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Five-year clinical outcomes and intracoronary imaging findings of the COMFORTABLE AMI trial: randomized comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction

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Aims The long-term outcomes of biolimus-eluting stents (BESs) with biodegradable polymer as compared with bare-metal stent (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) remain unknown.

Methods and results We performed a 5-year clinical follow-up of 1157 patients (BES: $N = 575$ and BMS: $N = 582$) included in the randomized COMFORTABLE AMI trial. Serial intracoronary imaging of stented segments using both intravascular ultrasound (IVUS) and optical coherence tomography performed at baseline and 13 months follow-up were analysed in 103 patients. At 5 years, BES reduced the risk of major adverse cardiac events [MACE; hazard ratio (HR) 0.56, 95% confidence interval (CI): 0.39–0.79, $P = 0.001$], driven by lower risks for target vessel-related reinfarction (HR 0.44, 95% CI: 0.22–0.87, $P = 0.02$) and ischaemia-driven target lesion revascularization (HR 0.41, 95% CI: 0.25–0.66, $P < 0.001$). Definite stent thrombosis (ST) was recorded in 2.2% and 3.9% (HR 0.57, 95% CI: 0.28–1.16, $P = 0.12$) with no differences in rates of very late definite ST (1.3% vs. 1.6%, $P = 0.77$). Optical coherence tomography showed no difference in the frequency of malapposed stent struts at follow-up (BES 0.08% vs. BMS 0.02%, $P = 0.10$). Uncovered stent struts were rarely observed but more frequent in BES (2.1% vs. 0.15%, $P < 0.001$). In the IVUS analysis, there was no positive remodelling in either group (external elastic membrane area change BES: -0.63 mm^2, 95% CI: -1.44 to 0.39 vs. BMS -1.11 mm^2, 95% CI: -2.27 to 0.04, $P = 0.07$).

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Conclusion Compared with BMS, the implantation of biodegradable polymer-coated BES resulted in a lower 5-year rate of MACE in patients with STEMI undergoing primary percutaneous coronary intervention. At 13 months, vascular healing in treated culprit lesions was almost complete irrespective of stent type.

Clinical Trial Registration http://www.clinicaltrials.gov. Unique identifier: NCT00962416.

Keywords ST-segment elevation myocardial infarction • Coronary artery disease • Drug-eluting stent • Restenosis • Stent • Stent thrombosis

Introduction

New-generation drug-eluting stents (DES) reduce the risk of target lesion revascularization (TLR) and stent thrombosis (ST) in stable lesions up to 5 years as compared with first-generation DES and bare-metal stent (BMS).[1–7] Improved clinical outcomes of new-generation DES have been reported in patients undergoing primary percutaneous coronary intervention (PCI) for treatment of the culprit lesion in the setting of acute ST-segment elevation myocardial infarction (STEMI) throughout 2 years of follow-up.[8–11] Recently, 5-year results of the EXAMINATION trial comparing durable polymer everolimus-eluting stent with BMS in patients with STEMI showed continued benefit of everolimus-eluting stent.[12]

Biolimus-eluting stent (BES) was designed as a stainless-steel stent platform with 120-µm thickness that coated with a biodegradable polymer (polylactic acid) on the abluminal surface providing controlled release of highly lipophilic sirolimus analogue of biolimus. In the exploratory analysis of the LEADERS trial, superiority of BESs with biodegradable polymer compared with first-generation sirolimus-eluting stents with regard to 5-year major adverse cardiac events (MACE) was more pronounced in patients presenting with STEMI ($P_{interaction}$ = 0.03).[2] The long-term effects of a DES with a biodegradable polymer as compared with BMS in STEMI patients after cessation of dual antiplatelet therapy (DAPT) has not been investigated in a large-scale randomized controlled trial to date.

A principal cause for ST occurring beyond the first year after stent implantation (i.e. very late ST) is delayed arterial healing in response to stent implantation,[13–17] an issue that is particularly pronounced in culprit lesions of patients with STEMI.[18] Biolimus-eluting stent has been designed with the objective to improve the arterial healing response by avoiding a permanent polymer beyond the period of controlled drug release. Whether these hypothetical benefits translate into improved arterial healing has not been previously investigated by intracoronary imaging in STEMI lesions *in vivo*.

We performed a clinical follow-up of patients included in the COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial[8,19] up to 5 years. In addition, in patients who were included in a nested imaging substudy, we performed and analysed serial intracoronary imaging of the stented segments with both optical coherence tomography (OCT) and intravascular ultrasound (IVUS).[20]

Methods

Patient population

The design and methods of this multicentre, randomized, assessor-blinded, superiority trial have been reported previously.[8,19] In brief, 1161 patients presenting with STEMI and undergoing primary PCI were randomly assigned to treatment with BES (N = 575) or BMS (N = 582) between 19 September 2009 and 25 January 2011 in 11 centres (*Figure 1*). The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent.

Clinical outcomes

Follow-up visits were scheduled at prespecified time intervals at 30 days and 1, 2 and 5 years. The results of clinical follow-up at 1 year and 2 years have been reported previously.[8,9] The prespecified primary endpoint was the composite of MACE including cardiac death, target vessel-related reinfarction, and ischaemia-driven TLR within 12 months. Detailed definitions of all primary and secondary endpoints were reported previously.[19] Data were stored in a central database (Cardiobase, Clinical Trials Unit and Department of Cardiology, Bern University Hospital, Switzerland and 2mT, Ulm, Germany), and independent study monitors verified source data to assess all the primary and secondary endpoints.[19]

Intracoronary imaging subgroup

A total of 103 patients were enrolled in the intracoronary imaging substudy at five predefined centres and were scheduled to undergo imaging at baseline (immediately following successful primary PCI) and 13 months using both IVUS and OCT. Patients qualified for imaging in case of the following criteria: haemodynamically stable, age <90 years, preserved renal function, TIMI flow ≥2 following primary PCI and anatomy suitable for imaging. Intravascular ultrasound and OCT recordings were stored on DVDs and were sent to an independent Core Laboratory (Cardialysis B.V., Rotterdam, The Netherlands) for analysis using a validated software (QIVUS, Medis, Leiden, The Netherlands).

