Editorial

Living the Dream of No Restenosis
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"I f I am in a dream, please don’t wake me" are the now-fabled words spoken by Patrick Serruys while viewing follow-up intravascular ultrasound images of sirolimus-eluting stents. The dream of an effective treatment for restenosis has eluded decades of effort by an army of investigators. Scores of devices, hundreds of drugs, and innumerable revascularization “strategies” have failed to eliminate the 10% to 50% risk of recurrence after angioplasty. The wasteland of failed anti-restenosis trials was expanded this summer by the 11 500-patient, hundred million dollar, mega-trial Prevention of Restenosis with Trial and its Outcomes (PRESTO), which demonstrated that tranilast (a cytokine inhibitor showing superb results in smaller pilot studies) was no better than placebo. When you take out a gallbladder, it doesn’t grow back. Yet, no matter how much skill, experience, time, and effort the interventionist brings to the table, restenosis can entirely reverse a perfect procedural result within months. Until now, only the efficacy provided by vascular brachytherapy has offered hope to patients with in-stent restenosis.

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In the present issue of Circulation, Sousa et al1 provide a first glimpse at the 1-year data after the implantation of sirolimus-eluting stents. The report describes a very small, noncontrolled registry, yet the results are striking. After 12 months of follow-up in 30 patients and 6 months of follow-up in an additional 15 patients, the authors demonstrate a uniquely stable result. Using the highly sensitive technique of intravascular ultrasound, only a very minor proliferative response to injury was observed (<3% luminal volume obstruction). By angiography, the percent diameter stenosis increased only slightly from a mean of near 10% at the procedure’s conclusion to ~20% at 1 year. By the 12-month follow-up time point, not a single patient had sustained clinical or angiographic restenosis. These results are amplified by the recently reported, 238-patient, double-blind, randomized trial in Europe and Latin America, Randomized Double-Blind Study with the Sirolimus-Eluding BX Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Lesions (RAVEL), which found restenosis at 6 months was reduced from 26% in patients receiving placebo to 0 in those receiving sirolimus-eluting stents (P = <0.001). These dramatic results have created a stir in cardiology. Ever since angioplasty’s invention, almost 25 years ago, restenosis has pulled on its reins, holding it back by denying patients a predictably long-lasting result. If the present data continue to be supported by ongoing, placebo-controlled, randomized trials (ie, Sirolimus-Coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions [SIRIUS] in the United States), our patients may finally receive the benefit of a minimally invasive revascularization technique that is also durable.

Of course, amid the fireworks, we should maintain our skepticism. The results are very preliminary, the number of patients studied small, the lesions enrolled simple, and the follow-up period still short. Indeed, one patient experienced a myocardial infarction at 14 months. The authors ascribe this to an “unstable plaque” proximal to the stent, but a pessimist might argue that sirolimus eluting from the adjacent stent may have weakened the fibrous cap that protects the underlying lipid pool. There is also a possibility that stent thrombosis, so crippling to early stenting and brachytherapy, could stymie the medicated stent model. Other toxicities may emerge, either from the medication itself or the polymer delivery vehicle. Preclinical trials of stents using different coatings and drugs have reported adverse reactions such as intimal hemorrhage, incomplete healing, intimal fibrin deposition, adventitial inflammation, and medial necrosis. These toxic effects could translate into clinical complications. Aneurysm, pseudoaneurysm, perforation, thrombosis, accelerated atherosclerosis, fibrosis, and systemic disorders are all potential adverse effects of drug-coated stent implants. The consequences for angioplasty patients are compelling because so many lives are involved. Worldwide, >1.5 million percutaneous coronary and peripheral angioplasty procedures are performed annually. Add our aging population and the kind of technological leap this study represents and that number could easily grow to >2 million. It is a bit intimidating to imagine that a serious late complication with an incidence of only 0.5% could affect >10 000 lives each year.

