

# Balancing Efficacy and Safety of Drug-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention

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Drug-eluting stents reduce the occurrence of in-stent restenosis and the need for subsequent target vessel revascularization compared with bare-metal stents. However, the safety of drug-eluting stents has been called into question because of an apparent increase in late stent thrombosis, a frequently fatal event. A substantial body of research has focused on determining the magnitude of these competing events, often reaching contradictory results even with analyses of the same data. Although larger, adequately powered, randomized trials are needed to fully assess the net clinical effects of drug-eluting stents compared with bare-metal stents, the evidence seems to suggest that the net clinical benefit of drug-eluting stents may outweigh their risks. The evidence is clearer that premature

discontinuation of antiplatelet therapy is an important trigger for stent thrombosis; therefore, patients who are candidates for implantation of drug-eluting stents should be screened for their ability to receive and tolerate uninterrupted antiplatelet therapy longer than is necessary with bare-metal stents. The evidence suggests that drug-eluting stents relieve obstructive coronary artery disease, provide durable mechanical results, and do more good than harm, but all patients also should be given antiplatelet and other optimal medical therapies to achieve the best outcomes.

*Ann Intern Med.* 2008;148:234-238.

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Few areas of medicine have evolved as rapidly as coronary artery revascularization procedures. Percutaneous coronary intervention, which began as an experimental procedure, is now performed in more than 1 million patients per year in the United States alone. Drug-eluting stents, which were developed to address the problem of in-stent restenosis with bare-metal stenting, are the most recent addition to the interventional armamentarium. After their approval by the U.S. Food and Drug Administration, drug-eluting stents were so rapidly assimilated that the devices were used in 80% to 90% of revascularization procedures in the United States in 2005. However, reports of an increased incidence of late stent thrombosis, defined as thrombosis occurring more than 30 days after implantation, have raised concerns about a safety tradeoff with this technology and have led to much public debate. We provide a perspective on the benefits and risks of drug-eluting stents, based on current clinical data.

## EFFICACY OF DRUG-ELUTING STENTS

### Mechanisms and Pivotal Clinical Trial Data

The principal mechanism of action of the 2 drug-eluting stents currently on the U.S. market is the controlled release (via a polymer carrier on the stent) of an antiproliferative or immunomodulatory compound that accumulates locally and inhibits the proliferative process responsible for restenosis. Initial first-in-man studies dem-

onstrated dramatic suppression of neointimal hyperplasia, and randomized clinical trials of drug-eluting stents (Table 1) eventually demonstrated 70% or greater reductions in the rate of target lesion revascularization compared with bare-metal stents, an effect that was consistently observed across all patient and lesion subgroups. However, the benefit of drug-eluting stents may have been overestimated because these trials involved routine angiographic follow-up and the use of “thick-strut” bare-metal stents in the bare-metal stent control groups (10).

### “Off-Label” Use of Drug-Eluting Stents

The pivotal clinical trials were for the most part restricted to low-risk patient and lesion subsets that are not completely representative of those seen in routine clinical practice. Specifically, the “on-label” indications for use of drug-eluting stents include only symptomatic patients with ischemic disease due to a single de novo lesion less than 30 mm in native coronary arteries, with a reference vessel diameter of 2.5 to 3.5 mm. Because the use of bare-metal stents in more complex lesion and patient subgroups is typically associated with higher rates of restenosis, many interventionalists have hypothesized that the efficacy of drug-eluting stents may be more pronounced in this population, with greater absolute reductions in repeated revascularization. Initial data from some of the pivotal randomized studies that included more complex lesion subsets have demonstrated this benefit (8). Additional studies are emerging about the use of drug-eluting stents for various “off-label” indications, including acute myocardial infarction (MI), chronic total occlusion, in-stent restenosis, diffuse disease, saphenous vein grafts, bifurcation lesions, and left main coronary artery stenting. In addition, several ongoing registries have provided “real-world” data that show favorable long-term outcomes and statistically significant reductions in major adverse cardiac events (11).

See also:

