

# Pathological assessment of very late bare metal stent thrombosis in the left main coronary artery: a case report

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## Background

Late catch-up phenomenon following stent implantation is a well-known complication. However, no report has evaluated thrombosis after 9 years with multi-modality and pathological evaluation.

## Case summary

A 71-year-old man with stable angina underwent elective percutaneous intervention of the left main coronary artery with implantation of a bare metal stent (BMS) 9 years ago. At the 9-year follow-up, coronary computed tomography (CCT) and coronary angiography (CAG) findings revealed a thrombus-like structure in the BMS slightly protruding into the sinus of Valsalva. Therefore, the previously prescribed double-antiplatelet therapy was replaced with an anticoagulant and clopidogrel, and a potent statin treatment was initiated. After the changes in drug treatment, follow-up examinations with CCT at 1 and 3 months suggested a decrease in the size of the thrombus; however, it appeared to increase after 6 months. Subsequently, the patient underwent surgical intervention. Pathological assessment of the explanted stent showed a proteoglycan-dominated extracellular matrix with few smooth muscle cells suggesting an organized thrombus.

## Discussion

It should be emphasized that multiple factors might be responsible for very late stent thrombosis, such as persistent strut chronic inflammation involving proteoglycans, stent protrusion, and poorly controlled type 2 diabetes mellitus, possibly further inducing inflammatory cells.

## Keywords

Case report • Very late stent thrombosis • Left main coronary artery • Pathology • Proteoglycan

## Learning points

- Thrombus formation inside a bare metal stent strut protruding from left main coronary artery ostium may occur as late as 9 years post-implantation.
- Very late stent thrombosis may occur due to mechanisms similar to acute stent thrombosis.

## Introduction

The later occurrence of restenosis ('late catch-up phenomenon') after bare metal stent (BMS) implantation is a well-known complication.<sup>1,2</sup> However, no published reports are available on very late thrombosis in the left main coronary artery (LMCA) of surviving patients with silent ischaemia. Herein, we report a rare case of very late thrombosis in the LMCA along with multiple modalities, including

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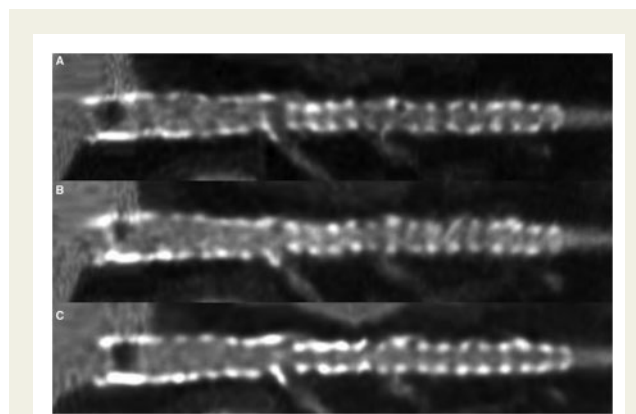
changes over time and pathological evaluation of surgically extracted the stent.

## Timeline

Date	Event
29 December 2008	Drug-eluting stent (3.5 mm × 23 mm Cypher <sup>®</sup> Cordis, Johnson & Johnson) implantation in the left main coronary artery (LMCA) to the left anterior descending artery for stable angina.
29 June 2009	Bare metal stent (4.0 mm × 8 mm Vision <sup>®</sup> Abbott Vascular) implantation in LMCA ostium for stable angina.
11 June 2014	Coronary angiography (CAG) was performed for routine follow-up purpose, and it did not reveal any significant in-stent thrombosis.
July 2018	Due to the positive result of exercise stress electrocardiogram test, coronary computed tomography (CCT), CAG, intravascular ultrasound, and optical coherence tomography were performed. These findings suggested stent thrombosis.
July 2018 to April 2019	Patient refused invasive therapy because he was asymptomatic. Therefore double-antiplatelet therapy was replaced with an anticoagulant and clopidogrel, and high-intensity statin and ezetimibe were conducted. In addition, intensified glycaemic control treatment was provided.
04 October 2018	CCT at 3 months after changing drugs suggested a decrease in the size of the thrombus.
28 February 2019	CCT at 6 months after changing drugs suggested re-growth of the thrombus.
01 April 2019	Surgical removal of the LMCA stent and coronary artery bypass grafting.

