Incidence of Late Stent Thrombosis With Bare-Metal, Sirolimus, and Paclitaxel Stents

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Stent thrombosis has become a major concern for interventional cardiology. Although infrequent, it is associated with significant morbidity and mortality. Recent attention has focused on the frequency of this complication with drug-eluting stents compared with bare-metal stents in regard to the timing (early, late, or very late) of the event, underlying mechanisms involved, and preventive strategies. Although dual antiplatelet therapy (aspirin plus thienopyridine) is crucial in mitigating the problem, there are significant issues with this management strategy, including the duration of dual antiplatelet treatment, patient compliance, variability in individual response to therapy, bleeding risk, and management of subsequent noncardiac surgical procedures. Newer strategies being evaluated to enhance the safety of drug-eluting stents include different alloys and stent designs, revisions in the polymer or drug utilized, and, ultimately, bioabsorbable platforms.

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The issue of stent thrombosis has attracted great interest and is the subject of intense debate and controversy, particularly as it relates to drug-eluting stents (DES).[1-4] This debate must be framed against the background of stent thrombosis evident with bare-metal stents (BMS). Both single center registries and multicenter randomized trials have shed light on this issue. Orford and colleagues[5] evaluated the Mayo Clinic (Rochester, MN) database of

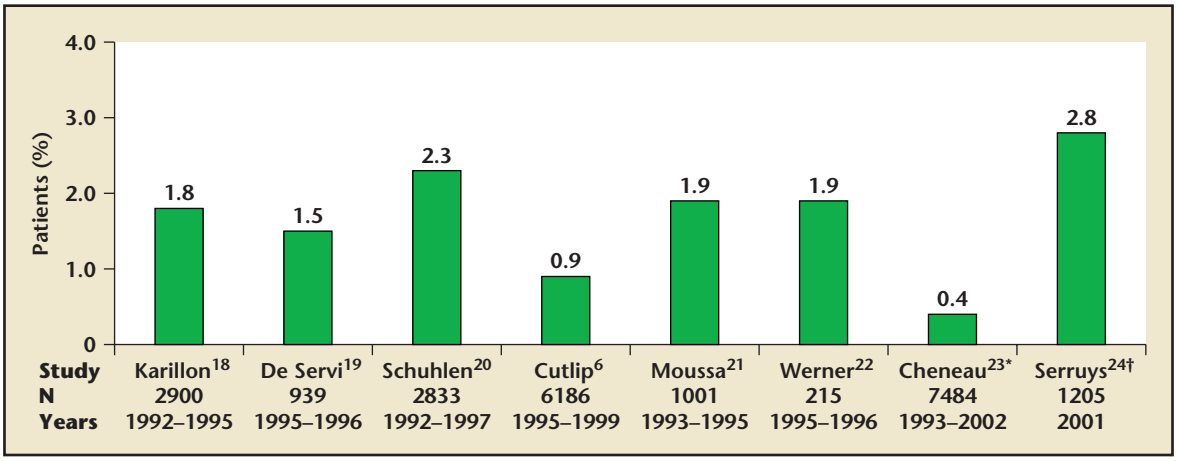

Figure 1. *Clinical experience of stent thrombosis with bare-metal stents. The average was about 1.2% to 30 days in approximately 20,000 patients. *IVUS-guided. †Multi-vessel stenting. IVUS, intravascular ultrasound. Adapted with permission from Honda Y and Fitzgerald PJ[17] and Kereiakes DJ et al.[7]*
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4509 patients treated with dual antiplatelet therapy after successful BMS implantation from 1994 to 2000. These authors considered stent thrombosis to have occurred when "confirmed angiographically (intraluminal filling defect within the stent resulting in Thrombosis In Myocardial Infarction [TIMI] 0 or 1 flow), when death was sudden and unexplained, or when a myocardial infarction (MI) occurred in the territory of the treated vessel." Twenty-three patients developed stent thrombosis within 30 days of the index procedures (0.51%). In this series of 23 patients with stent thrombosis, 48% had a fatal outcome and 39% had a nonfatal MI.

