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Review Article

The Current Status of Coronary Drug-Eluting Stents

Chih-Wei Chen[1,2], *Chin-Lon Lin*[1,2]*

[1]*Division of Cardiology, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan*
[2]*Division of Cardiology, Department of Internal Medicine, College of Medicine, Tzu Chi University, Hualien, Taiwan*

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Abstract

Percutaneous coronary intervention is currently the most common revascularization procedure for coronary artery stenosis. Bare metal stents effectively reduce the rates of acute closure and restenosis more successfully than balloon angioplasty. However, the rates of restenosis remain high. Local delivery of drugs using drug-eluting stents to inhibit neointimal proliferation was proven to be an effective method to reduce in-stent restenosis and hence the rates of target lesions and target vessel revascularization. At present, four drug-eluting stents have been approved by the Food and Drug Administration, including the sirolimus-eluting stent (Cypher), paclitaxel-eluting stent (Taxus), zotarolimus-eluting stent (Endeavor) and everolimus-eluting stent (Xience V). These four drug-eluting stents are effective in reducing in-stent restenosis, and target vessel and lesion revascularization in comparison with bare metal stents. However, the mortality and myocardial infarction rates were similar between bare metal stents and drug-eluting stents. Recently, late and very late stent thrombosis resulting in high rates of mortality and myocardial infarction have become important issues. Discontinuation of dual antiplatelet therapy appeared to be the main etiology of late and very late stent thrombosis. Dual antiplatelet therapy for at least 12 months after deployment of drug-eluting stents is currently recommended by the ACC/AHA guidelines. (*Tzu Chi Med J* 2009; 21(1):18–27)

*Corresponding author. Division of Cardiology, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital, 2, Min-Sheng Road, Dalin, Chiayi, Taiwan.
E-mail address: cllinmd@mail.tcu.edu.tw

1. Introduction

Since the first report of coronary angioplasty by Gruentzig et al in 1987, percutaneous coronary intervention (PCI) has become the most common revascularization procedure for occluded coronary artery disease (1). The procedure provides a novel technique to expand the stenotic coronary lesion with a balloon catheter and thereby relieving the myocardial ischemia, which was only treated by coronary artery bypass graft surgery prior to the discovery of this technique. However, the rate of restenosis for patients undergoing balloon angioplasty was as high as 30–50% within 6 months of the PCI (2–4). Coronary stents were developed to provide an intracoronary scaffolding device to reduce elastic recoil and remodeling, thus reducing the rate of restenosis. The stents did reduce the rate of restenosis. However, the rate of restenosis remained

unacceptably high (at about 10–30% of patients receiving PCI). This results in recurrent angina, impaired quality of life and the need for repeat PCI [4–6]. In 2003, drug-eluting stents (DES) were approved by The Food and Drug Administration (FDA) and became commercially available to overcome the main defect of bare metal stents (BMS), that is, restenosis. The DES releases high local concentrations of immunosuppressive or antiproliferative drugs into the coronary vessel wall at the site of stent deployment. The use of DES did reduce the rate of in-stent restenosis and the rate of reintervention [7–9]. Nevertheless, the answers to some issues, such as late thrombosis, duration of dual-antiplatelet therapy, and mortality benefits remained unclear.

2. Pathophysiology of restenosis

The pathophysiology of restenosis after PCI is not well understood. It is well accepted that restenosis is a maladaptive response to the trauma induced during angioplasty, which results in inflammation, thrombosis, cellular proliferation and extracellular matrix production. Inflammation and thrombosis occur at the time of vascular injury and are maximal within hours after the injury, resulting in acute closure after PCI. Cellular proliferation activity peaks at about 7 days post-injury. Finally, there is matrix formation from 1 week onward [10]. The lumen loss after PCI can come in three distinct stages: early loss associated with elastic recoil, which usually occurs within 1 hour, late loss due to negative remodeling, and neointimal hyperplasia [11]. Negative remodeling results from collagen deposition in the matrix and adventitia thickening. Neointimal hyperplasia results from the proliferation and migration of smooth muscle cells and extracellular matrix formation. Negative remodeling and neointimal proliferation may occur within 1–6 months after angioplasty [11]. Artery remodeling plays an important role in restenosis after angioplasty without stenting, and implantation of BMS reduces the impact of elastic recoil and negative remodeling [2]. On the other hand, in-stent stenosis arises mainly from neointimal hyperplasia [2]. Damage to the vascular wall results in endothelial damage and loss, endothelial dysfunction, vasoconstriction and inflammation. This starts the atherothrombotic cascade including platelet activation and adhesion [12]. This contributes to the release of mitogens including thromboxane A2, serotonin and platelet-derived growth factors. These factors then promote smooth muscle cell migration and proliferation, matrix formation, and cell proliferation [13].

