Journal of the American Heart Association

CONTEMPORARY REVIEW

Intravascular Imaging for Guiding In-Stent Restenosis and Stent Thrombosis Therapy

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ABSTRACT: Advances in stent technology and the design of endovascular devices with thinner struts, anti-inflammatory and antithrombotic polymers, and better drug kinetics have enhanced the safety and efficacy of the second-generation drug-eluting stents and broadened their use in the therapy of high-risk patients and complex anatomies. However, despite these developments, in-stent restenosis and stent thrombosis remain the Achilles' heel of percutaneous coronary intervention, with their cumulative incidence reaching up to 10% at 5 years following percutaneous coronary intervention. The treatment of stent failure poses challenges and is associated with a worse prognosis than conventional percutaneous coronary intervention. Several studies have recently highlighted the value of intravascular imaging in identifying causes of stent failure, underscored its role in treatment planning, and registries have shown that its use may be associated with better clinical outcomes. The present review aims to summarize the evidence in the field; it discusses the value of intravascular imaging in identifying the mechanisms of in-stent restenosis and stent thrombosis in assessing the morphological characteristics of neointima tissue that appears to determine long-term outcomes in evaluating procedural results, and presents the findings of studies supporting its value in guiding therapy in stent failure.

Key Words: in-stent restenosis ■ intravascular ultrasound ■ optical coherence tomography

New developments in percutaneous coronary intervention (PCI) technology, including the design of efficient guidewires, adjunctive PCI devices, and advances in stent technology, have simplified the procedure, reduced the risk of complications, increased procedural success, and improved long-term outcomes, especially in high-risk patients and complex lesions. Nevertheless, in selected patients and in challenging anatomies, the event rate remains high.[1] In-stent restenosis (ISR) constitutes the most common cause of stent failure in the United States and United Kingdom,[2,3] and its management is challenging because reintervention is needed in 10.3% to 36.8% of the patients at 3-year follow-up.[4,5] Although the incidence of stent thrombosis (ST) has been considerably reduced after the introduction of the second-generation drug eluting stents (DES) as shown in clinical trials, in clinical practice, the ST rates are higher and are associated with devastating consequences, because in such cases the clinical presentation is often death or myocardial infarction.[6–8]

Over the past years, several endovascular therapies have been introduced to successfully treat ISR that were evaluated in numerous randomized control studies (Figure S1, Table S1). Despite the undoubted value of these studies in clinical practice, they all had a significant limitation: they did not use intravascular imaging to identify the underlying mechanisms of stent failure and assess neointima characteristics that are likely to affect clinical outcomes. Intravascular imaging studies have underscored the importance of correcting causes of stent failure and the role of neointima composition on vessel wall response after repeat revascularization. Consequently, the routine use of intravascular imaging has IIa/C indication in the European Society of Cardiology guidelines for detecting causes

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026492

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

DCB	drug-coated balloon
DES	drug-eluting stent
ISR	in-stent restenosis
IVBT	intravascular brachytherapy
POBA	plain old balloon angioplasty
ST	stent thrombosis
TLR	target lesion revascularization
WSS	wall shear stress

of stent failure and personalizing therapy.[9] This review aimed to provide a comprehensive overview in the field, discusses the potential value of intravascular imaging in identifying causes of ISR and ST, presents clinical outcomes from small-scale studies assessing different interventional strategies in challenging scenarios, and proposes a treatment algorithm that relies on the information derived from intravascular imaging to effectively treat ISR and ST.

UNDERLYING MECHANISMS OF IN-STENT RESTENOSIS

The introduction of DES and developments in stent polymers and drug kinetics have significantly reduced the incidence of ISR and improved prognosis.[10] Despite these advances, however, ISR remains the Achilles' heel of DES, with the number of procedures performed for this reason continuing to rise over recent years. According to the British Cardiovascular Intervention Society audit data in 2008, approximately 4000 PCIs were performed to treat ISR in the United Kingdom, a number that rose to 5215 in 2018. This rise can be attributed to the increase of the number of PCIs (from 80 331 to 102 258) and the complexity of the procedures performed.

Several studies have demonstrated that patient demographics (eg, diabetes, renal failure, previous bypass operation) and complex lesion anatomy (eg, bifurcation lesions, long lesions, presence of moderate/severe calcification, chronic total occlusions, and small vessel disease) are predictors of ISR.[1,11] The use of intravascular imaging to guide revascularization in complex lesions appears to improve short- and long-term outcomes and reduce the incidence of stent failure.[12,13] This should be attributed to the fact that intravascular ultrasound (IVUS) and optical coherence tomography (OCT) allow optimal stent sizing, detailed assessment of procedural results, and identification of potential causes of ISR (Figure 1).[14] Therefore, it has been argued that routine use of intravascular imaging is the best way to prevent ISR by identifying the causes of stent failure and optimizing PCI results.

EVIDENCE SUPPORTING THE USE OF INTRAVASCULAR IMAGING TO GUIDE TREATMENT IN ISR

There are no randomized data today to support the prognostic value of intravascular imaging in guiding revascularization in ISR. This could be attributed to the relatively small incidence of ISR and also to the fact that it is unclear how to use the information provided by intravascular imaging to guide revascularization in this setting. The RIBS III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) study provided some evidence about the potential value of IVUS in treating ISR. This study was designed to examine the value of a switch strategy (ie, use of a different DES in 363 patients admitted with DES-ISR).[15] IVUS was used to guide revascularization in 38.0% of the patients and was associated with a larger acute gain (1.55±0.6 versus 1.35±0.6 mm, $P<0.01$) and minimum lumen diameter at 9-month follow-up (1.89±0.8 versus 1.68±0.7 mm, $P<0.01$); however, it did not reduce the incidence of target lesion revascularization (TLR) at 2 years. These findings, however, should be interpreted with caution, because in RIBS III, the use of IVUS depended on operator preference. In addition, the recently published iOPEN-ISR (Impact of Intravascular Ultrasound on Outcomes Following Percutaneous Coronary Intervention for In-Stent Restenosis) registry was the first that demonstrated a prognostic benefit of the use of IVUS in guiding revascularization of lesions with ISR. In this report, 1522 patients with ISR were treated with either IVUS (65.9%) or angiography alone guidance (34.1%). The primary end point was the rate of major adverse cardiac events at 1 year, described as the composite of all-cause mortality, Q-wave myocardial infarction, and target vessel revascularization, that occurred in 18.0% of patients treated with IVUS and 24.5% of patients treated with angiography guidance ($P<0.01$). Q wave myocardial infarction (0.3% versus 1.6%, $P=0.010$) and target vessel revascularization (14.5% versus 19.2%, $P=0.021$) occurred less often in the IVUS than the angiography cohort, but there was no difference between groups in the incidence of all-cause mortality. Results were similar at 2- and 3-year follow-ups. In multivariate analysis, IVUS guidance was independently associated with a reduced incidence of major adverse cardiac events at 1-year follow-up.[16] Limitations of this analysis included the differences in the baseline demographics between the 2 groups, the fact that IVUS was used at the discretion of the operator, which is likely to introduce bias, and the lack of a