BMS Thrombosis

Cutlip and colleagues[6] performed a pooled analysis of multicenter BMS trials that enrolled patients from 1995 to 1999. Thirty-day clinical stent thrombosis was defined as angiographic documentation of stent occlusion, unexplained sudden death when the stent was not known to be patent, MI, or urgent target lesion revascularization. This study, which included 6186 patients and 6219 treated vessels, demonstrated that clinical stent thrombosis occurred within 30 days in 53 patients (0.9%). Similar to the results seen in the single center experience reported by Orford and colleagues,[5] of those patients with angiographic stent thrombosis, 64.4% of patients died or suffered an MI.

Other experiences with BMS demonstrate similar results (Figure 1).[7] Stent thrombosis with BMS, although associated with a marked increase in morbidity and mortality, was not the focus of attention. Instead, the majority of active investigation centered on the problem of in-stent restenosis, which occurred with far greater frequency. It was in-stent restenosis that drove the development of DES, which have dramatically improved the clinical outcomes for patients and have become predicate devices. As the issue of in-stent restenosis became much less frequent, the problem of stent thrombosis associated with DES became more important, beginning with early reports of late stent thrombosis (LST) occurring beyond 1 year after the index procedure.[2,3] As was true following BMS, stent thrombosis is associated with a marked increase in morbidity and mortality. The issue of LST with DES has now moved to center stage in the field of interventional cardiology.

DES Stent Thrombosis

Evaluating the issues surrounding DES thrombosis has been complex. This is the result of several factors, including:

- The incidence of stent thrombosis is low to very low, and no trials have been adequately powered to use this event as a primary endpoint.
- Stent thrombosis may occur late in clinical follow-up. This is difficult because coronary artery disease is a progressive disease, and events may occur late that are not related to the DES-treated sites. For example, a patient may die suddenly several years after implantation of a DES, and whether that sudden death is a primary arrhythmic event or whether it relates to stent thrombosis is very difficult or even impossible to determine. Indeed, this patient population experiences a 1% to 2% annual "background" incidence of death or MI due to progression of disease at non-treated sites.

- The histopathology of patients dying from stent thrombosis may be very different than the underlying pathologic/histologic events that occur in patients who do not die. Although inflammation and delayed healing are found at autopsy in patients who die after stent implantation, it is not known how often these events occur in patients who remain alive and asymptomatic.
- The definition of stent thrombosis and its timing has varied in the trials and clinical experiences evaluated to date. This latter problem is of fundamental importance in trying to compare frequencies between different devices.

Recently, a standardized set of definitions has been proposed, which should facilitate the study of stent thrombosis.[8] The timing of stent thrombosis has been classified as:

- *Acute* if it occurs within 24 hours of the index procedure.
- *Subacute* if it occurs from 1 to 30 days after the index procedure.
- *Late* if it occurs between 30 days and 1 year after the index procedure.
- *Very late* if it occurs 1 year after the index procedure.

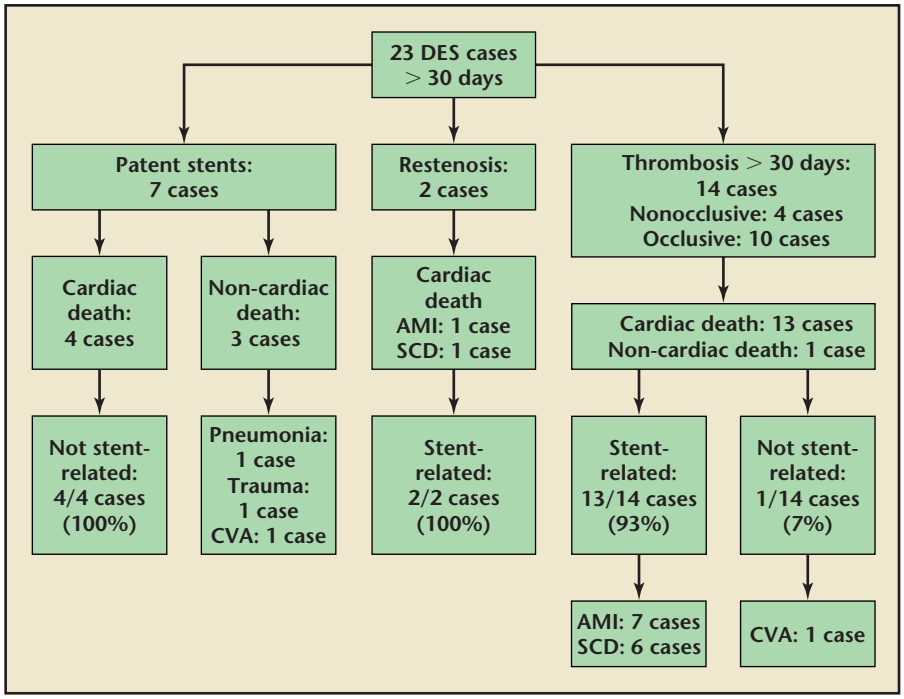
In addition to stratifying the timing of stent thrombosis, the definition of stent thrombosis has also been addressed.

