanisms to support these concerns, including delayed endothelialisation, enhanced agonist-induced platelet aggregation and hypersensitivity reaction to the polymer. In addition, there are theoretical concerns that stent deployment in the context of a pro-thrombotic, inflammatory state in acute coronary syndrome (ACS) patients may compromise vessel healing and re-endothelialisation, and hence could increase the risk of LST – concerns supported by published histological data.[21] SIRTAX was an RCT in which 1,012 patients were assigned to treatment with either an SES or a PES. The primary clinical end-point, a composite of cardiac death, MI and target lesion revascularisation (TLR) at nine months, was published in the *New England Journal of Medicine* in 2005,[22] and showed a significantly lower rate of major adverse cardiac events (MACE) with SES than with PES, a difference that was largely driven by a significant reduction in TLR (8.3 versus 13.8%; p<0.01). Findings from the SIRTAX-LATE data presented at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in 2009 also highlighted that vascular healing in response to first-generation DES is not complete, and in some patients may be ongoing up to five years after device implantation. The risk of very LST continued between one and five years, with a cumulative rate of definite stent thrombosis of 4.4% at five years. All of these issues with first-generation stents led to the development of second-generation DES.

Second-generation Stents

First-generation DES were considered to be essentially BMS that had been sprayed with polymer and drug. In the first-generation DES (Taxus and Cypher), 316L stainless steel was used as the platform and the strut thickness ranged from 130 to 140µm. With 316L stainless steel, the radial strength is dependent on the thickness of the stent's struts. Newer stent designs use cobalt–chromium, which has greater radial strength per thickness and is radio-opaque, and thus allows thinner struts. In fact, the second-generation DES – Endeavor®, a zotarolimus-eluting stent (ZES), and Xience V®, an everolimus-eluting stent – are constructed from cobalt–chromium and have thin stent struts (80–90µm) that result in a decrease in neointimal response and more rapid re-endothelialisation. Pre-clinical data have demonstrated that stents with thinner struts have a greater degree of re-endothelialisation compared with those with thicker struts.[23] Both second-generation DES, Endeavor and Xience V, are approved and now available in the US and Europe.

The Endeavor ZES system (Medtronic Vascular, The Netherlands) has been available in Europe since 2005 and received FDA approval in October 2007 for use in the US. The stent platform is composed of a cobalt alloy stent, a phosphorylcholine (PC) polymer and zotarolimus (ABT-578), a drug designed to inhibit smooth-muscle-cell proliferation.[24] The drug layer of the ZES is 90% zotarolimus and 10% PC; with full drug elution, this layer disappears, leaving behind only a 1µ PC base coat. Data from a series of large RCTs have demonstrated that not only is the ZES effective in preventing restenosis, with low rates of TLR, but also the incidence of LST and very LST is extremely low; indeed, in contrast to SES and PES, the rate of LST was no higher than with the comparator BMS.[25–27] The safety and efficacy of the Endeavor ZES platform has been established in stable *de novo* coronary artery lesions. The Endeavor I study[25] included 100 patients with a single coronary lesion and showed a MACE rate of 2% at 12 months. The Endeavor II study[26] in 1,197 patients with a single *de novo* coronary artery lesion demonstrated a low MACE rate (7.3%), a low TLR rate (4.6%) and a stent thrombosis rate of 0.5%, maintained out to two-year follow-up. The Endeavor III study[27] comparing ZES with SES in 436 patients showed no cases of stent thrombosis after nine months of follow-up. The results from these studies provided evidence that the ZES platform is safe and efficacious, and, because of the exceedingly low reported rate of stent thrombosis with the ZES platform, it was suggested that there may be a theoretical advantage to using ZES in acute, high-risk PCI such as ST-segment-elevation MI (STEMI).

Another member of the -olimus family is everolimus (Xience V, Abbott Laboratories), a sirolimus analogue with a single minimal alteration in its molecular structure (position 40) without a chemical modification of the mTOR binding domain.[28] Of interest is that, when implanted in rabbit iliac arteries, a more rapid endothelialisation was observed in the everolimus-eluting stent than in the SES, ZES or PES, demonstrated by a complete endothelialisation of the struts with exhibition of cd31 (an antigen surface marker of good endothelial functionality) in the cells at 14 days (R Virmani, unpublished data, 2006). The platform of the Xience V stent is an L-605 cobalt–chromium balloon-expandable stent built on the proven Multi-Link Vision® (Abbott Laboratories) BMS system, whose main characteristics are high flexibility and ease of deliverability. With a strut thickness of 81µm, it has the thinnest coronary stent struts.[29] The polymer coating in the Xience V stent is formed by two polymer layers: a primer adhesion layer of poly(n-butyl methacrylate) and a drug reservoir of poly(vinylidene fluoride co-hexafluoropropylene) combined with everolimus. The layer of everolimus–polymer matrix with a thickness of 5–6µ is applied to the surface of the stent and loaded with 100µg of everolimus per cm^2 of stent surface area, with no top coat polymer layer. Of interest, the coating thickness is lower for the Xience V (5.3µ) than for the Cypher (7.2µ) or Taxus (15.6µ) stents.

