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Intracoronary Imaging Assessment of Stent Thrombosis

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Abstract

Purpose of Review This review focuses on the benefits, limitations, and evidence regarding the use of various intravascular imaging modalities in evaluating the etiology of stent thrombosis (ST).

Recent Findings Intravascular ultrasound and optical coherence tomography can be used clinically to evaluate the etiology of ST including malapposition, underexpansion, stent fracture, and neoatherosclerosis. Near-infrared fluorescence has also been shown to have niche benefits in ST due to abnormal stent endothelization. Additionally, intravascular imaging also helps guide intervention depending on the etiology of stent thrombosis.

Summary Intravascular imaging has been shown to provide valuable information regarding the etiology of ST and helps in guiding intervention for these lesions.

Keywords Stent thrombosis · Intravascular imaging · Intravascular ultrasound · Optical coherence tomography · Near-infrared fluorescence · Percutaneous coronary intervention

Introduction

Stent thrombosis (ST) is a potentially life-threatening complication of percutaneous coronary intervention (PCI) with an overall reported prevalence of 0.5–3.3% in the drug-eluting stent era [1] [2]. Most patients with ST present with acute myocardial infarction and have a mortality rate reported between 20 and 45% [3] [4]. Timely diagnosis and optimal intervention of these patients are essential. ST has been defined and classified by the Academic Research Consortium based on documentation and timing [5••] (Figure 1). Based on clinical and angiographic documentation, ST is classified as definite (symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis (ST)), probable (unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of ST) and possible (any unexplained death after 30 days) [5••]. Additionally, based on timing of occurrence with respect to the index PCI, ST has been classified as acute (0 to 24 h), subacute (24 h to 30 days), late (30 days to 1 year) and very late (>1 year) [5••]. Etiology of ST can be multifactorial due to procedure or lesion related parameters (bifurcation lesion, use of multiple stents, small vessel diameter, coronary dissection, stent underexpansion, and stent malapposition), patient features (age, diabetes, chronic kidney disease, systolic dysfunction, and high platelet reactivity) and antiplatelet therapy (inadequate intensity or duration of therapy, patient noncompliance). Various imaging modalities including intravascular ultrasound (IVUS), optical coherence tomography (OCT), near-infrared fluorescence (NIRF), and cardiac computed tomography (CT) can provide better assessment of the etiology of ST and help with management.

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Intravascular ultrasound

IVUS provides detailed transmural coronary imaging, which helps in better understanding lesions and stent characteristics [6•]. IVUS-guided PCI has been shown to have significantly lower rates of all-cause mortality, myocardial infarction, target vessel revascularization, and ST [7] [8]. These beneficial effects of IVUS imaging have been attributed to the ability to identify and treat

