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As Time Goes By

Current Status and Future Directions in the Controversy Over Stenting

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Drug-eluting stents (DES) have dramatically transformed the landscape of interventional cardiology largely on the basis of empirical evidence showing profound reduction in angiographic and clinical restenosis without any significant increase in adverse events. Recent data, however, raise questions regarding the increased risk of late stent thrombosis associated with DES in more complex lesions and higher-risk patients than those evaluated in the initial clinical trials or Food and Drug Administration-approved indications, the challenge of continuing long-term antiplatelet therapy, and the danger of early discontinuation of antiplatelet therapy. We herein review the current status of this controversy, describe the additional evidence needed for its resolution, and offer recommendations for regulatory reform and 3 specific recommendations to encourage evidence-based patient management: 1) an emphasis on medical therapies with proven long-term benefit; 2) the use of kinetic modeling to estimate long-term outcomes of therapies based on the available near-term data; and 3) the restructuring of reimbursement incentives to encourage the use of evidence-based clinical management strategies. (J Am Coll Cardiol 2007;50:128–37) © 2007 by the American College of Cardiology Foundation

It's still the same old story
A fight for love and glory
A case of do or die. . .
The fundamental things apply
As time goes by. . .

Herman Hupfeld (1)

Drug-eluting stents (DES) have dramatically transformed the landscape of interventional cardiology largely on the basis of empirical evidence showing profound reduction in angiographic and clinical restenosis without any significant increase in adverse events. The justification for the enormous surfeit of DES use (totaling nearly 6 million patients globally to date at a cost of $4 to $5 billion annually) is founded on the notion that restenosis—although not a major impediment on survival—importantly impacts on quality-of-life and the need for repeat revascularization.

Restenosis

It has been argued that the clinical benefits of DES relative to restenosis and target vessel revascularization (TVR) have been overestimated in clinical trials compared with clinical practice (2–4). This might be a consequence of several factors: 1) the use of thick-strut stents in the former versus thin-strut stents in the latter; 2) protocol-driven angiography mandated in the former, which inflates restenosis rates by about 2-fold; and 3) attenuation of restenosis benefit in high-risk patients (diabetes, acute coronary syndromes, and renal failure) and complex lesions (multivessel disease, arterial bifurcations, left main disease, chronic total occlusions, and vein grafts) that were not evaluated in the pivotal clinical trials but represent >60% of patients undergoing stenting in clinical practice (2) (Table 1). As a result, substantial uncertainties remain regarding the safety and effectiveness of DES in these "real-world" settings:

- What is the clinical relevance of angiographic "late loss"?
- What is the impact on frequency or severity of angina, myocardial ischemia, myocardial infarction (MI), death, or quality-of-life (not objectively assessed in any trial)?
- What about late complications such as "aneurysms"?

Stent Thrombosis

Unlike restenosis, stent thrombosis is a rare but potentially life-threatening complication of coronary stents. In clinical trials, the cumulative incidence of stent thrombosis with DES at 9 to 12 months has ranged from 0.5% to 0.7%, roughly comparable to the incidence with bare-metal stent (BMS) (2,5,6). By contrast, the rate in registries more representative of clinical practice has been reported to be 2- to 3-fold higher (7–10). In addition, a key difference is that the temporal pattern with thrombotic events was not infrequently observed beyond 12 months (so-called "very late thrombosis") with DES but not with BMS (11). Very late stent thrombosis has been reported to occur at a rate of

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0.2%/year in clinical trials (12) and 0.6%/year with broader use of DES in clinical practice (13). Although rare, stent thrombosis can result in death in almost one-third to one-half of cases (7,8,10,14–17) (Table 2). Although several patient-, lesion-, and procedure-related predictors have been identified, the strongest independent predictor of stent thrombosis seems to be premature discontinuation of dual antiplatelet therapy (7,8) (Table 3).

Growing concerns about late thrombosis with DES have motivated an ad hoc change in clinical practice to continue dual antiplatelet therapy well beyond the 3 to 6 months recommended by treatment guidelines (although extension to 1 year in patients at low bleeding risk is considered optional [18]). However, the results of the PREMIER registry, in which nearly 1 in 7 patients discontinued treatment within 30 days of DES (these patients experiencing a 9-fold higher risk of an adverse event), underscore the challenge of adherence with such a strategy (19). Moreover, the long-term use of dual antiplatelet therapy is associated with an inherent risk of bleeding (20). These observations highlight several questions that warrant further study:

What is the magnitude and time-course of stent thrombosis in "real-world" clinical practice?

What are the mechanisms for its genesis?

What are the clinical and pathophysiologic predictors of risk?

What are safe and effective ways to mitigate or ameliorate this risk?

