Clinical efficacy of drug-eluting stents in patients with diabetes

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'Despite the widespread utilization of percutaneous procedures... restenosis remains a significant limitation to the long-term efficacy and durability of the treatment'

The achilles heel of coronary angioplasty is restenosis. This vexing problem is the result of a cascade of cellular and molecular events which leads to the migration of inflammatory markers to the site of injury in a vessel wall induced by balloon angioplasty. Although arterial remodeling and elastic recoil contribute to restenosis, the main phenomenon is neointimal proliferation. The ability of antineoplastic and antineoproliferative drugs such as sirolimus and paclitaxel, have become the cornerstone of drug-eluting stents (DESs), particularly in high-risk patients, such as those with diabeties.

Coronary artery disease (CAD) is the leading cause of death in developed nations. In the USA alone there are over 1.2 million myocardial infarctions (MIs) and 600,000 percutaneous revascularization procedures annually [1]. Despite the widespread utilization of percutaneous procedures for the treatment of CAD – particularly angioplasty and stenting – restenosis remains a significant limitation to the long-term efficacy and durability of the treatment [2].

Patients with diabetes are at a particularly high risk of complications from percutaneous coronary interventions (PCIs). Studies have consistently demonstrated that for both stable and unstable coronary lesions, patients with diabetes are more likely to suffer adverse events including repeat target-lesion revascularization (TLR) and target-vessel revascularization (TVR) [3]. Binary restenosis rates in patients without diabetes treated with bare-metal stents (BMSs) is approximately 25 to 30% [3,4]; however, this rate can almost double for those with diabetes, to between 33 and 50% [5]. Due to the high rates of restenosis following PCIs with a BMS, there has been a great deal of interest in the use of DESs for the treatment of patients with diabetes. Indeed diabetic subgroup analyses from large DES trials have demonstrated restenosis rates of between 6 and 18% [3–5]. Furthermore, the rates of repeat revascularization and subsequent repeat angiography and intervention have been reduced [6]. All of these advantages have translated to a lower cost in patient healthcare, despite the initially higher price of DESs compared with BMSs [7].

Pathophysiology of neointimal hyperplasia & targets of DESs

The use of stents during PCIs virtually eliminates acute vessel recoil and flow, limiting dissections which result from angioplasty. Stenting, however, can result in greater long-term stimulation of the arterial wall leading to chronic vessel injury. This chronic stimulation may result in neointimal proliferation, hyperplasia and restenosis. The area of restenosis has limited cellularity – it is principally a matrix of smooth muscle cells, proteoglycans and collagen.

During angioplasty and stenting, there is a disruption of the endothelium, leading to exposure of the contents of the subintimal space, such as von Willibrand's factor, collagen and lipids. This can result in local inflammation, the activation of circulating platelets, and cytokines as well as growth factors and adhesion molecules. Attempts at local vessel repair, such as fibrin deposition, platelet adhesion and thrombus formation can ultimately provide a matrix for cellular infiltration, chemotaxis and proliferation.

Efforts to control the injury process and limit the neointimal hyperplastic response have targeted pathways in the cell cycle. Due to the complexity of the cell cycle and the regulatory pathways, many attempts at reducing restenosis have failed. However, two drugs, sirolimus and paclitaxel, have significantly demonstrated positive results in limiting restenosis – even in high-risk patients with diabetes.

The use of a DES involves delivery of the drug from a polymeric scaffold. The encapsulated drug from the stent can either degrade and be released or can diffuse outward. Stent coatings include biocompatible polymers such as phosphorylcholine and depot-release coatings such as nanoporous ceramic [8,9]. Nonbiodegradable polymers are usually used for DESs and diffusion is the

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main mechanism of drug delivery [10]. Thus there are three principal components of a DES – the metallic stent, the drug carrier and the pharmacologic agent that prevents vascular neointimal proliferation [11].

The three polymers used for the CYPHER® sirolimus-eluting stent (SES) are parylene c, polyethylene-co-vinyl acetate and poly-n-butyl methacrylate. The polymer's coating is applied using a laser-cut stainless steel stent. The sirolimus drug is sandwiched between the layers of the polymer. Sirolimus, an immunosuppressive agent, interferes with cell proliferation early in the cell cycle (G1 phase arrest) and is a cytostatic agent.

Paclitaxel is an antiproliferative drug that stabilizes the microtubules and prevents depolymerization. Furthermore, paclitaxel inhibits reorganization of the microtubules during the cell's mitotic process. Hence, paclitaxel halts the accumulation of anti-inflammatory cells at the site of vessel injury that causes restenosis.

Drug-eluting stents in diabetes mellitus

Although various clinical trials have demonstrated the benefit of DESs in patients with CAD, their role in diabetes mellitus (DM) has been the topic of great interest.

The SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with *de novo* coronary artery lesions (SIRIUS) trial is the benchmark study that led to the use of DESs in patients with obstructive CAD [11]. A subset of the SIRUS study, Impact of Sirolimus-Eluting Stents on Outcome in Diabetic Patients, analyzed the effect of SESs in DM [4]. This study compared SES and BMS implantation in 1058 patients with *de novo* native coronary artery lesions – 279 patients had DM (26%) (among the DM group, 131 patients received SESs and 148 patients received BMSs). Follow-up at 9 months showed a TLR of 22.3% in BMS patients with diabetes versus 6.9% in patients who received SES ($p < 0.001$). The TLR in nondiabetic patients was 14.1% among BMS use and 2.99% ($p < 0.001$) in those patients with DESs. Major adverse cardiac events (MACEs) with BMSs were 25 versus 9.2% ($p < 0.001$) in the SES group of the diabetic population. In the nondiabetic population, MACE events were 16.5 to 6.5% ($p < 0.001$) with BMSs and SESs, respectively. This subset data demonstrated a reduction in TLR and MACEs in patients who received a SES compared with BMS. However, the rates of repeat revascularization in insulin-requiring patients compared with nondiabetic patients remained relatively high despite the use of SESs.

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Similarly, the efficacy of paclitaxel in patients with DM undergoing stent implantation was studied in the TAXUS™ IV trial, where 1,314 patients were prospectively randomized to the slow-release, paclitaxel-eluting TAXUS stent (PETS) or the bare-metal EXPRESS™ stent. Of the study group, 318 patients (24%) had diabeties [3]. At 9 months follow-up, angiographic restenosis was 6.4% with PETSs versus 34.5% with BMSs ($p < 0.001$). The TLR at 12 months was 7.4 versus 20.9% ($p < 0.001$) in the DES and BMS groups, respectively. MACEs were also reduced by 44% (11.3 vs 24%; $p < 0.004$). Various other events such as TVR, were reduced by 54% and cardiac death, MI and subacute thrombosis were comparable in the DES and the BMS groups. A significant reduction in angiographic restenosis was noted in the diabetic population who were insulin-requiring (7.7 vs 42.9%; $p = 0.0065$) and the TLR was 6.2 versus 19.4% ($p = 0.07$). TAXUS IV demonstrated a significant reduction in angiographic and clinical restenosis in patients with DM including those who were insulin-requiring.

Overall, in the various trials of the CYPHER stent, 5500 patients with diabetes received SESs. The randomized trials included the RAndomized study with sirolimus-eluting Bx VELocity balloon-expandable stent (RAVEL), SIRIUS, New SIRIUS, study in patients with *de novo* coronary artery lesions in Small VEsseLs TrEated with the CYPHER stent (SVELTE), direct stenting using the sirolimus-eluting Bx VELOCITY™ stent (DIRECT) and the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. The registries included CYPHER, BIDGE and the World Health Organization (WHO) study. All the trials showed a significant reduction in MACE in patients with diabetes and confirmed the inhibitory effect of rapamycin on the neointimal proliferation. Late lumen loss was noted as 0.07 mm in RAVEL and 0.029 mm in SIRIUS and DIABETES [12]. In the latter trial, a total of 302 patients were enrolled, and at 270 days the primary end point of 88% reduction in late lumen

loss was achieved. In-segment restenosis rates were 7.7 versus 33.3% ($p < 0.0.1$) and TLR was 7.5 versus 31.3% ($p < 0.0001$).

Similar results have been noted with paclitaxel-eluting stents. More than 2600 patients have received TAXUS stents in TAXUS I, II, IV and VI and the real-world registries (Web-based TAXUS Intercontinental observational Data transitional registry program [WISDOM], Milestone II, ARRIVE) have demonstrated low TLR and low reintervention rates in patients with diabetes.

Expert commentary & outlook

At present, there is no clear evidence that one DES is better than the other. However, recently there have been two head-to-head trials comparing sirolimus with paclitaxel in patients with diabetes. These trials both suggested that sirolimus is superior to paclitaxel in the high-risk subset of patients with diabetes. In-stent restenosis and TLR for paclitaxel was approximately twice that of sirolimus [13,14].

Despite reductions in clinical and angiographic restenosis and MACEs (including death and MI) restenosis rates continue to be high in patients with diabetes. However, DESs hold significant promise in treating this high-risk subset. While this article concentrated only on paclitaxel and sirolimus, there are a number of other candidate molecules being investigated for DESs and we anxiously await the results of trials evaluating them.

Highlights

- Restenosis remains a significant problem with bare-metal stents.
- Drug eluting stents with paclitaxel and sirolimus have greatly reduced the rates of restenosis.
- Patients with diabetes are at particularly high risk of developing restenosis.
- Recent studies suggest that sirolimus-coated stents may be superior to paclitaxel in preventing restenosis in patients with diabetes.

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