Since the United States Food and Drug Administration (FDA) approval of drug-eluting stents (DES) in 2003 as a treatment for coronary artery disease (http://www.fda.gov/bbs/topics/NEWS/2003/NEW00896.html), physicians have extended the use of these devices to patient and lesion complexities beyond those studied in pivotal randomized trials that compared their outcomes with bare metal stents. During the early period of enthusiastic adoption of DES, clinical decisions regarding DES implantation often exceeded the supportive evidence for a specific indication and instead were based on extrapolations of DES use in less complex patients, positive reports from subgroup analyses of subsequent trials, and anecdotal experience. Application of DES beyond the studied (and approved) indications, termed “off-label,” represents at least 60% of clinical practice patterns in contemporary percutaneous coronary intervention.1

In parallel with the increasing use of sirolimus- and paclitaxel-eluting stents, there emerged concern that DES may be associated with an increased incidence of late stent thrombosis (ST) and possibly increased rates of myocardial infarction (MI) and death.2–7 Although the pivotal trials evaluating DES were not statistically powered to identify differences in rare adverse events between DES and bare metal stents, the observation that ST, in particular late ST, was often associated with death or MI8–13 raised concerns among clinicians and regulators. In many instances, the limited data available obscured the differentiation of “evidence-based” medicine from clinical opinion and raised questions about the risk–benefit equation of DES use. The result was a return to increased use of bare metal stents and a relative decline in DES use from ≈90% of coronary stent revascularization procedures in 2006 to 60% by mid-2007.14

Because of these safety concerns, the FDA convened an expert advisory panel in December 2006 resulting in an updated statement that although the approved DES were associated with a small but measurable increase in the rate of ST compared with bare metal stents, “the concerns about thrombosis do not outweigh the benefits [of drug-eluting stents].”15 The panel also agreed that because of safety concerns, the DES labeling should state that when such stents are used off-label, patient outcomes may not be similar to those observed in the narrower patient populations reflected in the randomized trials used for device approval, indicating that in off-label use, “the safety and effectiveness of DES as compared with those of alternative treatments deserve continued study.”16 Although off-label use of a medical product by an individual physician for an individual patient should not be interpreted as inappropriate or substandard clinical practice, in many cases it does mean that data from well-designed clinical trials have not been developed which establish a reasonable assurance of safety and effectiveness for FDA approval of the specific condition.

Despite the benefit of DES in reducing the need for repeat revascularization in populations with variable risk,15 concern remained that this benefit may be outweighed by a higher risk of late ST. Further, uncertainties have been raised regarding the relative benefit of DES in “real-world” practice; the reduced rate of repeat revascularization associated with DES implantation might be attenuated by the absence of protocol-specified follow-up angiography.16,17 Still other studies have suggested that although DES implantation has early and intermediate term benefits, the relative efficacy may diminish over the long-term.18 Accordingly, as the focus of DES trials has shifted toward greater emphasis on clinical outcomes (e.g., cardiac death, MI, and coronary revascularization) rather than angiographic measures (such as late lumen loss and percent diameter stenosis), the experience of FDA with DES has motivated (1) the adoption of clinical trial end point definitions that are more specific to the coronary territory treated with the DES and (2) modifications to the review process that will ensure public safety of newly developed DES technologies.

**Lessons Learned From the DES Experience and Unresolved Dilemmas**

DES benefits and risks have heightened the responsibility among interventional cardiologists, industry, and regulators to better understand clinical trial design and methodology and their relevance to both device approval and clinical practice. Over the past 3 years, as clinical trial experience has shifted toward a greater emphasis on DES safety, both the clinical
trial and regulatory approaches to late DES outcomes have become more refined.

An important lesson in this experience has been that one trial alone may be insufficient to exclusively direct clinical decision making. Further, the potential for variable reporting of results within the same clinical study at different periods of follow-up,19 and the sheer number of DES trials, increase the probability by chance alone for inconsistent and unanticipated findings. In the latter example, clinicians must be able to critically appraise such trials in the context of a much larger evidence basis before routinely adopting changes in practice.

Accordingly, more recent investigations have focused on evaluating long-term outcomes after DES treatment in population-based studies involving large patient cohorts of appropriate size to examine low-frequency events, including death, MI, and ST. Beyond randomized trials with more restrictive enrollment criteria, observational studies, for example, typically evaluate outcomes in less controlled and more complex cohorts. These recent population-based studies, having the advantage of generalizability and statistical power, have contributed with greater precision to our understanding of the risks and benefits of DES across a broad range of practice. Overall, these studies have shown generally low rates of clinical restenosis, death, or MI as demonstrated in randomized trials. Furthermore, although adverse events may be more common after percutaneous coronary intervention in the clinical setting of off-label versus “on-label” use,20,21 in trials that include bare metal stent outcomes, an increased rate of death and MI (compared with bare metal stents) has usually not been found with DES, and a consistent DES-associated restenosis benefit has been observed.15,19–27 However, although statistical adjustments provide insights into treatment differences and serve to generate hypotheses, non-randomized studies are inherently limited because of unrecognized or unaccounted variables absent in the statistical modeling. In most instances, such trials examining outcomes in off-label indications are of single-arm observational design, which further limit the conclusions that may be drawn from study results. Thus, although off-label does not necessarily imply “unstudied,” the shortcomings associated with existing trials underscore the need for prospective, well-designed, and rigorously executed and monitored label expansion studies.

