Drug-Eluting Stent Restenosis
An Uncommon Yet Pervasive Problem

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In 1977, using a wire-tipped balloon, Dr Andreas Gruentzig performed the first percutaneous balloon coronary intervention on a blockage in Mr Adolph Bachmann’s left anterior descending coronary artery. The continued success of this pioneering event has been documented by follow-up angiography at 10 years and again at 23 years postprocedure. Mr Bachmann’s follow-up angiograms may be the most viewed on the planet, because they were obtained during dramatic, live demonstration conferences in front of thousands of physicians and were published in the New England Journal of Medicine.

In fact, Mr Bachmann was recently honored at an event attended by over 10 000 people at a large medical meeting. It is indeed very fortunate for the field of interventional cardiology that Mr Bachmann’s left anterior descending artery blockage did not recur.

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In 2010, despite all the promising technology and all the research, creativity, effort, and dollars poured into the field, the problem of restenosis, although vastly reduced, has not been eliminated. It is not an exaggeration to state that at my institution, Scripps Clinic, nearly every working day we see at least 1 patient with restenosis of a drug-eluting stent (DES). One report estimated 200 000 repeat revascularizations are performed every year in the United States for DES failure. Despite tremendous progress in lowering the incidence of restenosis with DES, given the large number of percutaneous coronary intervention procedures performed worldwide every year, even a low restenosis rate translates into a significant absolute number of patients experiencing this problem. The problem of DES restenosis is pervasive enough that all physicians caring for patients with coronary disease should be well versed in its treatment.

Early data from the bare-metal stent era informed us that if restenosis were to occur, we could expect it within 6 months of stent implantation. DES restenosis has been found to occur over a longer timeline, and restenosis rates are related to the complexity of the lesion and clinical risk factors. In simple lesions, one can expect restenosis rates of less than 5% at 1 year. At 5 years, repeat intervention rates are approximately 10%. However, in more complex lesions, restenosis has been documented at 10% at only 2 years, and repeat revascularization rates climbed to 17.2% by 5 years. In trials treating patients with ultracomplex disease, DES failure rates are even higher. For example, in the recent SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial, the repeat revascularization rate after multivessel or left-main DES implantation was 13.7% at 1 year and 17.4% after just 2 years (unpublished data from European Society of Cardiology conference, Barcelona, Spain, September 2, 2009). As follow-up continues to accrue, it is not unreasonable to expect published repeat procedure rates above 20% 5 years after complex percutaneous coronary intervention procedures.

The number of different technologies we can offer patients with DES restenosis has grown considerably. Although there are many options, unfortunately, there is more technology available than there are high-quality data to guide our decisions. Options within the United States include simple balloon dilation, cutting balloon, scoring balloon, restenting with the same DES, restenting with a new-generation DES, restenting with a DES with a different mechanism of action (ie, crossover from a “limus” [ie, mTOR inhibitor] to a paclitaxel stent or vice versa), redilation plus brachytherapy, redilation plus oral sirolimus, and of course, bypass surgery. Outside the United States, in 2010, one can add redilation with a drug-eluting balloon and implantation of a fully biodegradable stent to this long list. In total, the interventionalist is faced with >10 therapeutic options from which to choose. Despite many published reports, all comparisons between these revascularization strategies are either small, poorly powered, randomized trials or registries wherein the patient groups compared are not really similar.

In this issue of Circulation, Abe et al add another helpful but less than perfect data set to this troubled field. The authors use extended follow-up of the large, multicenter j-Cypher Registry to compare outcomes after treatment of Cypher in-stent restenosis with balloon angioplasty alone versus implantation of another sirolimus-eluting stent. At 2-year follow-up, there were no differences in mortality or stent thrombosis, but target-lesion revascularization rates were significantly lower in the sirolimus-eluting stent group (23.8% versus 37.7%, P<0.001).

This study is strengthened by its large size and multicenter design. Starting with 12 824 patients enrolled in the j-Cypher Registry, 1094 lesions with sirolimus-eluting stent restenosis in 990 patients (537 lesions treated with sirolimus-eluting stents and 557 with balloon angioplasty alone) were compared. Unfortunately, despite its size, owing to its many confounders and other limitations, the results of this large study are only modestly helpful to the physician community. At the time of initial treatment (before the restenosis),
patients in the balloon angioplasty group were more likely to have had a restenotic and a longer lesion and to have been treated without intravascular ultrasound or direct stenting. These factors are all associated with higher future rates of target-lesion revascularization. The investigators attempted to correct for these differences in baseline characteristics by using multivariable analysis; however, this kind of statistical adjustment is imperfect and especially prone to error due to unmeasured confounders. One example of an unmeasured confounder in this study is the physician’s own bias when selecting a treatment strategy. Clearly, each physician chose between balloon angioplasty and repeat sirolimus-eluting stent on the basis of their own experiences and predisposition. In addition to the significant differences in baseline characteristics, this study also suffers from a lack of randomization, a lack of study monitoring, and a lack of independent core laboratory assessment. In light of these weaknesses, the present report must be viewed as yet another imperfect addition to many other flawed studies in this field. It provides additional data but will only have a modest impact on patient care.

