# Optical coherence tomographic insights of very late stent thrombosis of a second-generation drug-eluting stent: a case report

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| **Background** | Very-very late stent thrombosis (VVLST) occurring more than 5 years after implantation of drug-eluting stent (DES) is extremely rare, being restricted to few case reports. Mainly described with first-generation stents, this life-threatening complication has not been described with later-generation stents. We describe the first case of VVLST occurring 3309 days (>9 years) after implantation of second-generation DES. |
| **Case summary** | A 62-year-old man presented with the acute coronary syndrome. He has a history of percutaneous coronary intervention (PCI) to the right coronary artery using the three second-generation DES more than 9 years ago. Coronary angiogram revealed in-stent restenosis (ISR) with doubtful angiographic thrombus. Optical coherence tomography (OCT) confirmed the diagnosis of stent thrombosis (STh) localized to the stent overlap zone with underlying ISR. Patient underwent OCT-guided PCI with DES implantation and was discharged on dual antiplatelet therapy including ticagrelor. He is doing well on follow-up at 6 months. |
| **Discussion** | Stent thrombosis can occur in second-generation stents nearly a decade after implant. Stent overlap segment is more prone to neo-atheroma formation and vulnerable plaque leading to STh. In addition to confirming the diagnosis, OCT provides exciting insights into the underlying mechanism. This has implications for long-term antiplatelet therapy in patients implanted with multiple stents. |
| **Keywords** | Very-very late stent thrombosis • Second generations stent • Optical coherence tomographic • Case report |
| **ESC Curriculum** | 3.1 Coronary artery disease • 3.2 Acute coronary syndrome • 3.4 Coronary angiography |

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## Learning points
- Stent thrombosis (STh) may occur years after implantation of second-generation drug-eluting stent.
- The stent overlap region appears more prone to lipid-rich neo-atheroma formation, plaque rupture, and consequent STh.
- Optical coherence tomography imaging helps understand the mechanism of stent failure and optimize interventional management.

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# Introduction

Stent thrombosis (STh) is an uncommon but life-threatening complication of percutaneous coronary intervention (PCI).[1] Although commonly encountered STh is acute (within 24 h), subacute (within 1–30 days), or late (1–12 months) in nature,[2] very late stent thrombosis (VLST) (more than 1 year) after stent implantation has been well reported. Stent thrombosis occurring more than 5 years after stent implantation, described as very-very late stent thrombosis (VVLST), had been limited to a few case reports. Since the first case report in 2009,[3] VVLST has been considered a class effect of first-generation drug-eluting stent (DES). However, we report a 62-year-old man presenting with STh over 9 years after implanting second-generation DES and discuss the optical coherence tomographic (OCT) insights into the underlying mechanism.

# Timeline

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| April 2011 | 62 years, male, chronic smoker, hypertensive, exertional angina |
| February 2012 | Angina refractory to medical therapy |
| | Coronary angiogram—diffuse critical stenosis of right coronary artery (RCA), percutaneous coronary intervention (PCI) using three drug-eluting stents (DES) |
| | Proximal RCA—3.5 × 30 mm Endeavor Spirit Second-generation |
| | Mid RCA—3.0 × 30 mm Stent (Zotarolimus-eluting Endeavor Spirit stent, |
| | Distal RCA—2.75 × 30 mm Medtronic Vascular, CA, USA) |
| Till February 2021 | Doing well, compliant to medications, continued to smoke |
| March 2021 | Unstable angina |
| | Coronary angiogram—diffuse in-stent restenosis |
| | Intracoronary optical coherence tomography (OCT) imaging |
| | Diffuse intimal hyperplasia, neo-atherosclerosis, and plaque rupture with white thrombus localized to stent overlap zone causing significant luminal stenosis (very-very late stent thrombosis) |
| | OCT-guided PCI—pre-dilation → third-generation DES 3.5 × 38 mm stent → high-pressure post-dilation, well-expanded and well-apposed stent, minimal stent area = 6.54 mm² |
| Follow-up at 2 months | Has quit smoking, compliant to medications, no angina |

# Case presentation

A 62-year-old Indian male, a chronic smoker, presented with three episodes of rest angina for the last 1 month. He was detected with

hypertension and was taking telmisartan hydrochloride, 40 mg once a day for the last 5 years. There was no history of any other comorbidity. At presentation, his blood pressure was 130/82 mmHg, and his pulse rate was 90 beats per minute. His cardiovascular examination was unremarkable. The electrocardiograph showed T-wave inversion in leads LII, LIII, and aVF (*Figure 1*). Echocardiography revealed a structurally normal heart with a left ventricular ejection fraction of 55%. Cardiac troponin-I level was normal.