One outstanding area of DES investigation has been whether the risk of late (30 days to 1 year) and very late (beyond 1 year) STs may be mitigated by extended use of dual antiplatelet therapy (DAPT, aspirin plus clopidogrel) beyond that described in the randomized trials performed for DES approval.9,28 Although a reanalysis of key randomized trials comparing sirolimus- and paclitaxel-eluting stents with bare metal stents through 4-year follow-up has demonstrated a numerically higher incidence of very late ST (ie, occurring 1 year after index revascularization),2–4 and observational studies have indicated a higher risk of ST in off-label indications for both bare metal stents and DES,20,21 few data are available to guide clinical decisions regarding long-term DAPT use. As a precautionary measure based on trials associating early (<6 months) thienopyridine discontinuation with an increased risk of DES thrombosis, an intersociety guideline recommendation advocated 12-month DAPT after DES placement in patients not at high risk for bleeding.29,30 In December 2006, after an extensive review of data indicating a numeric excess of late ST with sirolimus- and paclitaxel-eluting stents,2–4 the FDA advisory panel concurred with this empirical recommendation of 12-month DAPT after DES placement and recommended that these guidelines be incorporated into DES product labeling. The scientific rationale for extended DAPT use was based on evidence of delayed coronary endothelialization associated with DES that lengthens duration of thrombotic risk.31 This recommendation was subsequently reinforced by a multidisciplinary Science Advisory statement for instructing clinical practice.28 Importantly, however, this recommendation was based on consensus opinion, randomized pharmaceutical trials conducted in patients with acute coronary syndromes (involving bare metal stents and beyond any existing approved indications for DES),32,33 and observational studies indicating lower risk of death and MI with long-term DAPT,34 rather than on prospective randomized trial evidence.

At present, studies examining the relationship between DAPT and outcomes after percutaneous coronary intervention have been limited by trial design or methods that have restricted their applicability to clinical decision making in routine practice. Observational studies have consistently associated premature discontinuation of DAPT with a higher risk of ST.10,35–37 Although some studies have demonstrated that long-term DAPT may be associated with reductions in death and MI, a general benefit in patients with coronary artery disease rather than a specific reduction on the rate of DES thrombosis has not been excluded.34 Importantly, DES thrombosis may occur despite continued DAPT. In addition, few studies formally evaluated compliance with intended therapy or studied increased bleeding risks associated with long-term DAPT. As a result, despite guideline recommendations for extended DAPT after percutaneous coronary intervention with DES,28–30 few data are available to guide clinical decision making beyond consensus opinion. Accordingly, the FDA has supported the need for well-conducted studies to address the optimal duration of DAPT after DES placement. One example involves the planning of a large (~20 000 patients) randomized trial that is specifically intended to examine whether 30 versus 12 months of DAPT after drug-eluting stent and bare metal stent revascularization may impact the outcomes of death, MI, stroke, and ST (http://www.clinicaltrials.gov/ct2/show/NCT00977938). As such, investigations with DES may not only permit adequate study to merit device initial approval or label expansion but also inform existing clinical practice.

Guidance for DES Approval and Surveillance: An Adaptive Model

The experience with DES has presented an opportunity for the FDA to reappraise the review process of current United States market-available DES and to develop regulatory guidance for next generation DES. Although the public health responsibility of the Center for Devices and Radiological Health within the FDA is to ensure that new medical devices
Clinical Trial Development for DES: From Preclinical Study to Pivotal Trial

DES are regulated as class III (highest risk) devices, and any proposal for new device investigation in the United States must begin with an approved investigational device exemption application that includes a detailed device description, proposed indications for use, preclinical evaluation and previous clinical experience, summary of the manufacturing process, and proposed clinical trial protocol. Before marketing, approval of a premarket approval (PMA) application is required that is based on scientific evidence that supports reasonable assurance of safety and effectiveness of the device for its intended use. The FDA DES Guidance document outlines the comprehensive preclinical experimental and clinical elements to be submitted in an investigational device exemption (and subsequent PMA) application. The Table details the important aspects of preclinical bench testing, human clinical trial design, and conduct for new DES or iterative development of an existing DES platform. Once an acceptable standard of preclinical and early human clinical safety is established, a pivotal investigational device exemption trial should be of sufficient size to demonstrate either clinical superiority to bare metal stents or noninferiority (or even superiority) to an approved DES. Whether the statistical plan of an investigational device exemption trial is designed to test superiority or noninferiority, the relative margins of what determines trial success must be clinically relevant based on both prior clinical studies and expected performance. Noninferiority trials face an added limitation of the potential for outcome drift, in which after several noninferiority trials, a later generation DES could be no better (or even worse) than the initial predicate device (eg, a bare metal stent).

