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Bioabsorbable polymer drug-eluting stents with 4-month dual antiplatelet therapy versus durable polymer drug-eluting stents with 12-month dual antiplatelet therapy in patients with left main coronary artery disease: the IDEAL-LM randomised trial

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KEYWORDS

- adjunctive pharmacotherapy
- drug-eluting stent
- intravascular ultrasound
- left main

Abstract

Background: Improvements in drug-eluting stent design have led to a reduced frequency of repeat revascularisation and new biodegradable polymer coatings may allow a shorter duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI).

Aims: The Improved Drug-Eluting stent for All-comers Left Main (IDEAL-LM) study aims to investigate long-term clinical outcomes after implantation of a biodegradable polymer platinum-chromium everolimus-eluting stent (BP-PtCr-EES) followed by 4 months DAPT compared to a durable polymer cobalt-chromium everolimus-eluting stent (DP-CoCr-EES) followed by 12 months DAPT in patients undergoing PCI of unprotected left main coronary artery (LMCA) disease.

Methods: This is a multicentre randomised clinical trial study in patients with an indication for coronary artery revascularisation who have been accepted for PCI for LMCA disease after Heart Team consultation. Patients were randomly assigned in a 1:1 ratio to receive either the BP-PtCr-EES or the DP-CoCr-EES. The primary endpoint was a non-inferiority comparison of the rate of major adverse cardiovascular events (MACE), defined as all-cause death, myocardial infarction, or ischaemia-driven target vessel revascularisation at 2 years.

Results: Between December 2014 and October 2016, 818 patients (410 BP-PtCr-EES and 408 DP-CoCr-EES) were enrolled at 29 centres in Europe. At 2 years, the primary endpoint of MACE occurred in 59 patients (14.6%) in the BP-PtCr-EES group and 45 patients (11.4%) in the DP-CoCr-EES group; 1-sided upper 95% confidence interval (CI) 7.18%; p=0.04 for non-inferiority; p=0.17 for superiority. The secondary endpoint event of BARC 3 or 5 bleeding occurred in 11 patients (2.7%) in the BP-PtCr-EES group and 2 patients (0.5%) in the DP-CoCr-EES group (p=0.02).

Conclusions: In patients undergoing PCI of LMCA disease, after two years of follow-up, the use of a BP-PtCr-EES with 4 months of DAPT was non-inferior to a DP-CoCr-EES with 12 months of DAPT with respect to the composite endpoint of all-cause death, myocardial infarction or ischaemia-driven target vessel revascularisation.

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Abbreviations

BARC	Bleeding Academic Research Consortium criteria
BP	biodegradable polymer
CoCr-EES	cobalt-chromium everolimus-eluting stent
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DOCE	device-oriented composite endpoint
DP	durable polymer
IDEAL-LM	Improved Drug-Eluting stent for All-comers Left Main
LMCA	left main coronary artery
MACE	major adverse cardiac events
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PtCr-EES	platinum-chromium everolimus-eluting stent
TLR	target lesion revascularisation
TVR	target vessel revascularisation

Introduction

Randomised clinical trials of surgical and percutaneous revascularisation in patients with significant stenosis of an unprotected left main coronary artery (LMCA) have shown that percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has comparable clinical outcomes to bypass surgery in terms of death, all myocardial infarction and stroke, but a higher rate of repeat revascularisation and non-periprocedural myocardial infarction[1-3]. As such, PCI is an acceptable alternative therapy for patients with LMCA disease, especially for those considered unsuitable for surgery due to advanced age or multiple comorbidities. Given the potentially catastrophic consequences of stent thrombosis in the LMCA, 12 months of dual antiplatelet therapy (DAPT) is reasonable. Biodegradable polymer (BP)-coated DES were developed to decrease the risk of durable polymer (DP)-related delayed vascular healing, potentially reducing the risk of stent thrombosis and allowing a shorter duration of DAPT[4,5]. Additionally, during PCI of LMCA disease, a large size discrepancy exists between the proximal and distal segments of the left main bifurcation and represents a potential substrate for strut malapposition. Therefore, the ability to over-expand a stent whilst maintaining radial strength is also an important consideration. A novel BP-coated platinum-chromium everolimus-eluting stent (BP-PtCr-EES) combines these features and may offer advantages for PCI in the LMCA[6,7]. To test this hypothesis, the Improved Drug-Eluting stent for All-comers Left Main (IDEAL-LM) study investigated clinical outcomes after BP-PtCr-EES implantation followed by only 4 months of DAPT compared to durable polymer cobalt-chromium everolimus-eluting stent (DP-CoCr-EES) implantation followed by 12 months of DAPT for treatment of unprotected LMCA disease.

Editorial, see page 1457

Methods

STUDY DESIGN AND PATIENT POPULATION

The IDEAL-LM study is an investigator-initiated, international, multicentre, open-label randomised clinical trial comparing two stent designs coupled with two different durations of DAPT for PCI in LMCA disease. Patients had an indication for revascularisation according to current guidelines (LMCA >90% diameter stenosis or >50% diameter stenosis with documented ischaemia)[8]. PCI should be the revascularisation method of choice after discussion with the Heart Team. Patients with chronic and acute coronary syndromes were enrolled, excluding those with ST-elevation myocardial infarction within the prior 5 days. The complete inclusion and exclusion criteria are listed in **Supplementary Table 1**. Patients were randomly assigned in a 1:1 ratio to undergo PCI with either a BP-PtCr-EES followed by 4 months of DAPT or a DP-CoCr-EES followed by 12 months of DAPT. The use of intravascular ultrasound to optimise stent deployment was strongly recommended. Details of the main study design have been published[9]. All patients provided written consent before any study-specific procedures. Randomisation was performed immediately before the index procedure using web-based software (e-DREAM system; Diagram B.V.) with random blocks according to centre. Clinical follow-up was performed at discharge, 3 months, 6 months, 1 year and then annually through to 5 years. There was a prespecified substudy in 100 patients at 5 sites to assess vascular healing after 3 months using optical coherence tomography (OCT).

The study was initiated by the principal investigators and the protocol developed in consultation with the statistical committee. Boston Scientific provided funding, reviewed the protocol and participated in site selection but were not involved in any other aspect of the conduct of the study. Site monitoring, database management and statistical analyses were performed by the independent organisations listed in **Supplementary Table 2**. The study was approved by local institutional review boards, it adheres to the principles of the Declaration of Helsinki and Good Clinical Practice, and was registered at ClinicalTrials.gov (NCT02303717) before inclusion of the first patient.

STUDY DEVICES

The BP-PtCr-EES (Synergy; Boston Scientific) has a platinum-chromium alloy platform with a strut thickness of 74-81 µm and a 4 µm thick coating on the abluminal side only of a biodegradable polymer (DL-lactide-coglycolide) which is hydrolysed to carbon dioxide and water over a period of 120 days. The polymer is mixed with an everolimus to give a dose equivalent of 1 µg/mm^2 and is released over a period of 90 days. The DP-CoCr-EES (XIENCE; Abbot Vascular) has a cobalt–chromium alloy platform with a strut thickness of 81 µm and an 8 µm thick durable polymer coating. The polymer is polyvinylidene fluoride hexafluoropropylene and is loaded with everolimus[10].

PROCEDURAL CHARACTERISTICS

PCI for LMCA was performed according to the standard procedures. For LMCA bifurcation lesions, provisional stenting with side branch opening was the preferred approach, but two-stent strategies, such as T and protrusion, culotte and crush were all acceptable. Any additional non-left main lesions undergoing PCI were to be treated with the same stent to which the patient

had been assigned at randomisation. If a staged procedure was planned, treatment of the non–target vessel should have been performed within 30 days, again using the same stent type as the study stent. All procedural complications and adverse events were recorded throughout the PCI procedure and the follow-up period. Cardiac biomarkers (CK-MB or troponin) were measured before and at least 4 hours post-procedure.

