EDITORIAL COMMENT

Stenting for Small Coronary Vessels: A Contestable Winner*

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Stents were initially used to manage or prevent acute vessel closure after percutaneous transluminal coronary angioplasty (PTCA). The first direct randomized comparison with respect to restenosis showed the superiority of stenting to PTCA for de novo lesions situated in native vessels 3 mm or larger (1,2). In these trials, stenting was associated with a 25% to 30% reduction of restenosis as compared to PTCA (1,2). This represented the first of a series of battles won by stenting regarding restenosis. Trials that followed showed better results after stenting than after PTCA for bypass graft lesions (3), lesions situated in the proximal left anterior descending coronary artery (4), restenotic lesions (5), chronic occlusions (6) and in patients with acute myocardial infarction (7). Accordingly, stent placement was unanimously indicated for the treatment of de novo or restenotic lesions situated in large vessels (≥3 mm in size).

Smaller vessels constitute a large group in daily practice of percutaneous coronary interventions. Interventions in small coronary vessels (<2.8 to 3.0 mm) account for a considerable proportion (30% to 50%) of the >1 million coronary catheter-based procedures performed worldwide each year (8). Previous studies on balloon angioplasty without stent placement have identified small vessel size as an independent risk factor for the development of restenosis (8). After the introduction of coronary stents, several retrospective analyses have compared long-term results in small versus large vessels, indicating that restenosis rates differ significantly with vessel size. Elezi et al. (9) found that restenosis rate increased from 20.4% in vessels >3.2 mm to 28.4% in vessels 2.8 to 3.2 mm, and to 38.6% in vessels <2.8 mm. Similar findings were described by Akiyama et al. (10), with a rate of 19.9% in vessels ≥3 mm, and 32.6% in vessels <3 mm. Both studies have clearly indicated the mechanism of this negative effect: the absolute late lumen loss after six months in small vessels is equal to, or even higher, than in larger vessels and, as the initial acute gain in smaller vessels is significantly lower, net lumen gain decreases even more dramatically, leading to a significantly higher restenosis rate.

On the basis of the available evidence, small vessel size represents an important risk factor for an adverse outcome both after PTCA and stenting. Post hoc quantitative angiographic analyses of two randomized trials actually designed for large vessels have suggested that stenting might be a better option than PTCA for lesions in small coronary vessels (11,12). However, because the data of these post hoc analyses were not generated by specifically designed randomized studies comparing stenting with PTCA, small vessel size has not been considered an established indication for stenting. As a result of the growing interest in this topic in the last few years, more than half a dozen studies have been dedicated to the randomized comparison between stenting and PTCA for small coronary vessels, including about 2,000 patients.

Heparin-coated beStent versus PTCA for small vessels. The Stenting In Small Coronary Arteries (SISCA) study published in this issue of the Journal (13) reports on the results of one of the randomized trials comparing stenting with PTCA for lesions in small coronary arteries. De novo lesions situated in coronary vessels with a reference diameter of 2.1 to 3.0 mm and with a length that could be covered with a single 15-mm stent were included. For the comparison with PTCA, the investigators (13) chose the heparin-coated beStent. The primary end point of the trial was the minimal lumen diameter (MLD) at follow-up angiography after six months. On the basis of the sample size calculation the assumption was that the primary end point after stenting will be 0.2 mm greater than after PTCA. Accordingly, the study intended to enroll 200 patients (13). The trial was terminated by the sponsor after inclusion of 145 patients. Abciximab was administered in 5% of the procedures; 14% of the PTCA patients and 4% of the stent patients crossed over to the opposite treatment approach. By six months, only one patient had died and two patients had incurred myocardial infarction (13). At follow-up, the primary end point of the trial, MLD, was slightly better in the stent group but without achieving statistical significance (1.69 mm in the stent arm vs. 1.57 mm in the PTCA arm, p = 0.1).

A trend in favor of stenting was also seen regarding the incidence of angiographic restenosis at six months: 9.7% versus 18.8% in the PTCA group (p = 0.15). Target lesion revascularization due to restenosis was required in 8.1% of the patients of the stent group and 16.9% of those in the PTCA group between the first and sixth month (p = 0.13). Target vessel revascularization, a less sensitive index of target lesion restenosis—considering the high proportion of multileesion interventions in the study—was needed in 7.0% of the PTCA patients and in none of the patients in the stent arm. The only significant difference between the two

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groups was observed in the net lumen gain at six months, with 0.72 mm for stent patients and 0.55 mm for PTCA patients (p = 0.02) (13). Summarizing these results, the SISCA trial failed to achieve the target difference of 0.2 mm in MLD in favor of stenting defined during study planning, but showed a trend to less angiographic and clinical restenosis for stenting as compared to PTCA (13).

The SISCA trial has a number of strengths that deserve comment. Although the stent type selected is the same as that used in three other randomized trials dedicated to small vessel intervention, the use of heparin coating is a distinct characteristic of the SISCA trial. However, the extremely low restenosis rate found after stenting despite the small vessel size cannot be explained with the heparin coating of the stents used in this trial. In a porcine model, heparin coating indeed reduced stent thrombogenicity but was not able to decrease neointimal hyperplasia (14). These experimental results have recently been corroborated by a randomized clinical trial showing no influence on restenosis with heparin coating (15).