Drug-eluting stents may face other challenges. For example, longer-term follow-up may reveal results that are less permanent than anticipated. In fact, in the present study, if one looks critically at the minimal luminal diameter (MLD) changes over the 12-month follow-up period, subtle but noteworthy trends emerge. Two devices were evaluated, the “fast release” coated stents, wherein almost all drug was completely eluted by 15 days, and the “slow release” stent, which uses a polymer topcoat to slow drug release to 4 to 6 weeks. In fast release patients, the mean MLD was 2.67 mm

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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immediately after implantation, virtually unchanged (2.69 mm) at 4 months, and then dropped to 2.32 mm (a 13.8% reduction) between 4 and 12 months. Interestingly, in the slow release group (the same formulation that is being tested in the randomized RAVEL and SIRUS trials), MLD changes occurred over a very different time course. The mean MLD was 2.74 mm immediately after implantation, dropped to 2.55 mm (a 7% reduction) 4 months later, and then dropped only slightly more (2.48 mm; another 2.8% decrease) between 4 and 12 months. Thus, the fast release group demonstrated better efficacy at 4 months, but by 12 months, MLD loss in the fast group had “caught up” to and surpassed that of the slow release group. One wonders if, over a longer follow-up period, an even slower releasing stent would maintain a larger lumen. These data, although subtle and involving small numbers of observations, underscore the need for further follow-up and further development before we fully understand the pharmacokinetics of stent-based drug delivery. One should remember that it was only after we obtained angiograms 3 years after catheter-based brachytherapy that small trends toward late “catch-up” were observed. Current plans for 18- and 24-month angiographic follow-up in this first group of sirolimus-stented patients will provide important long-term surveillance data.

As we stand on the verge of a “cure” for restenosis, it is interesting to ask, “Why has it taken so long?” Since the late 1970s, mammoth efforts and resources have been directed at restenosis. Today, optimism for drug-coated stents can be credited to the efforts of a very large number of researchers. Our understanding of restenosis evolved slowly. It was not until the early 1990s that several pivotal studies distinguished basic restenosis mechanisms such as early recoil, unfavorable remodeling, and the proliferative response to injury. Other landmark studies established the concept that the extent of luminal “late loss” at follow-up is proportional to the amount of “acute gain” achieved during the initial procedure, which could be roughly described by the “late loss index.” These breakthroughs inspired an intense struggle to provide the largest possible initial lumen diameter under the banner “bigger is better.” Although this approach provided incremental reductions in restenosis, today it is hard to imagine our naiveté in thinking we might eliminate restenosis using only mechanical devices like bare stents and atherectomy catheters.

Developing the stent as a drug delivery vehicle posed substantial challenges. The stent’s stainless steel struts are poorly designed for drug delivery. Drugs do not bind readily to stent struts and, if bound, the surface area is not very large, providing only a limited drug reservoir. Thus, many researchers turned to stent coatings to facilitate the binding of drugs and to increase the available surface area. The initial stent coatings, however, were dismal failures. In early animal implant studies. This required the development of predictable animal models of restenosis that allow detailed, quantitative documentation of the in vivo response to injury. Another challenge was the difficult task of uniformly applying coatings to stent struts (typically accomplished by dipping) and then sterilizing the combination (usually with heat) without altering the properties of the coating or drug. Of course, a safe, biocompatible stent coating must be coupled with an efficacious drug. Manufacturers sprouted new divisions focused entirely on drug delivery to test scores of medications.

