

Insulin-Dependent. Rapamycin-Resistant?

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The development of drug-eluting stents has revolutionized interventional cardiology. In Spain, 25 148 drug-eluting stents were implanted in 2004, according to the Registro Español de Hemodinámica y Cardiología Intervencionista (Spanish Registry of Hemodynamics and Interventional Cardiology).¹ Based on the results of key randomized studies with sirolimus-eluting^{2,3} and paclitaxel-eluting stents,⁴⁻⁷ everything appears to indicate that the efforts to prevent the much-dreaded restenosis have finally been successful. In fact, when one reads or reviews the main large-scale, multicenter, multinational, often industry-sponsored studies, the conclusion is that these stents have a high level of efficacy and safety. A meta-analysis of 12 clinical studies⁸ showed a mean reduction in the revascularization incidence of 69% (relative risk [RR]=0.31; 95% confidence interval, 0.19-0.51). This benefit was associated with a mean additional cost of €818 718 per 1000 patients with a de novo lesion treated with a drug-eluting stent. Therefore, widespread use at market prices would imply an increase in healthcare costs for the different sensitivity scenarios assessed. It has recently been shown that the use of drug-eluting stents may have greater cost-effectiveness in scenarios where the risk of restenosis is higher.⁹ In this regard, all the subgroups analyzed in the SIRIUS and TAXUS studies^{10,11} show the unequivocal, uniform clinical benefit of using these stents. In addition, these stents appear to “neutralize” the detrimental effect of some clinical (e.g., diabetes mellitus) or anatomical conditions (long lesions, small vessels), with a comparably low failure rate, both among patients who present the adverse clinical condition and among those who do not (Table).

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To better explore the effectiveness of drug-eluting stents in the “real-world” of high-risk patients, we should focus on registry results.¹²⁻¹⁴ Unlike randomized studies, registries have almost no inclusion criteria, thus producing a larger study population that more closely resembles the population seen in daily practice. Since patient inclusion is generally voluntary, there may be an inherent patient enrollment bias in any registry. However, a registry is often the only way to create evidence in highly adverse clinical situations that are normally excluded in industry-sponsored randomized studies. The study from Berenguer et al¹⁵ published in this issue of our journal is a welcome addition to the literature.

Berenguer et al¹⁵ have assessed the usefulness of sirolimus-eluting stents among diabetic patients with complex lesions by conducting a substudy of a single-center registry of complex lesions treated with these devices.¹⁶ Complex stenosis was defined as stenosis presenting any of the following anatomical conditions associated with a high risk of restenosis: location in the left main sten, bifurcations, lesions longer than 18 mm, calcified lesions, stenosis of the proximal left anterior descending artery, restenotic lesions, total occlusions, ostial lesions, and stenosis in vessels of less than 2.75 mm. In all 260 lesions treated, target vessel failure at 1 year as the primary event and angiographic evidence of restenosis at 6 months were then compared between nondiabetic, non-insulin-dependent diabetic mellitus (NIDDM), and insulin-dependent diabetic mellitus (IDDM) patients. The patients with insulin-dependent diabetes presented significantly greater late luminal loss and a higher incidence of restenosis (trend at the limit of significance). Nevertheless, these findings did not result in an increase in the rate of target vessel revascularization (6.5% in type 1 diabetes, 5.8% in NIDDM, and 3.8% in non-diabetics; $P=NS$). Likewise, the incidence of target vessel failure showed only a tendency ($P=.07$) to be higher in patients with IDDM. Lastly, and most importantly, the multivariate analysis eliminated IDDM as an independent predictor of restenosis and target vessel failure. This fact is not as surprising if the baseline data are analyzed for both groups (Tables 1-4 of the study). Patients with IDDM were typically women, hypertensive, with a history of coronary artery bypass grafting, peripheral vascular disease, heart failure, and ejection fraction <50%, and presented significantly