Intravascular ultrasound

Intravascular ultrasound was performed using a 20-MHz ultrasound catheter (Eagle Eye, Volcano Cooperation, Rancho Cordova, CA, USA). The catheter was advanced at least 5 mm beyond the distal stent edge and a motorized pullback at a speed of 0.5 mm/s was performed after the administration of 200-µg intracoronary nitroglycerine. Images were acquired with 30 frames per second and recorded on a DVD. Intravascular ultrasound measurements from the stented, distal, and proximal regions measured at cross-sectional level (every 0.5 mm) were included in the analysis. For each cross-section, the lumen area, stent

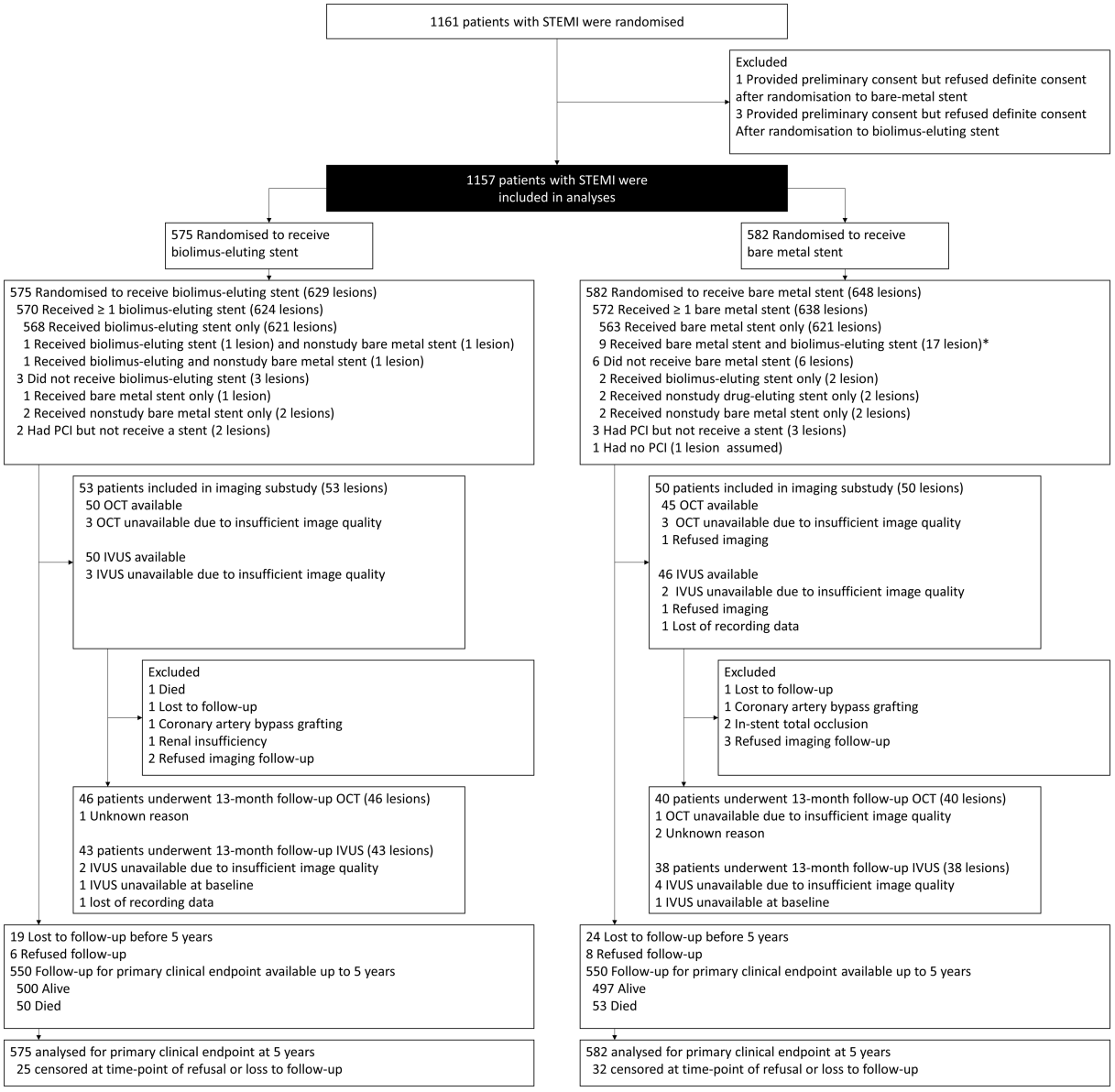

Figure 1 Study flowchart of COMFORTABLE AMI.

area, external elastic membrane area, and plaque and media area were measured. The plaque and media area was defined as external elastic membrane area - lumen area. Neointimal area was defined as stent area - lumen area, while negative values were set to 0.

Optical coherence tomography

Optical coherence tomography images were acquired with the Fourier-domain C7-XR imaging system using the Dragonfly^{TM} imaging catheter (St. Jude Medical, St. Paul, MN, USA) using a pullback speed of 20 mm/s immediately after primary PCI and at the 13-month follow-up. Optical coherence tomography was performed after the administration of 200-µg intracoronary nitroglycerine starting at least 5 mm distal to the stent and ending at least 5 mm proximal to the stent. Optical coherence tomography measurements from the stented region at lesion-level, cross-section-level (every 1 mm), and strut-level and were included in the analysis. Measurements from struts on side-branches and those from cross-sections, where the stent contour or the lumen contour was not available, were excluded. Uncovered struts were defined as struts with any part not covered by tissue. Malapposed struts were regarded as present, if distance from the endoluminal side of the strut and lumen contour was >0.130 mm for BMS, and >0.151 mm at baseline and >0.140 mm at follow-up for BES, considering absorption of the biodegradable polymer. Persistent malapposition was defined as malapposed struts at both baseline and follow-up; late-acquired malapposition was malapposed struts at follow-up, but not present at baseline; and resolved malapposition was those present only at baseline. Detailed methods for pairwise assessments of malapposition are described in Supplementary material online, Methods.