At the age of 52, he was diagnosed with chronic stable angina when a coronary angiogram revealed a diffuse lesion in the right coronary artery (RCA), causing critical stenosis (*Figure 2A*). PCI to RCA was done with implantation of three second-generation DES (zotarolimus-eluting Endeavor Spirit stent, Medtronic Vascular, CA, USA) with an adequate overlap of stent edges. Post dilation with a 3.0 × 15 mm non-compliant (NC) balloon in the distal RCA and a 3.5 × 15 mm NC balloon in mid-proximal RCA achieved good angiographic results (*Figure 2B*). Intracoronary imaging was not done at that time. He received dual antiplatelet therapy (DAPT), including aspirin and clopidogrel, for 1-year post-PCI, after which only aspirin was continued. He has also received metoprolol and atorvastatin since then. He did well for the last 9 years following PCI.

During the current presentation, he was diagnosed with non-ST-elevation acute coronary syndrome and was given 180 mg ticagrelor along with 75 mg aspirin. A coronary angiogram revealed diffuse in-stent restenosis (ISR) extending from proximal to the mid-stented segment of RCA with a focal haziness causing 90% stenosis (*Figure 2C*). This hazy lesion corresponds to the overlap segment of proximal-mid RCA stents (*Figure 2B* and *C*). An intracoronary OCT imaging of RCA was performed (ILUMIEN TM Optis systems, MA, USA) to elucidate the mechanism of stent failure. Longitudinal OCT image (*Figure 3*, middle panel) revealed well-apposed struts throughout the length of the stented segment, diffuse intimal hyperplasia, and neo-atherosclerosis, causing a variable degree of luminal stenosis. Furthermore, the OCT appearance of neo-atherosclerosis was variable. While predominantly fibrotic hyperplasia was noticed in the distal and proximal stent, neo-atheroma in the middle stent showed a predominantly lipid-rich plaque with minimal fibrous element, especially at the site of proximal stent overlap. This segment also revealed a thin overlying fibrous cap, plaque rupture, and a white thrombus causing significant luminal area reduction (*Figure 3*, upper and lower panels, *Videos 1* and *2*). Further analysis of the OCT images revealed a vessel diameter of 3.2 mm in the distal reference segment of RCA. This correlates well with the measured mean stent diameter of 3.18 mm in distal RCA, 3.51 mm at the distal stent overlap, and 3.55 mm at the proximal stent overlap segments of RCA, thereby ruling out under-expansion as a mechanism of stent malfunction in the index patient (*Figure 4A–E*).

