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Review

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Outcomes, risk factors, and procedural management of acute myocardial infarction caused by stent thrombosis

Emiliano Bianchini[1], Francesco Bianchini[1], Mattia Lunardi[1,2], Andrea Zito[1], Enrico Romagnoli[1,2], Cristina Aurigemma[1,2], Lazzaro Paraggio[1,2], Ilaria Dato[1,2], Francesco Burzotta[1,2], Carlo Trani[1,2]

[1]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy.
[2]Department of Cardiovascular Sciences, Policlinico A. Gemelli IRCCS, Università a Cattolica Sacro Cuore, Rome 00168, Italy.

Correspondence to: Dr. Francesco Burzotta, Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy; Department of Cardiovascular Sciences, Policlinico A. Gemelli IRCCS, Università a Cattolica Sacro Cuore, Rome 00168, Italy. E-mail: francesco.burzotta@policlinicogemelli.it

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Abstract

Coronary stent thrombosis (ST) is a rare but severe complication of percutaneous coronary interventions (PCIs) with significant implications for patient outcomes. Despite advancements in antiplatelet medications and drug-eluting stent (DES) technology, ST remains associated with considerable morbidity and mortality. Notably, ST is an adverse event arising from various factors, including patient characteristics, stent-related issues, and procedural complications. In such a context, intravascular imaging (IVI) plays a pivotal role in assessing the underlying mechanisms and guiding treatment decisions. The use of thrombus aspiration and intracoronary antithrombotic therapies have been debated in the context of de novo acute myocardial infarction, but they could have a remarkable role for ST. However, the optimal management of ST requires individualized approaches tailored to patient-specific factors. This review provides a comprehensive analysis of the current understanding of ST, encompassing its incidence, outcomes, and risk factors, focusing on procedural acute management.

Keywords: Stent thrombosis, acute myocardial infarction, percutaneous coronary intervention

INTRODUCTION

Coronary stent/scaffold thrombosis (ST) represents a rare but yet dramatic complication following percutaneous coronary intervention (PCI) involving stent implantation[1].

During the early stages of coronary stenting, bare-metal stents (BMS) were associated with up to 20% of ST[2]. The introduction of dual-antiplatelet therapy (DAPT) - instead of intensive anticoagulation therapy - together with adequate stent expansion via high-pressure balloon inflation lead to a favorable reduction of angiographically documented ST at 6-month follow-up[3,4].

Although rare nowadays, ST exerts a significant impact on patient outcomes, and from an epidemiological standpoint, it holds numerical importance because of the widespread utilization of PCIs worldwide. According to recent reports, the incidence of ST varies based on its timing of occurrence. Rates range from 0.5%-1% within the first year following PCI to 0.2%-0.6% in subsequent years[5].

Even with improvements in antiplatelet medications and drug-eluting stent (DES) technology, adverse cardiac events remain significant following an initial ST episode. Long-term cardiac mortality rates hover around 30%-40% for definite ST cases[6,7].

Most patients experiencing ST present with ST-elevation myocardial infarction (STEMI) and urgent rePCI is the primary management strategy[8,9]. In this context, STEMI caused by ST presents a higher risk of both short-term and long-term mortality compared to de novo STEMI[1].

Moreover, managing ST presents numerous challenges due to patient frailty and complexities in both procedural treatments (e.g., severe stent malapposition hindering device advancement, in-stent restenosis) and medical therapies (e.g., P2Y12 non-responsiveness, urgent need for rapid platelet inhibition). Given these uncertainties, the authors aimed to review the current evidence regarding ST, with a focus on its urgent procedural and pharmacological management.