#### Web-Only

Appendix Tables

Conversion of graphics into slides

**Table 1. Clinical Events in Pivotal Trials of Sirolimus- and Paclitaxel-Eluting Stents\***

Study (Reference)	Target Lesion Revascularization†, %		Stent Thrombosis, %		Myocardial Infarction, %		Total Mortality, %		Major Adverse Cardiac Events, %	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
<b>Sirolimus-eluting stent trials</b>										
RAVEL (1)	0.0	22.9	0.0	0.0	3.3	4.2	1.7	1.7	5.8	28.8
SIRIUS (2)	4.1	16.6	0.4	0.8	2.8	3.2	0.9	0.6	7.1	18.9
Canadian SIRIUS (3)	4.0	18.0	2.0	2.0	2.0	4.0	0.0	0.0	4.0	18.0
European SIRIUS (4)	4.0	20.9	1.1	0.0	4.6	2.3	1.1	0.6	8.0	22.6
<b>Paclitaxel-eluting stent trials</b>										
TAXUS I (5)	0.0	10.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	10.0
TAXUS II (6)	4.2	14.4	0.7	0.0	3.1	5.3	0.0‡	0.8‡	10.4	21.8
TAXUS IV (7)	3.0	11.3	0.6	0.8	3.5	3.7	1.4‡	1.1‡	8.5	15.0
TAXUS V (8)	8.6	15.7	0.7	0.7	5.4	4.6	1.3‡	1.4‡	15.0	21.2
TAXUS VI (9)	6.8	18.9	0.5	1.3	8.2	6.2	0.0	0.9	16.4	22.5

\* BMS = bare-metal stent; DES = drug-eluting stent; RAVEL = Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions; SIRIUS = Study of the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions.

† Repeated revascularization within the stent and 5 mm proximal and distal to the stent.

‡ Cardiac mortality.

## SAFETY OF DRUG-ELUTING STENTS

Despite the remarkably consistent benefit of drug-eluting stents in the reduction of repeated revascularization, a meta-analysis suggesting a statistically significant 2.4% increased risk for death or MI compared with bare-metal stents (12) has called the safety of these devices into question. Another meta-analysis demonstrated a statistically significant increase in noncardiac mortality at 2 to 3 years among patients receiving the sirolimus-eluting stent (13). Although both of these analyses were limited to aggregated trial data available from published manuscripts rather than patient-level data and combined varying definitions of end points from the included trials, they received widespread attention for questioning the long-term safety of drug-eluting stents. An initial analysis of an observational registry of Swedish patients reported additional adverse outcomes, indicating an increase in mortality with drug-eluting stents that became apparent 6 months after the procedure (14), and other recent studies have reported the development of coronary aneurysms 6 to 21 months after drug-eluting stent implantation (15).

### The Stent Thrombosis Debate

On the basis of the currently available data from clinical trials (2, 7) and registries (16), the overall rate of subacute stent thrombosis, defined as thrombosis occurring 24 hours to 30 days after stent implantation, appears to be similar for bare-metal and drug-eluting stents. However, several studies indicate a small but measurable increase in the rate of late stent thrombosis (thrombosis occurring 30 days to 1 year after stent implantation) in patients receiving drug-eluting stents, with an estimated incidence of 0.2% to 0.5% per year (17). One trial even showed an incidence of late stent thrombosis of 1.4% in the drug-

eluting stent group versus 0.8% in the bare-metal stent group (18). Although these rates appear to be unusually high (even in the bare-metal stent group), in the aggregate, these data suggest an increased rate of late stent thrombosis in patients receiving drug-eluting stents.

Patient-level data from the major randomized trials have subsequently been analyzed to specifically address the incidence of stent thrombosis with drug-eluting stents at 4-year follow-up. Overall, the frequency of protocol-defined stent thrombosis did not statistically differ with drug-eluting stents (1.2% for sirolimus-eluting stents versus 0.6% for bare-metal stents [ $P = 0.20$ ]; 1.3% for paclitaxel-eluting stents versus 0.9% for bare-metal stents [ $P = 0.30$ ]) (19). However, when very late stent thrombosis events (occurring >1 year after stent implantation) were analyzed separately, an increase in events was observed with sirolimus-eluting stents (5 events vs. 0 events with bare-metal stents;  $P = 0.025$ ) and paclitaxel-eluting stents (9 events vs. 2 events;  $P = 0.028$ ). Given the high incidence of death and MI associated with stent thrombosis, the expected mortality and MI rates should in theory be elevated in patients with drug-eluting stents. However, most studies (including meta-analyses of the studies on which these analyses were based) have found no statistically significant difference in death and MI even after years of follow-up (19–21). The question that naturally arises from this ostensible paradox is why the small but measurable increase in late stent thrombosis does not translate into an increased rate of death and MI.

### Is Restenosis a Benign Process?

It has been suggested that unlike native coronary artery disease, in which plaque rupture with subsequent thrombus formation can lead to acute MI and death,

restenosis due to gradual hyperplasia of neointima cannot result in acute coronary syndromes, and instead is a “stable,” nonfatal condition associated only with recurrent angina and myocardial ischemia. More recent studies have called this hypothesis into question, because approximately 10% of patients with restenosis have acute MI as their presenting symptom (22). Moreover, in this analysis, 8.9% of patients had a totally occluded vessel at angiography (19% of whom presented with ST-segment elevation MI). Nevertheless, MIs associated with restenosis are typically less severe and are therefore less likely to have the same prognostic impact as those related to stent thrombosis.