Table 1 Indications for DES Use

1. "On-label" or FDA-approved use
CYPHER Sirolimus-eluting Coronary Stent (5)
For improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions in native coronary arteries
• ≤30 mm in length
• 2.5–3.5 mm in diameter
• 50%–99% stenosis
TAXUS Express 2 Paclitaxel-Eluting Coronary Stent System (6)
For improving luminal diameter for the treatment of de novo lesions in native coronary arteries
• ≤28 mm in length
• 2.5–3.75 mm in diameter
• 50%–99% stenosis
2. "Off-label" or beyond FDA-approved use
Lesion subsets
• Multivessel disease
• Left main disease
• Bifurcation lesions
• Chronic total occlusions (CTO)
• In-stent restenosis (ISR)
• Small vessels (<2.5 mm in diameter) or large vessels (>3.75 mm in diameter)
• Long lesions requiring multiple or overlapping stents
• Saphenous vein grafts (SVG)
• Thrombus containing lesions (acute MI)
High-risk patient subsets
• Diabetics
• Renal dysfunction

DES = drug-eluting stent; FDA = Food and Drug Administration; MI = myocardial infarction.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CAD = coronary artery disease
CI = confidence interval
CMS = Center for Medicare and Medicaid Services
DES = drug-eluting stent(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)

Clinical Outcomes (Death or MI)

Even though randomized trials have consistently shown reductions in restenosis with DES, none of these trials was adequately powered to reliably evaluate relatively infrequent but clinically relevant end points such as death or MI. Key findings from long-term follow-up of major DES trials were presented recently at 2 key meetings, and these are summarized in Table 4.

European Society of Cardiology/ World Congress of Cardiology (September 2006)

The current firestorm regarding DES was ignited by the findings of 2 group-level meta-analyses first reported at the European Society of Cardiology (ESC)/World Congress of Cardiology (WCC) meeting in Barcelona in September 2006. In the meta-analysis reported by Camenzind et al. (21), significantly increased rates of death or Q-wave MI, presumably due to stent thrombosis, was reported at maximum follow-up with sirolimus-eluting stents (SES) (risk ratio 1.60; 95% confidence interval [CI] 1.06 to 2.43) but not with paclitaxel-eluting stents (PES) (risk ratio 1.15; 95% CI, 0.79 to 1.69). In a separate meta-analysis of 4 randomized trials, treatment with SES was not associated with a difference in total or cardiac mortality at 3 years, but noncardiac mortality was significantly increased compared with BMS (odds ratio 2.04; 95% CI 1.00 to 4.15) (22). Although this finding remains largely unexplained, interpretations range from a potential (but unlikely) direct systemic effect of the small amounts of drug or polymer leaching from the stent to a subtle influence of redefinition and readjudication processes across complex data sets, a restrictive definition of stent thrombosis requiring confirmation on angiography (for which the patient has to be alive) or autopsy (very low prevalence), an uncontrolled confounder, or simply a play of chance (23). Similar patterns were reported with long-term follow-up of SIRIUS (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions), RAVEL (Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent) (24), and BASKET (Basel Stent Kosten Effektivitäts Trial) (10) (Table 4). Even though the differences in death or MI were not statistically significant in any of the individual trials (likely owing to inadequate power), the number needed to

Table 2 Clinical Importance of Stent Thrombosis

Study	Stent Type	Confirmation of Stent Thrombosis	Duration	Death	Death or MI
Cutlip et al., 2001 (14) (n = 6,186)	BMS	Angiogram or clinical	6 months	21%	70%
Heller et al., 2001 (15) (n = 1,855)	BMS	Angiogram plus acute MI	9 months	17%	100%
Iakovou et al., 2005 (7) (n = 2,229)	DES	Angiogram or clinical	9 months	45%	93%
Ong et al., 2005 (16) (n = 2,016)	DES	Angiogram plus clinical	1 month	25%	100%
Kuchulakanti et al., 2006 (8) (n = 2,974)	DES	Angiogram	6 months	31%	72%*
BASKET-LATE, 2006 (10) (n = 746)	DES	Angiogram plus clinical	18 months	19%†	88%†
Mauri et al., 2007 (17) (n = 4,545)	DES	Angiogram plus clinical	4 yrs	31%	84%*

*Only MI rates reported; †cardiac death.
BMS = bare-metal stent; DES = drug-eluting stent.

harm (NNH) with DES ranged from 12 to 111, and the probability of any harm (ranging from 69% to 96%) exceeded the probability of any benefit (ranging from 4% to 31%) (Table 4) (25). Although these preliminary estimates had not yet been subjected to peer review, they nevertheless sounded a disquieting alarm, leading to the "demonization" of DES by the lay media and prompting the U.S. Food and Drug Administration (FDA) to convene a panel of experts to weigh the risk and benefits of these devices.

The FDA Circulatory System Devices Expert Panel (December 2006)

An open panel meeting of the FDA's Circulatory System Devices Expert Panel was held in Gaithersburg, Maryland on December 7 and 8, 2006. Data from a variety of randomized controlled trials and registries presented to the panel offered conflicting information about the benefit:risk ratio with DES. On the basis of these findings, the FDA panel summarized its views regarding so-called "on-label" use of these devices for approved indications derived from the pivotal clinical trials and for more widespread "off-label" use (Table 1) (26).