We pre-dilated the ISR lesion with a 2.5 × 15 mm semi-compliant balloon followed by a 3.0 × 15 mm NC balloon and a 3.5 × 15 mm NC balloon at high pressure. Our initial plan was to treat the lesion with a drug-eluting balloon as ISR was intrastent. However, OCT imaging after balloon angioplasty revealed a dissection flap at the upper edge of the proximal stent, extending from the neoatheroma. A review of OCT images revealed a predominantly fibrotic plaque at this site (*Figure 4F*). So, the diseased segment was treated with a 3.5 × 38 mm third-generation Sirolimus-Eluting Polymer Free
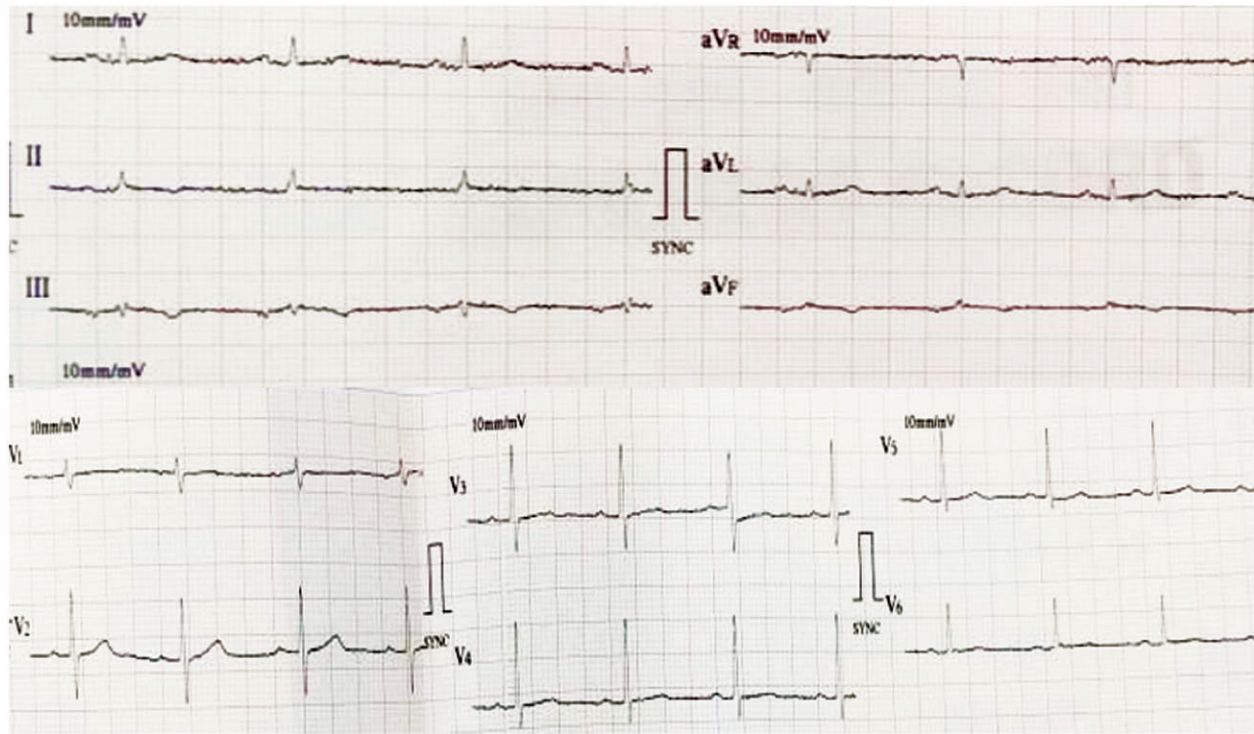
**Figure I** Electrocardiogram at presentation showing T-wave inversion in leads LII, LIII, and aVF.
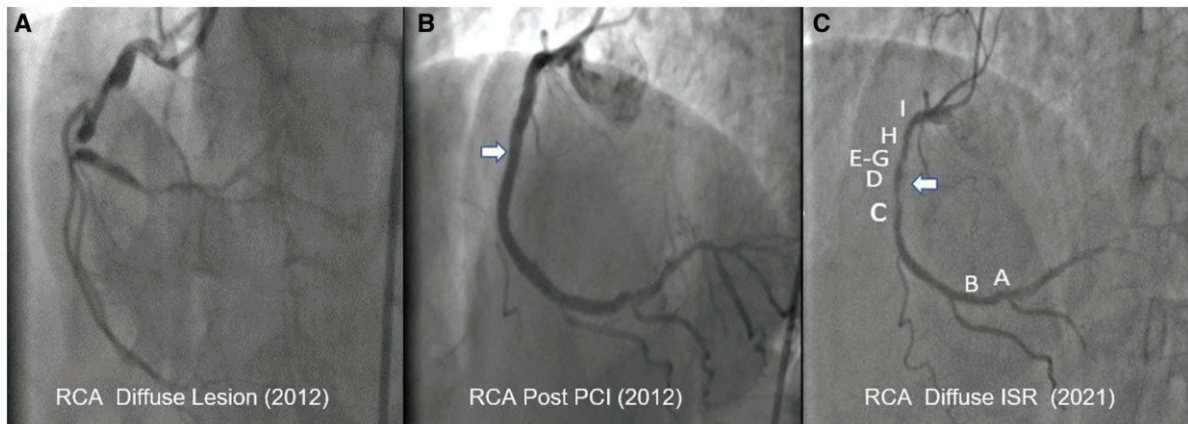


