

Stent Thrombosis in BMS and DES

More issues than answers.

BY MITCHELL W. KRUCOFF, MD, FACC

"Always remember that a medical device is the replacement of one disease with another...hopefully, a less severe one."

—William C. Roberts, MD

from a 1978 lecture at George Washington University

Percutaneous coronary intervention (PCI) has advanced during the past 30 years to become an effective nonsurgical revascularization technology that provides symptomatic relief for stable angina and reduces morbidity and mortality in acute coronary syndromes and ST elevation myocardial infarction (STEMI). Compared to plain balloon dilatation, bare-metal stents (BMS) constrained flow-limiting intimal dissection, produced more laminar luminal flow, and provided a scaffolding to resist elastic recoil at the dilatation site. This resulted in a significant reduction in 1-year restenosis, as well as in rates of periprocedural urgent bypass surgery.^{1,2}

The full benefits of BMS as an advance beyond plain balloon angioplasty were dependent on a number of lessons learned along the way. Both bleeding and early thrombosis rates improved as clinical trials added experience with new combinations of anticoagulant agents (unfractionated heparin, low-molecular-weight heparin, and direct thrombin inhibitors) and antiplatelet agents (IIb/IIIa inhibitors, thienopyridines, and aspirin) as PCI evolved from balloon to BMS, and such experience continues to evolve in the era of drug-eluting stents (DES).³⁻⁹ Outcomes have also benefited from angiographic and intravascular ultrasound observations on procedural technique, such as geographic miss with predilatation and the use of high-pressure balloon inflation to optimally deploy stent struts,^{10,11} supported by engineering advances such as thinner strut designs using alloys (ie, cobalt chromium). In all, adverse outcomes with BMS were considered narrowed

to a single most evident new challenge: the fibroproliferative response to stent implantation, or in-stent restenosis. In-stent restenosis became the primary target of the next generation of stent technologies—stent platforms loaded with drugs inhibitory to cellular reproduction cycles—the stents we know today as DES.

From the first reports in human subjects to the pivotal randomized trials that quickly followed, DES platforms consistently demonstrated a remarkable ability to diminish both angiographic and clinically driven in-stent restenosis compared to BMS, with relative reductions of more than 50% or absolute reductions of approximately 12%.¹²⁻¹⁸ A network meta-analysis of some 38 clinical trials has shown this particular clinical benefit to be sustained out to at least 4 years.¹⁹ With in-stent restenosis rates in simple lesions approaching single digits, global enthusiasm for DES technology was high, with 80% to 90% market penetration in some areas of the US and multiple "all-comers" registries exploring DES outcomes in more complex patients worldwide.^{20,21}

However, anecdotal reports of very late DES stent thrombosis²² were followed in the spring of 2006 by registry reports raising the concern that although DES reduced restenosis relative to BMS, an increase in rare but catastrophic late thrombotic complications might offset such early gains.²³⁻²⁵ Both the scientific community and the public and media took notice of these concerns,^{26,27} and the FDA convened a special 2-day Advisory Panel on the topic of stent thrombosis in December 2006.²⁸ Although the panel concluded that all data available supported that DES are safe and effective relative to BMS in the simple "on-label" patients studied in pivotal randomized trials, the panel also pointed to a number of important areas of unanswered questions and ongoing concern in understanding the