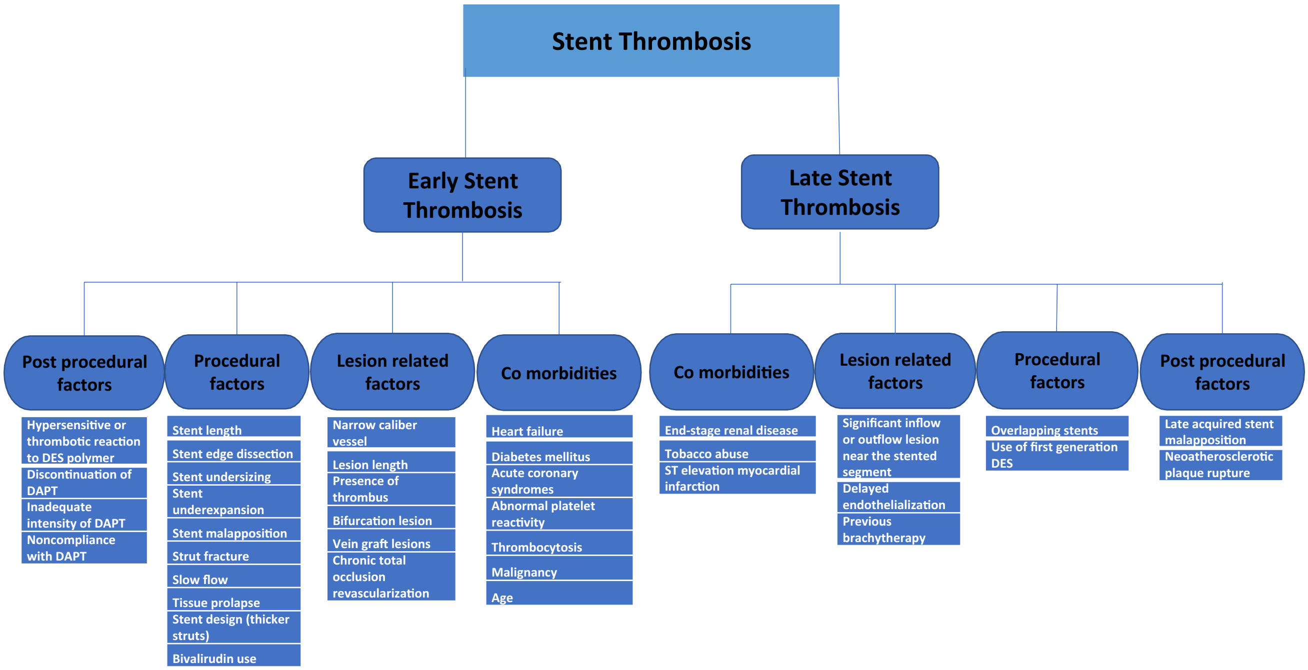

Fig. 1 Risk factors for stent thrombosis

stent underexpansion and incomplete stent apposition as well as periprocedural complications such as side branch occlusion, stent edge dissections, and hematoma.

IVUS has been used to assess pathophysiological mechanisms initiating ST, which are not well appreciated in conventional angiography [9] [10]. In a randomized study by Choi et al in ACS patients, predictors for early ST were identified using IVUS. They found that minimum lumen area <5 mm^2, significant residual stenosis, significant stent edge dissection, and significant tissue (plaque/thrombus) protrusion (more than the median that narrowed the lumen to <4 mm^2) were more prevalent in patients with early ST [9]. Interestingly, significant acute malapposition (more than the median) was not found in patients with early ST. Minimal luminal area was also noted to be a significant risk factor for ST in the follow-up study from the Syntax II trial population [11].

Vallejo et al reported that in patients with early ST, underexpansion and lesion at the stent border were the most common IVUS findings, whereas patients with late and very late thrombosis were most likely to show in-stent proliferation with severe stenosis and, in one case, malapposition due to positive vessel remodeling [10]. IVUS also helped in therapeutic management – ST examined by IVUS were treated less often with implantation of a second stent with no significant differences in angiographic outcome, mortality, or rethrombosis [10]. Neoatherosclerosis and malapposition demonstrated on IVUS have been shown to be associated with the development of very-late ST in two small patient population studies [12] [13]. Malapposition has been found to be common in patients with DES with very late ST (VLST), while neoatherosclerosis was exclusively observed in patients with BMS with VLST [14•]. Determining the etiology of ST by intravascular imaging helps make decisions regarding strategy for treatment. When IVUS reveals underexpansion and/or malapposition as the etiology for ST, balloon angioplasty has better outcomes and is favored over additional stent implantation [15]. Various etiologies of ST have been illustrated with IVUS imaging (Figs. 2, 3, 4).

Optical coherence tomography

OCT that utilizes near infra-red range light has a much higher spatial resolution compared to IVUS and has been widely used for intracoronary assessment [16] [17]. OCT provides better tissue differentiation, which helps in distinguishing the various mechanism of ST and optimizing intervention [16] [18]. Different types of ST and their etiology have been extensively evaluated using OCT in the PRESTIGE multi-center registry [19]. A majority of the patients in the registry presented with late and VLST (71.4%). The most common findings in these patients included underexpansion, uncovered stent struts, malapposition, and neoatherosclerosis. Stent underexpansion and uncovered struts were frequently seen in early ST. Malapposition was a frequent finding

