EDITORIAL COMMENT

Restenosis: Do We Need to Understand It to Treat It?*

David Faxon, MD, FACC
Chicago, Illinois

“There is, we believe, both in pathogenesis and in therapeutics: much remedy, little cure; much theory, little truth.”
—Pierre Marie, 1883, Archive de Neurologique

Restenosis has been the major therapeutic challenge of interventional cardiology over the past two decades. Andreas Grüentzig reported that restenosis occurred in 30% of his initial patient population (1). Since then, the number of patients developing restenosis has increased, largely because of the treatment of more complex cases. In the early to mid-1990s, coronary stents were introduced, and they have made a significant impact on the practice of interventional cardiology. Their popularity is due not only to the fact that they reduce restenosis, but also that they are relatively easy to use, they result in a reliable, superior angiographic result, and they have helped level the playing field among operators. Despite improved outcomes, coronary stents also develop restenosis within or adjacent to the stent. Although hyperplasia was dominant (3,4). In fact, numerous studies have demonstrated that stents actually result in more neointimal growth than does balloon angioplasty, but because of the larger final lumen diameter, restenosis at follow-up is significantly less.

Currently, stents are placed in 70% to 80% of patients. The factors that lead to subsequent restenosis after stenting are surprisingly similar to those that contribute to restenosis after balloon angioplasty. In an analysis of 6,180 patients pooled from six recent native artery coronary stent studies, Cutlip et al. (5) in this issue of the Journal have shown that clinical restenosis defined as target lesion revascularization, target vessel revascularization, or target vessel failure was related to the initial lumen diameter, the final lumen diameter, stent length, diabetes, unstable angina, and hypertension and inversely related to myocardial infarction and cigarette smoking. These factors, however, have only a fair discriminatory ability (C statistic of 0.68). In addition, most of these independent predictors are of limited value in selecting patients or altering the procedure, because it is now well accepted that every effort should be made to achieve a minimal residual stenosis. Another major contribution of the study, however, was the observation that clinical restenosis, as opposed to angiographic restenosis, has a more delayed presentation than previously appreciated. In this analysis, the rate of clinical restenosis (TVF) increased from 9.4% at six months to 16% at one year, emphasizing the need for more prolonged follow-up in trials evaluating new devices or drugs.

It is evident that restenosis continues to be a major clinical problem despite the introduction of stents. Even though stents have had a significant impact in reducing stenosis by 10% to 15%, restenosis continues to occur at a disturbingly high rate (6). However, further reduction has only recently been shown to be possible, with the use of intravascular radiation therapy or drug-eluting stents. Intravascular radiation, or brachytherapy, with beta or gamma sources has been shown to be an effective treatment for in-stent restenosis in native or saphenous vein grafts and has reduced the rate of subsequent restenosis by 40% to 60% (7–10). Radiation, however, has not been clearly shown to prevent restenosis in de novo lesions after balloon angioplasty or stent placement (11).

The most important recent development has been the preliminary results of drug-eluting stents (12–15). Stents eluting rapamycin or paclitaxel have been shown to reduce restenosis to <4% at six months in selected patients. Not all drugs appear to be effective; for instance, agents such as actinomycin D or QUA DDS-QP2 have failed to show long-term benefit. Unlike radiation, drug-eluting stents appear to be effective in the initial procedure, and early evidence suggests that they may also be effective in preventing subsequent restenosis after the development of in-stent restenosis (16). Much larger trials are currently ongoing, and the results of these studies will clearly be necessary for

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From the Section of Cardiology, University of Chicago, Chicago, Illinois.
us to fully understand the benefits and risks of these new devices; but there is little question that they appear to offer enormous promise.

The proposed mechanism of benefit of both radiation and drug-eluting stents is the inhibition of proliferation of smooth muscle cells, without the creation of excessive cell death, as it is the common belief that in-stent restenosis is largely due to smooth muscle cell proliferation. Although the proposed mechanism is supported by experimental studies, human pathologic data are lacking. The study by Chung et al. (17) in this issue of the Journal raises questions about the mechanism of in-stent restenosis. In this study, 29 coronary artery in-stent restenotic tissue samples retrieved by directional coronary atherectomy were analyzed. The authors found a low cell-proliferation rate, an increase in myxoid tissue, and cell-depleted areas in 57% of specimens. Although the study did not evaluate specimens obtained early after stenting, these findings suggest that extracellular matrix formation is a much more important component of in-stent restenosis than previously thought. These new findings again emphasize how limited our understanding of restenosis and in-stent restenosis is. It is not uncommon in cardiology to have effective treatments before we completely understand the mechanism of benefit. For instance, the mechanism of angioplasty was not understood for more than 10 years after its introduction, and stents were shown to be effective in reducing restenosis before we understood the role of remodeling in restenosis. Despite our therapeutic advances in dealing with restenosis, the challenge for the future is to obtain better understanding of the mechanisms involved, because this is the only way to optimize effective treatment and to prevent restenosis. In addition, this understanding will help us to understand the vascular response to injury and atherosclerosis. Even though current therapy for restenosis with drug-eluting stents may well be an effective treatment, the Holy Grail should perhaps shift to finding the means of avoiding the need to place stents in the first place.

Reprint requests and correspondence: Dr. David Faxon, University of Chicago, Section of Cardiology, Mail Code 6080, Room B608, 5841 S. Maryland Ave., Chicago, Illinois 60637-1463. E-mail: dfaxon@medicine.bsd.uchicago.edu.

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