Table 1 Clinical outcomes at 5 years and between 1 year and 5 years

	Biolimus-eluting stent (*N* = 575)	Bare-metal stent (*N* = 582)	HR (95% CI)	*P*-value
At 5 years				
Major adverse cardiac events[a]	48 (8.6)	84 (14.9)	0.56 (0.39–0.79)	0.001
Death, any reinfarction, any revascularization	127 (22.6)	159 (28.1)	0.77 (0.61–0.98)	0.031
Death	50 (8.9)	53 (9.4)	0.94 (0.64–1.39)	0.772
Cardiac death	27 (4.9)	31 (5.5)	0.87 (0.52–1.47)	0.611
Reinfarction	37 (7.0)	54 (10.1)	0.68 (0.45–1.03)	0.069
Q-wave	9 (1.7)	15 (2.8)	0.60 (0.26–1.37)	0.227
Non Q-wave	29 (5.5)	42 (8.0)	0.68 (0.43–1.10)	0.115
Target vessel-related reinfarction	12 (2.2)	27 (5.0)	0.44 (0.22–0.87)	0.018
Q-wave	5 (0.9)	9 (1.6)	0.56 (0.19–1.66)	0.294
Non-Q-wave	7 (1.3)	19 (3.6)	0.37 (0.15–0.87)	0.023
Cardiac death or target vessel-related reinfarction	38 (6.9)	55 (9.8)	0.69 (0.45–1.04)	0.073
Any revascularization	80 (14.9)	110 (20.2)	0.70 (0.53–0.94)	0.017
Any target lesion revascularization	29 (5.4)	63 (11.4)	0.45 (0.29–0.69)	<0.001
Ischaemia-driven target lesion revascularization	24 (4.4)	57 (10.4)	0.41 (0.25–0.66)	<0.001
Any target vessel revascularization	41 (7.6)	71 (12.9)	0.56 (0.38–0.82)	0.003
Ischaemia-driven target vessel revascularization	35 (6.5)	62 (11.3)	0.55 (0.36–0.83)	0.005
Stroke	9 (1.7)	16 (3.1)	0.56 (0.25–1.27)	0.167
Transient ischaemic attack	2 (0.4)	7 (1.3)	0.28 (0.06–1.37)	0.117
Definite stent thrombosis	12 (2.2)	21 (3.9)	0.57 (0.28–1.16)	0.120
Definite or probable stent thrombosis	23 (4.1)	34 (6.2)	0.67 (0.40–1.14)	0.144
From 1 year to 5 years (landmark at 1 year)				
Major adverse cardiac events[a]	24 (4.6)	35 (6.9)	0.65 (0.39–1.09)	0.105
Death, any reinfarction, any revascularization	80 (15.7)	90 (18.3)	0.85 (0.63–1.14)	0.277
Death	32 (6.0)	30 (5.6)	1.06 (0.65–1.75)	0.811
Cardiac death	11 (2.1)	11 (2.1)	1.00 (0.43–2.30)	0.992
Reinfarction	26 (5.1)	33 (6.7)	0.77 (0.46–1.29)	0.330
Q-wave	7 (1.3)	8 (1.6)	0.87 (0.32–2.40)	0.790
Non Q-wave	20 (3.9)	28 (5.6)	0.70 (0.40–1.25)	0.226
Target vessel-related reinfarction	9 (1.7)	12 (2.4)	0.74 (0.31–1.75)	0.488
Q-wave	4 (0.7)	2 (0.4)	1.99 (0.36–10.86)	0.427
Non-Q-wave	5 (1.0)	11 (2.2)	0.45 (0.16–1.29)	0.136
Cardiac death or target vessel-related reinfarction	19 (3.6)	23 (4.5)	0.81 (0.44–1.49)	0.499
Any revascularization	53 (10.6)	61 (12.7)	0.83 (0.57–1.20)	0.313
Any target lesion revascularization	20 (3.8)	29 (5.8)	0.65 (0.37–1.15)	0.143
Ischaemia-driven target lesion revascularization	15 (2.9)	25 (5.0)	0.57 (0.30–1.08)	0.087
Any target vessel revascularization	30 (5.8)	34 (6.8)	0.84 (0.51–1.37)	0.481
Ischaemia-driven target vessel revascularization	24 (4.7)	27 (5.4)	0.85 (0.49–1.47)	0.560
Stroke	4 (0.8)	14 (2.7)	0.28 (0.09–0.86)	0.027
Transient ischaemic attack	1 (0.2)	4 (0.8)	0.25 (0.03–2.22)	0.212
Definite stent thrombosis	7 (1.3)	8 (1.6)	0.86 (0.31–2.38)	0.774
Definite or probable stent thrombosis	9 (1.7)	13 (2.6)	0.68 (0.29–1.59)	0.373

Depicted are numbers of first events (incidence rates % from Kaplan–Meier) and hazard ratios HR (95% confidence intervals) from Cox's regressions with *P*-values.
[a]Major adverse cardiac event: cardiac death, target vessel-related reinfarction, and ischaemia-driven target lesion revascularization.

Statistical analysis

Baseline and angiographic characteristics were compared using the χ^2, the Fisher's exact tests, or the *t*-tests. Cumulative incidences were estimated by the Kaplan–Meier method. Hazard ratios (HRs) and their 95% confidence interval (CI) comparing BES, and BMS were calculated using Cox proportional hazard models. Detailed statistical methods for intracoronary imaging are provided in Supplementary material online, Methods.

Statistical analyses were performed with Stata (StataCorp, College Station, TX, USA) and the computing environment R (R Foundation for Statistical Computing, Vienna, Austria) with packages nlme, lme4, and geepack. All statistical analyses were two-tailed. *P*-values <0.05 were considered statistically significant.

