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Standards and Guidelines

SCAI Expert Consensus Statement on Management of In-Stent Restenosis and Stent Thrombosis

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ABSTRACT

Stent failure remains the major drawback to the use of coronary stents as a revascularization strategy. Recent advances in imaging have substantially improved our understanding of the mechanisms underlying these occurrences, which have in common numerous clinical risk factors and mechanical elements at the time of stent implantation. In-stent restenosis remains a common clinical problem despite numerous improvements in-stent design and polymer coatings over the past 2 decades. It generates significant health care cost and is associated with an increased risk of death and rehospitalization. Stent thrombosis causes abrupt closure of the stented artery and therefore carries a high risk of myocardial infarction and death. This Society for Cardiovascular Angiography & Interventions (SCAI) Expert Consensus Statement suggests updated practical algorithmic approaches to in-stent restenosis and stent thrombosis. A pragmatic outline of assessment and management of patients presenting with stent failure is presented. A new SCAI classification that is time-sensitive with mechanistic implications of in-stent restenosis is proposed. Emphasis is placed on frequent use of intracoronary imaging and assessment of timing to determine the precise etiology because that information is crucial to guide selection of the best treatment option. SCAI recommends image-guided coronary stenting at the time of initial implantation to minimize the occurrence of stent failure. When in-stent restenosis and stent thrombosis are encountered, imaging should be strongly considered to optimize the subsequent approach.

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Abbreviations: BMS, bare metal stents; DAPT, dual antiplatelet therapy; DCB, drug-coated balloons; DES, drug-eluting stents; ISR, in-stent restenosis; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; OCT, optical coherence tomography; RCT, randomized clinical trial; ST, stent thrombosis.

Keywords: coronary stenting; in-stent restenosis; major adverse cardiovascular events; stent thrombosis; target vessel failure.

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Introduction

Coronary stenting has transformed revascularization strategy, producing excellent procedural and clinical outcomes in myriad clinical settings. Despite proven short and long-term benefits, in-stent restenosis (ISR) and stent thrombosis (ST) continue to be limitations. There remains no definitive management approach for either condition despite a greater understanding of the underlying mechanisms ensuing from advances in intracoronary imaging.

In this Society for Cardiovascular Angiography & Interventions (SCAI) Expert Consensus Statement, practical algorithmic approaches to ISR and ST are offered. A pragmatic outline of assessment and management of patients presenting with stent failure is presented. A new SCAI classification that is time-sensitive with mechanistic implications of ISR is proposed. Emphasis is placed on frequent use of intracoronary imaging and assessment of timing to determine the precise etiology, as that information is crucial to guide selection of the best treatment option.

Methodology

This statement has been developed according to SCAI Publications Committee policies for writing group composition, disclosure and management of relationships with industry, internal and external review, and organizational approval. Detailed author disclosures are included as Supplemental Table 1. The work of the writing committee was supported exclusively by SCAI, a nonprofit medical specialty society, without commercial support. Writing group members contributed to this effort on a volunteer basis and did not receive payment from SCAI. Group members in each section performed literature searches, and the section leads in collaboration authored initial section drafts with other members of the writing group. The draft manuscript was peer reviewed in February 2023 and the document was revised to address pertinent comments. The writing group unanimously approved the final version of the document. The SCAI Publications Committee and Executive Committee endorsed the document as official society guidance in March 2023. SCAI statements are primarily intended to help clinicians make decisions about treatment alternatives. Clinicians also must consider the clinical presentation, setting, and preferences of individual patients to make judgments about the optimal approach.

In-stent restenosis

ISR remains a common clinical problem despite numerous improvements in-stent design and polymer coatings over the past 2 decades. ISR generates significant health care cost and is associated with an increased risk of death and rehospitalization. The incidence of ISR is 10%; 25% of ISR cases present with acute myocardial infarction (MI) with a 30-day mortality rate of 10% to 25%.[1–4]

Risk factors

Clinical. The incidence of ISR varies depending on individual patient, angiographic and procedural characteristics as listed in Table 1.[1–15] Second-generation drug-eluting stents (DES) have a 5.7% ISR rate in patients without diabetes, and 8.7% rate in those with diabetes.[5] Beyond 1 year, there is a gradual increase in major adverse cardiovascular events (MACE); the 5-year ISR rate is 9% to 12% in noncomplex lesions.[6]

Recurrent ISR is not unusual in contemporary practice. The failure to appreciate and address the original mechanism of ISR underlies refractory cases of recurrence. As in first ISR, the use of intracoronary imaging may provide insights into the underlying mechanisms. Recurrent ISR occurs in approximately 20% of all ISR cases.[7,8] Recurrence is independently predicted by the number of stents placed at the location.[9,10] The 1-year MACE (43.1%) and target lesion revascularization (41.2%) rates were significantly higher in the ≥3 stent layer group than in the 1-stent-layer and 2-stent-layer groups. Importantly, on multivariable analysis, the number of metallic layers and hemodialysis requirement were identified as independent predictors of MACE. A third layer of metal is almost always associated with underexpansion and should be avoided.

Table 1. In-stent restenosis risk factors[1–15]

Patient factors	Angiographic factors	Procedural factors
• Diabetes mellitus • Renal insufficiency • ACS presentation • Female • Recurrent ISR	• Lesion length >20 mm • Diameter <3 mm • Chronic total occlusion • Ostial location • Bifurcation • Saphenous vein graft • Severe Calcification • Multivessel CAD	• Underexpansion • Stent fracture • Bare metal stent • Stenoses proximal and distal to stent • Major arterial dissection involving media or >3 mm length • Multiple stent layers

ACS, acute coronary syndrome; CAD, coronary artery disease; ISR, in-stent restenosis.

Pathogenesis and contributory factors

The preferred treatment strategy depends on a precise diagnosis and understanding of the cause. Consequently, identifying the mechanism in each case using intracoronary imaging and optimizing the interventional result are critical steps (Table 1).

Biologic factors. The primary biologic mechanism of ISR is neointimal tissue proliferation or hyperplasia, an exaggerated homeostatic healing response to arterial wall damage sustained during stent implantation.[1] The distribution of neointimal tissue proliferation may be focal or diffuse along the length of the stent. Causative factors are local inflammation resulting from mechanical disruption of the intima/media leading to aggressive neointimal hyperplasia/proliferation that consists of smooth muscle cells and extracellular matrix. Hypersensitivity reactions to the metal and/or the polymer of early-generation DES are also recognized mechanisms of neointimal hyperplasia.[1]

Neoatherosclerosis is an increasingly recognized mechanism of stent failure seen with current generation DES. It is characterized by accumulation of lipid-laden foamy macrophages sometimes with necrotic core formation within stented segments.[16] Injury to the vessel by balloon inflation and stent deployment stimulates neointima formation. The subsequent intimal and medial damage leads to proliferation and migration of vascular smooth muscle cells, macrophages, and extracellular matrix formation. These activate the coagulation cascade and an inflammatory response. This combination of events, along with elution of antiproliferative drug, inhibits endothelialization. The lack of endothelium allows incorporation of low-density lipoprotein into the artery wall early after DES implantation. At later stages, the healed in-stent neointima is prone to atherosclerosis development.

Additional mechanisms of ISR include elastic recoil and relocation/subluxation of axially transmitted plaque (tissue intrusion) (especially early) and reorganization of thrombus, neointima formation, and remodeling (especially late).[6–16]

Mechanical factors. The primary mechanical cause of ISR is underexpansion. This may result from stent undersizing, low deployment pressures, or underlying calcified lesions. Other mechanical causes include stent recoil, longitudinal stent deformation, stent fracture, crushed stents, dislocated stents, and geographic miss. Geographic miss results from incorrect placement of the stent so that it does not fully

cover the diseased segment. Stent fracture may be seen at hinge points in the coronary artery and after stenting a calcified nodule. Other findings, such as early-stent malapposition, tissue prolapse, and asymmetry/eccentricity have little or no prognostic value. Stent underexpansion may occur as a result of undersizing, low deployment pressures, or heavily calcified lesions.[9–13]

Some interventional cardiologists favor routine poststent placement dilation with high-pressure balloons; while this can be an effective strategy, it can also lead to edge dissections. Instead, postprocedural imaging might be a more effective use of time and effort.

Definition and classification

In-stent restenosis is established angiographically as a binary event, defined as recurrent diameter stenosis at the stent segment >50% of the vessel diameter.[16] Additional criteria for clinically relevant ISR include: recurrent angina, objective signs of ischemia, or abnormal fractional flow reserve.[17–19]

Morphologic patterns. Coronary angiography remains the standard diagnostic method to determine ISR severity and morphologic pattern:

Mehran. The Mehran System[19] classifies restenotic lesions on the basis of morphology and extent of disease, with 4 subclasses based on location within the stented segment. Lesions were classified as focal (class I), diffuse intrastent (class II), diffuse proliferative (class III), and total occlusion (class IV). This schema was highly relevant to bare metal stenting (BMS), but its applicability to DES ISR is uncertain.

Waksman. The Waksman ISR Classification[20] is based on mechanistic considerations informed by intracoronary imaging. There are 5 groups of DES ISR identified: mechanical (type I; underexpansion I A, stent fracture I B), biologic (type II; intimal hyperplasia II A, neoatherosclerosis noncalcified II B, neoatherosclerosis calcified II C), mixed pattern (type III), chronic total occlusions (type IV), and lesions previously treated with >2 stents (type V).

Intravascular ultrasound- and optical coherence tomography-based classifications. Kang et al[21] has proposed an intravascular ultrasound (IVUS)-based classification that incorporates length of the restenosis as well as minimal luminal area. Gonzalo et al[22] and Ali et al[23] have proposed optical coherence tomography (OCT) classifications that rely on both quantitative and qualitative parameters.

Timing. Table 2 is the proposed new SCAI classification incorporating the cause of ISR based on time from implantation. SCAI recommends that early (<30 days), late (30 days to 1 year), and very late (>1 year) timing categories be adopted for all future diagnostic and therapeutic studies. By integrating mechanistic etiology with timing, this classification will be useful to determine best treatment options.

Table 2. SCAI classification of in-stent restenosis: a system based on time interval and causative factor

Classification	Time interval	Morphologic substrates
Early	<30 d	• Undersizing • Underexpansion • Stent fracture
Late	30 d to 1 y	• Delayed healing (including drug induced) • Uncovered stent struts • Intimal hyperplasia (especially in BMS ISR)
Very late	>1 y	• Neoatherosclerosis • Intimal hyperplasia • Stent fracture

BMS, bare metal stent; ISR, in-stent restenosis.

Imaging adjuncts to diagnosis

SCAI strongly recommends routine evaluation by intravascular imaging to determine the cause of ISR, to inform therapeutic strategy, and to confirm effective treatment after percutaneous coronary intervention (PCI).[24–29] Identifying the mechanism of stent failure is paramount because the causative factors will influence the selection of treatment and devices to manage the ISR, ultimately impacting the durability of the repeat revascularization. Despite being the primary means of assessing ISR in clinical practice, angiography alone is usually inadequate because of limited resolution and inherent deficiency in quantifying vessel size, stent size, stent expansion, number of stent layers, in-stent calcific neoatherosclerosis, and extrastent calcific disease. Identifying the mechanism of ISR depends on visualizing the stent and its relation to the arterial wall, rather than the lumen itself.

