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EDITORIALS

Drug eluting stents for patients with diabetes

The role of coronary revascularisation versus medical treatment needs clarification

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In general, drug eluting stents have improved outcomes after percutaneous coronary intervention (PCI).[1] However, more deaths were reported in patients with diabetes who received drug eluting stents than in those who received bare metal stents.[2] For several years, coronary artery bypass grafting has been the main method of coronary revascularisation in patients with diabetes and multivessel disease because of better survival and lower need for repeat revascularisation than with stenting.[3] The lower success rate and higher complication rate of coronary stenting procedures in patients with diabetes may be attributed to several factors—complex coronary anatomy, diffuse and extensive disease, presence of comorbidities, and problematic vascular access. Several mechanistic and cellular pathways accentuate inflammation, and oxidative stress may account for these poorer outcomes in patients with diabetes.

However, a network meta-analysis recently reported that drug eluting stents were safe and prevented target vessel revascularisation in patients with and without diabetes who were given dual antiplatelet treatment for more than six months.[4] Taking the evidence a step further, in a linked research paper (doi:10.1136/bmj.e5170), Bangalore and colleagues explored the relative differences in outcomes for various commercially available drug eluting stents that were impregnated with sirolimus, paclitaxel, everolimus, and zotarolimus.[5]

This mixed treatment comparative meta-analysis of 42 trials with 10 714 patients with diabetes found that everolimus eluting stents provided the lowest rate of target vessel revascularisation. Compared with bare metal stents, the number needed to treat to prevent a revascularisation procedure was 13.4. Importantly, drug eluting stents, especially everolimus eluting stents, did not increase stent thromboses, including late events. Indeed, the two year risk of stent thrombosis for everolimus eluting stents was about a third to half of that after implantation of a drug eluting stent in general.[6] Despite the complex statistical analysis, the findings provide a reasonable approach to guide clinicians in choosing a stent for their patients with diabetes undergoing PCI. However, the US Food and Drug Administration recently approved the second generation zotarolimus eluting stent (Resolute MicroTrac and Resolute Integrity) as the only limus eluting stent for use in patients with diabetes.

The reasons for the better outcome associated with everolimus eluting stents in the current study are not clear. In vitro studies found that everolimus was two to three times less potent than sirolimus.[7] Although sirolimus, everolimus, and zotarolimus have similar efficacy in preventing the proliferation of human coronary smooth muscle,[7 8] the amount of drug delivered on the stent is lower for everolimus and zotarolimus, and drug release kinetics also differ between stents (table⇓). In addition, the differences in performance extend beyond drug factors. Bangalore and colleagues selected studies that evaluated devices with durable polymer to carry the drug, but the thickness of the polymer varied between studies and devices (thinner for everolimus eluting stents and zotarolimus eluting stents; table). Some authors have suggested that the polymer induces inflammation and stent thrombosis.[9] Modifications in its composition and thickness may have a positive effect on outcomes. Other factors that might have affected restenosis rates include the thickness of struts on the stents and the nature of the stent's base material. Taken together, these drug and stent factors may account, at least in part, for the variation in outcomes.

Although the number of coronary stenting procedures fell from 399 558 in 2004 to 322 024 in 2009 in the United States (a 19% decline),[10] the burden of older patients with diabetes is expected to increase dramatically worldwide. Evidence of the efficacy of second and third generation drug eluting stents is beginning to affect the fundamental considerations that underpin the choice between surgical and percutaneous coronary revascularisation for patients with diabetes. The current study reports better outcomes with everolimus eluting stents, but whether the clinical efficacy of bioresorbable everolimus eluting stents is superior for patients with diabetes remains unclear.[11] Another problem that the current study did not investigate is the rate of late repeat revascularisation procedures.[12] The FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) study, which is currently investigating outcomes after sirolimus or paclitaxel eluting stents and bypass surgery in 1900 patients with diabetes, will provide further evidence to help clinicians when choosing between interventions for patients with diabetes.[13]

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The cost effectiveness of using drug eluting stents for patients with diabetes also requires further evaluation. A recent cost effectiveness analysis found that, over three years, the cost of preventing one target vessel revascularisation procedure was $6379 (£4036; €5083). This included the cost of the drug eluting stent and the incremental cost of treating a patient who has received such a stent (such as clopidogrel for at least a year).[14] A major drawback is that PCI in the non-acute setting, even with drug eluting stents, has not been shown to be superior to optimal medical treatment.[15] Optimal medical treatment will probably remain the core treatment for patients with diabetes, although the current role of coronary revascularisation and medical treatment in managing such patients needs to be better defined. Regardless of the revascularisation strategy chosen, doctors and patients with diabetes must remember that this high risk group will still need multifactorial interventions to achieve various therapeutic targets and improve survival.

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Table

Table 1| Characteristics of various drug eluting stents

Stent name	Drug (concentration, μg/cm^2)	Polymer	Polymer thickness (μm)	Release kinetics (28 days)	Platform*	Design	Strut thickness (μm)
Cypher	Sirolimus (140)	Polyethelyne co-vinyl acetate and poly-n-butyl methacrylate	12.6	80%	SS 316L	Closed cell	140
Taxus Express	Paclitaxel (100)	Poly(styrene-b-isobutylene-b-styrene)	16.0	<10%	SS 316L	Open cell	132
Endeavor	Zotarolimus (100)	Phosphorylcholine	5.3	95%†	MP35N CoCr	Hybrid	91
Xience V	Everolimus (100)	Polyvinylidene fluoride co-hexafluoropropylene and poly-n-butyl methacrylate	7.6	80%	L605 CoCr	Hybrid	81

*SS=stainless steel; CoCr=cobalt-chromium.

†At 14 days.