Focused Perspective

A Chicken in Every Pot and a Drug-Eluting Stent in Every Lesion

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A 78-year-old man is admitted with episodes of severe angina associated with hypotension. Urgent angiography finds critical left main stenosis with well-preserved left ventricular function (Figure 1). While discussing the treatment plan with the physician, the patient suddenly manifests sustained ventricular fibrillation. Prompt electrocardioversion restores sinus rhythm, but there is electromechanical dissociation and no blood pressure. Chest compressions are initiated. A guiding catheter quickly inserted into the left coronary finds total occlusion of the left main (Figure 2). Between chest compressions, the left main is opened with balloon angioplasty (Figure 3), and a stent is implanted, restoring flow, contractility, and blood pressure. The patient is discharged 3 days later, sustaining only a small rise in cardiac enzymes.

See p 1942 and p 1948

Is this case unusual? Some might argue “no.” Stents and balloon angioplasty have been used for decades to rescue patients from disaster. However, in one way, this 78-year-old man underwent a revolutionary procedure. This patient’s left main coronary artery was treated with a drug-eluting stent (DES). Three months later, a follow-up angiogram found no evidence of restenosis (Figure 4). If further follow-up of this and other patients enrolled in left main DES trials prove favorable, the paradigm could shift, making DES the treatment of choice for obstructive left main coronary disease.

In the present issue of Circulation, the results of 2 pivotal trials testing paclitaxel-eluting stents are presented. One underscores the important clinical benefits of DES, whereas the other provides insights into how this exceptional new technology can be improved. Stone et al1 present the 1-year results of the TAXUS IV randomized trial, which conclusively demonstrates the superiority of a polymer-based paclitaxel-eluting stent over a bare-metal stent. In this large, double-blind, randomized trial, the TAXUS stent (Boston Scientific) reduced ischemia-driven target-lesion revascularization at 1-year follow-up by 73% (from 15.1% to 4.4%; P<0.0001). TAXUS IV stands alongside the SIRIUS trial2 (which tested a polymer-based sirolimus-eluting stent) to provide a solid foundation of evidence supporting the near-exclusive use of DES. With 2 conclusive trials, the arguments against DES become increasingly awkward to justify. These arguments are almost always motivated by economic rather than clinical concerns. Indeed, DES is an extraordinarily expensive therapy. However, our patients’ needs must come first. In my opinion, unless it is unavailable or undeliverable or the patient has a clinical contraindication (usually to prolonged antiplatelet therapy), a DES should be implanted.

Implications for Your Clinical Practice

In light of the dramatically improved outcomes demonstrated in recent DES trials, physicians will need to rethink how they manage patients with obstructive coronary artery disease. At 1 year in TAXUS IV and SIRIUS, the need for revascularization of the target lesion in the DES arm was 4.4% and 4.9%, respectively.1,3,4 These numbers are even lower if one excludes patients with mandated angiographic follow-up. In fact, patients in SIRIUS who underwent DES of the left anterior descending artery had an angiographic restenosis rate (>50% diameter stenosis at follow-up) of only 2%.5 Thus, for many patients, DES now makes stenting competitive with the long-term outcome after internal mammary artery implantation. Indeed, at Scripps Clinic, since Food and Drug Administration (FDA) approval of the first DES in April 2003, referrals for stenting have increased by >40%, and correspondingly, bypass surgery rates have begun to decline. The benefits of a less invasive procedure to patients are obvious. Not so obvious is the profound programmatic impact such changes can have on the divisions of cardiology and cardiac surgery. The requirement for skilled physicians, resources, and space can shift dramatically, resulting in significant interpersonal and economic challenges. Surgery is of fundamental importance to the institution. Without a strong surgical program, there can be no stent program. Interventional cardiologists who jokingly claim they “want to put their bypass surgeons out of business” may be very sorry if they get what they ask for.

A shift away from bypass surgery to DES can also impact a hospital’s financial health. Bypass surgery is very well reimbursed. By contrast, DES reimbursement often does not adequately compensate the hospital’s expenses. Without question, current DES prices are still high at $2400 to $3000 per stent. The first stent is easy to swallow. It’s the second and especially the third, fourth, and fifth stents that become so economically unpalatable. Discussions with payers are now underway to improve reimbursement for multivessel...
DES implantation. Also, a second FDA-approved DES may exert some downward pressure on prices. Historically, however, we don’t usually begin to see serious discounts until there is a third (expected in 2006) or fourth (also expected in 2006) vendor in the marketplace. So what’s good for patients (fewer repeat procedures) and good for many insurance plans (less bypass surgery and fewer repeat stent procedures) is not necessarily good for hospitals.