## Case presentation

A 71-year-old man with stable angina underwent elective percutaneous coronary intervention (PCI) of the LMCA with implantation of a BMS (4.0 mm × 8-mm Vision<sup>®</sup>), due to proximal restenosis of a drug-eluting stent (3.5 mm × 23-mm Cypher Stent) implanted (Figure 2A). Routine follow-up coronary angiography (CAG) after 5 years did not reveal any significant restenosis (Figure 2B). Coronary computed tomography (CCT) and CAG were performed at 9 years due to a positive exercise stress electrocardiogram test performed in the routine (Figures 2C, D and 3A, and Video 1). The patient had no abnormal findings on physical examination. He had no history of myocardial infarction but had a history of poorly controlled diabetes mellitus (DM) (haemoglobin A1c 8.7%) treated with oral medicine. Coronary computed tomography and CAG revealed a thrombus-like structure in the BMS slightly protruding into the sinus of Valsalva. Intravascular ultrasound (IVUS) and optical coherence tomography

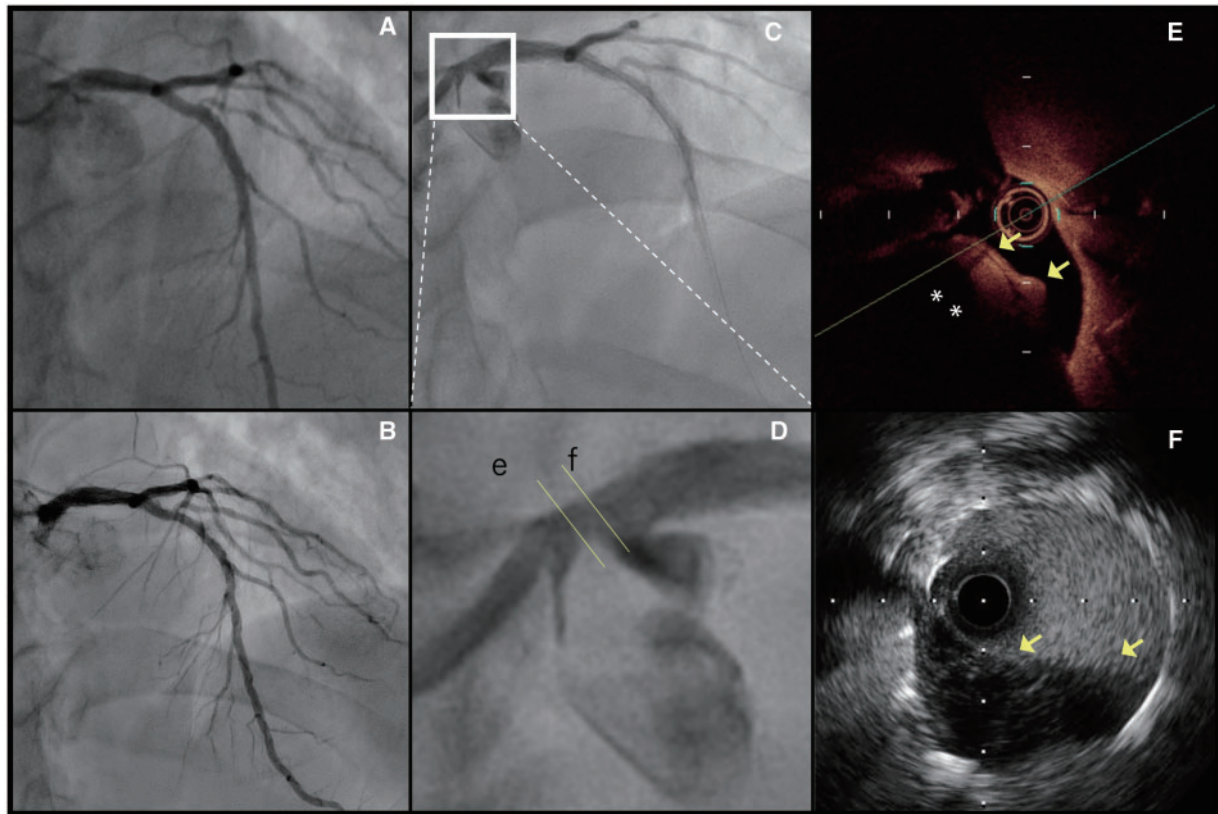


**Figure 1** Findings of pathological and macroscopic evaluations of the surgically removed stent. (A, B) Pathological examination surrounding the stent strut reveal a smooth muscle-rich neointimal tissue. Proteoglycan-rich extracellular matrix was observed on the luminal side. (C, D) Fibrinogen surrounding the stent struts suggest an organized thrombus. (E, F) Macroscopic evaluation of the surgically removed tissues involving the stent. (E) Long-axis direction and (F) transversal direction.