OBJECTIVES AND ENDPOINTS

The primary objective of the trial is to establish the non-inferiority of the BP-PtCr-EES group relative to the DP-CoCr-EES group for the composite primary endpoint of major adverse cardiac events (MACE), defined as all-cause death, myocardial infarction, and ischaemia-driven target vessel revascularisation (TVR) at 2 years. Secondary endpoints included individual components of the primary endpoint, a device-oriented composite endpoint (DOCE), defined as cardiac death, myocardial infarction not clearly attributable to a non-treated vessel and clinically-indicated target lesion revascularisation (TLR), stent thrombosis as per Academic Research Consortium criteria and bleeding as per Bleeding Academic Research Consortium criteria (BARC 1 to 5 and combined BARC 3 or 5)[11]. Procedural success was defined as attainment of a <30% diameter stenosis of the target lesion with no in-hospital DOCE. An independent Clinical Endpoint Committee adjudicated all study endpoints including bleeding events.

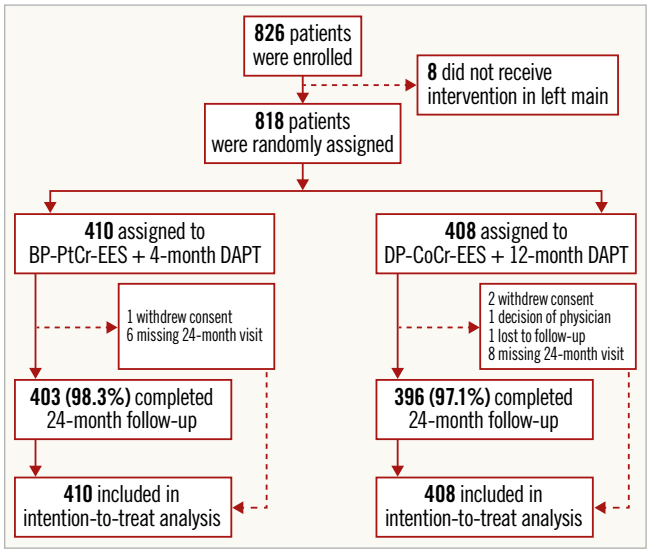
STATISTICAL ANALYSIS

The trial was powered to assess non-inferiority for the primary endpoint at 2 years post-procedure. Reviewing event rates from published data, the primary endpoint rates at 2 years for both treatment groups were predicted to be 20%[12,13]. Based on a prespecified absolute difference of 7.5% for the non-inferiority margin and a two-sided type I error of 0.05, a total of 818 patients provided 85% power. Non-inferiority would be shown if the upper limit of the 1-sided 95% confidence interval (CI) of the absolute risk difference was less than the non-inferiority margin of 7.5%. If non-inferiority was established, superiority testing would be performed, as well as calculation of 2-sided 95% CIs, both applied to the intention-to-treat population. Continuous variables are reported using descriptive statistics and compared using Wilcoxon's rank sum or Student's t-tests. Categorical variables are expressed as frequency (%) and compared using the likelihood-ratio chi-square or Fisher's exact tests. All statistical tests were interpreted at a 2-sided significance level of 0.05 and all CIs at a 2-sided level of 95% unless otherwise stated. Statistical analyses were performed by using SAS (version 9.4, SAS Institute Inc.).

Results

BASELINE PATIENT CHARACTERISTICS AND FOLLOW-UP

Between December 2014 and October 2016, 818 patients undergoing PCI for LMCA were randomly assigned to receive either BP-PtCr-EES (410 patients) or DP-CoCr-EES (408 patients). The study flow chart is presented in the **Central illustration**. Baseline



Central illustration. *Study profile. BP-PtCr-EES: biodegradable polymer platinum-chromium everolimus-eluting stent; DAPT: dual antiplatelet therapy; DP-CoCr-EES: durable polymer cobalt-chromium everolimus-eluting stent*

clinical characteristics were well balanced between the groups and are shown in **Table 1**. Participants were mainly male (79.6%), with a mean age of 66.4±10.3 years, 22.0% had diabetes, 33.1% had previous PCI and 40.5% presented with an acute coronary syndrome. All patients received at least a short term of DAPT post-procedure and, according to the protocol, a major shift in DAPT usage was in the period from 4 months to 12 months **(Supplementary Figure 1)**.

LESION AND PROCEDURAL CHARACTERISTICS

Lesion and procedural characteristics are summarised in **Table 2**. PCI for LMCA disease was performed in all patients. Isolated LMCA disease was present in 23.2% (95/410) of patients in the BP-PtCr-EES group and 25.5% (104/408) in the DP-CoCr-EES group. The SYNTAX score was 21.6±9.0 in the BP-PtCr-EES group and 20.9±9.1 in the DP-CoCr-EES group. Intravascular ultrasound was used in 39.5% and 42.2% of patients, respectively. Single-stent implantation was performed in the LMCA in 77.3% (317/410) and 81.8% (334/408) of patients in the BP-PtCr-EES and DP-CoCr-EES groups, respectively. Almost all patients (99.5%) received the assigned stent in the culprit lesion.

CLINICAL OUTCOMES

At 2 years, the primary endpoint of MACE occurred in 59 patients (14.6%) in the BP-PtCr-EES group and 45 patients (11.4%) in the DP-CoCr-EES group **(Table 3, Figure 1)**; 1-sided upper 95% CI 7.18%, p=0.04 for non-inferiority; p=0.17 for superiority. Rates of all-cause death (BP-PtCr-EES vs DP-CoCr-EES: 5.2% vs 5.3%; log-rank p=0.96), myocardial infarction (BP-PtCr-EES vs DP-CoCr-EES: 6.0% vs 3.5%; log-rank p=0.08) and ischaemia-driven TVR (BP-PtCr-EES vs DP-CoCr-EES: 7.4% vs 4.8%; log-rank p=0.15) did not significantly differ between groups through

Table 1. Patient baseline characteristics.

Characteristic	BP-PtCr-EES (n=410)	DP-CoCr-EES (n=408)	Total (n=818)
Patient measures			
Age (years)	66.8±10.2	66.0±10.5	66.4±10.3
Male	338/410 (82.4)	313/408 (76.7)	651/818 (79.6)
Body mass index (kg/m^2)	28.1±4.8	28.6±5.2	28.3±5.0
Current smoker	86/410 (21.0)	94/408 (23.0)	180/818 (22.0)
Diabetes mellitus	87/410 (21.2)	93/408 (22.8)	180/818 (22.0)
Hypertension	315/410 (76.8)	308/408 (75.5)	623/818 (76.2)
Hypercholesterolaemia	319/410 (77.8)	293/408 (71.8)	612/818 (74.8)
Family history of coronary artery disease	146/410 (35.6)	166/408 (40.7)	312/818 (38.1)
Previous ACS	163/409 (39.9)	155/407 (38.1)	318/816 (39.0)
Previous PCI	150/410 (36.6)	121/408 (29.7)	271/818 (33.1)
Previous CABG	29/410 (7.1)	29/408 (7.1)	58/818 (7.1)
Previous cerebrovascular accident	34/410 (8.3)	31/408 (7.6)	65/818 (8.0)
Clinical presentation			
Stable coronary artery disease	243/410 (59.3)	244/408 (59.8)	487/818 (59.5)
Acute coronary syndrome	167/410 (40.7)	164/408 (40.2)	331/818 (40.5)
Unstable angina	30/410 (7.3)	33/408 (8.1)	63/818 (7.7)
Non-ST-elevation MI	59/410 (14.4)	69/408 (16.9)	128/818 (15.7)
ST-elevation MI	78/410 (19.0)	62/408 (15.2)	140/818 (17.1)