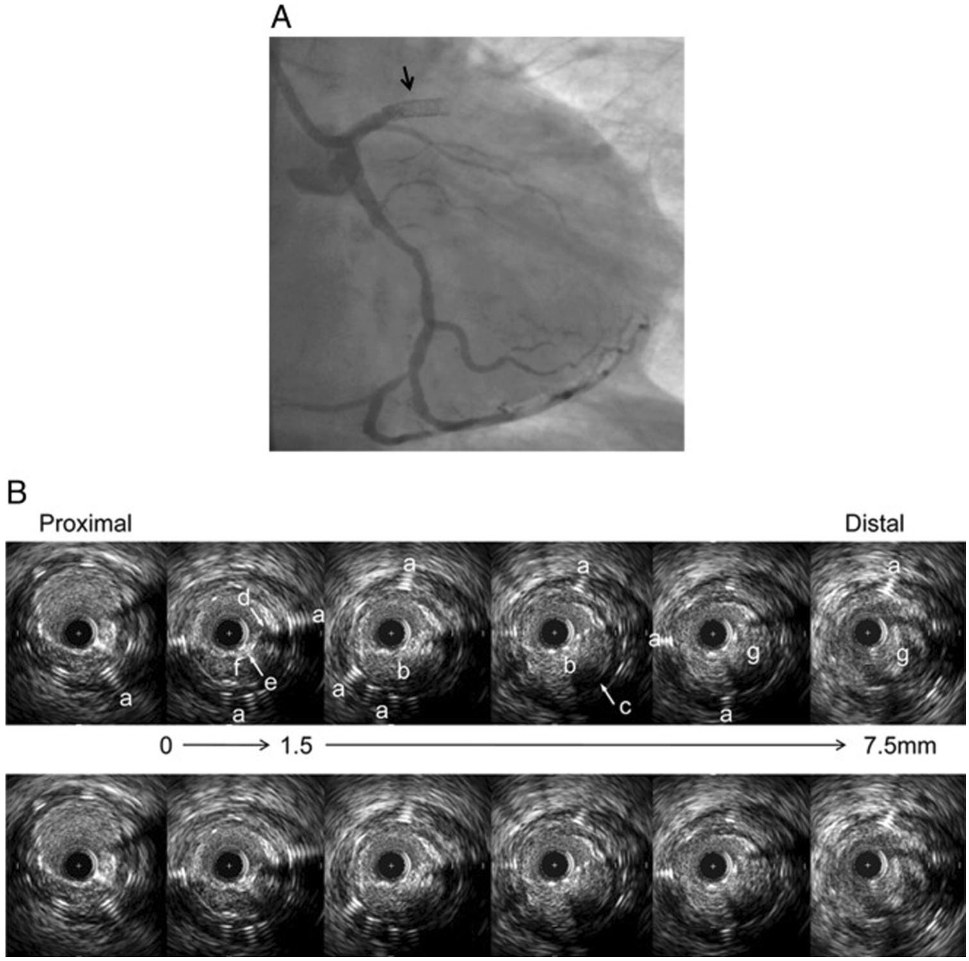

Fig. 2 Intravascular ultrasound (IVUS) images from the patient demonstrating very eccentric intra-stent plaque, fibrous cap rupture, evacuated intrastent plaque cavityand thrombus formation. Published with permission. Courtesy: Cheol Whan Lee, Su-Jin Kang, Duk-Woo Park, Seung-Hwan Lee, Young-Hak Kim, Jae-Joong Kim, Seong-Wook Park, Gary S. Mintz, Seung-Jung Park, Intravascular Ultrasound Findings in Patients With Very Late Stent Thrombosis After Either Drug-Eluting or Bare-Metal Stent Implantation, Journal of the American College of Cardiology, Volume 55, Issue 18, 2010, pages 1936-1942.

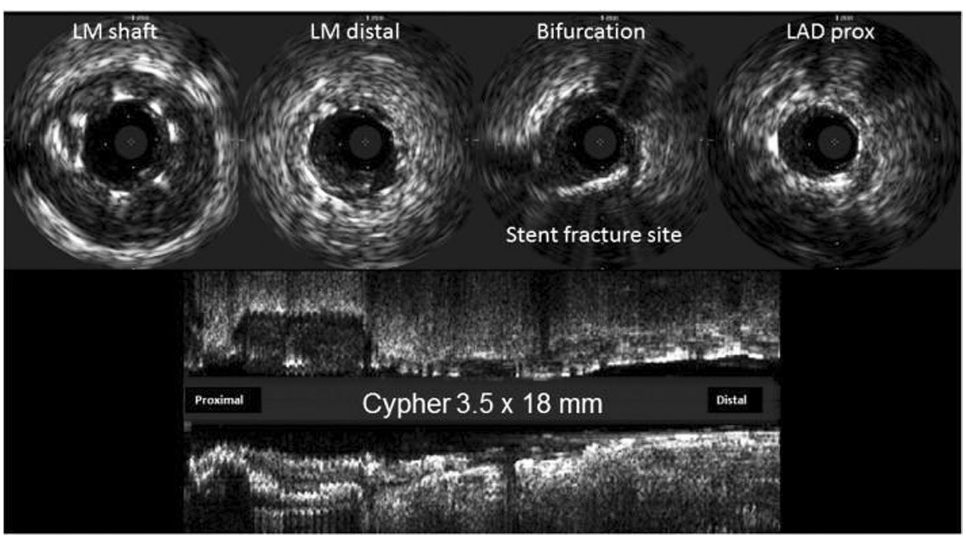

Fig. 3 Example of a 55-year-old male patient presenting with a left main stent thrombosis 2 174 days after left main/left anterior descending artery percutaneous coronary intervention. IVUS documented severe remodeling and incomplete stent apposition in the left main and a stent fracture at the bifurcation site (left main/left anterior descending artery). Published with permission. Courtesy: Petteri Kosonen, Saila Vikman, Lisette Okkels Jensen, Jens Flensted Lassen, Jan Harnek, Göran K. Olivecrona, Andrejs Erglis, Eigil Fossum, Matti Niemelä, Kari Kervinen, Antti Ylitalo, Mikko Pietilä, Jens Aaroe, Thomas Kellerth, Kari Saunamäki, Per Thayssen, Lars Hellsten, Leif Thuesen, Kari Niemelä, Intravascular ultrasound assessed incomplete stent apposition and stent fracture in stent thrombosis after bare metal versus drug-eluting stent treatment the Nordic Intravascular Ultrasound Study (NIVUS), International Journal of Cardiology, Volume 168, Issue 2, 2013, Pages 1010-1016,

