Diabetics and Drug-eluting Stents in ST Segment Elevation Myocardial Infarction: Confidence in Numbers

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Diabetes mellitus affects over 15 million adults in the United States and more than 180 million patients globally, including 25%-30% of all patients undergoing percutaneous coronary intervention (PCI).[1-3] Diabetic compared to non diabetic patients following PCI are at increased risk of death, myocardial infarction (MI), and stent thrombosis,[4-6] and the presence of diabetes is one of the strongest and most consistent risk factors for restenosis and target lesion revascularization (TLR) from excessive intimal hyperplasia.[7-9]

Experimental studies have demonstrated that in the presence of diabetes, vascular smooth muscle cells are hypersensitive to the stimulatory action of platelet derived growth factor released after balloon injury, and to the elevated levels of insulin and insulin like growth factors.[10-16] In addition, hyperglycemia may directly increase restenosis by increasing the expression of basic fibroblast growth factor, a potent mitogen for smooth muscle cell proliferation after balloon injury, and by inducing synthesis of extracellular matrix at the treatment site.[17,18] Advanced glycosylation of vessel wall proteins may augment the inflammatory reaction after vessel wall injury, further inducing release of stimulatory cytokines, and thus promoting smooth muscle proliferation.[19,20] Altogether, these mechanisms play an important role in the excessive intimal hyperplasia and the hyperthrombotic state present in diabetic patients, and may explain the worse outcomes seen after PCI in diabetics compared to non diabetics.

SEE ARTICLE ON PAGES 354-64

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Drug eluting stents (DES) in patients with stable coronary artery disease, especially among diabetic patients, have dramatically reduced the rates of angiographic restenosis and TLR, with reductions ranging from 50%-80% with both sirolimus-eluting stents (SES) as well as paclitaxel-eluting stents (PES) compared to bare metal stents (BMS).[20-23] In the diabetic substudy of the randomized SIRolImUS-coated Bx Venlocity balloon expandable stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial, 279 diabetic patients were treated with SES (n=131) or BMS (n=148). Compared to BMS, SES resulted in 9 month reductions in TLR (22.3% vs 6.9%; $P<.001$) and major adverse cardiac events (25% vs 9.2%; $P<.001$), with comparable rates of stent thrombosis.[22] The safety and efficacy of the PES was reported from a pooled analysis of 5 randomized clinical trials including 827 diabetic patients (n=408 PES; n=416 BMS). At 4 year follow-up there were no significant difference in the rates of death (8.4% vs 10.3%), MI (6.9% vs 8.9%), or stent thrombosis (1.4% vs 1.2%) with PES compared to BMS respectively (all P=NS). PES was, however, associated with a significant and durable 50% reduction in TLR compared to BMS (12.4% vs 24.7%; $P<.0001$).[23]

While the efficacy of DES in reducing angiographic and clinical restenosis among diabetic patients has been dramatic and consistent among trials, the safety of DES in this high risk patient subgroup is less well established, in part because of the relatively few patients studied with resultant wide confidence intervals. Diabetic patients are predisposed to thrombotic complications due to increased levels of plasminogen activator inhibitor type 1 (PAI-1),[24] reduced levels of platelet cNOS activity,[25] and greater endothelial dysfunction compared to non diabetic patients.[26] Iakovou et al showed that diabetes is a predictor stent thrombosis among DES treated patients.[27] In addition, a meta analysis of double blind randomized trials reported greater mortality among diabetics treated with SES rather than BMS at 4 year follow-up (12.2% vs 4.4%, P=.004), and a trend toward an increase in very late stent thrombosis (11 vs 3 events) with SES.[28]

Moreover, few studies have examined the safety and efficacy of DES in diabetic patients with ST-segment elevation acute myocardial infarction (STEMI), in which rates or death, reinfarction and stent thrombosis are increased with both BMS and DES compared to patients undergoing PCI with stable ischemic heart disease.

The meta-analysis by Iijima et al published in this edition of *Revista Española de Cardiología*[29] is an important step in assessing the role of DES in diabetics with STEMI. From a pooled patient level analysis of 7 randomized trials, the investigators compared TLR rates and clinical outcomes in 206 diabetics receiving DES (with either SES or PES) to 183 diabetics receiving BMS. Patients treated with DES had a significantly lower risk of TLR (HR=0.44; *P*=.02) without an increase in stent thrombosis or the combined endpoint of death or MI during a follow-up of 12-24 months. These data are reassuring that diabetic patients may safely benefit from DES therapy in the setting of a STEMI.

The results and conclusions of this pooled analysis are consistent with the findings of DES in the context of elective PCI,[22,23] as well as with the recently published large network meta-analysis by Stettler et al of 35 randomized controlled trials in which SES and PES were compared to each other as well as to BMS across a broader spectrum of patients (including those with acute coronary syndromes).[30] In this analysis the risk of TLR was significantly lower among diabetics who received DES (SES vs BMS, HR=0.29; PES vs BMS, HR=0.38). Among DES patients, those who received dual anti-platelet therapy with aspirin and clopidogrel for 6-months did not have increased mortality rates. Thus, these studies collectively suggest that DES use is safe and effective in diabetic patients across the spectrum of acute coronary syndromes, including STEMI, despite the general poor prognosis of this cohort.

While the analysis by Iijima et al is promising, definitive conclusions must be tempered by the limitations of the study. Although the data was pooled from 7 randomized trials, the number of diabetics enrolled in each trial was small. The baseline characteristics of the patients within this meta-analysis were not provided, and the possibility that an imbalance in one or more clinical or angiographic feature may have been present which may have influenced revascularization rates and safety outcomes, such as age, chronic kidney disease, vessel size, lesion length, etc, cannot be excluded. The repeat intervention curves diverge within 24 hours of the procedure, which suggests that the play of chance may have somewhat favored DES in the present analysis. Perhaps most importantly, despite pooling data from 7 trials, the entire study cohort of 389 patients is still well underpowered to reliably support a conclusion that safety of DES in diabetic patients with STEMI has been proven, or to examine the safety and efficacy of SES and PES in this patient population.

Additional questions remain to be addressed:

1. Do insulin dependent and non-insulin dependent diabetics benefit equally from DES, and are there benefits of tight glucose control following PCI in STEMI? It has been suggested that among diabetics, those requiring insulin have increased mortality and may achieve less relative benefit from PCI.[31,32]

2. What is the optimal thienopyridine regimen and duration of dual anti-platelet therapy? Diabetics have larger platelets and increased platelet activation and aggregation than non diabetics, and may benefit from more potent thienopyridine agents and extended dual antiplatelet therapy.[33-35]

3. What are the long-term outcomes of DES versus BMS implantation in diabetic patients? Studies regarding the durability of DES in diabetics have been conflicting. In one prospective study, DES use was no longer associated with decreased revascularization rates and clinical benefit after 3 year follow-up compared to BMS.[36]

4. What is the relative safety and efficacy profile of "new" DES in patients with STEMI (with or without diabetes), such as those eluting the antiproliferative agents zotarolimus and everolimus, and can outcomes be further enhanced by novel designs incorporating bioabsorbable polymers or even completely bioabsorbable stents?

In conclusion, the current study by Iijima et al[29] is encouraging and suggests that diabetics with STEMI benefit from DES therapy with improved efficacy without compromising safety. The major questions that remain regarding safety and long-term efficacy of DES in diabetics with STEMI will be answered as additional patients are studied and followed. In this regard, 478 patients with diabetes and STEMI were recently randomized to PES versus BMS in the international Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, the results of which when reported will provide significant new data to inform stent selection decisions in diabetics with STEMI.

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