- *Definite* thrombosis is deemed to have occurred if there is angiographic documentation of thrombus within the stented segment or pathologic documentation of thrombus in the stent that occurs in the setting of an acute ischemic syndrome.
- *Probable* stent thrombosis is defined as unexplained death within 30 days of the index procedure or if there was documentation of an MI in the distribution of the initial stented target vessel.
- *Possible* thrombosis is defined as any unexplained death that occurred beyond 1 month following the index procedure.

As previously mentioned, acute, subacute, and late thrombosis have very high morbidity and mortality; the combined endpoint of death and/or MI occurs in up to approximately 50% of patients.[2,3,5,6] The frequency of these adverse associated events is the same irrespective of whether the stent thrombosis occurs with a BMS or a DES. The clinical setting of very late stent thrombosis is less certain.[9,10] It may be that MI from late stent thrombosis is less frequently identified over the course of time due to collateral vessel development. The MI may be silent, or, conversely, the patient may present with sudden cardiac death. It is also possible that stent occlusion beyond 1 year or later may result from the gradual development of obliterative restenosis and not late stent thrombosis. These 2 conditions (obliterative restenosis, thrombosis) may be impossible to differentiate at the time of follow-up angiography.

The pathology of stent thrombosis has been studied in a small number of autopsy specimens.[4,11] Joner and colleagues[11] evaluated a registry experience of 40 autopsies from patients with DES. Twenty-three DES cases implanted for longer than 30 days were compared with 25 matched BMS controls. The cause of death in the 23 DES cases can be seen in Figure 2.[11] Both Cypher® and Taxus® stents were included in this study, while BMS stents served as controls. Of the patients with DES that had been placed longer than 30 days prior to death, 14 of 23

Figure 2. *Cause of death in patients dying more than 30 days after placement of a drug-eluting stent. DES, drug-eluting stent; AMI, acute myocardial infarction; SCD, sudden cardiac death; CVA, cerebrovascular accident. Reprinted with permission from Joner M et al.*[11] www.medreviews.com