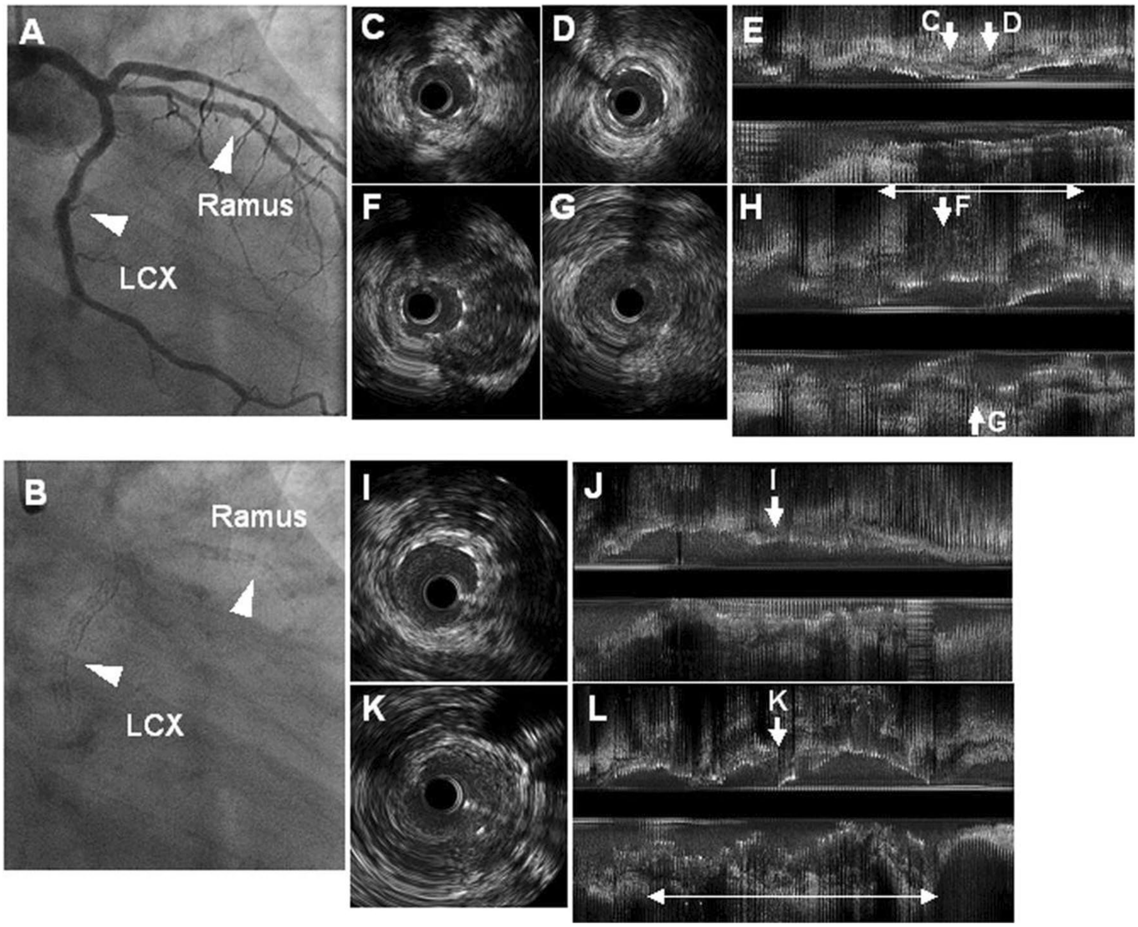

Fig. 4 IVUS findings in a patient with stent fractures in 2 vessels with aneurysm formation. A 57-year-old man received 1 Cypher stent in the ramus branch and 1 month later 2 Cypher stents in the left circumflex coronary artery (LCX). He had recurrent angina 14 months after the first Cypher stent implantation and underwent repeat angiography. *(A)* Angiogram shows haziness within the 2 stented segments. *(B)* Angiogram without dye injection shows stent fractures in the 2 Cypher stents *(arrowheads)*. *(C to E)* IVUS images of the ramus 1 month after the index procedure shows neither stent fracture nor aneurysm formation. *(F to H)* IVUS images of the ramus 14 months after the index procedure shows aneurysm formation *(F, which corresponds to C on 1-month IVUS study, double-headed arrow in H)* and stent fracture *(G, which corresponds to D on 1-month IVUS study)*. *(I, J)* Post-implantation IVUS study of the LCX. *(K, L)* Thirteen-month follow-up IVUS study of the LCX. Note the development of an aneurysm *(K, double-headed arrow in L)* and complete stent fracture *(K)*. *(I, K)* Same anatomic cross-section. Published with permission. Courtesy: Doi H, Maehara A, Mintz GS, Tsujita K, Kubo T, Castellanos C, Liu J, Yang J, Oviedo C, Aoki J, Franklin-Bond T, Dasgupta N, Lansky AJ, Dangas GD, Stone GW, Moses JW, Mehran R, Leon MB. Classification and potential mechanisms of intravascular ultrasound patterns of stent fracture. Am J Cardiol. 2009 Mar 15;103 [7]:818-23.

in early ST; however, it was also reported in few (14%) VLST patients. Neoatherosclerosis was noted frequently in late ST patients. Similar results were noted in multiple studies including the PESTO French registry [20–22].

Incidence of ST in bifurcation lesions has been previously studied by Bechiri et al [23]. Strut malapposition was noted to be the most frequent mechanism for ST in bifurcation lesions [23]. Length of malapposed or uncovered stent has also been corelated to incidence of ST [24]. Additionally, VLST has also been evaluated with OCT, and neoatherosclerosis has been frequently observed in these patients [25]. In-stent plaque rupture was the major cause for VLST in patients with neoatherosclerosis, and uncovered stent struts was the most frequent cause for VLST in patients without neoatherosclerosis [25]. Macrophage infiltration was significantly more frequent in OCT frames with plaque rupture compared with those without, whereas calcification was more often observed in frames without plaque rupture. Based on these findings, it was concluded that increased macrophage infiltration signals plaque vulnerability and might serve as an important indicator of ST. Patients who had imaging-guided intervention for late ST and VLST have been studied with follow-up OCT [26•]. A

