Paclitaxel-Eluting Stents in Complex Lesions

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ERCUTANEous CORONary INTERventions (PCIs) have become the dominant form of revascularization. This evolution has been based on the results of a large number of pivotal randomized trials. Since the pioneering work of Gruntzig,1 2 major developments have revolutionized clinical cardiology practice. The first was the introduction of bare metal stents by Sigwart and Puel in 1986 and results following use of stents to treat impending or acute vessel closure after balloon angioplasty were subsequently reported in 1987.2 Stent implantation improved both acute and long-term results following angioplasty, but perhaps more important from the patient’s perspective, dramatically reduced the need for emergency coronary artery bypass graft (CABG) surgery.

The second development was the advent of drug-eluting stents in an effort to prevent a need for repeat revascularization due to restenosis. Multiple studies comparing PCI with CABG surgery have shown that the superiority of CABG surgery predominately rests with its advantage in lower rates of repeat revascularization.3,4 Drug-eluting stents have the potential to redress this imbalance but only if effective in complex lesions.

To date, enthusiasm for use of drug-eluting stents is based on key trials involving use of the sirolimus-eluting stent5 and the polymer-based, paclitaxel-eluting stent.6 Both stents demonstrated a dramatic reduction in the need for revascularization when compared with the bare metal stent in relative simple coronary artery lesions (shorter than 18 mm and located in vessels ≥2.5 mm in diameter). Safety and efficacy were demonstrated with a more than 2-fold reduction in the need for repeat revascularization with the drug-eluting stent compared with the bare metal stent. Longer lesions (≤30 mm in length)7,8 were evaluated in subsequent trials and again safety and efficacy were confirmed.

In this issue of JAMA, Stone and colleagues10 report the results of a randomized trial evaluating the paclitaxel-eluting TAXUS stent (Boston Scientific Corp, Natick, Mass) in more complex lesions. This study, TAXUS V, follows the sequence of other paclitaxel-eluting stent trials that have included progressively more complex lesions than the first human paclitaxel-eluting stent trial.11 This trial enrolled patients with lesions as long as 46 mm and lesions located in smaller vessels with a minimal diameter of 2.25 mm and also allowed use of multiple stents (on the same lesion) with minimal overlap between 2 stents.

The study by Stone et al moves the field of drug-eluting stents closer to clinical practice but there is still a relatively long way to go. For instance, the investigators did not allow enrollment of patients with total occlusions, bifurcational, ostial, severely calcified, or thrombus-containing lesions. In addition, no multiple index lesions were included; this means that for the purpose of the end-point analysis only 1 lesion treated with the paclitaxel-eluting stent was evaluated. If drug-eluting stents were reserved only for lesions of this level of complexity, as many as 160 000 stents per month around the world10 might not have been implanted.

This large study randomized 1172 patients at 66 US centers and has a well-balanced and appropriate representation of patients with clinically relevant characteristics in both groups: 30% of the patients had medically treated diabetes mellitus and 30% had unstable angina. Moreover, there were high rates of clinical follow-up, nearly 98%, and angiographic follow-up, exceeding 85%. At least 200 patients had lesions in vessels smaller than 2.25 mm in diameter (high risk for adverse events), and at least 200 had lesions located in vessels with a diameter of 4.0 mm (low risk for adverse events). These 2 subgroups of patients with lesion characteristics at the opposite ends of the spectrum may make the overall results more difficult to interpret correctly, but on the other hand may stimulate interest in the specific evaluation of these 2 subgroups. A third, rather unique subgroup, from the perspective of randomized trials, is that 379 patients had multiple stents placed in the same lesion.

The primary end point evaluated is important and pertinent for any study of drug-eluting stents: ischemia-driven target vessel revascularization. In the entire study population, target vessel revascularization and target lesion revascularization at 9 months occurred in 17.3% and 15.7% of...
patients, respectively, in the bare metal stent group and in 12.1% and 8.6% of those, respectively, in the paclitaxel-eluting stent group. Most of the secondary end points (Table 3 in the article by Stone et al) such as the composite of “any major adverse cardiac event,” which includes death and myocardial infarction, also were reduced in the paclitaxel-eluting stent group, as was the more standard end point, the binary restenosis rate. However, the rate of myocardial infarction at 30 days was slightly (but not significantly) increased in the paclitaxel-eluting stent group.

While the study was not specifically powered to evaluate subgroups, the data reported provide important insights for 3 subgroups: vessels of 2.25 mm in diameter or smaller, vessels of 4.0 mm in diameter or larger, and multiple overlapping stents.

Patients with stents implanted in small vessels had a small reference vessel size (average of 2.08 mm). The findings in this subgroup demonstrate the advantage of the paclitaxel-eluting stent over the bare metal stent in terms of angiographic restenosis (31.2% vs 49.4%; \(P = .01\)) but also highlight the need for further improvement for the paclitaxel-eluting stent in the therapy of small vessels especially when patients with diabetes are highly represented. The temptation to compare these results with another study evaluating the sirolimus-eluting stent in small vessels is understandable but needs to be tempered by the presence of longer lesions (16.6 mm vs 11.8 mm) and a higher prevalence of diabetes (47.2% vs 24.9%) in the 2.25-mm stent group in TAXUS V.