DEFINITIONS, INCIDENCE AND OUTCOMES

As per the definition provided by the Academic Research Consortium (ARC), current studies must define ST based on the likelihood of its occurrence. This approach is necessary because a number of patients experiencing ST may pass away before receiving a diagnosis, underestimating the true occurrence of such an event[10]. Definite ST requires a clear diagnosis of intracoronary thrombus, typically confirmed through angiography or autopsy. In contrast, probable or possible ST diagnoses are based on the clinical likelihood of ST in patients who passed away during the trial follow-up (e.g., signs of ischemia in the previously treated myocardial territory). To mitigate the risk of underdiagnosis, most studies report ST as a composite of both probable and definite ST.

From a clinical standpoint, ST is categorized according to its timing relative to the index PCI. The ARC recommends its classification into early (0 to 30 days) - subclassified as acute (< 24 h) and subacute (< 31 days but > 24 h) - late (31 days to 1 year), and very late (> 1 year) ST, aiming to highlight differences in the underlying pathophysiological mechanisms during these distinct periods[10].

The majority of ST, whether with BMS or DES, typically occur within the initial 30 days, when the endothelization of most of the stent platform is still incomplete[11,12]. However, differently from first-generation DES, newer DES has been demonstrated to be safer in the setting of 1-month short DAPT in

high-bleeding-risk patients compared to BMS[13,14].

In the era of DAPT, the overall rate of ST is typically less than 1%. Higher rates, ranging from 2% to 3%, have been reported for patients undergoing PCI for acute coronary syndromes (ACS)[15,16]. In the "Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents" (ADAPT-DES) registry, the risk of probable/definite ST ranged from 0.8% to 2% within a 2-year follow-up period and there was a notable higher risk observed across the spectrum of ACS, with STEMI representing the most hazardous clinical setting[12].

ST, despite rare, imposes a significant mortality burden both at short-term and long-term follow-up. In the "Outcome of PCI for stent-ThrombosIs MultIcentre Study" (OPTIMIST) registry, nearly one-fifth of patients with ST died within a 30-day follow-up period. This mortality rate consistently rises after the 6-month follow-up, reaching as high as 30%[9]. Furthermore, the angiographic outcomes of PCI performed to treat ST frequently exhibit suboptimal results, and nearly 40% of patients display varying degrees of angiography-derived measures of coronary microvascular obstruction[9].

In a pooled analysis of the Patient Related Outcomes with Endeavour vs. Cypher Stenting Trials (PROTECT trials), half of the patients who experienced ST died within the 4-year follow-up period. Alarmingly, nearly two-thirds of these deaths occurred within the first day after undergoing urgent PCI[7]. This underlines the potential difficulty in managing such an acute event. Patients presenting with an early ST have a higher mortality compared to patients with late or very late ST. The latter, indeed, have comparable outcomes to de novo STEMI - underlying different aetiologic mechanisms and suggesting different management[7,17].

PATHOPHYSIOLOGY AND RISK FACTORS OF STENT THROMBOSIS

ST emerged as a major concern following the introduction of first-generation DES. Although these stents effectively reduced early in-stent restenosis compared to previous BMS, they also led to delayed reendothelialization caused by the release of antiproliferative drugs. Consequently, this prolonged exposure of the metallic platform to the bloodstream heightened the risk of platelet interaction, activation, and thrombosis. Contemporary DES consists of a metallic platform, an antiproliferative drug, and a drug carrier, offering improvements in each component compared to early-generation DES[18].

The cobalt-chromium or platinum-chromium composition of new DES enhances radial strength and reduces strut thickness. Compared to older stainless steel stents, the lower nickel content and the presence of fluoropolymer reduce platelet and inflammatory activation[19]. Accordingly, ST arises from various mechanisms, not limited to technical aspects, such as stent optimization, but also interactions among stent composition, drugs, drug carriers, patient biology, and antiplatelet regimens [Figure 1][1,20].