The Clinical Evaluation of the Xience V Stent System in the Treatment of Patients with *de novo* Native Coronary Artery Lesions First (SPIRIT) trial proved the superiority of everolimus embedded in a durable polymer on a cobalt–chromium stent compared with BMS (Multi-Link Vision). The SPIRIT-I FIM study was a prospective, single-blind, randomised trial performed in nine centres between December 2003 and April 2004. A total of 28 patients were randomly assigned to receive the everolimus-eluting stent and 32 were assigned to receive the BMS. Angiographic follow-up was performed at six and 12 months. In-stent late loss (the primary end-point) at six months was 0.10 and 0.84mm in the Xience V and control arms, respectively (p<.001), and remained relatively unchanged at 12-month follow-up (0.23 and 0.81mm, respectively). In addition, there was a 64% reduction in neointimal hyperplasia by intravascular ultrasound in patients randomised to the Xience V stent (36.4 and 13.3mm^2, respectively).[30]

The number of LSTs in the Xience V arm of the SPIRIT-I trial was zero out to three years of clinical follow-up.

In the SPIRIT-II trial in 300 patients, the Xience V stent proved to be superior to the PES for reduction of both late loss and binary restenosis. In-stent late loss was 0.12 for Xience V and 0.37 for Taxus (p<0.001). Similarly, in-stent binary restenosis occurred in three of 237 (1.3%) versus three of 86 (3.5%; p=0.194), and TLR in six of 223 (2.7%) versus five of 77 (6.5%; p=0.157). In addition, cardiac death occurred in none of 223 (0%) versus one of 77 (1.3%; p=0.257), MI in two of 223 (0.9%) versus two of 77 (2.6%; p=0.272) and stent thrombosis in one of 223 (0.5%) versus one of 77 (1.3%; p=0.448).[31]

Subsequently, the SPIRIT-III study included 1,002 patients at 65 US sites randomised in a 2:1 manner to the Xience V stent or the Taxus stent. At completion of the two-year follow-up, treatment with Xience V compared with PES resulted in a significant 32% reduction in target vessel failure (10.7 versus 15.4%, hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.48–0.98; p=0.04) and a 45% reduction in MACE (7.3 versus 12.8%, HR 0.55, 95% CI 0.36–0.83; p=0.004).[32] However, neither SPIRIT-II nor SPIRIT-III was powered to demonstrate superiority for clinical end-points, and the routine performance of angiographic follow-up may have artificially exaggerated the absolute benefits of the Xience V stent. Therefore, SPIRIT IV was designed without angiographic follow-up to further assess the differences between these two stent platforms.[33]

SPIRIT IV randomised 3,690 patients to receive the Xience V or the PES Express 2 stent. Three-year data were presented at the TCT meeting in 2009, and revealed a 43 and 39% reduction in MACE and TLR, respectively, in comparison with PES. No stent thromboses occurred in either stent between two and three years, and there were no differences in overall rates of stent thrombosis between the two stents (0.9 versus 1.6%; p=0.37). However, SPIRIT IV found a statistically significant difference in stent thrombosis between the two arms at one year: 0.29% for Xience V versus 1.06% for Taxus (p=0.003).

With results that back up those of SPIRIT IV, a second trial in real-life practice comparing Xience V with PES, COMPARE, randomised 1,800 consecutive patients undergoing elective or emergency PCI to blinded treatment. The primary end-point was a composite of all-cause mortality, non-fatal MI and TVR within 12 months. Follow-up was completed in 1,797 patients, and on the intention-to-treat analysis the primary end-point occurred in 56 of 897 patients (6%) in the Xience V group versus 82 of 903 (9%) in the PES group (relative risk [RR] 0.69, 95% CI 0.50–0.95; p=0.02 for superiority). One-year follow-up showed that, in addition to the 31% RR reduction (p=0.02) for the composite end-point in patients treated with the Xience V, the everolimus-eluting stent was associated with significantly less stent thrombosis (p=0.002).[34] This represents some very important progress with second-generation stents, as not only efficacy but also safety has improved, namely by a significant reduction in MI as well as stent thrombosis at one year.