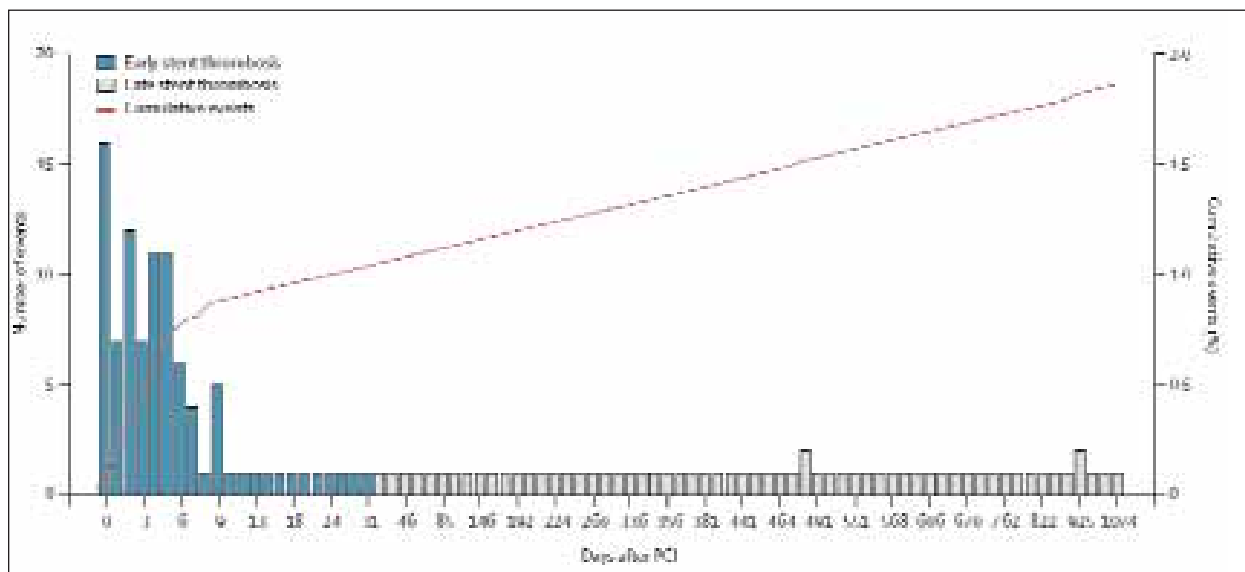


Figure 1. Cumulative frequency of stent thrombosis over time. Beyond 6 months, a linear hazard of 0.6% per year is evidenced. (Reprinted with permission from Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet*. 2007;369:667-678.³⁸)

possible tradeoff between long-term safety and short-term efficacy, including heterogeneity of more complex “real-world” patient and “off-label” coronary anatomy and optimal duration of dual-antiplatelet therapy.

Since the FDA panel meeting, more than 15 meta-analyses, as well as national and state registries, have been published intended to add insight into the risks and benefits of DES versus BMS used in PCI. With new, second-generation DES platforms emerging, as well as new medical adjunct agents, understanding the issues and data available is critical to informed practice of PCI going forward.²⁹

CLINICAL REPORTS OF STENT THROMBOSIS AFTER PCI

Reports contributing data on stent thrombosis now include experience in more than 100,000 patients, although heterogeneous features, such as inclusion and patient selection criteria, coronary anatomy, stent platform, duration of follow-up, duration of antiplatelet therapy, and definition of stent thrombosis events in human subjects, present profound challenges to efforts to pool, or even to interpret, the data available across the published literature.

Stent thrombosis in the first 30 days and out to 1 year after PCI have been most routinely reported with both BMS and DES platforms. In one overview of eight clinical reports involving more than 20,000 patients,

30-day stent thrombosis rates with BMS ranged from 0.4% to 2.8%.³⁰ Stent thrombosis rates within the first year with both first-generation (sirolimus-eluting stents [SES] or paclitaxel-eluting stents [PES]) and second-generation (zotarolimus-eluting stents [ZES] or everolimus-eluting stents [EES]) DES platforms appear comparable to rates reported with BMS. Pooling 10 studies of 2,602 PES and SES patients compared to 2,428 BMS patients followed for 9 months, stent thrombosis rates were 0.6% and 0.5%, respectively.³¹ Stone et al reported almost identical rates of approximately 0.6% at 1 year from a patient-level meta-analysis of 5,254 randomized and registry patients (878 with SES, 1,753 with PES, and 1,626 with BMS).³² Two patient-level meta-analyses of ZES and EES were presented to FDA Advisory Panels in 2007, in which stent thrombosis within the first year was 0.4% to 0.5% with ZES versus 1.2% to 1.3% with BMS, depending on the definition used, from 2,728 patients, including 2,132 with ZES and 596 with BMS,³³ and 0.7% with EES versus 0.8% with PES from 1,302 DES patients, 892 with EES, and 410 with PES, again depending on definition used.³⁴

The overriding concern with stent thrombosis for both BMS and DES in the first year relates to interruption of or nonresponsiveness to dual-antiplatelet therapy,^{35,36} with stent thrombosis rates in the first 6 months after implantation as high as 11.1% in the presence of dual nonresponsiveness to both aspirin and clopido-

grel. Such dual resistance was observed in 6% of 746 PCI patients in a recent report.³⁶ Conversely, stent thrombosis in the first year in 12,844 PCI stent patients with acute coronary syndromes in the TRITON-TIMI 38 study was reduced from 2.4% to 1.1% with the use of prasugrel, which has less measurable platelet nonresponsiveness, although this benefit was observed at the cost of some increase in bleeding.⁹

