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Drug-eluting Stents in Acute Coronary Syndrome: Is There a Risk of Stent Thrombosis with Second-Generation Stents?

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Abstract

Over the past decade, the advent of drug-eluting stents (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. A number of stents capable of delivering an anti-proliferative agent designed to prevent neointimal hyperplasia, the principal mechanism of restenosis after stenting, have been evaluated; four of these devices are currently approved by the U.S. Food and Drug Administration (FDA). Bare metal stent (BMS) and first-generation DES, such as sirolimus-eluting (SES-Cypher®) and paclitaxel-eluting stents (PES-Taxus®), have further improved results of percutaneous coronary intervention (PCI) by improving early results and reducing the risk of restenosis. However, there is currently debate on the safety of these first-generation DES, given the potential for late stent thrombosis (LST), especially after discontinuation of dual anti-platelet therapy. Second-generation DES, such as zotarolimus-eluting (ZES-Endeavor®) and everolimus-eluting stents (EES-Xience V®), are become available in the USA and/or Europe. Recently, long-term results comparing DES with BMS in patients with ST-segment-elevation MI (STEMI) have raised some questions about the long-term risks of the drug-eluting devices. It may be useful to pause, reflect for a moment, and consider some recent pertinent results regarding their wider use. This systematic review tries to provide a concise and critical appraisal of the data available to compare first and second generation stents especially to assess risk of stent thrombosis (ST) with second-generation DES.

Keywords

coronary disease; angioplasty; thrombosis; restenosis; stents

DES effectiveness is determined by the ability to limit neointimal hyperplasia and maintain vessel patency. Angiographic follow-up provides a means to assess this effect by measuring the loss of restored vessel lumen over time. Two continuous measures, late loss and percent diameter stenosis, provides statistically powerful endpoints for measuring differences between devices.

First-generation stents

Since DES received the CE mark in 2002 and US Food and Drug Administration (FDA) approval in 2003, there has been a significant increase in the use of these devices. The first of the Limus family drugs used on endovascular prosthesis was sirolimus, a natural macrocyclic lactone blocks the cell cycle mainly of the smooth muscle cell from the G1 to S phase ^(1,2), proved to have a 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 [C]-SIRIUS and European [E]-SIRIUS) (3–9).

Due to the polymer, 75% of the drug is released over the first 10 days. Although not a member of the limus family, the paclitaxel-eluting stent (PES) (Taxus®, Boston Scientific) was the second DES to receive FDA approval, one year after the SES. 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 months of follow-up (10). Thereafter, the TAXUS family trials expanded with the **II, IV, V,** and **VI** trials and confirmed the superiority of PES as compared with BMS in more complex patients and lesions (11–14).

In the **TYPHOON** trial (15), the use of SES vs. BMS resulted in significant reduction in combined Major Adverse Cardiac Event (MACE) (5.9% vs. 14.6%, $p < 0.001$) and target-lesion revascularisation (TLR) (3.7% vs. 12.6%, $p < 0.0001$). Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (**HORIZONS-AMI**) study (16) randomised 3006 patients undergoing primary PCI to receive either a PES or BMS, resulted in a significant reduction of ischaemia-driven TLR (4.5% vs. 7.5%, $p = 0.002$) at one year.

The findings from the HORIZONS-AMI trial will have a major impact on how decisions are made regarding DES and BMS in the highest risk patients, especially patients presenting with STEMI. 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, there is an increased risk of LST, which is of particular concern, especially after discontinuation of dual anti-platelet therapy (17).

Pooled clinical trials of SES and PES versus their BMS counterparts have shown no differences for death, MI or stent thrombosis during four years of follow-up. Both stents, however, were observed to have slightly more frequent ST events in the period beyond the first year; this is termed very late stent thrombosis (18) (Mauri et al, 2007). These differences were not statistically different but were determined to be potentially clinically meaningful and resulted in a recommendation by a special FDA advisory panel to extend dual antiplatelet therapy for a minimum of 12 months if there are no bleeding contraindications. Randomised trials comparing SES versus PES have generally not demonstrated any differences in death, MI or stent thrombosis. In the meta-analysis above, however, there was slightly increased risk of stent thrombosis for PES (HR, 0.66; 95% CI, 0.46–0.94; $p = .02$), with the difference beginning after six months. This effect was driven mostly by a single study and should be interpreted with the appropriate caution.

It is generally accepted that DES are associated with an increased incidence of LST compared to BMS (19), this excess risk appears to be small and not to translate into adverse clinical outcome. However, until now this has remained a concern, particularly in ACS patients. 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 may compromise vessel healing and re-endothelialisation; and hence could increase the risk of LST, concerns supported by recently published histological data (20). The extent of thrombus burden at the

time of stent implantation might also be a significant factor in the incidence of LST. Sianos et al ⁽²¹⁾ demonstrated a two-year rate of LST of 8.2% in patients with large thrombus burden vs. a rate of only 1.3% for those with a small thrombus burden.