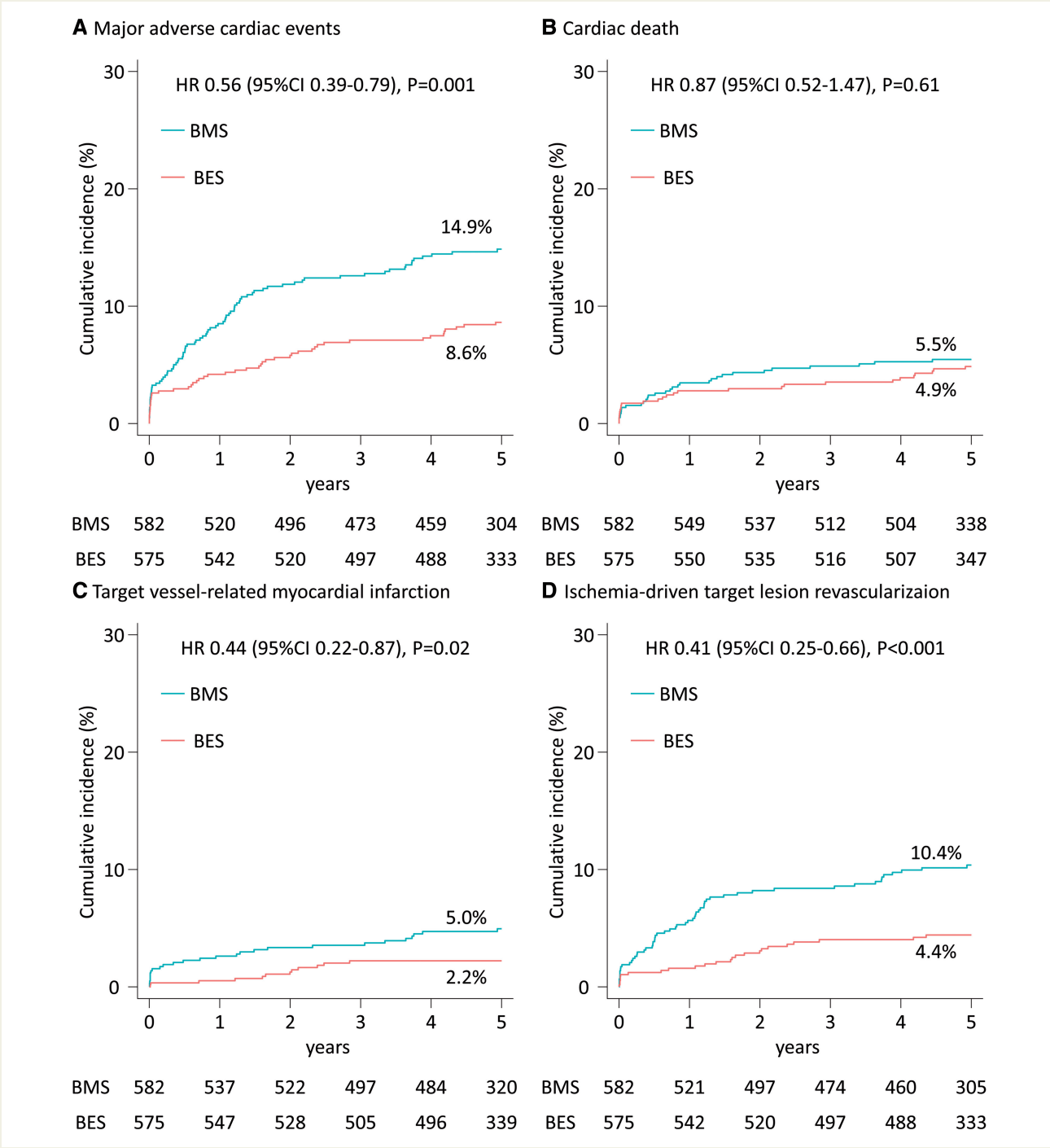

Figure 2 Cumulative incidence curves throughout 5 years for (*A*) major adverse cardiac events, (*B*) cardiac death, (*C*) target vessel-related myocardial infarction, and (*D*) ischaemia-driven target lesion revascularization. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; TLR, target lesion revascularization.

Results

Clinical outcomes

At 5 years, clinical follow-up information was obtained in 550 patients (95.7%) treated with BES and in 550 patients (94.5%) treated with BMS ($P = 0.42$) (*Figure 1*). Baseline clinical, procedural, and angiographic characteristics were similar for both groups (Supplementary material online, *Tables S1 and S2*). Cumulative cardiovascular event rates at 5 years and between 1 year and 5 years are summarized in *Table 1*. At 5 years, the primary endpoint of MACE occurred less frequently in BES (8.6%) as compared with BMS-treated patients (14.9%, HR 0.56, 95% CI 0.39–0.79, $P = 0.001$).

