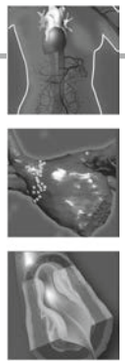

Avoiding stent thrombosis: advances in technique, antiplatelet pharmacotherapy and stent design

Stent thrombosis (ST) is major complication that can occur any time following stent placement. Many studies have advanced our understanding of the risk factors and mechanisms contributing to ST. Beyond identifying high-risk characteristics, such as premature discontinuation of dual antiplatelet therapy or acute coronary syndrome on presentation, insights from these studies have led to refinements in procedural technique and stent design. Second-generation drug-eluting stents are commonly used in practice today, and have improved some of the characteristics found to promote ST with first-generation drug-eluting stents, and have resulted in lower rates of ST. In addition, the use of a novel and more potent antiplatelet therapy in high-risk patients has led to a reduction in subsequent ischemic events, including ST. Despite these important gains, several issues remain unresolved. Studies continue to evaluate the optimal duration of dual antiplatelet therapy following stent placement, which is challenged by successive advancements in stent technology. Whether the next generation of stents utilizing bioabsorbable materials can succeed in reducing ST even further remains to be determined.

KEYWORDS: bioabsorbable stent ■ clopidogrel ■ dual antiplatelet therapy ■ first-generation DES ■ IVUS ■ mechanism ■ OCT ■ predictor ■ second-generation DES ■ stent thrombosis

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Definitions for stent thrombosis

Historically, stent thrombosis (ST) was proven angiographically by the demonstration of thrombus at the site of a previously placed stent with impaired downstream flow, or inferred clinically in patients with subsequent myocardial infarction (MI), target-lesion revascularization (TLR) or unexplained sudden death. While the angiographic definition of ST may underestimate the true incidence by not including patients who fail to survive to angiography, the clinical definition may overestimate the incidence by including events not attributable to ST. Definitions of ST, therefore, require a compromise between sensitivity and specificity. Clinical trials evaluating first-generation bare-metal stents (BMS) defined ST differently, leading to disparities in the reported incidence and making comparisons between studies problematic.

As the development and use of drug-eluting stents (DES) led to a perceived increase in rates of late and very late ST, the lack of uniformity in protocol definitions made comparisons of safety outcomes between different stents more problematic. Even prior to the 2006 European Society of Cardiology meeting that highlighted the issue of ST, a uniform and standardized definition was clearly necessary. To address this need, a group of clinical trialists, members of the US FDA and representatives from the major device manufacturers was assembled, known as the Academic Research Consortium (ARC). The document that resulted from this meeting incorporated terminology to reflect both the timing and the certainty of events and has since become a guide on how multiple clinical end points can be more effectively compared across trials [1].

By establishing uniform criteria for angiographic confirmation and maintaining the principle of intention-to-treat by not excluding patients with interval TLR, this new classification created standardized definitions that reconciled many of the inconsistencies of preceding protocol definitions (Box 1). These new definitions were not, however, without limitations. While the 'definite' label is highly specific due to the requirement of evidence of thrombus, the 'probable' and 'possible' labels allow for increasing levels of sensitivity to capture more events. The inclusion of all unexplained deaths occurring beyond 30 days under the possible label could potentially exaggerate rates of very late ST among patients whose death is without another clear etiology.

Subsequent trials have primarily reported on ARC-definite and/or probable (def/prob) ST rates, although some have advocated for expanded reporting to include ARC-possible events. In an effort to validate ARC definitions of ST among an autopsy registry of subjects with prior coronary

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Box 1. Academic Research Consortium definitions of stent thrombosis.

Timing

- Early: within first 30 days of PCI
  - Acute: within the first 24 h
  - Subacute: between 24 h and 30 days
- Late†: between 31 days and 1 year
- Very late†: more than 1 year after PCI

Certainty

- Definite‡: angiographic confirmation of thrombus originating within the stent or in the segment 5 mm proximal or distal to the stent and associated with at least one of the following criteria within a 48-h period
  - Acute onset of ischemic symptoms at rest, new ECG changes suggestive of acute ischemia or elevation in cardiac biomarkers to twice the normal value
  - In the presence of a pathological confirmation of ST (evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy)
- Probable: unexplained death within 30 days after stent implantation or in the presence of any MI related to documented ischemia in the distribution of the stented vessel, even in the absence of angiographic confirmation of ST and in the absence of any other obvious cause
- Possible: unexplained death occurring more than 30 days after PCI

†Late and very late ST includes primary and secondary events (ST after a target-lesion revascularization).
‡The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms (silent occlusion) is not considered a confirmed ST.
MI: Myocardial infarction; PCI: Percutaneous coronary intervention; ST: Stent thrombosis.

stenting, Cutlip *et al.* suggested that reporting only definite or def/prob events may result in substantial under-reporting of confirmed true ST events that may be captured by the ARC-possible designation [2]. A modification of the possible criteria to designate those events in which sudden cardiac death or acute ischemia was felt to be likely versus unlikely was found to allow for the expected increase in sensitivity by including such events together with def/prob events and with an increase in specificity compared with an inclusion of all possible events. While such criteria have yet to be adopted, the study highlights the ongoing limitations of accurately capturing the true occurrence of ST events.

Timing & incidence

Many factors influence the timing and incidence of ST. Early trials reported high rates of acute vessel closure reflective of the equipment, procedural techniques and pharmacotherapy of the time, all of which have since been greatly refined leading to much lower event rates in contemporary studies. Although the establishment of ARC definitions now allows for more meaningful comparisons of ST between trials, event rates continue to vary based on the study design (i.e., randomized controlled trial [RCT] vs registry analysis), the duration of follow-up and the clinical characteristics of the patient population.

The timing of ST is often the first clue to the underlying mechanism. The majority of events occur within the first 30 days with both BMS and DES, often relating to suboptimal procedural results. Data from over 21,000 patients in the Dutch Stent Thrombosis Registry provide insight into the timing of ST with a 2.1% incidence of definite ST at median follow-up of 31 months [3]. Nearly 75% of these 437 events occurred within the first 30 days (32% acute and 41% subacute) with the remainder occurring with similar frequency during the late period (13%) and very late period (14%). Beyond the early period, the risk for ST varies depending on the type of stent placed with unique risk profiles afforded by each successive generation of stents.

■ Bare-metal stents

Early investigational BMS were associated with rates of ST and acute vessel closure as high as 16–24% at 30-day follow-up [4,5]. The incorporation of anti-thrombotic therapy and high-pressure inflations to subsequent trials reduced the incidence to below 2% [6]. By 2001, a pooled analysis of six major trials and associated registries reported a 30-day ST rate of 0.9% [7], with the vast majority occurring within the first 48 h. Many of these trials did not report the incidence of ST beyond the early period due to the observation that such events were rarely observed to occur [1]. This attenuated risk results from the vascular response to stent deployment characterized by smooth muscle proliferation and neointimal hyperplasia leading to endothelialization of stent struts.

More recent data, however, suggest that the risks of late and very late ST with BMS are not negligible. The Coronary Angiography and Angioplasty Registery (SCAAR) reported comparable 30-day rates of definite ST (0.6%) to RCTs [8], but more pronounced 1-year (1.2%)

and 2-year (1.4%) definite ST rates among this large cohort of unselected patients [9]. A retrospective study of 4503 BMS patients found a cumulative incidence of 0.5% at 30 days, 0.8% at 1 year and 2.0% at 10 years [10]. This greater than twofold increase in events between years 1 and 10 suggests that BMS may not be as safe as many have assumed. Among these patients, clinical restenosis occurred in 18.1% at 10-year follow-up with 2.1% of patients presenting with MI, suggesting that the mechanisms of these late events may be different to those with DES [11].

■ First-generation DES

Compared with balloon angioplasty alone, the use of BMS resulted in a significant reduction in both abrupt vessel closure and restenosis at the site of the treated lesion, but at 1 year, revascularization rates remained as high as 21% [12]. This major limitation prompted the development of novel stents coated with durable biocompatible polymers that slowly release drugs capable of inhibiting smooth muscle cell proliferation and migration to the overlying endothelium [13]. In the pivotal SIRIUS trial, the Cypher® sirolimus-eluting stent (SES; Cordis, NJ, USA) was associated with a dramatic reduction in in-stent restenosis and repeat revascularization compared with BMS with low rates of ST observed in both arms (0.4% SES vs 0.8% BMS; p = nonsignificant [NS]) [14]. A similar reduction in revascularization favoring the TAXUS® paclitaxel-eluting stent (PES; Boston Scientific, MA, USA) compared with BMS was demonstrated in the TAXUS-IV trial with no appreciable difference in ST (0.8% PES vs 0.6% BMS; p = NS) [15].

Based on the dramatic reduction in restenosis, the cardiology community praised these first-generation DES as a transforming technology. By the end of 2004, they were used in nearly 80% of coronary interventions in the USA [16]. This early enthusiasm quickly evolved into concern, however, following an FDA advisory alerting physicians of a possible heightened risk associated with DES use based on nearly 300 episodes of reported (60 fatal) ST among SES recipients [17]. Concern intensified following the 2006 European Society of Cardiology Congress during which two meta-analyses reported an increased risk of death associated with DES use compared with BMS [18,19]. Follow-up data from the single-center BASKET–LATE trial also found DES use to be associated with higher rates of death or MI (4.9 vs 1.3%), as well as thrombosis-related clinical events (2.6 vs 1.3%) between 6 and 18 months compared with BMS use [20]. Despite receiving some methodological criticism, these studies had an immediate impact on clinical practice, reflected by a sudden and dramatic decrease in DES use.