Although these absolute event rates are fairly low compared to the 6% to 8% abrupt closure rates seen in the angioplasty era, the catastrophic nature of stent thrombosis is uniformly reported, with even higher MI and death rates likely in later events that occur outside of the hospital. STEMI rates of 45% to 80% of stent thrombosis cases, with mortality rates reported from 15% to 45%, provide clear cause for concern.^{35,37-39} Furthermore, as permanent coronary implants, with more than 10 million patients already treated with DES and an additional 750,000 treated annually, an ongoing linear hazard of 0.5% to 0.6% per annum out to at least 3 to 4 years³⁸ (Figure 1) would account for approximately 50,000 STEMIs and deaths each year. This is a significant public health issue regarding the safety of patients treated with PCI.

The late trajectory for stent thrombosis events has generated the most attention to potential differences between BMS and DES. In the Basel cost-effectiveness registry (Basel Stent Kosten Effektivitats [BASKET]), late follow-up in 499 DES and 244 BMS patients who were MACE free at 6 months described a 4.9% death and MI rate with DES versus 1.3% with BMS, with many caveats to this analysis.⁴⁰ Although questions remain, multiple independent registries and analyses reporting longer-term follow-up out to 3 to 4 years also suggests an ongoing linear hazard of stent thrombosis with DES in the range of approximately 0.4% to 0.6% per year.^{19,22,38,41-43} The challenging question has been, to what degree can either stent thrombosis rates or clinical outcomes be differentiated between BMS and DES through such reports and analyses?

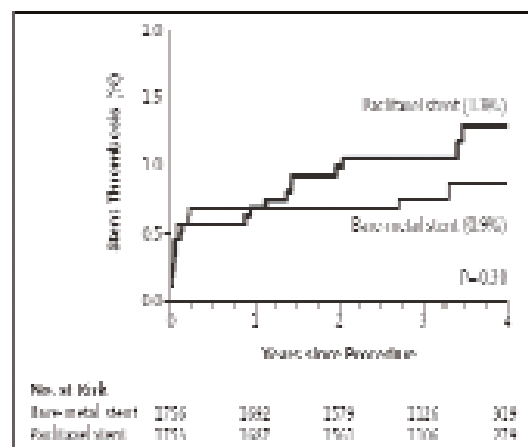
Spaulding et al⁴² analyzed 4-year outcomes in 1,748 patients from four studies of SES versus BMS, with stent thrombosis rates of 3.6% in 878 SES versus 3.3% in 870 BMS patients, whereas Kastrati et al⁴¹ expanded the analysis of these four trials in conjunction with 10 other SES/BMS reports and described an increasing trajectory of stent thrombosis in the SES group but only after the first year. Stone et al³² included the same four SES trials in a report also examining five studies randomizing patients to PES versus BMS. They concluded, like Kastrati, that while overall stent thrombosis rates were comparable, late thrombosis rates after year 1

were higher with both first-generation DES (SES and PES) platforms. Mauri and colleagues,⁴³ examining a similar array of randomized trials as Stone, compared different definitions for stent thrombosis (protocol definitions vs the Academic Research Consortium [ARC] definition),⁴⁴ finding that use of the ARC possible/probable late thrombosis definition raised the overall event rates reported but reduced any apparent difference between BMS and DES. In another meta-analysis of 38 trials randomizing either BMS versus DES or SES versus PES (including the previously mentioned analyzed studies), Stettler et al reported 4-year outcomes of 18,023 patients showing equivalent stent thrombosis rates, although MI rates were varied in BMS versus SES and SES versus PES comparisons.¹⁹