Farb et al conducted a study involving 56 patients with 116 stents. Neointimal thickness, inflammatory cell density, and neointimal vascular channel density were significantly greater when the struts were in contact with the ruptured arterial media compared with the fibrous plaque or intact fibrous caps [14]. The data suggested that coronary stenting accompanied by medial damage and penetration of the stent into a lipid core induces increased arterial inflammation, which is associated with increased neointimal growth.

3. Evolution of DES

Because of the high restenosis rate of BMS, many efforts have been made to reduce in-stent stenosis, including brachytherapy (radiation therapy) and many systemic pharmacological approaches. Local delivery of drugs to inhibit neointimal proliferation has been tried for more than 20 years. Catheter-based drug delivery was unsuccessful in humans, partly owing to the short period of time the compounds remained within the vascular wall. The problem was resolved by incorporating drugs into a polymer matrix encapsulated over the stents to provide the platform from which controlled drug delivery was available during a programmed period of time. Many drugs were studied in DES, including paclitaxel and Limus family-related drugs, such as sirolimus, zotarolimus, biolimus A9 and everolimus. Paclitaxel offers stabilization of microtubules and inhibits cell division in the G0/G1 and G2/M phases, and hence inhibits neointimal hyperplasia [15]. The Limus family-related drugs were found to be effective in the inhibition of neointimal hyperplasia via binding to FKBP 12 binding protein, which subsequently binds to the mammalian target of rapamycin (mTOR) and blocks the cell cycle, predominantly of smooth muscle cells, from the G1 to S phase. These drugs were incorporated into the polymer matrix on stents and were then delivered to coronary arteries. The results of clinical trials have shown that DES reduced neointimal proliferation effectively and reduced the incidence of restenosis in comparison with BMS. Until now, four DES have been approved by the FDA. Cypher sirolimus-eluting stent (Cordis Corp., Miami, FL, USA) was the first, followed by Taxus paclitaxel-eluting stent (Boston Scientific Corp., Natick, MA, USA), Endeavor zotarolimus-eluting stent (Metronic Vascular, Santa Rosa, CA, USA) and the latest Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA).

The sirolimus-eluting stent (SES) has a 5 μmol/L layer proximal to the metallic struts that is composed of a mixture of synthetic polymers blended with sirolimus and a diffusion barrier of drug-free polymer covering the sirolimus-containing layer, modulating the release of approximately 80% of the drug over approximately 30 days. The FDA-approved paclitaxel-eluting stent (PES) (TAXUS) is coated with paclitaxel (1 $\mu g/mm^2$ per unit area of the stent surface) in a slow- or moderate-release formulation of a proprietary

hydrocarbon-based elastomer [8]. The FDA-approved zotarolimus-eluting stent (ZES) (Endeavor) is coated with a phosphorylcholine polymer that is designed to target zotarolimus (10 μg/mm) delivery to the arterial wall [16]. Finally, the FDA-approved everolimus-eluting stent (EES) is coated with two polymers (an acrylic polymer and a fluoro polymer) loaded with 100 μg of everolimus per cm^2 of stent surface area with the first 25% of the stent drug released on the first day after stent implantation and the remaining amount of the drug released over the following 4 months [17].

4. Major clinical trials of DES

4.1. Sirolimus-eluting stent (SES)

Sirolimus was the first of the Limus family of drugs to be used for endovascular prosthesis and was proven to be effective in the suppression of neointimal proliferation via local or systemic delivery to the artery walls to inhibit mTOR activity [18–21]. A series of randomized controlled clinical trials were conducted to evaluate the efficacy and safety of SES in humans. The first landmark study was the RAVEL trial, which was a randomized controlled study to compare the in-stent restenosis rate and safety in native coronary arteries of angina patients who received SES or BMS [22]. A total of 238 patients with single, primary target lesions in native coronary arteries of 2.5–3.5 mm in diameter and less than 18 mm in length were randomized to receive implantation of the SES (n=120) or a BMS (n=118). At 6 months, the mean in-stent late loss was significantly lower in the SES group than in the BMS group (–0.01±0.33 mm *vs.* 0.80±0.53 mm; $p<0.001$). No cases of restenosis were observed in the SES group and 26.6% of cases in the BMS group had restenosis ($p<0.001$). A 3-year follow-up of the RAVEL trial showed sustained clinical benefits in the cumulative event-free survival rates (for incidence of target vessel revascularization [TVR], target vessel failure [TVF], and major adverse cardiac events [MACE], including death, Q-wave or non-Q wave myocardial infarction [MI] and target lesion revascularization [TLR]) at 1, 2, and 3 years in SES group [23]. At almost the same time, the randomized, double-blind, SIRIUS study compared the safety and efficacy of SES and BMS in 1058 patients (n=533 and 525 in the SES and BMS group, respectively) with native coronary artery stenotic lesions in which more patients with diabetes, long lesions (mean, 14.4 mm) and small vessels (mean, 2.8 mm) were included [24]. The primary end point was the failure of the target vessel (defined as death from cardiac causes, MI, revascularization, or repeat PCI) within 270 days of the procedure. A risk reduction of 58% was found in the SES group compared with the BMS group (4.1% *vs.* 16.6%; $p<0.001$) which was mainly due to a reduction in the number of patients requiring revascularization. The reduction in in-segment restenosis was significantly consistent among all subgroup analyses, including age, gender, diabetes mellitus, left anterior descending artery involvement, vessel size or length and stent overlapping. The differences were maintained during the 2-year follow up and no differences in death, MI or stent thrombosis were seen between the two groups [25].