"On-label" use. Both approved DES are associated with a small increase in stent thrombosis compared with BMS that emerges 1 year after stent implantation. However, on the basis of the data available, this increased risk of stent thrombosis was not associated with an increased risk of death or MI compared with BMS.

The concerns about thrombosis do not outweigh the benefits of DES compared with BMS when DES are implanted within the limits of their approved indications for use.

Larger and longer premarket clinical trials and longer follow-up for post-approval studies are needed, with uniform definitions of stent thrombosis and close attention paid to patient compliance with antiplatelet therapy.

"Off-label" use. Off-label use of DES is associated with an increased risk of stent thrombosis, death, or MI compared with on-label use.

The available data were insufficient to determine whether the increased risk in adverse events with off-label use was the same or different between the 2 currently approved DES.

Data on off-label use are limited, and additional studies are needed to determine optimal treatments for more complex patients. Until more data are available, the DES labels should state that when DES are used off-label, patient outcomes might not be the same as the results observed in the clinical trials conducted to support marketing approval.

Duration of antiplatelet therapy. Data from several studies suggest that a longer duration of antiplatelet therapy than is currently included in the DES labeling might be beneficial.

The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown, and DES thrombosis might still occur despite continued therapy.

The labeling for both approved DES should include reference to the 2005 American College of Cardiology (ACC)/American Heart Association (AHA)/Society of Cardiovascular Angiography and Interventions (SCAI) percutaneous coronary intervention (PCI) Practice Guidelines (27), which recommend that patients receive aspirin indefinitely plus a minimum of 3 months (for SES) or 6 months (for PES) of clopidogrel, with therapy extended to 12 months in patients at a low risk of bleeding.

The detailed data presented at the FDA meeting supporting these key judgments were recently published en

Table 3 Premature Discontinuation of Clopidogrel Therapy and Risk of Stent Thrombosis With DES

	Premature Discontinuation			
Study	Yes	No	RR (95% CI)	PAR
Iakovou et al., 2005 (7)	5/17 (29%)	24/2,212 (1.0%)	27 (12, 63)	17%
Kuchulakanti et al., 2006 (8)	14/310 (4.5%)	24/2,658 (0.9%)	5 (3, 10)	29%

PAR = Pr × [(RR − 1)/Pr × (RR − 1) + 1].
CI = confidence interval; DES = drug-eluting stent; PAR = population attributable risk; Pr = prevalence of clopidogrel discontinuation; RR = relative risk.

Table 4 Long-Term Follow-Up of "On-Label" Use of DES (Randomized Clinical Trials)

Trial	End Point	Follow-Up	Incidence (%) DES	Incidence (%) BMS	p Value	NNH (NNT)*	Probability Benefit	Probability Harm
ESC/WCC, September 2006								
Camenzind et al. (21) meta-analysis								
SES vs. BMS (n = 1,748) (4 trials)	Death or Q-wave MI	Last F/U (>3 yrs)	6.3	3.9	0.03	42	1%	99%
PES vs. BMS (n = 3,364) (5 trials)	Death or Q-wave MI	Last F/U (>3 yrs)	3.3	2.8	0.46	227	23%	77%
Nordmann et al. (22) meta-analysis (4 trials)								
SES vs. BMS (n = 1,748)	Death	3 yrs	4.7	3.1	0.09	66	4%	96%
SES vs. BMS (n = 1,748)	Noncardiac death	3 yrs	3.2	1.6	0.04	66	2%	98%
SIRIUS (SES vs. BMS)	Death	4 yrs	6.0	4.6	0.30	71	15%	85%
	Death or MI	4 yrs	8.4	6.7	0.27	58	13%	87%
RAVEL (SES vs. BMS)	Death	5 yrs	12.1	7.1	0.26	20	13%	87%
	Death or MI	5 yrs	18.9	10.5	0.09	12	4%	96%
BASKET (SES or PES vs. BMS)	Death or MI	18 mo	8.4	7.5	0.63	111	31%	69%
FDA panel, December 2006								
Stone et al. (12) meta-analysis								
SES vs. BMS (n = 1,748) (4 trials)	Death	4 yrs	6.7	5.3	0.23	71	11%	89%
	Death or Q-wave MI	4 yrs	8.2	6.4	0.14	56	7%	93%
	ST	Day 0 to 4 yrs	1.2	0.6	0.20	167	10%	90%
	Late ST	1–4 yrs	0.6	0.0	0.025	167	1%	99%
PES vs. BMS (n = 3,513) (5 trials)	Death	4 yrs	6.1	6.6	0.68	(200)	66%	34%
	Death or Q-wave MI	4 yrs	7.3	7.5	0.93	(500)	54%	46%
	ST	Day 0 to 4 yrs	1.3	0.9	0.30	250	15%	85%
	Late ST	1–4 yrs	0.7	0.2	0.028	200	1%	99%
Kastrati et al. (28) meta-analysis								
SES vs. BMS (n = 4,958) (14 trials)	Death	1–5 yrs	5.9	5.9	0.80	1,428	40%	60%
	Death or MI	1–5 yrs	9.7	10.2	0.76	(200)	62%	38%
	ST	Day 0 to 1–5 yrs	1.4	1.2	0.75	500	37%	63%
	Late ST	1–5 yrs	0.6	0.1	0.02	182	1%	99%

*Numbers needed to treat for benefit are shown in parentheses (NNT or NNH values ranging from 30 to 80 are deemed clinically important).