In the wake of this controversy, multiple independently conducted meta-analyses of RCTs, comparing DES with BMS, were published (Table 1), each demonstrating there to be no significant increase in the overall rates of death or MI among DES recipients [21–24]. Depending on whether protocol definitions of ST were used, some identified a small, but significant, difference in very late ST (~0.2% per year) between groups based on a small number of events occurring beyond the first year [22,24]. A network meta-analysis including 38 trials, 18,023 patients and up to 4-year follow-up data found similar rates of short- and long-term mortality, regardless of the type of stent placed, and no significant differences in the overall risk of definite ST between either DES and BMS [23]. Five-year follow-up from the TAXUS and SIRIUS family of trials have since been reported. Compared with BMS, neither PES nor SES were found to have a statistically significant difference in cumulative def/prob ST, but a trend towards more very late ST with PES compared with BMS (1.4 vs 0.9%; p = 0.18) [25] and with SES compared with BMS (1.4 vs 0.7%; p = 0.22) [26] was found, again corresponding to a 0.2–0.3% rate of very late ST with these first-generation DES.

ST rates reported from registries are slightly higher due to more complex anatomy, medical comorbidities and off-label DES use, compared with clinical trials. Analysis of the Bern–Rotterdam registry revealed late and very late ST rates of 0.4–0.6% per year, persistent for up to 4 years [27,28] with a similar rate of 0.3–0.4% per year reported from the SCAAR registry [8]. SIRTAX–LATE, which randomized 1012 high-risk patients to SES versus PES, found similar overall rates of definite ST (4.6 vs 4.1%; p = NS) between years 1 and 5, translating to a higher (0.65% per year) rate of very late ST that are more consistent with findings from these registries [29].

■ Second-generation DES

As will be discussed in greater detail, second-generation DES have incorporated multiple design improvements that have resulted in lower rates of ST compared with first-generation DES [9]. No RCTs have directly compared second-generation DES with BMS, but indirect comparisons have suggested that the likelihood

Table 1. Meta-analyses evaluating the safety of first-generation drug-eluting stents.

Study (year)	Stents evaluated	Enrollment (n)	ST definitions	ST rate at 1 year, % (p-value)	ST rate beyond 1 year, % (p-value)	Ref.
Stone *et al.* (2007)	PES vs BMS SES vs BMS	3513 1748	Protocol	1.2 vs 0.6 (0.2) 1.3 vs 0.9 (0.3)	0.6 vs 0 (0.02) 0.7 vs 0.2 (0.03)	[22]
Spaulding *et al.* (2007)	SES vs BMS	1748	ARC def/prob	0.8 vs 1.8 (NS)	2.8 vs 1.7 (NS)	[164]
Mauri *et al.* (2007)	PES vs BMS SES vs BMS	2797 1748	ARC def/prob	0.9 vs 0.8 (NS) 0.6 vs 1.3 (NS)	0.9 vs 0.6 (NS) 0.9 vs 0.4 (NS)	[21]
Kastrati *et al.* (2007)	SES vs BMS	4958	Protocol	Not applicable†	0.6 vs 0.05 (0.02)	[24]

†*Hazard reported with drug-eluting stent use: 1.09 [0.64–1.86].*
ARC: Academic Research Consortium; BMS: Bare-metal stent; Def/prob: Definite and/or probable; NS: Nonsignificant; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; ST: Stent thrombosis.

of ST associated with some of these new stents is comparable or even lower than BMS [30,31]. Rates of ST also appear to be lower with novel stents utilizing bioabsorbable materials, although these data are currently limited to patients of lower risk and complexity.

Mechanisms of ST

The mechanisms underlying ST are multifactorial and differ based on the timing of stent placement. ST in the early period is often attributable to suboptimal periprocedural results and/or early discontinuation of dual antiplatelet therapy (DAPT), while ST occurring in the late period is more often related to delayed arterial healing caused by a reaction to one ore more stent components. Very late ST can result from the same factors causing late ST and may also be related to late acquired stent malapposition or neoatherosclerosis with plaque rupture. Pathologic studies and *in vivo* imaging studies utilizing intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have provided unique insight into many of these mechanisms, particularly among recipients of first-generation DES in whom a growing incidence of late and very late ST were increasingly recognized.

■ Insights from pathologic studies

One of the first case reports described a patient death as a direct result of ST occurring 18 months after being treated with a Cypher DES, Virmani *et al.* described the findings of an extensive inflammatory infiltration with a predominance of eosinophils, probably caused by a localized hypersensitivity response to the stent polymer [32]. Just prior to this publication, the FDA reported up to 50 possible cases of a generalized hypersensitivity reaction occurring in SES recipients, although many were later attributed to probable reactions to clopidogrel. However, in reviewing 262 cases of possible hypersensitivity reactions from the Research on Adverse Drug Events and Reports (RADAR) project, which investigates causality between therapeutic agents and potentially fatal adverse events, clopidogrel was only implicated in two cases, whereas 17 cases were attributed to the stent itself [33].

In a more robust examination of 14 cases of late ST, DES patients exhibited more evidence of persistent fibrin deposition and incomplete endothelialization compared with matched autopsies of BMS patients, in whom the majority of stent struts have been shown to be endothelialized by 3 months [34]. This delay in arterial healing is now recognized as a probable nidus for thrombosis. Additional risk factors identified in this small series included local hypersensitivity reactions, malapposition, penetration of stent struts into a necrotic core, ostial or bifurcation stenting and early withdrawal of antiplatelet therapy. In another evaluation of patients who had died 30 days after DES placement, Finn *et al.* identified 28 out of 62 coronary lesions associated with thrombus and confirmed the extent of endothelial coverage to be the best histological predictor of ST [35]. This study also observed a greater degree of nonuniform healing among DES-treated lesions compared with BMS-treated lesions.

■ Insights from IVUS

IVUS reveals details of lesion morphology beyond those that angiography alone can provide. This that can assist the operator in choosing appropriately sized stents, detecting mechanical problems after stent deployment and understanding mechanisms contributing to ST. IVUS has played an instrumental role in identifying predictors for both early ST due to suboptimal procedural results and late and very late ST due to mechanisms unique to DES.

Incomplete stent apposition (ISA) is characterized by a lack of contact between stent struts

and the underlying vessel wall that may be present soon after stent deployment or develop later as a consequence of positive remodeling and/or thrombus resorption [36]. While ISA occurring early after stent placement has not been clearly linked to ST, late-acquired ISA has been identified as an independent risk factor for late and very late ST post-DES [37]. In a series of patients presenting with very late ST who were evaluated with IVUS, ISA was detected more frequently compared with matched controls (77 vs 12%; $p < 0.001$) [38]. In another series of 30 patients (23 DES and seven BMS), ISA was present exclusively among DES recipients (74 vs 0%) with BMS recipients more commonly exhibiting evidence of disease progression or neointimal rupture within the stent (100 vs 43%) [39]. The etiology of late ISA remains incompletely understood, but pathologic evidence of medial necrosis of the arterial wall is believed to promote focal positive remodeling [40]. Such features may be seen angiographically as either peristent contrast staining or aneurysm formation. Histopathological evaluation of thrombus aspirates from patients presenting with very late ST after DES placement have found eosinophil counts to be three-times higher compared with patients with other causes of acute MI, correlating with the extent of ISA and suggestive of a delayed-type hypersensitivity mechanism, in keeping with pathologic studies [41].

■ Insights from OCT

While IVUS provides excellent tissue penetration to characterize plaque morphology, OCT offers up to ten-times greater resolution that clearly delineates the interface of the vessel lumen and overlying stent struts, making it an attractive tool for assessing post-percutaneous coronary intervention (PCI) results and complications. The high level of detail provided by OCT allows it to quantify the degree of neointimal stent coverage and detect ISA [42]. In a multimodality imaging study of 18 patients with late ST of DES compared with matched controls, the presence of uncovered stent struts, as assessed by OCT, and positive vessel remodeling, as imaged by IVUS, were associated with late ST [43]. This study also demonstrated the ability of OCT to detect in-stent neoatherosclerosis and plaque rupture as potentially important mechanisms for very late ST occurring in both BMS and DES recipients [43]. OCT can distinguish between red blood cell-rich red thrombi, which appear as high-backscattering protrusions with signal-free shadowing and platelet-rich white thrombi, which appear as low-backscattering structures [44]. However, the strong degree of signal attenuation caused by a red thrombus can limit the ability to assess the underlying stent struts among patients presenting with ST. This presents a practical limitation of using this modality to elucidate the underlying mechanism of ST [42]. Future studies may expand the role of OCT but its role in assessing and reducing ST remains largely investigative at this time.

Predictors of stent thrombois

Risk factors for the development of ST are often categorized as being patient related, procedure related and lesion related (Figure 1). The risk of ST increases in accordance with the complexity of each of these features.

Patient-related predictors

■ Demographics & comorbidities

Among the many risk factors for ST reported in different registries, renal insufficiency [45–48], diabetes mellitus [28,46–51], multivessel coronary artery disease (CAD) [48,51] and left ventricular dysfunction [3,46,50,52] are the most consistently identified comorbidities associated with ST. The DESERT registry, the largest case–control registry of ST to date with over 500 cases of definite late or very late ST, has identified multiple additional independent risk factors including younger age, current smoking and African–American race [53]. Other studies have implicated both cocaine abuse [54] and malignancy [3]. Although many of these risk factors are not readily modifiable, physicians caring for these patients should be aware of the risk they may pose prior to making decisions regarding stent placement in order to maximize the benefit of revascularization and minimize the potential for harm.