The most investigated risk factors for ST depend on its timing. Early discontinuation of DAPT, particularly in patients undergoing PCI for ACS, as well as small vessel diameter, stent undersizing/underexpansion/fracture, early in-stent restenosis, and suboptimal procedural results (i.e., slow flow/no-reflow), are the most influential factors for early ST[12,21,22]. Among them, an early interruption of DAPT is the strongest risk factor, especially within the first month after PCI. In the recent STOPDAPT 3, a more conservative aspirin-free strategy with a single potent P2Y12 during the first month after a PCI was not superior to a standard DAPT regimen in terms of both bleeding and ischemic events[23]. However, specifically in ACS patients, a higher incidence of ST was noted in the aspirin-free regimen compared to standard DAPT within the first month. This underscores the necessity for more effective platelet reactivity inhibition following PCI for ACS, especially within the first month. Furthermore, the use of potent P2Y12 inhibitors (such as Prasugrel

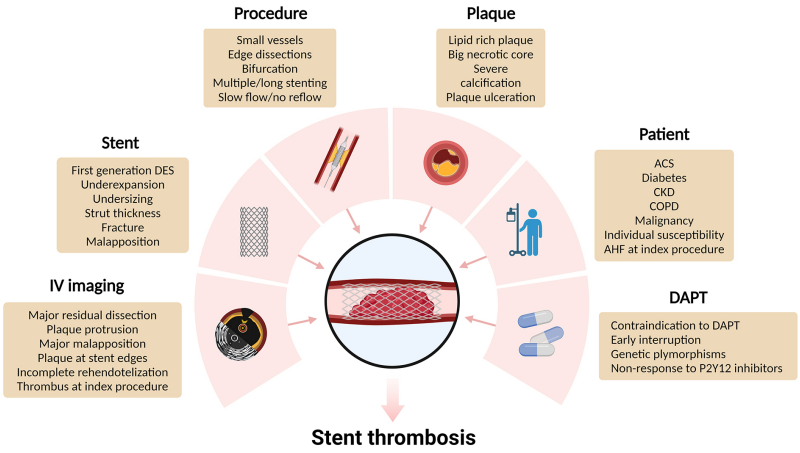

Figure 1. Principal risk factors for ST. ACS: Acute coronary syndrome; AHF: acute heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DES: drug-eluting stent; DAPT: dual antiplatelet therapy; ST: stent thrombosis. Created by BioRender.com.

or Ticagrelor) should be the preferred choice as the second antiplatelet drug in patients at a heightened risk of recurrent ischemic events, such as those undergoing PCI for ACS[24,25]. In light of a well-balanced bleeding and ischemic risk, the use of long-lasting antiplatelet regimens with aspirin plus a potent P2Y12 inhibitor after 1 year in ACS patients was also tested to reduce ischemic events[26]. On the other hand, in patients undergoing PCI for chronic coronary syndrome (CCS), where a default strategy with clopidogrel plus aspirin for 3-6 months is normally adopted, the occurrence of early ST suggests a non-response to clopidogrel[27,28].

Conversely, the primary contribution to late-onset ST is subjective. Despite the evolution of DES to address the inflammatory response of coronary vessels to metals and polymer coatings, late-onset ST is mainly attributed to patient susceptibility to stent failure, mediated by in-stent restenosis and impaired reendothelization, which involve a prothrombotic status, a predisposition for aggressive atherosclerosis, and clinical conditions that contraindicate a longer dual DAPT regimen (e.g., malignancy). Patient characteristics such as chronic kidney disease (CKD), diabetes, obesity, chronic obstructive pulmonary disease and malignancy - favoring a long-lasting vessel inflammation and in-stent restenosis - emerge as the most robust risk factors for late ST[20,21]. Stent restenosis can itself lead to ST, mainly with late and very late onset: in the U.S. CathPCI registry, among more than 500,000 patients with in-stent restenosis, 25% presented with acute MI[29]. Specifically, in-stent restenosis can be classified as either resulting from neointimal hyperplasia or neoatherosclerosis, and although their pathophysiology differs, both can lead to ST[5,20]. Neointimal hyperplasia is a reparative mechanism wherein a combination of coagulation and inflammatory factors induces the proliferation of vascular smooth muscle cells and extracellular matrix at the site of stent implantation. An “allergic” reaction to the stent metals and polymers, associated or not with an individual resistance to antiproliferative drugs, could lead to an abnormal reparative process and restenosis[30,31]. Otherwise, neoatherosclerosis is a progression of coronary disease in response to ongoing endothelial dysfunction and incomplete stent endothelization. Vulnerable plaques with larger necrotic cores, commonly encountered during ACS, are particularly susceptible to the progression of neoatherosclerosis. After PCI of ruptured plaques, LDL accumulation accelerates within the exposed necrotic core, a process further exacerbated by the pro-inflammatory environment characteristic of ACS[32,33]. This partially explains the higher risk of ST in patients undergoing PCI for ACS.