Table. Key Regulatory Considerations for Development of a DES Trial Program

<table>
<thead>
<tr>
<th>Preclinical study</th>
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<tbody>
<tr>
<td>1. Characterization of pharmacology and toxicity associated with the antiproliferative drug, the drug and polymer coating process, and the drug–device combination in terms of biologic compatibility and drug-release kinetics</td>
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<tr>
<td>2. Preclinical evaluation using animal implants to inform stent mechanics and handling and enable assessment of stent endothelialization, reduction in neointimal hyperplasia, inflammation, and arterial injury</td>
</tr>
<tr>
<td>3. Histopathologic review at 180 to 360 days, dose-ranging and overlapping stent studies to establish safety margin</td>
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Human clinical trial design

1. “First in Human” often useful to characterize device performance, expectation of biologic efficacy (eg, by angiographic and intravascular ultrasound measures), and safety
2. For pivotal trials of a new DES that use a new molecular entity or a combination of drugs, novel elution kinetics, coating, or platform, a randomized controlled trial is the recommended pivotal clinical study design
3. For serial iterations of an approved DES (eg, a change in the configuration of the stent platform with the same polymer and drug), a single-arm clinical trial with a historical control may be acceptable

Selection and definition of study end points

1. For IDE pivotal trials, a device-oriented hierarchical composite primary end point of “target lesion failure,” defined as cardiovascular death, target vessel-related MI, and target lesion revascularization
2. Evaluation of the primary (clinical) end point at 12 months
3. Secondary end points relevant to early and late clinical safety and efficacy, procedural-related events, and angiographic and intravascular ultrasound measures of biologic effectiveness and arterial wall remodeling
4. Performance of scheduled follow-up angiography and intravascular ultrasound studies in selected patients after clinical end point ascertainment to avoid bias related to angiographically driven, but nonclinically driven, repeat revascularization; alternatively, follow-up angiography may be performed in a separate patient cohort independent of the pivotal study

Statistical considerations

1. Formal null and alternative hypotheses related to the primary end point
2. Secondary end points generally expected to be descriptive and not lead to additional efficacy or safety claims in the DES product labeling
3. Methods to minimize missing data and a prospective plan to handle missing data in the statistical analyses to support validity of study results

main coronary disease) or clinical equipoise regarding the safety and efficacy of DES (eg, acute MI), a randomized controlled trial would be recommended. In other instances, if there is no established standard of care and no approved device for particular lesion (eg, total coronary occlusions and bifurcation disease), either a randomized or a single-arm study that uses historical control data to formulate either objective performance criteria or a performance goal may be acceptable. Further, any labeling claims or expanded indications based on secondary end points should be prespecified in the protocol with the provision of formal hypothesis testing, adequate statistical power, and control...
of type I error. In summary, trial design proposals for substantive changes to existing commercialized DES or their indications for use are considered on a case-by-case basis depending on whether proposed modifications raise new questions of device safety or effectiveness.

Evaluation of DES-Specific Outcomes and Therapies: Late ST and Antiplatelet Therapies

Considering the clinical implications of ST, a comprehensive assessment of ST over the long-term is a focus for existing and new DES PMA applications. Previously, accurate estimation of late ST was confounded by nonuniformity of definitions across early DES trials, either limiting events to those identified angiographically or excluding patients who underwent prior target lesion revascularization. As a result, the FDA has recommended the use of ST definitions established by the Academic Research Consortium (ARC) that classify events according to the level of evidence and timing of the event (early, <30 days; late, 31 days to 1 year; very late, >1 year).

Also important is a determination of the relationship between ST and what has been termed “obligatory” DAPT. Therefore, a requirement for approval of new DES is that clinical studies closely monitor: patient compliance with the recommended DAPT regimen; frequency, duration, and implications of DAPT interruption; deferral of invasive procedures because continued DAPT is essential; and the rate of bleeding complications associated with DAPT. In addition, the FDA supports the conduct of investigator-initiated and industry-sponsored trials that are specifically intended to examine whether extended durations of DAPT after DES implantation impact the outcomes of cardiovascular death, MI, stroke, and ST.

