

Stent Thrombosis Management

How to predict and manage stent thrombosis and the effect of newer-generation DES.

BY DONALD E. CUTLIP, MD

Stent thrombosis (ST) is a catastrophic complication of coronary stenting, presenting as sudden death or nonfatal myocardial infarction (MI) in almost all cases.^{1,2} Despite a decreasing frequency of ST in the current era, these dire consequences have generated intense clinical and research interest in prevention and management. In the early period of bare-metal stenting, ST occurred in approximately 3% to 4% of patients despite aggressive anticoagulation regimens.^{3,4} Subsequent studies employing routine high-pressure dilation showed improved ST rates (< 1%) with dual-antiplatelet therapy (DAPT) compared to systemic anticoagulation.⁵ Throughout this period, ST was considered a time-limited event, with occurrences reported only during the first 30 days after stenting and confirmation of most cases within the first week.⁶

The first substantial concern of ST beyond 30 days occurred with the use of intracoronary brachytherapy. Stent placement in the same setting as intracoronary brachytherapy has been associated with persistent risk of

ST beyond 30 days in 5% to 10% of patients.^{7,8} This risk was mitigated by prolonging DAPT from the standard 30 days to 3 or 6 months.^{9,10} Thus, when clinical trials of drug-eluting stents (DES) were designed, there was awareness of late ST, and DAPT was planned accordingly. It is interesting to note now that randomized DES clinical trials did not show a difference in ST rates at any time interval for DES versus bare-metal stents (BMS), partly due to the previously underappreciated risk for late ST after routine BMS use, as well as the low-risk clinical trial populations (Figure 1).^{11,12} In contrast, the risk for ST beyond 1 year was substantially higher with first-generation DES when used in higher-risk routine practice patients and lesions (Figure 2).^{13,14}

CLASSIFICATION OF STENT THROMBOSIS

Against the backdrop of increasing risk for late ST with first-generation DES, in 2007, the Academic Research Consortium (ARC) proposed a standardized classification to allow for comparison of rates and related out-

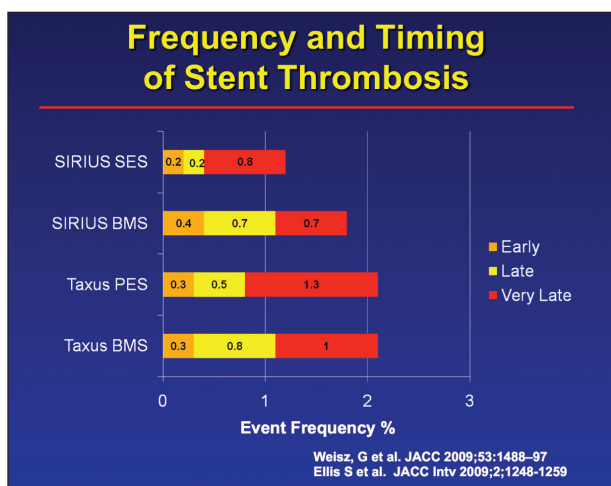


Figure 1. Five-year ST results of SES, PES, and BMS in randomized controlled trials. Data from Weisz G et al. J Am Coll Cardiol. 2009;53:1488-1497¹¹; and Ellis S et al. JACC Cardiovasc Interv. 2009;2:1248-1259.¹²