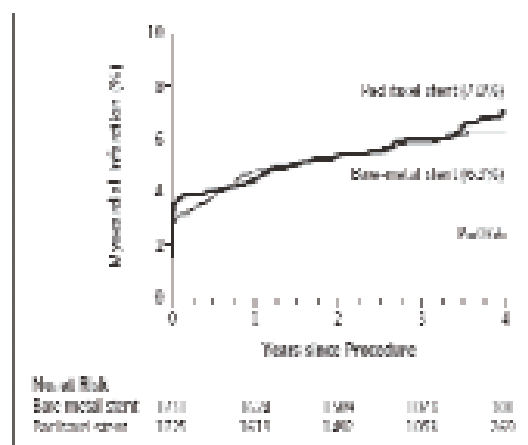
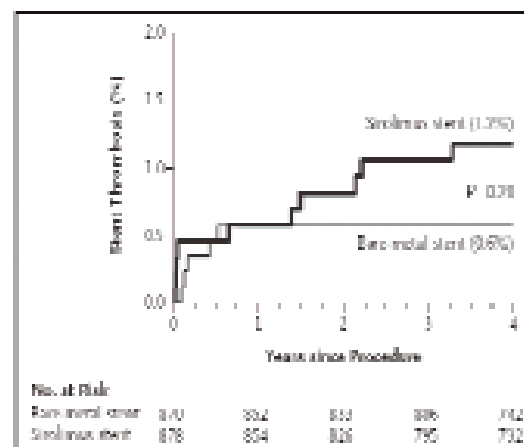
Other large registry reports add information but not necessarily clarity. In 2007, Laegerquist et al²⁵ published up to 3-year follow-up data from the Swedish national SCAAR (Swedish Coronary Angiography and Angioplasty Registry) on 19,771 patients treated with PCI in 2003 and 2004, including 6,033 patients with DES and 13,738 with BMS. As reported, possible benefit with DES early on was lost in a landmark analysis from 6 months to 3 years, in both unadjusted and propensity-adjusted cohorts, with adjusted 3-year mortality relative risk with DES of 1.32 (95% CI, 1.11–1.57). Significant heterogeneity of results in restenosis rates and clinical event rates have been described across specific brands of BMS, as well as across specific DES, within the registry itself, suggesting that a “class effect” assumption across BMS or across DES per se may be misleading, and/or that operators may intuitively select different brand name stent products for different kinds of patients or lesions. Furthermore, in an initial report from the SCAAR group, with the addition of patients treated through to 2005 (totaling 35,262 from 2003 to 2005), the overall results change, and the incidence of death and of death and MI were similar between DES and BMS up to 4 years of follow-up.⁴⁵

Two additional large registries are notable. The Western Denmark registry⁴⁶ of 12,305 patients and the Ontario provincial registry⁴⁷ of 13,353 patients both suggest early beneficial trends with DES that persist relative to BMS out to about 2 years.

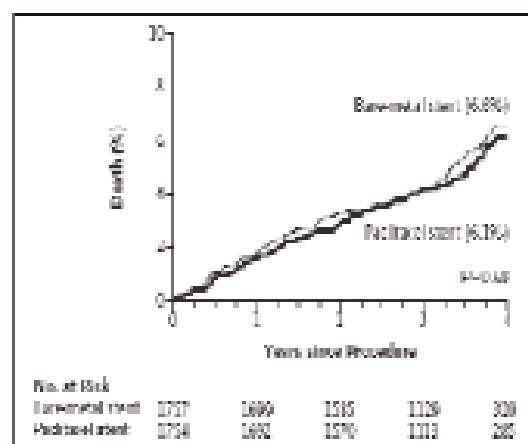
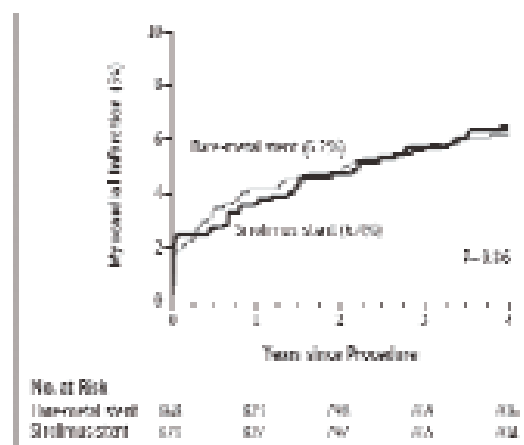
Thus, almost paradoxically, while meta-analyses of randomized data and several large longitudinal registries suggest an ongoing linear, and apparently, increased absolute stent thrombosis rate of 0.1% to 0.2% with DES over BMS from 1 year to at least 4 years after PCI,⁴⁸ the clinical outcomes of cardiac death and MI observed appear to be equivalent or even slightly favorable to DES patients (Figure 2). Although in part