**Figure 2** A selective coronary angiogram (A) In 2012 revealed diffuse lesion in the right coronary artery, causing critical stenosis. (B) A metal jacket right coronary artery after implantation of a 3.5 mm × 30 mm stent in the proximal-right coronary artery, 3.0 mm × 30 mm stent in mid-right coronary artery, and a 2.75 mm × 30 mm stent in the distal-right coronary artery (zotarolimus-eluting Endeavor Spirit stents, Medtronic Vascular, CA, USA) with adequate overlap (arrow indicate proximal overlap) at stent edges are shown. (C) In the year 2021, reveals diffuse in-stent restenosis extending from proximal to middle stented segment with slight haziness at the proximal stent overlap (arrow), causing 90% stenosis. Points marked A to G correspond to cross-sectional optical coherence tomographic images in *Figure 3*. The point marked D corresponds to the arrow in B, indicating a proximal stent overlap segment.

Coronary Stent (Coroflex ISAR-Neo Stent, B. Braun, Melsungen, Germany) followed by high pressure (18 atm) post-dilatation with a 3.5 × 12 mm NC balloon. Repeat OCT imaging showed a well expanded and well-apposed stent with minimal stent area (6.54 mm$^2$) (*Figure 5A–E*), except at the proximal part where it was malapposed (*Figure 5F, Video 3*). This segment was further
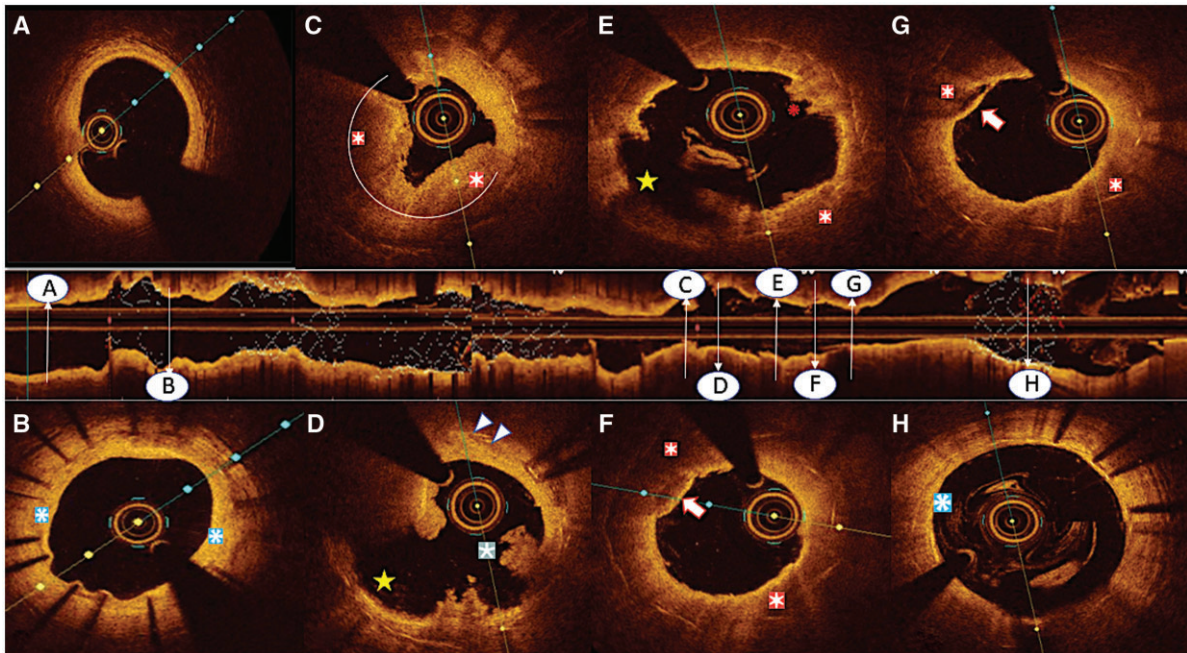