■ Clinical presentation/acute coronary syndrome

Acute coronary syndrome (ACS) is characterized by a state of increased platelet activity that creates an environment in which ST is more prone to occur [7,8,28,45,47,50,55,56]. Findings such as the presence of thrombus at the site of plaque rupture or impaired flow due to distal embolization or spasm may lead to stent undersizing and poor stent expansion at the time of deployment. The penetration of stent struts into the necrotic core of the overlying lesion may also trigger a maladaptive vascular response [57]. Autopsy studies in acute MI have observed substantial delays in culprit site vessel healing among DES recipients characterized pathologically by increased inflammation,

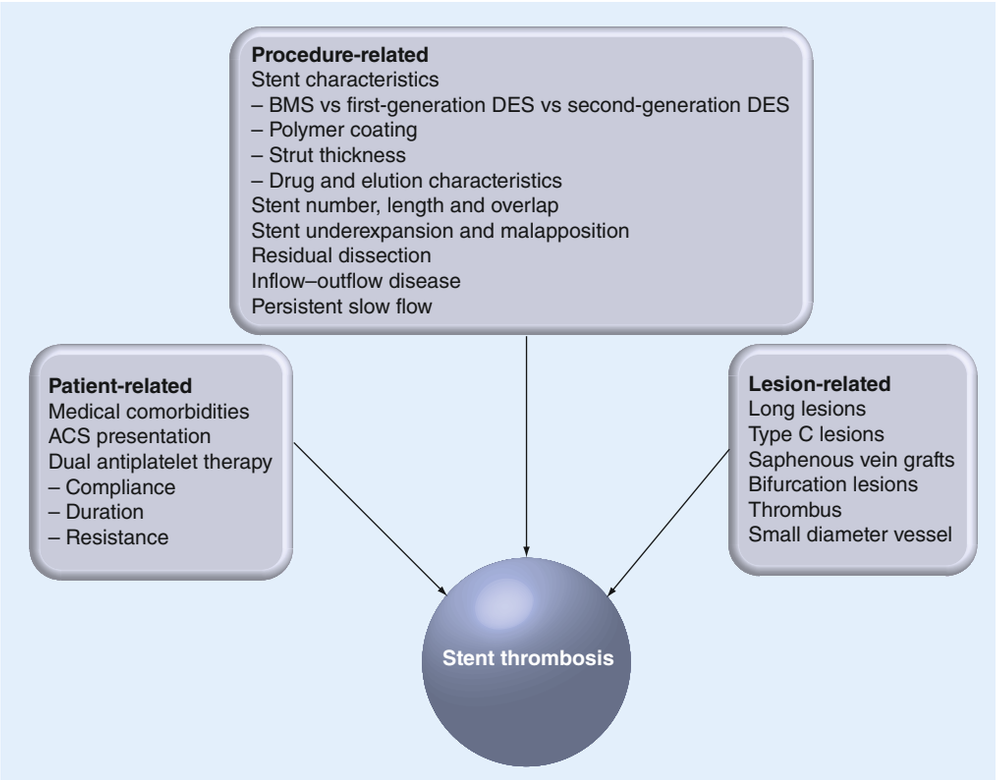

Figure 1. Stent thrombosis risk factors.
ACS: Acute coronary syndrome; BMS: Bare-metal stent; DES: Drug-eluting stent.

increased fibrin deposition and more uncovered stent struts [58].

Non-ST-elevation–ACS

In the ACUITY trial, which enrolled 13,819 patients with moderate-to-high risk ACS, ST occurred in 1.4% at 30 days [48] and 2.2% by 1 year with similar rates between BMS and DES. These rates are much higher than rates observed in trials conducted in patients with stable CAD [21,22], but are comparable with rates in observational studies that included patients with ACS [27,49]. Subsequent trials evaluating newer P2Y12 inhibitors in a similar population of moderate-to-high-risk ACS patients have also demonstrated elevated ST rates ranging between 2.3 and 2.9% at 12- to 15-month follow-up among patients randomized to clopidogrel, with significant reductions in ST in favor of both prasugrel [59] and ticagrelor [60].

ST-elevation MI

As one might expect, ST rates are even higher among patients who present with ST-elevation MI (STEMI). In the HORIZONS–AMI trial, 3602 patients undergoing primary PCI for acute STEMI were randomized to either unfractionated heparin and glycoprotein IIb/IIIa inhibitors or bivalirudin monotherapy [61]. Among the 3202 patients who received a stent (2261 DES and 861 BMS), def/prob ST occurred in 137 (4.4%) patients with 28 (0.9%) acute, 49 (1.6%) subacute, 32 (1.0%) late and 33 (1.1%) very late [57]. The overall incidence of ST was not affected by the anticoagulation strategy, but acute ST (within 24 h) occurred more often among patients randomized to bivalirudin (1.4 vs 0.3%; $p < 0.001$), whereas subacute ST occurred more often among those who received unfractionated heparin/glycoprotein IIb/IIIa inhibitors (2.8 vs 4.4%; $p < 0.02$). ST occurred frequently during the index hospitalization (in over 33%) and was associated with a higher mortality rate compared with events that occurred postdischarge (27.8 vs 10.8%) [62]. The administration of unfractionated heparin prior to randomization and the use of a 600-mg loading dose of clopidogrel (as opposed to 300 mg) were identified as independent predictors of reduced acute and subacute ST, respectively, suggesting that the number of early ST events in this high-risk population may be reduced by these management strategies [57,63].

Prior to the publication of HORIZONS–AMI, the use of BMS over DES was thought to afford greater safety. Although the randomized TYPHOON trial [64] and PASSION trial [65], both comparing DES versus BMS in acute MI, found

no differences in rates of ST at 1-year follow-up, other data suggested a higher risk associated with DES use in this population [27]. A subsequent meta-analysis of 13 trials and 7352 STEMI patients (including HORIZONS) found nearly equivalent rates of ST at 1 year, regardless of DES versus BMS (2.7 vs 2.6%, respectively) despite a 56% reduction in target-vessel revascularization (TVR) in favor of DES [66].

Emerging data now suggests that outcomes in STEMI patients may be enhanced with the use of current second-generation and next-generation stents. The EXAMINATION trial, a randomized comparison of everolimus-eluting stents (EES) versus BMS in patients presenting with STEMI, found a reduction in definite ST (0.5 vs 1.9%; p = 0.01) and def/prob ST (0.9 vs 2.6%; p = 0.01) among EES patients [67]. Similarly, the COMFORTABLE–AMI trial, a randomized comparison of a next-generation biolimus-eluting stent (BES) with a biodegradable polymer versus BMS in 1161 patients with STEMI, found a significant reduction in 1-year major adverse cardiac events (8.7 vs 4.3%; hazard ratio [HR]: 0.49 [95% CI: 0.30–30.80]; p = 0.004) in favor of BES driven by a lower risk of target vessel-related reinfarction (0.5 vs 2.7%; p = 0.01) and ischemia-driven TLR (1.6 vs 5.7%; p < 0.001) [68]. Rates of cardiac death and definite ST were not significantly different, although a higher number of ST events occurred among BES patients (12 vs 5; p = 0.10).

■ Antiplatelet therapy: noncompliance, duration, dose & resistance

Antiplatelet therapy after PCI plays an essential role in the prevention of subsequent ST. Both noncompliance with and resistance to DAPT have been shown to be important risk factors for ST, particularly with first-generation DES. The recommended duration of DAPT has evolved from shorter periods employed in the trials leading to the approval of first-generation DES to longer durations based on the recognition of many events occurring soon after DAPT cessation. The optimal duration continues to be debated due to the ever-changing risks and efficacy associated with newer devices and drugs.

Noncompliance with DAPT

As cases of late ST associated with first-generation DES began to accumulate, multiple studies identified premature cessation of DAPT as an independent predictor for these events. Premature discontinuation of clopidogrel was associated with a greater than 30-fold increase in the risk of ST in a single-center study of 652 SES patients, with nearly 25% of such patients experiencing an event within the first month [69]. Among a cohort of 2229 DES patients, 29 (1.3%) experienced ST by 9 months, with premature discontinuation of DAPT found to be among the most powerful independent predictors of ST to date (HR: 89.8 [95% CI: 29.9–269.6]) [46]. An analysis of the PREMIER registry, which included 500 patients treated with DES during an acute MI, found nearly one in seven was noncompliant with thienopyridine therapy at 30 days [70]. Although ST was not specifically reported, noncompliance with DAPT was associated with higher mortality (7.5 vs 0.7%) during the next 11 months.