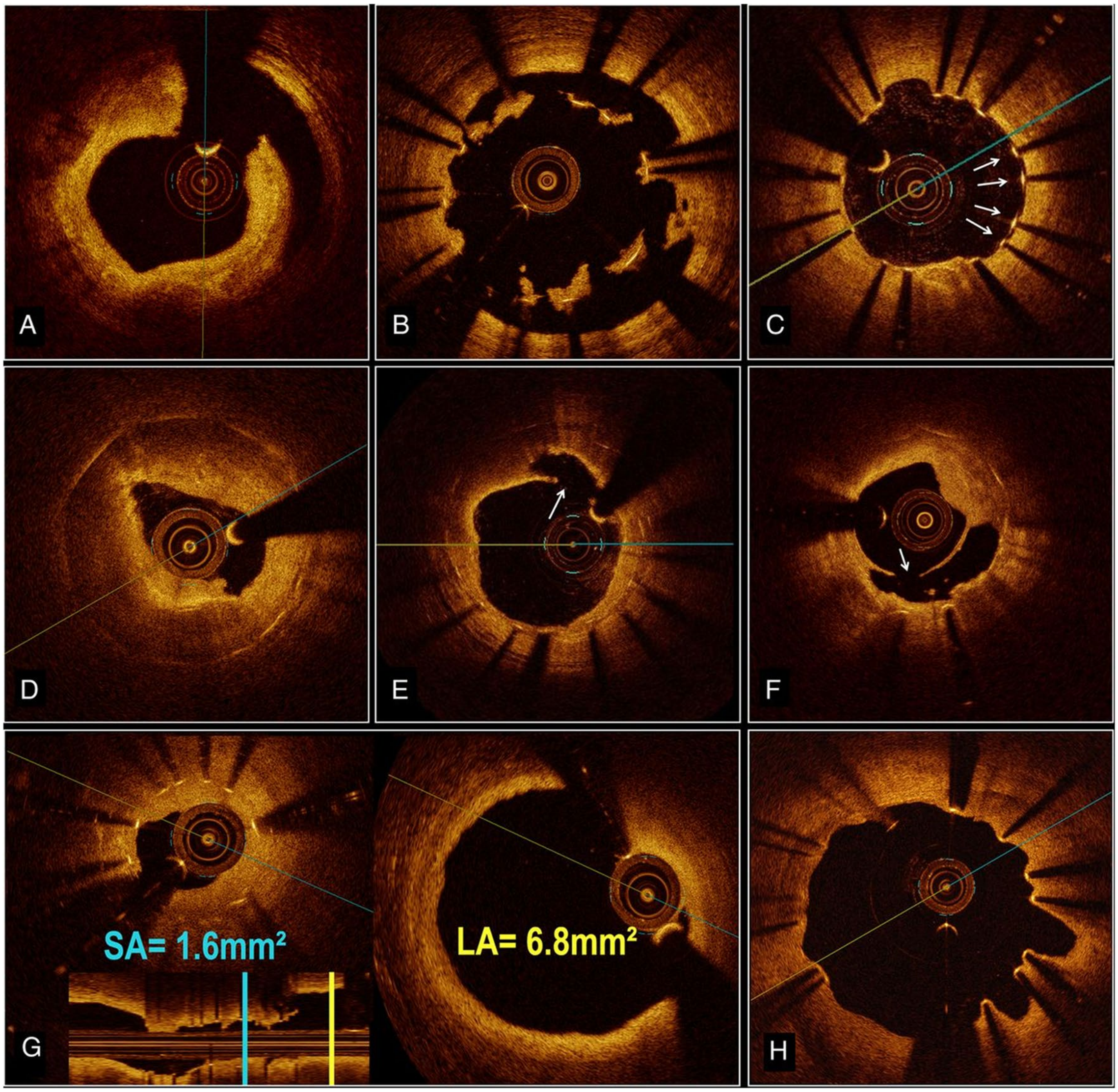

Fig. 5 Representative examples of stent thrombosis underlying mechanisms explored by optical coherence tomography imaging after optimal thrombus resorption: acute stent thrombosis: edge dissection (*A*); subacute stent thrombosis: stent major malapposition (*B*); late stent thrombosis: isolated uncovered struts (*C*); very late stent thrombosis: neoatherosclerosis lesion (*D*); ruptured neoatherosclerotic lesion (*E* and *F*); major stent underexpansion with stent area and reference lumen area measurements (*G*); coronary evaginations related to underlying positive remodeling (*H*). Published with permission. Courtesy: Geraud Souteyrand, Nicolas Amabile, Lionel Mangin, Xavier Chabin, Nicolas Meneveau, Guillaume Cayla, Gerald Vanzetto, Pierre Barnay, Charlotte Trouillet, Gilles Rioufol, Gregoire Rangé, Emmanuel Teiger, Regis Delaunay, Olivier Dubreuil, Thibault Lhermusier, Aurélien Mulliez, Sebastien Levesque, Loic Belle, Christophe Caussin, Pascal Motreff, the PESTO Investigators, Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry, *European Heart Journal*, Volume 37, Issue 15, 14 April 2016, Pages 1208–1216

majority of the patients who had initial stent malapposition were noted to have persistent malapposition and had poor rehealing [26•].

Imaging with IVUS and OCT has been compared in the past with each having specific benefits and indications. In lesions with late-acquired stent malapposition, IVUS is considered better than OCT because of its greater axial resolution and ability to evaluate the entire vessel wall [27]. In VLST with neocalcification, OCT is likely to be a better modality to assess the lesion compared to IVUS [27]. OCT is a better modality in evaluating uncovered stent struts which could be a potential culprit for late ST [28]. Overall, OCT provides detailed information in ST lesions, which helps in better treating these lesions. Various etiologies of ST have been illustrated using OCT images (Figs. 5, 6, 7, 8).