**Figure 3** Optical coherence tomography imaging of right coronary artery. *Middle Panel*: Longitudinal image reveals well-apposed stent struts throughout the length with intimal hyperplasia and/or diffuse neo-atherosclerosis extending from the distal to the proximal stented segment, causing a variable degree of luminal area reduction with maximal luminal area stenosis of 88% at the point marked C. A to H correspond to cross-sectional optical coherence tomography images in the upper and lower panel of this figure as well as to the angiographic image of *Figure 2C. Upper and Lower Panel*: Cross-sectional optical coherence tomography images show (A) distal normal reference segment with the vessel diameter of 3.2 mm measured from external elastic lamina to external elastic lamina. (B) Predominantly a fibrotic neo-intimal hyperplasia (⊛) within the distal right coronary artery stent. (C) Heterogeneous fibro-lipidic (⊠) neo-atheroma (covering > 180° arc) causing in-stent restenosis with 88% luminal area stenosis. (D) Proximal stent overlap segment (arrowheads) with plaque rupture (★) in a predominantly lipid-rich neo-atheroma and an extensive white thrombus (⊠). (E) Fibro-lipidic plaque (⊠) with erosion (✳) and thrombus adjacent to the plaque rupture (★). (F and G) Proximal stent lipid-rich plaque (⊠) with thin cap fibro-atheroma. (G) Thin cap fibro-atheroma with an intimal tear. (H) Proximal part of the stent shows minimal neo-intimal fibrotic hyperplasia.
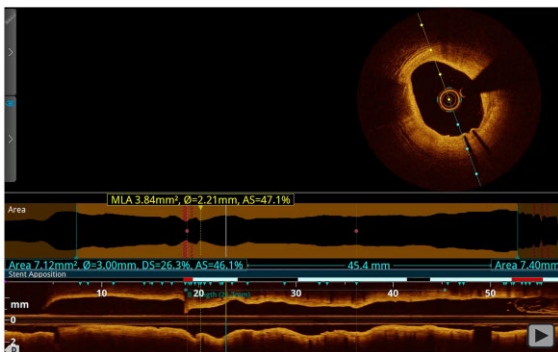


