Drug-eluting stents (DES) were introduced to the coronary artery disease treatment market in 2003 with much exuberance and fanfare. With >70% reduction in restenosis and no apparent safety concerns in 1-year reports from large randomized clinical trials,\textsuperscript{1-2} the opportunity for expansion of the technology seemed limitless. Interventional cardiologists responded with confidence and quickly expanded use to a wide array of off-label indications, limited only by initial inventory constraints.\textsuperscript{3,4} Some even considered DES as a potential therapy for vulnerable lesions or regions that were not yet hemodynamically significant, and there were concerns by hospitals and others that widespread use of these devices for treatment of traditional surgical disease would place cardiac surgery programs in jeopardy.\textsuperscript{5,6} The realization of an increased risk of late and very late stent thrombosis with the first-generation DES, especially in patients with increased lesion complexity, dampened this enthusiasm.\textsuperscript{7,8}

In the years since we have also learned that many patients with symptoms and angiographic evidence of coronary artery disease do as well on medical therapy alone as with stenting, or perhaps even worse with stenting if hemodynamic significance of a coronary lesion is not confirmed.\textsuperscript{9,10} Furthermore, among most patients with 3-vessel coronary artery disease, coronary artery bypass surgery has demonstrated clear benefit in comparison with the first-generation paclitaxel-eluting stent (PES).\textsuperscript{11} Within this context, the use of DES has equilibrated to ≈70% of stent procedures, appropriate-use criteria are widely discussed, and cardiac surgery and surgeons have survived. Meanwhile, new generations of DES have been developed and approved for use with modification of the design flaws that were implicated as factors in the delayed healing and ongoing risk of thrombosis with the first-generation devices. These improvements include polymers that are applied in thinner layers and are more biocompatible, stents with thinner struts, and lower doses of the antiproliferative drugs.

In this issue of Circulation, Räber et al\textsuperscript{12} report that, in a cohort of unselected, routine clinical practice patients, the second-generation everolimus-eluting stent (EES) demonstrated significantly lower risk of stent thrombosis compared with groups who had received either the sirolimus-eluting stent (SES) or PES. The report expands on previous work from this group, which was among the first to note an ongoing risk of very late stent thrombosis after SES or PES that was much higher (≈0.6% per year) among patients in routine clinical practice than had been reported from initial randomized clinical trials (≈0.2% per year).\textsuperscript{13,14} The study includes 12 339 patients who were treated during 3 discrete intervals, in each of which either SES, PES, or EES was the default DES strategy. The authors adjusted for potential differences in baseline characteristics between the intervals by using propensity score methods and reported events as incidence rates per 100 patient-years to correct for differences in follow-up between the older devices and the newer EES. The results included a significant reduction in risk of Academic Research Consortium definite stent thrombosis after 4 years for EES in comparison with either SES (hazard ratio 0.41; 95% confidence interval, 0.27–0.62) or PES (hazard ratio 0.33; 95% confidence interval, 0.23–0.48) mostly because a lower risk of stent thrombosis beyond 1 year (very late stent thrombosis). Along with the reduction in definite stent thrombosis, EES were associated with a reduced adjusted risk of myocardial infarction (MI) in comparison with either SES or PES, a trend toward a reduced adjusted risk of cardiac death or MI in comparison with SES, and a significantly reduced adjusted risk of cardiac death or MI in comparison with PES. The differences in cardiac death or MI were due almost entirely to preventing those events that occurred surrounding a stent thrombosis, with almost no difference in cardiac death or MI that did not occur at the time of stent thrombosis. The results are dramatic and suggest that EES use may be expanded to more complex lesions and patients with a safety profile that is similar to that observed in clinical trials of simple lesion treatment and probably not different from bare metal stents.