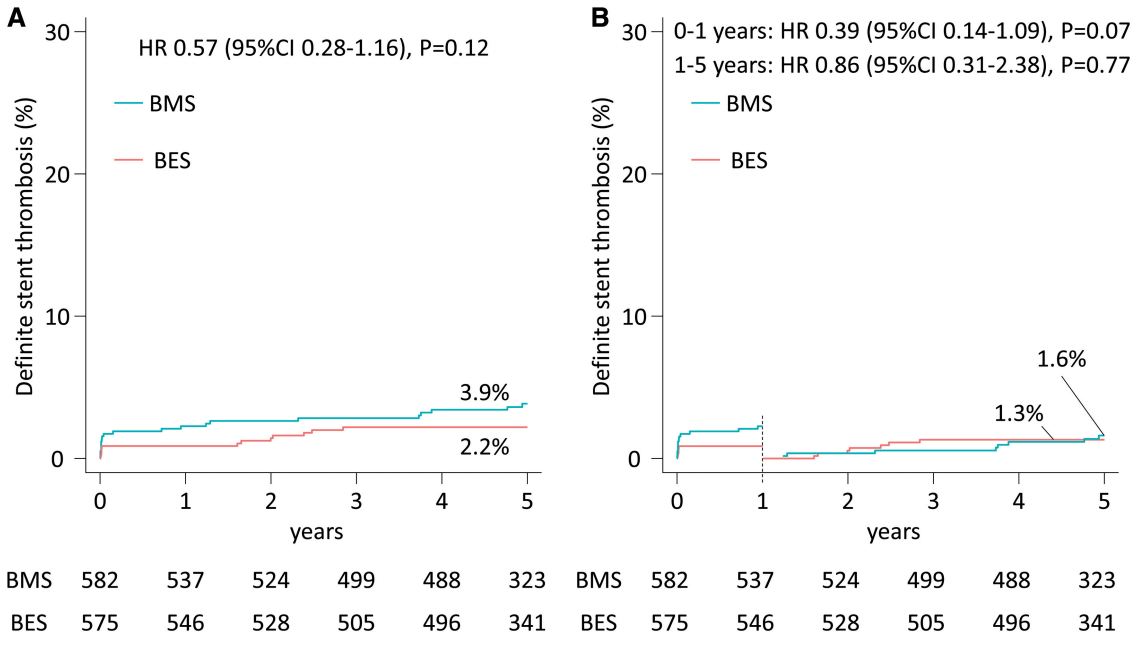

Figure 3 Cumulative incidence curves (*A*) throughout 5 years and (*B*) landmark analyses beyond 1 year and 5 years for definite stent thrombosis. CI, confidence interval; HR, hazard ratio.

Numerically fewer MACE were observed beyond the first year among patients allocated to BES without reaching statistical significance (BES 4.6% vs. 6.9%, HR 0.65, 95% CI 0.39–1.09, $P = 0.105$) (*Table 1*, *Figure 2A*). The *P*-value for interaction between the first and subsequent years of follow-up did not indicate a significant interaction by time ($P = 0.42$). While cumulative rates of cardiac death were similar for the BES and BMS groups throughout 5 years (HR 0.87, 95% CI 0.52–1.47, $P = 0.61$), the 5-year cumulative rates of target vessel-related myocardial infarction (HR 0.44, 95% CI 0.22–0.87, $P = 0.018$) and ischaemia-driven TLR (HR 0.41, 95% CI 0.25–0.66, $P < 0.001$) were significantly lower among patients allocated to BES as compared with those who had BMS implanted (*Figure 2B–D*). No significant difference in these endpoints was observed beyond the first year.

Dual antiplatelet therapy was prescribed in 90.4% of patients receiving BES and 87.3% of patients receiving BMS at 1 year ($P = 0.12$), while only few continued DAPT beyond 2 years (2 years: 17.5% vs. 17.6%, $P = 1.00$; 5 years: 6.8% vs. 6.9%, $P = 1.00$) (Supplementary material online, *Table S3*). The cumulative rate of definite ST tended to be lower in the BES compared with the BMS group at 1 year (HR 0.39, 95% CI 0.14–1.09, $P = 0.07$). Between 1 year and 5 years, no difference was observed for this endpoint (BES 1.3%, BMS 1.6%, HR 0.86, 95% CI 0.31–2.38, $P = 0.77$) (*Figure 3A* and *B*).

Intracoronary imaging outcomes

A total of 53 patients in the BES arm and 50 patients in the BMS arm were included in the prespecified imaging substudy. Patients included in the imaging substudy were younger, more likely male, more obese, and had a lower frequency of hypercholesterolaemia compared with those participating in the clinical follow-up protocol (Supplementary material online, *Table S4*). There were no significant differences in baseline clinical, lesion, and procedural characteristics, as well as in medication status between the two groups (Supplementary material online, *Tables S5–S7*).

Serial IVUS was performed at baseline and 13-month follow-up in 81 patients (43 in the BES arm and 38 in the BMS arm). Lumen area at follow-up was larger in BES as compared to BMS-treated patients (8.01 mm^2 vs. 6.70 mm^2, $P < 0.001$), in conjunction with smaller neointimal area (0.00 mm^2 vs. 1.39 mm^2, $P < 0.001$) (*Table 2*). The external elastic membrane area decreased in both groups [change BL to FUP in BES -0.63 mm (-1.44 to 0.39) vs. BMS -1.11 mm (-2.27 to 0.04, $P = 0.07$], indicative of the absence of positive remodelling in both treatment arms.

Optical coherence tomography was performed in 95 patients (BES $N = 50$ and BMS $N = 45$) at baseline and in 86 patients (BES $N = 46$ and BMS $N = 40$) at 13-month follow-up. Optical coherence tomography assessments are summarized in *Table 3*. Optical coherence tomography showed overall consistent results with IVUS in terms of larger lumen area and smaller neointimal area in lesions treated with BES as compared with BMS. Neointimal thickness (*Figure 4*) was lower in BES [65.8 µm (58.1–74.4)] as compared to BMS [243.9 µm (213.7–278.4), $P < 0.001$]. Malapposed struts were an infrequent finding at baseline in both groups (BES 2.6% vs. BMS 2.5%, $P = 0.87$), and most malapposed struts resolved at follow-up. Since late-acquired malapposition was infrequently observed in both arms, malapposed struts at 13-month follow-up were exceedingly rare (BES 0.08% vs. BMS 0.02%, $P = 0.10$). Uncovered struts at 13-month follow-up were rare but more frequently observed in BES (2.1%) as compared to BMS (0.15%, $P < 0.001$).

Table 2 Changes in intravascular ultrasound measurements from baseline to 13-month follow-up