(OCT) revealed an arteriosclerotic lesion with an organized thrombus (Figure 2E and F, and Videos 2 and 3). Hence, our heart team recommended coronary artery bypass grafting (CABG) to avoid the risk of embolization during repeat PCI. However, the patient refused this procedure as he was asymptomatic. Therefore, the previously prescribed double-antiplatelet therapy was replaced with an anticoagulant (apixaban 10 mg/day) and clopidogrel, and the standard statin therapy was replaced with a combination of high-intensity statin and ezetimibe. In addition, intensive glycaemic control with additional drugs was provided. After a change in drug treatment, follow-up CCT examination at 3 months showed a decrease in thrombus size (Figure 3B). However, thrombus size appeared to increase after 6 months (Figure 3C). Echocardiography showed preserved left ventricular systolic function (LVEF = 65%) over time. Subsequently, surgical removal of the stent, LMCA ligation, and CABG including left internal mammary artery anastomosed to left anterior descending artery, saphenous venous graft anastomosed to obtuse marginal, and posterior lateral artery were performed. Pathological assessment of the extracted stent revealed a proteoglycan-rich extracellular matrix on the lumen side with few smooth muscle cells, indicating an organized thrombus (Figure 1A and B). The patient was asymptomatic to date, approximately 1 year after surgery.

## Discussion

Very late stent thrombosis (VLST) is an extremely rare phenomenon,<sup>2,3</sup> and it is even rarer with a BMS.<sup>1</sup> To the best of our knowledge, no study has assessed thrombosis at 9-year follow-up with multiple modalities and pathological examination. A previous study indicated that VLST after BMS implantation might be caused by thrombus formation after the rupture of a calcified atherosclerotic plaque.<sup>4,5</sup> However, we would like to emphasize that multiple factors



**Figure 2** Serial angiography findings and follow-up intravascular ultrasound and optical coherence tomography findings. (A) Angiography during percutaneous coronary intervention with stent implantation. (B) Angiography at 5-year follow-up showing no significant LMCA thrombosis. (C, D) Angiography at 9-year follow-up showing a significant thrombosis at the left main ostium. Angiographic diameter stenosis due to the thrombosis was about 50%. (E) optical coherence tomography examination of the LMCA thrombosis. A structure protruding inward in the stent was observed. It was observed as a high-intensity area (arrows) similar to a thrombus, attenuated, and a relatively signal-poor region (asterisks). Hence, the possibility of a mixed thrombus was considered. No exposed/malapposed stent struts were observed in the visible range. (F) IVUS examination of the LMCA thrombosis. An echolucent structure was observed inside the stent, which was consistent with the identification of a thrombus (arrows). IVUS, intravascular ultrasound; LMCA, left main coronary artery; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

such as peri-stent strut chronic inflammation involving proteoglycans,<sup>6,7</sup> stent strut protrusion,<sup>8</sup> and poorly controlled type 2 DM involving induction of inflammatory cells<sup>9</sup> might be responsible for VLST.

### Proteoglycans

Proteoglycan-rich tissue, observed as an echolucent zone on IVUS<sup>10</sup> and a relatively signal-poor region on OCT,<sup>11</sup> is observed in the vascular wound healing process, including thrombus absorption.<sup>12</sup> Its presence has been reported to be associated with early in-stent restenosis (ISR).<sup>6,7</sup> In our case, both intravascular imaging modalities suggested the presence of proteoglycans, which was confirmed by pathological examination. Therefore, we hypothesize that a process similar to early ISR, in which a thrombus is adhered and absorbed, occurred over the 9 years.