Two smaller studies of SES were performed in Europe (European SIRIUS [E-SIRIUS] trial) [26] and Canada (Canada SIRIUS [C-SIRIUS] trial) [27].

The E-SIRIUS trial enrolled 352 patients with single *de novo* lesions of 15–32 mm in diameter. The minimum lumen diameter was significantly greater in the SES group than in the BMS group (2.22 mm *vs.* 1.33 mm; $p<0.0001$) after 8 months of follow up and fewer patients had MACE in the SES group, mainly due to a lower rate of TLR. The C-SIRIUS trial randomized 100 patients with small target vessels to SES and BMS. At 9 months of follow up, late loss of lumen diameter (in-stent luminal diameter, 2.46 mm *vs.* 1.49 mm; $p<0.001$), angiographic in-lesion restenosis (2.3% *vs.* 52.3%; $p<0.001$) and clinically driven TLR (4% *vs.* 18%; $p=0.05$) were significantly lower in the SES group than in BMS group.

In a pooled analysis of the three SIRIUS trials with a total number of 1510 cases, the in-stent restenosis was reduced from 38.5% in the BMS group to 3.1% in the SES group and in-lesion restenosis was reduced from 39.8% in the BMS group to 7.5% in the SES group ($p<0.0001$ for both comparisons) [28].

The Stenting Coronary Arteries in Non-Stress/Benestent Disease (SCANDSTENT) trial included patients with more complicated lesions, including total occlusion (n=115), bifurcations (n=109), ostial lesions (n=73), or angulations (n=25) [29]. In-stent restenosis rates at the 6-month follow up favored the SES group (16.4% *vs.* 43.1%; $p<0.001$). A continued benefit was observed for up to 3 years after stent implantation [30]. The rate of late adverse events was similar between the two groups and TLR was performed fewer times in the SES group than in the BMS group (4.9% *vs.* 33.8%; $p<0.001$).

The results of the studies of SES consistently demonstrated its effectiveness in reducing in-stent or in-lesion restenosis, TLR and TVR in comparison with BMS. These effects have been demonstrated in patients with variable vessel sizes, lengths and complexities.

4.2. Paclitaxel-eluting stent (PES)

The PES, which is coated with paclitaxel, is currently available worldwide. There are other PES under investigation, such as the V-Flex Plus coronary stent (Cook Inc., Bloomington, IN, USA) and the 7-hexanoyltaxol

(QP2)-eluting polymer stent (QuaDS) (Quanam Medical Corp., Santa Clara, CA, USA). The first evidence that PES is effective in preventing in-stent restenosis was the results of the TAXUS 1 trial [31]. A total of 61 patients (31 received slow-release PES and 30 received BMS stents) with *de novo* or restenotic lesions (<12 mm) and diameters of 3.0 mm or 3.5 mm were compared. Six-month angiographic restenosis rates were 0% for the PES group and 10% for the BMS group (p=not significant). There were significant improvements in minimal lumen diameter (2.6 mm *vs.* 2.2 mm; $p<0.01$), diameter stenosis (13.6% *vs.* 11.8%; $p<0.01$) and late lumen loss (0.36 mm *vs.* 0.78 mm; $p<0.01$). No difference in the 30-day and 12-month MACE were found between the two groups. A similar study (TAXUS II), which included more patients (n=536), was conducted to compare the slow-release (SR; n=131) and moderate-release (MR; n=135) PES with BMS (n=270) [32]. Significantly lower rates of angiographic in-stent restenosis were found in the SR group than in the BMS group (2.3% *vs.* 17.9%; $p<0.0001$) and in the MR group than in the BMS group (4.7% *vs.* 20.2%; $p=0.0002$) after 6 months of follow-up. The incidence of MACE (a composite of cardiac death, MI and repeat revascularization) at 12 months was significantly lower ($p=0.0192$) in the SR (10.9%) and MR (9.9%) groups than in the BMS group (22.0% and 21.4%, respectively), which was predominantly due to a significant reduction in repeat TLR in the PES-treated patients.