Data are mean±SD or counts (percentage). ACS: acute coronary syndrome; BP-PtCr-EES: biodegradable polymer platinum-chromium everolimus-eluting stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DP-CoCr-EES: durable polymer cobalt-chromium everolimus-eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention

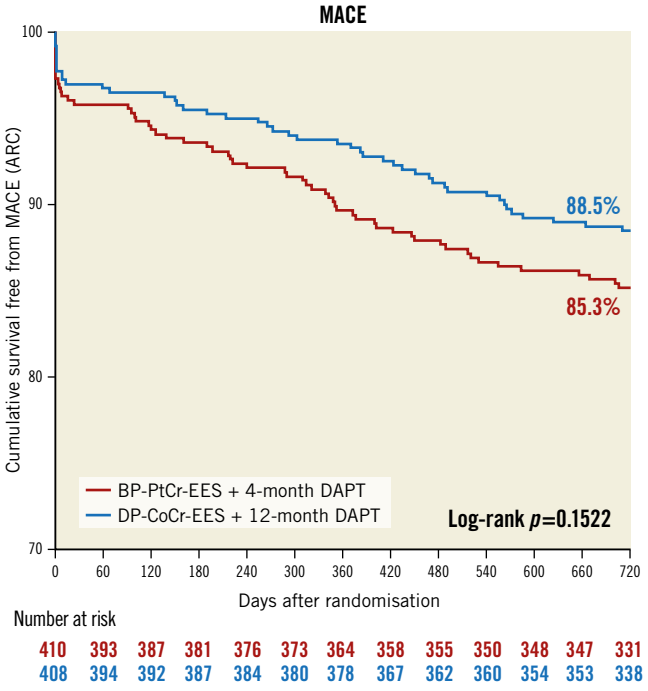


Figure 1. *Cumulative event-free survival plot for primary endpoint over 2 years of follow-up. ARC: Academic Research Consortium; BP-PtCr-EES: biodegradable polymer platinum-chromium everolimus-eluting stent; DAPT: dual antiplatelet therapy; DP-CoCr-EES: durable polymer cobalt-chromium everolimus-eluting stent; MACE: major adverse cardiovascular events*

2 years of follow-up. Rates of definite or probable stent thrombosis were not significantly different between groups (BP-PtCr-EES vs DP-CoCr-EES: 2.7% vs 1.3%; log-rank p=0.14). BARC 3 or 5 bleeding occurred in 11 (2.7%) patients assigned to the BP-PtCr-EES and 2 (0.5%) patients assigned to the DP-CoCr-EES (log-rank p=0.02) **(Table 3, Figure 2)**. Of the 11 events in the BP-PtCr-EES group, 7 occurred when the patients were off DAPT and 4 occurred in patients also taking oral anticoagulant therapy (2 on-DAPT and 2 off-DAPT). There was no evidence for any treatment-by-subgroup interaction with respect to MACE across all prespecified subgroups **(Figure 3)**. Landmark analyses up to 4 months, from 4 months to 1 year, and from 1 to 2 years showed no significant differences between groups with respect to MACE **(Supplementary Figure 2)**.

Discussion

In this all-comers, multicentre, single-blind, randomised clinical trial, LMCA PCI with BP-PtCr-EES followed by 4 months of DAPT was non-inferior to DP-CoCr-EES followed by 12 months of DAPT in terms of MACE at 2 years. No significant differences were documented in the individual components of the primary endpoint, but they all trended numerically higher in the BP-PtCr-EES with 4-month DAPT group than in the DP-CoCr-EES with 12-month DAPT group. The rates of definite and probable stent thrombosis were low and did not differ between groups. Counterintuitively, BARC 3 or 5 bleeding occurred more commonly in the short-duration DAPT group but the study was not powered to show

Table 2. Angiographic and procedural characteristics.

		BP-PtCr-EES (n=410)	DP-CoCr-EES (n=408)	*p*-value
PCI procedure performed		410/410 (100.0%)	408/408 (100.0%)	1.00
Access site	Radial	335/410 (81.7%)	334/408 (81.9%)	0.826
	Femoral	70/410 (17.1%)	69/408 (16.9%)	
	Brachial	5/410 (1.2%)	5/408 (1.2%)	
Number of diseased vessels	Left main only	95/410 (23.2%)	104/408 (25.5%)	0.469
	Left main+one vessel disease	171/410 (41.7%)	175/408 (42.9%)	
	Left main+two vessel disease	106/410 (25.9%)	87/408 (21.3%)	
	Left main+three vessel disease	38/410 (9.2%)	42/408 (10.3%)	
SYNTAX Score		21.6±9.0	20.9±9.1	0.310
Predilatation performed		301/410 (73.4%)	303/408 (74.3%)	0.811
Post-dilatation performed		363/410 (88.5%)	361/408 (88.5%)	1.00
Largest balloon size		4.3±0.6	4.2±0.6	0.351
Maximum pressure used (atm)		17.0±3.6	16.8±3.8	0.660
Number of stents used		1.3±0.6	1.2±0.5	0.148
Number of stents used in the left main	1	317/410 (77.3%)	334/408 (81.8%)	0.346
	2	76/410 (18.5%)	59/408 (14.5%)	
Number of stents used outside left main		1.2±0.6	1.1±0.5	0.1319
IVUS performed post-procedure		162/410 (39.5%)	172/408 (42.2%)	0.476
MSA >8.5 mm^2 in carina		154/158 (97.5%)	165/169 (97.6%)	1.00
MSA >5.5 mm^2 in both the ostium of LAD and LCx		150/158 (94.9%)	156/168 (92.9%)	0.494
Procedure success		410/410 (100.0%)	407/408 (99.7%)	1.00
IABP support		2/410 (0.5%)	2/408 (0.5%)	0.895
DAPT at discharge	Clopidogrel	259/410 (63.2%)	263/407 (64.6%)	
	Ticagrelor	52/410 (12.7%)	60/407 (14.7%)	
	Prasugrel	28/410 (6.8%)	29/407 (7.1%)	
Monotherapy (±[N]OAC)		69/410 (16.8%)	53/407 (13.0%)	
OAC		21/410 (5.1%)	27/408 (6.6%)	

Data are mean±SD or counts (percentage). BP-PtCr-EES: biodegradable polymer platinum-chromium everolimus-eluting stent; DAPT: dual antiplatelet therapy; DP-CoCr-EES: durable polymer cobalt-chromium everolimus-eluting stent; IABP: intra-aortic balloon counterpulsation; IVUS: intravascular ultrasound; LAD: left anterior descending artery; LCx: left circumflex artery; MSA: minimal stent area; (N)OAC: (novel) oral anticoagulants; PCI: percutaneous coronary intervention

a difference in bleeding events and so this could be the play of chance. Moreover, all 4 patients who experienced BARC 3-5 bleeding whilst taking an oral anticoagulant were in the BP-PtCr-EES group.