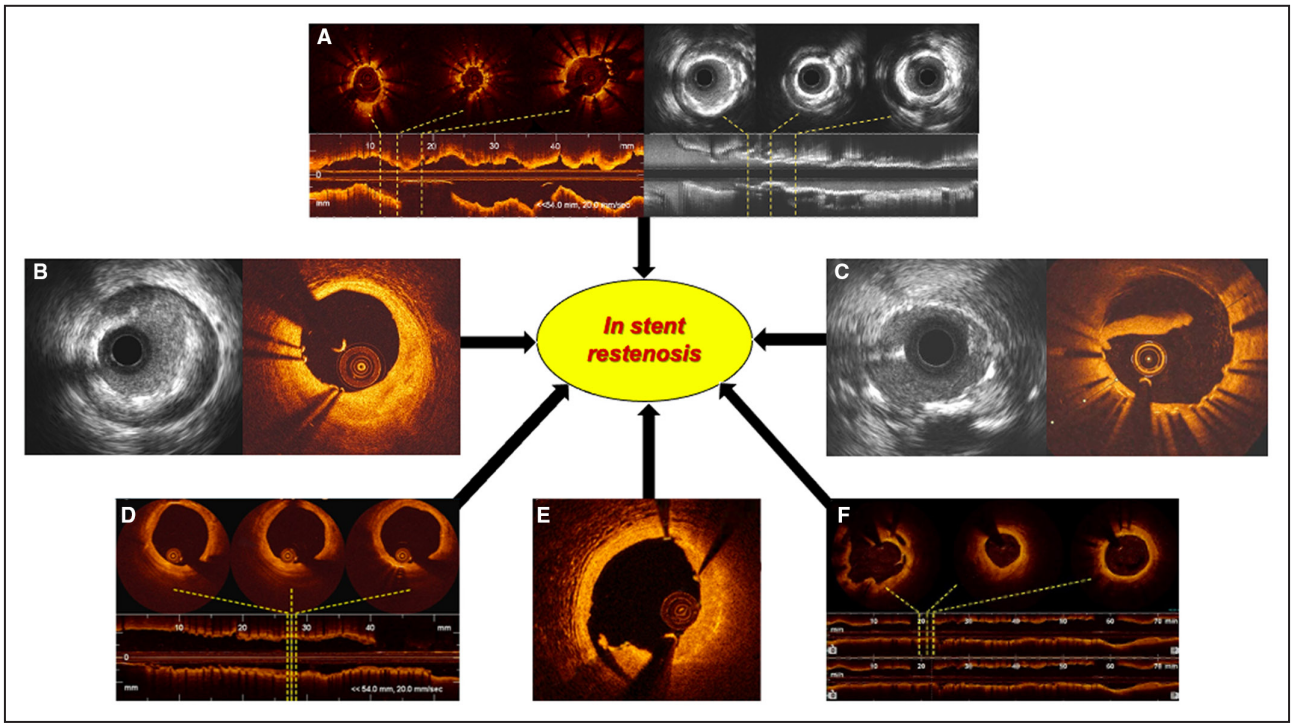

Figure 1. Common causes of in-stent restenosis.
A, Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) cross-sections of stent underexpansion. **B**, Significant plaque at the stent edge is seen on IVUS and OCT. **C**, Thrombus extends into the lumen on IVUS and OCT. **D**, Nonoverlapping stents. There are no stent struts on the middle cross-section of OCT. **E**, A dissection flap extends into the lumen on OCT. **F**, Fractured stent struts are seen.

standardized protocol to guide revascularization in the 2 groups.

Recently, a classification scheme has been proposed to categorize ISR based on the underlying pathological mechanisms that contributed to its development, and a treatment algorithm has been developed for personalized treatment.[17] In the following section we present the evidence supporting the role of IVUS or OCT for optimizing revascularization in ISR and propose an updated algorithm that takes into account recently published studies to guide therapy in this setting (Table S2).

Stent Underexpansion

Stent underexpansion constitutes a common cause of ISR[18]; this should be attributed not only to the resulting smaller lumen area that makes even a small neointima proliferation clinically relevant, but also to the fact that a suboptimal stent expansion is likely to create an unfavorable hemodynamic environment with high wall shear stress (WSS) at the underexpanded segment and low WSS upstream and downstream of the stenosis, which promotes neointima proliferation and neoatherosclerotic lesion formation in bare metal and DES.[19]

The definition of optimal stent expansion varies in different studies; in the recently published expert consensus document of the European Association of PCI, stent underexpansion was defined as stent expansion (ie, a minimum stent area versus average reference lumen area ratio) ≤80%, or a minimum stent area ≤5.5 mm^2 by IVUS and ≤4.5 mm^2 by OCT.[14]

Assessment of stent expansion in ISR using intravascular imaging is of the utmost importance for guiding therapy. In the study of Yin et al, the presence of stent underexpansion, defined as a stent expansion <70% and minimum stent area <4.5 mm^2, multiple layers of stent and a calcified underlying plaque were predictors of new DES underdeployment, defined again as a stent expansion <70% and minimum stent area <4.5 mm^2, which was associated with a higher risk of myocardial infarction (9.7% versus 1.9%, P=0.046) and TLR (32.4% versus 13.3%, P=0.010) at 2-year follow-up.[20] Therefore, it is essential to evaluate stent expansion and optimize lesion preparation, especially in restenotic lesions with increased calcific burden. In this setting, off-label use of debulking techniques, such as rotational atherectomy, orbital atherectomy, excimer laser, or intravascular lithotripsy, may be considered.[21–23] In the absence of randomized data, debulking device selection should be individualized depending on lesion

characteristics that can be assessed by intravascular imaging. Rotational atherectomy can be used in severely calcified restenotic lesions, but this technique as well as orbital atherectomy should be avoided in case of extensive stent malapposition, because there is a risk of burr entrapment. Intravascular lithotripsy balloons may not be able to cross severely restenotic lesions and appear effective only in lesions with circumferential calcium, whereas excimer laser seems to perform well in most cases, but it is not available in many catheterization laboratories. Intravascular imaging can also be used to assess procedural results, modify treatment strategy in case of suboptimal lesion preparation, and in case of optimal results, guide implantation and aggressive postdilatation of another DES.[24]

Nonoverlapping Stents

A gap between serially implanted stents can potentially increase the incidence of ISR; the vessel wall trauma during lesion preparation as well as the lack of drug delivery in this segment can promote intima proliferation leading to restenosis.[25] Intravascular imaging can accurately detect the gap between stents and estimate their length. Implantation of an additional stent to cover the gap is the plausible treatment.

Stent Fracture

Stent fracture is a well-recognized cause of stent failure and ISR. Several studies have shown that its incidence is lower in the second-generation DES and confirm that it is an instigator of ISR and ST in these devices.[26–28] In the study of Kuramitsu et al, the incidence of stent fracture was 2.9% at 6- to 9-months follow-up and was associated with a higher incidence of myocardial infarction and TLR (5.1% versus 0.4%, P=0.018 and 25.6% versus 2.0%, P<0.001).[28] It is believed that the absence of metal scaffolding to support the underlying plaque, as well as the limited drug delivery in this segment, provide the substrate for neointima proliferation. IVUS and especially OCT, with its higher resolution, can be used to detect stent fracture in case of ISR.[29,30] A retrospective analysis comparing outcomes following treatment of ISR attributed to stent fracture using drug-coated balloon (DCB) or DES showed no difference in restenosis (37.5% versus 44.4%, P=0.58) or TLR (31.9% versus 43.9%, P=0.31) rates between these 2 groups at 1-year follow-up.[31]

Edge Dissection and Increased Plaque at the Stent Edge

Several studies have shown that an increased plaque (>54.5%) or lipid burden (lipid arc ≥185°) at the edge of the stent and the presence of edge dissections are predictors of ISR and future revascularizations.[32–36] Intravascular imaging enables evaluation of plaque morphology at the landing zones; IVUS, with its high penetration depth, is the ideal modality for quantifying plaque burden, whereas OCT, with its greater resolution, appears superior to IVUS in assessing plaque composition and detecting vessel wall dissection. Therefore, in case of ISR with residual plaque at the stent edge or major edge dissections, with length >3 mm or circumferential extent >60°, implantation of an additional stent to cover the plaque or edge dissection should be considered.[37]

Neointima Characteristics and Revascularization Strategy

Although OCT has limitations in assessing neointima characteristics,[38] there is evidence that specific morphological features, detected by OCT, determine vessel wall response following an interventional therapy. In the study of Tada et al, which included 214 restenotic lesions, OCT was used to classify ISR as homogeneous, heterogeneous, layered, lipid rich, and non–lipid rich (Figure S2).[39] Lesions were treated with either combined therapy with plain old balloon angioplasty (POBA) and DCB or standalone POBA. DCB therapy was associated with a lower incidence of ISR and TLR compared with standalone POBA at 6- to 8-months follow-up. Analysis based on neointima morphology showed that ISR and TLR rates were lower in the DCB group when neointima had a homogeneous or lipid-rich morphology, but there was no difference between groups in lesions with a heterogeneous or layered morphology (Table S2).