With the advent and widespread adoption of intravascular imaging (IVI), several procedural outcomes have been investigated - and quantified - as risk factors for ST [Figure 2]. The absence of adequate stent apposition (> 350 μm distance of the struts from intima or > 200 μm for a length > 600 μm), or significant underexpansion (cross-sectional area < 75% of the reference lumen area) are among the primary findings associated with ST, particularly in early presentations[34-36]. Additionally, stent malapposition can also occur later because of positive vessel remodeling. Uncovered stent struts were largely observed even in cases of late ST, suggesting causes other than the release of antiproliferative drugs[29]. This phenomenon has been attributed to the elevated shear rates occurring in stented small vessels or vessels that are inadequately expanded following stent deployment, hindering complete reendothelialization over the struts. Thinner struts and greater distance between them - facilitated by optimal stent expansion - are associated with improved reendothelialization and subsequent reduced risk of ST[34,37]. Furthermore, unapposed stent struts create local front-facing obstacles that disrupt the blood flow stream and generate high shear rates. The distance between the struts and vessel wall correlates with the extent of flow disturbances, posing a tangible risk of ST following the discontinuation of DAPT[35,38]. Moreover, impaired reendothelialization resulting from suboptimal stent optimization in "high-risk" locations, such as coronary bifurcations, can create an even more hazardous thrombogenic source. Consequently, PCI on coronary bifurcations is identified as one of the risk factors for future ST[39,40]. Other features - not directly related to the stent expansion - were identified through IVI and were associated with a heightened risk of stent failure and ST. These include major plaque protrusion between the stent struts, particularly irregular protrusion with significant luminal extension (> 0.5 mm), major edge dissection (defined as a dissection penetrating into the media, longer than 3 mm, and extending more than 60°), or significant residual plaque burden at the stent edges (5-mm edge zones adjacent to the stent with more than 30% stenosis of the reference diameter and major lipid plaque or plaque rupture). These factors have been considered in current randomized controlled trials (RCTs) involving IVI guidance to optimize stent implantation and minimize the risk of ST[36,41-45].

MANAGEMENT

The management of acute MI following ST should involve a meticulous evaluation of the underlying mechanisms, considering the timing of ST occurrence - whether early or late - to guide clinical decision-making and determine the most appropriate pharmacological and interventional treatments [Figure 3].

Pharmacological management

Given that early discontinuation of DAPT or biological non-response to P2Y12 inhibitors are primary causes of ST, obtaining precise information and rapidly reinstating an adequate antiplatelet regimen are essential. During the acute phase, promptly addressing platelet aggregation through intravenous administration of antiplatelet medications - such as Glycoprotein (GP) IIbIIIa inhibitors or Cangrelor - may prove advantageous, especially in DAPT-naïve patients[46,47]. Cangrelor, an adenosine triphosphate analog, selectively and reversibly inhibits platelet activation mediated by the P2Y12 receptor. Currently, it stands as the sole intravenous P2Y12 inhibitor approved for clinical use by the Food and Drug Administration[46]. Rapid and potent platelet inhibition is observed within minutes, and platelet function typically recovers within 60 min after discontinuation. In a comprehensive meta-analysis of patient-level data from three phase III trials involving 24,910 patients, Cangrelor demonstrated a significant reduction in the rate of stent thrombosis at 48 h compared to Clopidogrel[48].