In contrast to angiography, IVUS and OCT provide detailed assessment of the native artery and stented segment (Figure 1A, B). Recent intravascular imaging studies demonstrate that suboptimal stent deployment is common—occurring in 31% to 58% of patients—and that suboptimal stent deployment confers an increased risk of adverse events.[30–33] The relative advantages of IVUS and OCT are summarized in Table 3.[34,35]

Suboptimal minimal stent area (MSA) is a major predictor of stent failure, and an IVUS optimized MSA of >5.0 mm^2 or OCT optimized MSA of >4.5 mm^2 are optimal goals. Another useful criterion is to achieve a target MSA >90% of the closest proximal or distal reference segment. In addition, intraluminal diagnostic imaging should be performed to ensure that there are no inflow or outflow obstructions within 5 mm of the proximal or distal stent edge. In particular, any major edge dissections (defined as >60°, >3 mm in length, or penetrating the media) should be stented.[33–35]

Physiologic assessment

Patients with ISR of intermediate range severity on coronary angiography present a clinical challenge because of potential short and long-term complications, and it is recommended that objective evidence of myocardial ischemia is demonstrated prior to proceeding with repeat intervention. Even though there are no randomized clinical trials (RCTs) assessing coronary physiology to guide management of ISR, there are several retrospective observational trials that suggest that it may assist in clinical decision-making.[36,37] Deferral of coronary revascularization in patients with ISR and fractional flow reserve >0.80 was associated with similar outcomes over 36 months to patients with de novo coronary stenosis.[37] Further studies may define the value of coronary physiology assessment in developing decision strategy before and after intervention.

Proposed treatment strategies

A summary of existing RCTs and registries,[20,38–51] including clinical situations in which particular treatment modalities have been shown to be advantageous, are presented in Table 4.[52–55] The most common treatment approach for the first episode of ISR is to implant a second DES, based on the rationale that DES therapy has superior efficacy over balloon angioplasty alone. However, this is not always necessary and may not be the best solution, particularly when the reference vessel and the resultant minimal lumen area are small.[20] If the underlying etiology is not directly addressed and corrected, there is a high likelihood of recurrent ISR, and the rate of ISR in second layer DES is high: 12% to 16% at 12 months and 33% at 3 to 5 years.[56–58]

General strategic approach. The critical principle is to obtain the largest acute lumen gain as possible by maximizing the immediate

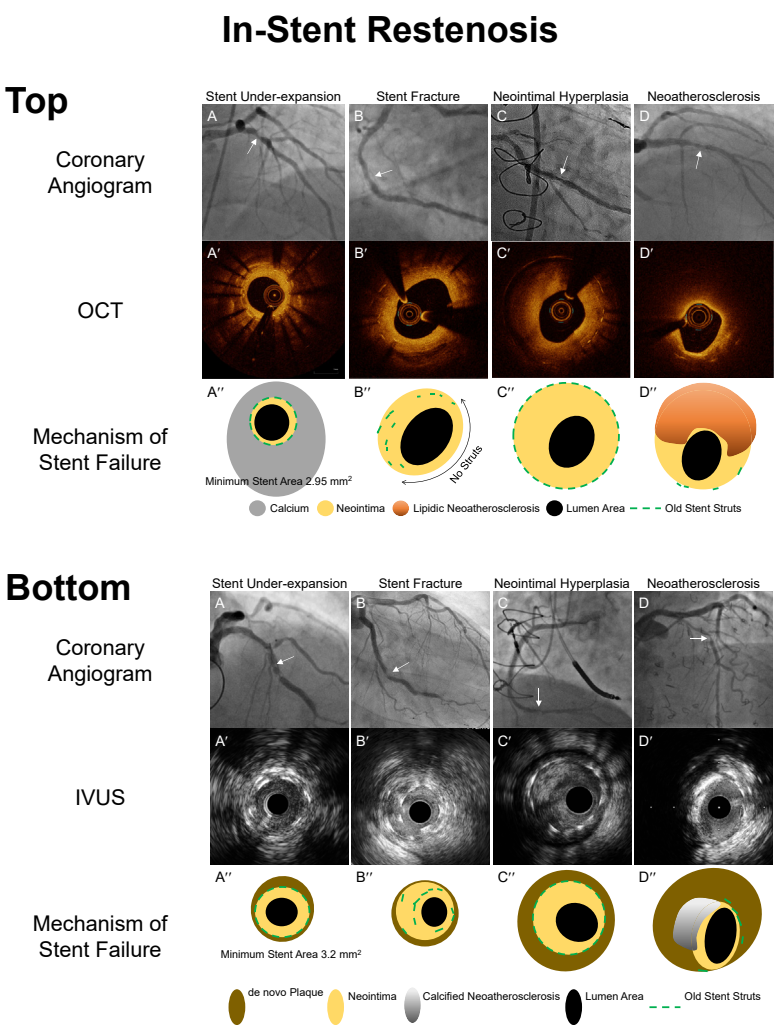

Figure 1.
Mechanisms of in-stent restenosis evaluated by intravascular imaging. A′-D′ are optical coherence tomography (OCT) or intravascular ultrasound (IVUS) images corresponding to the in-stent restenosis seen in the angiographic images (**A-D**, white arrows). **A″-D″** are representative diagrams provided to clarify the intracoronary images, **A′-D′**. **Top**. Mechanisms of in-stent restenosis evaluated by OCT. (**A**) A patient experienced recurrent in-stent restenosis (ISR), and OCT visualized a severely underexpanded stent because of circumferential thick calcium behind stent with only a minimum amount of neointimal hyperplasia. (**B**) This patient was treated with a single drug-eluting stent. At the time of ISR, the OCT image showed a lack of stent struts over half of the arterial circumference (double headed arrow) while stents struts were overlapped at 7 to 9 o'clock. These are typical features of stent fracture. (**C**) Excess amount of neointimal hyperplasia within a well-expanded stent. (**D**) Lipidic neointima (strong signal attenuation) within the stent struts indicating neoatherosclerosis. **Bottom**. Mechanisms of in-stent restenosis evaluated by IVUS (**A**) IVUS visualized an underexpanded stent with a minimum amount of neointimal hyperplasia. By looking at the adjacent segment, the cause of underexpansion was a small vessel with a myocardial bridge. (**B**) IVUS delineates overlapped struts within a single stent at 7 to 10 o'clock indicating stent fracture. (**C**) Excess amount of neointimal hyperplasia within a well-expanded old stent. (**D**) Calcified plaque (superficial hyperintensity with acoustic shadow from 8 to 12 o'clock) within the stent indicates neoatherosclerosis.

postprocedural minimal luminal area. To operationalize this concept, a complete diagnostic evaluation of the cause of ISR must be pursued.[59] An algorithmic approach is provided in Figure 2. Repeat PCI should be routinely performed following intracoronary imaging assessment. The mechanism of the initial ISR should be determined, with correction of any underlying mechanical factors with image guidance to ensure optimal sizing and expansion. A second stent should be image-guided to ensure correct stent expansion to ensure appropriate stent expansion.

Besides repeat DES, a number of adjunct treatments exist that may be highly effective.[58–69] If there is significant underexpansion, it is critical to increase expansion by applying high-pressure balloons. If there is additional hyperplasia, perhaps preparation with scoring/cutting balloons, rotational atherectomy (RA), orbital atherectomy (OAS), drug-coated balloons (DCBs), vascular brachytherapy (VBT), excimer laser coronary angioplasty (ELCA), or intravascular lithotripsy (IVL) may be useful.

When ISR is predominantly because of neointimal hyperplasia, treatment is dependent on the pattern of ISR. For focal ISR, a high-pressure or scoring/cutting balloon may be sufficient; ELCA or atherectomy may be beneficial in selected cases. For diffuse ISR, atherectomy or scoring/cutting balloon angioplasty followed by repeat DES implantation is typically advised.

If stent underexpansion is not because of calcification, atheroablation should be used only if significant neointimal hyperplasia is also present. RA, OAS, and ELCA may debulk neointima hyperplasia, although mechanistic evaluations fail to demonstrate this effect. In cases where intravascular imaging identifies an arc of calcium >270° or >0.67 mm in thickness, atherectomy vessel preparation should be considered to optimize lesion and stent expansion.[60–69]

If stent underexpansion is due to significant peri-stent calcium (>90°), RA, OAS, and ELCA may be employed to improve stent underexpansion by disrupting the calcified plaque behind the stent. IVL may also be useful. These techniques are associated with calcium modification and/or fracture, and when followed by high-pressure inflations may reduce stent underexpansion. However, if unsuccessful, coronary artery bypass grafting may be necessary (see Figure 3).

Balloon angioplasty. Balloon angioplasty should be the initial step in focal lesions or if short dual antiplatelet therapy (DAPT) duration is required. In the setting of stent underexpansion, high-pressure noncompliant balloon inflations are the preferred strategy.

Super high-pressure balloons. Double layer, noncompliant coronary balloons (OPN NC, SIS Medical) capable of inflation pressures ranging from 35 to 55 atm have recently become available in the United States. This class of percutaneous transluminal coronary angioplasty balloon has performed favorably in severely calcified de novo lesions and may be a consideration in ISR secondary to an underexpanded stent.

Table 3. Applications of OCT vs IVUS[34,35]

	IVUS	OCT
Assessing lesion severity in left main disease	+++	+
Assessing de novo lesion characteristics		
Thin cap fibroatheroma	–	+++
Thrombus	+	+++
Plaque rupture	++	+++
Calcified nodule	+	+++
Dissection	++	+++
Positive remodeling	+++	+
Plaque burden	+++	+
Aorto-ostial disease	+++	–
Stent optimization		
Expansion	++	+++
Apposition	++	+++
Stent failure		
Neointimal hyperplasia	+	++
Underexpansion	++	+++
Malapposition	++	+++
Renal impairment	+++	+

+++ Excellent; ++ Good; + Poor; – Not advised
IVUS, intravascular ultrasound; OCT, optical coherence tomography.

Repeat DES. In general, repeat DES implantation has historically shown superior results compared with balloon angioplasty alone. However, this approach should only be undertaken once appropriate sizing and expansion of the original stent has been assured using intravascular imaging. A second stent may not be necessary if the original stent was underdeployed and can be corrected.

If focal edge restenosis, stent gap, or stent fracture is identified, conventional or high-pressure balloon dilation at the site of the mechanical complication should be the initial treatment. This should then be followed by repeat DES implantation when the ISR is focal. Repeat DES to cover the entire diseased segment can be performed when the ISR is diffuse or proliferative, but care should be taken to minimize the stent coverage as much as possible.[44–52] There is no definitive evidence regarding which type of DES should be used to treat ISR of a previously implanted DES, and there is no consensus on whether a different stent type or drug should be used when an additional DES is implanted. However, the RIBS III trial[38] assessed the impact of selecting a different DES for treatment of ISR and demonstrated better angiographic and clinical outcomes at 9-month follow-up in the cohort that received a different DES than the first implanted stent.