Similar findings were reported in an updated analysis from the same research group that also included restenotic lesions treated with DES.[40] In this study, which included 428 lesions, ISR and TLR rates were considerably higher at 6- to 8-months follow-up in the homogeneous and layered lesions treated with POBA compared with the DCB and DES groups. Conversely, in lesions with heterogeneous neointima, the incidence of ISR and TLR was numerically higher in the DCB than the POBA or DES group (Table S2).

The above findings were also confirmed by a retrospective analysis of 222 restenotic lesions treated with paclitaxel-eluting DCB,[41] and by the study of Lee et al that included 122 restenotic lesions treated with DCB, which showed worse prognosis in heterogeneous than in nonheterogenous neointima (43.7% versus 19.6%, P=0.018).[42] In that study, a numerically higher event rate was reported in lipid-rich neoatherosclerotic plaques compared with nonneoatherosclerotic lesions, but this difference was not statistically significant, probably because of the small sample size (Table S2). These findings are also supported by the analysis of Xhepa et al that included 197 ISR lesions treated with either DCB

or DES.[43] The lesions were classified as lesions with a high or low inhomogeneity depending on the number of quadrants that had a heterogeneous, layered, or neoatherosclerotic pattern. Lesions with high inhomogeneity treated with DCB had higher major adverse cardiac events and TLR rates than those treated with a DES; conversely, there was no difference in the outcomes between the 2 treatment strategies in lesions with low inhomogeneity.

A possible explanation of the high event rate noted after treatment of restenotic lesions with high inhomogeneity with DCB is the fact that this morphological type has features associated with increased instability, such as increased fibrin deposition and peristrut inflammation, is seen more often after stenting of plaques that caused an acute coronary syndrome, and is associated with worse prognosis.[14,44,45] In this setting, DES implantation should be considered, because it enables its invasive passivation. In calcific-rich neoatherosclerotic lesions and calcific nodules, efforts should be made to optimally prepare these lesions using multiple debulking techniques to minimize the risk of implanting an underexpanded stent.[24]

Recurrent Restenosis

The treatment of recurrent restenosis is one of the challenges in interventional cardiology, because the event rate has been reported in up to 20% of patients at 1-year follow-up.[46] Several treatment strategies have been proposed in this setting, such as DCB, implantation of second-generation DES, and intravascular brachytherapy (IVBT). In the New Tokyo Registry that included 304 patients, clinical outcomes were compared between patients with a different number of metallic layers of stent that were treated with DCB. Patients with ≥3 layers had a higher TLR rate at 1-year follow-up than those with 1 or 2 layers (Table S2).[47] The study of Varghese et al provided additional insights about the optimal treatment strategy of recurrent restenosis.[46] The authors included patients who had at least 2 layers of stent and classified them in 2 groups; the first included patients treated with IVBT and the second patients receiving any other therapy. This analysis demonstrated a high event rate in both groups but a better prognosis at 1 year in the IVBT group than the control group (13.2% and 28.2%, P=0.01) with or without propensity matching (Table S2).

Summarizing the evidence, it can be argued that in recurrent restenosis because of aggressive neointima proliferation, DCB can be used in cases with ≤2 layers of stent, whereas in cases with ≥3 layers, IVBT should be preferred when available. Intravascular imaging, and in particular OCT, is an excellent tool for assessing stent layers and planning treatment.[14]

UNDERLYING MECHANISMS OF STENT THROMBOSIS

The development of first-generation DES considerably reduced the incidence of ISR, but studies have shown that their implantation was associated with a higher incidence of ST that has been attributed to the delayed endothelial coverage and the persistent inflammatory reaction to the durable polymer, raising concerns about their safety.[48] Advances in stent technology and the advent of second-generation DES have reduced the incidence of ST to <1% per year, but it did not eliminate it.[49] Reports have shown that specific patient characteristics (eg, presentation with an acute coronary syndrome, history of diabetes, impaired left ventricular systolic function, impaired platelet reactivity) and lesions with a high anatomical complexity are associated with a higher incidence of ST, and intravascular imaging studies have provided unique insights about the mechanisms of ST (Figure 2).[11,50] The Bern, the PESTO (Morphological Parameters Explaining Stent Thrombosis Assessed by OCT), and the PRESTIGE (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort) registries, which are the largest in the field, showed that OCT performed at the time of the event is capable of detecting the underlying cause of ST in the vast majority of the cases. In these studies, suboptimal image quality, not allowing image analysis, was seen in only 5.5% of the cases, whereas in interpretable OCT, a cause of ST was identified in 98.2% of the cases in the Bern registry, in 87% of the cases in the PESTO registry, and in all the cases in the PRESTIGE registry (Figure 3).[51–53] This information is clinically relevant because the cause of ST determines treatment planning.

Stent Underexpansion

Stent underexpansion is a well-recognized cause of ST and has a high prevalence in patients admitted with subacute (24 hours to 30 days), late (>30 days to 1 year), or very late (>1 year) ST. Computational fluid dynamic studies have shown that stent underexpansion is associated with increased WSS and shear rate at the stenosis site.[54] High shear rate causes platelets and adhesion protein displacement near the vessel wall, creating a prothrombotic environment. The contact of adhesion proteins like the von Willebrand factor and fibrinogen with the thrombogenic stent struts can trigger a clot cascade that includes platelet stimulation. In a high shear rate milieu, the von Willebrand factor elongates, allowing a larger number of platelets to bind sites of the molecule leading to thrombus formation and stent occlusion.[55]

Treatment of stent underexpansion, whenever this is detected, is therefore essential. IVUS and OCT have