However, it is worth noting the absence of studies examining Cangrelor as an upfront treatment for patients with ST and the relatively low average percentage of patients presenting with STEMI in the cited pooled analysis (12%). Nonetheless, in a nationwide real-world registry, Cangrelor was predominantly used in patients with STEMI (> 98%), demonstrating optimal short-term outcomes[49]. Operators could have

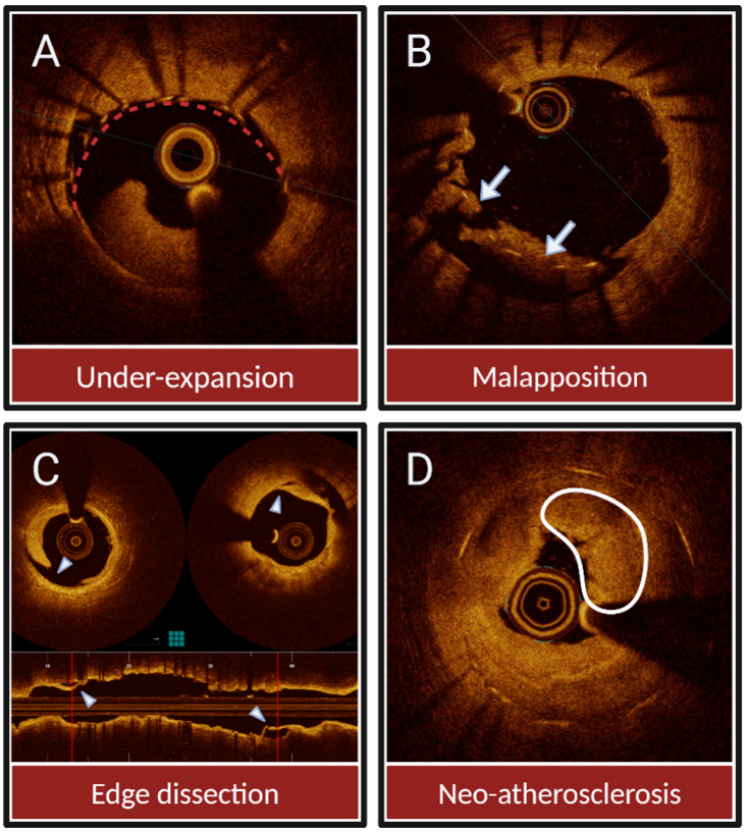

Figure 2. Examples of intravascular imaging findings in patients presenting with ST and acute myocardial infarction. (A) Stent underexpansion (dashed red line). (B) Stent malapposition with thrombus (white arrows). (C) Major edge dissections (white triangles). (D) Neo-atherosclerosis mixed with thrombus (white circle). ST: Stent thrombosis. Created by BioRender.com.

benefited from the flexible and rapid platelet inhibition offered by Cangrelor, without the need to administrate oral P2Y12 inhibitors before coronary angiography. However, it is important to note that Cangrelor has not been adequately investigated in direct comparisons with Ticagrelor and Prasugrel in P2Y12 inhibitors-naïve patients undergoing PCI for ACS, and the potential add-on of Cangrelor to patients treated with oral loading doses of these agents remains uncertain. In the FABOLUS-FASTER trial conducted by Gargiulo *et al.*, the use of Cangrelor in P2Y12 inhibitors-naïve patients presenting with STEMI was found to be superior to a loading dose of 60 mg of prasugrel in terms of inhibiting platelet aggregation at 30 min[50]. Therefore, in individuals who have not received P2Y12 inhibitors or GP IIb/IIIa inhibitors, Cangrelor may represent a favorable option to rapidly achieve an adequate antiplatelet effect before undergoing a complex and high-risk PCI.