Cutting and scoring balloons. The use of balloons incorporating cutting or scoring elements has been shown in very small series to result

Table 4. Summary of in-stent restenosis and stent thrombosis management strategies

Modalities of treatment	When to consider	Other considerations
In-stent restenosis[1,2,20,38–51]		
Balloon angioplasty	• Focal, discrete lesions • Stent underexpansion • Need for short DAPT	• Risk of recurrence and edge dissection high • Use of DCB associated with lower risk of TLR and binary restenosis
Repeat DES	• If only one prior layer, may consider over balloon angioplasty alone[a] • Focal edge restenosis, stent gap, stent fracture	• Reduction in need for target revascularization compared with angioplasty alone • No definitive consensus for change in-stent type but RIBS III trial showed reduction of restenosis rate and improved event-free survival in cohort receiving a different DES platform
Cutting and scoring balloons	• May modify neointimal growth • May help to avoid additional stent layer	• Scoring balloon angioplasty superior to PTA alone at 6-8 mo (improved angiographic outcomes and reduced stenosis)
Atheroablation	• Should be considered if mode of stent underexpansion calcification and resistant to high-pressure balloons • Should be considered when significant neointimal hyperplasia present	• Clinical trials for use of atheroablation for ISR negative
DCB	• May help to avoid additional stent layer	• Treatment with DCB non-inferior to DES in terms of 6-mo MLD
Vascular brachytherapy	• Refractory ISR • Limited availability	• Due to delay in endothelialization, patients may need lifelong DAPT • Treatment can be repeated every 12 mo
Intravascular lithotripsy	• May be considered when there is highly calcified neoatherosclerosis	• Limited data to suggest proper case selection
Stent thrombosis[52–55]		
Balloon angioplasty	• May be needed in addition to repeat DES and/or aspiration thrombectomy to restore coronary blood flow	
Repeat DES	• May be needed in addition to PTA and/or aspiration thrombectomy to restore coronary blood flow • Should normally limit to significant residual dissections after PTA	• No stent type associated with reduction in ST
Aspiration thrombectomy	• Consider when heavy thrombus burden present • Consider adjunctive glycoprotein IIb/IIIa inhibitors if persistent heavy thrombus burden after aspiration	• Associated with improved microvascular perfusion during STEMI because of ST • Majority of patients undergoing aspiration thrombectomy had successful recanalization
Pharmacologic therapies	• Consider glycoprotein IIb/IIIa inhibitor infusion • Assess compliance and consider switch to higher potency antiplatelet therapy if the patient was compliant and still taking DAPT • May consider drug resistance testing and prolonged DAPT duration	• Consider patient's renal function and bleeding risk when continuing glycoprotein IIb/IIIa inhibitor after PCI • Prolonged anticoagulation and antiplatelet therapy may be beneficial when residual thrombus is detected following intervention

DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization.
[a] Avoid when there are already 2 layers of stent

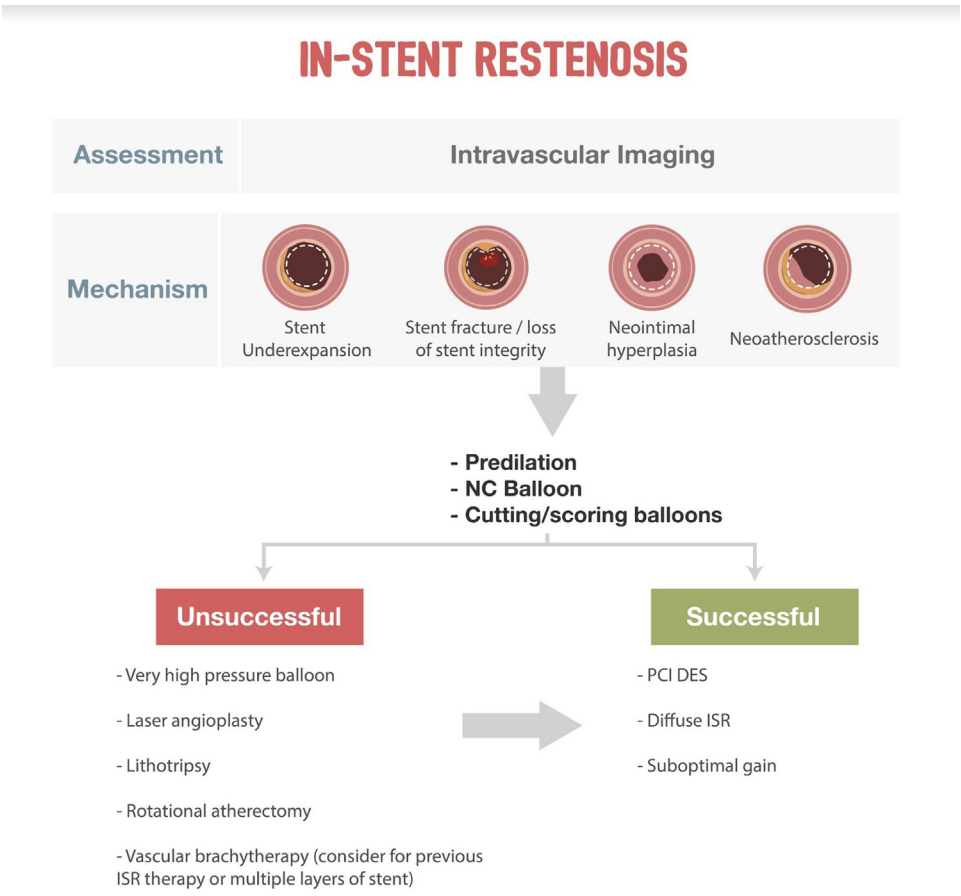

Figure 2.
SCAI algorithmic approach to in-stent restenosis. DES, drug-eluting stents; ISR, in-stent restenosis; PCI, percutaneous coronary intervention.

in better acute angiographic outcomes in ISR compared with BA.[58,59] Small IVUS-guided studies suggest that the use of cutting compared with traditional balloons is associated with larger lumen gain, lower lumen loss, and preserved angiographic result at follow-up.[45,69] However, a randomized study comparing standard balloons vs cutting balloons for the treatment of ISR failed to demonstrate superiority of the cutting balloon in terms of recurrent ISR and MACE.[58]

Atheroablation. Despite the appealing concept of atheroablation, clinical trials for the treatment of ISR have been negative.[62–64] The utilization of RA when IVUS or OCT confirms the presence of calcium within neoatherosclerotic plaques is reasonable, but no controlled trials exist. RA might also have value in lesions refractory to high-pressure balloon angioplasty. However, the use of mechanical atheroablative technologies within stents poses risks of device entrapment, and some suggest reserving mechanical atherectomy for bailout use. Excimer laser has similarly shown no special benefits.[61,64,67]

DCBs. Preliminary clinical studies using sirolimus-based DCBs showed promising preliminary results; however, randomized trials are needed to demonstrate efficacy with DES in ISR. Most data are with paclitaxel DCBs. Several trials and meta-analyses have demonstrated similar outcomes of DCB compared with DES in the management of ISR[44,45,70,71–83] and are summarized in Table 5. Although coronary DCBs are not available in the United States, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines[65] give DCBs a class I indication for the treatment of ISR. DCB outcomes may be optimized with inflation time >60 seconds and a balloon: artery ratio >0.91. Neointimal modification with RA improves acute luminal improvement over DCB therapy alone, with lower late lumen loss; however, there are similar clinical outcomes at 6 months.[50]

VBT. Vascular brachytherapy inhibits neointimal formation within the stent by delivering radioactive Strontium-90 β-radiation locally, decreasing proliferation. This treatment modality was commonly employed for bare metal ISR 2 decades ago, with minimal long-term benefit demonstrated. The use of VBT has undergone resurgence in use for DES ISR.[86,84,87] The more overlapping stent layers there are, the less effective brachytherapy is for ISR. With 3 or more stent layers, the 3-year target lesion failure rate exceeds 50%. Accordingly, many centers consider recurrent ISR after failure of 2 DES layers to be an indication for intraventricular block.

IVL. Intravascular lithotripsy is a promising new approach in calcified lesions and has been evaluated in nonrandomized series as a treatment for highly calcified neoatherosclerosis causing ISR.[45,51,88] The mechanism of action is emission of an electrical charge from a pair of lithotripters resulting in generation and collapse of vapor bubbles within a pressurized, fluid-filled semicompliant balloon. This results in acoustic shockwaves that exert an instantaneous field force of up to 50 atm creating fractures within intimal and medial calcium, facilitating subsequent stent expansion as assessed by IVUS and OCT. Whether this device provides a long-term benefit, alone or in combination, in this difficult morphologic subset will require RCTs. IVL has also been combined with VBT.[50]

Management of recurrent ISR. Patients with recurrent ISR are refractory to usual treatment modalities.[60] The rates of repeat revascularization have been reported to exceed 50% within 2 years. For this

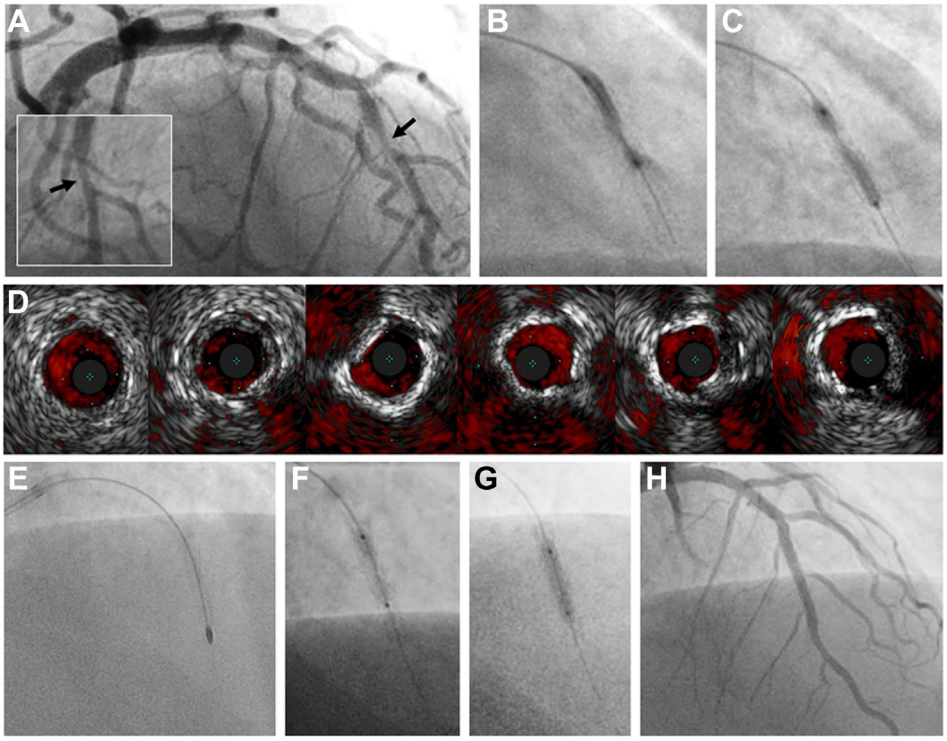

Figure 3.
Stepwise, imaging-guided treatment of a calcified ISR lesion. In-stent restenosis of a first-generation drug-eluting stent (Taxus, Boston Scientific) in the mid LAD, implanted 18 years prior and confirmed patent several years afterward. Intrastent (type II) restenosis (**A**, inset with orthogonal view) was noted on angiography with multiple unsuccessful attempts made at dilatation (**B**, **C**) using noncompliant balloons (24-26 atm). Subsequent IVUS imaging (**D**, distal to proximal) reveals both calcified and noncalcified tissue within an appropriately sized stent, likely representing neoatherosclerosis. Despite successful rotational atherectomy (**E**: 1.5 mm burr, 160-170,000 rpm × 8 passes), non-compliant balloon dilation still revealed a focal waist (**F**). Complete expansion of a 2.5 × 12 mm Shockwave C2 IVL balloon was achieved after 80 pulses at 6 atm (**G**) and confirmed with IVUS. A 2.75 × 26 mm drug-eluting stent was implanted at 20 atm with excellent angiographic (**G**) and IVUS results. IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; LAD, left anterior descending artery.

reason, new approaches are often tried in these cases, but typically published results are anecdotal reports and uncontrolled series, rather than controlled trials.

