



Double-vessel very late stent thrombosis following Resolute Onyx zotarolimus eluting stents implantation in an octogenarian

George Kassimis^{1,2,*}, Tushar Raina¹

¹Department of Cardiology, Cheltenham General Hospital, Gloucestershire Hospitals NHS Foundation Trust, Cheltenham, United Kingdom

²Second Department of Cardiology, Hippokraton Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

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Compared with bare-metal stents (BMS), drug-eluting stents (DES) have shown better clinical outcomes for patients undergoing percutaneous coronary intervention (PCI) by inhibition of neo-intimal hyperplasia.^[1] However, early-generation DES produced late thrombotic events, more than 1-year, by delaying arterial healing of stented vessels.^[2–5] New-generation DES have been developed with thinner stent struts, more biocompatible polymer coatings for drug release, and a variety of antiproliferative agents with similar or superior anti-restenotic efficacy.^[6] This development has led to a significant improvement in the efficacy and safety of new-generation DES, and consistently lower rates of very late stent thrombosis (VLST).^[7,8] In fact, use of new-generation DES is the standard treatment in contemporary PCI practice.^[9]

VLST (> 1year)^[10] is an infrequent, but potentially fatal complication due to acute vessel closure. Several potential factors are most closely related to the risk of developing VLST, including procedural (multiple stenting, longer stented length, overlapping stents, prior coronary artery bypass grafting), lesion (bifurcation and vein graft lesions, multivessel disease), and patient factors [presence of renal disease, prior history of myocardial infarction, current smoking, depressed left ventricular systolic function, discontinuation of dual antiplatelet therapy (DAPT)].^[11–13] Furthermore, neo-atherosclerotic plaque rupture is now acknowledged as a potential contributing factor.^[14,15]

Although atrial fibrillation (AF) remains the most frequent cardiac cause of coronary embolism (CE) in ST-segment-elevation myocardial infarction (STEMI) patients, etiopathogenesis of CE implies multiple mechanisms leading to an increased systemic pro-thrombogenicity.^[16]

We describe the first reported case of an octogenarian patient presenting with anterior STEMI and newly diagnosed AF who experienced VLST in two coronary vessels simultaneously which occurred 16 months after Resolute Onyx zotarolimus eluting stents (RO-ZES) (Medtronic) implantation.

An 80-year-old man presented to the emergency department with severe chest pain within 2 h after onset of symptoms. The electrocardiogram (ECG) showed newly diagnosed AF and ST-segment elevation in the anterior leads. The patient had undergone elective PCI in our centre using RO-ZES in the proximal left anterior descending (LAD) [2.75 × 22 mm; post-dilated with a non-compliant (NC) 3.0 × 12 mm balloon at 16 atm] and in the right coronary artery (RCA) (5.0 × 26 mm proximally post-dilated with a 5.0 NC balloon; 3.0 × 26 mm and 2.75 × 18 mm distally post-dilated with 3.0 × 15 mm NC balloon at 14 atm) 16 months prior to admission (Figures 1A and 1B magnified pictures respectively). DAPT consisting of 75 mg aspirin and 75 mg clopidogrel was prescribed for an intended period of 12 months following PCI.

Transradial cardiac catheterization revealed a thrombotic occlusion at the site of the stent implanted in the proximal LAD with Thrombolysis In Myocardial Infarction (TIMI) 0 flow (Figure 1A) and a thrombus at the site of the proximal stent in the mid RCA with TIMI 2 flow (Figure 1B, white arrow) and a moderate to severe focal lesion just before the 3.0 × 26 mm stent (Figure 1B, black arrow). Following oral administration of 300 mg of aspirin and 180 mg of ticagrelor loading doses and 9000 u of unfractionated heparin through the radial sheath, primary PCI was performed in the blocked LAD which was felt the culprit lesion of this presentation. An XB 3.5 6F guide catheter (Cordis) gave good support, and a Sion blue wire (Asahi) crossed the LAD occlusion easily. Thrombus aspiration was then performed