ESC/WCC = European Society of Cardiology/World Congress of Cardiology; F/U = follow up; NNH = numbers needed to harm; NNT = numbers need to treat; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; ST = stent thromboses; other abbreviations as in Tables 1 and 2.

masse online as a series of articles in the *New England Journal of Medicine* (12,17,28–30). A close scrutiny of these data offer critical insights and raise additional important questions.

"ON-LABEL" USE. In contrast to the group-level meta-analyses presented by Camenzind et al. (21) and Nordmann et al. (22) at the ESC/WCC meeting, the results of 3 meta-analyses presented at the FDA meeting were both based on individual patient-level data. Examination of the meta-analysis by Stone et al. (12) suggested a nonsignificant increase in the cumulative 4-year risk of death or Q-wave MI with the SES compared with BMS (hazard ratio 1.30, 95% CI 0.91 to 1.86). In contrast, no excess in death or Q-wave MI was reported for PES (12). The meta-analysis by Kastrati et al. (28) included 14 trials (both pivotal and post-marketing trials) and reported virtually no difference with respect to mortality (hazard ratio 1.03, 95% CI 0.82 to 1.30) and death or MI (hazard ratio 0.97, 95% CI 0.81 to 1.16) with SES compared with BMS. Overall, with respect to death or MI, the probability of any benefit exceeded probability of any harm with PES and with SES in the meta-analysis by Kastrati et al. (28) but not in the meta-analysis by Stone et al. (12) (Table 4). Another pooled analysis of data from the 4 pivotal SES trials reported that although overall survival and event rates were not significantly different at 4 years, among diabetic patients (25% of total population), use of SES was associated with increased occurrence of very late stent thrombosis and almost a tripling of mortality (hazard ratio 2.9; 95% CI 1.38 to 6.10; p = 0.008) (29).

With respect to stent thrombosis, the cumulative incidence of stent thrombosis was numerically greater but not statistically significant with both types of DES (12,28,29). Of note, the incidence of very late stent thrombosis (>1 year) was significantly greater with both DES compared with BMS. However, despite this increase in stent thrombosis, risk of death or MI was not significantly increased with either DES. A likely explanation might be related to insufficient pooled sample size resulting in a β (false-negative) error of about 60% to 70%. An adequately powered study would require a sample size >10,000 patients to permit detection of differences in risk (29).

In an attempt to establish the precise incidence of stent thrombosis, a new standardized hierarchical definition proposed by Academic Research Consortium (ARC)—a roundtable of investigators, industry representatives, and

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regulators—was applied retrospectively to the DES trials (17). Stent thrombosis was classified as definite (angiographic or pathologic confirmation of acute thrombosis in acute coronary syndromes), probable (any unexplained death within 30 days or as target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion), or possible (any unexplained death after 30 days) by the ARC definition (17).

There are several potential limitations of the ARC definitions for stent thrombosis: 1) they are derived primarily from the results on the basis of clinical trials with little or no insights into the risk of stent thrombosis in "real world" patients; 2) the inclusion of any unexplained death within 30 days as probable stent thrombosis might be biased in favor of DES, owing to a higher frequency of late thrombosis (>30 days) compared with BMS; 3) the inclusion of all unexplained deaths beyond 30 days as possible stent thromboses might be overly inclusive, because a number of factors other than stent thrombosis (including natural history events) might result in an unexplained death, thus diluting out true stent thrombosis signal; 4) in contrast to the original protocol-defined criterion, events occurring after intervening target lesion revascularization (TLR) (secondary thrombosis) are not censored in the ARC definitions, thereby introducing confounding due to treatment-related complications (for example, brachytherapy used to treat restenosis is known to predispose to late stent thrombosis); 5) the ARC definitions have not been vetted by the professional societies, such as the AHA, ACC, and SCAI; and 6) the ARC definitions require prospective evaluation and validation in ongoing trials.

The results of post hoc re-adjudication of the ARC definitions (on the basis of "definite" or "probable" thrombosis) to pooled data from the pivotal SES trials are shown in Figures 1A and 1B. Three key observations are worth noting. First, the majority of death (88% SES [50 of 57] and 78% BMS [35 of 45]) and death or MI (83% SES [83 of 100] and 68% BMS [61 of 89]) were not attributable to TLR or stent thrombosis, suggesting other potential causes such as progression of disease in non-culprit lesions or incomplete capture of etiology due to lack of angiographic or autopsy confirmation in all cases. This is consistent with the observation that stent thrombosis accounted for <8% of overall deaths (21 of 280) and <18% of all MIs (57 of 324) reported in the pivotal SES and PES trials (17). Second, death or MI rate associated with stent thrombosis is 100% (13 of 13 SES, 15 of 15 BMS) compared with about 6% with restenosis (4 of 67 SES, 13 of 202 BMS), thereby confirming the relatively "benign" nature of the latter compared with the former. Third, a nearly significant increase in the rate of death or MI unrelated to stent thrombosis or TLR (2.5% absolute risk difference) was observed with SES that was partially (<50%) offset by a reduction in adverse events associated with TLR (1.0% absolute risk difference) (Fig. 1B). This offset would have been substantially attenuated if events secondary to inter-