GP IIb/IIIa inhibitors target the final pathway of platelet aggregation, inhibiting their binding mediated by von Willebrand factor and fibrinogen[51]. These drugs inhibit platelet activation mediated by all agonists, and their antiplatelet activity is almost immediate and more potent than that provided by Cangrelor[50]. Most of the data on upfront GP IIb/IIIa inhibitors administration are limited to the pre-P2Y12 antagonists era, and nowadays, their routine use is no longer recommended[52]. Recent studies conducted in the era of potent P2Y12 inhibitors have shown conflicting results regarding the benefits of GP IIb/IIIa inhibitors, raising concerns about an increased risk of thrombocytopenia and bleeding events[47,53]. Shortening the infusion duration of GP IIb/IIIa inhibitors to less than 18-24 h, as tested in most prior trials, may be considered safer in patients at low risk of bleeding, especially when PCI is performed via a radial approach[54]. Another

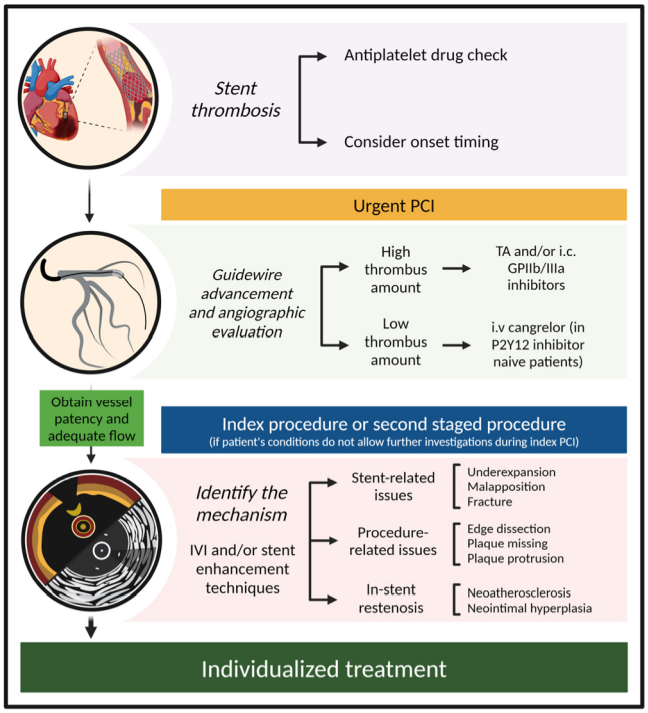

Figure 3. Procedural management algorithm for ST. GP: Glycoprotein; IVI: intravascular imaging; TA: thrombus aspiration; ST: stent thrombosis; PCI: percutaneous coronary intervention. Created by BioRender.com.

alternative is to administer the drug directly into the coronary circulation to minimize systemic adverse effects[55,56]. According to current guidelines, GP IIbIIIa inhibitors are recommended as bail-out drugs if there is evidence of no-reflow or a thrombotic complication during PCI[52]. Hence, in the context of ST, particularly when a large amount of thrombus is observed during angiography, the use of rapid-onset GP IIb/IIIa inhibitors may be beneficial. The intracoronary administration of Abciximab - an irreversible GP IIbIIIa binder - is one of the most studied strategies, partly due to its claimed favorable effects on microvascular function and inhibition of the inflammatory cascade compared to small molecules such as Eptifibatide and Tirofiban[55]. Intracoronary Abciximab, whether combined with prior mechanical removal of thrombus by manual thrombus aspiration (TA) or not, has been demonstrated to be superior to standard PCI in terms of angiographic surrogate endpoints for myocardial perfusion and infarct size[57-61].

