Randomized clinical trials of new coronary devices, as with other novel therapies, are generally conducted in a homogeneous and usually low-risk population. There is valid statistical and methodological justification for this approach, including lower variances (resulting in increased statistical power) and increased probability that observed differences are due only to the study therapy. Although such trial designs generally increase the chances of a positive result, they result in a limited ability to generalize the findings to the broader population of patients encountered in routine clinical practice. Furthermore, the quality of evidence required for reasonable assurance of safety and effectiveness, the benchmark for regulatory approval of a new device, is necessarily in equilibrium with the desire to bring novel designs to market and meet the clinical needs of the population for whom therapy may be beneficial as expeditiously as possible. The resulting limited complexity of the study population and relatively short duration of follow-up after study therapy increase the risk of failing to detect important safety concerns in the premarket period.

The short history of drug-eluting stents (DES) is a classic example of this paradigm. Early randomized clinical trials of the first 2 DES, the sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES), were conducted in relatively low-risk patients and lesions and showed overwhelming efficacy compared with bare metal stent (BMS) controls without apparent safety concerns during a 1-year follow-up. 

Three years after marketing of these devices in the United States, there were warnings from 2 informal meta-analyses—presented originally at the European Society of Cardiology (ESC) congress in 2006—of a possible late increased risk for death or myocardial infarction. Even though the mortality increase was noncardiac in one of these reports and subsequent detailed patient-level analyses from the randomized clinical trials of SES and PES showed no increase in risk for death, myocardial infarction, or stent thrombosis compared with BMS for either DES in this population, these warnings, the so-called ESC firestorm, sparked a fear of late thrombotic events beyond the 3 to 6 months of prescribed dual antiplatelet therapy. This concern was heightened by reports from real-world nonrandomized studies that included more complex patients and lesions and suggested a substantially higher risk of DES thrombosis between 30 days and 1 year (late) and beyond 1 year (very late) than had been previously reported. On the basis of these observations, a special session of the US Food and Drug Administration Circulatory System Devices Advisory Panel concluded that concerns about thrombosis do not outweigh the benefits of DES compared with BMS when DES are implanted within the limits of their approved indications. The panel issued cautions, however, in extending the use of DES to more complex patients and lesions that were not represented adequately in the randomized clinical trials.

Although considered as a class during these deliberations and still frequently grouped together as first-generation DES, the SES and PES are different in all aspects of the 3-component DES design: stent structure, polymer, and drug type. These design variations have been associated with clear and consistent differences in angiographic outcomes, measured most reliably by late lumen loss during 9 months of follow-up, with SES showing rates of 50% lower than PES. Despite these angiographic differences, the individual device studies have suggested similar clinical safety and efficacy for SES and PES compared with their BMS counterparts, at least within the lower-risk populations included in the pivotal randomized clinical trials. Two subsequent randomized trials, Siroliimus- versus Paclitaxel-eluting Stents in de novo Coronary Artery Lesions (REALITY) and Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) assessed whether differences might exist between SES and PES when tested in the more complex patients and lesion types encountered in routine practice. The SIRTAX trial showed a significant reduction in the clinical end point of binary angiographic restenosis at 8 months or any of the secondary clinical end points at 1 year. In contrast, the SIRTAX trial showed a significant reduction in the clinical primary end point of major adverse cardiac events at 9 months for SES, with most of the difference resulting from a 44% reduction in target lesion revascularization (TLR). Perhaps because of the conflicting results, these studies did not have a major impact on use of SES over PES in simple or complex lesions. Shortly after publication of REALITY and SIRTAX, the initial enthusiastic use of both DES declined
amid the controversy of a possible increased risk for very late stent thrombosis and concerns over histopathological reports of ongoing vascular inflammation and persistent delayed healing for both devices.\textsuperscript{11} Meanwhile, the introduction of newer, second-generation DES, which have been approved on the basis of noninferiority to PES in populations very similar to the initial SES and PES pivotal clinical trials and without convincing superiority in more complex patients and lesions,\textsuperscript{12,13} has rekindled enthusiasm in DES almost to pre–ESC firestorm levels and led to replacement of SES and PES in most centers with these newer devices. There seems to have been little interest in fact that the 5-year analyses from the original pivotal clinical trials have reported continued effectiveness and no excess hazard, including very late stent thrombosis, for either SES or PES compared with the BMS controls.\textsuperscript{14,15}

In the current issue of Circulation, Räber et al report the 5-year results from the SIRTAX trial.\textsuperscript{16} The study is important as the best available data on late outcomes of SES and PES in the more complex patients of routine clinical practice, and the results have implications beyond the actual comparison of SES and PES.

There are 2 major findings to consider. First, patients in both groups continued to require repeat TLR during late follow-up. This was slightly more frequent for SES (2.0%/y versus 1.4%/y) and abolished the early difference in favor of SES for TLR and the primary end point composite of major adverse cardiac events. Does this represent a late catch-up phenomenon that is more apparent for SES and is due to differences in DES-related biology? It is possible that this is the case, but among the small group of patients with paired angiograms at 8 months and 5 years, a continued increase in neointimal hyperplasia is suggested by excess late lumen loss in both devices. The slight increase for SES is not statistically significant. In any case, it is clear that late TLR occurs for both devices and that, as a result, after 5 years there is no longer a significant difference in TLR or major adverse cardiac events.