Drug-coated balloons may have a beneficial effect in recurrent ISR, but more investigation is needed. Adverse events are significantly higher in patients treated with DCBs with >2 stent layers versus no significant differences in patients with 1 or 2 prior stents. Atheroablative modalities are often employed, but published reports are anecdotal. Multilayer (>2 stents) underexpanded ISR is particularly recalcitrant to standard treatment. VBT is often reserved for refractory ISR and might be considered when multiple layers of stent are present.[50,84,87]

Surgical revascularization should be considered in discussion with the patient after several interventional procedures have failed. Although no studies have supported a specific approach as to when repeat procedures should be avoided, Table 6 lists key considerations to assist in deciding which patients might be better treated with coronary artery bypass graft surgery or optimal medical therapy. A heart team approach may be advisable to consider all of the relevant factors in an individual case.

Stent thrombosis

ST is an acute or subacute thrombotic occlusion that usually presents as an acute MI or acute coronary syndrome and is associated with high rates of morbidity and mortality. These thrombi can be notoriously difficult to treat with traditional interventional techniques because they tend to be large, friable, and adherent.[89]

Incidence and clinical presentation

The overall incidence of ST is 0.5% to 1.0% in the first year and 0.2% to 0.6% in every subsequent year.[90–92] The rate is lower for elective stent placement (0.3%-0.5%) but higher in acute coronary syndrome (3.4%) and MI. In contemporary practice, the observed mortality rate (~30%) is high, although recent clinical trials and studies requiring autopsy confirmation suggest a better survival, with an average rate of <10%.[90–92] The ST rate is higher in ST-elevation myocardial infarction presentations treated with primary stenting.[93–95]

Stent thrombosis causes abrupt closure of the stented artery, and therefore carries a high risk of MI and death. As with any acute vessel closure, the clinical ramifications of ST are influenced by the amount of threatened myocardium, the degree of myocardial viability, the presence and adequacy of collaterals, and the speed and success of revascularization. Approximately 20% of patients with a first ST experience a recurrent ST episode within 2 years.[92]

Classification

Stent thrombosis is classified by the Academic Research Consortium criteria[96] based on the presenting clinical scenario and timing after initial stent placement. Timing is classified as acute, subacute, early, late, and very late. ST occurring within 24 hours is acute; 24 hours to 30 days is subacute; from 30 days to 1 year is late; and >1 year is defined as very late. Early ST is defined as occurring within 30 days (ie, acute plus subacute). The clinical presentation defines whether the likelihood of ST is definite, probable, or possible. This categorization accurately portrays ST and is important in investigating its pathophysiologic associations.[97]

Pathogenesis

Numerous clinical and technical risk factors have been associated with ST, as summarized in Table 7.[98–105] Prevention of ST is dependent on optimal stent implantation and the duration and compliance with DAPT. Premature or patient-initiated termination of DAPT, sometimes because of bleeding or perioperative concerns, is responsible for most cases of ST.[100,101,106–112] Congenital or acquired hyporesponder DAPT status seen with clopidogrel is uncommon with prasugrel or

Table 5. Selected Trials Evaluating Management Strategies for In-stent Restenosis

Trial, publication year	Investigation Time	No. of lesions centers, region	Design	Drug-coated balloon, carrier agent, commercial name	Control device	Restenotic stent	Endpoint(s)	Follow-up (mo)	Principal findings	*P*-value
PCB vs Uncoated balloon										
PACCOCATH ISR I&II, 2012[75]	Dec 2003 - Dec 2005	54/54 Multicenter, Germany	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, PACCOCATH	Uncoated balloon	BMS, DES	LLL (mm)	6	0.11 ± 0.44 vs 0.80 ± 0.79	.001
							TLR (%)	12/60	4 vs 37 / 9 vs 39	.001/.004
							MACE (%)	12/60	9 vs 44 / 28 vs 59	.001/.009
Habara et al, 2011[86]	Sep 2008 - Nov 2009	25/25 1, Japan	—	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	Uncoated balloon	SES	LLL (mm)	6	0.18 ± 0.45 vs 0.72 ± 0.55	<.01
							TLR (%)	6	4 vs 42	<.01
							MACE (%)	6	4 vs 40	<.01
PEPCAD-DES, 2012[72,76]	Nov 2009 - Apr 2011	72/38 Multicenter, Germany	Core lab	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	Uncoated balloon	DES	LLL (mm)	6	0.43 ± 0.61 vs. 1.03 ± 0.77	<.01
							TLR (%)	6/36	15 vs 37 / 19 vs 37	<.01/<.01
							MACE (%)	6/36	17 vs 50.0 / 21 vs 53	<.01/<.01
PCB vs DES										
PEPCAD II, 2009[70,77]	Jan 2006 - Dec 2006	66/65 10, Germany	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	PES, durable polymer, stainless steel (132 μm)	BMS	LLL (mm)	6	0.17 ± 0.42 vs 0.38 ± 0.6	.03
							TLR (%)	12	6 vs 15	.15
							MACE (%)	12/36	9 vs 22 / 35 vs 42	.08/–
SEDUCE, 2014[74]	Jun 2009 - Oct 2011	24/25 2, Belgium	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	EES, durable polymer, CoCr (81 μm)	BMS	LLL (mm)	9	0.28 vs 0.07	.1
							TLR (%)	12	4.2 vs 8	.576
RIBS V, 2014[73]	Jan 2010 - Jan 2012	95/94 25, Spain	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	EES, durable polymer, CoCr (81 μm)	BMS	LLL (mm)	6 to 9	0.14 ± 0.5 vs 0.04 ± 0.5	.14
							TLR (%)	12/36	6 vs 1 / 8 vs. 2	.09/.04
							MACE (%)	12/36	8 vs 6 / 12 vs 10	.60/.64
TIS, 2016[78]	Jan 2012 - Aug 2014	74/74 1, Czech Rep.	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	EES, durable polymer, CoCr (81 μm)	BMS	LLL (mm)	12	0.02 vs 0.19	<.01
							TVR (%)	12	7.4 vs 16.2	.110
							MACE (%)	12	10.3 vs 19.1	.213
ISAR-DESIRE3, 2013[71,79]	Aug 2009 - Oct 2011	137/131/134 3, Germany	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	1) PES, durable polymer, stainless steel (132 μm) 2) Common balloon	DES	ISR diameter (%)	6 to 8	38% vs 37.4% vs 54.1%	<.01[a]
							TLR (%)	12/36	22 vs 14 vs 44 / 33 vs 24 vs 51	.09/.11[b]
							MACE (%)	12/36	24 vs 19 vs 46 / 38 vs 38 vs 56	.5/.91[b]
PEPCAD China ISR, 2014[80]	Mar 2011 - Apr 2012	113/108 17, China	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	PES, durable polymer, stainless steel (132 μm)	DES	LLL (mm)	9	0.46 ± 0.51 vs 0.55 ± 0.61	.0005[a]
							TLR (%)	12/24	15.6 vs 12.3 / 15.9 vs 13.7	.48/.66
							TLF (%)	12/24	16.5 vs 16 / 16.8 vs 18.6	.92/.73
RIBS IV, 2018[44]	Jan 2010 - Aug 2013	154/155 23, Spain	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	EES, durable polymer, CoCr (81 μm)	DES	Binary restenosis	6 to 9	19% vs 11%	.27
							TLR (%)	12	16.2 vs 21.8	.26
							MACE (%)	12	18.4 vs 23.3	.35
RESTORE, 2018[81]	Apr 2013 - Oct 2016	86/86 10, South Korea	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2	EES, durable polymer, CoCr (81 μm)	DES	LLL (mm)	9	0.15 ± 0.49 vs 0.19 ± 0.41	.54
							TLR (%)	12	7 vs 5	.51
							MACE (%)	12	6 vs 1	.10
DARE, 2018[47]						BMS, DES	MLD (mm)	6		<.01[a]

(*continued on next page*)

Table 5 (*continued*)

Trial, publication year	Investigation Time	No. of lesions centers, region	Design	Drug-coated balloon, carrier agent, commercial name	Control device	Restenotic stent	Endpoint(s)	Follow-up (mo)	Principal findings	*P*-value
	May 2010 - Jun 2015	137/141 8, Netherlands	Core lab, CEC	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	EES, durable polymer, CoCr (81 μm)				1.71 ± 0.51 vs 1.74 ± 0.61	
							TVR (%)	12	7.1 vs 8.8	.65
							MACE (%)	12	10.9 vs 9.2	.66
BIOLUX-RCT, 2018[82]	Aug 2012 - Jan 2015	163/80 14, Germany, Latvia	Core lab, CEC	Paclitaxel, BTHC 3 μg/mm^2, Pantera Lux	DES, bioresorbable polymer, CoCr (60–80 μm)	BMS, DES	LLL (mm)	6	0.03 ± 0.40 vs 0.20 ± 0.70	.40
							TLR (%)	12	12.5 vs 10.1	.82
							TLF (%)	12	16.9 vs 14.2	.65
DAEDALUS, 2020[83]		Pooled analysis of 10 RCT[c]	Core lab, CEC	Paclitaxel, iopromide/BTHC 3 μg/mm^2	DES	BMS, DES	TLR (%)	36	16 vs 12, HR 1.27 (0.90-1.79)	.17
							Safety endpoint[d]	36	9 vs 11, HR 0.79 (0.58-1.10)	.16
SCB vs PCB										
FIM LIMUS DCB, 2019[84]	Dec 2015 - Jan 2017	25/25 5, Malaysia	Core lab, CEC	Sirolimus, crystalline coating 4 μg/mm^2, SeQuent SCB	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	DES	LLL (mm)	6	0.21 ± 0.54 vs 0.17 ± 0.55	.794
							TLR (%)	12	16 vs 12	>.99
							MACE (%)	12	16 vs 12	>.99
Scheller et al. 2022[85]	Dec 2015 - Feb 2020	50/51 10, Malaysia, Germany, Switzerland	Core lab, CEC	Sirolimus, crystalline coating 4 μg/mm^2, SeQuent SCB	Paclitaxel, iopromide 3 μg/mm^2, SeQuent Please	DES	LLL (mm)	6	0.25 ± 0.57 vs 0.26 ± 0.60	<.35[a]
							TLR (%)	12	16 vs 10	.39
							MACE (%)	12	18 vs 14	.60

BMS, bare metal stent; BTHC, butyryl-tri-hexyl citrate; CEC, clinical events committee; CoCr, cobalt-chromium; DES, drug-eluting stent; EES, everolimus-eluting stent; ISR, in-stent restenosis; LLL, late lumen loss; MACE, major adverse cardiovascular events; MLD, minimal lumen diameter; PCB, paclitaxel-cboated balloon; PES, paclitaxel-eluting stent; SCB, sirolimus-coated balloon; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization;

[a] Non-inferiority. [b] PCB vs PES. [c] PEPCAD II, ISAR-DESIRE 3, PEPCAD China ISR, RIBS V, SEDUCE, RIBS IV, TIS, DARE, RESTORE, BIOLUX-RCT. [d] All-cause death, myocardial infarction, or target lesion thrombosis.