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TABLE. Relative Risk Reduction in Target Vessel Revascularization Using a Drug-Eluting Stent Among the Different Patient Subgroups in the SIRIUS and TAXUS IV Studies*

	Relative Risk Reduction, SIRIUS study†	Relative risk reduction, TAXUS IV study‡
All patients	75%	73%
Nondiabetics	79%	76%
Diabetics	68%	IDDM: 68%; NIDDM: 67%
Vessel size	<2.75 mm: 71% ≥2.75 mm: 83%	≤2.5 mm: 76% >2.5-3.0 mm: 71% >3.0 mm: 68%
Lesion length	>13.5 mm: 73% ≤13.5 mm: 79%	>20 mm: 77% 10-20 mm: 70% <10 mm: 73%
Left anterior descending artery	74%	69%
Not left anterior descending artery	77%	76%

*ID indicates insulin-dependent diabetes mellitus; NID, non-insulin-dependent diabetes mellitus.

†SIRIUS study.¹⁰

‡TAXUS IV study.¹¹

longer lesions. Finally, an analysis of the cause of target vessel failure (Table 5 of the study) showed that this was basically due to a trend toward a higher incidence of cardiac death that was not related to a higher incidence of infarction in the target vessel (stent thrombosis) or a higher incidence of clinical restenosis. This appears to be logical, when considering that this patient group has poorer clinical characteristics. Therefore, in my opinion, the data from this registry do not show that sirolimus-eluting stents imply a poorer clinical progress in patients with IDDM, but rather that these patients are those who worsen (greater number of deaths) despite receiving a stent, with an incidence of clinical restenosis similar to that of nondiabetic or NIDDM patients.

Although a decrease in the efficacy of sirolimus-eluting stents could not be proven among IDDM diabetics due to the design of this registry, we should ask whether or not the clinical data support the concept of sirolimus resistance in these patients.

In the SIRIUS study, insulin-dependent patients did not present any improvement in the angiographic restenosis parameters when the stent was analyzed together with its margins. Nevertheless, when the analysis only looks at the stent, which is where the antiproliferative potency of the drug is determined, there was a significant decrease in late luminal loss and incidence of restenosis. This “margin effect” is attributed to technical problems (geographic miss) rather than ineffectiveness of the drug.¹⁷

The randomized, multicenter DIABETES study¹⁸ included high-risk diabetic patients, a group that is highly comparable to the patients in the present study. The mean reference diameter was 2.34 mm for all patients and 2.24 mm for insulin-dependent patients. Contrary to the authors’ description, chronic total occlusions (13% of the lesions included) and patients with renal failure (32% of the patients) were not excluded. In addition, 43% of the lesions were longer than 20 mm and 65% of the patients presented multivessel disease. In this context, the

incidences of restenosis and late luminal loss were comparable among IDDM and NIDDM patients. In reality, the decrease in risk was greater in insulin-dependent patients due to an increase in the incidence of restenosis in the group treated with conventional stents. Therefore, this is further evidence for the “neutralizing” effect of sirolimus-eluting stents in a high-risk group.

Finally, if we analyze the results of the 293 diabetic patients included in the Research and T-Search registries,¹⁹ similar data are obtained to those of the Berenguer et al study.¹⁵ The patients with insulin-dependent diabetes presented a worse clinical outcome (27% of major cardiac adverse events at 1 year versus 14.6% in patients with type 2 diabetes; $P=.091$). In the multivariate analysis, however, treatment of the left main sten and the left anterior descending artery, renal failure, and female sex were identified as independent predictors of failure at 1 year of follow-up, whereas the need for insulin was not statistically significant.

Based on the current evidence, because of their greater comorbidity, diabetic patients who require insulin should benefit from integral medical treatment beyond a purely cardiology approach, in which treatment is more careful, more controlled and probably multidisciplinary. Likewise, from the standpoint of percutaneous revascularization, they should receive, almost universally and as standard therapy, implantation of a drug-eluting stent.

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