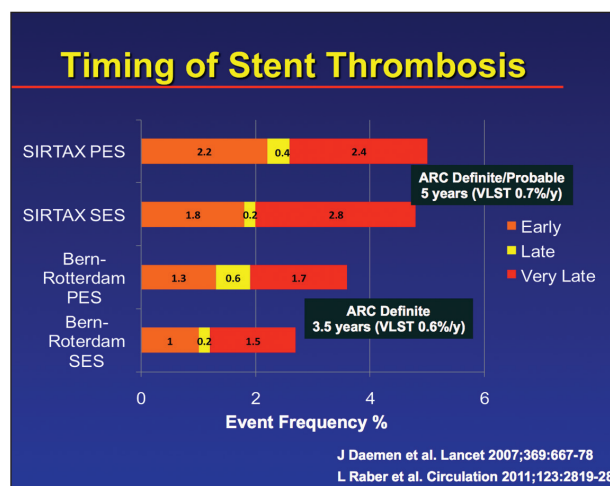


Figure 2. Late ST results in high-risk patients. VLST = very late stent thrombosis. Data from Daemen J et al. Lancet. 2007;369:667-678¹³; and Raber L et al. Circulation. 2011;123:2819-2828.¹⁴

TABLE 1. ARC CLASSIFICATION OF ST INCLUDING MODIFIED POSSIBLE CRITERIA

Classification	Criteria
Definite	Acute coronary syndrome with angiographic or pathologic confirmation of thrombus
Probable	Unexplained death within 30 d or MI involving target vessel territory without angiographic confirmation
Possible	Any unexplained death beyond 30 d
Timing*	
Early	0–30 d • 0–24 h = acute • > 24 h–30 d = subacute
Late	31 d–1 y
Very late	> 1 y
*Timing begins after completion of the procedure. Intraprocedural thrombotic events are not considered ST.	

comes across clinical trials and device iterations (Table 1).¹⁵ This classification allows for a specific level of confirmatory evidence and denotes the importance of event timing. Given the increased uncertainty regarding ST as a cause of death with longer time from stent implantation, the ARC classification of possible ST has not been widely accepted, and most reports rely on only definite or probable ST. It should be recognized, however, that this limited classification does underreport those events presenting with late unexplained death.

IMPROVED OUTCOMES WITH NEWER-GENERATION DES

There is evidence that ST rates have significantly declined with the use of newer-generation DES. Although most of the data are for everolimus-eluting stents (EES) and come from meta-analyses,^{16–18} similarly low rates have been shown for the Resolute zotarolimus-eluting stent (Medtronic) and the Nobori (Terumo Interventional Systems) biolimus-eluting stent in head-to-head comparisons with EES.^{19–21} It is reassuring that ST rates for the newer-generation DES are lower compared with first-generation DES, but indirect evidence from network meta-analyses and observational studies suggesting lower rates, even compared with BMS, is especially intriguing.^{17,18,22} Improvements in both stent design and polymer technology with thinner struts and thinner, more durable, biocompatible polymer coatings are likely the major factors, with durable polymers actually offering protection against thrombus.²³

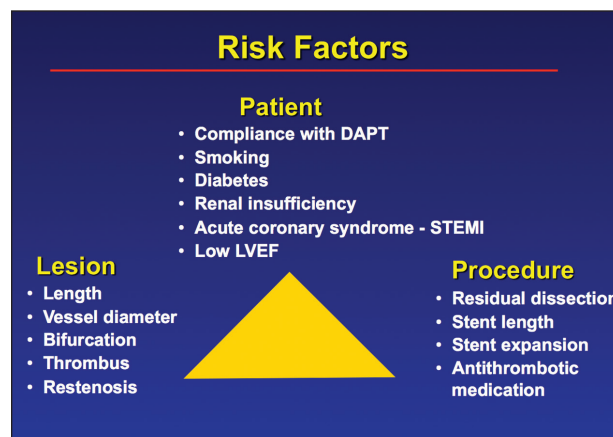


Figure 3. Risk factors for early and late ST. Abbreviation: LVEF, left ventricular ejection fraction.