The specific design of the BP-PtCr-EES platform, as well as the polymer degradation kinetics, has been reported to provide favourable vascular healing in non-LMCA lesions, with rates of strut coverage and apposition at 3 months of 94.5% and 93.8%, respectively[14]. In the TRANSFORM-OCT (TRiple Assessment of Neointima Stent FOrmation to Reabsorbable polyMer With Optical Coherence Tomography) study, BP-PtCr-EES and DP-zotarolimus-eluting stents showed a similar healing response at 3 months[15]. The OCT substudy of the IDEAL-LM study showed similar and near complete vascular healing with both stents 3 months after implantation, with a strut coverage >20 µm for over 96% of the individual struts[16]. These findings support the view that the biodegradable and durable polymers utilised in contemporary DES are associated with favourable vascular healing, even in LMCA disease. Nevertheless, little is known about the efficacy and safety of a short duration of DAPT after PCI with contemporary DES in LMCA. Current guidelines from the ACC/AHA recommend at least 6-12 months of DAPT in patients undergoing PCI with DES[17]. The European Society of Cardiology Guidelines recommend a 3-month period of DAPT in patients at high bleeding risk (e.g., PRECISE-DAPT score ≥25) undergoing PCI for stable coronary artery disease[18]. The European Bifurcation Club recently consulted worldwide opinion leaders for a detailed DAPT strategy proposal involving bleeding risk, patient characteristics and procedural characteristics, such as imaging guidance and bifurcation approach[19].

Recently, several large-scale randomised trials investigated the efficacy and safety of a short duration of DAPT (1 to 3 months) after PCI in specific study populations (e.g., all-comers, elderly, or high risk for bleeding or an ischaemic event)[20-22]. Overall, a short duration of DAPT after PCI did not increase the incidence of ischaemic events and may reduce the risk of bleeding events. Nevertheless, it

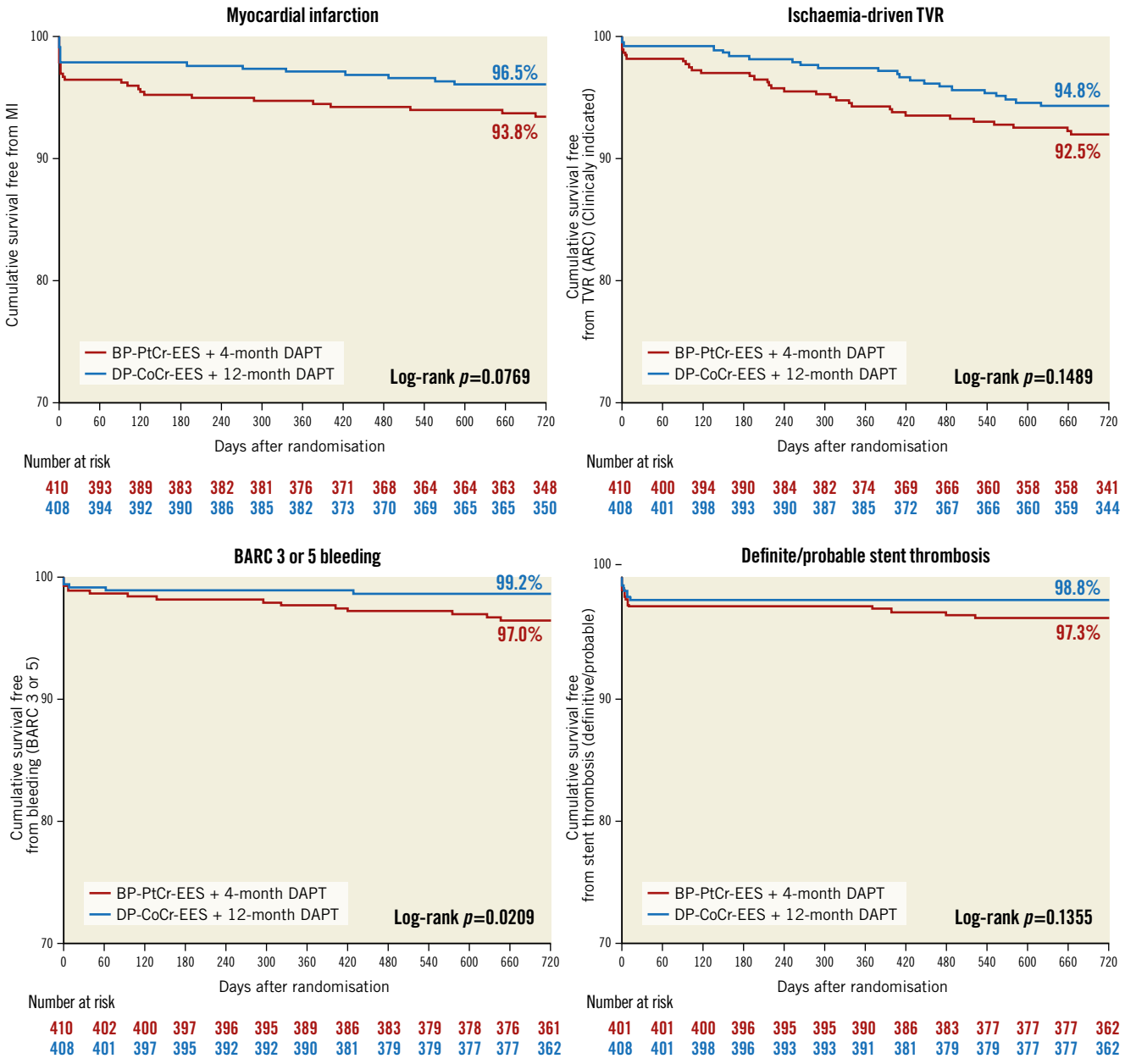


Figure 2. *Cumulative event-free survival plot for secondary endpoint over 2 years of follow-up. ARC: Academic Research Consortium; BARC: Bleeding Academic Research Consortium; BP-PtCr-EES: biodegradable polymer platinum-chromium everolimus-eluting stent; DAPT: dual antiplatelet therapy; DP-CoCr-EES: durable polymer cobalt-chromium everolimus-eluting stent; MACE: major adverse cardiovascular events; MI: myocardial infarction; TVR: target vessel revascularisation*

is noteworthy that only a small proportion of patients (from 1.8% to 8.2%) with LMCA disease were included in the aforementioned studies. Although no significant differences were observed in the ischaemic endpoints in IDEAL-LM, they all trended numerically higher in the BP-PtCr-EES/short DAPT group and bleeding was not reduced. Accordingly, the risks and benefits of a short duration of DAPT after PCI for LMCA disease need to be further investigated, taking into account the personalised risk of bleeding and ischaemic events.

In the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, PCI with the same DP-CoCr-EES used in IDEAL-LM, coupled with a minimum of 12 months of DAPT, was non-inferior to CABG at 5 years with respect to a composite endpoint of all-cause death, stroke, or myocardial infarction[2]. The SYNTAX scores and the incidence of diabetes were similar in EXCEL to the patient population in IDEAL-LM. Continuation of DAPT beyond 1 year in EXCEL did not reduce the rate of death, myocardial infarction or stroke[23].

In a patient-level pooled analysis of five multicentre registries including 700 patients treated for LMCA disease, the rate of target

Table 3. Clinical outcomes at 2 years after stent implantation.