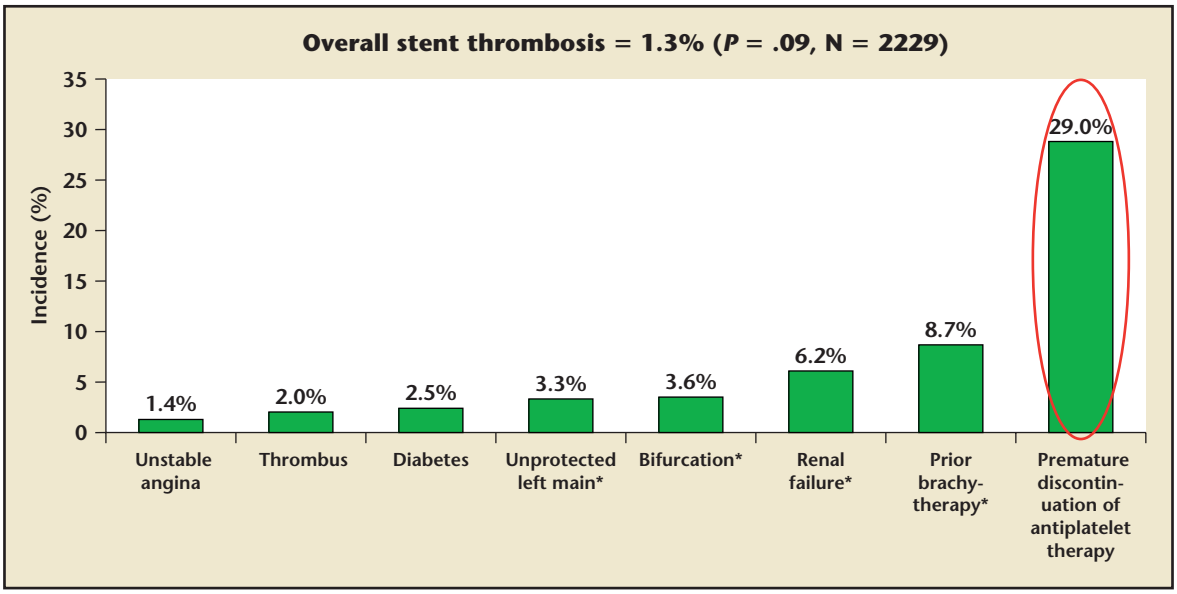


Figure 3. *Early discontinuation of antiplatelet therapy is one of the strongest risk factors for stent thrombosis. *The safety and effectiveness of the Taxus® Express2™ stent have not been established in patients with an unprotected left main, prior brachytherapy, diabetes, or lesions located at a bifurcation. Adapted with permission from Iakovou I et al.*[2] www.medreviews.com

had evidence of LST. The robustness of healing with DES versus BMS was assessed by analysis of fibrin deposition and the extent of endothelialization. As a group, the DES patients had more persistent fibrin deposition and poorer endothelialization compared with the BMS patients. In the DES patients who had evidence of LST, there was more delayed healing than in the DES patients without LST. The authors also identified other factors associated with LST, including hypersensitivity (perhaps related to the polymer), excessive wall injury, and complex disease, including a large necrotic atherosclerotic core and bifurcation lesions.

Clinical risk factors for stent thrombosis have also been assessed. The most common of these has been discontinuation of dual antiplatelet therapy (Figure 3).[2,3,9,10] It must be remembered, however, that stent thrombosis may occur even while the patient is on dual antiplatelet therapy. In the largest autopsy series published to date, Joner and colleagues[11] found that of the 14 patients with LST of a DES, only 5 had discontinued antiplatelet therapy. Therefore, discontinuation of dual antiplatelet therapy does not account for the majority of events. In many DES patients, additional mechanisms may be dominant. Nevertheless, dual antiplatelet therapy is currently a practical and prudent approach until further understanding is gained on this important clinical issue, and the duration of vulnerability for LST is better defined.

There is controversy about the optimal duration of dual antiplatelet therapy to prevent stent thrombosis. Patients in the initial randomized trials of DES versus BMS typically received dual antiplatelet therapy for only 2 to 6 months. With the current recognition of LST, however, the duration of therapy is now often extended to 12 months or longer. Whether 12 months of antiplatelet therapy will be sufficient to prevent very late stent thrombosis remains unknown. Even after 1 year, there has been pathological documentation of delayed endothelialization.[4] Indeed, very late stent thrombosis has been reported following BMS. As previously discussed, a rather ubiquitous finding in autopsy specimens has been the lack of endothelialization. What is not known, however, is how many patients who never experience stent thrombosis have delayed endothelialization.

The incidence of LST within the first year after placement of stents has been studied in multiple series.[12] Most randomized trials to 1-year follow-up have not demonstrated a difference in stent thrombosis rates between BMS and DES, with the caveat that the definitions used have not been uniform between studies. Moreno and colleagues,[12] in a pooled analysis of 10 randomized trials of DES versus BMS, identified 9-month stent thrombosis rates of 0.6% in DES patients versus 0.5% in BMS patients (Figures 4 and 5). In another meta-analysis confined to