Table 6. Considerations for CABG in refractory/recurrent in-stent restenosis

- Multivessel CAD especially LM or proximal LAD involvement
- Prior CABG
- Suitability of distal vessel for grafting (including diffuseness of CAD, extent of "metal jacket," and size of vessel)
- Global and regional LV function including viability (especially the segment subtended by the involved vessel)
- Comorbid conditions (including age, frailty, life expectancy, and activity level)
- Anticipated completeness of revascularization
- Response to optimal medical therapy

CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending coronary artery; LM, left main coronary artery; LV, left ventricular.

ticagrelor.[107,108] Prior generation stents were susceptible to ST with discontinuation of DAPT out to 5 years and longer in anecdotal cases. With the newest generation of stents, the duration of treatment can be decreased safely to 3 months[113] or 1 month.[114]

Circumstances that abet stasis and turbulence, such as underexpanded stents, stents in small vessels, or long lesions, are associated with ST.[115–121] These common mechanical etiologies of ST are associated with stent underexpansion in both early and late ST. A second concern is injury or endothelial disruption caused by edge dissection. The delayed healing and endothelial in-growth observed with early-generation DES are now less common. Early, late, or very late ST can be associated with a calcified nodule, perhaps because of consequent underexpansion.

Neointima containing smooth muscle cells develops beginning 2 weeks after BMS.[106,121] However, DES, depending on the antiproliferative drug and generation, demonstrate delayed endothelial maturation as compared with BMS.[107] When there is an intense neointimal growth reaction to the stent, which is an exaggerated response to arterial healing that peaks at 30 days to 6 months after implantation, vascular narrowing, which can precipitate ST, may occur. Neointimal thickness at stent strut sites is increased when there has been damage to the tunica media. Drug elution and coating polymers may delay this time frame.[98,103,105,121,122]

Correlates of timing of ST and mechanism

The incidence of Academic Research Consortium definite or probable ST within 2 years is 4.4% and is distributed among the acute, subacute, late, and very late time periods. Each time frame is associated with somewhat different mechanistic circumstances.[99–103,105,121–124]

Early ST. The strongest predictor of early ST is premature discontinuation of DAPT in the first 30 days following stent implantation.[122] Mechanical predictors of early ST are similar to those associated with ISR—underexpansion and inflow-outflow problems, including geographic miss, significant residual dissections, and especially occult intramural hematomas—especially at the distal stent edge. Early-stent occlusion is usually the consequence of platelet-rich thrombi forming on an inadequate procedural result. The adequacy of stent expansion and the presence of an occult intimal dissection should be specifically evaluated when the etiology is unclear.

Acute ST. The incidence is 0.2% to 0.6%.

Subacute ST. The incidence is 1.0% to 1.3%.

Late ST. The incidence is 0.4% to 0.6%. The unifying morphologic finding is impaired neointimal healing, defined as delayed development of an endothelialized layer of smooth muscle cells and extracellular matrix that completely covers the stent.[123]

Several morphologic substrates have been associated with late ST. Stenting across major arterial side branches is well recognized. Overlapping and bifurcation stenting[125] are prone to underexpansion and malapposition; careful technique and close attention to adjunct imaging are essential. Stent struts that are not apposed to the vessel wall, which can be because of malapposition or late remodeling, produce increased blood flow turbulence and low-flow foci at the margins of the stent. Low-flow velocity increases fibrin and platelet deposition. Intimal dissection and plaque disruption in the arterial segments adjacent to stents can progress and cause flow obstruction. Stenting of lipid-rich plaques with plaque prolapse also increases risk of ST. Lipid-rich plaques with significant necrosis are prone to stent struts penetrating deeply into the lipid core, thus losing contact with the vessel wall. Also, stents placed in a stenosis with large lipid core might delay the development of a fully endothelialized neointima because of scarcity of migrating and proliferating smooth muscle cells in proximity to the stent. Finally, diffuse ISR with thrombosis can occur because of overproduction of intimal hyperplasia and neoatherosclerosis.[103,118–121]

Residual stent edge dissection has been associated with target lesion revascularization.[101,123,124] Edge dissections are defined as being major by OCT when they extend in an arc of >60° and are >3 mm in length. Intimal dissection and plaque disruption in the arterial segments adjacent to stents can progress and cause flow obstruction.

Very late ST. The incidence has been reported between 0.4% to 0.8%. Very late ST (VLST) occurs 1 to 5 years after stent implantation at a rate of 2% per year. The most commonly identified causes of VLST are malapposition, uncovered struts, neoatherosclerosis, and stent underexpansion. The degree and extent of malapposition and uncovered stent struts are the most important correlates of thrombus formation in VLST.[101,124] Intravascular imaging can identify suboptimal stent deployment.

Diagnostic imaging modalities

Intravascular imaging is crucial to developing rational individual case strategy because the causative mechanism is highly influential in selecting treatment strategy to manage the thrombus and prevent its recurrence. Although no imaging modality is rated in the class I

Table 7. Risk factors for stent thrombosis[98–105]

Clinical risk factors	Procedure related	Lesion related	Stent related	Antiplatelet related
• ACS (STEMI/NSTEMI)	• Stent length	• Necrotic core	• Bio-compatible polymers	• Adherence
• Left ventricular dysfunction	• Stent underexpansion	• Bifurcation lesions	• Polymer/stent thickness	• CYP2C19 polymorphisms
• Chronic kidney disease	• No reflow	• Prior brachytherapy	• Drug dosage	• High on-treatment platelet reactivity
• Diabetes mellitus	• Residual stenosis	• Multivessel disease		• Antiplatelet type
• COVID-19	• Dissection	• Inflow and outflow obstruction		• Dual antiplatelet therapy duration
	• Multiple stents			
	• Bifurcation stenting			

ACS, acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

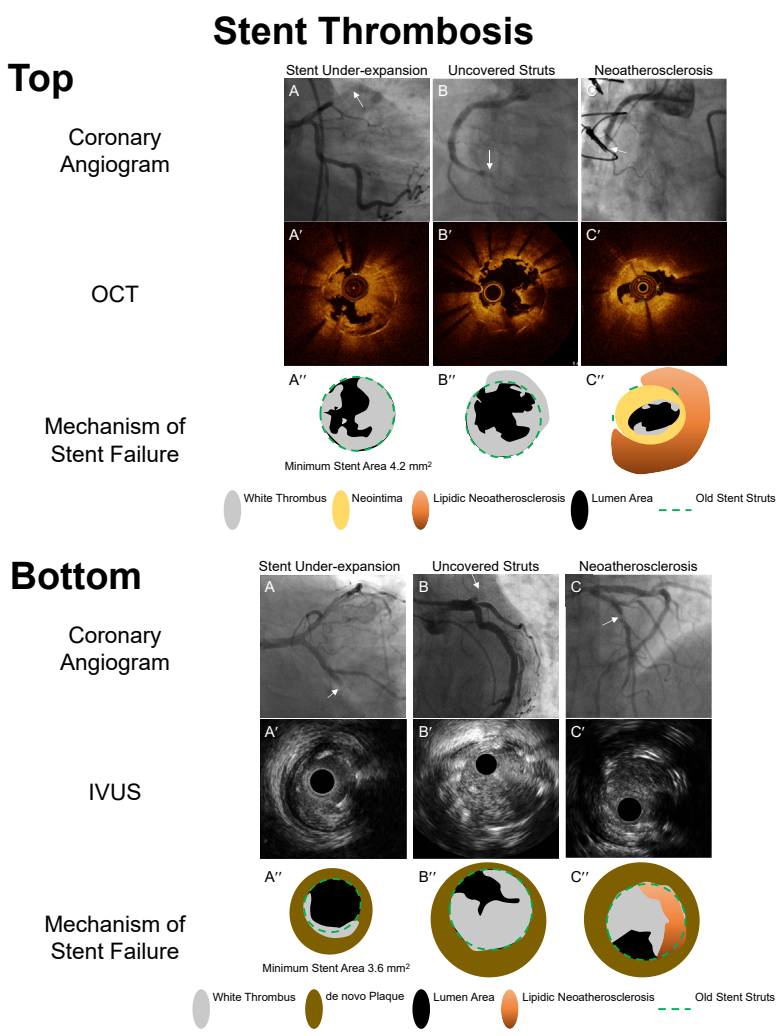

Figure 4.
Mechanisms of stent thrombosis evaluated by intravascular imaging. A′-C′ are optical coherence tomography (OCT) or intravascular ultrasound (IVUS) images corresponding to stent thrombosis seen in the angiographic images **A-C** (white arrows). **A″-C″** are representative diagrams provided to clarify the intracoronary images **A′-C′**. **Top**. Mechanisms of stent thrombosis evaluated by OCT (**A**) Subacute stent thrombosis in which OCT showed a severely underexpanded stent occupied by white thrombus in the mid left anterior descending artery. (**B**) Very late stent thrombosis occurred 2 hours after noncardiac surgery and after discontinuation of antiplatelet therapy. OCT showed uncovered stent struts occupied by white thrombus. (**C**) Lipidic plaque (strong signal attenuation) within stent struts indicating neoatherosclerosis resulting in plaque rupture with thrombus. **Bottom**. Mechanisms of stent thrombosis evaluated by IVUS (**A**) Subacute stent thrombosis in which IVUS showed a severely underexpanded stent and thrombus in the mid left circumflex artery. (**B**) Very late stent thrombosis in which IVUS showed a well-expanded stent occupied by thrombus. Because there is no neointimal hyperplasia, it was speculated that uncovered stent struts were the cause of stent thrombosis. (**C**) Lipidic plaque (strong signal attenuation) appeared within the stent struts indicating neoatherosclerosis resulting in plaque rupture with thrombus.

category by existing guidelines because of an absence of randomized trials, angiography alone is clearly inadequate because of its intrinsic inadequacy to assess stent expansion, neoatherosclerosis, calcification, and remodeling. IVUS and OCT provide detailed assessment of the stented segment and accurately identify the underlying mechanisms. For these reasons, SCAI recommends that imaging be strongly considered when the etiology of ST is uncertain from clinical and angiographic information.