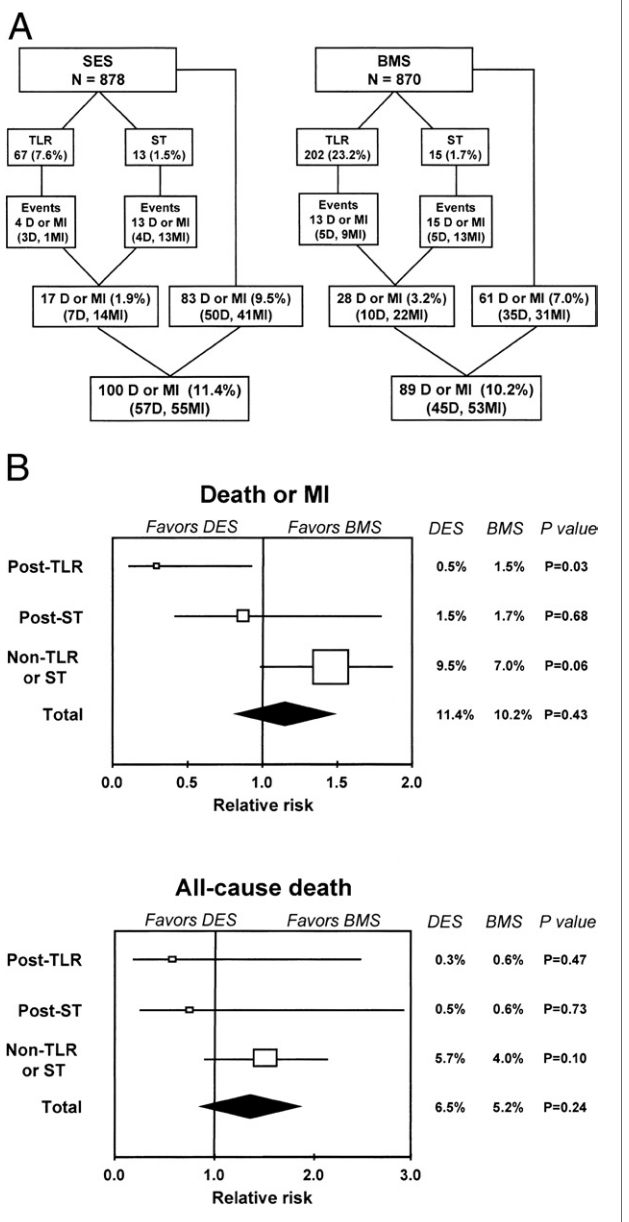

Figure 1 **Pooled Analysis of RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials**

(A) Data regarding clinically-driven target lesion revascularization (TLR), stent thrombosis (ST), based on definite or probable cases (as a reliable approximation of the true incidence of stent thrombosis) according to the Academic Research Consortium (ARC) definition and includes events post-TLR (secondary thrombosis), death (D) or myocardial infarction (MI) are shown for sirolimus-eluting stents (SES) and bare-metal stents (BMS). There were 3 additional cases of stent thrombosis in the SES and 10 in the BMS group resulting in a total of 13 versus 15 cases (compared to 10 vs. 5 cases using the protocol-defined criterion). Six out of the 10 additional thrombotic episodes in the BMS group occurred after intervening TLR (5 related to brachytherapy) compared to none in the SES group. There were a total of 100 death or MI events in the SES group (11.4%) compared to 89 in the BMS group (10.2%). **(B)** Attributable cause of death or myocardial infarction following stenting. Differences in the rates of all-cause death or myocardial infarction **(top panel)** and all-cause death **(bottom panel)** between SES (n = 878) and BMS (n = 870) attributable to clinically-driven target lesion revascularization (post-TLR), stent thrombosis (post-ST) based on definite or probable cases according to ARC definition, and other (non-ST or TLR). Data are shown as relative risk and 95% confidence intervals.

vening TLR (6 BMS vs. 0 SES) were not counted per protocol. Furthermore, the notion that reduced risk secondary to reduced restenosis might be offset by increased risk associated with late stent thrombosis (12) is not apparent from these data. It is also not clear whether the excess deaths with SES (57 vs. 45) were cardiac or noncardiac in origin. On the basis of these observations, several lingering questions remain:

- How and why do the results of individual patient-level meta-analysis differ from group-level meta-analysis (commonly reported in published literature and typically used for formulating treatment guidelines)?
- Why is there no significant increase in death or MI with DES despite increase in late stent thrombosis?
- What is the impact of censoring or counting events (death, MI, or stent thrombosis) related to intervening repeat revascularization?
- What is the impact of end point criterion on outcomes (Q-wave MI vs. non–Q-wave MI, procedural vs. non-procedural MI)?
- What is the mechanism of death (cardiac vs. noncardiac) or MI after stenting?
- What is the optimal measure of overall risk and benefit of stenting?
- What is the temporal relation between stent thrombosis, death, or MI and discontinuation of clopidogrel treatment?