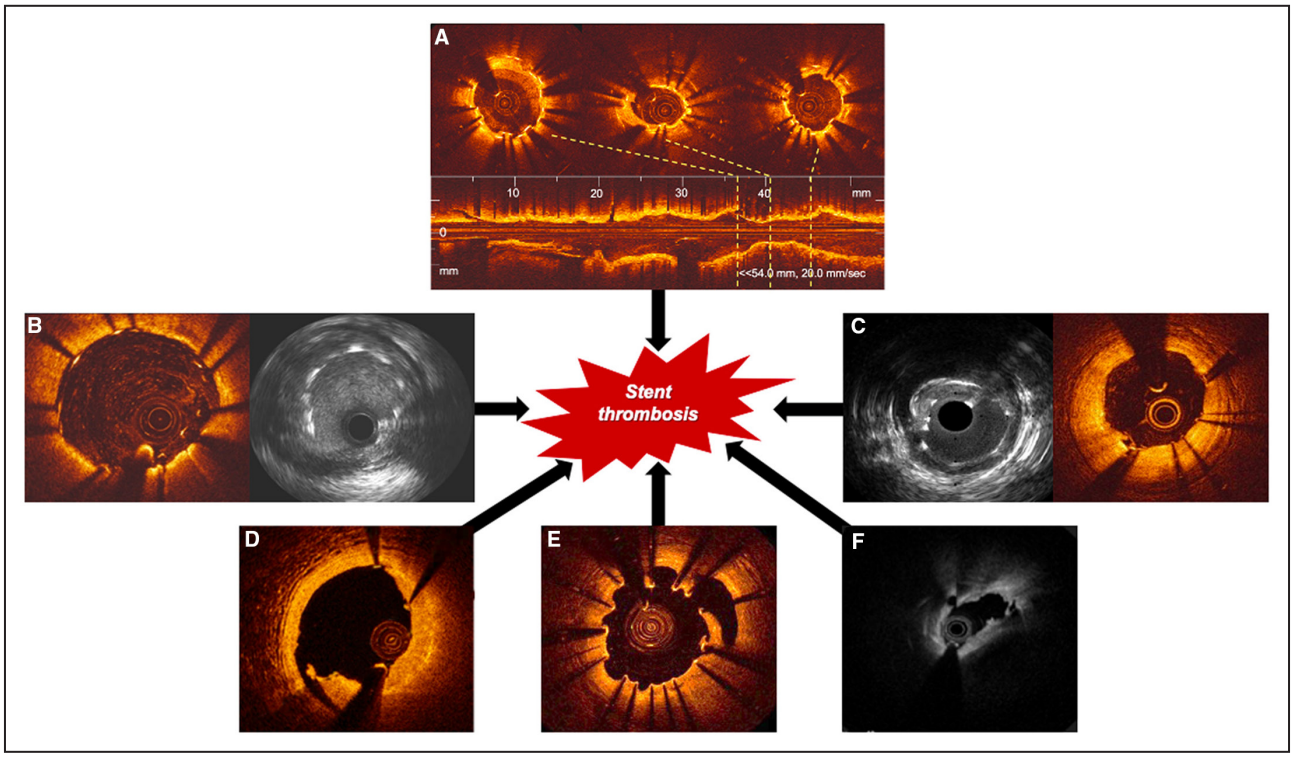

Figure 2. Common causes of stent thrombosis.
A, Optical coherence tomography (OCT) cross-section of stent underexpansion. **B**, Malapposed stent struts are seen with a significant distance from the vessel wall on OCT and intravascular ultrasound (IVUS). **C**, Significant plaque at the stent edge is seen on IVUS and OCT. **D**, A dissection flap extends into the lumen on OCT. **E**, Evagination and vessel wall bulging pushing the stent struts into the lumen is seen on OCT. **F**, Lipid-rich neoatherosclerotic plaque appears on OCT.

excellent efficacy in evaluating stent expansion and the composition of the underlying plaque and guiding aggressive dilatation.[14] If there is no significant ISR, and the stent expansion is achieved using noncompliant balloons, excimer laser, or intravascular lithotripsy, there is no need to deploy another stent.[23] Conversely, stent implantation should be considered when rotational atherectomy or orbital atherectomy are used that dismantle the implanted stent.[22]

Uncovered Struts

Newer-generation DES, designed with thinner struts and better healing profiles, have enabled faster stent endothelization[56,57]; despite these advances, however, persistent uncovered stent struts are often seen today in clinical practice and constitute a common cause of ST.[51–53] Protruding uncovered stent struts affect the local hemodynamic microenvironment, creating recirculation zones proximally and distally to the strut that are likely to promote thrombus formation.[58] Stent characteristics, and in particular strut thickness and shape as well as strut connector alignment and interstrut distance, determine local hemodynamic forces and to a certain extent the risk of ST.[55] OCT is the preferred modality for assessing strut endothelization, despite the fact that it often overestimates strut coverage because it is unable to differentiate fibrin from endothelium.[59] In the study of Won et al, a cutoff of uncovered stent struts of 5.9% was associated with a higher incidence of death, myocardial infarction, and ST.[60]

There is lack of evidence on how to treat patients admitted with ST attributed to uncovered stent struts; it appears plausible in this setting to avoid implantation of another stent and use OCT to aggressively dilate the deployed stent, aiming to increase the struts' embedment and facilitate their endothelization.

Malapposition

Stent strut malapposition can be classified as early malapposition and is caused by suboptimal procedural results or late strut malapposition that can be further differentiated to late persistent, when inadequately apposed stent struts following PCI remain malapposed at follow-up, or late acquired malapposition when this occurs at follow-up despite optimal stent deployment. Several intravascular imaging studies have reported a high incidence of stent strut malapposition in patients admitted with ST,[51–53] whereas recently, the Yonsei OCT registry showed that significant malapposition (malapposition volume ≥7 mm^3) is an independent

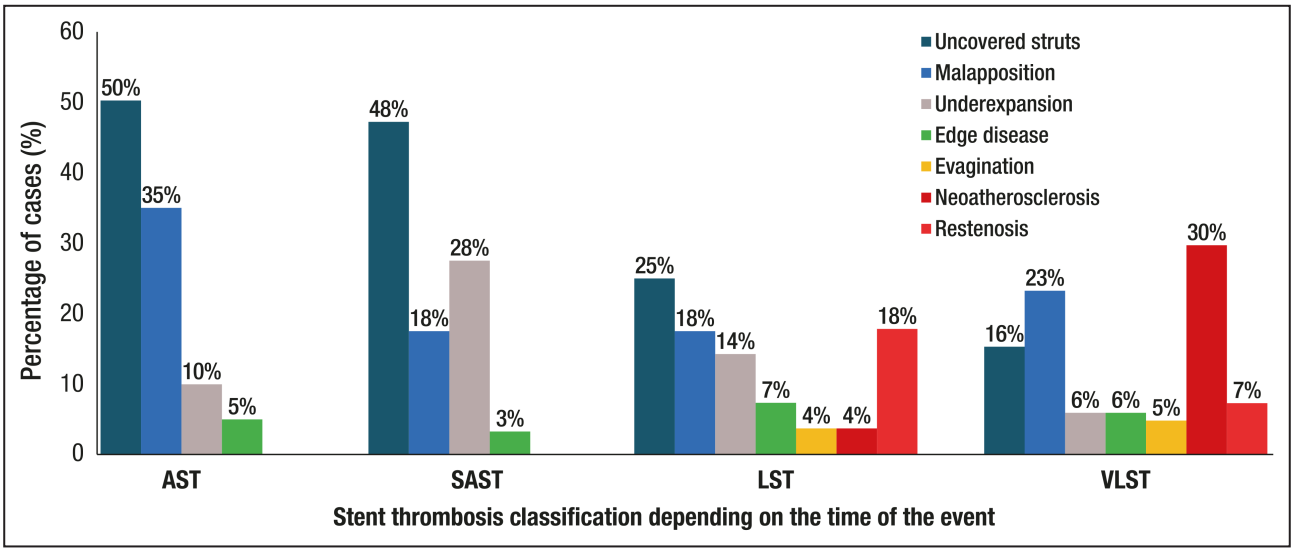

Figure 3. Incidence of the most common causes of stent thrombosis according to the time of the event; a combined analysis of the PESTO (Morphological Parameters Explaining Stent Thrombosis Assessed by OCT), PRESTIGE (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort), and Bern registry studies.
AST indicates acute stent thrombosis; LST, late stent thrombosis; SAST, subacute stent thrombosis; and VLST, very late stent thrombosis.

predictor of ST (hazard ratio, 5.79; 95% CI, 1.50–22.39; *P*=0.004).[61]

Strut malapposition affects the local hemodynamic forces; malapposed struts increase WSS and shear rate, creating an unfavorable hemodynamic environment that can promote thrombus formation leading potentially to stent occlusion. The effect of stent strut malapposition on local hemodynamic forces and the formed thrombus in ex vivo studies is related to the malapposed distance, with higher WSS and shear rate values reported in larger malappositions.[62,63]

Late acquired stent malapposition has been associated with an inflammatory response of the vessel wall to the deployed stent that can activate a clotting cascade leading to thrombus formation.[48] Intravascular imaging usually shows a well-expanded stent with evidence of positive remodeling and strut malapposition in the middle of the stent; nevertheless, it has to be acknowledged that differentiation of late acquired from late persistent malapposition may be challenging, especially when IVUS or OCT have not been performed following PCI.

Irrespective of the underlying mechanism that strut malapposition leads to ST, another stent implantation should be avoided, and treatment should focus on aggressive stent dilatation to diminish malapposition and its unfavorable implications the on local hemodynamic forces.[14]

Edge Dissection and Increased Plaque at the Stent Edge

There are convincing data to suggest that increased plaque burden at the edge of the stent or the presence of edge dissection are associated with a higher risk of ST.[51–53] Intravascular imaging (IVUS and OCT) is capable in detecting these and guiding implantation of another stent.