**Video 1.** Pre-PCI OCT pullback (Distal Stent, Distal Overlap Zone and Mid Stent).
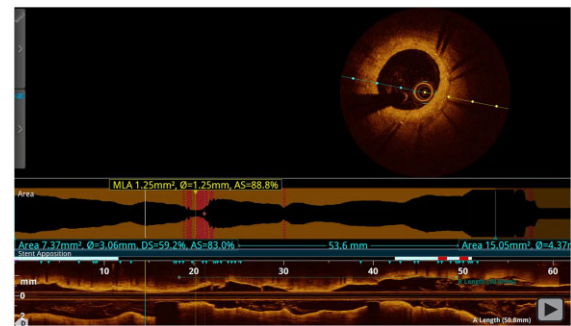


**Video 2.** Pre-PCI OCT pullback (Mid Stent, Proximal Overlap Zone and Proximal Stent).

post-dilated with a 4.5 mm NC Balloon at 14 atm as guided by OCT. The final angiogram showed thrombolysis in myocardial infarction III flow (*Figure 5G*). No further OCT imaging was done in view of contrast load. He was discharged on metoprolol, telmisartan, atorvastatin, and DAPT, including 75 mg of aspirin once a day and 90 mg of ticagrelor twice a day. Being a candidate with high thrombotic risk, he was prescribed an extended duration of DAPT as per current guidelines.[4] He is doing well on follow-up at 6 months after discharge.
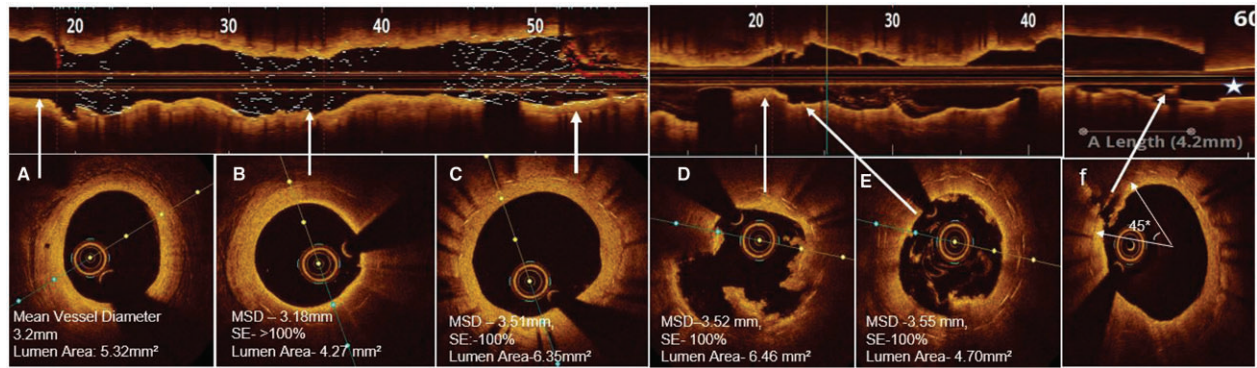
**Figure 4** Optical coherence tomographic images of right coronary artery illustrating no under-expansion (A–E) and dissection (F). (A) Distal normal reference diameter as measured from external elastic lamina to external elastic lamina is shown. (B–E) Neo-atheroma segment showing mean stent diameter and stent expansion of the distal right coronary artery stent (B), distal-mid stent overlap segment (C), and mid-proximal stent overlap segment (D, E). Overlap segment is evident by double layer of stent struts (C–E). (F) Dissection after balloon dilatation near the proximal edge of the stent covering an angle of 45° and extending proximally towards the guide catheter tip (star) for a length of 4 mm (corresponding longitudinal image), which required stenting are shown. White arrows indicate corresponding points in the longitudinal image.
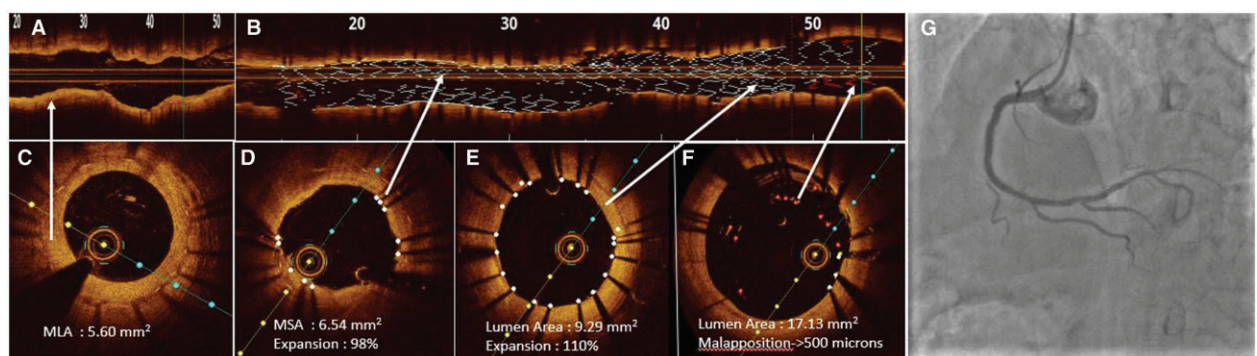


**Figure 5** Post-percutaneous coronary intervention optical coherence tomographic and angiographic images of right coronary artery. Longitudinal image of distal (A) and proximal (B) part of right coronary artery with corresponding cross-sectional images indicated by arrows. (C) A minimal lumen area of 5.60 mm² is shown. (D) Minimal stent area of 6.54 mm² and stent expansion of 98% in the newly stented segment. (E) Well-expanded and well-apposed stent in a part of proximal right coronary artery are shown. (F) Stent malapposition in the upper part, which was later dilated with a 4.5 mm balloon guided by OCT. (G) Final post-PCI angiographic image with thrombolysis in myocardial infarction 3 flow and no residual stenosis.