The TAXUS IV trial was designed to evaluate single *de novo* coronary lesions of 10–28 mm in length and 2.5–3.75 mm in diameter covered using a single study stent [33]. A total of 662 patients were assigned to the SR PES group and 652 patients were assigned to the BMS group. At 12 months of follow up, in comparison with BMS, PES reduced TLR by 73% (4.4% *vs.* 15.1%; $p<0.0001$), TVR by 62% (7.1% *vs.* 17.1%; $p<0.0001$), the TVF rate by 52% (10.0% *vs.* 19.4%; $p<0.0001$), and composite major adverse cardiac events by 49% (10.8% *vs.* 20.0%; $p<0.0001$). The rates of subacute thrombosis were similar between the two groups. There were fewer episodes of MI in the PES group than in the BMS group (0% *vs.* 1.1%; $p=0.007$), TVR (2.4% *vs.* 6.3%; $p=0.0009$) and MACE (2.4% *vs.* 6.3%; $p=0.0009$) between 9 and 12 months after implantation.

The later TAXUS V and TAXUS VI trials were designed to evaluate the safety and efficacy of the SR- and MR-PES in more complex lesions [34,35]. About half of the lesions in the TAXUS V study (n=1156) were complex, previously unstudied, long lesions (10–46 mm in length), requiring stent diameters of 2.25 mm or 4.0 mm, and/or multiple stents. At the 9-month angiographic follow-up examinations, the rates of TVR and in-stent restenosis were lower in the PES group than in the BMS group (12.1% *vs.* 17.3%; $p<0.02$ and 13.7% *vs.* 31.9%; $p<0.001$, respectively). The TAXUS VI trial enrolled 446 high-risk patients, including those with lesion lengths >20 mm, vessel diameters <2.5 mm, overlapping stents, ACC/AHA type C lesions, and those being treated for diabetes. At 9 months, a 53% risk reduction in TVR (9.1% *vs.* 19.4%; $p=0.0027$) and 64% risk reduction in TLR (6.8% *vs.* 18.9%; $p=0.0001$) were found in the PES group compared with the BMS group.

The results of these studies demonstrated the beneficial effects of PES in reducing in-stent restenosis. TVR and TLR were consistent in variable lesion lengths, lesion sizes, stent diameters, lesion complexity and even in diabetic patients in comparison with the effects of BMS.

4.3. Zotarolimus-eluting stent (ZES)

Zotarolimus, a Limus family related drug, has antiproliferative and anti-inflammatory effects. Incorporation of the tetrazole ring within the zotarolimus chemical structure increases lipophilicity and facilitates its ability to cross the membranes of smooth muscle cell to initiate the blockage of normal cell-cycle division.

The ENDEAVOR I trial was a first-in-human, nonrandomized, prospective, single-arm study (n=100), which was designed as a preliminary feasibility study to evaluate the safety and efficacy of the ZES in the treatment of single, *de novo*, native coronary lesions of less than 15 mm in length and 3.0–3.5 mm in diameter [36]. The binary angiographic restenosis rates (defined as >50% diameter stenosis) at 4 and 12 months were 2.1% and 5.4%, respectively. The cumulative incidence of MACE (defined as death, MI, emergent cardiac surgery or repeat revascularization of the index lesion) was 1% at 30 days and 2% at 4 and 12 months. The results demonstrated that the ZES is reliable and safe for treating obstructive coronary artery disease. The incidence of MACE was 3% at 2 years, 6.1% at 3 years and 7.2% at 4 years. From 2–4 years, there was only one additional reported case of TLR [36]. Only one case of stent thrombosis occurred at 10 days after the index procedure, but no cases occurred thereafter.