Recently long-term results from two studies comparing DES with BMS in patients with STEMI have raised some questions about the long-term risks of DES. In one study known as **PASSION** trial, conducted in two centres between 2003 and 2004, the researchers enrolled 619 patients with STEMI and followed them for up to five years. All patients were treated with 75mg of clopidogrel daily for at least six months and 80 to 100mg aspirin indefinitely. At five years, the composite end point of cardiac death, recurrent MI and TLR was 22.0% in the BMS arm and 18.3% in the DES arm, a non-significant difference. Unlike the **DEDICATION** study, there was no statistically significant difference in the rates of cardiac death-11.5% in the BMS and 8.9% in the DES arms. Rates of TLR at five years were 10.5% and 7.3% in the BMS and DES arms, respectively.

There was a trend toward increased rates of definite stent thrombosis among those treated with the PES. At five years, ST was double that of the BMS treated patients, although this increased risk was not statistically significant. The increased risk appeared between years one and five of follow-up, according to investigators. In the **DEDICATION** trial, investigators report an increased risk of cardiac death at three years in patients treated with a DES compared with patients treated with a BMS.

The **DEDICATION** trial randomised 626 STEMI patients either to a BMS or a DES. Eight-month follow-up results hinted at an increased risk of cardiac mortality. During follow-up at three years, this risk was maintained, with a 6.1% cardiac death rate in those treated with the DES and a 1.9% cardiac death rate in the BMS arm. Major adverse cardiovascular events (MACE), which included cardiac death, re-infarction and TLR, were significantly lower in the DES arm, a result that was driven by a reduction in TLR.

Second-generation Stents

First-generation DES were considered to be essentially BMS that have been sprayed with polymer and drug. In the first generation of DES (Taxus and Cypher), 316L stainless steel was used as the platform and the strut thickness ranged from 130 to 140µm. In fact, the second generation of DES (Endeavor with zotarolimus eluting stent-ZES and Xience V with Everolimus eluting stents-EES) are constructed from cobalt-chromium and have thinner stent struts (80–90µm) that result in a decrease in neointimal response and more rapid re-endothelialisation.

This design improves flexibility and stent delivery and may be associated with reduced vessel injury. Preclinical data have demonstrated that stents with thinner struts have a greater degree of re-endothelialisation compared to those with thicker struts ⁽²²⁾.

ZES is marketed as Endeavor (Medtronic, Santa Rosa, CA) 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 ⁽²³⁾. The drug layer of the ZES is 90 percent zotarolimus and 10 percent PC; with full drug elution, this layer disappears, leaving behind only a 1-micron PC base coat. EES is marketed as both **XIENCE V** (Abbott Vascular Devices, Redwood City, CA) and **Promus** (Boston Scientific, Natick, MA).

It is a thin-strut cobalt-chromium stent coated with a thin durable fluoropolymer that elutes everolimus, an analogue of sirolimus, with an elution profile similar to that of SES. The layer of everolimus-polymer matrix with a thickness of 5–6 microns is applied to the surface of the stent and is loaded with 100 µg of everolimus per cm² of stent surface area with no

top coat polymer layer. Of interest, coating thickness appears less for the Xience V (5.3 microns) than for Cypher (7.2 microns) or Taxus (15.6 microns).

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 late and very LST is extremely low; indeed in contrast to SES and PES, LST was no higher than with the comparator BMS^(24–26). The safety and efficacy of the Endeavor™ ZES platform has been established in stable de novo coronary artery lesions. The **Endeavor I** study (24) included 100 patients with a single coronary lesion and showed MACE rate of 2% at 12 months.

The **Endeavor II** study⁽²⁵⁾ in 1,197 patients with single de novo coronary artery lesion, demonstrated low MACE (7.3%), low TLR (4.6%) and stent thrombosis rate of 0.5%, maintained out to two years follow-up. The **Endeavor III** study (26) comparing ZES with SES in 436 patients, showed no cases of stent thrombosis after nine months follow-up. Results from these studies provided evidence that the ZES platform was 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 of using ZES in acute, high-risk PCI such as STEMI.

Recently, the 18 months results from **SORTOUT III** trial (Danish Organization for Randomized Trials with Clinical Outcomes) which represents real world experience, favoured the SES above the ZES. Results of the trial were presented in Atlanta at the American College of Cardiology (ACC) meeting 2010 and have recently been published in *The Lancet*⁽²⁷⁾. Out of 2332 patients, 1162 patients (1619 lesions) were assigned to receive the ZES, and 1170 patients (1611 lesions) to receive the SES. Within nine months, MACE occurred more often in ZES patients than in SES patients (6% vs 3%, HR 2•15, 95% CI 1•43–3•23; p=0•0002).