*Correspondence to: Email: gksup@yahoo.gr

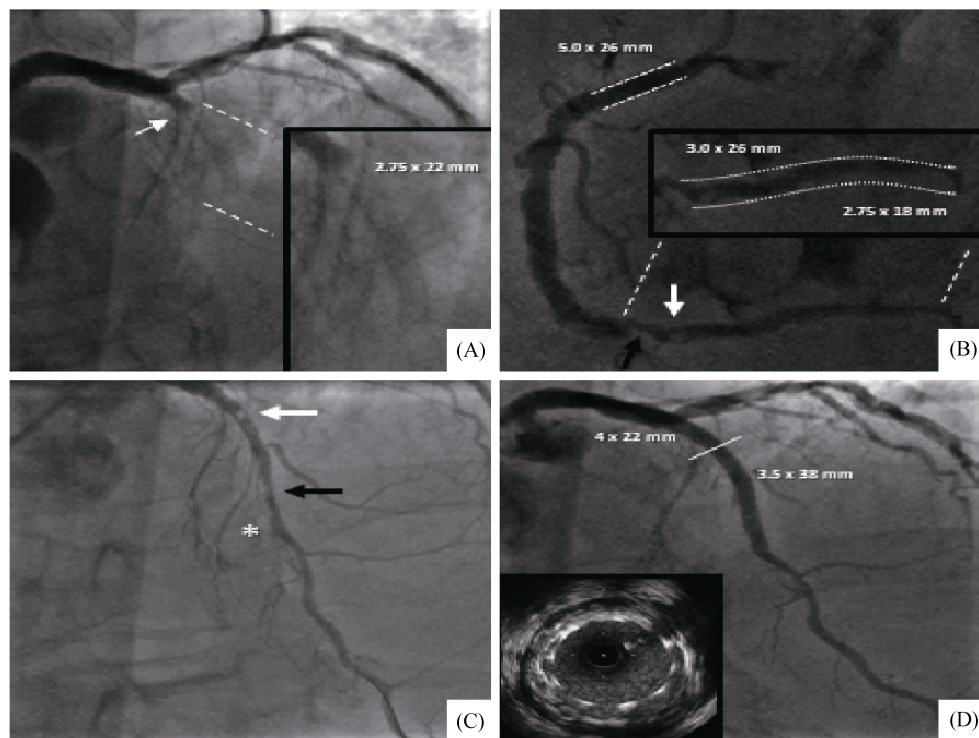


Figure 1. Coronary angiography and IVUS-guided LAD primary angioplasty. Thrombotic occlusion at the site of the proximal LAD stent with TIMI 0 flow (A, white arrow, magnified picture) and evidence of thrombus at the site of the proximal stent in the mid RCA with TIMI 2 flow (B, white arrow) with a moderate to severe focal lesion just before the 3.0×26 mm stent (B, black arrow). Following thrombus aspiration and restoration of TIMI 3 flow in the LAD, there was evidence of remaining thrombus (C, white arrow) in the LAD stent, which was clearly undersized in angiography and further disease after the stent (C, black arrow) with good “landing zone” (C, white asterisk). Deployment of 2 EES (4.0×22 mm proximally and 3.5×38 mm mid) in LAD with a good final angiographic (D) and IVUS result (white line, small picture). IVUS: intravascular ultrasound; LAD: left anterior descending.

with a thrombus aspiration device (Export Catheter, Medtronic) restoring TIMI 3 flow in the LAD. There was evidence of some remaining thrombus (Figure 1C, white arrow) in the LAD stent, which was clearly undersized in angiography and some further disease after the stent (Figure 1C, black arrow) with a good “landing zone” (Figure 1C, white asterisk). We proceeded with predilation of the LAD stent with a semi-compliant balloon 2.5×20 mm balloon (Sprinter Legend, Medtronic) and a 2.75×20 mm NC Quantum Apex (Boston Scientific), and we deployed 2 everolimus eluting stents (EES) (4.0×22 mm proximally and 3.5×38 mm mid, post-dilated with a 4.0×15 mm NC at 16 atm) with a good final angiographic result (Figure 1D) and resolution of the anterior ST elevation ECG changes. We performed an intravascular ultrasound (IVUS) study using the OptiCross™ (Boston Scientific) imaging catheter which confirmed good stent apposition and expansion (Figure 1D, white line). The procedure was covered with tirofiban bolus and 12 h intravenous infusion post-PCI due to the significant amount of thrombus found on both LAD and RCA. The patient remained pain-free and we brought him

electively for an IVUS-guided PCI deferred strategy of the RCA thrombotic lesion 2 weeks after the index event following oral anticoagulation with rivaroxaban 15 mg od and DAPT with aspirin 75 mg o.d. and ticagrelor 90 mg b.d.