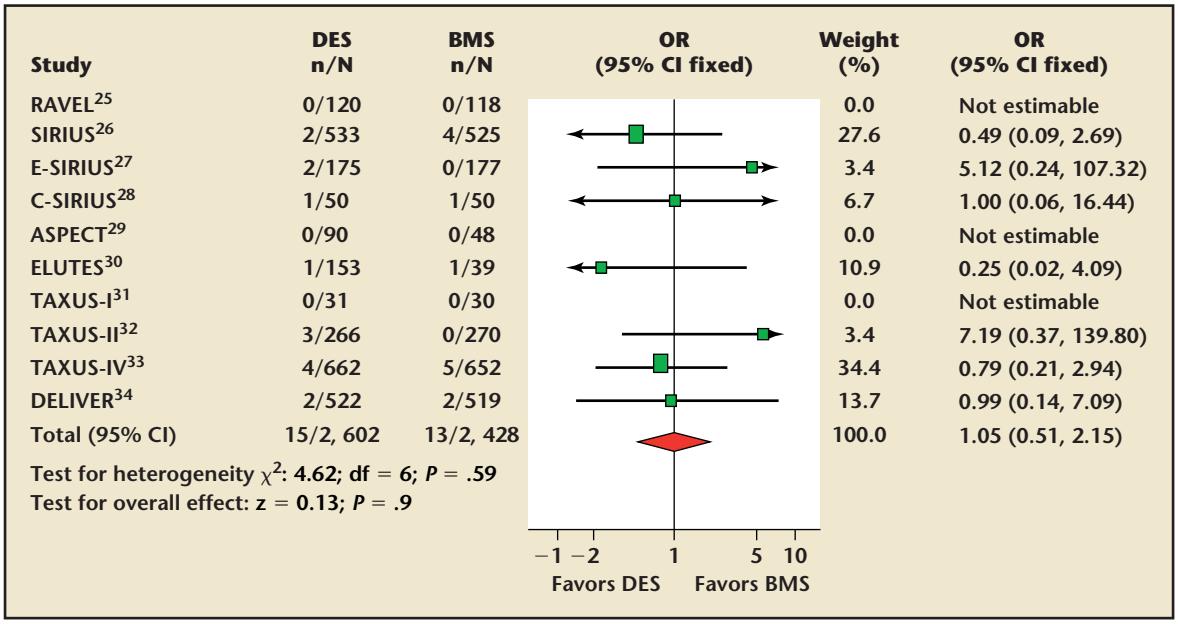
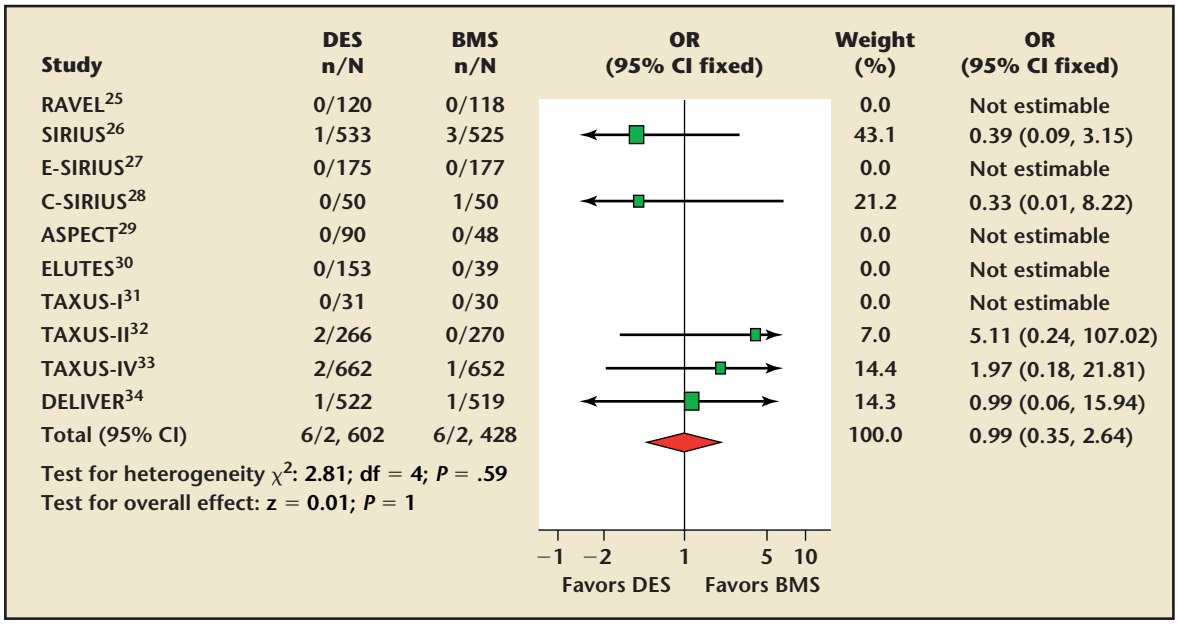