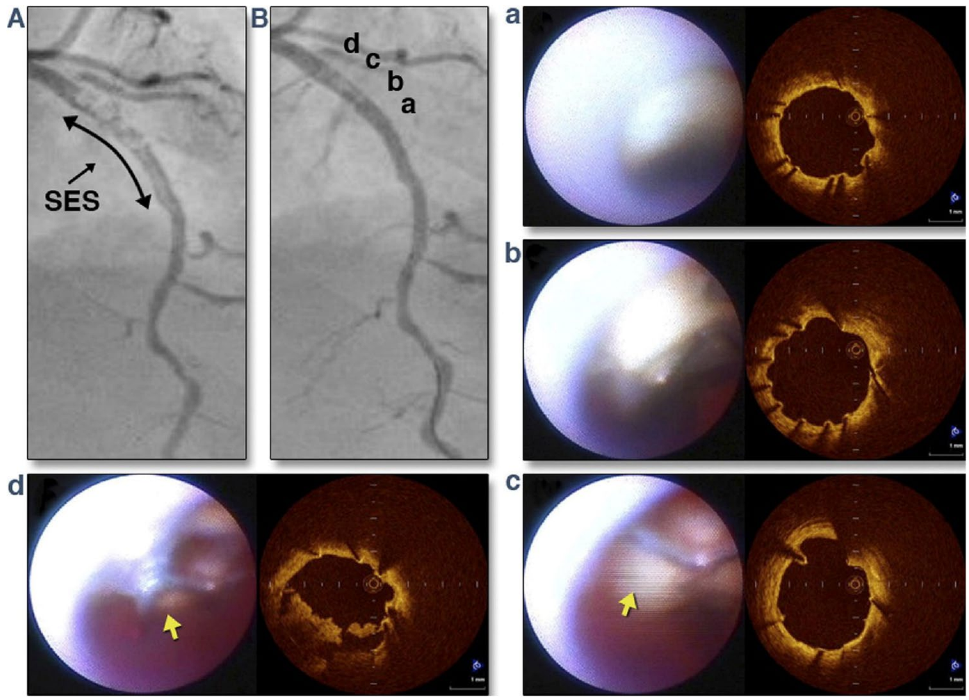

Fig. 6 A 70-year-old man underwent a 2.5 mm × 28 mm sirolimus-eluting stent (SES) implantation in the mid-left anterior descending artery (LAD) for acute myocardial infarction (AMI). Aspirin (100 mg/day) with clopidogrel (75 mg/day) was prescribed, but clopidogrel was stopped because of drug-induced liver injury 1 month after SES implantation. Thirty-four months after SES implantation, the patient suddenly suffered from recurrence of angina and was admitted to our hospital. Emergent coronary angiography (CAG) showed thrombus-like shadow in SES **(A)**. After aspiration thrombectomy **(B)**, optical coherence tomography (OCT) and coronary angioscopy (CAS) were performed. OCT and CAS revealed no coverage of neointima over stent struts in the distal and proximal portion of stent **(a)**. At thrombus sites, OCT revealed malapposition and red and white thrombus on the stent struts which were not covered by neointima **(b, c and d)**. CAS revealed malapposition and yellow plaque under stent struts **(b, c and d, yellow arrow)**. Published with permission. Courtesy: Ikenaga H, Ishihara M, Dai K, Nakama Y, Ohtani T. Mechanisms of very late stent thrombosis after drug-eluting stent implantation: findings from coronary angioscopy and optical coherence tomography. JACC Cardiovasc Imaging. 2011 Nov;4 [13]:1217-9. doi: 10.1016/j.jcmg.2011.05.008. PMID: 22093273.

Near-infrared fluorescence

Near-infrared fluorescence (NIRF) imaging is an optical-based intravascular approach that utilizes near-infrared light to excite targeted or activatable fluorophores that illuminated specific molecules, cells, or biological processes [29–31] whose iterative advances have demonstrated significant utility in the realm of intravascular stent imaging. Successive iterations of NIRF have advanced the modality from a one-dimensional to a two-dimensional platform, allowing sensing of NIRF signals in vessels of diameters more typical of the human coronaries [32]. The current platform couples third-generation combined NIRF-OCT to provide simultaneous molecular and microstructural imaging and enabling distance-based compensation of the NIRF signal in an in vivo single pullback [33, 34]. As previously discussed, inflammation within a neoatherosclerotic plaque is associated with increased risk of plaque rupture leading to ST. Coupled OCT-NIRF allows identification and characterization of such in vivo scenarios, by allowing the visualization of fibrin deposition on the stent [35] particularly in stents with absent endothelium. Jaffer et. al. demonstrated that the tissue coverage traditionally visualized via OCT of bare metal stents and drug-eluting stents did not always represent healthy tissue coverage, and that often stents with variable NIRF-detected fibrin deposition were at risk for progression of the inflammatory cascade leading to ST [36].

Conclusion

ST is a potentially fatal complication of PCI, and efforts should be made to prevent its occurrence by utilizing intravascular imaging to optimize PCI results. IVUS, OCT, and