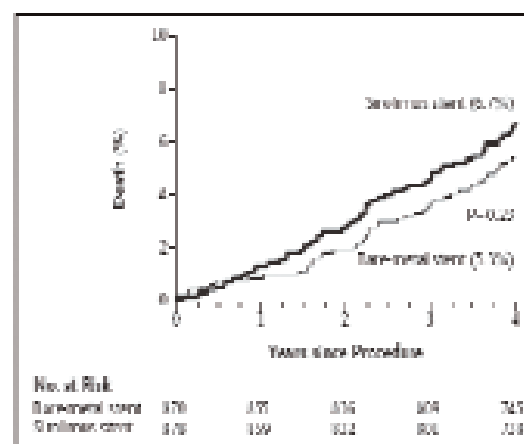
A



B



C



PES vs BMS

SES vs BMS

Figure 2. Four-year follow-up stent thrombosis rates in pooled patient cohorts randomized of PES versus BMS and SES versus BMS for stent thrombosis (A), MI (B), and death (C). (Adapted and reprinted with permission from Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356:998-1008.³²)

this paradox might be explained by adverse outcomes stemming from higher revascularization rates seen with BMS,⁴⁹ or by the fact that some trial reports censored patients with repeat revascularization from late stent thrombosis calculations, there is still no clear explanation for, or even certainty about, whether this pattern of early benefit/late hazard with DES versus BMS is universal to platforms, patients, or physician practice patterns.⁵⁰ This is but one of many critical areas that present confounding issues to retrospective recalculations and adjustments of existing data sets, and it should be considered imperative that greater clarity on these points is developed in work going forward.

ISSUES IN BMS AND DES COMPARISONS ACROSS THE LITERATURE

Mechanistic Versus Outcome Concerns

Stent thrombosis is so frequently clinically catastrophic that, in many overviews, the difference between mechanistic concerns with a device and the clinical well-being of a patient is blurred. As follow-up tracks PCI patients out toward 5 years and beyond, the natural history of the disease and the behavior of a stented coronary site may become more difficult to discriminate from one another because both are capable of producing STEMI and death. Diligence with regard to the specificity of definition of stent thrombosis per se is critical, and has been a criticism of the ARC “possible” stent thrombosis⁴⁴ (eg, all patients treated with a DES will ultimately die of “possible” stent thrombosis). On the other hand, equivalent rates of death and MI between BMS and DES—as most large reports reassuringly suggest is the case, with markedly lower restenosis using DES—do not necessarily represent the same mechanistic behavior over time. Large longitudinal analyses showing early benefit and late hazard temporal patterns suggest that equivalent long-term outcomes from BMS and DES are achieved through different mechanisms of device safety and performance. BMS clearly have higher repeat revascularization rates, which bring periprocedural complications and may create substrates for later complications as well. With lower restenosis rates, mechanistic insight into how and why DES “catch up” late to yield numerically similar overall outcomes is an area to be explored, not overlooked with oversimplified statements that “safety is similar” between BMS and DES.

DES platforms have novel components not seen with BMS, including the drug eluted and polymer used to load the drug. Although obviously successful in reducing fibrocellular proliferation, associated local inflammation and drug toxicity have been implicated in endothelial nonhealing and metabolic abnormalities as mechanistic features unique to DES that may be exacerbated in settings such as overlapping stents.⁵¹⁻⁵³

In addition to better understanding of DES versus BMS comparisons, attention to the mechanism and timing of events is critical to DES versus new DES comparisons as a means of understanding not only how well patients do but the role of the stent design in influencing both short- and long-term outcomes. The ARC definitions of time periods for early, late, and very late stent thrombosis were developed specifically to address the likelihood that thrombotic events in these different time periods are likely to occur through importantly different mechanisms.⁴⁴

Finally, patients and the cardiology community are not well prepared to deal with equipoise in clinical outcomes with permanent coronary implants, with which restenosis, stent thrombosis, STEMI, and death are actually a spectrum of outcomes varying in incidence and severity, not a dichotomy of efficacy and safety endpoints. “How many rehospitalizations and repeat revascularizations is worth one life?” is not a question the public, the media, and the scientific and regulatory community are comfortable answering, even though all experts, including the FDA, know well that no medical device in cardiology can ever be perfectly safe.²⁹

MIXING INFORMATION FROM RANDOMIZED STUDIES AND REGISTRIES AND RELATED STATISTICAL ISSUES IN BMS VERSUS DES EVALUATION

Randomized studies provide the most robust head-to-head comparisons, but randomized trials often use restrictive enrollment criteria and, due to logistical challenges in randomized device studies (such as the need for QCA core laboratories, IVUS core laboratories, and more intense and expensive on-site quality control and procedural consents), study cohorts are relatively small in size. Stent thrombosis, particularly stent thrombosis beyond 1 year, is a very rare endpoint and very difficult to evaluate in small trials, even with long follow-up periods. Meta-analytic pooling of randomized trials may help with population size issues but still may not predict device safety in more complex “real-world” populations and beg other questions of clinical and statistical assumptions on poolability. Furthermore, if studies have prospectively used different definitions for stent thrombosis, even independent adjudication of events using a consensus definition (as has widely been done in applying the ARC definitions) to make them more poolable still represents a retrospective ad hoc statistical methodology with potentially suspect reliability, as shown in the Mauri meta-analyses.⁴³