In the quest for the holy grail in percutaneous coronary intervention (PCI), namely a therapy with low rates of both restenosis and stent thrombosis, do the data from Räber et al provide convincing evidence that a device has emerged that allows discussion of this possibility? There are, of course, several concerns that require consideration. First, because the study was not a randomized trial, it is subject to the criticisms of observational data, most notably the likelihood of measured and unmeasured confounding. The authors have ad-
dressed measured confounding through appropriate statistical adjustment, which actually resulted in larger and more significant benefits for EES. Unmeasured confounding is also diminished by a strategy in which consecutive patients were enrolled in specific time intervals, during which 1 of the 3 devices was the default DES. This removes the potential bias in selection of 1 DES over another. It does not, however, account for differences in practice between these intervals. Such differences might have included differing thresholds for use of bare metal stents over DES or referral for coronary artery bypass surgery over PCI and could have resulted in a population at lower risk for stent thrombosis in the later interval. It is likely this occurred to some degree. In particular, the increased frequency of multivessel treatment and longer total stent length in the PES group are consistent with this time interval reflecting less discriminate use of DES. Although such a bias cannot be excluded, the increased effect in favor of EES after adjustment for known predictors of stent thrombosis and the magnitude of the difference suggest that a true difference exists. It is also likely that duration of dual-antiplatelet therapy varied between the time intervals, with more patients in the EES group receiving therapy beyond 6 months. The data for dual-antiplatelet therapy compliance beyond 6 months or 1 year were not provided, but it is noteworthy that antiplatelet therapy at the time of stent thrombosis as shown in online-only Data Supplement Table III suggested a higher risk for SES or PES whether on dual-antiplatelet therapy or not. Moreover, given that most of the increased risk was beyond 1 year, it is unlikely that differences in dual-antiplatelet therapy duration had a significant impact.

The interval method of patient selection also raises concerns about duration of available follow-up. As the authors note, the issue of variable duration of risk or cumulative follow-up is addressed, in part, by the reporting of incidence rates per 100 patient-years. This does not account for differences, however, that may occur because of the nonlinearity of relative risk over time. For example, in the recent 4-year report from the Limus Eluted from a Durable versus Erodable Stent Coating (LEADERS) trial, a significant reduction in very late stent thrombosis for the biodegradable polymer biolimus-eluting stent in comparison with SES emerged only after 2 years. It is reassuring that, in the current report, the differences in favor of EES were similar or greater when the analysis was restricted to those patients with at least 2 years of follow-up, as shown in online-only Data Supplement Table IV.

Despite the limitations of making treatment effect comparisons within an observational study, the data provided by Rüber et al provide credible evidence that the second-generation EES has a significantly better safety profile than first-generation SES and PES. Taken together with other studies that have demonstrated at least equivalent efficacy, it appears that a new bar has been set for PCI treatment of coronary artery disease. How should interventional cardiologists respond to this new information? Of course, we will want to see corroborating data from other observational datasets and longer-term follow-up of patients in randomized clinical trials. Some will then likely consider a return to the exuberant acceptance of the first DES and again expand their use to a wider and wider population of patients and lesions. Many will fear a déjà vu experience with the bad news of an unforeseen late complication yet to be unveiled. Hopefully, most will simply incorporate the encouraging findings into an individual patient-based treatment algorithm that allows estimation of a lower risk-to-benefit ratio for most patients.

The response must recognize, however, that even the best PCI treatment is only truly safe and effective with appropriate use. Incorporation of medical therapy and surgical options based on current evidence strengthens rather than weakens the impact of PCI. Importantly, the new higher bar being established for PCI must not diminish development efforts for an even safer and more effective percutaneous option. Because demonstrating improvement or even noninferiority to this high standard will be onerous, these future evaluations will require novel clinical trial designs, including the possibility of establishing objective performance criteria rather than concurrent controls for comparison of new treatments. As we move forward, the field should be congratulated for the process of innovation and development that when faced with a problem seeks solutions and then tests them rigorously. Once again, the future appears bright. This time our response should be one that tempers enthusiasm with recognition of limitations and a passion to be even better.

Disclosures
Dr Cutlip is a Principal Investigator, Medtronic Endeavor Drug Eluting Stenting: Understanding Care, Antiplatelet Agents and Thrombotic Events (EDUCATE) trial.

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Evidence of Safety and Effectiveness for a Drug-Eluting Stent: How Should We Respond This Time?
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