Evaginations

Coronary evagination is defined as an outward bulge of the vessel wall between well-apposed stent struts with maximum depth higher than the strut thickness and has been attributed to an inflammatory response of the vessel wall to the implanted stent. The presence of coronary evaginations seems to be associated with thrombus formation,[64] and have been recognized as a common cause of ST.[51–53] Possible mechanisms that lead to thrombosis include the presence of vascular inflammation, the presence of uncovered struts, as well as the unfavorable hemodynamic milieu noted in these segments, with areas of recirculation and flow stagnation that can facilitate microparticle accumulation and trigger a clotting cascade.[45,65] OCT is regarded today as the ideal modality for detecting the presence of evaginations. There is a lack of evidence on how to treat ST in this setting; it would appear reasonable to avoid implanting the same type of stent that was deployed in the index procedure and consider prolonged antithrombotic therapy to minimize the risk of ST. Aggressive postdilatation of the deployed stent is expected to reduce the incidence of malapposed struts and the size of the evaginations, and thus minimize the flow disturbances noted in these segments that are instigators of thrombus formation.[65] However, this strategy is also likely to increase vessel wall trauma

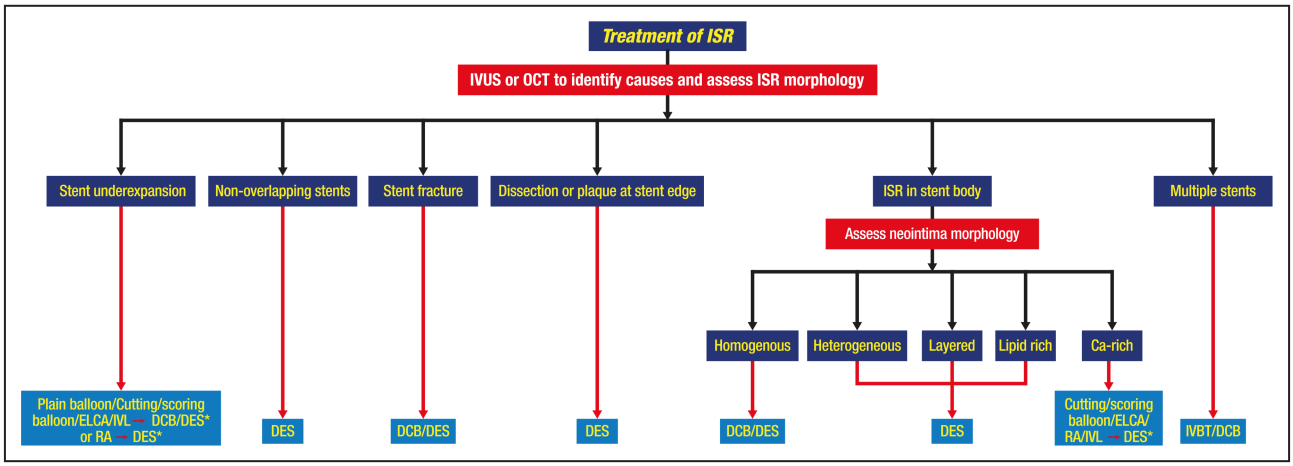

Figure 4. In-stent restenosis (ISR) treatment strategies according to the underlying mechanism and neointima characteristics assessed by intravascular imaging.
*Indicates use of DES only if there is optimal lesion preparation and expected optimal stent expansion. Ca indicates calcific; DCB, drug-coated balloon; DES, drug-eluting stent; ELCA, excimer laser coronary atherectomy; IVBT, intravascular brachytherapy; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; OCT optical coherence tomography; and RA, rotational atherectomy.

and vascular inflammation caused by the stent components, and therefore it should be reserved only in case of stent underexpansion.

Neoatherosclerosis and Neointima Proliferation

Neoatherosclerotic plaque rupture is one of the most common causes of late and very late stent thrombosis.[51–53] OCT is superior to IVUS for identifying neoatherosclerotic plaques and the presence of thrombus.[66] Similar to native plaque rupture, treatment of a ruptured neoatherosclerotic lesion should include its sealing with another stent.

ST can also occur in the presence of neointima hyperplasia without evidence of rupture.[51–53] Neointima erosion or excessive neointima proliferation leading to lumen stenosis and flow obstruction can be the underlying mechanism in this setting. In the absence of clinical evidence, treatment should be individualized. In case of mild neointima proliferation, no flow obstruction, and suspected erosion, conservative management can be considered as it was proposed in the Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based managementin plaque erosion study[67]; conversely, in cases with increased neointima burden leading to lumen obstruction, lesion dilatation and implantation of another stent appears to be the ideal treatment.

CONCLUSIONS AND FUTURE PERSPECTIVES

Summarizing the evidence of published studies, it is apparent that intravascular imaging enables identification of the underlying mechanisms of ISR and ST, information that can be useful in treatment planning.

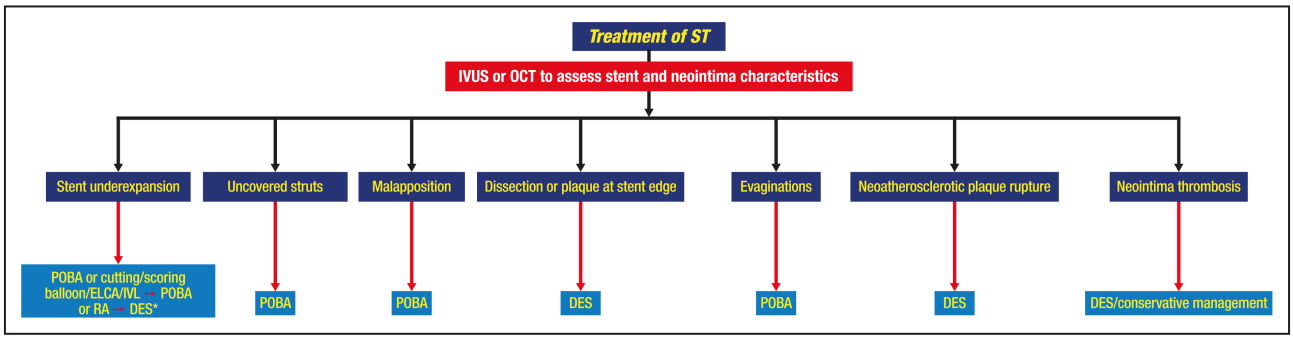

Figure 5. Stent thrombosis (ST) treatment strategies according to the underlying mechanism and neointima characteristics assessed by intravascular imaging.
*Indicates use of DES only if there is optimal lesion preparation and is expected optimal stent expansion. DES indicates drug-eluting stent; ELCA, excimer laser coronary atherectomy; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; OCT optical coherence tomography; POBA, plain old balloon angioplasty; and RA, rotational atherectomy.

Modality	Neointima morphology	Neo atherosclerosis	Stent underexpansion	Malapposed struts	Non-overlapping stents	Stent fracture	Multiple stent layers	Presence of evaginations	Late expansive remodelling	Plaque at stent edge	Lipid core at stent edge	Edge dissection
IVUS	✗	✓	✓✓✓	✓✓	✓✓✓	✓✓	✓✓	✓✓	✓✓✓	✓✓✓	✗	✓✓
OCT	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓	✓✓	✓✓	✓✓✓

Figure 6. Advantages and limitations of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) in assessing neointima features and detecting causes of stent failure.
✓✓✓ indicates excellent ability of the modality to detect the specific feature; ✓✓, moderate ability of the modality to detect the specific feature; ✓, weak ability of the modality to detect the specific feature; and ✗, the modality is unable to detect the specific feature.

Although there are no robust outcome data, reports indicate that neointima morphology and vessel wall pathology determine vessel response following treatment with different endovascular devices and support the image-guided personalized therapy of ISR and ST outlined in Figure 4 and Figure 5.