The ENDEAVOR II trial compared ZES (n=598) with BMS (n=599) in *de novo* native coronary lesions with diameters of 2.25–3.5 mm and lengths of 14–27 mm [37]. At 9 months, TVR had reduced from 15.1% to 7.9%, TLR had reduced from 11.8% to 4.6% and the rates of MACE had reduced from 14.4% to 7.3% ($p=0.0001$ for all). Stent thrombosis was similar in the ZES and BMS groups (0.5% *vs.* 1.2%; p=NS). In the 531 patients who underwent angiographic follow-up, late loss was reduced from 1.03 to 0.61 ($p<0.001$) in the stent and from 0.72 to 0.36 ($p<0.001$) in the segment. The rate of in-segment restenosis had

reduced from 35.0% to 13.2% with ZES ($p<0.0001$). Differences in clinical outcomes were maintained at 12 and 24 months ($p<0.0001$).

The results of the two studies demonstrated the effects of ZES on restenosis and TLR/TLR. Other studies of ZES are still ongoing.

To conclude, these three DES (SES, PES and ZES) consistently demonstrated the clinical benefits of DES in reducing restenosis in addition to preventing TVR and TLR. Thus the short-term safety profile is acceptable.

4.4. Everolimus-eluting stent (EES)

Everolimus is another Limus family-related drug and is a powerful anti-proliferative agent that forms a complex with the cytoplasmic protein FKBP12. It can inhibit growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1. Moreover, it can bind to and interfere with the function of FKBP12-rapamycin associated protein (FRAP), which is a key regulatory protein of cell metabolism, growth and proliferation. By this process, everolimus can cause cell-cycle arrest during the late G1 stage.

The main clinical data for EES is the SPIRIT clinical trial program. The SPIRIT first-in-man trial was a prospective single-blind, randomized, controlled multicenter study [17]. A total of 60 patients with single *de novo* lesions of 3.0 mm in diameter and less than 12 mm in length were randomly assigned to receive EES (28 patients) or BMS (32 patients). At 6 months, angiographic results showed significantly less in-stent late loss in the EES group than in the BMS group (0.10 mm *vs.* 0.87 mm; $p<0.001$) and in-segment late loss (0.07 mm *vs.* 0.61 mm; $p<0.001$). At 1 year, TLR was 7.7% *vs.* 21.4% ($p<0.001$) and MACE was equivalent (15.4% *vs.* 21.4%; p=not significant).

5. Head to head comparison of DES

The first randomized, controlled trial of a head-to-head comparison of SES and PES was the TAXi trial [38]. At 7 months of follow up, there were no significant differences between the PES group ($n=100$) and the SES group ($n=102$) in MACE (4% *vs.* 6%; $p=0.8$) or TVR (1% *vs.* 3%). Later, three large-scale studies were conducted to assess the differences between these two DES. The first trial compared MACE (death, MI, and ischemia-driven revascularization of the target lesion) between the SES ($n=503$) and PES groups ($n=509$) at 9 months [39]. The SES group had lower MACE at 9 months compared with that in the PES group (6.2% *vs.* 10.8%; $p=0.009$). The differences were driven mainly by a lower rate of ischemia-driven target-lesion revascularization in the SES group. Follow-up angiography was performed in 53.4% of cases and lower rates of angiographic restenosis were found in the SES group than in the PES group (6.6% *vs.* 11.7%; $p=0.02$). The second study was the REALITY trial, which was a prospective, randomized, multicenter study that assessed SES and PES in 1386 patients with moderate complex lesions. No differences in the primary end points (in-lesion binary restenosis) between the SES and PES groups (9.6% *vs.* 11.1%; $p=0.31$) were found. Rates of MACE (TLR, TVR, and composite end point of cardiac death, Q-wave or non Q-wave MI, coronary artery bypass graft surgery, or repeat TLR) at 1 year were similar between the SES and PES groups (10.7% *vs.* 11.4%; $p=0.73$). In-stent late loss (0.09 mm *vs.* 0.31 mm; $p<0.001$) and in-stent diameter stenosis (23.1% *vs.* 26.7%; $p<0.001$) were lower in the SES compared with the PES groups [40].

The third study was the SORT OUT II randomized trial, which compared PES ($n=1033$) with SES ($n=1065$). All patients were observed from randomization to death, emigration, or for up to 18 months after randomization [41]. There were no differences in the primary end points (MACE, including cardiac death, acute MI, TLR, or TVR: 9.3% *vs.* 11.2%; $p=0.16$) or stent thrombosis (2.5% *vs.* 2.9%; $p=0.60$) between the SES and PES groups. Two meta-analyses of randomized trials demonstrated that the SES group had a significantly lower risk of restenosis and TVR compared with the PES group. Rates of death or MI were similar [42,43].