Beyond procedural alternatives to manage ST and its related issues, one of the initial steps to prioritize is maintaining adequate antithrombotic status throughout the entire procedure. Unfractionated heparin (UFH) remains the primary anticoagulant in patients with STEMI undergoing primary PCI. In case of thrombotic complications, operators should administer a full dose of UFH based on the patient's weight (100 IU/kg) and verify adequate anticoagulation by assessing the activated clotting time (ACT). Notably, heparin acts on the coagulation cascade triggered by thrombin activation, preventing the formation of new fibrin clots, but it does not have an effect on already formed thrombi[62]. Recently, the use of intracoronary fibrinolytic therapy has been reconsidered as a potential option in STEMI cases with high thrombus burden, showing promising angiographic results compared to conventional PCI[63]. Its intracoronary administration minimizes systemic adverse effects, and could function as a solution to dismantle an already formed clot during ST. Importantly, the combination of intracoronary fibrinolysis and manual TA may exert a synergistic effect in cases of ST with a large thrombus burden[64]. However, a totally conservative stent-free strategy for ST, which involves a combination of intracoronary pharmacological therapies plus mechanical thrombus removal by TA, has yet to be tested in a large multicenter RCT.

Interventional management

After ST angiographic diagnosis, manual TA serves as a valuable tool to mechanically remove the thrombus and prevent distal embolization. Despite the absence of clinical advantage demonstrated in large RCTs in patients with STEMI, TA represents an effective strategy in preventing distal embolization, improving myocardial perfusion, and, as demonstrated by a recent patient-level data meta-analysis, potentially reducing cardiovascular mortality at both 30 days and 1-year follow-up, in cases of large thrombus burden[65-69]. Five observational studies have evaluated the role of routine TA soon after guidewire passage through the thrombus in patients with definite ST. Out of these, four studies reported a favorable effect of TA on angiographic outcomes compared to standard PCI, despite a lack of clear clinical advantage[70-74]. The combined treatment of GP IIb/IIIa inhibitors and TA in a specific context such as ST may represent a safe option when a stent-free strategy is chosen by the operator[58]. TA during ST may also offer advantages for the use of IVI, which is the most reliable tool to evaluate the underlying mechanisms of ST. A "cleaner" intravascular image facilitates a better understanding of stent failure mechanisms. Moreover, the use of IVI allows the optimization of PCI, thereby reducing the risk of further stent failures[75]. When major edge dissections, plaque missing, or severe plaque protrusions are observed, it is recommended to consider a new stent implantation: the goal is to maintain the vessel patency and a lumen surface as much regular as possible, minimizing potential flow-disrupting factors that could trigger further thrombus formation, especially in a pro-inflammatory and prothrombotic environment often present in patients experiencing ST. If high-pressure non-compliant (NC) balloon inflation proves ineffective in cases of severe stent underexpansion, IVI may suggest the presence of severe calcified atherosclerosis that could have hindered optimal expansion during the previous PCI. This underscores the need for advanced techniques that can be safely employed beneath the stent struts, such as super-high-pressure NC balloons or intravascular lithotripsy[76,77]. Prompt recognition and mechanical management with high-pressure inflated NC balloons are imperative for addressing stent underexpansion or major malapposition, which are significant drivers of early ST. It is noteworthy that failure to recognize more severe stent distortion, such as fracture or crush, could result in detrimental complications during the procedure, including additional device damage, dissections, and perforations[22,78]. Currently, advanced fluoroscopic imaging techniques, also referred to as "stent enhancement" techniques, are available to visualize the geometrical distortion of previously implanted stents (e.g., StentBoost [Philips]). These techniques have shown comparable performance to IVI in detecting underexpansion[79]. Even though macroscopic fluoroscopic findings are often observed in early ST and can be promptly recognized through fluoroscopy alone, a combination of stent-related features and other mechanisms (i.e., early in-stent restenosis, dissections) is not uncommon and only the use of IVI can provide a comprehensive evaluation of the underlying mechanisms of ST.