"OFF-LABEL" USE. Information related to broader clinical use of DES is primarily derived from uncontrolled registries. Data from the 7,393-patient ARRIVE registry of "real-world" experience with the PES showed that at 2 years the major cardiac events in PES recipients with more complex lesions (including multiple stents) were higher than in PES recipients with simple lesions (death: 6.5 vs. 4.6%, $p = 0.08$; MI: 3.6 vs. 2.1%, $p < 0.0001$; stent thrombosis: 3.0 vs. 1.4%, $p < 0.0001$) (31). In addition, stent thrombosis rates through 12 months in selected complex patient or lesion subsets ranged from 2.9% (acute MI) to 6.3% (insulin-requiring diabetics) (31). Other registry data from SCAAR (the Swedish Coronary Angiography and Angioplasty Registry), suggested an overall 18% relative increase in adjusted mortality with DES (risk ratio 1.18, 95% CI 1.04 to 1.35) in nearly 20,000 patients (both "on-label" as well as "off-label") followed for 3 years (30). Of note, a 32% relative increase in mortality (presumably related to stent thrombosis) was observed between the time of cessation of clopidogrel treatment at 6 months and 3 years, corresponding to a yearly absolute increased risk of 0.5% with DES. A major limitation inherent in such nonrandomized comparisons is the confounding due to selection bias and imbalances in measured and unmeasured prognostic variables. Thus, larger randomized trials with longer follow-up that include a broad "real-world" population and that evaluate hard clinical outcomes of death or MI are warranted to inform clinical practice.

One observational study of 4,666 stent recipients followed for 24 months reported that clopidogrel use predicted the incidence of death and the composite of death or nonfatal MI for patients who received DES but not BMS (32). At 24 months, the absolute difference in death was 3.5% lower and the absolute difference in death or MI (presumably related to stent thrombosis) was 4.5% lower for those taking clopidogrel. On the basis of these findings, the Advisory Panel endorsed the ACC/AHA recommendation that treatment with aspirin and clopidogrel for up to 1 year (in patients not at high bleeding risk) might be warranted to mitigate the increased risk for late stent thrombosis (27). However, clopidogrel use was not randomized and the results might be confounded by imbalances in unmeasured prognostic factors, small sample size, self-reporting of clopidogrel use, lack of accounting for bleeding and cost, and the failure to directly assess the risk of stent thrombosis. Furthermore, registry data in 3,021 patients from Italy and Germany suggest that discontinuation of clopidogrel therapy was an independent predictor of thrombosis within the first 6 months but not beyond 6 months (9 of 16 cases of thrombosis after 6 months occurred while receiving clopidogrel therapy) (33). These findings, along with the observations that: 1) the majority (71% to 83%) of late stent thromboses are not attributable to clopidogrel nonadherence (Table 3), and 2) the wide window of thrombotic risk—the median time to late stent thrombosis of 55 days (8) to 16 to 18 months (11) after clopidogrel discontinuation—call into question the assertion that extending dual antiplatelet therapy to 12 months will mitigate or ameliorate the risk of stent thrombosis. Thus, the risk-benefit-cost profile of dual antiplatelet therapy is not clear enough to warrant definitive recommendations. Clearly, randomized clinical trials are warranted to confirm these observations and to clarify the remaining uncertainties.

The AHA/ACC/SCAI/American College of Surgeons (ACS)/American Dental Association (ADA) Science Advisory (January 2007)

After the FDA deliberations, a science advisory endorsed by 5 major professional societies was published in January 2007 (34). This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating the patient and healthcare providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year and, if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents. Although these recommendations are based on what can most charitably be described as "inconclusive" data, they nevertheless do seem to appropriately address the concerns of antiplatelet therapy. However, it could be argued that given our limited understanding of the exact mechanism and incidence of stent thrombosis, our

inability to accurately identify at-risk patients, and the lack of effective and safe therapies to mitigate this risk, the most prudent strategy to limit this rare but potentially life-threatening complication at the "current" time is a selective, thoughtful, and evidence-based use of DES—at least, until the next generation of stents that are more pro-healing and less or non-thrombogenic become available. Thus, providing guidance for optimal indications for DES in clinical practice should merit equal if not more important and urgent consideration. In this regard, it might be advisable that the medical professional societies should collaborate with the regulators, device sponsors, and reimbursing agencies on the development and implementation of new tools and programs that not only help mitigate unnecessary risk but also promulgate best practice standards. Otherwise, a potential consequence might be that the prolonged use of dual antiplatelet therapy might be used inappropriately to rationalize the overuse of DES (a "band-aid" solution). A number of other relevant questions remain unaddressed:

- What precedent(s) support the recommendation for "off-label" use of a drug (clopidogrel use in non-emergent PCI not being a labeled indication) to mitigate the adverse effects of similarly "off-label" use of a device?
- What is the definition of "elective" with respect to the recommendation that such procedures be deferred for 1 year after stenting, and who is responsible for making the determination (the patient, the cardiologist, or the surgeon)? Does (arguably elective) stenting for chronic stable angina trump (arguably non-elective) knee replacement in an orthopedically disabled patient or renal transplantation in one on dialysis?
- What are the medicolegal consequences of these recommendations?