In this context, treatment strategies that failed to be proven superior over conventional therapies in randomized controlled trials should not be abandoned but considered in specific clinical scenarios. For example, the RESCUT (Restenosis Cutting Balloon Evaluation Trial) study failed to demonstrate the superiority of cutting balloons compared with POBA in the treatment of ISR (Table S1). Despite this, cutting balloons can be used in case of dense fibrotic ISR or in calcific neoatherosclerosis to optimize lesion preparation. Similarly, the TAXUS V ISR (Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis) and the SISR (Sirolimus-Eluting Stent Versus Intravascular Brachytherapy in In-Stent Restenotic Coronary Artery Lesions) studies showed that IVBT is inferior to DES for treating ISR (Table S1); nevertheless, IVBT seems to have a role in cases of recurrent ISR and especially when there are multiple layers of stents.[46] Several randomized controlled trials and metanalyses have also shown that second-generation DES are superior to DCB in the treatment of ISR (Table S1); however, reports indicate that DCB can be equally effective to DES in fractured stents and in lesions with a homogeneous neointima, whereas the recently published European guidelines on myocardial revascularization have given to DCB a class I recommendation and level of evidence A for the treatment of ISR.[9,68–70]

OCT appears superior to IVUS for guiding therapy in ISR and ST because it allows accurate assessment of lumen pathology and enables more detailed visualization of stent architecture and strut apposition and reliable characterization of neointima morphology (Figure 6).[14] However, it has to be acknowledged that there are no outcome data to support the value of OCT in this setting, whereas for IVUS, there are only registry data showing that its use is associated with better prognosis in patients suffering from ISR.[16]

Two randomized studies, ILUMIEN IV OPTIMAL PCI (Optical Coherence Tomography Guided Coronary Stent Implantation Compared to Angiography: A Multicenter Randomized Trial in PCI),[71] and IMPROVE (Impact on Revascularization Outcomes of IVUS Guided Treatment of Complex Lesions and Economic Impact),[72] which are currently ongoing, are expected to provide additional insights about the value of OCT and IVUS imaging in guiding therapy and improving outcomes in ISR. However, both studies will include a small number of patients with ISR and mandate DES implantation; therefore, they will not test the value of OCT or IVUS in selecting treatment strategy (ie, DCB versus DES) and guiding DCB therapy. Future analyses of IVUS or OCT registry data are anticipated to provide additional insights and define criteria for deferring DES implantation and for optimal PCI results with DCB. This is of utmost importance because often multiple causes of stent failure coexist, posing a challenge in deciding the ideal intervention and defining procedural success. These data are expected to enrich our understanding and provide the substrate for the conduction of adequately powered randomized controlled studies that will examine the value of intravascular imaging in guiding revascularization in stent failure and dictate its regular use in this setting.

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Sources of Funding

R.B., A.M., C.V.B., and A.B. are funded by research funds from the Biomedical Research Centre, Queen Mary University of London, London, United Kingdom.

Disclosures

None.

Supplemental Material

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Supplemental Material

Table S1. Landmark prospective randomised control studies evaluating the efficacy of different strategies in the treatment of ISR*

Study	Objectives	Studied patients	Follow-up period	Study endpoints	Results
ARTIST[73]	To compare the safety and efficacy of combined RA and POBA against POBA for the treatment of BMS-ISR	298	6 months	• Net lumen gain • Binary restenosis • MACE defined as death, tamponade, MI and TVR	• The net gain was higher in the POBA group than the RA plus POBA group (0.67±0.54mm vs 0.45±0.57, P=0.0019) • Binary restenosis was lower in the POBA group (51.2% vs 64.8%) • MACE rate was also lower in the POBA group than the RA plus POBA (8.9% vs 20.4%, P=0.005)
RIBS[74]	To compare the efficacy of POBA and of BMS implantation for treating BMS-ISR	450	12 months	• Restenosis rate at 6 months follow-up • MLD at 6 moths follow-up • MACE defined as death, MI and TVR	• Restenosis rate was similar in the two groups (38% vs 39%, P=0.92) • There was no difference in the MLD between groups (1.63±0.80mm vs 1.52±0.70mm, P=0.17) • MACE rate was similar in the two groups (23% vs 29%, P=0.19) at 1 year follow-up
RESCUT[75]	To compare the efficacy of CBA	428	7 months	• Binary restenosis	• Binary restenosis was similar in the CBA and in the POBA group (29.8% vs 31.4%, P=0.82)

	and of POBA in treating BMS-ISR			• MACE defined as death, MI, TLR	• There was no difference in the MACE rate between groups (16.4% vs 15.4%)
ISAR DESIRE[76]	To compare the effectiveness of treatment with POBA, SES and PES in patients with BMS-ISR	300 patients randomised in 3 groups	1 year	• Binary restenosis at 6 months follow-up • Net lumen gain • TVR • The combined endpoint of death – MI	• Binary restenosis was lower in the SES and PES than the POBA group (14.3% vs 21.7% vs 44.4%). • Net gain was also higher in the two DES groups than the POBA group (SES: 1.12mm, PES: 1.02mm, POBA: 0.41mm) • TVR was lower in the SES and PES groups compared to the POBA group (8% vs 19% vs 33%) • There was no difference between groups in the incidence of death – MI
TAXUS V ISR[77]	To examine the efficacy of PES and of IVBT for treating BMS-ISR	396	9 months	• Ischemia driven TVR • MACE defined as death, MI and TVR	• TVR was significantly lower in the PES group than the IVBT group (10.5 vs 17.5%, P=0.046) • A lower incidence of MACE rate was noted in the PES group compared to the IVBT group (11.5% vs 20.1%, P=0.020)
SISR[78]	To evaluate the efficacy of SES and of IVBT in the treatment of BMS-ISR	384	9 months	• MACE defined as cardiac death, MI, TVR • In-stent and in-lesion MLD, %DS, LLL and	• MACE rate was lower in the SES than the IVBT group (12.4% vs 21.6%, P=0.02) • MLD was larger and %DS was lower in the SES but there was no difference between groups in the LLL or binary restenosis rate at 6 months

				binary restenosis rate at 6 months	
RIBS II[79]	To compare the efficacy of POBA and of SES implantation for treating BMS-ISR	150	12 months	• Binary restenosis at 9 months • MLD and LLL at 9 months • IVUS-derived lumen and neointima volume at 9 months • MACE defined as death, MI and TVR	• Binary restenosis rate was lower in the SES than the POBA group (11% vs 39%, P<0.001) • MLD was higher and LLL was lower in the SES group • Lumen volume was higher and neointima proliferation was reduced in the SES group • MACE rate was lower in patients treated with SES than those undergoing POBA (11.8% vs 31%, P=0.004)
ISAR DESIRE II[80]	To compare SES and PES implantation for treating SES-ISR	450	12 months	• LLL at 6-8 months • Binary restenosis at 6-8 months • TLR • Death, MI and ST	• LLL was similar in the SES and PES groups (0.40±0.6mm vs 0.38±0.59mm, P=0.85) • There was no difference between groups in the incidence of binary restenosis • TLR and the incidence of death, M and ST were similar in the two groups
PEPCAD [81]	To compare the efficacy of PES	131	12 months	• LLL at 6 months follow-up • Binary restenosis	• LLL was higher in the PES than the DCB group (0.38±0.61mm vs 0.17±0.42mm, P=0.03)

	and of DCB for the treatment of BMS-ISR			• MACE defined as death, MI, TLR and ST at 12 months	• Restenosis rate was numerically higher in the PES group but this did not reach a statistical significance (20% vs 7%, P=0.06) • MACE rate was numerically but not statistically higher in the PES than the DCB group (21.5% vs 9.1%, P=0.08)
ISAR DESIRE III[82]	To investigate the efficacy of DCB, PES and POBA in treating limus-eluting stent-ISR	402	12 months	• %DS at 6-8 months • MLD at 6-8 months • In segment restenosis • TLR • The combined endpoint of death, MI and the incidence of ST	• %DS was similar in DCB and PES and higher in the POBA group (38.0±21.5% vs 37.4±21.8% vs 54.1±25%) • MLD was similar in the DCB and PES and lower in the POBA group (1.79±0.74mm vs 1.82±0.74mm vs 1.26±0.75mm) • The TLR rate was higher in the POBA group and similar in the DCB and PES groups (43.5% vs 22.1% vs 13.5%) • There was no difference between groups in the incidence of death, MI or the incidence of ST
RIBS V[83]	To evaluate the efficacy of DCB and of EES for treating BMS-ISR	189	12 months	• MLD at 9 months • MACE defined as cardiac death, MI and TLR	• MLD was higher in the ESS than the DCB group (2.36±0.6mm vs 2.01±0.6mm, P<0.001) • There was no difference in the MACE rate between the two groups (6% vs 8%, P=0.60)
RIBS IV[70]	To compare the efficacy of DCB	309	12 months	• In segment MLD at 6-9 months follow-up	• In segment MLA was larger in the DES compared to the DCB group (2.03± 0.7mm vs 1.80±0.6mm; P <0.01)