The two DES have also been compared in different patient groups or vessel situations. The ISAR-DIABETES study assessed the use of SES and PES in diabetic patients [44]. In a total of 250 patients with diabetes and coronary artery disease, 125 were randomly assigned to receive PES and 125 to receive SES. Angiographic follow up at 6.5 months (mean duration) demonstrated a 0.24 mm increase in in-segment late lumen loss ($p=0.002$) in the PES group. In-segment restenosis was lower in the SES group than in the PES group (6.9% *vs.* 16.5%; $p=0.03$) and no differences were noted in the TLR (6.4% *vs.* 12.0%; $p=0.13$). The Long-DES II study assessed the use of long SES and PES (stent length >32 mm) in 500 patients with long coronary artery lesions (>25 mm) [45]. The follow-up angiography at 6 months demonstrated a lower rate of angiographic in-segment binary restenosis (3.3% *vs.* 14.6%; $p<0.001$) and in-stent late loss of lumen diameter (0.09 mm *vs.* 0.45 mm; $p<0.001$) in the SES than in the PES group. At 9 months, the TLR was lower in the SES group than in the PES group (2.4% *vs.* 7.2%; $p=0.012$). There were no differences in the incidence of death (0.8% *vs.* 0%; $p=0.049$) or MI (8.8% *vs.* 10.8%; $p=0.452$) between the PES and SES groups. The ISAR-SMART 3 study also demonstrated that PES was

associated with a greater late luminal loss and was less effective in reducing restenosis in small coronary vessels than SES [46].

Until now, only one study (ENDEAVOR III) has compared the safety, clinical efficacy and angiographic outcomes between ZES and SES [47]. A total of 436 patients with *de novo* native coronary lesions with diameters 2.5–3.5 mm and lesion lengths 14–27 mm were randomized to the ZES (n=323) and SES (n=113) groups. The primary end point, 8-month angiographic in-segment late lumen loss, was significantly higher in the ZES group than in the SES group (0.34 mm *vs.* 0.13 mm; p<0.001). Inhospital MACE was lower in patients treated with ZES (0.6% *vs.* 3.5%; p=0.04). Higher in-segment binary angiographic restenosis and TLR were found in the ZES group at 9 months (11.7% *vs.* 4.3%; p=0.04 and 9.8% *vs.* 3.5%; p=0.04, respectively). No significant differences in clinically driven TLR or TVF were found [47]. The ENDEAVOR IV trial was designed to compare the primary noninferiority endpoints of TVF among 1548 patients randomized (1:1) to treatment with ZES or PES. The study is still going on [48].

The SPIRIT II and III trials compared EES and PES. In the SPIRIT II trial, a total of 300 patients with *de novo* native coronary artery lesions with diameters of 2.5–3.75 mm and lengths less than 28 mm were randomized to the EES group or the PES group at a 3:1 ratio [49]. At 6 months of follow up, in-stent late loss was 0.12 mm for the EES group and 0.37 mm for the PES group (p<0.0001). Similar results were found for in-stent binary restenosis (1.3% *vs.* 3.5%; p=0.194), TLR (2.7% *vs.* 6.5%; p=0.157), cardiac death (0% *vs.* 1.3%; p=0.257), MI (0.9% *vs.* 2.6%; p=0.272) and stent thrombosis (0.5% *vs.* 1.3%; p=0.448). SPIRIT III was a prospective, randomized, single-blind, multicenter, controlled trial that enrolled 1002 patients with *de novo* coronary artery lesions with diameters of 2.5–3.75 mm and lengths less than 28 mm [50]. Patients were randomized 2:1 to receive EES or PES. The angiographic follow up at 8 months showed less in-segment late loss in the EES group than in the PES group (0.14 mm *vs.* 0.28 mm; p<0.004). EES was non-inferior to PES for TVF at 9 months (7.2% *vs.* 9%; p<0.001). A significant reduction in MACE was found in the EES group than in the PES group at 9 months (4.6% *vs.* 8.1%; p=0.03) and at 12 months (6.0% *vs.* 10.3%; p=0.02), due to fewer episodes of MI and TLR.

In brief, SES does not seem to be inferior to PES in terms of in-stent restenosis rates. In addition, the rates of TVR and TLR, as well as mortality and MI, were similar. In comparison with ZES, patients receiving SES also showed better clinical outcomes in terms of restenosis and TVR/TLR with borderline higher in-hospital MACE. Patients who received EES did better in late loss than those who received PES.

