

## A Friend In Need Is a Friend Indeed: the Case of Drug-Eluting Stents, Diabetes, and Small Vessel Size

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Patients with diabetes mellitus consistently have shown a less favorable angiographic and clinical outcome after balloon angioplasty with or without bare metal stents (BMS) as compared to nondiabetic patients.<sup>1,2</sup> Diabetic patients have an increased risk for restenosis and the clinical follow-up is characterized by a higher incidence of death, myocardial infarction and reinterventions.<sup>3</sup> Thus, diabetes itself and the frequent coexistence of other important risk factors label individuals with this disease as highly complex patients and represents a challenging problem in modern invasive cardiology. In recent years, drug-eluting stents (DES) are increasingly being used in diabetic patients. Several well designed trials investigated outcomes after DES implantation in diabetic patients. Consistently, RAVEL subset analysis,<sup>4</sup> DIABETES trial,<sup>5</sup> subset analysis from TAXUS II, IV, V and VI,<sup>6</sup> and SIRIUS<sup>7</sup> demonstrated the superiority of DES over BMS in reducing the need for target vessel revascularization without showing, however, a clear mortality benefit in diabetic patients within the examined follow-up period.

In addition to diabetes, small vessel size also presents a significant challenge; treatment of lesions in small coronary arteries is difficult and often disappointing with various interventional modalities. Revascularization by aorto-coronary bypass surgery (CABG) is technically difficult and is associated with high failure rates, while revascularization by plain balloon angioplasty<sup>2</sup> and BMS<sup>1,8</sup> is associated with high complication and restenosis rates. The major problem with small size vessels is their limited

capacity to accommodate for late lumen loss after stenting, the extent of which is independent of vessel size. Thus, the superiority of DES over BMS shown in dedicated studies and subset analyses focused on small coronary vessels<sup>9-11</sup> comes not unexpected.

Abundant evidence is thus available in support of the increased risk of restenosis associated with diabetes and small vessel size; both these factors may serve as a “stress test” helping the evaluation of the relative performance of coronary devices including DES.<sup>12,13</sup>

The authors of the article that is published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA<sup>14</sup> are to be commended for having combined both diabetes and small vessel size in their analysis creating a particularly high-risk scenario that is not unusual in the every-day practice of interventional cardiology. Patients with both these factors are those most in need of a treatment modality able to reduce effectively their inherently high risk of restenosis. For the first time we are provided with an analysis addressing interventions in a very small vessel size showing an average value of only 1.9 mm. To date, even dedicated studies on interventions in small vessels have reported average values of vessel size that were well above the 2 mm threshold. To realize the terrain on which Jiménez-Quevedo and colleagues<sup>14</sup> have been operating, it is sufficient to consider that with a 1 mm late loss typical for BMS, more than half of their patients might have been at risk of restenosis if assigned to BMS. We are happily surprised to see an in-stent late lumen loss of 0.64 mm and an incidence of angiographic restenosis of 39.1% among BMS patients, although the BMS type they received has not the reputation of a “low-loss” stent.<sup>15</sup> On the contrary, we are not surprised to see an irrelevant late lumen loss in the DES group of the study of Jiménez-Quevedo et al.<sup>14</sup> In line with the described relationship between late lumen loss and restenosis,<sup>16</sup> there was more than 75% risk reduction in angiographic and clinical restenosis with the use of this particular DES (sirolimus-eluting stent [SES]).<sup>14</sup> The data presented do not show an advantage in

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mortality with DES in this high-risk subset of patients, but both the limited number of patients and duration of follow-up do not enable a comprehensive assessment of this issue. Previously, the absence of restenosis has been reported to translate in improved long-term survival after stenting<sup>17</sup>; we have to wait for larger and long-term studies with the hope that DES will be able not only to improve the quality but also the length of life. Our enthusiasm in this sense is somehow abated by the intravascular ultrasound finding of an elevated incidence of late malapposition of DES.<sup>14</sup> Although the clinical significance of this finding is unknown in this particular subset of diabetic patients with DES in small vessels, there is a theoretical increase in risk of late stent thrombosis which justifies a prolonged dual antiplatelet therapy.

As appropriately acknowledged by the authors, it is a subset analysis including a limited number of patients. Although it is scientifically correct to call for large randomized studies in diabetic patients with lesions in small vessels as the authors do in the discussion of their article,<sup>14</sup> there is little chance that this will be done in the future. Available evidence is so overwhelmingly in favor of DES that no one will take the initiative of exposing a large number of such complex patients to the high risk of restenosis connected with BMS. The findings of Jiménez-Quevedo et al<sup>14</sup> should be seen in the context of other studies exemplarily showing the higher the risk of restenosis, the larger the benefit with DES. In the randomized trial of Pache et al,<sup>18</sup> compared to BMS, DES reduced restenosis by 80% in vessels <2.8 mm in size, but by a mere 14% in vessels  $\geq 2.8$  mm in size. Later randomized trial confirmed that high-risk subsets of patients create an optimal setting that permits differentiation of various DES in terms of performance. Although there were no significant differences when SES were compared to paclitaxel-eluting stents (PES) in relatively selected cases,<sup>19</sup> there were exactly high risk subsets such as diabetic patients,<sup>20</sup> lesions in small vessels<sup>21</sup> and restenotic lesions<sup>22</sup> that accentuated these differences by evidencing the superiority of SES which was thereafter validated by a formal meta-analysis.<sup>8</sup> Choosing the highly challenging combination of diabetes and very small vessel size, Jiménez-Quevedo and colleagues have pushed DES almost into the very extreme of the "uncharted territory."<sup>23</sup> It is intuitive to believe that the magnitude of benefit shown in this analysis with SES<sup>14</sup> would have been a difficult target to achieve by other DES platforms. Currently, there are DES in use that provoke a late lumen loss not very different from that observed in the BMS group of the present study (0.64 mm),<sup>14</sup> which represents a considerable handicap for vessels <2 mm in size.

The role of an optimized adjunct antiplatelet therapy may be more crucial in patients with diabetes and

lesions in small vessels. There are little doubts about the benefit of pretreatment with clopidogrel loading in a 600 mg dose at best and, if this is timely done, glycoprotein IIb/IIIa inhibitors might not be needed in all situations. Abciximab has improved outcomes in patients with acute coronary syndromes, particularly if they present with positive cardiac biomarkers.<sup>24</sup> In addition, it has reduced restenosis in diabetic patients receiving BMS,<sup>17</sup> but it is still not known whether this beneficial effect is also observable in those receiving DES. Patients with diabetes mellitus and coronary artery disease require, independently of the PCI procedure, careful glycemic control and intensive management of all other risk factors including dyslipidemia, hypertension, smoking, and obesity. The role of the quality of glycemic control and the therapeutic options to achieve it are being tested as a standalone strategy or in combination with revascularization procedures (PCI or CABG) in a large randomized clinical trial including diabetic patients with coronary artery disease.<sup>25</sup>

This subset analysis of the DIABETES trial clearly shows that we are currently approaching patients with a very high risk profile, a profile that only a few years ago would have been prohibitive for the majority of interventional cardiologists. This has been enabled by the availability of new effective DES technology. High-risk patients are those most in need of this technology and a friend in need is a friend indeed.

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