Duration & dose of DAPT

Other registries that have correlated early discontinuation of DAPT with ST have suggested that the impact becomes less pronounced as the time after PCI increases (Table 2). In a series of 3021 DES patients, 42 (1.4%) experienced ST by 6 months, with premature DAPT cessation found to be the strongest predictor of ST during this period (HR: 13.7 [95% CI: 4.0–46.7]) [71]. Although 16 additional events occurred beyond this time period, these were not predicted by thienopyridine cessation. A larger cohort of 6816 DES patients also found a strong association between definite ST (0.8% at 1 year and 1.2% at 4 years) and clopidogrel discontinuation that appeared to be confined to the first 6 months of follow-up [72]. An analysis of the Dutch Stent Thrombosis Registry found the lack of clopidogrel use at the time of ST to be the strongest predictor of ST in the first 30 days (HR: 36.5 [95% CI: 8.0–167.5]) with continued, but more modest risk up to and beyond 6 months [3]. Among 1903 DES patients who were stratified into four groups based on duration of clopidogrel therapy until cessation post-PCI (group 1: within 30 days; group 2: 1–6 months; group 3: 6–12 months; and group 4: after 12 months), the composite of death/MI/ST both at 30 days and between 31 and 60 days post-DAPT cessation were indexed [73]. Within the first 30 days postclopidogrel cessation, event rates were higher for group 1 (5.2%) compared with other groups (group 2: 1.2%, group 3: 0.9% and group 4: 0.6%; p = 0.004) with similarly low rates seen in all groups between days 31 and 60. When the time between the index PCI and cessation of clopidogrel was analyzed as a continuous variable, the probability of events occurring within the first 30 days became similar to that observed in

Table 2. Registries evaluating optimal duration of dual antiplatelet therapy.

Study (year)	Enrollment (n)	Follow-up	End point	ST incidence (%)	Duration of DAPT suggested by results	Ref.
Iakovou *et al.* (2005)	2229	9 months	ST	1.3	9 months	[46]
Park *et al.* (2006)	1911	19.4 months	ST	0.8	6 months	[45]
Airoldi *et al.* (2007)	3021	6 months 18 months	ST	1.4 1.9	6 months	[71]
Eisenstein *et al.* (2007)	1501	24 months	Death, MI	Not reported	At least 1 year, possibly longer	[74]
van Werkum *et al.* (2009)	21,009	31 months	ST	2.1	Up to 1 year	[3]
Schultz *et al.* (2009)	6816	4 years	ST	1.2	6 months	[72]
Kimura *et al.* (2009)	10,778	2 years	Death, MI, ST	0.77	6 months	[165]
Lemesle *et al.* (2011)	1901	60 days after cessation	Death, MI, ST	Not reported	10.2 months	[73]

DAPT: Dual antiplatelet therapy; MI: Myocardial infarction; ST: Stent thrombosis.

the 31–60-day interval following cessation after a minimum of approximately 10.2 months.

In contrast to these studies, other registries have suggested benefit from extended durations of DAPT. In BASKET–LATE, 746 patients were randomized to DES versus BMS with DAPT for 6 months post-PCI followed by aspirin (ASA) monotherapy [20]. Although the 30-day rate of composite death and MI was lower for the DES group (2.0 vs 4.7%, p = 0.05), late ST occurred twice as frequently (2.6 vs 1.3%). Similarly, in an observational study of 4666 patients utilizing the Duke database, extended use of clopidogrel at 6, 12 and 24 months in DES patients was associated with lower rates of death and MI at all time intervals, a finding not observed in patients treated with BMS [74].

Given these conflicting findings, RCTs have been conducted to test the hypothesis that extended regimens of DAPT may reduce ischemic events (Table 3). Although these trials have important differences with regards to the patient population, the duration of DAPT and the clinical end points, those that have been published to date (REAL–LATE and ZEST–LATE [75], PRODIGY [76], EXCELLENT [77] and RESET [78]) found no significant difference in outcomes between shorter and extended durations of DAPT. In fact, the PRODIGY study reported a significant increase in major bleeding associated with prolonged DAPT to 24 months (3.5 vs 7.4%; p = 0.0002) [79]. While none of these were adequately powered to individually determine if ischemic end points may be lowered with extended DAPT, some found that shorter durations of DAPT following placement of second-generation DES are not associated with an appreciable increase in ischemic events, suggesting that these devices may be safer than first-generation stents [78].

The use of differing durations and different stents adds to the difficulty of directly comparing results. Nevertheless, as a whole they signal that the risk-to-benefit ratio does not favor extended therapy, particularly when considering the elevated bleeding risks of prolonged DAPT. Fortunately, results from larger trials are forthcoming and may provide answers. The largest of these, the DAPT study, recently completed enrollment of over 25,000 patients across a broad spectrum of clinical conditions and stents with planned randomization to 12 versus 30 months of DAPT [80]. Other studies currently enrolling include ISAR–SAFE [81] and OPTIMIZE [82], which are comparing shorter durations of DAPT post-PCI with a DES to the currently recommended duration of 1 year.

The optimal dose of ASA and clopidogrel after PCI has also been debated. A 600-mg loading dose of clopidogrel provides more potent, rapid and uniform platelet inhibition compared with a 300-mg dose, establishing it as the recommended loading dose (along with ASA 325 mg) prior to PCI in most patients [83]. Varying durations of higher maintenance doses of both clopidogrel and ASA have been used after these loading doses, primarily to reduce the risk of subacute ST. CURRENT–OASIS-7 sought to determine the comparable efficacy and safety of different post-PCI DAPT regimens in the first 7 days on short- and long-term outcomes [84]. A total of 25,087 patients with ACS, of whom 70% underwent PCI, were randomized in a 2 × 2 factorial design to higher versus lower dose ASA (325 vs 81 mg) and/or double- versus standard-dose clopidogrel (600-mg load followed by 75 mg twice daily vs 300-mg load followed 75 mg daily). While the primary end point of composite death, MI or stroke did not

Table 3. Randomized trials evaluating optimal duration of dual antiplatelet therapy.

Study (year)	Enrollment (n)	Regimens (months)	Stents	Primary end point	Results, % (p-value)	Ref.
REAL–LATE ZEST–LATE (2010)	2701	12 vs 24	DES	2 years CV death or MI	1.8 vs 1.2 (NS)	[75]
PRODIGY (2010)	1357	6 vs 24	SES, EES	2 years death, MI, or CVA	10.0 vs 10.1 (NS)	[166]
EXCELLENT (2011)	1443	6 vs 12	DES, BMS	1 year CV death, MI, or TVR	4.7 vs 4.4 (NS)	[77]
RESET (2012)	2117	3 vs 12	ZES (3 months) vs other DES (12 months)	1 year CV death, MI, ST, TVR or major bleed	4.7 vs 4.7 (NS)	[78]
DAPT (2010)	>25,000	12 vs 30	DES, BMS	33 months death, MI or CVA 33 months def/prob ST	Ongoing	[80]
ISAR–SAFE (2009)	6000	6 vs 12	All DES	15 months death, MI, CVA or major bleed	Ongoing	[81]
OPTIMIZE (2012)	3120	3 vs 12	ZES	1 year death, MI, CVA or major bleed	Ongoing	[82]

BMS: Bare-metal stent; CV: Cardiovascular; CVA: Cerebrovascular accident; Def/prob: Definite and/or probable; DES: Drug-eluting stent; EES: Everolimus-eluting stent; MI: Myocardial infarction; NS: Nonsignificant; SES: Sirolimus-eluting stent; ST: Stent thrombosis; TVR: Target-vessel revascularization; ZES: Zotarolimus-eluting stent.

differ between higher versus lower ASA, or double versus standard clopidogrel strategies in the overall population, a 46% reduction in definite ST (0.7 vs 1.3%; p = 0.0001) in favor of double-dose clopidogrel was observed in the PCI-subgroup translating into a 14% reduction in the primary end point, albeit at the expense of a 41% increase in major bleeding (1.6 vs 1.1%; p = 0.001) [85]. Although this trial has to be viewed as showing no efficacy in favor of extended durations of higher dosages of ASA and clopidogrel, the ability to reduce ST is an important finding that may allow for targeted therapy among populations at lower risk for bleeding.

Clopidogrel resistance & the role of platelet function testing

While noncompliance with DAPT appears to be responsible for many ST events, variability in response to clopidogrel may contribute to ischemic events among patients adhering to therapy [86]. Clopidogrel requires activation before inhibiting platelet P2Y12 receptors. Variability in intestinal absorption, drug interactions affecting hepatic cytochromes and genetic polymorphisms of genes encoding CYP450 isoenzymes are among the more studied mechanisms that contribute to the variable pharmacologic action of clopidogrel. Up to one-third of the population may exhibit significant hyporesponse to clopidogrel, reflected by high on-treatment platelet reactivity (HTPR) [87]. HTPR is an independent risk factor for the occurrence of ischemic events after PCI [86]. A pooled analysis of 20 trials and over 9000 patients found HTPR to increase the risk for ischemic events by fivefold and ST by fourfold [88]. Several studies have used receiver–operator curve analysis to define a threshold value of HTPR to identify thrombotic risk in patients undergoing PCI. Among those utilizing the more commonly used VerifyNow assay (Accumetrics, CA, USA), threshold values greater than 230–240 P2Y12 reaction units (PRU) have been shown to be the best predictors of subsequent ischemic events [89–91].

Despite the correlation between HTPR and ischemic events, the role of platelet function testing (PFT) in guiding the management of patients after PCI remains to be determined. Several studies have prospectively evaluated the role of PFT in guiding subsequent antiplatelet therapy (Table 4). The GRAVITAS trial compared standard-dose (300-mg load and 75-mg maintenance) versus high-dose (600-mg load and 150-mg maintenance) clopidogrel in patients with HTPR (PRU: >230) after elective PCI and found no reduction in the composite of cardiovascular death, MI and ST at 6 months (2.3 vs 2.3%) [92]. Despite a significant decrease in the proportion of patients with persistent HTPR at 30 days in the high-dose group, only a modest reduction in PRU levels was observed. Whether or not a more potent antiplatelet agent may improve outcomes in such a population was tested in TRIGGER–PCI, which randomized 423 patients with HTPR (PRU: >208) 1 day after elective PCI following a

Table 4. Randomized trials evaluating the role of platelet function testing.

