Drug-Eluting Stents — Pushing the Envelope beyond the Labels?

Joseph P. Carrozza, Jr., M.D.

Unlike jurors, clinicians frequently must make decisions without the luxury of the totality of evidence. When we speak of evidence-based medicine, it is important to remember that available data may be incomplete, outdated, and of questionable relevance to particular patients, especially those excluded from randomized trials. Nowhere is this more apparent than in the controversies surrounding the use of drug-eluting stents in patients with coronary disease.

Pivotal trials of drug-eluting stents reported significant reductions in the rate of repeat revascularization without excess adverse events in the first year after placement of the stent.[1,2] Although these randomized trials were well designed and executed, the extrapolation of findings was limited by the exclusion of patients with complex disease such as chronic occlusions, stenoses at vessel bifurcations, lesions in the left main coronary artery, and multivessel coronary disease. Nevertheless, interventional cardiologists made the leap of faith and extended these findings to off-label applications (i.e., applications beyond those approved by the Food and Drug Administration [FDA]).

The placement of drug-eluting stents became the default strategy for patients undergoing percutaneous coronary intervention (PCI), and most of the indications were off-label. Three years after FDA approval, emerging data suggested a higher rate of thrombotic occlusion with drug-eluting stents than with bare-metal stents, increasing the risk of myocardial infarction and death.[3,4] Reanalysis of the data from the pivotal trials reaffirmed the efficacy and safety of drug-eluting stents for labeled indications but left many questions unanswered for off-label use, especially after two registries reported higher rates of adverse events for stents used in an off-label fashion than for stents used according to the labeled indication.[5-7] The FDA urged caution when placing drug-eluting stents outside of approved indications.[8]

Two observational studies in this issue of the *Journal* contribute new and valuable insights into the appropriateness of off-label use of drug-eluting stents. Hannan et al. compare outcomes for drug-eluting stents and coronary-artery bypass grafting (CABG) among patients with multivessel disease,[9] using data on all patients in New York State who were undergoing CABG or PCI. These investigators previously reported greater risk-adjusted survival among patients with three-vessel disease and those with two-vessel disease (with or without involvement of the proximal left anterior descending artery) who were treated with CABG than among those who were treated with bare-metal stents.[10] Surgery was also associated with fewer revascularization procedures, a consistent finding in previous comparisons of CABG and PCI in patients with multivessel disease. With the promise of less restenosis, many people hoped a similar comparison would establish equipoise between the treatments and affirm multivessel treatment with drug-eluting stents as a viable alternative to CABG.

At first glance, the rate of repeat revascularization among patients in the drug-eluting–stent cohort did not differ from the rate among patients in the bare-metal–stent group in the 2005 registry. However, many of the repeat PCIs for the patients with drug-eluting stents occurred within the first 60 days after the procedure, suggesting that these events were staged interventions and not failures of the target vessel, which constituted only 25% of the total number of revascularizations. Despite this suggestion of reduced target-vessel failure, once again CABG was associated with significantly greater adjusted survival (94.0% vs. 92.7%) and freedom from death or myocardial infarction (92.1% vs. 89.7%) among patients with three-vessel disease and those with two-vessel disease than was PCI with drug-eluting stents. In contrast, a meta-analysis of 23 randomized trials found no difference between PCI and CABG in terms of mortality at 5 years, but surgery was associated with a greater risk of procedural stroke and a lower need for revascularization.[11]

The New York State registries are a sobering reality check for those who hoped the benefits

of drug elution would level the playing field between CABG and stents for patients with multivessel disease. But several important caveats are in order before a final verdict is rendered. In contradistinction to trials in which randomization minimizes bias, risk adjustment in observational studies may not account for unmeasured confounders. For example, dementia is not a covariate in this risk-adjustment model and would be likely to influence a clinician to choose PCI instead of CABG. When confounders are associated with an increased risk of the measured outcome (e.g., death), bias becomes clear. Factors precluding CABG include coexisting conditions that are linked to poor prognosis (e.g., dementia), whereas those precluding PCI are often lesion-based (e.g., chronic total occlusion) and have a lesser effect on prognosis after CABG. Thus, the presence of these unmeasured confounders may bias the outcome in favor of CABG.

It is important to remember that in this observational study, the physician, and sometimes the patient, chose the treatment and thus introduced selection bias. In a randomized design, patients must qualify for both treatments and assignment is by chance. This allows a purer comparison of two treatments but has practical limitations. Is it appropriate to remove physician and patient preferences from decision making when they are such important features of "real-world" medicine? Previous randomized trials that compared PCI with CABG enrolled only 4 to 8% of patients with multivessel disease.[12,13] These randomized trials often exclude patients who are at the highest risk, limiting the relevance of the findings to a minority of patients.