	BP-PtCr-EES (n=410)	DP-CoCr-EES (n=408)	Risk difference (95% CI)	*p*-value
Primary outcome				
MACE*	14.6% (59/403)	11.4% (45/396)	3.28 (–1.38-7.93)	0.1734
Separate endpoints for the primary outcomes				
All-cause death	5.2% (21/403)	5.3% (21/396)	–0.09 (–3.19-3)	1.0000
All MI	6.0% (24/403)	3.5% (14/396)	2.42 (–0.52-5.36)	0.1343
Ischaemia-driven TVR	7.4% (30/403)	4.8% (19/396)	2.65 (–0.67-5.96)	0.1404
Secondary outcomes				
DOCE**	11.9% (48/403)	9.6% (38/396)	2.31 (–1.98-6.61)	0.3060
Cardiac death	3.7% (15/403)	3.5% (14/396)	0.19 (–2.41-2.78)	1.0000
Periprocedural MI	2.2% (9/403)	1.8% (7/396)	0.47 (–1.47-2.41)	0.8017
Spontaneous MI	4.0% (16/403)	1.8% (7/396)	2.2 (–0.1-4.51)	0.0887
Ischaemia-driven TLR	6.0% (24/403)	4.6% (18/396)	1.41 (–1.68-4.5)	0.4291
Left main+5 mm	5.7% (23/403)	3.3% (13/396)	2.42 (–0.44-5.29)	0.1243
Thrombosis endpoints				
Definite or probable stent thrombosis	2.7% (11/403)	1.3% (5/396)	1.47 (–0.47-3.4)	0.2058
Acute (≤24 hours)	0.5% (2/403)	0.3% (1/396)	0.24 (–0.6-1.09)	1.0000
Subacute (>24 hours to 30 days)	1.2% (5/403)	1.0% (4/396)	0.23 (–1.23-1.69)	1.0000
Late (30 days to 1 year)	0.0% (0/403)	0.0% (0/396)	–	–
Very late (>1 year)	0.99% (4/403)	0.0% (0/396)	0.99 (0.02-1.96)	0.1241
Bleeding endpoints				
BARC 2	1.2% (5/403)	0.3% (1/396)	0.99 (–0.2-2.18)	0.2171
BARC 3	2.2% (9/403)	0.5% (2/396)	1.73 (0.13-3.33)	0.0637
3a	1.2% (5/403)	0.3% (1/396)	0.99 (–0.2-2.18)	0.2171
3b	0.5% (2/403)	0.3% (1/396)	0.24 (–0.6-1.09)	1.0000
3c	0.5% (2/403)	0.0% (0/396)	0.50 (–0.19-1.18)	0.4994
BARC 5	0.7% (3/403)	0.0% (0/396)	0.74 (–0.09-1.58)	0.2491
5a	0.3% (1/403)	0.0% (0/396)	0.25 (–0.24-0.73)	1.0000
5b	0.5% (2/403)	0.0% (0/396)	0.5 (–0.19-1.18)	0.4994
BARC 3 or 5 bleeding	2.7% (11/403)	0.5% (2/396)	2.22 (0.49-3.96)	0.0215

Data are percentage (counts). *All-cause death, myocardial infarction or ischaemia-driven TVR. **Cardiac death, target vessel myocardial infarction, or ischaemia-driven TLR. BARC: Bleeding Academic Research Consortium criteria; BP-PtCr-EES: biodegradable polymer platinum-chromium everolimus-eluting stent; CI: confidence interval; DP-CoCr-EES: durable polymer cobalt-chromium everolimus-eluting stent; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation

lesion failure in patients treated with two-stent techniques was significantly higher than in the one-stent group only when DAPT was interrupted before 1 year[24]. In IDEAL-LM, approximately 80% of patients underwent LMCA-PCI using a single-stent technique and we did not see an interaction between treatment with one or more stents and randomised treatment allocation.

Study limitations

Firstly, the observed rates of the primary endpoint were lower than predicted, with the difference being due to lower rates of all-cause death and ischaemia-driven TVR than in previous studies[12,13,25-27]. As a specific example, all-cause death at two years was 5.0% in IDEAL-LM, compared to 10.0% in the ISAR-LEFT-MAIN study[28]. Generally, of course, this is good news for patients undergoing LMCA-PCI, but it means that the result of IDEAL-LM is not particularly robust. The predicted event rate of 20% in both groups coupled with an absolute non-inferiority margin of 7.5% yield a relative non-inferiority margin of 7.5/20=0.375. This is similar to the EXCEL trial in which the predicted event rates were 11% in both groups (excluding repeat revascularisation) with a non-inferiority margin of 4.2%, yielding a relative non-inferiority margin of 4.2/11=0.38. If we apply this to the observed event rates in IDEAL-LM, the equivalent absolute non-inferiority margin would be 4.3% and non-inferiority would not be confirmed. Alternatively, and retrospectively, one can state that due to the lower-than-predicted event rates, the trial is now underpowered, though potentially the original power of 85% could be recovered during ongoing follow-up. Given the methodological limitations of the study, and the numerically higher number of events

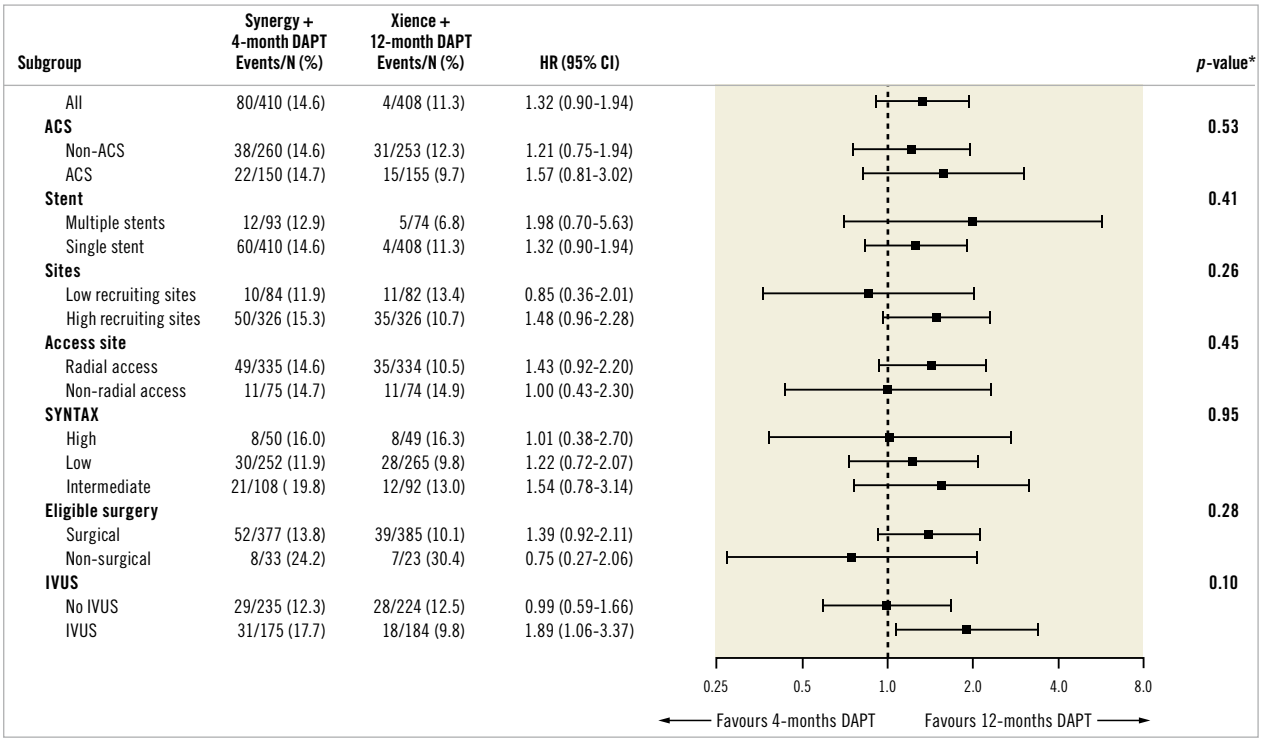


Figure 3. *Stratified analyses of the primary endpoint at 2 years across subgroups. * p-value is the test of interaction between treatment and subgroup, unadjusted for multiplicity. ACS: acute coronary syndrome; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IVUS: intravascular ultrasound*

in the BP-PtCr-EES followed by 4-month DAPT group, a larger dataset is required to evaluate this potentially concerning signal.