Next-generation Stents

In addition to the improvements that have been made in second-generation DES, there are currently newer approaches being tested such as biodegradable polymers and stents, polymer-free drug delivery and the pro-healing approach. Pro-healing technology, designed to enhance re-endothelialisation, is used in the Genous stent (coated with anti-CD34 antibody). Two-year follow-up data from the single-centre TRIAS-HR study were presented at the Euro-PCR meeting in 2009, showing similar mortality (5.1 versus 4.2%) and TLR rates (15.3 versus 13.7%) for the Genous stent versus the PES. However, the thrombosis rate with the PES was 5.3% compared with 0.0% in the Genous stent arm. In first-generation DES, non-erodable polymers were used in both the Cypher and Taxus stents: the Cypher stent used polyethylene-co-vinyl acetate (PEVA) and poly(n-butyl methacrylate) (PBMA) and the Taxus stent used poly(styrene-b-isobutylene-b-styrene) (SIBBS). However, as mentioned above, these polymers are likely to provoke an inflammatory reaction.[35]

The next major breakthrough could be bioabsorbable polymers and stents as a potential solution to avert the risks such as very LST and delayed vessel healing associated with currently available DES. Compared with metallic stents, there are several potential advantages, including complete absorption of stent material, a phenomenon that may facilitate repeat treatments to the same site and allow restoration of vasomotion with enhanced potential for vessel remodeling. Among the polymers suggested for bioabsorbable stents are poly-L-lactic acid (PLLA), polyglycolic acid (PGA), poly(D,L-lactide/glycolide) copolymer (PDLA) and polycaprolactone (PCL). One such stent, the BVS (Abbott, Abbott Park, IL, US), is a polylactic acid polymer everolimus-eluting stent. Polylactic acid polymer is degraded in the body via the Krebs cycle into CO_2 and water, and no drug or polymer is left behind after the elution period. The rationale for the biodegradable polymer is to reduce the risk of LST and enhance vascular remodelling. One such trial has been performed with the biolimus-eluting stent with an abluminal biodegradable polymer compared against the SES with a durable polymer. Biolimus is a highly lipophilic sirolimus analogue that is immersed into a polylactic acid biodegradable polymer and applied to the abluminal surface of a stainless steel stent. The polymer breaks down after six to nine months. The Limus Eluted from a Durable versus Erodable Stent Coating (LEADERS) trial, a head-to-head study that investigators say is representative of real-world clinical practice, resulted in non-inferior safety, efficacy and angiographic outcomes at nine months.[36] The LEADERS study was conducted in 10 European centres and enrolled 1,707 patients with chronic stable coronary artery disease or ACS. The primary end-point – a composite of cardiac death, MI and TVR at nine months – as reported in *The Lancet* showed event rates of 9.2% for the biolimus-eluting stent and 10.5% for the SES, fulfilling non-inferiority, with a risk difference of 1.3%, which was significant at a p-value of 0.0034 for achieving non-inferiority. The two-year follow-up data were presented at TCT 2009. For the end-point of definite stent thrombosis, the rate was 2.0% for both platforms at one year, and the rate between one and two years was 0.2% for biolimus-eluting stents and 0.5% for SES. The clinical implications are that these findings attest that biolimus eluted from a biodegradable polymer is at least as safe and effective as sirolimus eluted from a durable polymer at two-year follow-up.

ABSORB is one of the recent clinical trials that has looked at the benefits of using bioabsorbable stents. The ABSORB trial was a prospective, multicentre, open-label FIM study that assessed the BVS stent tested originally in just 30 patients with single *de novo* lesions in 3.0mm vessels.[37] Two-year imaging results (intravenous ultrasound [IVUS], multislice computed tomography [CT] and optical coherence tomography [OCT]) have been published recently indicating that at least one-third of the stent has been absorbed by the vessel wall.[38] Three-year data from the first phase of the ABSORB trial were recently presented at American Heart Association (AHA) scientific sessions, and showed no

cases of stent thrombosis out to three years and no new MACE between six months and three years (3.6% at three years).

Conclusion

Newer DES are proving to be significantly more effective and safer than the first-generation DES. While the buzz surrounding bioabsorbable stents continues to build, there are new evolutions within DES technology, and the everolimus-eluting Xience V stent is among the most promising of the second-generation DES.

The second generation DES, with better stent design and greater biocompatibility with release kinetics, have shown promising results, but larger RCTs are needed in patients with ACS and real-world situations of patients with long lesions, calcifications or bifurcations.

As with all DES platforms, longer-term follow-up is required to assess their safety, especially with respect to very LST and the requirement for prolonged dua-antiplatelet therapy. ■

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