**Varying Definitions of Stent Thrombosis**

Another explanation for the lack of an association between possible increases in late stent thrombosis and other end points, such as death or MI, is the way in which stent thromboses were defined in the pivotal randomized trials. In the published analyses of these trials, stent thrombosis events occurring after an intervening revascularization were censored (that is, not counted). For example, if a patient was randomly assigned to a bare-metal stent, developed restenosis that was treated by repeated revascularization, and then developed acute stent thrombosis, the latter was not reported as a protocol-defined event in the trial. This definition allowed the researchers to directly attribute the stent thrombosis event to the index revascularization. However, on an intention-to-treat basis, all events should ideally be attributed to the index revascularization, rather than being censored or otherwise excluded.

The censoring of stent thrombosis events that occur after an intervening revascularization is particularly prob-

lematic when one considers that this happened far more frequently with bare-metal stents. This practice is known as “informative censoring,” and in this case it led to substantial underestimation of the rate of stent thrombosis in the bare-metal stent group. Indeed, in an analysis based on a new definition of stent thrombosis proposed by the Academic Research Consortium (Appendix Table 1 and Appendix Table 2, available at www.annals.org) that counted all events regardless of past revascularization, the occurrence of stent thrombosis on an intention-to-treat basis was similar with drug-eluting and bare-metal stents at 4 years of follow-up (Table 2) (23). Even with the inclusion of possible stent thrombosis (which represents the most inclusive definition), the thrombosis rate was almost identical between the 2 groups.

**Do We Truly Know the Incidence of Stent Thrombosis with Drug-Eluting Versus Bare-Metal Stents?**

Although the incidence of stent thrombosis with drug-eluting versus bare-metal stents has been widely discussed in the lay press and in clinical circles over the past year, there are remarkably few data to draw on for this debate. The overall rarity of these events (<2%) makes it very difficult to be definitive about differences between drug-eluting and bare-metal stents when assessing the true relative incidence of these events. For instance, if one were to design an adequately powered clinical trial to demonstrate even a doubling of the stent thrombosis rate with drug-eluting stents, the trial would have to enroll approximately 8000 patients to adequately detect a 50% relative increase (1% absolute increase) in the rate of stent thrombosis,

**Table 2. Pooled Data from Pivotal Trials of Sirolimus- and Paclitaxel-Eluting Stents\***

Data	Sirolimus-Eluting Stents	Bare-Metal Stents	P Value	Paclitaxel-Eluting Stents	Bare-Metal Stents	P Value
Stent thrombosis† (definite and probable), %						
Early (0–30 d)	0.5	0.3	–	0.5	0.5	–
Late (31–360 d)	0.1	1.0	–	0.4	0.3	–
Very late (>360 d)	0.9	0.4	–	0.9	0.6	–
All	1.5	1.7	0.70	1.8	1.4	0.52
Stent thrombosis† (definite, probable, and possible), %						
Early (0–30 d)	0.5	0.3	–	0.5	0.5	–
Late (31–360 d)	0.2	1.3	–	0.9	0.9	–
Very late (>360 d)	2.9	1.7	–	1.8	2.1	–
All	3.6	3.3	0.80	3.2	3.5	0.84
All-cause mortality	6.7	5.3	0.23	6.1	6.6	0.68
Cardiac mortality	3.5	2.7	0.40	2.4	3.0	0.51
Death or myocardial infarction	11.6	10.4	0.44	12.4	11.8	0.79
Target lesion revascularization‡	7.8	23.6	<0.001	10.1	20.0	<0.001
Target vessel revascularization§	12.1	27.5	<0.001	17.2	24.7	<0.001

\* Data are adapted from references 19 and 23 and include unrestricted physician-directed analysis of the major trials comparing sirolimus-eluting stents (RAVEL [Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions], Canadian and European SIRIUS [Study of the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions], [n = 1748]) and paclitaxel-eluting stents (TAXUS I, II, IV, V, and VI [n = 3513]) with bare-metal stents. The latest available follow-up used for analysis was 4 years.

† Defined according to the Academic Research Consortium criteria.

‡ Repeated revascularization within the stent and 5 mm proximal and distal to the stent.

§ Any revascularization of the previously stented vessel.

assuming a baseline rate of 2% in the group with bare-metal stents. In comparison, all 9 major randomized trials comparing sirolimus-eluting stents with paclitaxel-eluting stents enrolled a total of 5261 patients, and thus the available published data remain greatly underpowered to address the comparative stent thrombosis incidence.