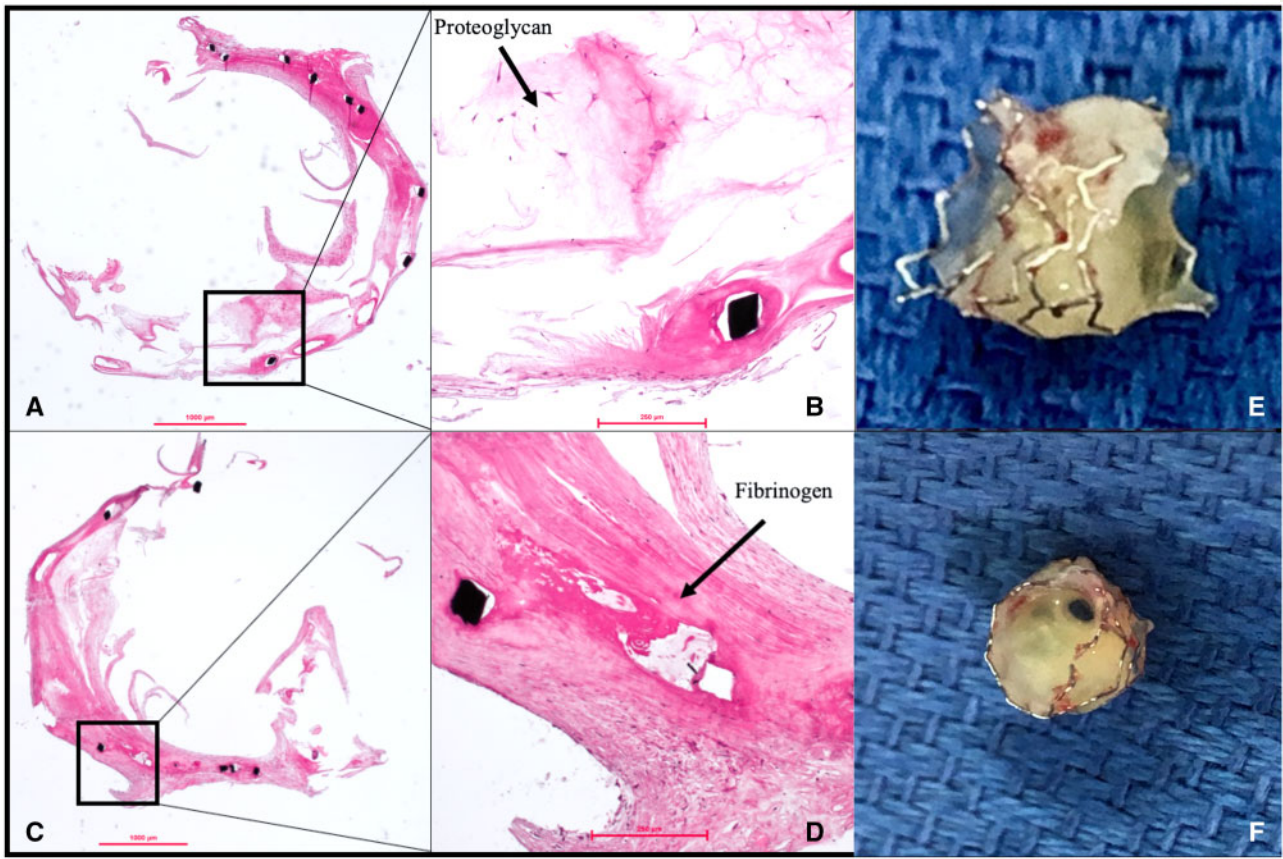
### Stent protrusion/malapposition

Stent strut malapposition and late-acquired stent malapposition have been suggested as probable aetiologies for VLST after BMS