	and of EES for treating DES-ISR				
ISAR-DESIRE IV[84]	To examine the value of scoring balloon before DCB angioplasty in patients with DES-ISR	252 randomised to DCB therapy with or without scoring balloon pre-dilation	12 months	• MACE rate defined as cardiac death, MI, TVR • In segment %DS at 6-8 months follow-up • Binary restenosis at 6-8 months follow-up • LLL at 6-8 months • The combined incidence of death, MI • TLR and ST rates	• MACE rate was statistically lower in the DES compared to the DCB group (10% vs 18%, P=0.04) • In segment %DS was lower in the scoring balloon group (35.0±16.8% vs 40.4±21.4%, P=0.047) • Binary restenosis rate was lower in the scoring balloon group (18.5% vs 32.0%, P=0.026) but there was no difference between groups in the LLL (P=0.27) • There was no difference between groups in the incidence of the combined endpoint of death, MI • TLR and ST rates were also similar in the two groups
DARE[85]	To compare the effectiveness of DCB and EES for treating BMS- and DES-ISR	278	12 months	• MLD at 6 months • Binary restenosis at 6 months • %DS • Cardiac death, MI, TVR and ST	• MLD was similar in the two groups (1.71±0.51mm vs 1.74±0.61mm) • Binary restenosis rate and the %DS values were similar in the two groups • The incidences of cardiac death, of MI and of TVR were similar in the two groups; no ST occurred in the studied patients

BIOLUX [86]	To evaluate the efficacy of BTHC-DCB and of BP-SES in treating BMS and DES-ISR	229	18 months	• LLL at 6 months • MLD at 6 months • %DS at 6 months • MACE rate defined as cardiac death target vessel MI and TLR • ST rate	• LLL was similar in the two groups (P=0.40) • MLD and %DS were also similar in the two groups • There was no difference between groups in the MACE rate at follow-up (17.9% vs 18.6%) • The incidence of ST was similar in the two groups

BMS, bare metal stent; BP, biodegradable polymer; BTHC, butyryl-tri-hexyl citrate; CBA, cutting balloon angioplasty; DCB, drug coated balloon; DES, drug eluting stent; DS, diameter stenosis; EES, everolimus eluting stent; ISR, in-stent restenosis; IVBT, intravascular brachytherapy; IVUS, intravascular ultrasound; LLL, late lumen loss; MACE, major adverse cardiovascular events; MI, myocardial infarction; MLD, minimum lumen diameter; PES, paclitaxel eluting stent; POBA, plain old balloon angioplasty; RA, rotational atherectomy; SES, sirolimus eluting stent; ST, stent thrombosis; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

* In case of multiple studies investigating the efficacy of the similar treatment strategies only the largest study is reported.

Table S2. Intravascular-imaging-based studies examining the efficacy of treatment strategies.

Study	Objectives	Follow-up period	Number of patients	Results
Lee et al[23]	To compare outcomes in patients with ISR due to underexpansion caused by peri-stent calcium after treatment with and without excimer laser	N/A	81 patients (23 treated with and 58 without excimer laser)	• Excimer laser was associated with a higher incidence of per-stent calcium fracture (61% vs 12%, P<0.01) that resulted in a larger minimum lumen area (4.76mm^2 vs 3.46mm^2, P=0.004) than treatment without excimer laser
Yin et al[20]	To identify predictors and examine the prognostic implications of newly implanted stent underexpansion for treating ISR	2 years	143 patients (143 lesions; newly stent underexpansion was noted in 33 lesions and optimal stent expansion in 110)	• Old stent underexpansion, double layers of stent, calcific arc >180^o and maximum calcific thickness >0.5mm were independent predictors of newly stent underexpansion (defined as minimum lumen area 4.5mm^2 and stent expansion <70%) • New stent underexpansion was associated with a higher MACE rate at 2 years follow-up (35.5% vs 14.3%, P=0.009)
Sakamoto et al[31]	To compare outcomes in patients with ISR attributed to stent fracture treated with DCB or DES	12 months	47 patients (69 lesions, 24 treated with DCB and 45 with DES)	• The ISR (37.5% vs 44.4%, P=0.58) and TLR (31.9% vs 43.9%, P=0.31) rates were similar in patients treated with DCB and in those implanted with DES at 12 months follow-up

Tada et al[39]	To examine the effect on neointima morphology on ISR and TLR rates following treatment with POBA or POBA plus DCB	6-8 months	195 patients (234 lesions, 146 treated with POBA and DCB and 68 treated with POBA)	• The ISR (23.3% vs. 45.6%, P =0.001) and TLR rates (17.8% vs. 36.8%, P=0.003) were lower in the DCB group • The ISR and TLR rates were lower in restenotic lesions with homogeneous (ISR: 20.0% vs 55.6%, P=0.002; TLR: 12.7% vs 37.0%, P=0.019) or lipid-rich (ISR: 22.1% vs 58.6%, P=0.001; TLR: 13.2% vs 41.5%, P=0.006) neointima in the DCB group • No difference was noted between groups in lesions with a heterogeneous (ISR: 35.0% vs 37.5%, P=0.100; TLR: 25.0% vs 37.5%, P=0.651) or layered morphology (ISR: 22.5% vs 39.4%, P=0.100; TLR: 19.7% vs 36.4%, P=0.089)
Tada et al[40]	To assess the impact of neointima morphology on clinical outcomes following treatment of ISR with POBA, DCB and DES	7 months	379 patients, 428 lesions (78 treated with POBA, 202 lesions with DCB and 148 with DES)	• The TLR rate was higher in the POBA than the DCB (33.3% vs 16.8%, P=0.004) or the DES group (12.8%, P<0.001) • The ISR rates in lesions with homogeneous (54.8% vs 19.1% vs 19.6%) and layered (43.2% vs 22.0% vs 15.8%) structure were higher in the POBA group than the DCB and DES groups • Conversely the ISR rate was numerically higher in lesions with a heterogeneous neointima treated with DCB than those treated with POBA or DES (38.5% vs 20.0% vs 18.8%)

Miura et al[41]	To identify predictors of recurrent ISR after treatment with paclitaxel eluting DCB	Coronary angiography at 6-month follow-up	222 patients	• Post-procedural stent underexpansion (OR: 2.20, 95%CI: 1.04-4.60; P=0.040), previous stent fracture (OR: 2.46, 95%CI: 1.03-5.72; P=0.040) and heterogeneous neointima pattern (OR: 3.21, 95%CI: 1.39-7.30; P=0.006) were independent predictors of recurrent restenosis at 6 months
Lee et al[87]	To examine the implications of neointima morphology on long-term clinical outcomes following treatment of ISR with DCB	53 months	122 patients	• Patients with heterogeneous neointima had a higher MACE rate that those with homogeneous or layered neointima (43.7% vs 19.6% vs 10.8%) • MACE rate was numerically but not statistically higher in patients with neoatherosclerotic lesions that those (33.4% vs 18.4%, P=0.168)
Xhepa et al[43]	To evaluate the prognostic implications of neointima inhomogeneity following treatment with DCB and DES	24 months	197 patients	• Patients with low inhomogeneity ISR had similar MACE (27.5% vs 26.6%, P=0.917) and TRL (22.5% vs 25.0%, P=0.797) rates after treatment with DES and DCB • Conversely, MACE (40.8% vs 12.5%, P=0.004) and TRL (38.7% vs 12.5%, P=0.006) rates were higher in the DCB group in ISR lesions with increased inhomogeneity
Yabushita et al[47]	To examine the prognostic implications of the number of layers of stents in patients with recurrent ISR treated with DCB	12 months	304 patients (333 lesions (166 patients with 1 layer of stent, 87 with 2	• MACE (43.1% vs 16.1% vs 16.9%, P<0.01) and TLR (41.2% vs 14.9% vs 14.5%, P<0.01) rates were statistically higher in patients with ≥3 layers of stents than those with 1 or 2 layers

			and 51 with ≥3 layers of stent)	• In multivariate analysis the number of metallic layers was independent predictor of MACE (HR of ≥3 layers compared to 1 layer: 3.17, 95%CI: 1.75-5.76, P<0.01)
Varghese et al[46]	To compare outcomes in patients with recurrent ISR treated with and without IVBT	12 months	328 patients (197 treated with and 131 without IVBT)	• IVBT was associated with a lower incidence of MACE (13.2% vs 28.2%, P=0.01) and numerically lower TLR rate (10.7% vs 22.1%; P=0.07) at 1 year follow-up • Results were unchanged after propensity matching (MACE rate in IVBT group 13.2% vs 30.8% in the non-IVBT-group, P<0.01)

CI, confidence interval; DCB, drug coated balloon; DES, drug eluting stent; HR, hazard ratio; ISR, in-stent restenosis; IVBT, intravascular brachytherapy; MACE, major adverse cardiovascular events; OR, odds ratio; POBA, plain old balloon angioplasty; TLR, target lesion revascularization.