Angiographic factors. The extent of coronary artery disease is an independent predictor of ST.[105,122] The Dutch Stent Thrombosis Registry included 21,009 consecutive patients and showed that multivessel disease, long lesions, and multiple lesions (total stent length) are independent determinants of ST.[117] The volume of thrombus burden is important in appraising the risk of distal embolization, as is the degree of residual flow, presence of collaterals, and status of the microvasculature.[53–55] The size of the jeopardized myocardial segment and the residual left ventricular function are also critical factors.

Intravascular imaging. There is substantial data suggesting that intravascular imaging improves outcomes (see Figures 4A, B and 5). IVUS has been considered the standard imaging modality for ST.[101,102,122] OCT, which has 10-fold higher axial resolution, has more recently shown great promise.[115,119,126,127] Although the absence of a multicenter, controlled trial limits a formal level of indication,[24] these modalities appear to be useful in optimal lesion preparation strategies.

There are several well-defined imaging criteria to optimize stenting (Table 8).[115–120] IVUS can be of great value during stent placement to assess stent sizing, expansion, and apposition. Several studies suggest that IVUS-guided stent placement reduces ST, restenosis, and repeat revascularization.[101,102,116,118,128–130] Stent undersizing occurs frequently when visual estimation alone is used for size selection, and this is a major contributor to the risk of ST (and ISR). The incidence of ST is significantly reduced when IVUS is used to guide stent placement and optimize expansion.[128] In the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) study,[129] at 1 year, there was a significant reduction in definite/probable ST (0.52% vs 1.04%, $P = .01$) and MI (2.5% vs 3.7%, $P = .002$)[128] when IVUS guidance was employed.

Optical coherence tomography may be superior to IVUS in assessing the cause of ST. In particular, uncovered struts and underexpansion are seen in acute and subacute ST, and neoatherosclerosis, uncovered struts, and malapposition are seen in late and very late ST.[126,131,132] OCT has been shown to be highly effective in determining the underlying cause of VLST in >98% of cases, and multiple mechanisms are usually present (55%). OCT demonstrates malapposition, neoatherosclerosis, uncovered struts, and stent underexpansion underlying ST.[127] OCT identified adverse features requiring further intervention in 35% of cases, with significantly lower risk of death and MI at 1 year in the CLI-OPCI trial.[97]

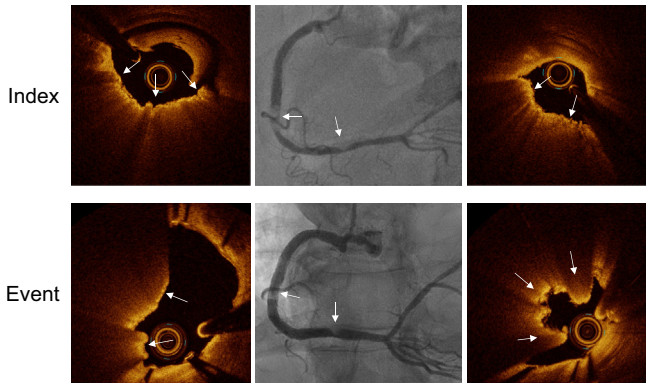

Figure 5.
Early restenosis due to re-protrusion of a calcified nodule. This patient underwent percutaneous coronary intervention to treat lesions in the distal and mid right coronary artery. Optical coherence tomography (OCT) showed an eruptive calcified nodule (white arrows) in both lesions. A calcified nodule is characterized by an accumulation of small calcium fragments typically with strong signal attenuation due to accompanying and overlying fibrin. The patient came back for staged procedure of LAD (left anterior descending artery) 6 weeks later. OCT showed reprotruding calcified nodules within the stent.

In ULTIMATE,[130] IVUS-guided PCI was associated with important reductions in target vessel failure (cardiac death, MI, or target vessel revascularization). At 3 years, target vessel failure occurred in 47 patients (6.6%) in the IVUS-guided group and in 76 patients (10.7%) in the angiography-guided group ($P = .01$), driven mainly by the decrease in clinically driven target vessel revascularization (4.5% vs 6.9%; $P = .05$). Both OPINION[133] and ILUMIEN III[131] compared IVUS and OCT and concluded that these methods have similar treatment outcomes.

Mechanical and pharmacologic treatment of ST

Balloon inflation, aspiration thrombectomy and pharmacologic treatment with anticoagulants and antiplatelet drugs are the mainstays of treatment (Table 4).[52–55] Emergent PCI is indicated when the presentation is acute, although optimal reperfusion is achieved in only 2/3.[89] The SCAI recommended algorithm to organize these approaches is provided in Figure 6.

Table 8. Intravascular imaging correlates of stent thrombosis[103,105,115–120]

- Small cross-sectional area of <5 mm
- Underexpansion
- Malapposition or incomplete stent apposition
- Correct stent sizing
- Late positive remodeling or aneurysm formation
- Inflow/outflow lesions proximal or distal to the stented segment
- Plaque prolapse or protrusion
- Edge dissection
- Significant residual stenosis
- Stent overlap
- Plaque characteristics: lipid content; delayed or absent endothelialization of stent struts
- Hypersensitivity or inflammatory reactions
- Strut fractures
- Neoatherosclerosis (very late stent thrombosis)

Following diagnostic angiography, most ST occlusions can be treated initially with balloon angioplasty alone, sometimes with adjunctive thrombus aspiration when the clot burden is large. Additional stent implantation should ordinarily be limited to significant residual dissections, especially if recent DAPT has been discontinued. High-pressure inflations with noncompliant balloons to assure stent apposition may be necessary in some cases. At this time, no particular stent design or polymer coating has been shown to prevent ST more than others.

Glycoprotein IIb/IIIa antagonists should be considered to improve microvascular reperfusion because of distal embolization, and prolonged infusions up to 72 hours have been successful in anecdotal cases. Prolonged anticoagulation and antiplatelet therapy may be beneficial when residual thrombus is detected following intervention. Compliance and drug resistance should be evaluated in detail. More potent antiplatelet therapy should be considered, including aspirin, prasugrel, or ticagrelor.[107,108,134] If platelet aggregation studies are available and reveal insufficient (<50%) inhibition of platelet aggregation with standard DAPT, the sustained administration of 150 mg/d clopidogrel may be considered. Long-term non-vitamin K oral anticoagulants or warfarin are rarely necessary but may be considered for selected cases of recurrent ST. Although mechanical and extraction thrombectomy have been employed anecdotally, there are

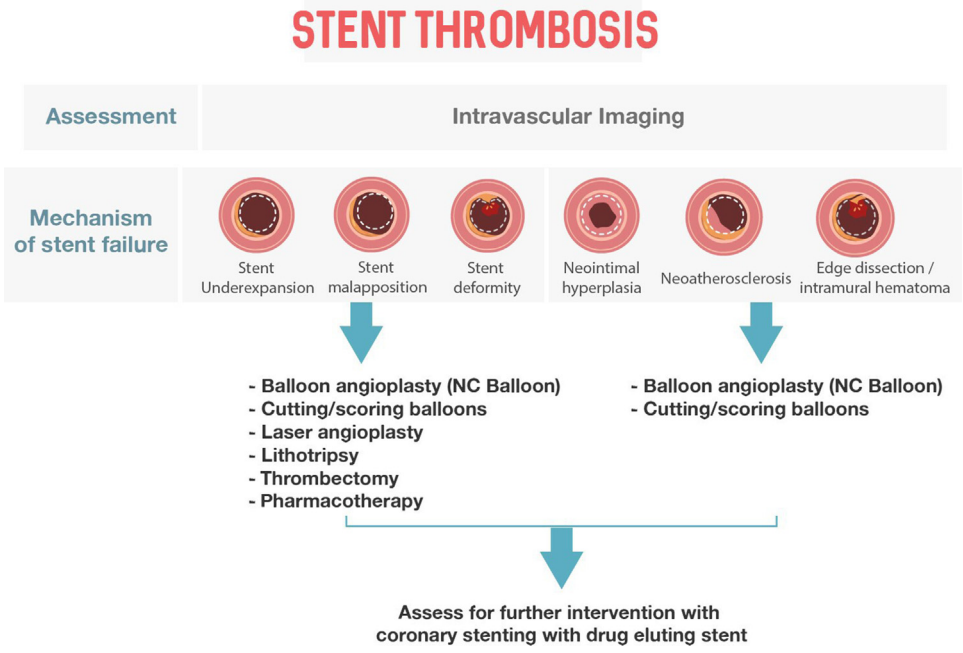

Figure 6.
SCAI algorithmic approach to stent thrombosis.

no large-scale studies to evaluate their benefit or subgroups of most/least promise.[135]

After flow is re-established and the thrombus is no longer angiographically visible, angiographic and clinical circumstances that reflect distal embolization should be sought and treated. Once the patient is stabilized, the etiology of the stent closure should be pursued. If DAPT has not been interrupted, the stent should be assessed with either IVUS or OCT to determine the adequacy of stent apposition, expansion, and the presence of edge dissections or intramural hematomas. Optimization of stent deployment with appropriate high-pressure balloon expansion should be performed. Additional stent implantation should be avoided if possible because the probability of recurrent ST increases proportionately to the stent length; however, treatment of edge dissections and progression of disease with additional stents are imperative to prevent repeat ST.

Conclusion

Stent failure remains the major drawback to the use of coronary stents as a revascularization strategy. Recent advances in imaging have substantially improved our understanding of the mechanisms underlying both ISR and ST, which have in common numerous clinical risk factors and mechanical elements at the time of stent implantation. SCAI recommends image-guided PCI at the time of initial stent implantation to minimize the occurrence of ISR and ST. When ISR or ST is encountered, imaging should be strongly considered to optimize the subsequent approach to these challenging cases.

Peer review statement

Given his role as associate editor, Sandeep Nathan had no involvement in the peer review of this article and has no access to information regarding its peer review.