The National Heart, Lung, and Blood Institute (NHLBI) Interventional Cardiology Working Group (January 2007)

On January 30, 2007, the NHLBI convened a panel of representatives from academia, industry, and the FDA to clarify its potential role in the debate over DES. The general sense of the group was that there was no need for a large, NHLBI-sponsored randomized clinical trial at the present time but that a number of more basic questions should be addressed such as:

- What are the frequency, time course, cause, clinical predictors, and long-term clinical consequences of restenosis and thrombosis, and can these dynamics be accurately modeled?
- What are the safety and efficacy of the various treatment alternatives (medical therapy and bypass surgery) in patients with chronic stable angina and acute coronary syndromes?
- What are the kinetics of drug release and vascular healing in atherosclerotic vessels compared with non-atherosclerotic vessels?
- What are the optimal type, dose, and duration of antiplatelet therapy?
- How should patients requiring premature termination of antiplatelet therapy for non-elective surgery be managed ("bridging" therapy)?

Where Do We Go From Here?

So far, all of this activity has done little more than clarify the extent of the debate. On the one hand, advocates of DES argue that the available data are sufficient to continue "business as usual" while supporting on-going trials and clinical registries to monitor long-term outcomes as the technology continues to mature. On the other hand, critics argue that the level of uncertainty is such that use of DES should be limited to "on-label" indications until sufficient evidence of long-term safety and efficacy are available to resolve the uncertainties. Although both views can be justified as prudent and responsible, it will take a long time for the practical and economic consequences to play out. Until then, we recommend a return to epigraphic "fundamentals" in the form of regulatory reforms summarized in Table 5 (35) and the following evidence-based proposals.

Proposal #1: Evidence-Based Medical Management

Evidence-based medical therapy is a rational alternative to stenting, at least in mild to moderate chronic stable angina and asymptomatic patients with coronary artery disease (CAD) and evidence of myocardial ischemia on functional assessment (comprising the majority of patients undergoing elective stenting). The theoretical basis for considering revascularization versus medical therapy in chronic stable CAD can be distilled into one simple motto—palliation versus protection. Although restoring flow via revascularization might be protective in acute CAD, evidence so far indicates that it is largely palliative in chronic CAD. A meta-analysis of 11 trials comparing PCI with or without stenting versus optimal medical therapy demonstrated no reduction in mortality, an increase in MI, and no increase in need for repeat revascularization with PCI (36). These observations were recently reinforced by the results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, which demonstrated that as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy. Although a small but statistically significant improvement in anginal relief was observed in favor of PCI at 1 and 3 years, the differences were no longer significant at 5 years of follow-up (37). However, DES were not routinely used in this study. In contrast, disease modifying therapy (life-style changes, aspirin, lipid-lowering,

Table 5 Recommended Reforms

1. Approval process
Larger and longer pre-approval randomized clinical trials
Broad spectrum of patients representative of clinical practice
Hard clinical endpoints of all cause death or Q-wave myocardial infarction
Adequately powered to address death or Q-wave myocardial infarction
Post-approval device registries with extended follow-up (>5–10 yrs) and greater and timely public access to data
2. Operational standards
Explicit standards of evidence
Robust trial design and statistical methodology
Emphasis on clinical importance ≫ statistical significance
Universal criteria adopted by principal stakeholders
Sponsors, investigators, regulators, reimbursers/payors, professional/technical societies, guideline committees
3. Administrative reforms
Comprehensive post-marketing surveillance
Accurate, user-friendly, point-of-care, easily trackable, electronic
Resultant labeling changes (if warranted)
Balancing private versus public interests
Encourage innovation without compromising public safety
Incentives to encourage compliance and education
Consistent public policy
"Off-label" use of drug (clopidogrel) to optimize "on-label" use of DES
4. Additional targets
Therapeutic reform
Emphasize medical therapy over revascularization strategy for stable CAD
Tort reform
Change the current standard of evidence from the "community" to "evidence-based, best clinical practice" standard
Fiscal reform
Reimbursement incentives to encourage optimal utilization
Full reimbursement for "on-label" use
Scaled-down reimbursement for "off-label" use
Reward evidence-based best clinical practice

Adapted from Kaul and Diamond (35).
CAD = coronary artery disease; other abbreviations as in Table 2.

beta-blockers, angiotensin-converting enzyme inhibition) is both palliative and protective for both acute and chronic CAD.

