No development in interventional cardiology has created a stir like the drug-eluting stent for preventing restenosis. The attention of the medical community, the press, and the public has been intense and rightfully so, because restenosis has been the bane of interventional cardiology for the past 25 years. As we cardiologists celebrate the potential demise of our nemesis restenosis, we should also be honest in assessing how serious a villain he currently is.

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Although preclinical studies showed modest improvements in restenosis, the first human trials of drug-eluting stents promised its complete demise. The first experience in humans and the RAVEL trial (RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent)1 showed no restenosis and pointed mechanistically to almost complete inhibition of neointimal formation. With the broader application of the technique in the SIRIUS trial (multicenter randomized double-blind study of the SIROImUS-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions),2 cardiologists discovered that restenosis was markedly reduced but was not eliminated. Now in the first post-market experiences, we are beginning to learn something of the mechanisms by which restenosis occurs. This is essential if further progress is to be made on establishing the cause of the residual restenosis and potential solutions. Lemos et al3 have provided some valuable early insights into the pattern of restenosis occurring following the use of drug-eluting stents. The article by Lemos et al3 examines the follow-up angiographic and intravascular ultrasound findings in patients who were treated with drug-eluting stents after approval in Europe. An intentional commitment was made at his institution to change completely to drug-eluting stents to understand the relative benefit in a registry-type format. Among >600 patients treated, 121 have undergone repeat angiography to assess the pattern of restenosis. These representations patients with recurrent symptoms and others with “complex” lesion morphology. The restenosis rate of 15.7% is obviously inflated because of the limited number of follow-up studies and is not of primary interest, but the pattern of restenosis may give clues to improving the technique. Lemos et al3 found that the locations of neointimal formation were relatively discrete and were primarily located at points of small gaps between stents or at stent fractures or were at the ostium of bifurcation lesions. They speculate that inadequate stent coverage, rather than systemic resistance to sirolimus, is the likely explanation for the restenosis.

Such observations are, of course, critical as investigators examine methods of improving any technique. My concern is that major changes in the application of stents may occur without waiting for the data to support them. Already, extensive alterations of deployment methods of drug-eluting stents are being proposed. Some of these include extending the stents to very long lengths to cover any potential injury area at edges, applying bifurcation stents with the “crush” technique, which results in extensive metal coverage of the ostium of side branches but also results in a meshwork of stent material lying in the main channel, and other such approaches. Although some of these approaches may prove to be safe, this is still unclear.

In the attempt to reduce restenosis further to near zero, it is most important to consider safety issues first. Restenosis has not been shown to be the major contributor to survival. Patients who developed restenosis were compared with those who did not develop restenosis at Emory University.4 Long-term follow-up showed no difference in survival between these 2 cohorts. The complications of acute vessel closure, however, markedly reduce the long-term survival of patients; therefore, any efforts to control restenosis must be balanced by an avoidance of any increase in complication rates. I have several concerns regarding the enthusiasm for the broadened use of drug-eluting stents. As yet, there is little long-term data regarding the malapposition of the struts and the vessel wall resulting from the inhibition of vascular healing by newly positioned drug-eluting stents. Will the polymer coating remain permanently or will there be any increased risk of erosion and late thrombosis in the years to come? Will the recommendations to seat the stent deeply to avoid malapposition increase risk? High-pressure deployment and generous sizing of stents, as well as using longer stents, may liberate more atheroembolic material, resulting in more microembolization. Adequate comparative enzymatic data following stent deployment is still lacking. Will the use of stenting in conditions such as acute myocardial infarction result in late malapposition due to clot resorption, leaving wires exposed? Acute myocardial infarction often results in arteries appearing angiographically smaller than they actually are, which could lead to undersizing of stents. Will the enthusiasm for the reduction in restenosis lead to a much more extensive application of stenting “full metal jacket” that precludes the possibility of subsequent surgery? What is the long-term effect of stenting eliminating the possibility of positive

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remodeling if atherosclerosis progresses? These kind of questions may not be answerable in the near future, but they should be considered when selecting patients who will receive drug-eluting stents or non–drug-eluting (regular) stents.

During the first 6 months of the routine use of drug-eluting stents, Serruys\textsuperscript{5} reported a subsequent 6-month return reintervention rate of 2.7\%. This is impressive, and this rate was compared with the period before the availability of the drug-eluting stent. The subsequent 6-month reintervention rate for that group was 7.1\%. This means that, on average, 4.4 reinterventions per 100 patients were prevented by the routine use of drug-eluting stents. It is likely that the selective use of drug-eluting stents for lesions that have a higher restenosis risk, such as small vessels and longer lesions, will result in an even narrower gap between the routine use of drug-eluting stents versus the selective use of drug-eluting and regular stents.

What does one give up by selective use of drug-eluting stents? The avoidance of \textless{}5 reinterventions per 100 patients treated. There is no evidence that there will be any improvement in survival, myocardial infarction, or the need for urgent bypass surgery. In fact, the concern might be in the other direction, because long-term safety has not yet been fully confirmed. What will be gained by the selective use of drug-eluting stents? First, a very low reintervention rate can be anticipated if proper selection is performed for patients to receive either a drug-eluting or regular stent. Once healing has occurred, the ample data on regular stents would suggest long-term safety.

Understanding the pattern of restenosis from drug-eluting stents will certainly contribute to the understanding of the causes of the few cases of restenosis and ultimately lead to solutions. In the meantime, selective usage of these stents can further improve the already excellent outcome seen with regular stent technology. Finally, in our excitement about the potential for interventional cardiology, we must remember that atherosclerosis will not be cured by drug-eluting stents. Prevention of progression of this disease requires changing the metabolic milieu of the patient who has it. Interventional procedures are superb for alleviating the current ischemia and related symptoms, but a concerted effort by the healthcare team and the patient are necessary to change the ultimate outcome. Although the restenosis mouse “has roared,” it may not be necessary in all cases to use an elephant gun to eliminate him. Because we can no longer claim a zero restenosis rate, careful selection of drug-eluting or regular stents will help assure our patients of good clinical results. The future for controlling coronary artery disease looks bright. Progress will not stop here.

**References**

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