Study (year)	Enrollment (n)	PRU threshold	Intervention	Findings	Ref.
GRAVITAS (2011)	2214	>230	High-dose clopidogrel	No clinical benefit	[92]
TRIGGER–PCI (2012)	423	>208	Prasugrel	No clinical benefit	[93]
ARCTIC (2012)	2440	>235	High-dose clopidogrel plus glycoprotein IIb/IIIa or prasugrel	No clinical benefit	[94]
TRILOGY–ACS (2012)	2564	>208 >230	Prasugrel	No clinical benefit	[95]

PRU: P2Y12 reaction units.

600-mg loading dose of clopidogrel to continued clopidogrel versus prasugrel [93]. Prasugrel was shown to be very effective at lowering PRU levels but the extremely low event rate observed in both arms (only one periprocedural MI; no ST events), likely due to the low-risk population and high use of next-generation EES (~50%), prompted early termination of the study due to futility. Consistent with these findings, the ARCTIC trial prospectively tested a strategy of tailored antiplatelet therapy both before and after PCI based on results of PFT, but found no difference in clinical outcomes [94]. Similarly disappointing results in the medically managed ACS population were also reported from the TRILOGY–ACS substudy examining the role of PFT [95]. Although associated with lower PRU versus clopidogrel, no correlation between ischemic outcomes and platelet reactivity was present at 30-month follow-up. The 1-year follow-up results from the prospective observational ADAPT–DES study of patients undergoing PFT with VerifyNow before and after DAPT loading were also recently reported. Among the 70 patients (0.84%) who experienced def/prob ST by 1 year, HTPR (PRU: >208) was shown to be an independent predictor of MI and ST, but was also protective against major bleeding, thus it was not associated with a mortality reduction [96].

A loss-of-function polymorphism in the *CYP2C19* gene has been associated with decreased activation of clopidogrel, a reduced antiplatelet effect and increased cardiovascular events in patients receiving clopidogrel [97]. A meta-analysis of nine studies evaluating the impact of *CYP2C19* genotype on clinical events demonstrated an increased risk of ST in carriers of both one (HR: 2.67 [95% CI: 1.69–64.22]) and two (HR: 3.97 [95% CI: 1.75–79.02]) reduced-function alleles compared with noncarriers, identifying nearly 30% of patients as potentially less protected on clopidogrel therapy [98]. The role of genetic testing to identify such patients with *CYP2C19* polymorphisms is not recommended as a routine strategy based on the most current PCI guidelines [83]. Since these guidelines were published, the RAPID–GENE study established that point-of-care genetic testing following PCI can accurately identify *CYP2C19*2* carriers leading to subsequent reductions in PRU levels with prasugrel [99]. These results lay the foundation for larger studies to evaluate the role of pharmacogenomics in guiding antiplatelet selection post-PCI.

Lesion-related predictors

Specific findings on angiography are predictive of ST regardless of the procedural strategy. Longer lesions [7,45,52], smaller pre-PCI vessel diameters [49], bifurcation lesions [46,49], type C lesions [100], saphenous vein graft lesions [53] and the lesions associated with thrombus [46,101] have all been found to be associated with future episodes of ST after PCI.

Thrombus burden, in particular, is among the most high-risk lesion-related characteristics. In a retrospective analysis of 812 patients treated with DES for STEMI, patients with a large thrombus burden (defined as ≥2 vessel diameters) experienced higher mortality (HR: 1.76; p = 0.023) compared with patients with a smaller thrombus burden [101]. ST occurred in 1.1% of patients at 30 days and 3.2% at 2 years with significantly more events occurring among patients with larger thrombus burden (8.2 vs 1.3% at 2 years, respectively; p < 0.001). In this study, thrombectomy was associated with fewer ST events during follow-up (HR: 0.11; p = 0.03).

Procedure-related predictors

Achieving optimal technical results during PCI is perhaps the single most important way to avoid ST. Based on studies evaluating findings on angiography and IVUS after stent deployment, numerous predictors for ST have been identified. Angiographic findings associated with ST include evidence of residual dissection [7,48,50,52,102], smaller luminal dimensions [52,102,103] and persistent slow flow [52,103]. In addition, the use of longer stents [7,45,47,50,55,71,104], multiple stents [38,51,52] and overlapping stents [38,50] increases the potential for subsequent events. All of these risk factors have also been

shown to predict early ST in the BMS era based on studies utilizing IVUS [50,52]. Among 53 cases in the POST registry, designed to identify IVUS predictors of acute and subacute ST, 94% exhibited at least one significant abnormality on IVUS (including stent underexpansion, stent malapposition, inflow–outflow disease, dissection or thrombus) with only 32% having such abnormalities appreciated on angiography [105]. A smaller series of 12 patients presenting with acute ST identified most as having severe stent underexpansion with no patient fulfilling criteria for optimal stent implantation [106].

Studies utilizing IVUS to evaluate deployment of early BMS found that over 80% of these stents were poorly expanded despite seemingly adequate results on angiography [107,108]. Soon thereafter, Colombo *et al.* demonstrated that a strategy utilizing routine IVUS to optimize PCI results with adequately sized balloons (balloon-to-vessel ratio 1.17 ± 0.19) and high-pressure inflations (14.9 ± 3.0 atmospheres) can achieve optimal stent expansion in 96% of patients [6]. Subsequently, the CRUISE study the use of IVUS to be associated with larger stent diameters post-PCI and a 44% relative risk reduction (RRR) in the need for repeat revascularization at 9-month follow-up [109], while the OPTICUS study found no reduction in clinical events or restenosis rates with routine IVUS use [110].

In the DES era, the routine use of IVUS to optimize stent deployment and clinical end points was evaluated in an examination of 884 patients [111]. Rates of definite ST were significantly lower compared with propensity score-matched patients who underwent PCI without the aid of IVUS both at 30 days (0.5 vs 1.4%; p = 0.046) and 1 year (0.7 vs 2.0%; p = 0.014). Patients undergoing IVUS-guided PCI underwent less direct stenting, more postdilatation and had greater cutting balloon and rotational atherectomy use. Although there were no significant differences in the rates of death, Q-wave MI or TVR between groups, IVUS guidance was an independent predictor of freedom from cumulative ST at 12 months (adjusted HR: 0.5 [95% CI: 0.1–0.8]; p = 0.02) and was associated with a trend towards lower TLR. A meta-analysis of 11 studies comparing PCI with and without routine IVUS found IVUS-guided DES implantation to also be associated with a reduced ST (HR: 0.58 [95% CI: 0.44–40.77]; p < 0.001) as well as a lower incidence of death (HR 0.59 [95% CI: 0.48–40.73]; p < 0.001) and major adverse cardiac events (HR: 0.87 [95% CI: 0.78–70.96]; p = 0.008) [112]. More recently, results from the IVUS study of ADAPT–DES, a prospective multicenter registry designed to determine the frequency, timing and correlates of DES thrombosis, found that IVUS guidance was independently associated with a reduced 1-year rate of ST (HR: 0.37 [95% CI: 0.20–0.68]; p = 0.0014) with nearly a 50% reduction in nonperiprocedural MI [113]. These data suggest that information gained with IVUS may lead to important differences in procedural approach, which may in turn reduce thrombotic events.

As stent technology and technique has advanced, the majority of stents are adequately and safely deployed without the need for routine IVUS guidance. Indeed, the use of IVUS varies greatly from one center to another. However, emerging data suggest that IVUS can play an important role in optimizing procedural results in order to reduce future clinical events, ST in particular. If IVUS is utilized, the operator should aim to achieve a lumen inside the stent of at least 60–70% of the media–media cross-sectional area. If IVUS is not used, achieving a small 'step up' at the entrance of the stent and a 'step down', at the exit of the stent along with liberal postdilatation with a noncompliant balloon is likely to achieve similar results [114].

Advances in stent technology

■ First-generation DES

As discussed previously, the development of first-generation DES heralded a breakthrough in our ability to treat severe coronary lesions while minimizing the need for repeat revascularization. The panic caused by the European Society of Cardiology Firestorm followed by the dissemination of data on the efficacy and safety of these devices soon resulted in the acknowledgement that, although associated with a greater hazard of ST beyond the first year, first-generation DES provide superior clinical outcomes with an overall excellent safety profile that justifies their use among appropriately selected patients.

■ Second-generation DES

Newer stents have since been designed with novel metal–alloy platforms, biocompatible polymers and improved antiproliferative agents that have resulted in thinner struts, a more open-cell design and greater deliverability. In addition, these devices elicit less inflammation and result in more rapid endothelialization compared with first-generation DES, translating into reduced rates of restenosis and ST [115]. The most commonly used platforms of these so-called 'second-generation' DES, along with the data supporting their use, are discussed below.