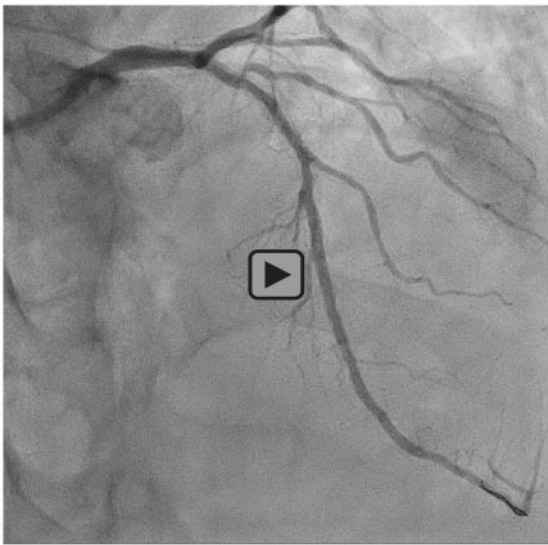
implantation.<sup>8</sup> A study reported that flow disturbance, especially the occurrence of non-streamlined flow along the malapposed stent struts, is relevant to stent thrombogenicity.<sup>13</sup> In our case, IVUS and OCT confirmed that the major portion of the thrombus was in the stent, protruding from the LMCA. The flow disturbance due to stent protrusion may have contributed to stent thrombosis in a manner similar to that due to malapposed stent strut.

### Poorly controlled diabetes mellitus

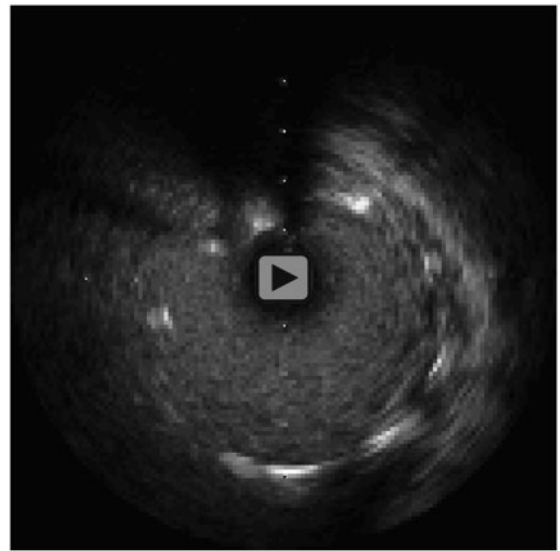
Core metabolic defects occurring in DM are impaired glucose tolerance, insulin resistance, and proinflammatory and prothrombotic states. These defects may lead to endothelial dysfunction and accelerated atherogenesis.<sup>9</sup> A study reported that high-mobility group box 1 (a thrombus-promoting factor) protein was more abundant in patients with type 2 DM than in patients without DM.<sup>14</sup> Other studies assessing the coronary atherectomy specimens of stenotic lesions from symptomatic patients with DM revealed that the total area percentage occupied by the thrombus was larger in specimens from patients with DM than in those without DM.<sup>15</sup> Therefore, patients



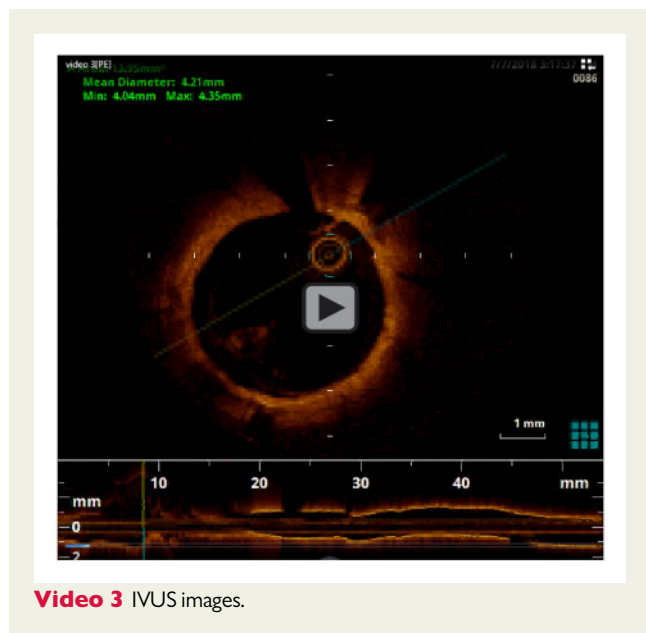
**Figure 3** Coronary computed tomography images of changes at treatment site over time. (A) Coronary computed tomography image just before the thrombosis was identified on coronary angiography. (B) Coronary computed tomography image at 3-month follow-up. The thrombus size decreased after treatment with an anticoagulant (apixaban 10 mg/day) and clopidogrel, a high dose of strong statin and ezetimibe, and DDP-4 and metformin hydrochloride. (C) Coronary computed tomography image at 6-month follow-up. Regrowth of the thrombus was observed after previous decrease in size. CCT, coronary computed tomography; CAG, coronary angiography.