**DES Caveats**

Although for many patients the results of DES are competitive with bypass surgery, one must keep in mind the fundamentals of applying clinical trial results to clinical practice. The first step is to compare the study inclusion criteria with the characteristics of the patient you are treating. TAXUS IV and SIRIUS treated patients with single, de novo, native coronary lesions of “intermediate” (10- to 30-mm) lengths. How then does a physician treat a patient with 2- or 3-vessel disease, diabetes, bifurcation disease, left main lesions, long lesions requiring a “full metal jacket,” total occlusions, saphenous vein graft stenoses, acute myocardial infarction, or in-stent restenosis? Clearly, the current evidence base to support DES in complex patient and lesion subsets is lacking. For now, physicians have 3 choices: (1) Wait for the data. Stick to the indications described in the package labeling and only apply DES in patients for whom it has been extensively studied. (2) Help create the data. Contribute to randomized trials and registries designed to evaluate DES in complex clinical scenarios. (3) Cautiously extrapolate the currently available DES data to patients who do not fit study entry criteria but for whom a better therapy is not apparent. This latter approach is the most controversial and should be applied with heavy doses of circumspection, continuous reevaluation, and oversight by one’s colleagues.

Fortunately, much of the data we need will soon be forthcoming. Some patient subsets have already been studied in small DES registries—some demonstrating low recurrence rates, ie, acute myocardial infarction and in-stent restenosis, and some with less pristine findings, ie, bifurcation lesions.6–10 Future registries are planned for left main, bypass grafts, bifurcations, and long lesions. Two large randomized trials of DES for in-stent restenosis are currently underway. Perhaps most exciting is the soon-to-be-initiated Future REVascularization Evaluation in Diabetes Optimal Management with surgery versus drug-eluting stents (FREEDOM) trial, a National Institutes of Health–sponsored randomized trial of DES versus bypass surgery in diabetic patients with multivessel disease. It is gratifying to observe the tremendous effort and resources being mobilized to build and critically evaluate the evidence base for DES.

**Do We Need a Better DES?**

With 2 FDA-approved DES systems demonstrating excellent efficacy and safety, do we need to do better? Target-vessel revascularization rates are already close to 5%. Stent throm-
bosis has been nearly eliminated by antiplatelet therapy. What more do we need?

Actually, we need much more. First, not all patients have the same dramatic results described above. For example, in some DES studies, diabetic patients (particularly insulin-dependent diabetics) have recurrence rates above 15%. Similarly, in some series, small-diameter vessels and longer lesions have higher rates of failure compared with more straightforward targets. We still have no consistently reliable solution for the side branch of bifurcation lesions, and bifurcations represent a substantial proportion of our patients. Brachytherapy failure patients have proven particularly susceptible to recurrent restenosis, and saphenous vein graft disease, not yet studied, also likely will pose durability challenges for DES. Although most of these patient subsets do better with current DES than bare-metal stents, these patients clearly need a more potent antiproliferative therapy.

Second, the long-term results of current DES systems are still not in. The 1- and 2-year data are very encouraging, but later failures could jeopardize the benefits of DES, particularly in comparison to bypass surgery. The coronary brachytherapy experience provides a telling example. The dramatic efficacy of brachytherapy at 1 and 2 years was found to significantly erode by 4 and 5 years as more radiation-treated patients than control subjects required late revascularization.11,12 Similarly, longer follow-up of DES patients may reveal less permanent results than anticipated. Any antirestenosis therapy is destined to encounter a certain number of late failures.

Some theoretical considerations from the radiation oncology world may be relevant to DES. Restenosis within a stented artery is due to smooth muscle cell proliferation and matrix production. Brenner et al.,13 after making some geometric assumptions, estimate that implanting a stent in a typical 3-mm-diameter vessel stimulates about 1 million clonogenic smooth muscle cells to replicate in response to the injury. These cells require about 1.7 months (the doubling time) to divide. After about 4 months (the usual time course for restenosis), slightly more than 2 such doublings have occurred, and the 1 million cells have turned into about 5 million cells, roughly enough to cause restenosis in the 3-mm vessel. Now, let’s assume a paclitaxel or sirolimus, eluting from a stent, with its excellent tissue penetration (both are lipophilic), is able to reach and inhibit 99.9% of those initial 1 million cells. Perhaps a minute fraction of smooth muscle cells escape because they are located deep within an eccentric plaque or are hiding behind a rock of calcium or in a region of poor stent–vessel wall contact. This leaves about 1000 uninhibited cells remaining (0.1% of initial 1 million cells). Perhaps a minute fraction of smooth muscle cells escape because they are located deep within an eccentric plaque or are hiding behind a rock of calcium or in a region of poor stent–vessel wall contact. This leaves about 1000 uninhibited cells remaining (0.1% of 1 million cells). These 1000 cells then begin to double. After 4 months (slightly more than 2 doublings), there are only 5000 cells, not enough to cause restenosis or even to show up on an intravascular ultrasound image. However, after about 22 months (12 doublings), these 1000 cells have multiplied to just over the magic 5 million number, causing the same tight restenosis; it

Figure 3. Emergency balloon angioplasty during cardiopulmonary resuscitation improves left main flow (note wrist watch on individual performing cardiopulmonary resuscitation at right upper corner of image). A DES is then implanted.