A coronary angiogram demonstrated complete resolution of the RCA thrombus (Figure 2A). An IVUS study confirmed an eccentric plaque before the mid RCA stents with stent undersizing, and severe malapposition throughout the entire length of the RCA stents (Figure 2A, 1-3). Subsequently, we used a 3.25×15 mm and 3.5×15 mm NC balloons Quantum Apex (Boston Scientific) to post-dilate the undersized stent and a Magic Touch sirolimus(s) coated balloon 3.5×20 mm (Concept Medical) for the malapposed part and finally implanted a 4.0×22 mm EES post-dilated with a 4.0 NC at 16 atm of pressure to cover the lesion just before the previous mid RCA stents, giving an excellent final angiographic and IVUS result (Figure 2B, 4-6). The patient was discharged on aspirin 75mg od for 1 month, ticagrelor 90 mg b.d. for 12 months and rivaroxaban 15 mg o.d. lifelong.

VLST is a clinical manifestation that is of specific inter-

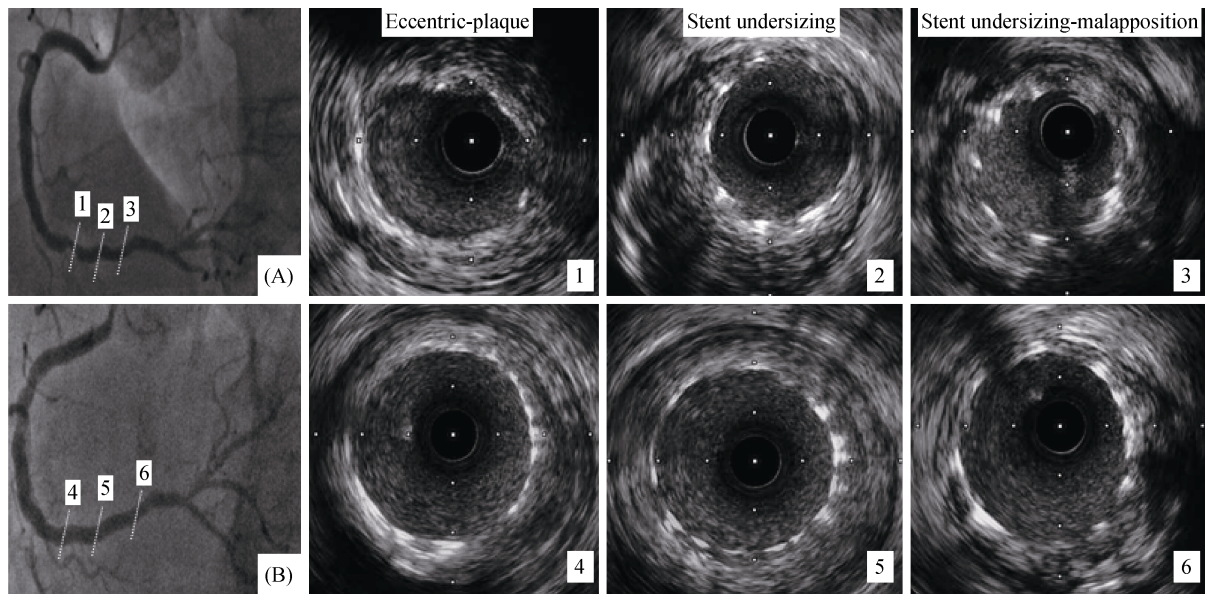


Figure 2. Complete resolution of the RCA thrombus (A). An IVUS study confirmed an eccentric plaque before the mid RCA stents (A1) with stent undersizing (A2), and severe malapposition throughout the entire length of the RCA stents (A3). Subsequently, we used a 3.25×15 mm and 3.5×15 mm NC balloons Quantum Apex to post-dilate the undersized stent (B5) and a Magic Touch sirolimus coated balloon 3.5×20 mm (B6) for the malapposed part and finally implanted a 4.0×22 mm EES to cover the lesion just before the previous mid RCA stents (B4), giving an excellent final angiographic and IVUS result (B, 4-6). EES: everolimus eluting stent; NC: non-compliant; RCA: right coronary artery; IVUS: intravascular ultrasound.

