Drug-Eluting Stents Are Safe and Effective

Right or Wrong?

Ulrich Sigwart, MD, FACC, FESC, FRCP
Geneva, Switzerland

Coronary stents were conceived to make transluminal angioplasty safer and more effective (1). When abrupt closure after balloon angioplasty of a proximal left anterior descending coronary artery stenosis in a patient with double vessel coronary artery disease was reversed for the first time by the implantation of a self-expanding mesh stent during a live demonstration in Lausanne in 1986, it became clear that arterial scaffolding might present a significant step forward on the road to predictable endoluminal therapy.

During the years to come, some sobering facts emerged. Even if most clinicians accepted the general concept of stenting, two problems relating to safety and efficiency were impeding the universal acceptance of this new revascularization modality: 1) a relatively high thrombotic occlusion rate (safety), and 2) a one-in-three recurrence rate (restenosis), reducing efficiency.

The purely mechanical solution to an important biological problem received mixed reports. As late as 1991, stenting was considered “futile” by some experts in the field (2). Stent thrombosis remained a major preoccupation until, after a long and frustrating battle with different anticoagulation regimens, platelet inhibition (3) presented as the solution to the safety problem; problem number two (efficiency) defied all attempts using systemic therapy. Local treatment appeared as a possible way out. Brachytherapy was hailed in the mid-1990s as an effective means of suppressing the exuberant healing response initiated by trauma and the implantation of a foreign body (4).

The border zone of the irradiated segment, however, remained worrisome, because it seemed to stimulate proliferation rather than stop it (5). The regulatory strings attached to this treatment option also prevented its wide adoption. Apart from the difficult task of choosing the right compound, drug-eluting stents (DES) imposed a number of technological challenges, including 1) how to fix a sufficient amount of medication onto the stent surface; 2) how to guarantee even distribution of drugs into the adjacent tissue; 3) how to retain the drug for the required period of time; and 4) how to make sure the carrier matrix would do no harm. These issues presented a formidable task to industry and researchers alike.

At the present time, two drugs—rapamycin (also called sirolimus) and its derivatives, and paclitaxel—have made it into large clinical trials and seem to have fundamentally changed the way coronary artery disease is being treated. Other potentially promising compounds have quickly fallen by the wayside, mainly because of a too-narrow therapeutic margin. Both of the successful candidates have been used previously to treat neoplastic disease or modulate the immune response in autoimmune disease and after transplantation. Although trials using stents coated with drugs locked into biodegradable polymers are under way, both currently used stents use drugs embedded in a nonresorbable polymer matrix, completely covering the stent struts.

The positive clinical results using this approach are undeniable. Even if the very first euphoria that followed the presentation of the Randomized Study with the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) (6) data—a proof of concept and safety trial with sirolimus-eluting stents—was little by little corrected by a somewhat-more realistic appreciation in larger trials with longer follow-up (7). The two-year follow-up after implantation of sirolimus-eluting stents presented by Ong et al. (8) and Weisz et al. (9) in this issue of the Journal fails to show any undue side effects of the DES during years one and two after the index revascularization. The initial reduction in the rate of restenosis in the 508 patients of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry (8), compared with similar patients treated during the pre-DES era and observed over the first six to nine months, was maintained up to two years. The recipients of these stents were unselected, consecutive “real-world” patients with a rather large variety of coronary artery disease.

The two-year follow-up of the SIRIUS trial seems to confirm this impression (9). The follow-up of the initial 1,058 patients assigned randomly to bare metal or sirolimus-eluting stents showed equal distribution of clinical events between year 1 and 2 in either group. When one examines the entire two-year follow-up, the difference in recurrence between active stents and bare metal stents is striking: target lesion revascularization rate was 21.3% in the bare metal stent group as compared with only 5.8% in the sirolimus-eluting stent group. Also, there was no difference in purely clinical hard end points such as death, stent thrombosis, and myocardial infarction. Unfortunately, possibly because the original trial was conceived for eight-month angiographic follow-up, clinical follow-up was only 92%.

Are DES safe and effective, then? The answer seems yes, but, in medicine and biology nothing is just black or white. Although the patients in the SIRIUS trial received clopidogrel only for three months, longer treatment is now recommended.
For practical purposes, DES may be considered safe if the patient can continue taking his or her double antiplatelet medication without interruption for at least six months, probably longer. Any planned or unplanned surgery presents a real threat to this strategy (personally, I have made it a habit to always ask patients before implantation of a DES if any type of surgery is planned or pending). As to the effectiveness, a clear reduction in clinical events, primarily target lesion revascularization—without the dreaded increase in sub-acute and late thrombosis rate—has been demonstrated.

Although not yet tested in a randomized controlled trial, percutaneous interventions with much lower morbidity are now playing in the same league as bypass-surgery. But will they remain there? Will bypass-surgery become history?

All will depend on the long-term performance of DES. Admittedly, the four-year follow-up data of the first 30 patients who received a sirolimus-eluting stent looked reassuring (10). And, the first substantial two-year data from two independent centers showing no excess in late thrombosis have been published in this issue of the Journal (8,9). So far so good; no reason for panic.

However, there is little doubt that the metal skeleton carrying the drug is not always state of the art and that the polymer matrix (which clearly induces inflammatory responses) may still be good for unpleasant surprises. The event rate in patients outside the large trials (11) seems higher than expected, and some patients, potentially important ones, have been lost to follow. A meta-analysis of the randomized Taxus trials also suggests a small but significant increase in rate of late stent thromboses (G. W. Stone, personal communication, 2005).

Despite all reassurances the race for the optimal antiproliferative drug and the best way to put this drug to work is not over yet. The two-year clinical follow-up presented in this issue of the Journal is the second act of the DES story. The play will go on, and we have to remain as vigilant as ever. Present-generation DES create a unique medium for thrombosis after the first few weeks after implantation (12). Delayed healing, inflammation and hypersensitivity, lack of endothelialization, and malapposition are some of the potential trouble spots involved. Four years of follow-up should be the minimum before any close-to-definite conclusion can be drawn. Interventional cardiology does not need Vioxx-type publicity!

There is still mileage in optimizing stent design and reducing the significant risk of late thrombotic complication by new ways of delivering appropriate softer drugs without the use of inert polymers. We ought to be reminded that some of the first bare metal stents implanted 20 years ago are still doing fine. It seems unlikely that currently used nonerodable polymers as drug delivery matrix will survive for the coming 20 years.

Reprint requests and correspondence: Ulrich Sigwart, Professor and Chairman, Centre and Division of Cardiology, University Hospital, CH-1211 Geneva, Switzerland. E-mail: Ulrich.Sigwart@hcuge.ch.

REFERENCES