Registries can be quite large, and “all-comers” post-market, national, and regional/state registries can better capture real-world practice. Registries, however, often suffer quality control issues, may be too large to affordably employ core laboratories, and so again present interpretability issues, especially for ad hoc queries. Furthermore, registries capture the practice of medicine, including any intrinsic bias in that practice in deciding what brand of stent to use in individual PCI cases. Statistical adjustments of registry populations comparing BMS to DES outcomes can only be driven by data fields captured in the registry, such as age, gender, clinical presentation, and so forth. More intuitive bias based on likelihood of compliance with dual-antiplatelet therapy, personal experience of the operator with a stent platform, or subtle aspects of anatomy not captured in case report forms cannot be statistically adjusted, making registry-based comparisons among real-world patients still hazardous to supporting robust real-world stent safety and performance conclusions.

The subtle bias of device selection in clinical practice also affects the presumptions of a “class effect” across DES platforms or, for that matter, across BMS platforms. Where it is conceivable that first-generation durable polymer DES (SES or PES) might have similar rates of very late stent thrombosis, in nonrandomized registries individual operators may tend to select one in side branch settings, or in longer lesions, based on their own personal experience, with the potential to create apparent differences in data sets where such bias may not be definable—a dilemma for instance with differences among brand name platforms noted by the SCAAR group.

Compounding these concerns is the important desire to progress in the understanding of relative risk/benefits in the use of DES versus BMS in key patient subgroups, such as for small vessel, bifurcations, or long lesion anatomy, or in high-risk groups such as the elderly, STEMI intervention, left main disease, degenerated vein grafts, diabetics, and patients with low ejection fraction or renal failure. In all of these groups, the early outcomes from 30 days through 1 year remain fairly straightforward to define and exciting to consider. However, reliably tracking and interpreting late catastrophic complication rates in any one of these groups are greatly limited by the rarity of the events themselves.

DUAL-ANTIPLATELET THERAPY

From animal and necropsy findings, the end-common pathway of stent thrombosis triggers off the exposed and inflammatory prosthetic material of a slowly or non-healing stent site. In the most stimulated, early postimplantation phase, medical platelet inhibition plays an

unequivocal role in promoting the safety of patients during and after PCI. But for how long after presents another dimension of the stent thrombosis conundrum: when it is challenging to evaluate rare, late safety events in device comparisons, how do we factor in such an obligatory drug-device safety relationship that may, or may not, wane over time? Dual-antiplatelet therapy for 1 year has been shown beneficial to clinical outcome in patients presenting with ACS, with some increased risk of bleeding,^{9,54} and possibly more beneficial to patients with DES than BMS.⁶ Currently, the FDA has endorsed the recommendations of US professional societies to continue clopidogrel for at least 1 year in patients who tolerate the drug after DES in “on-label” or simple lesions.⁵⁵ Whether a longer course or a more potent thienopyridine would have more benefit than risk, in whom, and with which DES platforms constitute a true challenge to clinical science to define in future studies.

GOING FORWARD WITH DES, PCI, AND THE ISSUES OF STENT THROMBOSIS

In summary, three things are clear: (1) efforts to learn more or gain certainty about DES and BMS thrombosis from existing data have been extensively addressed and yielded confusing results; (2) the emergence of new, hopefully better and safer second-generation DES platforms will generally not be assessed in superiority study comparisons to BMS, but in equivalence studies to “active control” first-generation DES,²⁹ as exemplified by the recently FDA-approved ZES and EES programs;^{33,34} and (3) to support and continue innovation in percutaneous revascularization, new research paradigms will be necessary. For medical devices used as widely as DES, with obligate safety dependence on medical therapy to inhibit platelets, such programs will face many challenges. To succeed, novel approaches will need to be developed to bridge pre- and postmarket research infrastructure, drug and device industry, regulatory and research culture, and international collaborations on an ongoing basis.^{29,56} For both randomized trials and nonrandomized registries, prospective designs and integrated research and analysis plans using common definitions will provide far more fertile and efficient growth of knowledge going forward than can be obtained by revisiting previous work. ■

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