6. Long-term outcomes and late/very late thrombosis

As shown in previous studies, in comparison with BMS, DES reduced in-stent restenosis, TVR and TLR effectively. However, long-term safety is another concern. The REAL multicenter registry trial assessed the 2-year safety and efficacy of DES [51]. The researchers assessed a total of 10,629 patients who underwent elective PCI with either DES (n=3064) or BMS (n=7565). The 2-year cumulative incidence of death was 6.8% in the DES group and 7.4% in the BMS group (p=0.35) and the rates of MI were 5.3% in the DES group and 5.8% in the BMS group (p=0.46). MACE was lower in the DES group than in the BMS group (16.9% *vs.* 21.8%; p<0.0001), which was mainly due to lower rates of TVR in the DES group (9.1% *vs.* 12.9%; p<0.00001). No significant differences were found but there was a trend for higher rates of angiographic stent thrombosis in the DES group (1.0% *vs.* 0.6%; p=0.09). The data demonstrated similar safety profiles between DES and BMS. A 4-year follow up also demonstrated an equivalent safety profile between SES and BMS [52]. In this pooled analysis of 1748 patients, both the SES and BMS groups had similar survival rates (93.3% *vs.* 94.6%; p=0.28), MI (6.4% *vs.* 6.2%; p=0.86) and stent thrombosis, as defined by the Academic Research Consortium (ARC) [53] (3.6% *vs.* 3.3%; p=0.8). In a large outcome study, researchers assessed 6033 patients treated with DES and 13,738 patients with BMS. At a 3-year follow up examination, a significantly higher event rate after 6 months was found in the DES group with 12.7 more events per 1000 patients per year (adjusted relative risk, 1.20; 95% confidence interval, 1.05–1.37). At 3 years of follow up, the mortality rate was significantly higher in the DES group (adjusted relative risk, 1.18; 95% confidence interval, 1.04–1.35) and from 6 months to 3 years, the adjusted relative risk for death in this group was 1.32 (95% confidence interval, 1.11–1.57). The results of this study showed that DES was associated with an increased rate of death, as compared with BMS, and this trend appeared after 6 months when the risk of death was 0.5% higher and a composite of death or MI was 0.5–1.0% higher per year [54].

Even with the safety profile reports and fewer revascularizations after using DES, the use of DES has raised some concerns about late and very late stent thrombosis. The classification of stent thrombosis was provided by the ARC, which defined the occurrence of late stent thrombosis as events occurring between 1 month and 1 year after PCI and very late stent thrombosis as events occurring more than 1 year after PCI [53]. Stent thrombosis resulted in a high rate of death (31% *vs.* 3%; p<0.001) [55].

Stone et al also demonstrated a 91.1% of death or MI within 7 days of stent thrombosis [56].

Although some studies showed that the rates of stent thrombosis were similar with DES and BMS [51,52,57], many studies showed higher rates of late and very late stent thrombosis in patients who underwent DES. In a meta-analysis study of SES, PES and BMS with 4 years of follow up, more very late thrombosis was observed in both the SES and PES groups than in the BMS group (0.6% *vs.* 0.0%; $p=0.025$ and 0.7% *vs.* 0.2%; $p=0.028$, respectively) [58]. Another 3-year follow-up study also demonstrated higher stent thrombosis in the SES and PES groups than in the BMS group (2.7%, 2.9% and 1.6%, respectively). Cumulative mortality rates were similar in these three groups [59]. According to data from a large two-institutional cohort study, late thrombosis was encountered steadily with no evidence of diminution at up to 3 years of follow up. Late thrombosis occurred at a steady rate of 0.6% per year [60]. Real world data also demonstrated an average stent thrombosis rate of 1.3% during a 9-month follow-up period [61].

7. Mechanism and predictors of late stent thrombosis

Many studies have been designed to evaluate the mechanism of late stent thrombosis. In an animal study, SES, PES, and BMS (BxVelocity or Express) were examined using the arterial reaction in rabbits [62]. Stented arteries were harvested at 28 and 90 days after insertion for histology. The results showed that the BxVelocity stent (BMS) group had significantly higher endothelialization than the SES group (96% *vs.* 75%; $p=0.04$) and the Express stent (BMS) showed a trend towards higher endothelialization than the PES (80% *vs.* 67%; $p=$not significant) at day 28. The study also showed higher levels of inflammation parameters, such as fibrin scores, struts with fibrin, giant cells per strut and luminal heterophils and eosinophils in the DES overlap site than in the BMS. In comparison with BMS, DES delayed arterial healing and promoted inflammation. Hofma et al also compared the endothelial function between the SES ($n=7$) and the BMS ($n=5$) [63]. Endothelium-dependent vasomotion of a coronary segment of 15 mm in length at 2 mm distal to the stent was assessed with intracoronary infusion of acetylcholine. Significant vasoconstriction was seen in the SES group (median 32% diameter reduction from baseline) but not in the BMS group (median 2% reduction) after acetylcholine infusion ($p=0.03$). There were no differences in endothelium-independent vasodilatation to nitrate between the two groups. The results illustrated that SES implantation may have adverse effects on local endothelium-dependent vasomotor responses compared with BMS implantation at 6 months. This may partially explain the phenomenon of late stent thrombosis. Kotani et al also demonstrated that SES had incomplete neointimal coverage at 3–6 months after implantation, according to angioscopic findings [64]. All these phenomena, including incomplete neointimal coverage, endothelial dysfunction and less endothelialization with higher rates of inflammation, are associated with subclinical thrombus formation. Autopsy data from 23 patients with DES (SES and PES) and 25 matched autopsies of BMS implantation also showed greater delays in healing in those who received DES, characterized by persistent fibrin deposition and poorer endothelialization [65].