This difference was maintained at 18 months (9.7% vs. 4.5%, respectively). Although there was no difference in all cause-mortality at nine months, at 18 months there was a significant advantage for SES (4% vs 3%; 1•61, 1•03–2•50; p=0•035). The results of SORT OUT III differ from the results observed in the Endeavor clinical trial program. SORT OUT III study differed in that it included patients with complex lesions, such as bifurcations, ostial lesions, left main lesions, long lesions and chronic total occlusions, as well as patients with ACS and STEMI, and that it was powered to address clinical end points.

The Clinical Evaluation of the Xience V (EES) 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 as compared with BMS (multi-Link Vision). Neither SPIRIT II nor III trial was powered for superiority for clinical end points, and the routine performance of angiographic follow-up may have artificially exaggerated the absolute benefits of Xience V stent. Therefore, **SPIRIT IV** trial was designed⁽²⁸⁾ without angiographic follow-up to further assess the differences between these two stent platforms.

SPIRIT IV had randomised 3690 patients to receive the Xience V or the PES Express 2 stent. Three years data was presented at the TCT meeting 2009 which revealed 43% and 39% reduction in MACE and TLR, respectively, in comparison to 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% vs 1.6%, p=0.37). Whereas in 3690 patients, SPIRIT IV trial (also presented at TCT meeting 2009) found a statistically significant difference in stent thrombosis between the two arms at one year: 0.29% for Xience V vs. 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 called **COMPARE** randomised 1800 consecutive patients to blinded treatment undergoing elective or emergency PCI. The primary endpoint was a composite of all-cause mortality, non-fatal MI and TLR within 12 months. Follow-up was completed in 1797 patients and on the intention to treat analysis, the primary endpoint occurred in 56 (6%) of 897 patients in the Xience V group versus 82 (9%) of 903 in the PES group (relative risk [RR] 0.69; 95% CI 0.50 to 0.95, $p = 0.02$ for superiority).

One year follow-up showed that in addition to the 31% relative risk reduction ($p=0.02$) for that composite end point in patients treated with the Xience V in the trial, the EES was associated with significantly less ST ($p=0.002$)⁽²⁹⁾. 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 through 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 prohealing approach. Prohealing 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, presented at the Euro-PCR meeting 2009, showed similar mortality (5.1% vs. 4.2% and TLR rates (15.3% vs. 13.7%) for the Genous stent versus PES. However, the thrombosis rates in PES were 5.3% vs. 0.0% in Genous stent arm. The ABSORB is one of the recent clinical trials that has looked at the benefits of using bio-absorbable stents. The **ABSORB** trial was a prospective, multicentre, open-label, first-in-man study that assessed the bioabsorbable polymer drug-eluting stent (BVS) tested originally in just 30 patients with single, de novo lesions in 3.0-mm vessels⁽³⁰⁾. Two years imaging results {IVUS, multislice-CT, optical coherence tomography} has been published recently indicating that at least one-third of the stent has been absorbed by the vessel wall⁽³¹⁾. Three years data from ABSORB 1st phase clinical trial was recently presented at AHA scientific sessions which showed no case of stent thrombosis out to three years and no new MACE between six months and three years (3.6% at 3 years).

CONCLUSION

Soon after their commercial launch, DES have demonstrated dramatic reductions in the requirement for repeat revascularisation of the stented segment (TLR) compared with BMS or balloon angioplasty. The first-generation devices, SES (Cypher) and PES (Taxus) appear to have an ongoing risk for ST beyond one year after stenting that may be related to inflammatory effects of the drug itself, drug dose or release kinetics or late effects of the polymer. However, alarming reports on potential increases in death, early and late stent thrombosis which mandate prolonged dual anti-platelet therapy, led to a decrease in use and stimulated the development of second-generation DES- EES (Xience V or Promus) and ZES (Endeavor).

They differ mainly in polymer technology and metallic stent structure. Until recently, they were proving to be significantly more effective and safer compared to the first-generation DES to reduce risk of ST in ACS patients with better stent design, greater biocompatibility with release kinetics. However, the most recent break through SORT OUT III trial which represents real-world experience, showed increase risk of ST with ZES well as there is increased risks of MACE and TLR in ZES compared to SES without any difference in all cause mortality. However, larger randomised and longer term controlled studies are needed

in patients with ACS and real world situations of patients with long lesions, calcification or bifurcations to assess their safety, especially in respect of very LST and the requirement of prolonged dual anti-platelet therapy.

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