est because it represents a low but continued risk during long-term follow-up. The incidence rate per 100 person-years of early (0–30 days), late (31 days–1 year), and VLST amounted to 0.6, 0.1, and 0.6 among EES-treated patients; 1.0, 0.3, and 1.6 among SES-treated patients; and 1.3, 0.7, and 2.4 among PES-treated patients.^[8] The Resolute ZES was compared with the EES in two large-scale trials, which showed similar risks of cardiac death, MI, repeat revascularization, and ST throughout a 2-year period.^[17,18] Regarding the safety and efficacy of RO-ZES, RO-ZES showed 1-year target lesion failure (TLF) rate of 4.5% and similar efficacy and safety compared with most contemporary DES.^[19,20] RO-ZES demonstrated superiority for eight-month in-stent late lumen loss compared with the historical control R-ZES in the RESOLUTE ONYX core trial (0.24 ± 0.39 mm with O-ZES vs. 0.36 ± 0.52 mm with R-ZES, $P = 0.029$).^[20] Moreover, 2.0 mm RO-ZES was associated with a low rate of TLF and late lumen loss without definite/probable ST at 12-month follow up for treatment of coronary lesions with a very small reference vessel diameter, less than 2.25 mm in the recent study.^[21] Lastly, in the recent BIONYX trial, the incidence of definite-probable ST at 1 year was very low in the RO group (0.1%).^[22]

These favourable clinical and angiographic benefit regarding RO-ZES could be explained by its characteristics. RO-ZES has a swaged shape and a larger strut width-to-

thickness ratio (strut width 91 μ m and thickness 81 μ m) to maintain radial strength despite thinner strut when compared with R-ZES. RO-ZES also has a dense inner core composed of the platinum-iridium alloy for increased radiopacity. The enhanced radiopacity of RO-ZES might have contributed to less geographic miss which was associated with increased target vessel revascularization^[23] and could have facilitated the recognition of stents that were not well expanded or incompletely apposed to the arterial wall^[22].

The mechanism of VLST is not fully understood. Delayed endothelialisation and polymer induced inflammation,^[24] stent fracture,^[25] late stent malapposition, stent,^[26] incomplete neointimal coverage over stent struts, and neo-atherosclerotic plaque rupture^[15] may play a vital role in the progression of VLST. Taniwaki, *et al.*^[27] investigated 64 patients at the time point of VLST as part of an international optical coherence tomography (OCT) registry. A total of 38 early- and 20 newer-generation DES were suitable for analysis. VLST occurred at a median of 4.7 years (interquartile range, 3.1–7.5 years). The most frequent findings were strut malapposition (34.5%), neoatherosclerosis (27.6%), uncovered struts (12.1%), and stent underexpansion (6.9%). Uncovered and malapposed struts were more frequent in thrombosed compared with non-thrombosed regions [ratio of percentages(%), 8.26; 95% confidence interval (CI): 6.82–10.04; $P < 0.001$ and 13.03; 95% CI:

10.13–16.93; $P < 0.001$, respectively]. The maximal length of malapposed or uncovered struts (3.40 mm, 95% CI: 2.55–4.25; vs. 1.29 mm, 95% CI: 0.81–1.77; $P < 0.001$), but not the maximal or average axial malapposition distance, was greater in thrombosed compared with non-thrombosed segments. The associations of both uncovered and malapposed struts with thrombus were consistent among early- and newer-generation DES. The combination of multiple mechanisms of VLST within the same lesion was observed more frequently (55%) than the presence of a single cause (43%). Third, the longitudinal extension of malapposed and uncovered struts, but not the incomplete stent malapposition distance or area, was related to the occurrence of VSLT.^[27] Multiple mechanisms of VLST were also present in our extreme case.

Although the occurrence of VLST has been shown to decline with the use of new-generation DES compared with early-generation DES in large clinical studies and meta-analyses,^[28,29] the occurrence of the complication per se appears to be triggered by largely the same stent-related abnormalities as identified by OCT.^[27]

Reported cases of VLST occurring in second-generation DES in the literature are rare. Puri, et al.^[30] reported a case of simultaneous two-vessel VLST after EES implantation. IVUS showed stent malapposition with positive remodelling of the vessel wall. A previous study^[31] indicated that the incidence of late acquired peri-stent contrast staining with EES was lower than that with SES. Peri-stent contrast staining has been reported to be associated with VLST. Simultaneous VLST in two or three coronary vessels has also been documented.^[32-34] However, this case, to the best of our knowledge, is the first reported case of double simultaneous VLST occurring at the site of stents in LAD and RCA 16 months after RO-ZES implantation in a Caucasian patient. Stent undersizing, underexpansion and malapposition were identified by IVUS.

This case brings various issues to question. Since both stents became thrombosed, it is possible the precipitating factor may be systemic rather than lesion-related. In this case, the mechanisms of VLST most likely were a combination of mechanical factors (severe stent undersizing and malapposition during the index procedure) and systemic factors (atrial fibrillation). IVUS plays an important role in identifying mechanical factors related to stent thrombosis as well as guiding its therapy accordingly.

Acknowledgment

We declare that we have no conflict of interest.

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