Figure 4. Surveillance angiogram at 3 months documents excellent patency of the DES within the left main coronary artery.
just took longer to get there. This theory must be modified by
the expectation that most stimulated smooth muscle cells
have a finite number of divisions in them (the “Hayflick
limit,” which begins with 50±10 divisions in embryonic cells
and decreases to just a few in old age14), so the restenosis
process often will peter out before the lumen is compromised.
Also, we can assume that some of the initially uninhibited
cells will come into contact with drug as they divide and
migrate toward the coated stent (assuming that by the time
they get there, drug is still eluting). In most patients, there-
fore, we can expect a long-lasting result. However, there is
always the possibility that some clonogenic cells will initially
be situated out of range and that by the time they migrate to
the coated stent, the drug will be gone. In addition, some cells
could be resistant to the antiproliferative drug. Through a
variety of mechanisms, therefore, some late failures are
bound to occur.

Designing a Better DES
Failures often provide important insights that help progress.
In this week’s Circulation, Lansky et al15 report the results of
the large, double-blind, randomized DELIVER trial which,
like the TAXUS IV trial, used paclitaxel but with a very
different clinical outcome. The paclitaxel stent used in
DELIVER reduced clinical recurrence and angiographic re-
stenosis, but the improvement was not sufficient to meet the
study’s primary and secondary end points. Target-lesion
revascularization was reduced by only 28% (from 11.3% to
8.1%; P=0.09). The observed decrease in repeat revascular-
ization and restenosis, though trending in a favorable direc-
tion, did not have enough clinical meaning to merit further
development, and this device has been abandoned by its
primary sponsor.

Why was the outcome of these 2 studies so different? The
stents used in the 2 trials were fairly similar. The dose density
of paclitaxel on the stent was actually higher (3.0 µg/mm²) on
the less effective stent used in DELIVER compared with the
more effective TAXUS stent (1.0 µg/mm²). Interestingly, the
most compelling distinction was the different drug-release
kinetics provided by the 2 delivery systems. The DELIVER
trial used a nonpolymer coating system, applying paclitaxel
directly to the stent struts. The TAXUS IV trial used a
polymer-based system that first mixes (“matrixing”) pacli-
taxel with a nonerodable polymer and then applies the
mixture to the stent. With the nonpolymer system, paclitaxel
is released relatively quickly. In vitro studies indicate that
40% of the drug is lost during stent delivery, and the
remainder elutes over the next 1 to 2 weeks. With the
polymer-based matrix system, the polymer acts like a sieve to
slow drug elution. Drug is released over a time course of
about 30 days. Interestingly, only 10% of the drug is believed
to ever be released from this particular system, with the
remaining 90% permanently bound in the polymer, empha-
sizing that it is the longer duration of drug elution rather than
total drug dose that explains the improved results obtained
with the polymer-based system. The FDA-approved sirolimus
DES system also uses a nonerodable polymer-drug matrix
and also releases drug over a time course of about 4 to 6
weeks, further supporting the theory that slow drug release
over a minimum of about 4 weeks is important.

The relative benefit of slow drug release should stimulate
investigation of even more programmable release mecha-
nisms. For example, several DES systems currently in trials
use noninflammatory biodegradable polymers that can be
formulated to release drug over a longer time period. An
added benefit is that once the polymer has completely
degraded, all of the drug is released, alleviating concerns
about potential long-term adverse consequences of retained
drug or polymer.

Another sophisticated DES release system under investi-
gation covalently bonds drug to a biodegradable polymer.
Drug release can then be precisely controlled by enzymatic
degradation of the polymer. Drug elution with such a system
can be extended to 3 or 4 months.

Improved drug carriers are one of many possible DES
improvements. Combination drugs, similar in concept to the
cocktails found beneficial for cancer chemotherapy, will soon
be tested. One creative approach is the combination of a cell
cycle inhibitor (like sirolimus or paclitaxel) with a vascular-
protective agent that promotes healing and stent endotheli-
alization. In theory, a rapidly endothelializing stent should
resist thrombosis and neointima formation. Polymers that
release nitric oxide and estrogen to improve endothelial
function have already shown benefit in clinical trials. Systems
providing unidirectional drug release, so that a cell cycle
inhibitor is released on the abluminal side of the stent to travel
into the vessel wall, while a bio-beneficial drug is released on
the luminal side to encourage endothelialization, are currently
under development.

Another part of the drug delivery system ripe for improve-
ment is the stent itself. Numerous new platforms, such as
ultra-low-profile, thin-strut stents built from cobalt chromium
and other novel materials, may reduce vascular injury and
improve deliverability. One unique design incorporates mul-
tiple drug “reservoirs” within stent struts to allow increased
drug loading and controlled release.

In the quarter-decade since its birth, coronary intervention
has been pushed forward by a series of astounding techno-
logical breakthroughs. DES represents the latest and perhaps
most dramatic advance. As described in this week’s Circu-
lation, when exciting new technology is coupled with rigor-
ous investigation, coronary intervention gets better. And with
it, so do our patients.

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