Declaration of competing interest

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Supplementary material

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References

1. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56(23):1897–1907.
2. Moussa ID, Mohananey D, Saucedo J, et al. Trends and outcomes of restenosis after coronary stent implantation in the United States. *J Am Coll Cardiol*. 2020;76(13):1521–1531.
3. Palmerini T, Della Riva D, Biondi-Zoccai G, et al. Mortality following nonemergent, uncomplicated target lesion revascularization after percutaneous coronary intervention: an individual patient data pooled analysis of 21 randomized trials and 32,524 patients. *J Am Coll Cardiol Intv*. 2018;11(9):892–902.
4. Nakatsuma K, Shiomi H, Natsuaki M, et al. Second-generation versus first-generation drug-eluting stents in patients with and without diabetes mellitus: pooled analysis from the RESET and NEXT trials. *Cardiovasc Interv Ther*. 2018;33(2):125–134.
5. Iqbal J, Serruys PW, Silber S, et al. Comparison of zotarolimus- and everolimus-eluting coronary stents: final 5-year report of the RESOLUTE all-comers trial. *Circ Cardiovasc Interv*. 2015;8(6), e002230.
6. Piraino D, Cimino G, Buccheri D, Dendramis G, Andolina G, Cortese B. Recurrent in-stent restenosis, certainty of its origin, uncertainty about treatment. *Int J Cardiol*. 2017;230:91–96.
7. Cassese S, Xu B, Habara S, et al. Incidence and predictors of reCurrent restenosis after drug-coated balloon angioplasty for restenosis of a drUg-eluting stent: the ICARUS cooperation. *Rev Esp Cardiol (Engl Ed)*. 2018;71(8):620–627.
8. Song L, Mintz GS, Yin D, et al. Characteristics of early versus late in-stent restenosis in second-generation drug-eluting stents: an optical coherence tomography study. *EuroIntervention*. 2017;13(3):294–302.
9. Yabushita H, Kawamoto H, Fujino Y, et al. Clinical outcomes of drug-eluting balloon for in-stent restenosis based on the number of metallic layers. *Circ Cardiovasc Interv*. 2018;11(8), e005935.
10. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol*. 2014;63(24):2659–2673.
11. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57(11):1314–1322.
12. Bossi I, Klersy C, Black AJ, et al. In-stent restenosis: long-term outcome and predictors of subsequent target lesion revascularization after repeat balloon angioplasty. *J Am Coll Cardiol*. 2000;35(6):1569–1576.
13. Zahn R, Hamm CW, Schneider S, et al. Incidence and predictors of target vessel revascularization and clinical event rates of the sirolimus-eluting coronary stent (results from the prospective multicenter German Cypher Stent Registry). *Am J Cardiol*. 2005;95(11):1302–1308.
14. Costa MA, Angiolillo DJ, Tannenbaum M, et al. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol*. 2008;101(12):1704–1711.
15. Kobayashi Y, De Gregorio J, Kobayashi N, et al. Stented segment length as an independent predictor of restenosis. *J Am Coll Cardiol*. 1999;34(3):651–659.
16. Nusca A, Viscusi MM, Piccirillo F, et al. In stent neo-atherosclerosis: pathophysiology, clinical implications, prevention, and therapeutic approaches. *Life (Basel)*. 2022;12(3):393.
17. Huang S, Houghton PJ. Mechanisms of resistance to rapamycins. *Drug Resist Update*. 2001;4(6):378–391.
18. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47(1):175–181.
19. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100(18):1872–1878.
20. Shlofmitz E, Iantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review. *Circ Cardiovasc Interv*. 2019;12(8), e007023.
21. Kang SJ, Mintz GS, Park DW, et al. Tissue characterization of in-stent neointima using intravascular ultrasound radiofrequency data analysis. *Am J Cardiol*. 2010;106(11):1561–1565.
22. Gonzalo N, Serruys PW, Okamura T, et al. Optical coherence tomography patterns of stent restenosis. *Am Heart J*. 2009;158(2):284–293.
23. Ali ZA, Roleder T, Narula J, et al. Increased thin-cap neoatheroma and periprocedural myocardial infarction in drug-eluting stent restenosis: multimodality intravascular imaging of drug-eluting and bare-metal stents. *Circ Cardiovasc Interv*. 2013;6(5):507–517.
24. Lotfi A, Davies JE, Fearon WF, Grines CL, Kern MJ, Klein LW. Focused update of expert consensus statement: use of invasive assessments of coronary physiology and structure: a position statement of the Society of Cardiac Angiography and Interventions. *Catheter Cardiovasc Interv*. 2018;92(2):336–347.
25. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2013;82(4):E266–E355.
26. Kang SJ, Mintz GS, Park DW, et al. Mechanisms of in-stent restenosis after drug-eluting stent implantation: intravascular ultrasound analysis. *Circ Cardiovasc Interv*. 2011;4(1):9–14.
27. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE Trial. *J Am Coll Cardiol*. 2018;72(24):3126–3137.
28. Jensen LO, Vikman S, Antonsen L, et al. Intravascular ultrasound assessment of minimum lumen area and intimal hyperplasia in in-stent restenosis after drug-eluting or bare-metal stent implantation. The Nordic Intravascular Ultrasound Study (NIVUS). *Cardiovasc Revasc Med*. 2017;18(8):577–582.
29. Prati F, Romagnoli E, Burzotta F, et al. Clinical impact of OCT findings during PCI: the CLI-OPCI II Study. *J Am Coll Cardiol Img*. 2015;8(11):1297–1305.

30. Alfonso F, Cuesta J. The therapeutic dilemma of recurrent in-stent restenosis. *Circ Cardiovasc Interv*. 2018;11(8), e007109.
31. Alfonso F, Scheller B. Management of recurrent in-stent restenosis: onion skin full metal jacket? *EuroIntervention*. 2013;9(7):781–785.
32. Alfonso F, García J, Pérez-Vizcayno MJ, et al. New stent implantation for recurrences after stenting for in-stent restenosis: implications of a third metal layer in human coronary arteries. *J Am Coll Cardiol*. 2009;54(11):1036–1038.
33. Maejima N, Hibi K, Saka K, et al. Relationship between thickness of calcium on optical coherence tomography and crack formation after balloon dilatation in calcified plaque requiring rotational atherectomy. *Circ J*. 2016;80(6):1413–1419.
34. Maehara A, Matsumura M, Ali ZA, Mintz GS, Stone GW. IVUS-guided versus OCT-guided coronary stent implantation: a critical appraisal. *J Am Coll Cardiol Img*. 2017;10(12):1487–1503. https://doi.org/10.1016/j.jcmg.2017.09.008
35. Maehara A, Ben-Yehuda O, Ali Z, et al. Comparison of stent expansion guided by optical coherence tomography versus intravascular ultrasound: the ILUMIEN II study (observational study of optical coherence tomography [OCT] in patients undergoing fractional flow reserve [FFR] and percutaneous coronary intervention). *J Am Coll Cardiol Intv*. 2015;8:1704–1714.
36. Nam CW, Rha SW, Koo BK, et al. Usefulness of coronary pressure measurement for functional evaluation of drug-eluting stent restenosis. *Am J Cardiol*. 2011;107(12):1783–1786.
37. McInerney A, Travieso Gonzalez A, Castro Mejía A, et al. Long-term outcomes after deferral of revascularization of in-stent restenosis using fractional flow reserve. *Catheter Cardiovasc Interv*. 2022;99(3):723–729.
38. Alfonso F, Perez-Vizcayno MJ, Hernandez R, , et allnvestigators R-I. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. *J Am Coll Cardiol*. 2006;47(11):2152–2160.
39. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005;293(2):165–171.
40. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (intracoronary stenting and angiographic results: drug eluting stents for in-stent restenosis 2) study. *J Am Coll Cardiol*. 2010;55(24):2710–2716.
41. Kokkinidis DG, Prouse AF, Avner SJ, Lee JM, Waldo SW, Armstrong EJ. Second-generation drug-eluting stents versus drug-coated balloons for the treatment of coronary in-stent restenosis: A systematic review and meta-analysis. *Catheter Cardiovasc Interv*. 2018;92(2):285–299.
42. Navarese EP, Austin D, Gurbel PA, et al. Drug-coated balloons in treatment of in-stent restenosis: a meta-analysis of randomised controlled trials. *Clin Res Cardiol*. 2013;102(4):279–287.
43. Goel SS, Dilip Gajulapalli R, Athappan G, et al. Management of drug eluting stent in-stent restenosis: a systematic review and meta-analysis. *Catheter Cardiovasc Interv*. 2016;87(6):1080–1091.
44. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. *J Am Coll Cardiol*. 2015;66(1):23–33.
45. Kufner S, Joner M, Schneider S, et al. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: a randomized controlled trial. *J Am Coll Cardiol Intv*. 2017 10;10(13):1332–1340.
46. Vom Dahl J, Dietz U, Haager PK, et al. Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). *Circulation*. 2002;105(5):583–588.
47. Baan Jr J, Claessen BE, Dijk KB, et al. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. *J Am Coll Cardiol Intv*. 2018;11(3):275–283.
48. Megaly M, Glogoza M, Xenogiannis I, et al. Outcomes of intravascular brachytherapy for recurrent drug-eluting in-stent restenosis. *Catheter Cardiovasc Interv*. 2021;97(1):32–38.
49. Varghese MJ, Bhatheja S, Baber U, et al. Intravascular brachytherapy for the management of repeated multimetal-layered drug-eluting coronary stent restenosis. *Circ Cardiovasc Interv*. 2018;11(10), e006832.
50. Chen G, Zrenner B, Pyxaras SA. Combined rotational atherectomy and intravascular lithotripsy for the treatment of severely calcified in-stent neoatherosclerosis: a mini-review. *Cardiovasc Revasc Med*. 2019;20(9):819–821.
51. Tovar Forero MN, Sardella G, Salvi N, et al. Coronary lithotripsy for the treatment of underexpanded stents: the international and multicentre CRUNCH registry. *EuroIntervention*. 2022;18(7):574–581.
52. Mahmoud KD, Vlaar PJ, van den Heuvel AF, Hillege HL, Zijlstra F, de Smet BJ. Usefulness of thrombus aspiration for the treatment of coronary stent thrombosis. *Am J Cardiol*. 2011;108(12):1721–1727.
53. Reeves RR, Patel M, Armstrong EJ, et al. Angiographic characteristics of definite stent thrombosis: role of thrombus grade, collaterals, epicardial coronary flow, and myocardial perfusion. *Catheter Cardiovasc Interv*. 2015;85(1):13–22.
54. Armstrong EJ, Feldman DN, Wang TY, et al. Clinical presentation, management, and outcomes of angiographically documented early, late, and very late stent thrombosis. *J Am Coll Cardiol Intv*. 2012;5(2):131–140.
55. Claessen BE, Henriques JP, Jaffer FA, Mehran R, Piek JJ, Dangas GD. Stent thrombosis: a clinical perspective. *J Am Coll Cardiol Intv*. 2014;7(10):1081–1092.
56. Goto K, Zhao Z, Matsumura M, et al. Mechanisms and patterns of intravascular ultrasound in-stent restenosis among bare metal stents and first- and second-generation drug-eluting stents. *Am J Cardiol*. 2015;116(9):1351–1357.
57. Albiero R, Silber S, Di Mario C, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol*. 2004;43(6):943–949.
58. Park SJ, Kim KH, Oh IY, et al. Comparison of plain balloon and cutting balloon angioplasty for the treatment of restenosis with drug-eluting stents vs bare metal stents. *Circ J*. 2010;74(9):1837–1845.
59. Claessen BE, Kini AS, Mehran R, Sharma SK, Dangas GD. Coronary in-stent restenosis: an algorithmic approach to the treatment of coronary in-stent restenosis. *J Invasive Cardiol*. 2019;(suppl):9–12.
60. Theodoropoulos K, Mennuni MG, Dangas GD, et al. Resistant in-stent restenosis in the drug eluting stent era. *Catheter Cardiovasc Interv*. 2016;88(5):777–785.
61. Lee T, Shlofmitz RA, Song L, et al. The effectiveness of excimer laser angioplasty to treat coronary in-stent restenosis with peri-stent calcium as assessed by optical coherence tomography. *EuroIntervention*. 2019;15(3):e279–e288.
62. Sharma SK, Kini A, Mehran R, Lansky A, Kobayashi Y, Marmur JD. Randomized trial of rotational atherectomy versus balloon angioplasty for diffuse in-stent restenosis (ROSTER). *Am Heart J*. 2004;147(1):16–22.
63. Ferri LA, Jabbour RJ, Giannini F, et al. Safety and efficacy of rotational atherectomy for the treatment of undilatable underexpanded stents implanted in calcific lesions. *Catheter Cardiovasc Interv*. 2017;90(2):E19–E24.
64. Latib A, Takagi K, Chizzola G, et al. Excimer laser lesion modification to expand non-dilatable stents: the ELLEMENT registry. *Cardiovasc Revasc Med*. 2014;15(1):8–12.
65. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165.
66. Rhee TM, Lee JM, Shin ES, et al. Impact of optimized procedure-related factors in drug-eluting balloon angioplasty for treatment of in-stent restenosis. *J Am Coll Cardiol Intv*. 2018;11(10):969–978.
67. Ashikaga T, Yoshikawa S, Isobe M. The effectiveness of excimer laser coronary atherectomy with contrast medium for underexpanded stent: the findings of optical frequency domain imaging. *Catheter Cardiovasc Interv*. 2015;86(5):946–949.
68. Rheude T, Fitzgerald S, Allali A, et al. Rotational atherectomy or balloon-based techniques to prepare severely calcified coronary lesions. *J Am Coll Cardiol Intv*. 2022;15(18):1864–1874.
69. Muramatsu T, Tsukahara R, Ho M, et al. Efficacy of cutting balloon angioplasty for in-stent restenosis: an intravascular ultrasound evaluation. *J Invasive Cardiol*. 2001;13(6):439–444.
70. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis: the three-year results of the PEPCAD II ISR study. *EuroIntervention*. 2015;11(8):926–934.
71. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial (restenosis intra-stent of bare metal stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol*. 2014;63(14):1378–1386.
72. Adriaenssens T, Dens J, Ughi G, et al. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug elUting balloon in Coronary artery rEstenosis) randomised clinical trial. *EuroIntervention*. 2014;10(4):439–448.
73. Scheller B, Clever YP, Kelsch B, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *J Am Coll Cardiol Intv*. 2012;5(3):323–330. https://doi.org/10.1016/j.jcin.2012.01.008
74. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119(23):2986–2994.
75. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the treatment of in-stent restenosis study. *Circ Cardiovasc Interv*. 2016;9(4), e003316.
76. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381(9865):461–467.
77. Xu B, Qian J, Ge J, et al. Two-year results and subgroup analyses of the PEPCAD China in-stent restenosis trial: a prospective, multicenter, randomized trial for the treatment of drug-eluting stent in-stent restenosis. *Catherer Cardiovasc Interv*. 2016;87(suppl 1):624–629.
78. Wong YTA, Kang DY, Lee JB, et al. Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: a randomized RESTORE Trial. *Am Heart J*. 2018;197:35–42.
79. Jensen CJ, Richardt G, Tölg R, et al. Angiographic and clinical performance of a paclitaxel-coated balloon compared to a second-generation sirolimus-eluting stent in patients with in-stent restenosis: the BIOLUX randomised controlled trial. *EuroIntervention*. 2018;14(10):1096–1103.
80. Giacoppo D, Alfonso F, Xu B, et al. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J*. 2020;41(38):3715–3728.