Two other limitations of the study by Hannan et al. are worth mentioning. Patients were enrolled before widespread use of extended dual antiplatelet therapy as prophylaxis against late-stent thrombosis. Finally, the mean follow-up times for both treatments were only 19 months, a period that captures the majority of clinical events related to the major hazards of stenting — thrombosis and restenosis — but does not include events driven by atherosclerosis of saphenous-vein grafts, a process that begins several years after surgery.

In another important observational study in this issue of the *Journal,* Marroquin et al. compare outcomes of patients who received drug-eluting stents with those who received bare-metal stents, using data from the National Heart, Lung, and Blood Institute Dynamic Registry for approved and off-label indications.[14] Patients who received stents for off-label indications had more coexisting conditions and poorer in-hospital and 1-year outcomes than did patients whose stents were for approved indications. Operators were more likely to use drug-eluting stents than bare-metal stents for off-label indications.

Were these choices appropriate? Although overall survival and freedom from death and myocardial infarction were lower for off-label than for on-label use of drug-eluting stents, the adjusted outcomes did not differ significantly as compared with bare-metal stents. Furthermore, adjusted rates of repeat revascularization were significantly lower for patients treated with drug-eluting stents than for those treated with bare-metal stents. Prespecified analyses suggested that for all off-label subgroups, the use of drug-eluting stents was at least as safe as the use of bare-metal stents and — except for large vessels, lesions in the left main coronary artery, and previous restenosis — was more efficacious at reducing the need for repeat revascularization. These findings appear to validate off-label use of drug-eluting stents. Once again, caution must be urged before the results of a single observational study are accepted. Unmeasured confounders, such as the risk of bleeding, which may have engendered reluctance to treat patients with the prolonged antiplatelet therapy that is prescribed for drug-eluting stents, may be associated with a poorer prognosis.

These two observational studies should provide valuable guidance regarding off-label use of drug-eluting stents. The New York State registries affirm that CABG remains the standard of care for patients who require multivessel coronary revascularization. However, stents may be an alternative for patients at high risk for surgical complications or when an informed patient chooses a less invasive option. Additional studies are needed before the findings for off-label use reported by Marroquin et al. can be considered the final word. Randomized trials provide complementary data and address some of the limitations of these observational studies. Although we confront clinical decisions in the absence of the totality of data, these two studies go a long way toward making these decisions more evidence based.

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From Harvard Medical School and the Cardiovascular Division, Beth Israel Deaconess Medical Center — both in Boston.

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Immunosuppressive Therapy and Tolerance of Organ Allografts

Thomas E. Starzl, M.D., Ph.D.

In this issue of the *Journal*, three articles describe several organ-transplant recipients in whom allografts have maintained good function for up to 5 years without immunosuppressive treatment.[1-3] In two articles concerning combined kidney and hematopoietic stem-cell transplantation, the authors attributed the successful outcome in their patients to the cotransplantation of donor stem cells.[1,2]

The third report, by Alexander et al., concerns a young girl who received a completely HLA-mismatched liver from a deceased male donor but did not receive a donor stem-cell infusion.[3] The cause of the fulminant hepatic failure with which the patient presented was never firmly established. However, a viral infection was thought to have caused lymphopenia that was noted at the initial hospital admission and persisted for a half year after liver transplantation. During the post-transplantation phase, passenger leukocytes from the graft largely replaced the recipient's leukocytes. In addition to the presence of male chromosomes in leukocytes from the girl's blood, the recipient's RhD-negative blood subgroup switched to the RhD-positive blood subgroup of the donor. Severe hemolytic anemia, which developed 10 months after transplantation, was attributed to anti-RhD antibodies produced against the donor's RhD-positive erythrocytes by residual B cells in the recipient. This condition prompted the patient's physicians to discontinue all immunosuppressive therapy so that the donor's hematopoietic cells might eliminate all of the recipient's residual B cells. The net effects of this action were resolution of the patient's hemolytic anemia and retention of the graft without immunosuppression.

In one article concerning combined kidney and hematopoietic stem-cell transplantation, reported by Scandling et al.,[1] tolerance was thought to be due to the stem-cell cotransplantation. The recipient of a kidney from an HLA-matched brother began to receive cyclosporine at the time of renal transplantation. During the next 2 weeks, he received 10 doses of total lymphoid irradiation, 5 doses of antithymocyte globulin, and a 10-day course of prednisone. On postoperative day 14, he received an infusion of donor hematopoietic stem cells, and a 1-month course of mycophenolate mofetil was initiated. Within