# Discussion

The initial higher STh rate with steel-based bare-metal stents and first-generation DES has dramatically reduced to as low as 0.7% at 12 months with the current generation DES.[5] The contributing innovations in second-generation DES include switching to cobalt alloy with thinner stent struts that allowed relatively rapid endothelization while maintaining the required radial strength. Predominant abnormalities causing early STh include uncovered struts, malapposition, underexpansion, and edge dissection, while malapposition, neo-atherosclerosis, uncovered struts, and under expansion are frequently observed in patients with late DES thrombosis.[6] Other factors predisposing to late STh include delayed arterial healing, hypersensitivity reactions, stent strut penetrating a necrotic core, overlapping stents,

longer stent lengths, and bifurcation stenting.[7,8] Important contributing patient-related factors include smoking, multivessel disease, younger age, and diabetes.[8] Despite a favourable impact of newer antiplatelet agents and intracoronary imaging for procedural optimization on the incidence of early STh, delayed healing, non-uniform endothelization, and recently described neo-atherosclerosis remain essential mechanisms for VLST.[9] Recruitment of macrophages and circulating monocytes with high lipid contents at the site of stent implantation is known to cause neoatherosclerosis.[10] Imaging studies have confirmed that stent under-expansion, strut malapposition, geographic plaque miss, and non-endothelialization are known to predispose neoatheroscleloris formation.[10] The largest available study evaluating the OCT characteristics of STh in the current generation stents has shown neoatherosclerosis and uncovered struts to be the
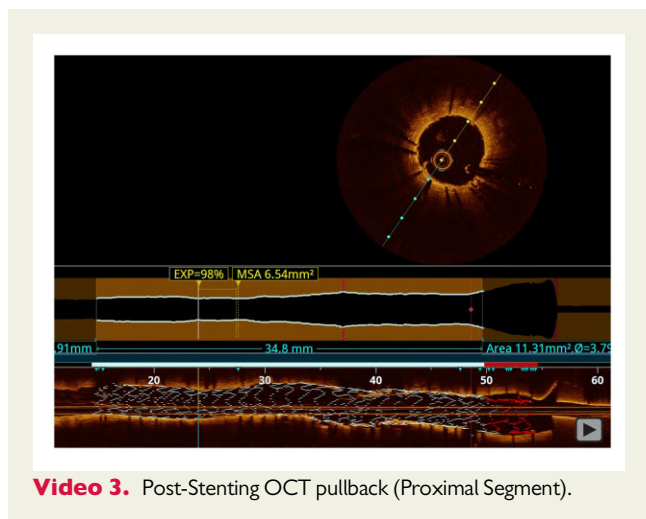
**Video 3.** Post-Stenting OCT pullback (Proximal Segment).

most common findings in VLST.[11] Despite this, the published reports on OCT insights into the underlying mechanism of STh beyond 5 years of PCI are few and restricted to BMS or first-generation DES. The index patient is the first report of VVLST of second-generation DES described in the literature, supported with OCT insights.

Intracoronary imaging is essential to elucidate the exact mechanism of stent failure. In the PESTO Registry, OCT identified a morphological abnormality associated with STh in 97% of the cases.[12] OCT is a preferred imaging modality for detecting plaque erosion, thin cap fibroatheroma, neo-atheroma formation, and characterization of thrombus compared to intravascular ultrasound. OCT in our case showed a spectrum of findings, including neointimal hyperplasia, fibrotic and lipid-rich neo-atheroma causing ISR, and plaque rupture leading to STh. Whereas predominantly fibrotic neointimal hyperplasia was noticed in the segment with a single layer of the stent, the significant component of neo-atheroma around the stent overlap segment was lipid-rich core with a thin fibrous cap associated with plaque rupture causing STh. This variability in the composition of neo-atheroma and its vulnerability for plaque rupture may be hypothetically explained by non-uniform drug delivery due to multiple overlapping DES. In addition to the physical burden posed by the excessive metal, exposure of the vessel wall to a high concentration of the antiproliferative drug in areas of stent overlap may hamper the healing process and inhibit fibrosis for an extended period thus leading to a vulnerable plaque. Various *in vivo* and imaging studies have reported delayed endothelialization, increased inflammation, and impaired vessel remodelling in the overlapped segments of DES.[13] These changes have increased major adverse events in clinical studies, although the risk of STh appears similar to non-overlapped revascularization.[14] Stent under-expansion, especially in the overlap zone, is another described mechanism of late STh. However, our patient has achieved a mean stent diameter that correlates well with the reference vessel diameter throughout the stented vessel length as measured with current OCT imaging. Therefore, underexpansion is unlikely a contributing mechanism of VVLST in the index patient.