	Biolimus-eluting stent (*N* = 43)	Bare-metal stent (*N* = 38)	*P*-value
Number of frames			
Baseline	59 (35.5–73)	52.5 (40.25–72.75)	0.74
Follow-up	48 (38–66.5)	52 (37.25–70.75)	0.43
Change	0 (-15 to 10), *P* = 0.24	-4.5 (-14 to 12.25), *P* = 0.51	0.87
Stent length (mm)			
Baseline	22.27 (16.07–27.67)	24.88 (18.57–28.92)	0.14
Follow-up	20.71 (17.89–26.88)	25.74 (17.4–32.26)	0.18
Change	1.05 (-1.04 to 2.36), *P* = 0.18	0.85 (-1.33 to 3.32), *P* = 0.24	0.89
External elastic membrane area (mm^2)			
Baseline	18.03 (16.55–22.33)	19.45 (14.62–24.16)	0.88
Follow-up	18.18 (15.85–22.33)	18.17 (14.34–21.76)	0.36
Change	-0.63 (-1.44 to 0.39), *P* = 0.049	-1.11 (-2.27 to 0.04), *P* < 0.001	0.07
Lumen area (mm^2)			
Baseline	8.21 (6.81–8.98)	7.67 (6.09–10.17)	0.65
Follow-up	8.01 (6.86–9.38)	6.07 (4.67–7.77)	<0.001
Change	0.1 (0–0.32), *P* = 0.003	-1.37 (-2.47 to -0.65), *P* < 0.001	<0.001
Stent area (mm^2)			
Baseline	8.21 (6.85–9.17)	7.75 (6.1–10.17)	0.55
Follow-up	8.07 (6.95–9.43)	7.8 (6.12–10.22)	0.49
Change	0.05 (-0.05 to 0.15), *P* = 0.08	0.06 (-0.16 to 0.21), *P* = 0.82	0.50
Plaque and media area (mm^2)			
Baseline	10.34 (9.18–12.81)	10.94 (8.33–13.88)	0.94
Follow-up	10.25 (8.76–12.58)	9.61 (7.46–12.23)	0.30
Change	-0.71 (-1.57 to 0.38), *P* = 0.03	-1.25 (-2.18 to -0.16), *P* < 0.001	0.08
Neointimal area (mm^2)			
Baseline	0.01 (0–0.06)	0.01 (0–0.05)	0.71
Follow-up	0 (0–0.03)	1.39 (0.86–2.28)	<0.001
Change	0 (-0.04 to 0.01), *P* = 0.157	1.34 (0.77–2.28), *P* < 0.001	<0.001

Area was normalized for length. Data were presented as median (25–75% quantiles). Paired IVUS imaging at baseline and 13-month follow-up were analysed.

Discussion

The long-term clinical follow-up of the COMFORTABLE AMI trial throughout 5 years and the nested serial imaging substudy resulted in the following salient findings:

(1) Biolimus-eluting stent significantly reduced the risk of MACE (HR 0.56, 95% CI 0.39–0.79, *P* = 0.001), mainly driven by lower risks for target vessel-related reinfarction (HR 0.44, 95% CI 0.22–0.87, *P* = 0.02), and ischaemia-driven TLR (HR 0.41, 95% C 0.25–0.66, *P* < 0.001) throughout 5 years.
(2) Very late definite ST (>1 year) rarely occurred without differences between BES and BMS (1.3% vs. 1.6%, *P* = 0.77).
(3) The clinical observation of improved efficacy observed in BES as compared to BMS patients is substantiated by less neointimal tissue at 13 months as assessed by both IVUS and OCT.
(4) The favourable safety profile of BES is paralleled by an almost complete arterial healing as evidenced by the absence of positive vessel remodelling and a low frequency of uncovered and malapposed stent struts at 13 months.

The benefits of BES in reducing the device-oriented primary endpoint was maintained throughout 5 years without attenuation and a number needed to treat of 24 to prevent one MACE. The improved outcome was driven by both a lower rate of target-vessel myocardial infarction (safety) and TLR (efficacy). Of note, there was no evidence of a delayed catch-up in event rates, but there were rather numerically fewer events in the BES group beyond the first year of follow-up. Similarly, the patient-oriented endpoint consisting of death, any myocardial infarction, and any revascularization was significantly reduced in favour of BES-treated patients. Although the study was not powered for safety endpoints, the observation of a numerically lower risk of ST at 1 year and similar event rates throughout the additional 4 years is relevant in view of previous concerns regarding the long-term safety of DES particularly among STEMI patients undergoing DES implantation of culprit lesions.

The concept of the investigated device is the resolution of the polymer beyond 9–12 months rendering the stent surface similar to a BMS. The clinical outcome data support this notion as no excess in adverse events potentially attributable to the polymer could be observed compared to the BMS group. Unlike the present investigation, the LEADERS trial compared BES against a first-generation sirolimus-eluting stent with a durable polymer in an all comers setting

Table 3 Optical coherence tomography measurements at baseline and 13-month follow-up

	Baseline			13-month follow-up		
	Biolimus-eluting stent	Bare-metal stent	*P* value	Biolimus-eluting stent	Bare-metal stent	*P*-value
Lesion level	***N* = 50**	***N* = 45**		***N* = 46**	***N* = 40**	
Lesion length (mm)	20.7 (18.2–23.3)	22.9 (20.2–25.6)	0.25	20.4 (17.6–23.3)	23.4 (20.3–26.4)	0.17
Minimal luminal area (mm^2)	7.28 (6.69–7.86)	6.98 (6.37–7.6)	0.49	7.01 (6.34–7.68)	3.74 (3.02–4.46)	<0.001
Minimal stent area (mm^2)	7.67 (7.07–8.27)	7.51 (6.88–8.14)	0.71	7.75 (7.06–8.43)	7.15 (6.42–7.88)	0.24
Stent volume (mm^3)[a]				173.34 (150.69–197.57)	190.17 (159.68–223.33)	0.40
Lumen volume (mm^3)[a]				160.37 (139.48–182.73)	128.64 (105.98–153.5)	0.06
Neointimal volume (mm^3)[a]				11.89 (9.32–14.76)	57.37 (45.85–70.17)	<0.001
Percent volume obstruction (%)[a]				6.73 (5.63–7.93)	30.45 (26.38–34.81)	<0.001
Cross-sectional level	***N* = 939**	***N* = 957**		***N* = 845**	***N* = 869**	
Number of frames per lesion	18.8 (16.4–21.2)	21.3 (18.7–23.8)	0.16	18.4 (15.9–20.8)	21.7 (19.1–24.3)	0.07
Neo-intimal area (mm^2)[b]				0.55 (0.47–0.65)	2.25 (1.9–2.66)	<0.001
Frames with any malapposition (%)	15.25 (11.06–20.66)	10.82 (7.53–15.31)	0.16	0.68 (0.27–1.68)	0.19 (0.04–0.78)	0.14
Mean malapposition area (mm^2)[b]	0.41 (0.33–0.51)	0.46 (0.36–0.59)	0.50	0.84 (0.42–1.65)	0.92 (0.31–2.77)	0.89
Luminal area (mm^2)[b]	8.57 (7.94–9.24)	8.30 (7.67–8.98)	0.57	8.17 (7.43–8.98)	5.39 (4.86–5.97)	<0.001
Stent area (mm^2)[b]	8.79 (8.15–9.49)	8.61 (7.94–9.32)	0.70	8.82 (8.14–9.56)	8.29 (7.6–9.03)	0.30
Strut level	***N* = 9504**	***N* = 10 114**		***N* = 8788**	***N* = 9495**	
Number of struts per lesion	190.1 (161.8–218.4)	224.8 (194.9–254.6)	0.10	191 (160.8–221.3)	237.4 (205–269.8)	0.04
Number of struts per frame	10 (9.5–10.5)	10.4 (9.8–10.9)	0.30	10.3 (9.8–10.8)	10.7 (10.2–11.3)	0.28
Uncovered struts (%)	85.727 (80.291–89.852)	74.221 (65.742–81.202)	0.01	2.064 (1.039–4.058)	0.146 (0.058–0.365)	<0.001
Malapposed struts (%)	2.663 (1.78–3.968)	2.534 (1.663–3.843)	0.87	0.076 (0.029–0.202)	0.017 (0.004–0.075)	0.10
Neointimal thickness (μm)[b]	54.48 (47.92–61.94)	51.81 (45.61–58.85)	0.59	65.75 (58.1–74.4)	243.92 (213.69–278.42)	<0.001
Malapposition distance (μm)[b]	231.47 (214.56–249.7)	221.88 (204.63–240.58)	0.46	338.88 (257.8–445.45)	404.9 (268.57–610.44)	0.49
Malapposed struts[c]	425	457	0.79	46	24	0.91
Resolved	387	434				
Persistent	38	23		38	23	
Late acquired				8	1	