Secondly, the IDEAL-LM study was designed to compare two therapeutic strategies for LMCA-PCI. The duration of DAPT was coupled to and determined by the randomly assigned stent type but we acknowledge that this may hinder the interpretation of any between-group differences in outcomes. Finally, the majority of patients were treated using one-stent techniques and therefore more data are required for a more robust recommendation on DAPT duration for patients treated with two-stent strategies.

Conclusions

PCI with the BP-PtCr-EES followed by 4 months of DAPT was non-inferior to the DP-CoCr-EES followed by 12 months of DAPT with respect to MACE at 2 years in an all-comers population with LMCA disease. However, due to event rates that were lower than predicted, the trial is underpowered and the individual components of MACE all trend numerically higher in the BP-PtCr-EES with 4-month DAPT group. The findings of this trial should be interpreted only as hypothesis generating. The efficacy and safety of a short duration of DAPT after LMCA PCI requires further investigation and future studies should focus on the individual patient risk for bleeding and ischaemic events.

DATA SHARING

All data, including study participant data, data dictionary, statistical analysis plan, and informed consent, will not be shared.

Impact on daily practice

PCI for left main disease is frequently a primary strategy due to relative contraindications for bypass surgery. Stent design iterations intend to improve outcomes and minimise antiplatelet therapy for these patients where comorbidity is frequently present. This study demonstrated that a strategy of using a biodegradable polymer-coated platinum-chromium everolimus-eluting stent followed by four months of dual antiplatelet therapy was non-inferior to a strategy with a durable polymer-coated cobalt-chromium everolimus-eluting stent followed by 12 months dual antiplatelet therapy. Superiority in bleeding events was not achieved. As the overall event rate was low, this study cannot make definite conclusions, yet both strategies provided state-of-the-art outcomes.

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Conflict of interest statement

R. van Geuns reports receiving grants and personal fees from Boston Scientific, during the conduct of the study; grants and personal fees from Abbott Vascular, AstraZeneca, and Amgen; and personal fees from Sanofi, outside the submitted work. M. Lesiak has received speaker's honoraria from Abbott Vascular, and Boston Scientific. Y. Onuma was an advisory board member of Abbott Vascular. M.B. McEntegart has a proctoring agreement with Boston Scientific and Vascular Perspectives. K.G. Oldroyd reports receiving grant support and lecture fees from AstraZeneca and lecture fees from Biosensors, Abbott Vascular, and GE. The other authors have no conflicts of interest to declare.

References

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-72.

2. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogats G, Mansour S, Noiseux N, Sabate M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Page P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N Engl J Med.* 2016;375:2223-35.

3. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sorensen HT, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE study investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2016;388:2743-52.

4. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From a Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv.* 2013;6:777-89.

5. Hagiwara H, Hiraishi Y, Terao H, Hirai T, Sakaoka A, Sasaki M, Murota S, Inoue K, Kimura J. Vascular responses to a biodegradable polymer (polylactic acid) based biolimus A9-eluting stent in porcine models. *EuroIntervention.* 2012;8:743-51.

6. Ng J, Foin N, Ang HY, Fam JM, Sen S, Nijjer S, Petraco R, Di Mario C, Davies J, Wong P. Over-expansion capacity and stent design model: An update with contemporary DES platforms. *Int J Cardiol.* 2016;221:171-9.

7. Fam JM. Defining optimal stent overexpansion strategies for left main stenting: insights from bench testing. *AsiaIntervention.* 2017;3:110-20.

8. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

9. Lemmert ME, Oldroyd K, Barragan P, Lesiak M, Byrne RA, Merkulov E, Daemen J, Onuma Y, Witberg K, van Geuns RJ. Reduced duration of dual antiplatelet therapy using an improved drug-eluting stent for percutaneous coronary intervention of the left main artery in a real-world, all-comer population: Rationale and study design of the prospective randomized multicenter IDEAL-LM trial. *Am Heart J.* 2017;187:104-11.

10. Saez A, Moreno R. Everolimus-eluting coronary stents. *Med Devices (Auckl).* 2010;3:51-6.

11. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-47.

12. Mehilli J, Kastrati A, Byrne RA, Bruskina O, Iijima R, Schulz S, Pache J, Seyfarth M, Massberg S, Laugwitz KL, Dirschinger J, Schömig A; LEFT-MAIN IntracoronaryStenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions Study Investigators. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol.* 2009; 53:1760-8.

13. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Gwon HC, Jeong MH, Jang YS, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol.* 2010;56:117-24.

14. de la Torre Hernandez JM, Tejedor P, Camarero TG, Duran JM, Lee DH, Monedero J, Laso FS, Calderon MA, Veiga G, Zueco J. Early healing assessment with optical coherence tomography of everolimus-eluting stents with bioabsorbable polymer (synergy™) at 3 and 6 months after implantation. *Catheter Cardiovasc Interv.* 2016;88:E67-73.

15. Guagliumi G, Shimamura K, Sirbu V, Garbo R, Boccuzzi G, Vassileva A, Valsecchi O, Fiocca L, Canova P, Colombo F, Tensol Rodriguez Pereira G, Nakamura D, Attizzani GF, Cereda A, Satogami K, De Luca L, Saia F, Capodanno D. Temporal course of vascular healing and neoatherosclerosis after implantation of durable- or biodegradable-polymer drug-eluting stents. *Eur Heart J.* 2018;39:2448-56.

16. Chang CC, Onuma Y, Lesiak M, Merkulov E, Anderson R, Kretov E, Barragan P, Oldroyd KG, van Geuns RJ. Optical Coherence Tomography Assessment for Percutaneous Coronary Intervention of the Left Main Artery: The IDEAL-LM Trial. *JACC Cardiovasc Interv.* 2020;13:401-2.

17. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68:1082-115.

18. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213-60.

19. Zimarino M, Angiolillo DJ, Dangas G, Capodanno D, Barbato E, Hahn JY, Giustino G, Watanabe H, Costa F, Cuisset T, Rossini R, Sibbing D, Burzotta F, Louvard Y, Shehab A, Renda G, Kimura T, Gwon HC, Chen SL, Costa RA, Koo BK, Storey RF, Valgimigli M, Mehran R, Stankovic G. Antithrombotic therapy after percutaneous coronary intervention of bifurcation lesions. *EuroIntervention.* 2021;17:59-66.

20. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet.* 2018;392:940-9.

21. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrie D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR; SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet.* 2018;391:41-50.

22. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Džavík V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med.* 2019;381:2032-42.

23. Brener SJ, Serruys PW, Morice MC, Mehran R, Kappetein AP, Sabik JF 3rd, Liu Y, Dressler O, Ben-Yehuda O, Stone GW. Optimal Duration of Dual Antiplatelet Therapy After Left Main Coronary Stenting. *J Am Coll Cardiol.* 2018;72:2086-7.

24. Rhee TM, Park KW, Kim CH, Kang J, Han JK, Yang HM, Kang HJ, Koo BK, Kim HS. Dual Antiplatelet Therapy Duration Determines Outcome After 2- But Not 1-Stent Strategy in Left Main Bifurcation Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2018;11:2453-63.

25. Mehilli J, Richardt G, Valgimigli M, Schulz S, Singh A, Abdel-Wahab M, Tiroch K, Pache J, Hausleiter J, Byrne RA, Ott I, Ibrahim T, Fusaro M, Seyfarth M, Laugwitz KL, Massberg S, Kastrati A; ISAR-LEFT-MAIN 2 Study Investigators. Zotarolimus- versus everolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol.* 2013;62:2075-82.

26. Kim YH, Park DW, Ahn JM, Yun SC, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Jang Y, Jeong MH, Kim HS, Hur SH, Rha SW, Lim DS, Her SH, Seung KB, Seong IW, Park SJ; PRECOMBAT-2 Investigators. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. *JACC Cardiovasc Interv.* 2012;5:708-17.

27. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation.* 2014;129:2388-94.

28. Tiroch K, Mehilli J, Byrne RA, Schulz S, Massberg S, Laugwitz KL, Vorpahl M, Seyfarth M, Kastrati A; ISAR-LEFT MAIN Study Investigators. Impact of coronary anatomy and stenting technique on long-term outcome after drug-eluting stent implantation for unprotected left main coronary artery disease. *JACC Cardiovasc Interv.* 2014;7:29-36.

Supplementary data

Supplementary Appendix 1. Endpoint definitions.
Supplementary Appendix 2. CONSORT 2010 checklist.
Supplementary Table 1. Inclusion and exclusion criteria.
Supplementary Table 2. Study organisations.
Supplementary Table 3. Number of patients randomised per site.
Supplementary Figure 1. DAPT usage from 0 to 24 months.
Supplementary Figure 2. Landmark analysis for primary endpoint over 2 years of follow-up.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00514

Supplementary data

Supplementary Appendix 1. Endpoint definitions

1.1.1 Study endpoints

Clinical study endpoints will be assessed according to the definitions below. The Central Endpoint Committee (CEC) will adjudicate all efficacy clinical study endpoints and may overrule the investigator. Detailed procedures for the adjudication of each of the events as well as the procedure will be laid down in a CEC charter prior to start of the study.

1.1.1.1 Death

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac death: any death due to immediate cardiac causes (e.g., MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death.

Vascular cause death: death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-cardiovascular death: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

1.1.1.2 Myocardial infarction

Type 1. Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, assuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD)but on occasion non-obstructive or no CAD.

Type 2. Myocardial infarction secondary to an ischaemic imbalance.

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3. Myocardial infarction resulting in death when biomarker values are unavailable.

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers are not collected.

Type 4a. Myocardial infarction related to percutaneous coronary intervention (PCI)

Periprocedural myocardial infarction will be defined according to the following definitions:

SYNTAX I

After allocation but before treatment	Q MI: new Q Waves not present on baseline ECG with CKMB levels elevated above normal compared to baseline (or cTn >7URL if CKMB is not available) Non-Q MI: elevation of CK levels to >2ULN with positive CKMB compared to baseline (or cTn >7URL if CKMB is not available)
Within 7 days' post-intervention	New Q-waves* and one plasma level of CK-MB ≥5 ULN or (cTn ≥35 URL if CKMB is not available)
At least 7 days after any intervention procedure	Either new Q-waves* OR one plasma level of CK-MB ≥5 ULN or (cTn ≥35 URL if CKMB is not available)

SCAI

Patients with normal baseline CK-MB	Peak CK-MB within 48 hours of the procedure ≥10 times the local laboratory ULN or Peak CK-MB within 48 hours of the procedure ≥5 times the local laboratory ULN with New pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB
	or In the absence of CK-MB measurements and a normal baseline cTn: cTn (I or T) level measured within 48 hours of the PCI ≥70x the local laboratory ULN, or cTn (I or T) level measured within 48 hours of the PCI ≥ 35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB
Patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent preprocedure level
Patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension

Type 4b. Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5. Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10x99th percentile URL in patients with normal baseline cTn values (>99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

1.1.1.3 Revascularisation

The location of revascularisations will be adjudicated per the Academic Research Consortium (ARC) definition.

- Target lesion revascularisation (TLR): TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.
- Target vessel revascularisation (TVR): TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself
- Non target lesion revascularisation (Non-TLR): any revascularisation in the target vessel for a lesion other than the target lesion is considered a non-TLR.

- Non target vessel revascularisation (Non-TVR): revascularisation of the vessel identified and treated as the non-target vessel at the time of the index procedure.

1.1.1.4 Stent thrombosis

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the patient left the catheterisation lab.

1. Timing:
   - Acute stent thrombosis: 0-24 hours' post stent implantation
   - Early stent thrombosis: >24 hours-30 days' post stent implantation
   - Late stent thrombosis†: 30 days-1-year post-stent implantation
   - Very late stent thrombosis†: >1-year post-stent implantation

   † Including "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis is a stent thrombosis after a target segment revascularisation.

2. Categories:
   - Definite
   - Probable
   - Possible

   Definitions of each category are as follows:

   Definite stent thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

*Angiographic confirmation of stent thrombosis**

The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:

- Acute onset of ischaemic symptoms at rest
- New ischaemic ECG changes that suggest acute ischaemia
- Typical elevation or depression in cardiac biomarkers (refer to definition of spontaneous MI)
- Non-occlusive thrombosis
    - Thrombus intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream.
- Occlusive thrombus
    - TIMI 0 or TIMI 1 in-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

Notes:

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis.

† Intracoronary thrombus.

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

Either of the following occurred after stent implantation will be considered a probable stent thrombosis:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

1.1.1.5 Bleeding

Bleeding will be assessed in accordance with the Bleeding Academic Research Consortium (BARC) Definition [3]. The patient will be questioned at each follow-up visit or telephone call if any bleeding episodes have occurred and these will be recorded in the eCRF.

Type 0:

No bleeding

Type 1:

Bleeding that is not actionable and does not cause the patient to

seek unscheduled performance of studies, hospitalisation, or treatment by a

healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.

Type 2:

Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional; (2) leading to hospitalisation or increased level of care; or (3) prompting evaluation

Type 3:

Type 3a

- Overt bleeding plus haemoglobin drop of 3 to <5 g/dL *(provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus haemoglobin drop ≥5 g/dL *(provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal).
    - Subcategories; confirmed by autopsy or imaging or LP
- Intra-ocular bleed compromising vision

Type 4: Coronary artery bypass graft–related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output ≥2 L within a 24-hour period

Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Type 5: Fatal bleeding

Type 5a. Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious

Type 5b. Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL haemoglobin). † Cell saver products will not be counted

Supplementary Appendix 2. CONSORT 2010 checklist

Section/Topic	Item no	Checklist item	Reported on page no
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results and conclusions (for specific guidance see CONSORT for abstracts [21,31])	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important charges to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participations	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation, details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for primary outcome	Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9

	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Number analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcomes, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes in recommended	9
Ancillary analyses	18	Results of any other analyses perform, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms [28])	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6

Supplementary Table 1. Inclusion and exclusion criteria.