Everolimus-eluting stents

The Xience V EES (Abbott Vascular, IL, USA; also distributed as Promus™ by Boston Scientific) is composed of a cobalt–chromium (CoCr) alloy platform coated with a thin layer of fluoropolymer that elutes everolimus, a sirolimus analog, over a period of several months [116]. The SPIRIT family of trials established the safety and efficacy of EES with a significant reduction in late lumen loss (LLL) and clinical events (MI and TVR) at 1 year compared with PES [117,118]. A pooled analysis of SPIRIT II and III found a sustained 44% RRR in major adverse cardiac events in favor of EES at 3-year follow-up and comparable rates of def/prob ST between EES and PES (n = 10, 1.2% vs n = 7, 1.9%; p = 0.43) [119]. The larger SPIRIT IV trial randomized 3687 patients with greater clinical complexity 2:1 to EES versus PES and found a 38% RRR in target-lesion failure (TLF) favoring EES (4.2 vs 6.8%, p = 0.001) and a 75% RRR in protocol-defined ST (n = 4, 0.17% vs n = 10, 0.85%; p = 0.004) at 1-year follow-up [120]. The incidence of ST in the EES group (0.17% protocol, 0.29% ARC def/prob) was among the lowest reported with any DES at the time [120], with a persistent 64% RRR in ST favoring EES at 2-year follow-up [121]. Published alongside SPIRIT IV, the COMPARE trial randomized 1800 nonselected patients to EES versus PES and demonstrated a 31% RRR in composite death, MI or TVR at 1-year (6 vs 9%, p = 0.02) with a significantly lower rate of ST (n = 6, <1% vs n = 23, 3%; p = 0.002) favoring EES, similar to SPIRIT IV [122]. At 2-year follow-up, the rates of ST continued to be significantly lower in the EES group with an impressive 79% RRR compared with PES (n = 8, 0.9% vs n = 35, 3.9%; p = 0.02) [123].

Further modifications have resulted in the next iteration of EES that are commonly used today. The Promus Element™ EES (Boston Scientific) utilizes a modified platinum–chromium alloy scaffold, but the same drug and polymer as Xience V EES. The incorporation of platinum into the platform results in a stent with better deliverability, radiopacity and fracture resistance [124]. This enhanced design was evaluated in the PLATINUM trial, which randomized 1530 low-risk patients to PCI with a Promus Element platinum–chromium EES versus Xience V CoCr EES, and showed comparably low rates of TLF and ST (0.4 vs 0.4%), supporting noninferiority [124]. The Xience Prime EES (Abbott Vascular) utilizes the same CoCr alloy scaffold, drug and polymer as the Xience V EES, but is designed with a slightly different link configuration, resulting in a longer and taller cell that promotes enhanced flexibility and deliverability. In the SPIRIT PRIME trial, the Xience Prime EES was shown to have comparable rates of TLF to historical events rates with Xience V from the SPIRIT family of trials and included a subset of long lesions during which no ST events occurred [125].

Zotarolimus-eluting stents

The Endeavor® zotarolimus-eluting stents (E-ZES; Medtronic, MN, USA) are also composed of a CoCr alloy platform but coated with a thinner polymer that releases an alternative sirolimus derivative, zotarolimus, more rapidly than other DES, with 95% released within 2 weeks. Angioscopic and OCT images revealed greater endothelial coverage of E-ZES struts compared with SES and PES [126], supporting the concept of E-ZES exhibiting intermediate behavior between BMS and DES. The ENDEAVOR family of trials established the safety of E-ZES, but noted higher rates of LLL and TLR compared with SES (9.8 vs 3.5%; p = 0.04) [127] and PES (15.3 vs 10.4%; p = 0.284) [128] despite comparable clinical outcomes. Extended follow-up from ENDEAVOR III and IV suggested E-ZES to be safe based on a reduction in mortality and MI compared with SES [129] and PES [128], and significantly less very late ST compared with PES (0.1 vs 1.6%; p = 0.004) [128]. SORT-OUT III subsequently randomized 2332 unselected patients to E-ZES versus SES and found composite cardiac death, MI or TVR to be twice as high in the E-ZES group at 18 months (10 vs 5%; p = 0.0002) with higher mortality in the E-ZES group (4 vs 3%; p = 0.035) [130]. Among this mixed ACS/stable CAD population with more complex lesions than the prior ENDEAVOR trials, ST was not significantly different at 18-month follow-up.

These disappointing results led to design modifications of the E-ZES, resulting in the Resolute ZES (R-ZES) with a unique blend of three polymers allowing for more delayed drug release [131]. Following the reassuring results in initial feasibility studies [132], the RESOLUTE–US observational study evaluated 1402 patients treated with R-ZES and found a 12-month rate of TLF of just 3.7%, much lower than the historical 6.5% rate of E-ZES controls, and an extremely low 0.1% incidence of ST [133]. When pooled with data from other trials evaluating R-ZES, extremely low rates of def/prob ST (1-year 0.78% and 2-year 0.96%) have been reported [134].

To date, only two trials have directly compared different second-generation DES in a randomized fashion. The Resolute All-Comers trial randomized 2292 patients to EES versus R-ZES and found similar rates of 13-month TLF (8.3 vs 8.2%, respectively; p = NS) with significantly fewer episodes of ST favoring EES (definite: 1.2 vs 0.3%; p = 0.01 and def/prob: 1.6 vs 0.7%; p = 0.05) [135]. The TWENTE trial randomized 1391 patients to EES versus R-ZES and found no difference in TVF at 1 year (8.1 vs 8.2%, respectively; p = NS) and similarly low rates of ST in both groups (definite ST: 0 vs 0.58%; p = 0.12 and def/prob: 1.2 vs 0.9%; p = 0.59) [136]. The exclusion criteria of both trials were very limited, with over half with ACS and over three-quaters with at least an 'off-label' feature for stenting. ST rates among unselected patients treated with ZES and EES are higher than those in RCTs, but remain considerably low compared with rates previously reported for first-generation DES. An analysis of the ESTROFA-2 registry, including 4768 patients treated with either ZES (2549) or EES (2219), found a cumulative incidence of def/prob ST of 1.3% at 1 year and 1.7% at 2 years for ZES, and 1.4% at 1 year and 1.7% at 2 years for EES (p = 0.8) [137]. The increment of definite ST between the first and second year was 0.2 and 0.25%, respectively.

■ Impact of second-generation DES

A consistent theme among all trials evaluating EES is the low rate of ST. Multiple meta-analyses have now been published that suggest EES to possess a superior profile in terms of both efficacy and safety (Table 5). Reductions in ST ranging from 45 [115] to 54% [138] compared with other DES have been suggested on the basis of these studies, an impressive finding when considering the greater complexity of patients in contemporary trials. Utilizing methods capable of comparing multiple stents both directly and indirectly by way of a common reference stent, two independently conducted network meta-analyses have recently added to these findings [30,31]. In what may be regarded as a paradigm shift, Palmerini *et al.* found EES to not only be associated with the lowest rates of definite ST at 1-year of all DES, but also lower rates of definite ST compared to BMS both at 1-year and 2-year follow-up [30]. The reduction in ST with EES compared to BMS was apparent after only 30 days of follow-up and continued to be present between 31 days and 1 year. In a similar analysis of 76 RCTs and 117,762 patient-years of follow-up, Bangalore *et al.* reported EES to have an 86% probability of having the lowest rate of ST of all stents [31]. Multiple EES components may be contributing to the reduction in thrombotic events including thinner stent struts, polymer characteristics and drug effect. In particular, the fluoropolymers used in EES have been demonstrated to have greater biocompatibility and less thrombogenicity as evidenced by a reduction in platelet adhesion *in vitro* [139].

Registries comparing outcomes of patients treated with second-generation DES versus first-generation DES in the modern era also support the superior safety and efficacy of newer devices. An analysis of SCAAR demonstrated the risk of definite ST to be 61% lower among second-generation DES recipients compared with BMS and 43% lower compared with first-generation DES [9]. Patients treated with a second-generation

Table 5. Meta-analyses evaluating safety of everolimus-eluting stents.

Study (year)	Methodology	RCTs (n)	Enrollment (n)	Follow-up	ST definition	Hazard ratio (95% CI) of ST for EES	Ref.
Baber *et al.* (2011)	Meta-analysis	13	17,101	21.7 months	Def/prob	0.55 (0.38–30.78) vs other DES†	[115]
Palmerini *et al.* (2012)	Meta-analysis	11	16,755	2 years	Definite Def/prob	0.38 (0.24–20.59) vs other DES† 0.46 (0.33–30.66) vs other DES†	[138]
Palmerini *et al.* (2012)	Network meta-analysis	49	50,844	1 year	Definite	0.23 (0.13–10.41) vs BMS 0.28 (0.16–10.48) vs PES 0.41 (0.21–20.70) vs SES 0.21 (0.10–10.44) vs E-ZES 0.14 (0.03–00.17) vs R-ZES	[30]
Bangalore *et al.* (2012)	Network meta-analysis	76	57,138	2.1 years	Any ST	0.51 (0.35–30.73) vs BMS 0.59 (0.41–40.83) vs SES 0.44 (0.31–30.60) vs PES	[31]

†*PES, SES or ZES.*
BMS: Bare-metal stent; Def/prob: Definite and/or probable; DES: Drug-eluting stent; EES: Everolimus-eluting stent; E-ZES: Endeavor zotarolimus-eluting stent; PES: Paclitaxel-eluting stent; RCT: Randomized controlled trial; R-ZES: Resolute zotarolimus-eluting stent; SES: Sirolimus-eluting stent; ST: Stent thrombosis; ZES: Zotarolimus-eluting stent.

DES also had lower mortality compared with both BMS patients (45% RRR) and first-generation DES patients (23% RRR) [9]. An analysis of the Bern–Rotterdam registry found the 4-year incidence of definite ST to be significantly lower with EES (1.4 per 100 person-years) versus SES (2.9 per 100 person-years; HR: 0.41 [95% CI: 0.27–20.62]) and versus PES (4.4 per 100 person-years; HR: 0.33 [95% CI: 0.23–20.48]) [140]. Focusing beyond the first year, very late ST with EES was 67–76% compared with first-generation DES, with an annual incidence of only 0.2% (n = 12) in the EES group versus 0.47% (n = 49) in the SES group and 0.8% (n = 53) in the PES group [140].