### EVALUATING THE NET CLINICAL BENEFIT

The net clinical benefit of any medical device or pharmaceutical agent is best characterized by its beneficial properties relative to its adverse effects. When the net effect is being considered, however, the relative clinical benefit must be weighed against the severity of the adverse effects. In the case of drug-eluting stents, the clinical benefit is the relative reduction in revascularization by approximately 50% to 70% across most lesion subsets (translating into an absolute reduction of 5% to 20%, depending on patient and lesion characteristics). This benefit must be weighed against a possible absolute increase in late stent thrombosis by approximately 0.5%, although the CIs around this latter estimate remain wide in the absence of a large number of events. The number needed to treat to prevent 1 restenosis event ranges from 5 to 20, whereas the number needed to harm (causing 1 excess event of stent thrombosis) is 200. Of note, because stent thrombosis is a more dire event than restenosis in general, the directionality and magnitude of the net clinical effect of drug-eluting stents are influenced not only by the number needed to treat or the number needed to harm but also by the differing clinical consequences of each competing risk.

Subgroup analyses from all clinical trials and numerous registries have demonstrated that implantation of drug-eluting stents reduces angiographic and clinical restenosis to a similar extent in all analyzed patient and lesion subgroups (2, 7). In fact, higher-risk patients may experience a greater absolute reduction in revascularization because of their higher baseline risk for restenosis. Given that the rate of serious adverse events (death and MI) has not been demonstrated to differ from that for bare-metal stents (although studies have been underpowered to assess these end points as well), and considering that drug-eluting stents are very effective in the reduction of repeated revascularization, the net clinical benefit of drug-eluting stents appears to be favorable (19–21). A meta-analysis of all randomized trials comparing drug-eluting stents with bare-metal stents (as well as head-to-head trials comparing sirolimus-eluting stents with paclitaxel-eluting stents) demonstrated similar mortality rates for all groups (24). Nevertheless, certain patient subsets may be well served with the use of a bare-metal stent if either the frequency of restenosis is low or its clinical consequences are limited.

In addition, multiple studies have shown that the single most important predictor of stent thrombosis is the premature discontinuation of antiplatelet therapy, with a dramatic increase in stent thrombosis seen in patients

taken off therapy (16). Currently, uninterrupted dual antiplatelet therapy (typically consisting of aspirin and clopidogrel) is recommended for at least 30 days after implantation of bare-metal stents and for a minimum of 1 year after implantation of drug-eluting stents. Consequently, it is critical that before stent implantation, all patients be evaluated for their ability to continuously receive and tolerate dual antiplatelet therapy (25). Also, all patients should receive optimal medical therapy, including anti-ischemic therapy (such as long-acting metoprolol or isosorbide mononitrate) and aggressive therapy to decrease low-density lipoprotein cholesterol levels and increase high-density lipoprotein cholesterol levels, as either an adjunct to percutaneous coronary intervention or as an initial strategy in asymptomatic patients or carefully selected patients with symptoms of low-risk stable angina (26).

### CONCLUSION

Numerous studies and registries have demonstrated that when used for “on-label” indications, drug-eluting stents are effective at reducing restenosis and the need for repeated revascularization in all patient subgroups and lesion types, without an increase in late MI or excess mortality. However, there are few overall safety data from adequately controlled trials on the use of drug-eluting stents for “off-label” indications. Larger prospective studies with adequate power to detect small differences in stent thrombosis, MI, and mortality rates are required to address these issues definitively. In the meantime, all patients should undergo rigorous screening before coronary intervention to assess their ability to tolerate uninterrupted dual antiplatelet therapy for a minimum of 3 to 6 months and preferably 1 year, as suggested by the Society for Cardiovascular Angiography and Interventions (27). In addition, all patients should receive optimal medical therapy as either an adjunct to percutaneous coronary intervention or as an initial strategy in asymptomatic patients or carefully selected patients with symptoms of low-risk stable angina (26).

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**Potential Financial Conflicts of Interest:** *Consultancies:* A. Kirtane (Medtronic Vascular). *Honoraria:* A. Kirtane (Boston Scientific).

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**Appendix Table 1. Definition of Stent Thrombosis according to the Academic Research Consortium\***

Type of Stent Thrombosis	Timing
Acute	Within 24 h after stent implantation
Subacute	24 h to 30 d after stent implantation
Late	30 d to 1 y after stent implantation
Very late	>1 y after stent implantation

\* Based on data from reference 23.

**Appendix Table 2. Certainty of Stent Thrombosis Events**

Certainty of Stent Thrombosis Event	Criteria
Definite	Angiographic evidence of stent thrombosis with clinical evidence of myocardial ischemia within past 48 h (chest pain with new ischemic echocardiographic changes or elevation of cardiac biomarkers) Pathologic evidence of stent thrombosis
Probable	Unexplained death within 30 d after stent implantation Myocardial infarction in territory supplied by the target vessel
Possible	Unexplained death >30 d after stent implantation