DES Evaluation: Implications for Clinical Research and Public Policy

Experience with DES both within and beyond the context of clinical trials has motivated the requirement for studies of DES in larger numbers of patients followed for a prolonged period of time. When low-frequency late-occurring outcomes are of interest, there is no substitute for the performance of clinical studies in large diverse patient populations and in varied clinical settings. At the time of PMA submission to the FDA, it is recommended that 12-month primary end point data from the pivotal trial be supplemented with 18- to 24-month follow-up data on an adequate number of patients to provide a reasonable assessment of safety, particularly after thienopyridine discontinuation. Patient outcomes should also be assessed annually through a minimum of 5 years after the index procedure.

Expansion of requirements for DES approval also has implications for clinical trial conduct. Enrolling sites may need to dedicate resources for long-term follow-up and encourage study subject retention. However, trial results must inform current clinical practice, and regulatory guidance of the FDA is not intended to compromise the real-time clinical relevance of trial results by overextending trial duration. Global trials conducted both within and outside of the United States can provide a valuable source of PMA data using statistical methods specified to address poolability among study subjects. Moreover, globalization of trial conduct may present advantages for trial sponsors seeking approval in other countries through harmonization of trial design and performance through collaboration with foreign regulatory agencies having more varied device approval requirements.

Any requirement for long-term (and more detailed) follow-up could potentially stifle innovation, hinder new product availability, and impede the introduction of improved medical devices. However, a reasonable assurance of safety and effectiveness of a new DES requires a comprehensive evaluation of late-occurring infrequent serious adverse events that affect both on-label patients and a broader population with clinical features more complex than those observed in initial clinical trials. In this regard, the DES regulatory guidance seeks efficiencies in clinical trial design and conduct to allow improved medical devices to reach patients without compromising the mission of FDA to protect U.S. public health. Such efficiencies include global trials, single-arm studies (when appropriate), broadening inclusion criteria to better reflect a real-world population, and adaptive trial designs.

An additional lesson of the DES regulatory experience is that once a DES has been approved for marketing, swift implementation of a large postapproval study provides an opportunity for timely public access to promising therapies and satisfies requirements for continued study. The principal objective of a postapproval DES study is to provide greater detail regarding the rates of ST and cardiovascular death and MI at 1-year follow-up in an on-label (intended use) population. The yearly rate of ST—the recommended primary end point of the postapproval study—should be evaluated in a study population of sufficient size to permit precise estimates of its occurrence. Specifically, the sample size should ensure an upper boundary for the 1-sided 95% CI around the observed rate of ST from 12- to 60-month postprocedure of ≤1% for each yearly interval, with at least 80% statistical power for patients treated according to the on-label indication. Commitment for 5-year follow-up in the postapproval study should also clarify whether annualized rate of ST remains constant or plateaus over time. Pooling of these patients with the preapproval pivotal study population will enable greater precision in assessing safety outcomes and an assurance of device safety. In addition, such studies contribute to our understanding of DES in more complex off-label indications as well as inform patterns of and outcomes relative to DAPT use.

Conclusion

Treatment with DES is the most common method of percutaneous coronary revascularization and represents a therapeutic advance by a reduction in restenosis rates and the need for repeat revascularization procedures. Amid widespread enthusiasm for DES, however, identification of late ST and uncertainties regarding the appropriate duration of DAPT underscore the need for a pre- and postapproval regulatory process capable of evaluating low-frequency late-occurring event rates. Regulation of medical devices of FDA encompasses the total product life cycle (Figure), from early device
inception through preclinical medical device testing, clinical trials, marketing application, postmarket monitoring of de-
vice performance, and eventual withdrawal from the market
because of obsolescence. Accordingly, fueled by DES expe-
rience in both clinical trials and real-world practice, the FDA
has adapted the process for device approval and surveillance
to assure continued safety and effectiveness. Although revis-
ion of the review process was needed to adapt to newly
identified concerns, the primary mission of the FDA remains
unchanged: to apply exacting criteria to evaluate medical
product safety and effectiveness in a least burdensome
manner to the benefit of patients.

Disclosures
Dr Kandzari serves as a consultant to the FDA Circulatory System
Devices Panel under special government employee status. Dr
Kandzari receives research/grant support from Cordis Corpora-
tion/Johnson & Johnson but has no equity conflict. Dr Farb
and Medtronic Vascular and is a former employee of Cordis
Devices Panel under special government employee status. Dr
Kandzari serves as a consultant to the FDA Circulatory System

References


Key Words: delivery of health care ■ public policy ■ government regulation ■ stents
Percutaneous Coronary Intervention in Perspective: Drug-Eluting Stents as a Model for Regulatory Review
David E. Kandzari, Andrew Farb and Ashley B. Boam

doi: 10.1161/CIRCINTERVENTIONS.109.871996
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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