Furthermore, the utilization of IVI improves the assessment of neoatherosclerosis calcification, suggesting the need for calcium-debulking techniques (e.g., rotational and orbital atherectomy). A systematic and repeated application of IVI is imperative to steer this off-label utilization and enhance safety under the stent struts[80-82]. Obviously, the use of IVI should be considered in the context of procedural safety, weighing the advantages of the obtainable information against the associated risks.

After the restoration of vessel patency and adequate flow, current evidence supports the use of drug-coating balloons (DEBs) in STEMI patients as a safe alternative to DES in selected cases, particularly when lesion preparation with pre-dilation and thrombus remotion results in adequate lumen patency (< 30% residual stenosis)[83,84]. Notably, in late ST, the presence of in-stent restenosis is frequent and the use of DEB angioplasty could serve as an alternative to stent-in-stent implantation, especially in small vessels (mean diameter < 2.75 mm) and in patients with suboptimal response to the stents[85]. The most extensive meta-

analysis on this topic demonstrated comparable outcomes between the use of DEB or DES concerning the composite endpoint of all-cause death, myocardial infarction, and target lesion thrombosis[86]. Of note, the implantation of a DES-in-stent yielded a lower incidence of target lesion failure in comparison to DEB treatment, particularly in the management of DES restenosis. It was postulated that DES restenosis mainly stems from neoatherosclerosis, in contrast to the more prevalent neointimal proliferation observed in BMS restenosis. Hence, the efficacy of DEB might be diminished in such cases. On the other hand, the predominance of neointimal proliferation may indicate a patient-specific predisposition to stent failure, particularly among "frequent flyers". Following a conservative balloon angioplasty, prescribing novel medications such as anti-inflammatory drugs could prove to be a promising strategy[87]. However, the optimal management of in-stent restenosis falls outside the aim of the present review.

Ultimately, a prompt diagnosis and a comprehensive understanding of the underlying mechanisms are essential to personalize either the revascularization treatment or the follow-up management, particularly in cases of late and very late ST. Indeed, while evident stent-related issues can be addressed in the cath lab, the presence of neoatherosclerosis warrants a more aggressive control of cardiovascular risk factors, handled through medical and lifestyle optimization. On the other side, ineffective DAPT regimens deserve specific investigations to rule out patient's resistance to P2Y12 inhibitors, or to verify adequate absorption of antiplatelet molecules. However, reiterative restenosis suggests particular attention to comorbidities such as CKD, COPD and heart failure, which can further disrupt such a delicate inflammatory and coagulative balance.

CONCLUSION

A comprehensive approach encompassing precise diagnosis, urgent procedural interventions, and tailored pharmacological treatments is essential for optimizing patient outcomes during ST. Intracoronary antithrombotic therapies combined with TA and IVI guidance play pivotal roles in achieving optimal outcomes, particularly in cases with a high thrombus burden and complex stent-related issues. Given the heterogeneity of ST mechanisms and possible management, future investigations should focus on refining existing approaches for optimal individualized treatment.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the review: Bianchini E, Bianchini F, Lunardi M, Dato I, Burzotta F

Provided technical and material support and made substantial contributions to the revision of the work: Romagnoli E, Zito A, Aurigemma C, Paraggio L, Trani C

Availability of data and materials

Not applicable.

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Conflicts of interest

Bianchini F received a research grant from Abbott Vascular. Romagnoli E received speaker fees from Abbott, Abiomed, and Terumo. Aurigemma C has been involved in advisory board activities by Abbott, Abiomed, Medtronic, and Biotronic. Paraggio L received speaker fees from Abiomed and Terumo. Lunardi M received speaker fees from Medtronic. Trani C and Burzotta F received speaker fees from Abbott Vascular, Abiomed, Medtronic, and Terumo. The other authors have no conflicts of interest to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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