Data were presented as mean (95% CI) or *n* (%).
[a]Square root transformed for analysis; all point estimators and CIs were back transformed to the original scale.
[b]Log transformed for analysis; all point estimators and CIs were back transformed to the original scale.
[c]OCT findings were analysed separately at baseline and follow-up, except that malapposed struts were analysed if both baseline and 13-month follow-up available.

and found a significantly lower rate of very late ST, suggesting a relevant role of the durable polymer in the induction of these events.[2]

While the LEADERS trial assessed all-comer patients with a limited proportion of STEMI patients, the only primary PCI trial investigating a new-generation DES vs. BMS was the EXAMINATION trial.[12] The results were comparable to our study showing improved patient and device-oriented cardiovascular outcomes. Thus, the EXAMINATION and COMFORTABLE AMI studies provide solid and consistent evidence indicating that new-generation DES do not only favourably impact long-term efficacy but also safety in the setting of STEMI patients undergoing primary PCI. Accordingly, the most recent European guidelines on STEMI recommend the use of DES over BMS.[21]

No previous study has investigated the *in vivo* arterial healing response of newer generation DES compared with BMS using serial intracoronary imaging in STEMI patients. Delayed arterial healing due to chronic vascular inflammation was identified as a hallmark of first-generation DES as compared to BMS and identified as one of the culprits for the increased risk of very late ST. Indicators of vascular inflammation can be detected *in vivo* by IVUS (i.e. positive remodelling) and OCT (i.e. uncovered stent struts, late acquired malapposition). In a previous intracoronary imaging sub-study of the HORIZONS-AMI trial (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), paclitaxel-eluting stents showed higher rates of uncovered and malapposed struts at 13-month follow-up, as assessed by OCT, and positive vessel wall remodelling as well as more frequent late acquired malapposition, as assessed by IVUS.[15] In the present intracoronary imaging sub-study, there were more uncovered stent struts in the BES group at 13 months follow-up (2.1% vs. 0.15%, $P < 0.001$). Notwithstanding, the absolute frequency of uncovered struts was reassuringly low indicating favourable healing when compared with the only DES data obtained in a comparable setting, i.e. the aforementioned primary PCI trial with reportedly 5.7% uncovered stent struts in the DES group.[15]

According to multiple recent OCT studies, malapposition is one of the predominant causes of very late ST.[16,22,23] In this study,

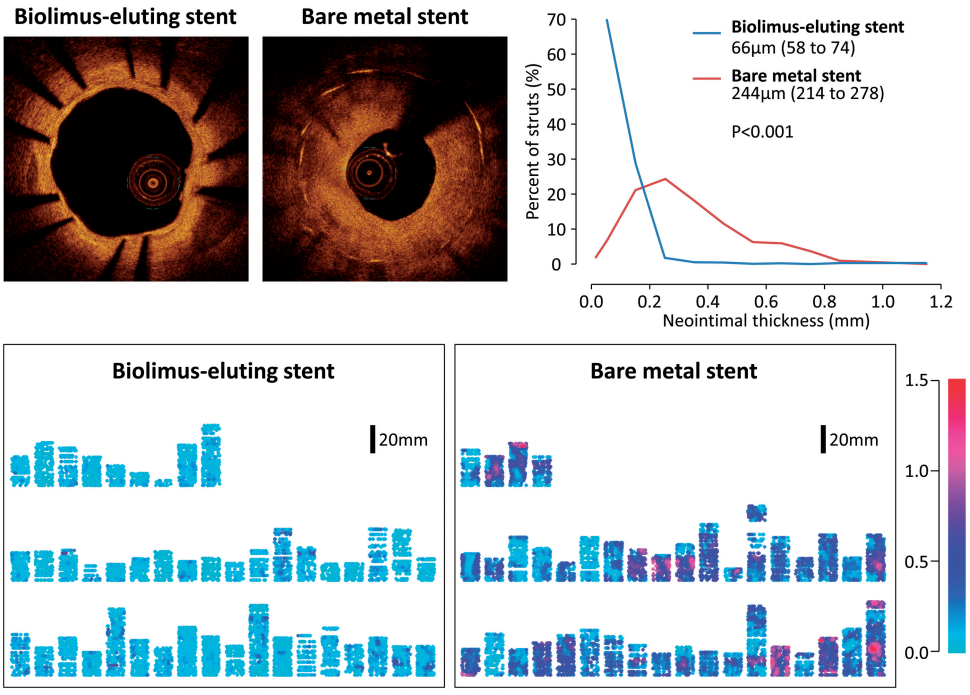

Figure 4 The primary endpoint of the imaging analysis neointimal thickness is demonstrated in this figure. The left panel shows two representative optical coherence tomography cross-sections of a biolimus-eluting stent (left) and bare-metal stent (right) treated lesion. The distribution of the neointimal thickness in biolimus-eluting stent, and bare-metal stent is shown in the histogram in the upper right panel. Geographical maps of all assessed lesions using colours to code the neointimal thickness (light blue, low neointimal thickness and red, high neointimal thickness). A more heterogeneous pattern is noted in the bare-metal stent group.