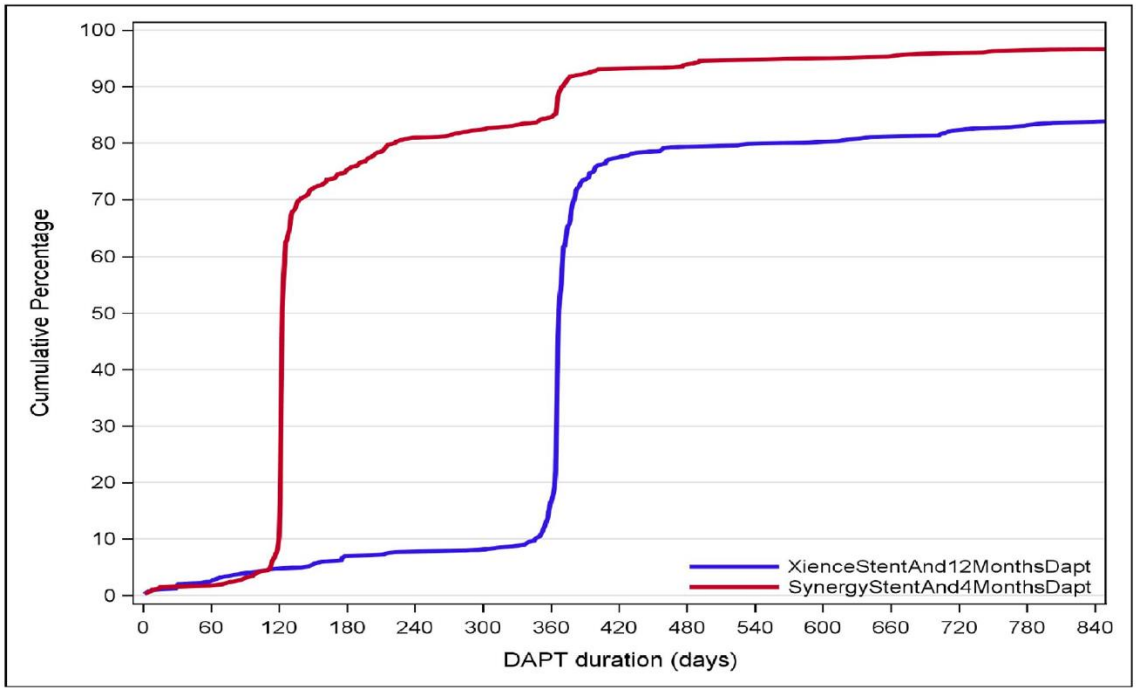
Inclusion criteria
1. Patient has an indication for revascularisation of left main coronary artery in accordance with ESC guidelines.
2. Patient has been discussed in the Heart Team with the cardiac surgeon prior to percutaneous coronary intervention procedure.
3. Patient is accepted for percutaneous coronary intervention.
4. Patient is at least 18 years of age.
5. Patient understands and accepts the meaning and aims of the study and is willing to provide written informed consent.
6. Patient is willing to comply with specified follow-up evaluation and can be contacted by telephone.
Exclusion criteria
1. Patient is not able to receive antiplatelet treatment due to contraindications.
2. Patient has a known allergy to acetylsalicylic acid, clopidogrel, prasugrel, or ticagrelor.
3. Patient is in cardiogenic shock at the time of treatment.
4. Patient had an ST-elevation MI within the last 5 days before treatment.
5. Patient has planned surgery within 12 months after stent implantation.
6. Patient has a history of bleeding diathesis or active major bleedings.
7. Patient had major surgery within 15 days before treatment.
8. Patient participates in other trial, which has not yet reached its primary endpoint.
9. Patient has a life expectancy <12 months.
10. Patient has a hypersensitivity or contraindication to everolimus or structurally related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers.
11. Patient is female with childbearing potential and not taking adequate contraceptives or is currently breastfeeding.

Supplementary Table 2. Study organisations.

Co-principal investigators
Professor Robert-Jan van Geuns, Professor Keith G Oldroyd
Data Safety Monitoring Board (DSMB)
Chair Professor Jan Tijssen
Safety Reporting and Monitoring
The Clinical Research Organisation (CRO) Venn Life Science, Belfast, UK. is responsible for entering all Serious Adverse Events (SAEs) including the assessment regarding relationship to the device (SADEs) or to the procedure from the eCRF in a safety database and for reporting these SAEs and SADEs according to the MEDDEV 2·7/3 guidelines and national requirements.
Data management and statistical analysis
Data management and statistical analysis were conducted by the CRO: Diagram, Zwolle, NL.
Clinical Event Adjudication Committee
Chair Dr. Eugene McFadden
Core laboratories
The independent angiography and intravascular ultrasound imaging Core Lab at Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, the Netherlands) analysed angiograms obtained during and/or before procedure· Members of the Angiographic/IVUS core lab were not involved as investigators or co-investigators in this study.

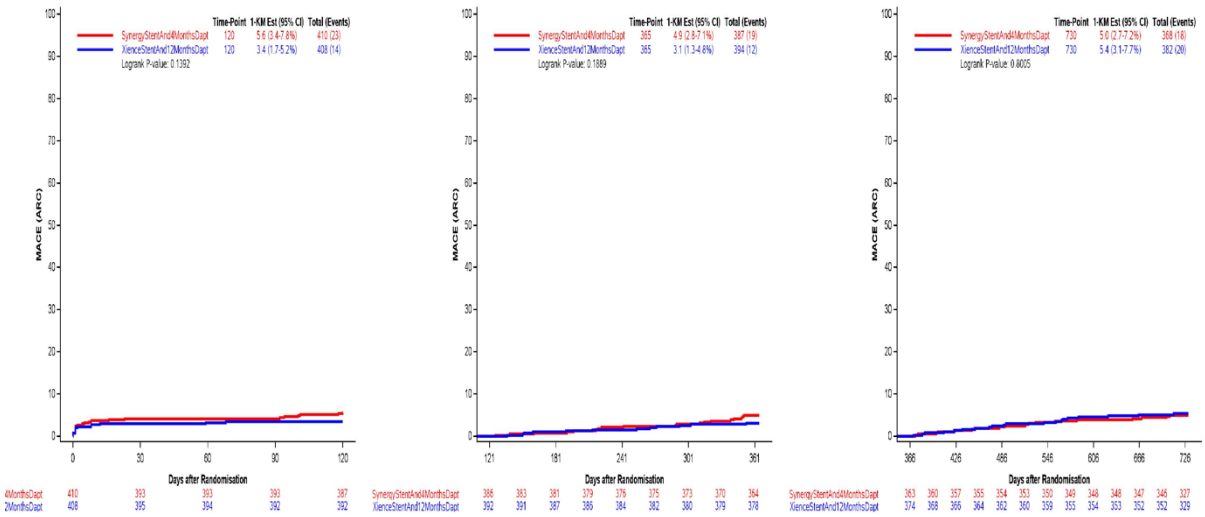
Supplementary Table 3. Number of patients randomised per site.

Site name	Principal investigator	Patients enrolled	Site name	Principal investigator	Patients enrolled
Russian Cardiology Research Center	Merkulov	105	Clinique-Saint Hilaire Rouen	Berland	19
Novosibirsk Research Institute	Kretov	103	Morriston Hospital	Chase	18
Golden Jubilee National Hospital	Oldroyd	83	Erasmus MC Rotterdam	van Geuns	13
Szpital Kliniczny Przemienienia Panskiego UM w Poznaniu	Lesiak	71	Polyclinique Les Fleurs Ollioules	Barragan	13
Royal Bournemouth Hospital	O Kane	47	Clinique St Martin à Caen	Morelle	13
Belfast City Hospital	Hanratty	46	Northern General Hospital	Gunn	10
Clinique des Nouvelles Cliniques Nantaises	Bressollette	42	Clinique Rhone Durance Avignon	Sainsous	10
Clinique Axium	Silvestri	37	CHU Rangueil	Carrie	10
Krasnoyarsk Regional Vascular Centre	Wlodarczak	30	Polsko Amerykanskie Kliniki Serca	Buszman	7
University Hospital of Wales	Anderson	25	State Budegatery Healthcare Institution	Osiev	5
Miedziowe Centrum Zdrowia	Protopopov	24	Clinique St Augustin	Darremont	4
Altnagelvin Hospital	Peace	23	Royal Infirmary of Edinburgh	Behan	3
Craigavon Area Hospital	Menowen	22	Wielospecjalistyczny Szpital Miejski im. J. Strusia w Poznaniu	Rzezniczak	2
John Radcliffe Hospital	Banning	20	Onze Lieve Vrouwe Gasthuis	Slagboom	2
Essex CTC	Kelly	19	**Total**		**826**



Supplementary Figure 1. DAPT usage from 0 to 24 months.

17.2.9 Landmark analysis MACE (ARC)



Supplementary Figure 2. Landmark analysis for primary endpoint over 2 years of follow-up.