PREDICTORS OF STENT THROMBOSIS

Given the poor outcomes despite early recognition and treatment, the most important step in managing ST is prevention. This requires an understanding of the usual predictors and taking appropriate precautions to limit those factors that can be avoided. For early and late ST, there has been consistency in identifying the common risk factors after BMS or DES implantation.^{2,6,24–26} These factors have been classified as those related to the patient, the lesion, or the procedure (Figure 3). The most important risk factor for early or late ST after BMS or first-generation DES implantation is premature discontinuation of DAPT. For BMS, this period appears to be 30 days, and for first-generation DES, it is at least 6 to 9 months.^{2,6} The minimum duration of DAPT for newer-generation DES remains controversial, but unplanned interruptions during the first 6 months appear to be associated with a significantly increased risk for ST.^{27,28} Interruptions related to major bleeding complications appear to be associated with a particularly high risk. Implantation of a BMS with 1 month of DAPT may be a better option in patients who are at very high risk for bleeding, especially if the restenosis risk is not high.²⁹ On the other hand, there is an ongoing benefit of reducing ST risk with continued DAPT well beyond 12 months in patients who are free from bleeding complications during the first 12 months.³⁰

Another important avoidable risk factor is stent underexpansion. In an intravascular ultrasound analysis of ST after sirolimus-eluting stenting, stent underexpansion and residual stenosis were the most significant predictors.³¹ Routine postdilation or intravascular ultrasound guidance should be considered in every case to mitigate this risk.

The predictors of very late ST have been more difficult to define, but share a common pathway of delayed

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healing, ongoing inflammatory changes, and development of neoatherosclerosis. Much of the inflammatory milieu and impaired healing have been overcome with improved stent design and polymers, although in a recent autopsy study of pathologic correlates, neoatherosclerosis remained a common finding, even with the newer-generation EES.³² To the extent that neoatherosclerosis may be a manifestation of stent-related endothelial dysfunction, it will be of interest whether bioabsorbable scaffold technology may sufficiently limit this phenomenon or whether more complex bioengineering will be required.³³ Again, continued DAPT appears to be helpful in preventing these very late ST events, regardless of stent type.³⁰

MANAGEMENT OF DEFINITE STENT THROMBOSIS

Most cases of ARC definite ST present as acute MI (> 60% ST-elevation MI [STEMI]) with < TIMI 3 flow in more than 80% of cases (TIMI 0 in 62% to 80%).³⁴ Thus, emergent cardiac catheterization with restoration of coronary flow is the mainstay of acute management. Despite successful revascularization, however, outcomes for acute MI due to ST remain poor,³⁵ even in comparison with de novo STEMI.³⁶ This is likely due to the sudden complete occlusion and high thrombus burden. Time to reperfusion may be even more critical, and in cases where any delays are anticipated, intracoronary fibrinolysis has been successful.³⁷

In a report from the CathPCI Registry involving more than 7,000 cases of ARC definite ST treated between 2009 and 2010, aspiration thrombectomy was performed in one-third of cases, and a new stent was implanted in 64%.³⁴ Successful recanalization (defined as TIMI 3 flow) was achieved in more than 90% of cases. Aspiration thrombectomy has been associated with improved microvascular perfusion in STEMI due to ST.^{38,39}

It is recommended to perform intracoronary imaging to assess for ST risk factors such as underexpansion, malapposition, or stent fractures, as this may guide

revascularization and future management. Subsequent antiplatelet therapy is an important consideration. In general, we prescribe a more potent P2Y₁₂ inhibitor such as prasugrel or ticagrelor, especially if the event occurred while on clopidogrel. Therapy is usually planned indefinitely, depending on timing of the event, other potential contributing risk factors, and subsequent risk for bleeding.

CONCLUSION

Risk for ST has significantly decreased with newer-generation DES, but remains a critical determinant of stent-related outcomes. Risk factors for early and late ST are well known, with DAPT compliance and optimal stent expansion among the most important correlates. The optimal duration of DAPT is likely contingent upon the patient's bleeding risk, with at least 6 months of therapy being a plausible standard if the bleeding risk is high. For patients without bleeding complications at 12 months, DAPT should be continued for at least 30 months. Rapid restoration of coronary flow is the mainstay of acute management, which should also include an assessment for potential causes. After ST, DAPT should be tailored to the specific patient and circumstances, but will usually result in lifelong therapy and consideration of a more potent P2Y₁₂ antagonist. ■

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