malapposed struts were rarely observed at 13 months (i.e. the time-point at which most patients have stopped DAPT) and the frequency was similar between BES and BMS. The similarity in malapposition is in part the consequence of a low number of struts developing late acquired malapposition in both stents (i.e. as a consequence of a vessel growth induced by inflammation). Consistent with this observation, the serial IVUS analysis demonstrated the absence of positive vessel remodelling in the BES group. Overall, the percentage of malapposed and uncovered struts in BES was lower than the 95% CI reported from a previous OCT analysis of very late ST cases.[16] This may explain the reassuringly low annual risks of very late ST (0.3%/year vs. 0.4%/year, $P = 0.77$) in a setting in which only few patients were on prolonged DAPT.

Study limitations

The results of the present study need to be interpreted in view of the following limitations. First, the study was an open label trial, while outcome assessors (e.g. angiography core-lab and clinical events committees) were blinded to the stent type implanted. Second, the study sample size was calculated estimating superiority for the overall composite endpoint of MACE, but was not powered to detect differences in individual safety or efficacy endpoints. Third, BES is currently less often used due to the availability of newer, thin-strut biodegradable polymer- and permanent polymer-DES. Fourth, according to the study protocol, intracoronary imaging was performed in ~10% of patients in five out of 11 study centres, suggesting that this substudy was performed in a selected group of patients.

Conclusions

Compared with BMS, the implantation of biodegradable polymer-coated BES resulted in a lower 5-year rate of MACE in patients with STEMI undergoing primary PCI, mainly driven by lower risks of target vessel-related reinfarction and ischaemia-driven TLR. Very late definite ST (>1 year) rarely occurred up to 5 years after BES and BMS implantation, which was in line with intracoronary imaging findings indicating almost complete vascular healing within 13 months.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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Acute coronary syndrome triggered by nitro-resistant triptan-induced coronary spasm

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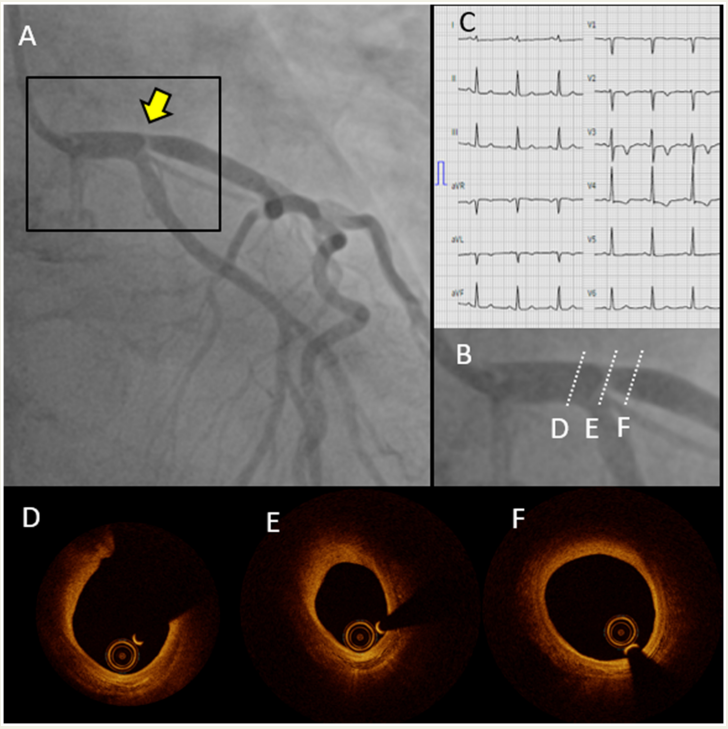
A 47-year-old woman was admitted with ongoing chest pain radiating to her left shoulder since 2 h. Prior to chest pain onset, she suffered from a migraine attack, which she treated for the first time with rizatriptan benzoate (20 mg). The electrocardiogram (*Panel C*) showed negative T waves in leads V2–4. Her risk factors were hyperlipidaemia (LDL-C: 210 mg/dL) and smoking. High-sensitive troponin T was elevated at 40 ng/L (ULN 14 ng/mL).



As the presentation was consistent with a non-ST-elevation myocardial infarction and emergent coronary angiography was performed. After intracoronary administration of 200 µg nitroglycerine, a hazy lesion in the ostial left anterior descending artery was found (*Panels A* and *B*), which persisted after an additional dose of 200 µg nitroglycerine, suggesting a plaque rupture. Intracoronary optical coherence tomography (OCT) was performed and allowed to rule out an atherosclerotic event (i.e. no thrombus or lumen disintegrity). Instead, a non-obstructive fibrous plaque with coronary spasm was found, suggesting the presence of a vasospastic angina induced by triptan intake and unresponsive to nitroglycerine (*Panels D–F*). As symptoms improved following calcium antagonist administration, the patient was discharged after 24 h on acetylsalicylic acid, statin and calcium antagonist, and she was advised to stop smoking. Without triptans, she remained free of symptoms and a treadmill test 6 months after the event was normal. This case illustrates that triptans can induce an acute coronary syndrome by coronary vasospasm and that these vasospasms may be irresponsive to nitroglycerine administration. The use of intracoronary OCT unravelled the underlying pathophysiology of the acute coronary syndrome and unnecessary stenting was avoided.