■ Stents with bioabsorbable polymers

A large body of evidence now supports superior efficacy and safety of second-generation DES compared with first-generation DES. However, one limitation continues to be the nonerodible polymer coating that persists for the life of the patient long after its role as a drug depot has been served. These polymers contribute to the delayed vascular healing and chronic inflammation linked with ST in pathologic studies [34,35]. In an effort to address this potential nidus for ST and restenosis in the long term, newer stents have replaced durable polymer coatings with bioabsorbable polymers (BP), allowing for controlled drug-release followed by subsequent degradation of the polymer coating and, thus, rendering the stent surface similar to that of a BMS. The potential clinical advantage of BP DES over durable polymer DES lies in the potential to reduce the incidence of late adverse events related to impaired vessel healing.

One of the first of these novel devices consists of a microporous stainless steel stent coated with a mixture of rapamycin, BP and resin that completely resorbs *in vivo* after a 6–9-week period and was evaluated in the ISAR stent project. After ISAR–TEST 3 demonstrated noninferiority of this BP stent compared with a Cypher SES [141], ISAR–TEST 4 randomized 2603 patients to receive a BP stent versus a durable polymer stent platform with an equal number of patients in the durable polymer group receiving either a first-generation Cypher SES or second-generation Xience EES [142]. The BP stent was found to be noninferior with respect to MI, death or TLR at 12-month follow-up with low rates of def/prob ST observed in both groups (1.0 vs 1.5%; p = 0.29). A 3-year follow-up has since reported no significant difference with respect to the primary end point (20.1 vs 20.9%, respectively; p = 0.59) or def/prob ST (1.2 vs 1.7%, respectively; p = 0.32) [143]. The type of durable polymer stent (EES vs SES) was not found to be associated with lower rates of def/prob ST (1.4 vs 1.9%, respectively; p = 0.51).

A large amount of data also exist for the BioMatrix™ family of stents (Biosensors International Ltd, Singapore). The polymer consists of a 50:50 matrix of polylactic acid and the antiproliferative agent, Biolimus A9, a semisynthetic sirolimus analog with tenfold greater lipophilicity, which is coated to the abluminal of a flexible stainless-steel stent. This BES polymer coating was previously shown to fully convert to lactic acid by 6 months, followed by further breakdown to water and carbon dioxide in the next few months. The LEADERS trial randomized 1707 patients to PCI with either a BES (n = 857) or SES (n = 850) and found similar rates of death, MI and clinical revascularization at 9-month follow-up [144]. The rate of definite ST at 1-year follow-up was 2.0% in both groups. However, extended follow-up has since demonstrated a 74% RRR in the incidence of very late ST between years 1 and 5 in favor of BES (0.7 vs 2.5%; p = 0.003) [145].

The Nobori BES (Terumo, NJ, USA) also utilizes a blend of Biolimus A9 and polylactic acid, and has been tested against various other DES platforms. After demonstrating noninferior angiographic outcomes compared with first-generation Taxus and Cypher stents in a smaller series of patients [146,147], the Noburi BES has been compared with more current second-generation stents in a randomized fashion. In COMPARE II, 2707 'all-comers' patients were randomized 2:1 to the Nobori BES versus Xience/Promus EES and were found to have comparable rates of composite cardiac death, MI or TVR at 1-year (5.2 vs 4.8%, respectively; p = NS) with very low rates of ST observed in both groups (definite ST: 0.7 vs 0.4%, respectively and def/prob ST: 0.8 vs 1.0%, respectively) [148]. Another large RCT reported less optimistic results based on the Noburi BES, failing to meet its prespecified end point of noninferiority compared with first-generation Cypher SES. The SORT OUT V trial randomized 1229 patients (1532 treated lesions) to BES and 1239 patients (1555 treated lesions) to SES and found a similar incidence of 9-month composite cardiac death, MI, definite ST and TVR (4.1 vs 3.1%, respectively) [149]. The observation that definite ST occurred more often among BES recipients (n = 9, 0.7% vs n = 2, 0.2%; p = 0.034) is a cause for concern given that a reduction in ST is a major objective of this technology but long-term

follow-up will be necessary to determine whether an advantage towards fewer very late ST events favoring BES becomes apparent, as seen in the LEADERS trial.

In a pooled analysis of three of these RCTs comparing stents with BP with stents with durable polymers (ISAR–TEST 3, ISAR–TEST 4 and LEADERS), the risk of definite ST was significantly reduced among patients randomized to a BP DES (HR: 0.56 [95% CI: 0.35–30.90]) driven by a lower risk of very late ST (HR: 0.22 [95% CI: 0.08–00.61]) and also with a lower incidence of MI among such patients (HR: 0.59 [95% CI: 0.73–0.95]) [150].

■ Stents with bioabsorbable scaffolds

Beyond stents with BP coatings, the concept of a fully bioabsorbable coronary stent has been a long-term goal of the interventional community that has recently been realized. By providing short-term lumen support during vessel healing prior to being completely resorbed over time, these stents can allow for a return of normal vascular function, avoidance of permanent side branch occlusion, and a reduction in restenosis and ST.

Several companies are developing and testing different bioabsorbable stent designs. Among them, the ABSORB™ Bioresorbable Vascular Scaffold (BVS; Abbott Vascular) has received considerable attention for reporting clinical and imaging outcomes similar to DES. Made out of poly-L-lactide and coated with everolimus, the Absorb BVS releases 80% of the drug by 30 days (similar to Xience) followed by gradual bulk erosion of the polymer over the next 2 years. The design is notable for having thicker stent struts, less tolerance for overexpansion compared with metal stents, but a variable rate of reabsorption. In the ABSORB trial, this novel stent was prospectively evaluated in 30 low-risk patients and was found to have a low 3.3% event rate (only one non-Q-wave MI) at 12-months with no episodes of ST during this period or at 5-year follow-up [151]. Imaging with IVUS and OCT detected an 11–12% reduction in stent area at 6 months raising concerns about stent recoil and prompting design modifications to improve radial strength. However, at 2-year angiographic follow-up, greater luminal area enlargement due to a decrease in plaque size was demonstrated with no change in LLL compared with 6-months [152]. In addition, approximately one-third of stent struts were no longer discernable and return of vasomotion in response to vasoactive agents was demonstrated. The design enhancements of the ABSORB BVS continue to be evaluated in a similarly low-risk cohort of patients and, thus far, has been associated with lower degrees of LLL compared with the previous cohort [153,154]. Further studies are underway to further evaluate the clinical safety and efficacy of these new devices, including the ABSORB II, which will compare BVS with Xience Prime EES.

Looking forward, although the potential advantages of fully bioabsorbable stents are clear, what remains unclear is whether the potential enhanced safety justifies the use of devices that are currently higher profile, less deliverable and untested in lesions of greater complexity. Issues related to the optimal duration of the scaffolding and drug elution also remain to be determined.

Advances in pharmacotherapy

■ Role of DAPT established

The feasibility of coronary stenting was accompanied by immediate recognition of the thrombotic properties of this new technology, prompting pharmacologic strategies to reduce platelet aggregation and subsequent thrombosis. Combinations of ASA and dipyridamole were first used followed by the addition of anticoagulants to reduce the unacceptable high rates of abrupt vessel closure [4,5]. Such regimens were plagued by high rates of bleeding and vascular complications leading to prolonged hospitalizations and prompting multiple trials to determine the optimal regimen to balance the risks of ST and bleeding. The combination of ASA and ticlopidine was shown to dramatically reduce ischemic events and hemorrhagic complications compared with conventional anticoagulant therapy in ISAR [155] and FANTASTIC [156]. Subsequently, the STARS trial evaluated three different anti-thrombotic regimens and found a significant reduction in 30-day ST with ASA and ticlopidine (0.5%) compared with ASA alone (3.6%) or ASA and warfarin (2.7%) [157]. ASA and ticlopidine was further shown to reduce vascular complications post-PCI in high-risk and unselected patients [156,158]. Soon thereafter, clopidogrel emerged as an alternative thienopyridine, offering advantages of greater potency, more rapid onset of action, and fewer and less serious adverse events compared with ticlopidine. Results from PCI–CURE and CREDO supported the benefit of prolonged treatment with clopidogrel and ASA based on a significant reduction in ischemic events without an increase in major bleeding [159,160], establishing this DAPT regimen as the cornerstone of post-PCI therapy.

■ Novel P2Y12 antagonists

Efforts to further reduce the incidence of ST have focused on achieving a more pronounced and consistent degree of platelet inhibition. Two P2Y12 receptor antagonists in particular, prasugrel and ticagrelor, have succeeded in this regard by demonstrating improved outcomes in the ACS population compared with clopidogrel.

In TRITON–TIMI 38, treatment of moderate-to-high risk ACS patients with prasugrel was associated with a 19% RRR (12.1 vs 9.9%; $p < 0.001$) in the incidence of cardiovascular death, MI or stroke compared with clopidogrel, albeit at the cost of more major bleeding (2.4 vs 1.8%; $p = 0.03$) [59]. Among patients who underwent PCI, the incidence of def/prob ST was significantly reduced with prasugrel (2.4 vs 1.1%; $p < 0.001$), a difference that persisted among those implanted with both DES (0.8 vs 2.3%) and BMS (1.3 vs 2.4%), and that was apparent both in the early period (71% RRR from 1.44 to 0.42%) and the late period (54% RRR from 0.91 to 0.42%) [161]. A striking reduction in ST was observed in subgroups of patients with diabetes (1.6% absolute risk reduction [ARR]), more than 20 mm of stent (1.5% ARR), bifurcation stents (3.2% ARR) and those with an MI prior to presentation (2.6% ARR).