Our observations may have important clinical implications. Firstly, the preferable use of a single long stent and minimizing the overlap zone of multiple stents during PCI of the diffuse coronary lesion appears reasonable. Secondly, the choice of antiplatelet therapy and its duration needs to be individualized. The current European Society of Cardiology guidelines recommends an extended duration of DAPT for patients with high thrombotic risk, as with three DES.[4] Additionally, the use of more potent drugs like ticagrelor as an alternative to aspirin for long-term therapy after PCI in such patients needs evaluation. Limited data suggest the use of GpIIbIIIa inhibitors is associated with better clinical outcomes in patients presenting with early STh.[15] Although we considered using Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor, it was not given in our patient due to active dental bleed during PCI.

## Conclusions

Our case illustrates that STh may occur many years after implantation of second-generation DES, especially involving the stent overlap region. OCT imaging elucidates the mechanism of stent failure and optimizes interventional management. Minimizing the number and degree of stent overlap during PCI using multiple stents is warranted. The use of DAPT in such patients should be carefully individualized. Future studies are required to validate these observations and avoid this catastrophic complication.

## Lead author biography



Parminder Singh Otaal graduated from the University of Rajasthan, Jaipur, India in 1997. After completing MD Internal Medicine and DM Fellowship Cardiology, he joined the Department of Cardiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, in 2008 as a Faculty. He completed a Course in Advanced Studies—Aortic Valve from University of Zurich in 2020. His areas of interest include coronary and structural heart interventions.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

# References

1. Tyczyński P, Karcz MA, Kalińczuk L, Fronczak A, Witkowski A. Early stent thrombosis. Aetiology, treatment, and prognosis. *Postepy Kardiol Interwencyjnej* 2014;**10**:221–225.

2. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA et al.; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–2351.

3. Layland J, Jellis C, Whitbourn R. Extremely late drug-eluting stent thrombosis: 2037 days after deployment. *Cardiovasc Revasc Med* 2009;**10**:55–57.

4. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.

5. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. *Eur Heart J* 2015;**36**:3320–3331.

6. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y et al.; ESC Scientific Document Group. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J* 2018;**39**:3281–3300. Erratum in: *Eur Heart J* 2019 Jan 14;**40**(3):308.

7. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;**48**:193–202.

8. Waksman R, Kirtane AJ, Torguson R, Cohen DJ, Ryan T, Räber L et al. Correlates and outcomes of late and very late drug-eluting stent thrombosis: results from DESERT (International Drug-Eluting Stent Event Registry of Thrombosis). *JACC Cardiovasc Interv* 2014;**7**:1093–1102.

9. Park SJ, Kang SJ, Virmani R, Nakano O, Ueda Y. In-stent neoatherosclerosis—a common pathway of late stent failure. *J Am Coll Cardiol* 2012;**59**: 2051–2055.

10. Borovac JA, D'Amario D, Vergallo R, Porto I, Bisignani A, Galli M et al. Neoatherosclerosis after drug-eluting stent implantation: a novel clinical and therapeutic challenge. *Eur Heart J Cardiovasc Pharmacother* 2019;**5**:105–116.

11. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E 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**: 1007–1021.

12. Souteyrand G, Amabile N, Mangin L, Chabin X, Meneveau N, Cayla G et al.; PESTO Investigators. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. *Eur Heart J* 2016;**37**:1208–1216.

13. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005;**112**: 270–278.

14. Räber L, Jüni P, Löffel L, Wandel S, Cook S, Wenaweser P et al. Impact of stent overlap on angiographic and long-term clinical outcome in patients undergoing drug-eluting stent implantation. *J Am Coll Cardiol* 2010;**55**:1178–1188.

15. Casserly IP, Hasdai D, Berger PB, Holmes DR, Schwartz RS, Bell MR. Usefulness of abciximab for treatment of early coronary artery stent thrombosis. *Am J Cardiol* 1998;**82**:981–985.