Another advantage of the SISCA trial is the very high reangiography rate at six months, with 141 of the 145 study patients having undergone the angiographic follow-up. This enables a highly reliable analysis of the primary end point. Angiographic indexes are sensitive markers of restenosis and carry a low risk of bias particularly when reangiography is routinely done and quantitative assessment is performed in an independent core laboratory. The alternative strategy of clinically driven reangiography may not be appropriate especially for patients who undergo interventions in small vessels because restenosis-induced symptoms may be less severe for small vessels as compared to larger vessels. In addition, stent versus PTCA trials are by nature open-label trials, and the inability to blind the operator as to the approach utilized can influence the decision to reintervene independently of the severity of angiographic restenosis and lead to a potential bias when target vessel revascularization serves as an isolated end point. Finally, Moer et al. (13) are to be commended for the overall low restenosis rate, both in the stent and in the PTCA group. These results are enviable even for interventions in larger vessels. The procedural data presented in their report (13) do not, however, provide insights into the potential mechanisms responsible for this excellent outcome.

Parallel to the strengths of the study of Moer et al. (13), there are also relevant limitations that should be accounted for before trying to draw conclusions. The only advantage with the use of MLD as the primary end point is that it allows for a smaller sample size in the trial. However, even if the investigators had found a significant difference in MLD between stent and PTCA alternatives, they would not have been able to convince interventional cardiologists about the superiority of stenting unless there was a significant difference in conventional indexes of restenosis such as the restenosis rate. Furthermore, both the protocol-mandated number of patients and the number of patients actually included are low. The premature termination of the trial by the manufacturer of the study device had a particularly negative impact in this regard. Did the company regret this act later, after the trend in favor of its product was found? We do not know, but this fact underscores the need for binding contracts between the investigators and manufacturers of study drug/device prior to initiation of patient enrollment.

Therefore, the SISCA trial alone is not able to solve the conundrum, which concerns what is the best interventional option for lesions in small coronary vessels due to the limited size of the population included and to the less than expected difference in the primary end point between the two treatment arms. However, six other randomized trials using four different stent types may help further in finding an answer. Common findings of all these trials are that stenting is associated with a significantly greater MLD at the end of the procedure and that provisional stenting is needed in about 20% of the patients initially assigned to PTCA.

**Other stents versus PTCA for small vessels.** In the study by Park et al. (16), 120 patients were randomly assigned to either placement of NIR stents or balloon angioplasty. At follow-up angiography, restenosis rates were 35.7% in the stent group and 30.9% in the PTCA group (p = NS) (16). In the ISAR-SMART (Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries) trial (17), 404 patients were randomly assigned to placement of a Multi-Link stent or PTCA. All patients received abciximab periprocedurally, which differs from other trials that did not give it systematically. At follow-up angiography, the restenosis rate was 35.7% among stent patients and 34.8% among PTCA patients (p = NS) (17). In the BESMART (BeStent in Small Arteries) trial, a total of 381 patients were randomized to either placement of a beStent or PTCA (18). After six months, the restenosis rate was 21% after stenting and 47% after PTCA (p < 0.001) (18). The SIS study (Stenting In Small Arteries) included 352 patients (19). The stent used for this trial was also the beStent. After six months, the restenosis rate was 28% after stenting and 32.4% after PTCA (p = NS) (19).

In the RAP study (Restenosis en Arterias Pequeñas), 426 patients were randomized to receive either a beStent or PTCA (20). At follow-up angiography, the restenosis rate was 27% among stent and 37% among PTCA patients (p < 0.05) (20). The CORDIS-MICA (MiniCrown stent In small Coronary Arteries) trial was performed with the MiniCrown stent (21). With 600 patients initially mandated by the protocol, the trial was stopped by the sponsor after randomization of 128 patients. The trial had a very high crossover rate of 37% in the PTCA arm. Based on a very low number of repeat angiographies, mainly driven by recurrent symptoms, restenosis rates were high but not significantly different, with 61% after stenting and 63% after PTCA (p = NS) (21).
certainly better to stent than to be satisfied with a suboptimal post-PTCA result.

In addition, as illustrated in Figure 2, the results of the trials clearly show that the maximum that can be expected after PTCA, even after achievement of an optimal result, is a long-term outcome equivalent to that achieved with a systematic stenting strategy. Thus, taken together, the results of the randomized trials including the present study of Moer et al. (13) do not discourage the routine use of stenting for lesions in small coronary arteries; they only show that a strategy based on optimal PTCA with provisional stenting is probably as effective over the long term as the alternative strategy of systematic stenting. Unless future studies show a benefit for brachytherapy in small vessels, the improvement potential of PTCA seems to be exhausted with the achievement of an optimal acute result. In contrast, coated and drug-eluting stents (25) represent promising new technologies that could turn stents into highly attractive devices for treating lesions in small coronary arteries.

Which option should be used in small coronary arteries?

Figure 1 summarizes the restenosis findings of the randomized trials stent versus PTCA for lesions in small coronary vessels. It is clearly evident that stenting of small vessels leads to results equivalent to or better than those achieved with PTCA. For the moment, it is difficult to explain the differences among the various trials regarding the extent of benefit with stenting. However, two factors deserve special attention as a potential explanation for the different results. First, the results suggest a role for the stent type used in small coronary arteries as it has already been demonstrated for larger vessels (22–24). The trials in which the beStent was used (13,18–20) showed better results for the stent arm than did the trials with stent types other than beStent (16,17,21). Second, the benefit with stenting in terms of restenosis reduction seems to be dependent on the final result achieved with PTCA. As shown in Figure 2, a good correlation existed between the residual stenosis after PTCA and the difference in restenosis rate in favor of stenting in the small vessel trials. This means that it is

REFERENCES