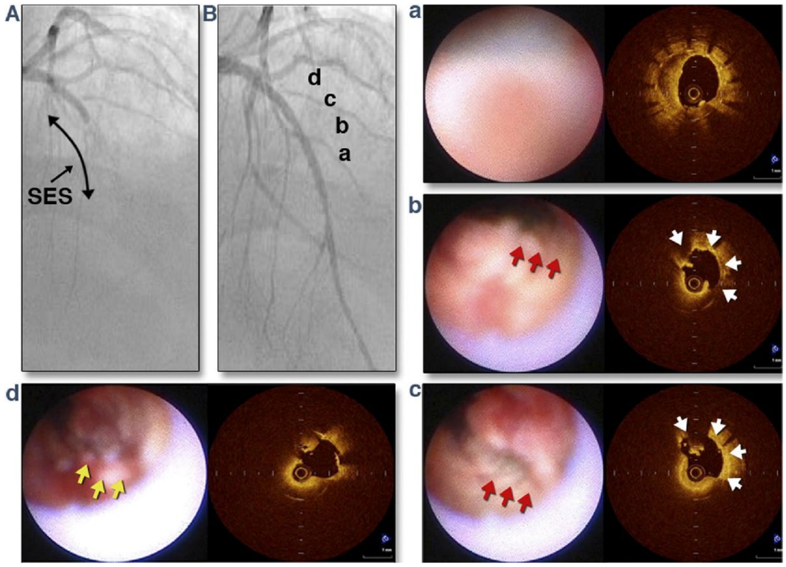

Fig. 7 A 68-year-old man underwent 2 SES implantations in the mid-LAD for AMI (2.5 mm × 18 mm and 2.5 mm × 18 mm). Aspirin (100 mg/day) with ticlopidine (200 mg/day) was prescribed. Aspirin and ticlopidine were stopped 1 year after SES implantation by a self-judgment. Fifty-four months after SES implantation, the patient suddenly suffered from recurrence of angina on exertion and was admitted to our hospital. Emergent CAG revealed total occlusion at proximal SES in the mid LAD (**A**). After balloon angioplasty (**B**), OCT and CAS were performed. OCT and CAS revealed neointimal coverage over stent in the distal and proximal portion of stent **(a)**. OCT revealed cavity formation **(white arrow)** over stent struts **(b, c)**. CAS revealed yellow plaque rupture **(C, yellow arrow)** and cavity formation **(b, c, red arrow)** over stent struts. Published with permission. Courtesy: Ikenaga H, Ishihara M, Dai K, Nakama Y, Ohtani T. Mechanisms of very late stent thrombosis after drug-eluting stent implantation: findings from coronary angioscopy and optical coherence tomography. JACC Cardiovasc Imaging. 2011 Nov;4 [13]:1217-9. doi: 10.1016/j.jcmg.2011.05.008. PMID: 22093273.

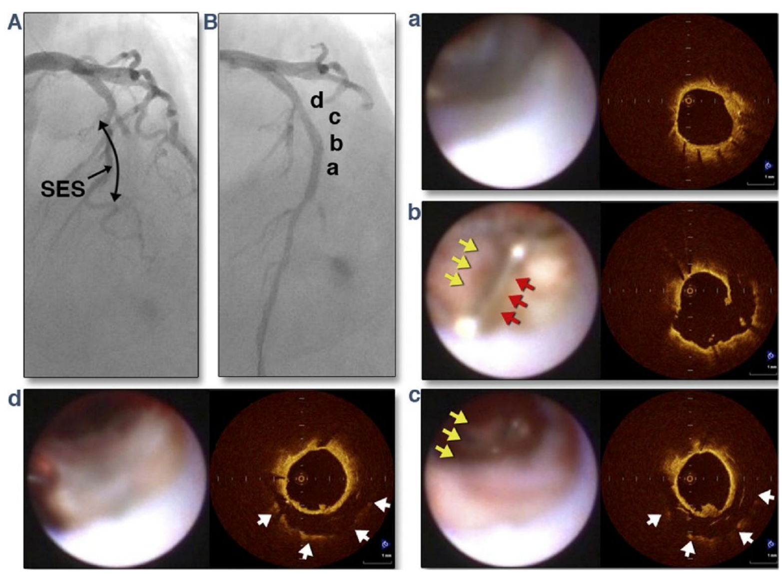

Fig. 8 A 70-year-old man underwent a 2.5 mm × 28 mm SES implantation in the mid-LAD for AMI. Aspirin (100 mg/day) and ticlopidine (200 mg/day) was prescribed thereafter. Ticlopidine was stopped 6 months after SES implantation. Fifty-nine months after SES implantation, the patient suddenly suffered from recurrence of angina and was admitted to our hospital. Emergent CAG showed total occlusion at the site of SES (**A**). After aspiration thrombectomy (**B**), OCT and CAS was performed. In the distal and proximal portion of stent, OCT and CAS revealed neointimal coverage over stent struts and no stent underexpansion **(a)**. OCT revealed mixed thrombus, plaque rupture **(b)**, and cavity formation behind neointima-covered stent (**c, d, white arrow**). CAS revealed ruptured yellow plaque under stent struts (**b, c, yellow arrow**). The stent struts were floating over the ruptured plaque (**b, red arrow**). Published with permission. Courtesy: Ikenaga H, Ishihara M, Dai K, Nakama Y, Ohtani T. Mechanisms of very late stent thrombosis after drug-eluting stent implantation: findings from coronary angioscopy and optical coherence tomography. JACC Cardiovasc Imaging. 2011 Nov;4 [13]:1217-9. doi: 10.1016/j.jcmg.2011.05.008. PMID: 22093273.

NIRF are the currently available intracoronary imaging modalities with individual relative advantages and disadvantages. Intravascular imaging is mandatory in case of ST to define the underlying mechanism and help tailor the therapy.

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Declarations

Conflict of Interest Amir Kaki reports work/support with/from Abbott, Abiomed, CSI, Terumo, Shockwave, Cathworks, all outside the submitted work. George Jolly, Nikhil Ghatnekar, and Aditya Bharadwaj declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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