After adding this report’s conclusions to the other published data, how should one treat a patient with DES in-stent restenosis? First, I believe it is important to provide a healthy dose of reassurance. Do not underestimate the emotional impact of repeated procedures on patients, particularly the “frequent flyers” who have experienced multiple visits to the catheterization laboratory. These patients often describe significant frustration and fear. They feel a loss of control, mostly due to an inability to plan their lives and predict when a restenosis will occur. It is helpful to reassure these patients by emphasizing they do not have an incurable, lethal disease. This is especially important to many active, younger patients, who are building and maintaining careers. Patients can be told if they stay in close contact with their cardiologist, the risk of death and infarction is low (not withstanding the present study’s quite anomalous 10% 2-year mortality rate in both groups). It may sound obvious to the physician, but most of our patients are seeking this kind of reassurance.

It is also helpful to explain the mechanism of restenosis. I use the “carpet” analogy. I often tell the patient, “After stenting, we want a carpet of cells to line and protect the stent. Unfortunately, we want a Berber carpet, and you have a shag carpet.” I also emphasize that recurrences are unlikely to go on forever. Finally, it is worth communicating that they are not the only patient to encounter this problem, and ultimately, patients with restenosis who seek treatment usually have good outcomes.

It is also wise to make the repeat percutaneous coronary intervention experience as “patient centered” as possible. Although this is recommended for every procedure, patients with restenosis are particularly sensitive. Frequent flyers often dread the little things about being hospitalized, such as interminable waiting, painful intravenous insertions, placement of a Foley catheter, or being awakened multiple times at night for blood pressures and blood draws. Patients with restenosis are often great candidates for outpatient procedures. If feasible, the radial access approach is often favored by the patient.

Despite the available literature, including the present study by Abe et al,7 the most appropriate technology to treat DES restenosis is poorly defined. Before a treatment strategy is selected, it is important to clearly document the patient’s “stentology”; in other words, exactly what kind of stents were placed in which vessel segment, at what time? This information is key to devising a treatment plan. Additionally, a pretreatment intravascular ultrasound examination can uncover surprises, such as poorly expanded stents that might indicate the need for simple redilation with a larger balloon, or higher balloon pressures. The time interval between restenoses is also helpful in choosing a therapy. In the present era, we found if the intraprocedural interval was >3 months, the risk of a further recurrence after another simple balloon angioplasty was low.8 It would have been very helpful if the authors of the present study had analyzed the time to first restenosis as a predictor of future restenosis with respect to the 2 treatment strategies. Without firm data, most interventionalists believe it is reasonable to apply a balloon-alone strategy if the interval between the previous DES procedure and the current restenosis is greater than about 6 to 9 months. Most will use another stent if this time interval is shorter, particularly if the vessel segment that contains in-stent restenosis is longer (ie, >10 mm) or involves the stent edge. For example, in 1 study of DES restenosis, subsequent revascularization was required in 51.1% of patients with diffuse restenosis (>10 mm in length) compared with only 17.8% of patients with focal (<10 mm) restenotic lesions.5

If repeat stenting is used, a DES is favored. The choice of DES has not been well studied. Several small and medium-sized randomized trials2-5,10-14 found no difference between sirolimus- and paclitaxel-eluting stents for the prevention of a subsequent DES restenosis. The Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis 2 (ISAR-DESIRE-2) study randomized 450 patients with restenosis after sirolimus-eluting stenting to repeat stenting with sirolimus- versus paclitaxel-eluting stents. Subsequent revascularization rates were similar at 16.1% versus 14.6%, respectively (P=0.52).2 Some prefer to “crossover” to a stent with a different mechanism of action compared with the DES that failed.15 Although not based on evidence, resistance to sirolimus has been reported in the cancer literature.16 It also makes common sense, and opting for a different kind of stent is easy for patients to understand. Other interventionalists prefer to use one of the newer, second-generation stents that have thinner stent struts and contain less polymer coating. Whatever stent is chosen, it is advisable to use intravascular ultrasound guidance to ensure optimal stent delivery, lesion coverage, and expansion.

Patients who sustain restenosis after 2 different DES implantations are considered multidrug failures. They require a lengthy discussion outlining the pros and cons of both bypass surgery and vascular brachytherapy. Often this includes a visit with a cardiac surgeon. The presence of diabetes mellitus often favors encouraging bypass surgery. Patients opting for further catheter-based therapy should consider brachytherapy.17 In my practice, patients who fail brachytherapy and are not candidates for bypass surgery (most patients
who get this far in the process have already had at least 1 bypass procedure) are treated with balloon angioplasty along with a 30-day course of sirolimus.18 The data supporting these choices are sparse. Fortunately, only a small number of patients sustain multiple recurrences.

Restenosis is frustrating for physicians as well as patients. It teaches humility and reminds us that although our current technology is elegant, there is much work to be done. Many promising solutions are on the horizon, such as polymer-free DESs, fully degradable DESs, and drug-eluting balloons. The persistence of restenosis in a small percentage but a large absolute number of patients underscores the critical need for continued research and development in our evolving healthcare system.

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