For avoidance of death or repeat revascularization, coronary artery bypass graft is a clear winner in some subsets (left main, multivessel disease with impaired left ventricular function). For ameliorating symptoms and improving quality of life (and perhaps avoidance of neurocognitive dysfunction), PCI (with or without stenting) might be preferable in patients with severe angina and documented ischemia. However, for improving survival and avoiding MIs without compromising quality of life, therapeutic life-style modification and optimal medical therapy might be the most desirable option overall. Thus, medical therapy is a rational and justifiable alternative to stenting unless there is a clear need for intervention (acute CAD). Even in these settings, no clear-cut advantage of DES over BMS is apparent from randomized clinical trials (38,39).

Proposal #2: Evidence-Based Kinetic Modeling of Outcomes

Once inserted, the stent cannot be removed (except through rather risky surgery). It is a life-long commitment on the part of the patient. Nevertheless, only relatively short-term data (1 to 5 years) are currently available on its safety and efficacy. In reviewing the available short-term data for purposes of regulatory approval, the FDA must ultimately make its judgments in the absence of direct long-term empirical evidence. Conventional wisdom, however, advises against extrapolation of short-term data beyond its immediate time horizon. As one does so, confidence intervals widen hyperbolically, thereby undermining the precision of such predictions. Clinical trials are not well suited to this task, because they are inefficient with respect to time and resource use. We therefore need alternative ways to make long-term predictions from near-term data for purposes of regulatory approval and clinical decision-making.

Kinetic models can serve this purpose (40,41). In contrast to a conventional statistical regression model, a kinetic model quantifies the time-dependent prevalence of alternative clinical states in terms of an inter-related network of state-to-state transitions. The rate of each of these transitions is quantified empirically by a kinetic rate constant or transition probability. One such model describing the pathophysiology of atherosclerotic events in terms of the inter-relation among cellular inflammation, vascular stenosis, and clinical outcomes has recently been proposed (40), and an analogous model based on the putative inter-relation among post-stent restenosis, thrombosis, and clinical events (Fig. 2) can be constructed. Such a model can potentially help answer a number of specific questions posed by the NHLBI Working Group, such as the projected clinical importance of restenosis and thrombosis over 5 to 10 years of follow-up, the predicted effect of alternative antiplatelet

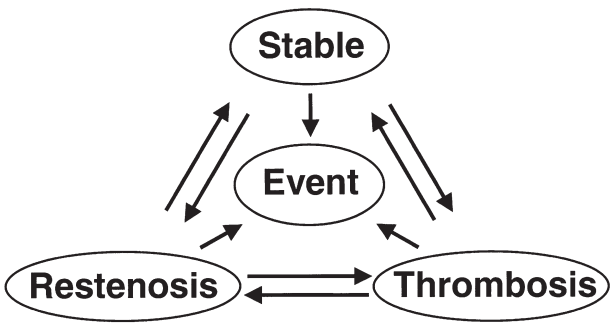

Figure 2 Schematic of a Kinetic Model of Restenosis, Thrombosis, and Adverse Events Post-Stenting

The **double arrows** indicate reversible state-to-state transitions and the **single arrows** indicate irreversible transitions. The rate of each transition can be quantified in terms of an empirical rate constant or transition probability (not illustrated). Such models can be used to predict the time-dependent prevalence of each state over relatively long periods of follow-up.

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strategies on these outcomes, and the design requirements of clinical trials to assess the accuracy of these predictions.

Proposal #3: Evidence-Based Reimbursement as the Driver of Quality

Currently, the Center for Medicare and Medicaid Services (CMS) pays for medical procedures deemed by it to be "reasonable and necessary." This determination is fundamentally different from that used by the FDA, through which drugs and devices are approved in terms of "safety and efficacy." As a result, a number of drugs and devices are (paradoxically) reimbursed by CMS without having proven "safety and efficacy"—the frequent off-label use of DES and clopidogrel being the most immediate examples.

It is generally acknowledged (even by the FDA) that physicians can legitimately employ approved drugs and devices in "off-label" ways. In fact, many consider such use to be guaranteed under the First Amendment and other legal precedents (42). But there is no similar guarantee that payers need to reimburse such "off-label" use at the same level of "on-label" use. Accordingly, CMS could rescale reimbursement schedules in proportion to the available evidence of clinical benefit (43), perhaps under the authority of the National Coverage Determination process (44). One simple way to begin could be to set reimbursement for "on-label" use at a higher level than that for "off-label" use—in line with the current emphasis on "pay-for-performance" (45).

Evidence-based reimbursement would thereby provide an incentive to physicians and industry alike to conduct the additional clinical trials documenting the benefit of such uses. On the basis of such new evidence, manufacturers could then petition the FDA for a new "on-label" indication—at which time CMS could rescale reimbursement accordingly. If the FDA and CMS require additional statutory authority to implement such reforms, that authority should be obtained through the passage of suitable Congressional legislation. Only by linking reimbursement directly to evidence of clinical benefit can we resolve current—and future—controversies such as that exemplified by DES.

At the very least, it should make for a stentorian shouting match!

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