81. Ali RM, Abdul Kader MASK, Wan Ahmad WA, et al. Treatment of coronary drug-eluting stent restenosis by a sirolimus- or paclitaxel-coated balloon. *J Am Coll Cardiol Intv*. 2019;12(6):558–566.
82. Scheller B, Mangner N, Abdul Kader MASK, et al. Combined analysis of two parallel randomized trials of sirolimus-coated and paclitaxel-coated balloons in coronary in-stent restenosis lesions. *Circ Cardiovasc Interv*. 2022;15(9), e012305.
83. Habara S, Mitsudo K, Kadota K, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *J Am Coll Cardiol Intv*. 2011;4(2):149–154. https://doi.org/10.1016/j.jcin.2010.10.012
84. Ho E, Denby K, Cheria S, et al. Intracoronary brachytherapy for drug-eluting stent restenosis: outcomes and clinical correlates. *JSCAI*. 2023;2(1), 100550.
85. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES Study. *J Am Coll Cardiol*. 2012;59(15):1377–1382.
86. Nikolakopoulos I, Vemmou E, Xenogiannis I, Brilakis ES. Combined use of intravascular lithotripsy and brachytherapy: a new approach for the treatment of recurrent coronary in-stent restenosis. *Catheter Cardiovasc Interv*. 2021;97(7):1402–1406.
87. Megaly M, Glogoza M, Xenogiannis I, et al. Coronary intravascular brachytherapy for recurrent coronary drug-eluting stent in-stent restenosis: a systematic review and meta-analysis. *Cardiovasc Revasc Med*. 2021;23:28–35.
88. Wańha W, Tomaniak M, Wańczura P, et al. Intravascular lithotripsy for the treatment of stent underexpansion: the multicenter IVL-DRAGON registry. *J Clin Med*. 2022;11(7):1779–1785.
89. Holmes Jr DR, Kereiakes DJ, Garg S, et al. Stent thrombosis. *J Am Coll Cardiol*. 2010;56(17):1357–1365.
90. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet*. 2008;371(9621):1353–1363.
91. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356(10):1020–1029.
92. Kirtane AJ, Stone GW. How to minimize stent thrombosis. *Circulation*. 2011;124(11):1283–1287.
93. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. *Circulation*. 2011;123(16):1745–1756.
94. Dangas GD, Claessen BE, Mehran R, Xu K, Stone GW. Stent thrombosis after primary angioplasty for STEMI in relation to non-adherence to dual antiplatelet therapy over time: results of the HORIZONS-AMI trial. *EuroIntervention*. 2013;8(9):1033–1039.
95. Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet*. 2016;387(10016):357–366.
96. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344–2351.
97. Cutlip DE, Nakazawa G, Krucoff MW, et al. Autopsy validation study of the academic research consortium stent thrombosis definition. *J Am Coll Cardiol Intv*. 2011;4(5):554–559.
98. Grewe PH, Deneke T, Machraoui A, Barmeyer J, Müller KM. Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. *J Am Coll Cardiol*. 2000;35(1):157–163.
99. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293(17):2126–2130.
100. Généreux P, Rutledge DR, Palmerini T, et al. Stent thrombosis and dual antiplatelet therapy interruption with everolimus-eluting stents: insights from the Xience V Coronary Stent System trials. *Circ Cardiovasc Interv*. 2015;8(5), e001362.
101. Uren NG, Schwarzacher SP, Metz JA, et al. Predictors and outcomes of stent thrombosis: an intravascular ultrasound registry. *Eur Heart J*. 2002;23(2):124–132.
102. Alfonso F, Suárez A, Angiolillo DJ, et al. Findings of intravascular ultrasound during acute stent thrombosis. *Heart*. 2004;90(12):1455–1459.
103. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol*. 2008;52(5):333–342.
104. Généreux P, Stone GW, Harrington RA, et al. Impact of intraprocedural stent thrombosis during percutaneous coronary intervention: insights from the CHAMPION PHOENIX Trial (clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention). *J Am Coll Cardiol*. 2014;63(7):619–629.
105. Aoki J, Lansky AJ, Mehran R, et al. Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation*. 2009;119(5):687–698.
106. Husted S, Boersma E. Case study: ticagrelor in PLATO and prasugrel in TRITON-TIMI 38 and TRILOGY-ACS trials in patients with acute coronary syndromes. *Am J Ther*. 2016;23(6):e1876–e1889.
107. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING study. *J Am Coll Cardiol*. 2005;46(10):1820–1826.
108. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST study. *J Am Coll Cardiol*. 2005;46(10):1827–1832.
109. Wenaweser P, Dörffler-Melly J, Imboden K, et al. Stent thrombosis is associated with an impaired response to antiplatelet therapy. *J Am Coll Cardiol*. 2005;45(11):1748–1752.
110. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006;48(12):2584–2591.
111. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297(2):159–168.
112. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J*. 2009;30(22):2714–2721.
113. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381(21):2032–2042.
114. Kandzari DE, Kirtane AJ, Windecker S, et al. One-month dual antiplatelet therapy following percutaneous coronary intervention with zotarolimus-eluting stents in high-bleeding-risk patients. *Circ Cardiovasc Interv*. 2020;13(11), e009565.
115. Gomez-Lara J, Salvatella N, Gonzalo N, et al. IVUS-guided treatment strategies for definite late and very late stent thrombosis. *EuroIntervention*. 2016;12(11):e1355–e1365.
116. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120(5):391–399.
117. Van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol*. 2009;53(16):1399–1409.
118. Pesarini G, Dandale R, Rigamonti A, et al. Late and very late coronary stent thrombosis: intravascular ultrasound findings and associations with antiplatelet therapy. *Catheter Cardiovasc Interv*. 2013;82(7):1056–1065.
119. Kang SJ, Lee CW, Song H, et al. OCT analysis in patients with very late stent thrombosis. *J Am Coll Cardiol Img*. 2013;6(6):695–703.
120. Murata A, Wallace-Bradley D, Tellez A, et al. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. *J Am Coll Cardiol Img*. 2010;3(1):76–84.
121. Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. *Circulation*. 1999;99(1):44–52.
122. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. *Circulation*. 2003;108(1):43–47.
123. Windecker S, Meier B. Late coronary stent thrombosis. *Circulation*. 2007;116(17):1952–1965.
124. Madhavan MV, Kirtane AJ, Redfors B, et al. Stent-related adverse events >1 year after percutaneous coronary intervention. *J Am Coll Cardiol*. 2020;75(6):590–604.
125. Franchin L, Kang J, De Filippo O, et al. Incidence and predictors of stent thrombosis in patients treated with stents for coronary bifurcation narrowing (from the BIFURCAT registry). *Am J Cardiol*. 2021;156:24–31.
126. Prati F, Di Vito L, Biondi-Zocca G, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention*. 2012;8(7):823–829.
127. Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation*. 2016;133(7):650–660.
128. Zhang Y, Farooq V, Garcia-Garcia HM, et al. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention*. 2012;8(7):855–865.
129. Witzenbichler B, Maehara A, Weisz G, et al. TCT-21 Use of IVUS reduces stent thrombosis: results from the prospective, multicenter ADAPT-DES study. *J Am Coll Cardiol*. 2012;60(17):B6 (suppl B):B6.
130. Gao XF, Ge Z, Kong XQ, et al. 3-year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *J Am Coll Cardiol Intv*. 2021;14(3):247–257.
131. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet*. 2016;388(10060):2618–2628.
132. Adriaenssens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE consortium (prevention of late stent thrombosis by an interdisciplinary global European effort). *Circulation*. 2017;136(11):1007–1021.
133. Otake H, Kubo T, Takahasi H, et al. Optical frequency domain imaging versus intravascular ultrasound in percutaneous coronary intervention (OPINION trial): results from the OPINION imaging study. *J Am Coll Cardiol Img*. 2018;11(1):111–123.
134. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. *J Am Coll Cardiol*. 2018;72(23 Pt A):2915–2931.
135. Jolly SS, James S, Džavík V, et al. Thrombus aspiration in ST-segment–elevation myocardial infarction: an individual patient meta-analysis: Thrombectomy Trialists Collaboration. *Circulation*. 2017;135(2):143–152.