The next questions are whether this phenomenon is unique to SES and PES, and whether it is exaggerated in the more complex population observed in SIRTAX. The 5-year reports of the SES (1.1%/y for SES versus 1.0%/y for BMS) and PES (1.5%/y for PES versus 2.0%/y for BMS) pivotal trials also reported late TLR in both the DES and BMS groups.\textsuperscript{14,15} Likewise, in a pooled analysis of BMS clinical trials, late TLR between 1 and 5 years occurred in 1.5%/y.\textsuperscript{17} There are a number of possible reasons for late TLR beyond stent-related alterations in the biology of the treated lesion, including progression of disease in surrounding segments and late clinical presentation of earlier restenosis. Regardless, it does not appear to be a clinical event that is unique to SES and PES or their use in more complex lesions, although it does reduce the late relative clinical benefit, and this effect may have a larger impact in more complex lesions.

The more serious concern from SIRTAX LATE is the ongoing hazard of stent thrombosis between 1 and 5 years. According to the Academic Research Consortium definite or probable criteria, the 5-year rate of stent thrombosis was 4.8% for SES and 4.9% for PES with a continuing rate of \(\approx 0.7%/y\) for very late stent thrombosis with either device. Although similar for SES and PES, these rates are alarming and clearly above the 0.2%/y reported for these devices in the pivotal clinical trials.\textsuperscript{6} The remaining questions are to what extent these rates may exceed that of a BMS and whether new DES will fare more favorably in similar patients and lesions. These missing data are crucial in deciding between medical therapy and revascularization and in choosing a revascularization strategy in these higher-risk patients and lesions.

It is of special concern that long-term safety and effectiveness outcome data comparing the first available DES in patients likely to be encountered in routine clinical practice are only available \(>8\) years after initial device approval. These important findings arrive at the end of what has been a fairly typical new technology development cycle in which there was a period of overwhelming enthusiasm and adoption, followed by reduced use owing to a fear of adverse outcomes, in this case based on registry data including at least partially inaccurate reports, and finally by a plateau phase reconciling these extremes. The plateau phase for DES was brief with a new upward slope related to enthusiasm for new and improved devices, notably also without convincing proof based on similar routine practice populations. The results of SIRTAX LATE also call attention to the fact that the delay in this knowledge may have subjected thousands if not millions of patients to an increased risk for late thrombotic complications, an adverse circumstance that is compounded by recognizing that the benefit of avoiding repeat revascularization may have been less than believed on the basis of earlier studies.

In this regard, the implications of SIRTAX LATE surpass the original objectives of comparing late safety and effectiveness of SES and PES in more complex lesions. Among the population enrolled in SIRTAX, the results for the 2 DES are equal. The question is whether a TLR rate of \(\approx 13%/y\) at the cost of nearly 5% stent thrombosis after 5 years should be interpreted as equally good or equally bad. The more important question that will never be answered is how either DES would have fared in a randomized comparison against the best available BMS in the SIRTAX population, because this was not the paradigm for speedy regulatory approval. Looking forward, it must be questioned whether newer DES should continue to be approved on the basis of noninferiority in low-complexity patients and lesions with limited duration of follow-up or whether it is time to abandon this model in favor of pragmatic clinical trials that test new devices in an appropriately broad population.

As noted previously, the regulatory requirements for approval should meet the balanced objectives of high-quality evidence for safety and effectiveness and prompt approval of new technology. The current paradigm fails on both counts. Data at the time of approval are still limited to a low-risk population, and sample sizes are likely to increase as the event rate for noninferiority is lowered, further extending the time lines for completion. The Food and Drug Administration guidance document for industry on DES development has made some strides in the right direction for future DES trials. It is now required that a substantial proportion of patients have 2 years of follow-up data at the time of premarket approval.
application submission, allowing the combination of multiple studies that have the ability to evaluate DES performance across a broader population than can be achieved by 1 study and highlighting the need for postapproval studies that ensure the inclusion of a sufficient number of patients treated in accordance with the labeled indications and provide separate analyses for those patients with indications not included in the approved label. This may improve generalizability of study results and the detection of infrequent safety signals, especially in more complex patients, if the postapproval studies can be enforced as suggested. Unfortunately, it does not increase efficiency or ensure that the pivotal clinical trials include a broad population of patients. A larger shift is required to ensure that the best clinical trial data, including proper control groups and adequate duration of follow-up, will apply to the patients who will be encountered and treated after approval. Such a shift will require stepping away from current, overly simplistic trial designs that allow comparisons with historical results but fail to meet the needs of future patients. Novel designs, including large, simple trials with limited exclusions, earlier approval with postapproval study enrollment as a marketing and possibly reimbursement requirement, and better methods for subgroup analysis are all potential attributes of a successful clinical trial design and regulatory approval strategy. These methods and others merit careful consideration and should be studied through collaboration of clinical trialists, regulatory authorities, and industry. It is imperative that 5 to 10 years from now we avoid wondering if the next great developments in DES technology are equally good or equally bad.

Disclosures
None.

References

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