Many factors account for the higher rates of late stent thrombosis in those receiving DES. Discontinuation of thienopyridine therapy was thought to be a major determinant of stent thrombosis. In one study [66], 3021 patients with 5389 lesions who received DES were studied and the incidence of stent thrombosis during an 18-month follow-up period was analyzed. The rate of stent thrombosis was 1.9% and the strongest predictor for stent thrombosis within 6 months of stenting was discontinuation of thienopyridine therapy (hazard ratio, 13.74; 95% confidence interval, 4.04–46.68; $p<0.001$). Nevertheless, insufficient information is available to determine whether there is benefit in continuing thienopyridine beyond 6 months. Other risk factors predisposing to late and very late stent thrombosis included renal failure, treatment for in-stent restenosis and bifurcation lesions, diabetes, acute coronary syndrome at presentation, primary stenting in acute MI, total stent length and low ejection fraction [55,60,61,67].

8. Optimal duration of dual antiplatelet therapy

Late and very late stent thromboses almost always result in serious adverse events, including MI and death, and may outweigh the benefits of DES in reducing restenosis and TLR/TVR. Many studies demonstrated that the most predictable factor for late and very late thrombosis in DES implantation was discontinuation of dual antiplatelet therapy [55,61,66,67]. The BASKET-LATE trial evaluated the rates of cardiac death and MI for 18 months after clopidogrel discontinuation in DES and BMS patients [68]. The rates of cardiac death and MI over 18 months were not different between DES and BMS groups but the proportion of events was significantly higher in DES than in BMS (4.9% *vs.* 1.3%) after the discontinuation of clopidogrel (between months 7 and 18). In the PREMIER trial, the mortality and cardiac hospitalization rates during an 11-month period after stopping thienopyridine therapy were evaluated in people treated with DES [69]. Among 500 DES-treated MI patients, the patients

who stopped thienopyridine therapy by day 30 were more likely to die (7.5% *vs.* 0.7%; $p<0.0001$) or to be rehospitalized (23% *vs.* 14%; $p=0.08$) during the 11 months following the discontinuation. These two studies showed the importance of prolonged dual antiplatelet therapy in DES patients.

The optimal duration of dual antiplatelet therapy (aspirin and thienopyridine) is still a matter of ongoing debate. The most recent ACC/AHA guidelines published in 2008 recommended that 162–325 mg of aspirin should be given for at least 3 months after SES implantation and 6 months after PES implantation, after which daily long-term low-dose aspirin (75–162 mg) should be continued. In addition, a daily dosage of 75 mg clopidogrel should be given for at least 12 months in patients receiving DES (70). According to this recommendation, at least 12 months of dual antiplatelet therapy is warranted for DES implantation to prevent unfavorable clinical outcomes. DES can thus be limited to those suitable for long-term (at least 12 months) dual antiplatelet therapy. For those who are scheduled for surgery requiring premature discontinuation of dual antiplatelet therapy, those with poor drug compliance, those at high risk of bleeding and those who are intolerant of dual antiplatelet therapy, DES implantation should be avoided if possible.

9. Conclusion

At the present time, PCI is the most important strategy in the treatment of coronary artery diseases. BMS reduced the rate of restenosis and acute closure in comparison to balloon angioplasty. The rate of restenosis of patients receiving BMS remains high. DES effectively reduced the rate of in-stent restenosis, TVR and TLR without additional benefits in mortality rates and MI compared with BMS. Observational data have raised many concerns about late and very late stent thrombosis in those receiving DES. Discontinuation of dual-antiplatelet therapy was shown to be the main etiology. The optimal duration of dual antiplatelet therapy remains to be debated. Dual antiplatelet therapy for at least 12 months after DES implantation is recommended by the ACC/AHA guidelines. The development of newer generations of DES to further reduce in-stent restenosis and stent thrombosis is expected.

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