Figure 4. *Meta-analysis of 10 randomized trials of DES versus BMS documenting no overall significant difference in the frequency of stent thrombosis out of 9 months. DES, drug-eluting stents; BMS, bare-metal stents; OR, odds ratio; CI, confidence interval; RAVEL, Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Stent; SIRIUS, Sirolimus-Eluting Stent in de Novo Native Coronary Lesions; E, European; C, Canadian; ASPECT, Asian Paclitaxel-Eluting Stent; ELUTES, European Evaluation of Paclitaxel Eluting Stent. Reprinted with permission from Moreno R et al.*[12] www.medreviews.com

Figure 5. *Meta-analysis of 10 randomized trials of DES versus BMS documenting no overall significant difference in the frequency of late stent thrombosis out of 9 months. DES, drug-eluting stents; BMS, bare-metal stents; OR, odds ratio; CI, confidence interval; RAVEL, Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Stent; SIRIUS, Sirolimus-Eluting Stent in de Novo Native Coronary Lesions; E, European; C, Canadian; ASPECT, Asian Paclitaxel-Eluting Stent; ELUTES, European Evaluation of Paclitaxel Eluting Stent. Reprinted with permission from Moreno R et al.*[12] www.medreviews.com



paclitaxel-eluting stents, 3817 patients were analyzed.[13] The hazard ratio for paclitaxel-eluting stents was 1.06 (95% CI, 0.55-2.04), indicating no significant difference between paclitaxel-eluting stents and BMS in the incidence of stent thrombosis.

These randomized trials have typically included very select patient populations and often restricted lesion subsets. In non-randomized registry experiences, particularly those with longer follow-up, the incidence of stent thrombosis appears to be higher than that seen in the randomized clinical trials. In the e-Cypher registry postmarket surveillance study of 15,000 patients, the total thrombosis rate at 1 year was 0.87%.[14] In other high-risk patients (such as those with acute MI), the thrombosis rate may be higher, as was recently documented in the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) trial,[15] in which approximately 3.4% of patients treated with either BMS or DES developed LST. This increase in stent thrombosis in patients treated with DES for acute MI has not been uniformly identified.[16]

Given the tremendous interest in the problem of stent thrombosis, a uniform set of criteria has recently been adopted. Utilizing these definitions, more complete adjudicated assessments of 4-year clinical trial data have become available for DES. In a series of 1748 patients randomized to either a Cypher stent or a BMS, there was no difference in definite or probable stent thrombosis at 4-year follow-up (1.4% with sirolimus-eluting stents and 1.7% with BMS). Although the number of total events remains small, there does appear to be a difference in temporal distribution. At 1 year, there were more events in the BMS group ($P = .04$), whereas beyond 1 year there was a slight increase in stent thrombosis with DES. At 4-year follow-up, the events balance out, and overall thrombosis rates are very similar (Tables 1 and 2). In a 2-center experience, after the first year of follow-up, the annual incidence of LST following DES was 0.6% per year.[10] Whether this trend for a slight relative increase in incidence of LST with DES will continue indefinitely has great implications and is the focus of ongoing analysis.

Prevention of stent thrombosis is critical. The ability to predict LST in an individual patient is limited. In addition to the complex patient and lesion subsets that have been identified, there have been some procedural

Table 1
Incidence of Any Thrombosis*

	SES (N = 878 Patients)	BMS (N = 870 Patients)
ARC Definition Stent Thrombosis		
Thrombosis (0-3 months)	0.5% (4/874)	0.9% (8/870)
Thrombosis (0-6 months)	0.5% (4/872)	1.4% (12/868)
Thrombosis (0-9 months)	0.6% (5/872)	1.5% (13/867)
Thrombosis (0-1 year)	0.7% (6/871)	1.6% (14/864)
Thrombosis (0-4 years)†	3.2% (27/832)	3.3% (27/826)

*Incidence of any thrombosis using the ARC definitions on adjudicated data from day 0 out to 4 years in the combined data set of RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS. There is no difference between SES and BMS.
†Of the 54 subjects with thrombosis during 0 to 4 years, 10 underwent an intervening TLR prior to the thrombosis. However, only 1 of those 10 received any drug-eluting stent (the SES) during TLR.
ARC, Academic Research Consortium; SES, sirolimus-eluting stent; BMS, bare-metal stent; RAVEL, Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Stent; SIRIUS, Sirolimus-Eluting Stent in de Novo Native Coronary Lesions; E, European; C, Canadian; TLR, target lesion revascularization.