The story of sirolimus is illustrative. Rapamycin (the original name for sirolimus) was discovered in the mid 1970s by the microbiology program at Wyeth-Ayerst. Its antimicrobial activity, which was produced by Streptomyces hygroscopicus, was discovered in soil samples brought home by researchers from Easter Island (named on Easter Day, 1722, by Dutch explorers but better known as the Island of Rapa Nui by its Polynesian natives). Sirolimus development was soon abandoned, however, because its antifungal benefits were outweighed by its immunosuppressive toxicity. It was resuscitated years later in the late 1980s as a result of advances in transplant medicine. Suren Sehgal, at Wyeth-Ayerst, noted its structure and impact on T cells were similar to tacrolimus, a new T-cell inhibitor with 10 to 100 times more potency than cyclosporin. Investigation at Wyeth-Ayerst and several transplant centers eventually led to its Food and Drug Administration approval as a treatment for kidney transplant rejection. During these studies, transplant immunologists Randall Morris and Clare Gregory, at Stanford University, made the seminal observation that transplanted rat hearts treated with sirolimus had clean coronary arteries instead of the usual intimal thickening observed in allografts. Making a leap from transplant immunology to restenosis, they performed a series of experiments demonstrating reduced intimal proliferation in sirolimus-treated rats after carotid artery balloon injury. Although allograft rejection and balloon angioplasty injured arteries by different mechanisms, both resulted in intimal proliferation that could be inhibited by sirolimus. Soon thereafter, Gallo et al., at The Mount Sinai School of Medicine (who had described many of its molecular mechanisms), extended this observation, reporting a 52% reduction in intimal hyperplasia when sirolimus was delivered systemically in a porcine stent coronary restenosis model.

In 1996, as these early results emerged in the literature, a newly formed drug-device team at Johnson and Johnson’s Cordis division, led by Robert Falotico and Gerard Llanos, was evaluating numerous drugs and coatings in parallel development programs. Of the many drugs tested, attention focused on sirolimus because the initial systemic trials demonstrated efficacy, the hurdles of incorporating the desired dose into a biocompatible polymer were overcome, and a collaboration with its owner, Wyeth-Ayerst, was successfully forged. This led to a series of implants by Suzuki et al. in the porcine model documenting a 51% reduction in intimal proliferation within sirolimus-coated compared with control stents. These results were replicated in rabbit and canine models and ultimately inspired the small, safety registry described in the present article. Surprisingly, the animal
experiments with sirolimus, while encouraging, did not fore-
shadow the near absence of intimal proliferation seen in the 
human trial reported by Sousa et al. This observation 
highlights the differences between animal and human reste-
nosis models. Today, we still do not have an animal model 
that accurately mimics the human condition, and the best 
model to test coated stents remains controversial.

In summary, the success of sirolimus required a collabo-
rati on between experts in both drug and device development, 
a great deal of empiric, trial-and-error experimentation with 
multiple drugs and polymers, good timing, and a little bit of 
luck sprinkled in.

The sirolimus story implies we have not seen the end of 
drug-coated stent development. Indeed, different medicated 
stents are currently in clinical trials, including paclitaxel, 
actinomycin-D, c-myc antisense, estradiol, and many others. 
Stent coatings have also grown more sophisticated. For 
example, one novel device uses drugs that are covalently 
bound to biodegradable "smart" polymers. As the polymer 
degrades, the drug is programmed to release over months to 
years. These "designer" coatings can release multiple drugs at 
different rates on different timelines. Other approaches in-
clude absorbent hydrogels applied to the stent surface that can 
"soak up" and then slowly release antiproliferative medica-
tions. Some plans even call on the physician to provide final 
assembly by dipping the hydrogel-coated stent (like fondue or 
sushi) into a drug-containing liquid just before deployment.

The massive quantity of creative energy being applied to 
atherectomy. The excitement is well deserved, and our patients will 
likely be candidates for a percutaneous approach. With a stent that doesn’t renarrow, the threshold for intervention may 
be lowered. For example, as markers for vulnerable plaque 
are developed, one can envision non-renarrowing stents being 
used to launch a preemptive strike against minimally stenotic, 
yet "at-risk" lesions. With their newly acquired ability to 
suppress intimal proliferation, stents themselves will 
proliferate.

Physicians and patients can be grateful for the important 
technological leaps in medicine represented by drug-coated 
stents. The excitement is well deserved, and our patients will 
be the beneficiaries. To some it may seem like a dream, but 
in reality, it just may be sweet dreams for restenosis.

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