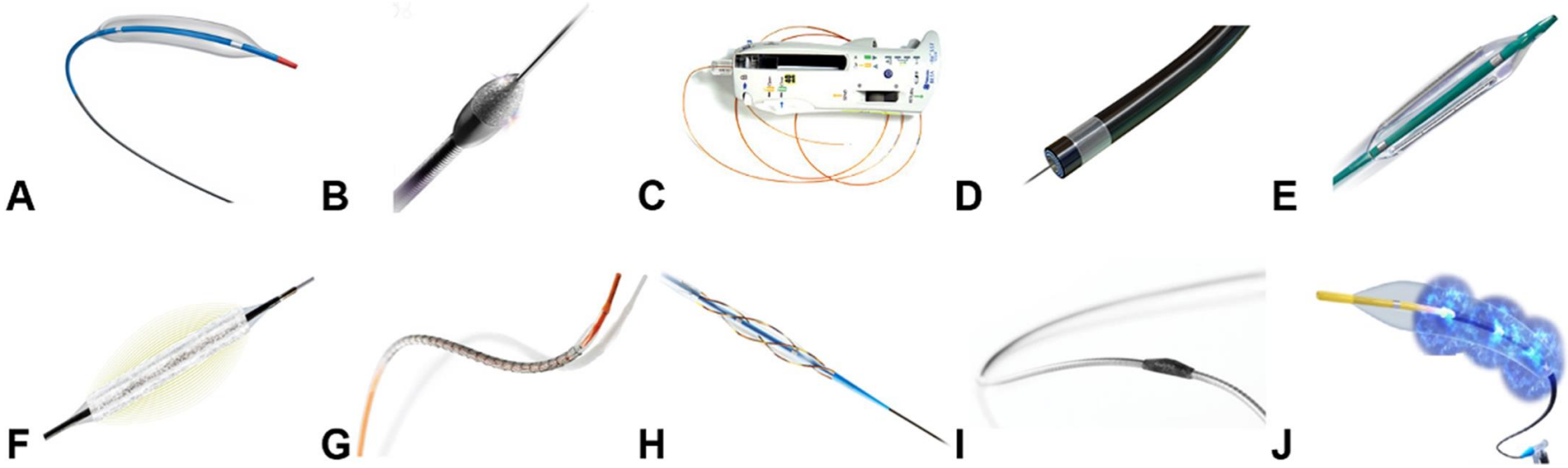

Figure S1. Existing treatment options for ISR. (A) plain old balloon angioplasty, (B) rotational atherectomy, (C) intravascular brachytherapy, (D) excimer laser, (E) cutting balloon, (F) drug coated balloon, (G) 2nd generation drug eluting stent, (H) scoring balloon, (I) orbital atherectomy and (J) intravascular lithotripsy. Bioresorbable scaffolds and 1st generation drug eluting stents are no longer available for the treatment of ISR.

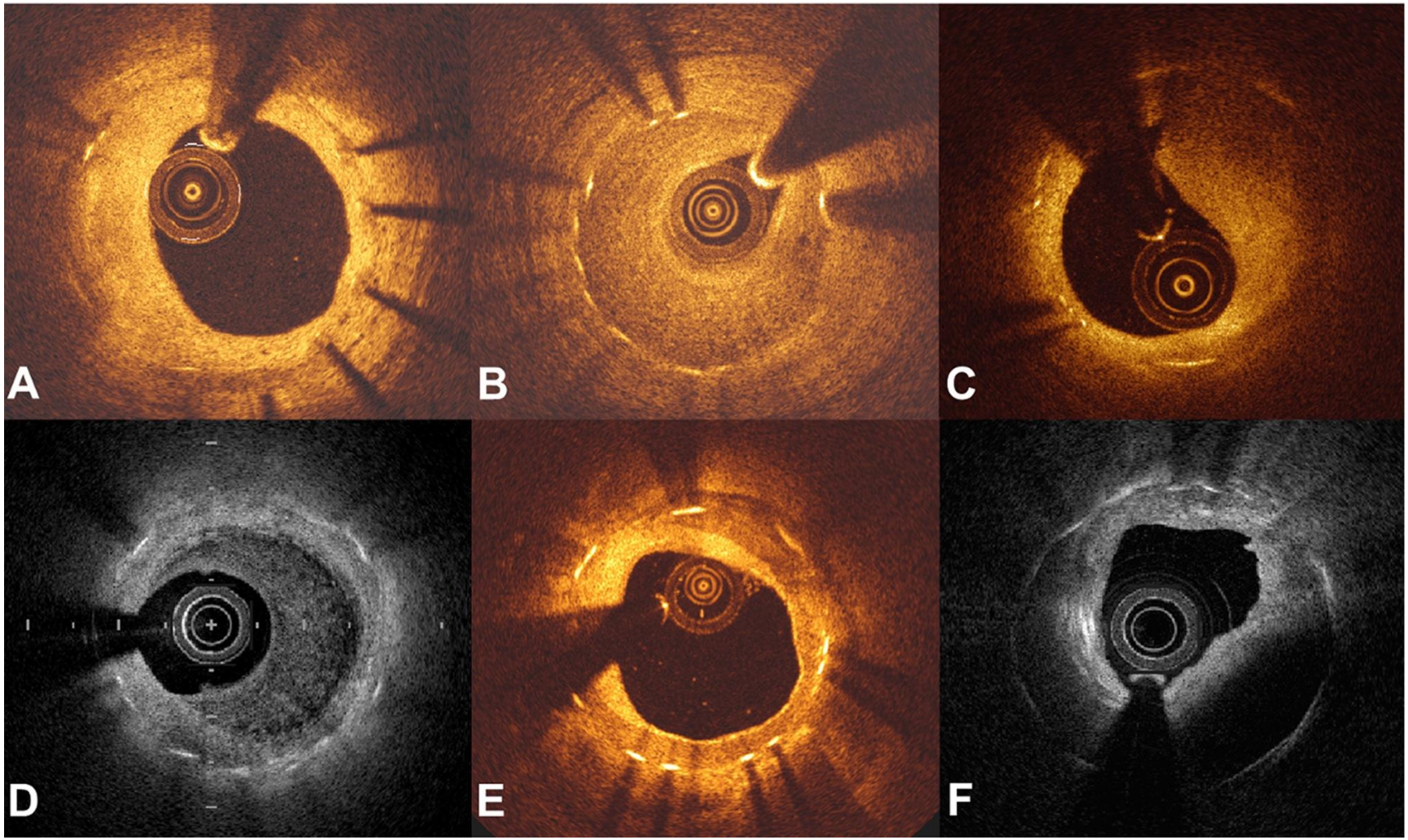

Figure S2. Neointima patterns. A) homogeneous neointima, B) heterogeneous neointima, C) layered neointima D) neointima with a heterogeneous and a layered pattern, E) calcific-rich neoatherosclerotic plaque and F) lipid-rich neoatherosclerotic plaque.