Influence of Residual Stenosis After Coronary Stent Implantation on Development of Restenosis and Stent Thrombosis

Sick et al,[1] report in a retrospective study on a selected population (only patients who underwent angiographic follow-up) the lack of any statistical significant association between stent overdilatatation, expressed as negative postprocedural stenosis, and the occurrence of thrombosis or stent restenosis. The authors conclude that ticlopidine treatment is the only condition to lower the risk of stent thrombosis and that stent overdilatation may actually be harmful by inducing more late loss, and hence, angiographic restenosis. Although I do not dispute the enormous importance of ticlopidine, demonstrated in observational and randomized trials,[2,3] to lower the risk of stent thrombosis, I do not think that the data reported support the conclusions of the authors in any way.

The 4 groups that were created in the study had a significant and rather large difference in reference vessel diameter (2.7 mm for the group with overdilatation and 3.0 mm for the group with moderate residual stenosis, $p = 0.012$). The value of reference vessel diameter to predict the risk of restenosis is one of the most solid findings throughout interventional cardiology.[4] Even the very powerful results obtained with drug-eluting stents seem to respect this association. It is impossible to draw any conclusions from the findings reported by Sick et al[1] due to the presence of a major bias in the constitution of the 4 groups. An immediate and striking observation is the very high restenosis (29.6%) reported in the group left with moderate poststenting residual stenosis. The relation the authors report between increase in percent follow-up stenosis and degree of residual postprocedural stenosis only confirms another major pillar in interventional cardiology, "the higher the gain, the higher the loss."[5,6] What the authors fail to point out is the value of the follow-up lumen diameter, which is functionally more important than the late loss. Incidentally, there is no difference in follow-up minimal lumen diameters in the 4 groups (1.7 mm for all of them, $p = 0.491$).

Regarding the issue of stent thrombosis, the reported data are even stronger to support an opposite conclusion. Small vessel size is another factor known to increase the risk of stent thrombosis.[7] Finding a trend toward a lower stent thrombosis in vessels with a lower residual stenosis, despite a significant smaller reference vessel sizes, may support the additional value of optimal stent dilatation. I think readers should consider these alternate interpretations.

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20 March 2003

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Reply: Dr. Colombo doubts the conclusions drawn from the results of our study with 2,523 quantitative angiographically analyzed lesions of 2,157 patients. The main conclusions were that optimal results with regard to stent thrombosis and restenosis were achieved with mild residual stenoses between 0% and 15% after single stent implantation. The study was a registry; its limitations are well known for such trials. In contrast, the large number of patients included in this study compensates, at least partly, for this. The first critical point mentioned in the commentary is the difference of reference diameter between the group with overdilatation and the moderate residual stenosis. It is well known that reference vessel diameter has great influence on the development of restenosis,[1–4] which was the reason we performed a multivariate analysis that could clearly demonstrate the independence of these 2 factors in predicting the development of restenosis, namely reference vessel diameter and residual stenosis or overdilatation. The statement of "the higher the gain, the higher the loss" is in total agreement with our statement except for the finding that the loss is much greater than the gain, leading to a significantly higher diameter stenosis at follow-up and the trend toward a higher restenosis rate. There is indeed no difference in minimal lumen diameter at follow-up, but there is a clearly higher standard deviation. This is due to an abnormal distribution of diameter stenosis at follow-up, which is presented as median and quartiles in Table 2 of our original article; it shows a highly significant difference with higher values for the more overdilated vessels. The criticized, relatively high restenosis rate of 29.6% is attributed to the study being performed in the late 1990s, and it

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also included hand-crimped stents. Restenosis rates during that time were comparably high with other trials.[5,6] Over the past few years, there was a restenosis rate decrease of around 20%, although there are still some famous current trials that show restenosis rates of 26% in control arms, like in the Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization (RAVEL) study[7]; this may be due to the specific patient cohort included in the different trials.

With regard to stent thrombosis, there is agreement in principle between the authors and the commentator. There was also a trend to a higher rate of stent thrombosis in our data with a higher degree of residual stenosis. However, most of the cases with stent thrombosis appeared with a lack of adequate ticlopidine and/or aspirin therapy. The total incidence of stent thrombosis with adequate dosage of both drugs in our study was extremely low, which supports our conclusion that adequate dosages of ticlopidine and aspirin are much more relevant for a decrease in stent thrombosis than oversizing of stents. This is comparable with the results of Schömig et al.[8] Their trial compared anticagulation therapy with antiplatelet therapy. These investigators also used routine clinical procedures in their trial, with only 10% to 12% intravascular ultrasound control and an accepted residual stenosis of up to 30% after successful stent implantation. The diameter stenosis after stent implantation in this trial was 2.4 ± 11.5% in the antiplatelet group and 2.9 ± 12.4% in the anticoagulant group. This rules out the notion that diameter stenosis was between 0% and 15% in most cases, which is comparable to our results. The authors agree with the aim to achieve an optimal stent dilatation, which, in our opinion, should be between 0% and 15% residual stenosis. This also helps to avoid dissections outside the stent that lead to multiple stenting, which is a well-known high-risk factor for restenosis.[9]

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