However, there are concerns about the effectiveness of paclitaxel-eluting stent in very small vessels, as shown by the 9-month, in-stent average late loss of 0.49 mm. The debate about the impact of differences in late loss between sirolimus-eluting and paclitaxel-eluting stents may become relevant when the reference vessel size decreases below a certain value not yet well defined. In this regard a similar in-stent late loss in large vessels translates into a restenosis rate of 3.5%. The SIR TAX (Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization) trial, which randomized 1005 unselected patients with a variety of lesions to sirolimus-eluting or paclitaxel-eluting stents seems to support the need to minimize late loss in more complex lesions. The primary composite end point of death, myocardial infarction, or target lesion revascularization at 9 months occurred in 10.8% of the paclitaxel-eluting stent group compared with 6.2% of the sirolimus-eluting stent group (hazard ratio, 0.56; 95% confidence interval, 0.36-0.86; \(P = .009\)). This difference was partly driven by a significantly greater need for revascularization in the paclitaxel-eluting stent group (8.3% vs 4.8% for sirolimus-eluting stent; \(P = .03\)).

The recently reported ISAR-DIABETES (Intracoronary Stenting and Angiographic Results-Do Diabetic Patients Derive Similar Benefits from Paclitaxel-Eluting and Sirolimus-Eluting Stents) trial, in which 250 patients with diabetes were randomized to receive a sirolimus-eluting stent or a paclitaxel-eluting stent, found a lower in-segment restenosis with the sirolimus-eluting stent (6.9% vs 16.5%; \(P = .03\)). The advantage demonstrated with the sirolimus-eluting stent occurred despite the reference vessel sizes that were not so small (2.75 mm with the paclitaxel-eluting stent and 2.70 mm with the sirolimus-eluting stent), a higher difference in late loss was used as the main explanation for a higher restenosis. This finding appears provocative and may suggest an overall advantage of the sirolimus-eluting stent compared with the paclitaxel-eluting stent, which becomes evident in patients with complex lesions. This advantage appears to be present even in more standard lesions in which large cohorts of patients are needed to demonstrate a difference.

Appropriately powered studies are necessary to clarify this area further.

Evaluating drug-eluting stents in large vessels may seem unnecessary in light of the need for prolonged antiplatelet therapy and the cost associated with modest advantages in terms of a lower need for revascularization. The current data provided in the trial by Stone et al are the only available information for the implantation of drug-eluting stents in very large vessels. A previous study comparing a thin-strut bare metal stent with a sirolimus-eluting stent reported results in small and large vessels and did not find any difference in terms of restenosis between the stents in vessels larger than 2.8 mm, but only 9 patients had postdilation of the sirolimus-eluting stent with a balloon larger than 3.5 mm. The 0% target lesion revascularizations in large vessels (ie, 4.0-mm stent) implanted with the paclitaxel-eluting stent in TAXUS V compared with the 5% rate for the bare metal stent would suggest 20 patients would need to be treated to prevent 1 repeat revascularization. As Stone et al point out, the approach of drug-eluting stent implantation in large vessels may not be cost-effective, but it may increasingly be so in the left main coronary artery or in saphenous vein grafts.

The increased incidence of periprocedural enzyme elevation in patients with overlapping paclitaxel-eluting stents is of concern. The precise etiology of this adverse event is unknown but may be caused by side-branch compromise. In the multiple stents subgroup, patients treated with paclitaxel-eluting stents had a higher incidence of side-branch slow flow, narrowing, and occlusion. These events may be related to the 30% increase in strut thickness caused by polymer coating (Mary Russell, MD, Boston Scientific, written communication, March 2005), which becomes more important in the areas of stent overlap. In the presence of a good angiographic outcome in the main vessel, it is not known whether long-term outcomes will be affected. It may be important to protect side branches during PCI by placing guide wires even if these vessels are small and will not be treated. These wires can be left in place during stent implantation and safely removed later. It is possible that this approach may attenuate the increased incidence of enzyme elevation seen with overlapping stents. An additional factor that may enhance safety could be a more liberal use of...
glycoprotein IIb/IIIa inhibitors, which were administered to less than half of the patients in this trial, or use of other potent antithrombotic agents such as direct antithrombins.

A final important point is the low thrombosis rate observed with paclitaxel-eluting stent even in the lesion subgroups at higher risk (1.1% with multiple overlapping stents). A possible concern persists for patients with lesions not evaluated in this study such as lesions at vessel bifurcations, patients with renal failure, or multiple drug-eluting stents in different vessels. Unfortunately, the last word about the risk of in-stent thrombosis with drug-eluting stents has yet to come. A much larger cohort of patients will need to be studied because small differences, which are clinically relevant due to the consequences of in-stent thrombosis, may only be shown with trials evaluating several thousand patients. In addition, patients will need to be evaluated for an extended period, at least 1 year following discontinuation of thienopyridine therapy.

It is becoming increasingly clear that drug-eluting stents have not abolished the restenotic process, and especially in high-risk lesions, target vessel revascularization rates exceed 10%. This suggests that while the 2 most studied stents are a vast improvement over the bare metal stent, there is still room for further progress. Perhaps thinner strut stents or drug combinations may hold the key to decrease restenosis even further. Finally, there is the huge challenge of reducing myocardial infarction and death following PCI and stent placement. The next step is to move from the complex lesion to the complex patient. This is a work in progress recently started with the enrollment of patients in the SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial comparing the paclitaxel-eluting stent with CABG surgery in patients with triple vessel disease and unprotected left main lesions.

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REFERENCES