Table 2
Incidence of Definite or Probable Stent Thrombosis*

	SES (N = 878 Patients)	BMS (N = 870 Patients)
ARC Definition Definite/ Probable Stent Thrombosis		
Thrombosis (0-3 months)	0.5% (4/874)	0.8% (7/870)
Thrombosis (0-6 months)	0.5% (4/872)	1.0% (9/868)
Thrombosis (0-9 months)	0.6% (5/872)	1.2% (10/867)
Thrombosis (0-1 year)	0.6% (5/871)	1.3% (11/864)
Thrombosis (0-4 years)	1.6% (13/832)	1.8% (15/825)

*Incidence of definite or probable stent thrombosis from day 0 out to 4 years in the combined data set of RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS. There is no significant difference.
ARC, Academic Research Consortium; SES, sirolimus-eluting stent; BMS, bare-metal stent; RAVEL, Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Stent; SIRIUS, Sirolimus-Eluting Stent in de Novo Native Coronary Lesions; E, European; C, Canadian.

factors that may impact the development of stent thrombosis, including the adequacy of initial deployment. When intravascular ultrasound is used after "routine" stent placement, many stents are found to be undersized or underdeployed, with poor wall apposition and expansion. In such cases, the use of slightly larger balloons or higher pressure may optimize the acute result and improve long-term outcome. New, more powerful antiplatelet strategies are also undergoing clinical evaluation. These new pharmacologic agents (discussed elsewhere in this supplement) may diminish the problems of aspirin and/or clopidogrel resistance, which may be important for certain subsets of patients undergoing stent placement.

New stent platforms to enhance DES safety are also being evaluated. These platforms are aimed at making percutaneous coronary intervention easier, more reliable, predictable, and safer. New biodegradable polymers may eliminate late polymer hypersensitivity or inflammation. Conversely, several platforms have eliminated the polymer entirely. Newer adjunctive therapeutic agents are also being tested to enhance healing and endothelial stent coverage. Finally, evolving approaches to the metal alloy platform involve biodegradable metals as well as absorbable polymer matrix stents and offer promise in improving the outcomes for patients.

Conclusion

Stent thrombosis remains a significant problem for a small percentage of patients undergoing coronary stent placement. In these patients, the risk of morbidity and mortality is high. Although stent thrombosis is observed following both BMS and DES, the temporal distribution of events differs with DES. Events are delayed and the risk may be protracted. Strategies that help predict patients at highest risk for LST as well as evolving therapies for mitigating thrombosis entirely are the focus of active investigation. ■

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Main Points

- The timing of stent thrombosis has been classified as acute if it occurs within 24 hours of the index procedure, subacute if it occurs from 1 to 30 days after the index procedure, late if it occurs between 30 days and 1 year after the index procedure, and very late if it occurs 1 year after the index procedure.
- Acute, subacute, and late thrombosis have very high morbidity and mortality; the combined endpoint of death and/or myocardial infarction occurs in up to approximately 50% of patients. The frequency of these adverse associated events is the same irrespective of whether the stent thrombosis occurs with a bare-metal stent (BMS) or a drug-eluting stent (DES).
- Discontinuation of dual antiplatelet therapy does not account for the majority of events.
- In a study of autopsy specimens, DES patients had more persistent fibrin deposition and poorer endothelialization compared with BMS patients.
- In a series of 1748 patients randomized to either a Cypher stent or a BMS, there was no difference in definite or probable stent thrombosis at 4-year follow-up (1.4% with sirolimus-eluting stents and 1.7% with BMS).
- Although stent thrombosis is observed following both BMS and DES, the temporal distribution of events differs with drug-eluting stents.

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