In the PLATO trial, a similar population of 18,624 ACS patients undergoing planned PCI was randomized to clopidogrel versus ticagrelor [60]. Treatment with ticagrelor was associated with a 16% RRR (11.7 vs 9.8%; $p < 0.001$) in the composite of vascular death, MI or stroke, again at the cost of more major noncoronary artery bypass graft-related bleeding (4.5 vs 3.8%; $p = 0.03$) [60]. The incidence of def/prob ST was significantly reduced among patients treated with ticagrelor (2.2 vs 2.9%; $p = 0.02$).

An adjusted indirect meta-analysis between ticagrelor and prasugrel utilizing patient data from TRITON, PLATO and DISPERSE-2 reported a 39% RRR in ST among patients receiving one of these more potent P2Y12 inhibitors compared with clopidogrel [162]. The data supporting the use of these more potent P2Y12 inhibitors is limited to patients presenting with ACS and has not yet been demonstrated to provide a similar benefit in patients undergoing PCI for stable CAD.

■ Novel oral anticoagulants

Although inhibition of the coagulation cascade with heparin products or direct thrombin inhibitors is a mainstay of therapy in the periprocedural period, few patients receive pharmacotherapy targeting the generation of thrombin in an outpatient setting after undergoing PCI. The emergence of novel oral inhibitors of the coagulation cascade for the reduction in embolic events in patients with atrial fibrillation and for the management of venous thromboembolism has renewed interest in the potential role of such therapy in patients with CAD who are being treated for ACS. Among these, the factor-Xa inhibitor rivaroxaban, was studied in the ATLAS ACS 2 TIMI 51 trial, which randomized 15,526 patients with recent ACS to receive twice-daily doses of either 2.5 or 5 mg of rivaroxaban or placebo in addition to standard therapy including low-dose ASA and a thienopyridine for a mean of 13 months [163]. Patients randomized to rivaroxaban experienced a 16% reduction in composite cardiovascular death, MI or stroke (8.9 vs 10.7%; $p = 0.008$) with similar efficacy seen in both doses. Patients who received rivaroxaban also experienced a 31% reduction in ST. Not unexpectedly, patients randomized to rivaroxaban experienced higher rates of noncoronary artery bypass graft major bleeding (2.1 vs 0.6%; $p < 0.001$) and intracranial hemorrhage (0.6 vs 0.2%; $p = 0.009$), but fewer fatal bleeding events were observed in patients taking the lower twice daily 2.5-mg dose compared with the 5-mg dose (0.1 vs 0.4%; $p = 0.04$). Although not yet FDA approved for the management of ACS, the addition of rivaroxaban as a potential adjunct to the current mainstay of DAPT will present new challenges for clinicians seeking to achieve a balance between reducing subsequent ischemic events and minimizing the potential for major bleeds.

Conclusion

ST is a rare, but devastating, complication associated with high morbidity and mortality. Patients typically present with acute MI and do not often survive long enough to present for clinical evaluation. Risk factors for ST include those relating to patient characteristics (comorbid clinical conditions, stable versus unstable presentation, antiplatelet therapy compliance and/or resistance), lesion characteristics (length, thrombus burden, bifurcation) and the procedural details (including stent characteristics). Recognition of these risk factors can aid the operator in reducing the incidence of ST with careful patient and stent selection and meticulous technique. Pathologic studies and coronary imaging modalities have advanced our understanding of the mechanisms contributing to ST during different time intervals. These insights have led to advancements in stent design and pharmacotherapy resulting in

a reduction in event rates. Despite these gains, ST continues to represent a threat, particularly among patients of greater complexity. Ongoing studies may help determine the optimal duration of DAPT following stent placement and the role of novel stents with bioabsorbable materials.

Executive summary

Definitions for stent thrombosis

- Academic Research Consortium definitions have standardized the way in which stent thrombosis (ST) is diagnosed and reported, allowing for more meaningful comparisons across clinical trials. These definitions characterize events based on degrees of certainty (definite, probable and possible), as well as timing (early: 0–30 days, late: 30 days to 1 year and very late: beyond 1 year).

Incidence & timing

- The timing and incidence of ST varies depending on the type of stent placed and the complexity of the patient population studied, with higher rates typically observed in registries of nonselected patient compared with rates reported from randomized controlled trials.
- Early and late ST occurs at similar rates with both bare-metal stents and first-generation drug-eluting stents (DES).
- First-generation DES are associated with a risk of very late ST, ranging from 0.2% in patients with noncomplex coronary artery disease to as high as 0.6% in higher risk patients.
- Second-generation DES have less long-term follow-up data available, but have been shown to have lower rates of ST across all time periods.

Mechanisms

- The underlying mechanisms of ST vary depending on the timing of the event and the type of stent placed.
- Early ST is often related to suboptimal procedural results or medical noncompliance, and is similar between recipients of both bare-metal stents and DES.
- Late and very late ST is often related to the inflammatory response to one or more components of DES that can manifest as hypersensitivity, delayed arterial healing and late acquired malapposition. Very late ST may also result from unique mechanisms such as neoatherosclerosis.

Predictors

- Multiple risk factors for ST have been identified based on retrospective and prospective registries and are often classified as being related to the patient, the lesion or the procedure.
- Acute coronary syndrome increases the risk for subsequent ST similarly for both bare-metal stents and first-generation DES. Emerging data suggest that this risk may be reduced with newer DES.
- Early discontinuation of dual antiplatelet therapy is the most consistent and powerful predictor of ST.
- Studies comparing shorter versus longer durations of dual antiplatelet therapy have not demonstrated a significant clinical benefit from longer prescriptions of dual antiplatelet therapy. Until the results of ongoing randomized controlled trials are able to provide further insight into the optimal duration, individual assessment of each patient's unique risks for both thrombosis and bleeding should be used to guide clinical decision-making.
- Clopidogrel hyporesponsiveness is associated with higher rates of ST post-percutaneous coronary intervention. Platelet function testing and genetic testing can identify patients at risk for ischemic events, but a routine testing strategy has not been demonstrated to improve clinical outcomes in randomized controlled trials.

Advances in stent technology

- Second-generation DES have incorporated design enhancements including thinner struts, more biocompatible polymers and enhanced deliverability that have contributed to their enhanced efficacy and safety compared with first-generation DES.
- Among the DES that are commonly used today, multiple analyses suggest everolimus-eluting stents to possess a superior profile in terms of efficacy and reduction in ST; however, head-to-head comparisons with Resolute zotarolimus-eluting stents demonstrate comparable clinical results.
- Novel stents with bioabsorbable polymers and scaffolds provide theoretical benefit in further reducing ischemic events during long-term follow-up, but more data are necessary before they replace the current generation of DES.

Advances in pharmacotherapy

- Both prasugrel and ticagrelor provide more rapid and intense platelet inhibition with less variability than clopidogrel and have been shown to significantly reduce subsequent ischemic events, including ST, in the acute coronary syndrome population.
- Rivaroxaban, a factor-Xa inhibitor, was shown to reduce ischemic events, cardiac death and ST in the acute coronary syndrome population. Novel oral anticoagulants may play an important role in the future as an adjunct to antiplatelet therapy.
- Among patients deemed to be at higher risk for ST based on other clinical characteristics, the benefit of intensifying P2Y12 inhibition must be carefully weighed against the risks of major bleeding.

Conclusion

- Advances in both stent technology and pharmacotherapy have reduced the incidence of ST, but the ongoing risk of events mandates a thoughtful assessment of risk factors for both thrombosis and bleeding in order individualize decision-making for each patient.

Future perspective

- Early studies of stents with bioabsorbable polymers have demonstrated promise in their ability to reduce the rates of very late ST. Long-term follow-up is necessary to fully assess the safety of these devices.
- Stents with fully bioabsorbable scaffolds represent an attractive concept to reduce the long-term burden percutaneous coronary intervention. Whether the current limitations of these devices can be overcome to realize these benefits remains to be determined.

Future perspective

Although ST continues to be a serious complication associated with PCI, advancements in stent technology and pharmacotherapy have progressively reduced the incidence to the lowest rates observed. The next generation of stents with BP coatings may potentially reduce ST even further by eliminating one of the remaining contributors to late events and have shown promise in early clinical follow-up. Beyond that, stents that fully degrade into nontoxic byproducts months-to-years after treating coronary lesions are currently being developed and tested, but are several years away from clinical practice. The reductions in ST observed with both prasugrel and ticagrelor highlight the benefits of more potent antiplatelet therapy among select populations. The addition of alternative antithrombotic agents, such as factor-Xa inhibitors, have the potential to further reduce ST but also afford greater risks of bleeding. Moving forward, clinicians will increasingly face challenges of balancing the risks of ischemic events and the risks of bleeding, both of which lead to adverse outcomes, as novel antithrombotic therapy is introduced. Expert operator techniques will always be needed to ensure good outcomes and to prevent complications with PCI, but ongoing improvements in stent design and pharmacotherapy promise to mitigate the effects of complex anatomy and other high-risk clinical features on the incidence of ST, allowing for the expanded use of stents in patients who can potentially benefit from coronary revascularization.

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