**Video 1** Coronary angiography at 9 years after stent implantation.



**Video 2** OCT images.



**Video 3** IVUS images.

with poorly controlled DM, as in our case, may be more prone to thrombosis. Hence, morphological and functional evaluation follow-up should be considered in addition to risk control in such cases.

## Lead author biography



Dr Yuki is a medical doctor working in the cardiology field for two years now. I want to become a cardiologist with specific interest in imaging in cardiology.

## Supplementary material

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

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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## References

1. Windecker S, Meier B. Late coronary stent thrombosis. *Circulation* 2007;**116**:1952–1965.
2. Park DW, Hong MK, Mintz GS, Lee CW, Song JM, Han KH et al. Two-year follow-up of the quantitative angiographic and volumetric intravascular ultrasound analysis after nonpolymeric paclitaxel-eluting stent implantation late “catch-up” phenomenon from ASPECT study. *J Am Coll Cardiol* 2006;**48**:2432–2439.
3. Naganuma T, Fujino Y, Tahara S, Mitomo S, Basavarajiah S, Nakamura S. Extremely late catch-up phenomenon after first generation sirolimus-eluting stent in the left main stem: insights from optical coherence tomography. *JACC Cardiovasc Interv* 2015;**8**:e237–e239.
4. Rao KR, Reddy S, Kashyap R, Vikas K, Reddy H, Ramalingam V. Acute coronary syndrome after 17 years of bare metal stent implantation: “very” very late stent thrombosis. *Case Rep Cardiol* 2020;**2020**:1–5.
5. Yumoto K, Anzai T, Aoki H, Inoue A, Funada S, Nishiyama H et al. Calcified plaque rupture and very late stent thrombosis after bare-metal stent implantation. *Cardiovasc Interv and Ther* 2011;**26**:252–259.
6. Skälén K, Gustafsson M, Rydberg EK, Hultén LM, Wiklund O, Innerarity TL et al. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. *Nature* 2002;**417**:750–754.
7. Riessen R, Isner JM, Blessing E, Loushin C, Nikol S, Wight TN. Regional differences in the distribution of the proteoglycans biglycan and decorin in the extracellular matrix of atherosclerotic and restenotic human coronary arteries. *Am J Pathol* 1994;**144**:962–974.
8. Caixeta A, Braga VCSP, Mintz GS. Very late stent thrombosis with bare metal stent: identifying severe stent malapposition and underexpansion by intravascular ultra-sound. *Einstein (São Paulo)* 2013;**11**:364–366.
9. Nesto RW. Correlation between cardiovascular disease and diabetes mellitus: current concepts. *Am J Med* 2004;**116**:11–22S.
10. Goto K, Shiode N, Shirota K, Fukuda Y, Kitamura F, Tominaga K et al. Pathological finding of sirolimus-eluting stent (SES) restenosis lesion with black hole appearance on intravascular ultrasound. *Circ J* 2009;**73**:1969–1971.
11. Onuma Y, Serruys PW, Perkins LE, Okamura T, González-García HM et al. Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. *Circulation* 2010;**122**:2288–2300.
12. Kay IP, Ligthart JM, Virmani R, van Beusekom HM, Kozuma K, Carter AJ et al. The black hole: echolucent tissue observed following intracoronary radiation. *Int J Cardiovasc Intervent* 2003;**5**:137–142.
13. Koppa T, Cheng Q, Yahagi K, Mori H, Sanchez OD, Feygin J et al. Thrombogenicity and early vascular healing response in metallic biodegradable polymer-based and fully bioabsorbable drug-eluting stents. *Circ Cardiovasc Interv* 2015;**8**:e002427.
14. Yamashita A, Nishihira K, Matsuura Y, Ito T, Kawahara K, Hatakeyama K et al. Paucity of CD34-positive cells and increased expression of high-mobility group box 1 in coronary thrombus with type 2 diabetes mellitus. *Atherosclerosis* 2012;**224**:511–514.
15. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, Fuster V et al. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation* 2000;**102**:2180–2184.