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A large, prospective, multicentre study of left main PCI using a latest-generation zotarolimus-eluting stent: the ROLEX study

Giuseppe Tarantini[1]*, MD, PhD; Luca Nai Fovino[1], MD, PhD; Ferdinando Varbella[2], MD; Daniela Trabattoni[3], MD, PhD; Giuseppe Caramanno[4], MD; Carlo Trani[5], MD, PhD; Nicoletta De Cesare[6], MD; Giovanni Esposito[7], MD, PhD; Matteo Montorfano[8], MD, PhD; Carmine Musto[9], MD; Andrea Picchi[10], MD; Imad Sheiban[11], MD; Valeria Gasparetto[11], MD; Flavio L. Ribichini[12], MD; Francesco Cardaioli[1], MD; Salvatore Saccà[13], MD; Enrico Cerrato[14], MD, PhD; Massimo Napodano[1], MD, PhD; Matteo Martinato[15], MSc, PhD; Danila Azzolina[15], MSc, PhD; Giuseppe Andò[16], MD; Antonio Mugnolo[17], MD; Marco Caruso[18], MD; Roberta Rossini[19], MD, PhD; Enrico Passamonti[20], MD; Rui Campante Teles[21], MD; Stefano Rigattieri[22], MD, PhD; Dario Gregori[15], MSc, PhD; Corrado Tamburino[23], MD, PhD; Francesco Burzotta[5], MD

The authors' affiliations can be found in the Appendix paragraph.

G. Tarantini and L. Nai Fovino contributed equally to this paper and are joint first authors.

GUEST EDITOR: Franz-Josef Neumann, MD; *Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany*

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KEYWORDS

- drug-eluting stent
- intracoronary imaging
- intravascular ultrasound
- left main
- percutaneous coronary intervention

Abstract

Background: Data on left main (LM) percutaneous coronary interventions (PCI) have mostly been obtained in studies using drug-eluting stent (DES) platforms without dedicated large-vessel devices and with limited expansion capability.

Aims: Our study aimed to investigate the safety and efficacy of LM PCI with the latest-generation Resolute Onyx DES.

Methods: ROLEX (Revascularization Of LEft main with resolute onyX) is a prospective, multicentre study (ClinicalTrials.gov: NCT03316833) enrolling patients with unprotected LM coronary artery disease and a SYNTAX score <33 undergoing PCI with the Resolute Onyx zotarolimus-eluting coronary stent, that includes dedicated extra-large vessel platforms. The primary endpoint (EP) was target lesion failure (TLF): a composite of cardiac death, target vessel myocardial infarction (TVMI) and ischaemia-driven target lesion revascularisation (ID-TLR), at 1 year. All events were adjudicated by an independent clinical event committee. An independent core lab analysed all procedural angiograms.

Results: A total of 450 patients (mean age 71.8 years, SYNTAX score 24.5±7.2, acute coronary syndrome in 53%) were enrolled in 26 centres. Of these, 77% of subjects underwent PCI with a single-stent and 23% with a 2-stent technique (8% double kissing [DK] crush, 6% culotte, 9% T/T and small protrusion [TAP] stenting). Intravascular imaging guidance was used in 45% (42% intravascular ultrasound [IVUS], 3% optical coherence tomography [OCT]). At 1 year, the primary EP incidence was 5.1% (cardiac death 2.7%, TVMI 2.7%, ID-TLR 2.0%). The definite/probable stent thrombosis rate was 1.1%. In a prespecified adjusted subanalysis, the primary EP incidence was significantly lower in patients undergoing IVUS/OCT-guided versus angio-guided PCI (2.0 vs 7.6%; hazard ratio [HR] 0.28, 95% confidence interval [CI]: 0.13-0.58; p<0.001).

Conclusions: In this large, multicentre, prospective registry, LM PCI with the Resolute Onyx DES showed good safety and efficacy at 1 year, particularly when guided by intracoronary imaging.

Corresponding author: Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Via Giustiniani 2, 35128 Padova, Italy. E-mail: giuseppe.tarantini.1@gmail.com

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Abbreviations

CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society Angina Score
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
EP	endpoint
IVUS	intravascular ultrasound
LM	left main
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
ST	stent thrombosis
TLF	target lesion failure
TLR	target lesion revascularisation
TVMI	target vessel myocardial infarction

Introduction

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is a guideline-recommended option to treat patients with unprotected left main (LM) coronary artery disease (CAD) and a low-intermediate SYNTAX score[1]. DES implantation in the LM is known to pose specific challenges due to the large target vessel size, the common involvement of bifurcation with large and important branches, and the potential major clinical impact of complications[2]. To date, available data on LM PCI derive from previous studies on patients mostly receiving DES without dedicated large-vessel platforms and with limited expansion capability[3-5]. In fact, only a few DES manufacturers provide large-diameter stents whose nominal range falls within the typical LM size (4.5-5.0 mm). The new-generation, Resolute Onyx (Medtronic) zotarolimus-eluting stent includes large (3.5-4.0 mm – expansion limit 5.0 mm) and extra-large vessel (4.5-5.0 mm – expansion limit 6.0 mm) stent platforms and is designed to optimise the treatment of larger vessels, such as the LM.

On such a basis, we designed a prospective, international, multicentre study aimed at assessing the results of LM PCI obtained with the Resolute Onyx DES.

Methods

STUDY POPULATION

The ROLEX (Revascularization Of LEft main with resolute onyX) registry is a prospective, international, multicentre study enrolling patients with LM *de novo* CAD undergoing PCI with the Resolute Onyx zotarolimus-eluting coronary stent at 26 centres. According to the study protocol, we included patients aged >18 years with unprotected LM CAD up to intermediate anatomical complexity (defined by a SYNTAX score <33) considered amenable for PCI with the Resolute Onyx DES. Significant LM CAD was defined as angiographic diameter stenosis >50%. If LM diameter stenosis was between 50% and 70%, evidence of ischaemia by fractional flow reserve (FFR) with intracoronary adenosine administration <0.80 or intravascular ultrasound (IVUS) minimal lumen area <6.0 mm^2 was recommended. The Heart Team was involved in every case and the decision to perform PCI was shared with the patient after informing them about all the therapeutic options (i.e., patients did not have to be refused for surgery to be enrolled in the study). The study inclusion and exclusion criteria are reported in **Table 1**. Patients with an indication for PCI of other non-LM lesions could be enrolled, as long as the SYNTAX score was <33 and all lesions were treated with the Resolute Onyx DES. The study received institutional review board/ethics committee approval at each participating site.

Table 1. Detailed study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Unprotected *de novo* LM CAD with angiographic diameter stenosis >50% (if stenosis 50-70%, evidence of FFR <0.80 or IVUS minimal lumen area <6.0 mm^2 is recommended)	– Prior LM PCI or CABG – Left main diameter stenosis <50% – SYNTAX score ≥33
Silent ischaemia, stable angina, unstable angina or non-ST elevation myocardial infarction	– Concomitant indication to cardiac surgery (severe heart valve disease, etc.)
Ability to provide written informed consent and comply with follow-up for at least 2 years	– Cardiogenic shock (Killip >2)
Age >18 years	– Severe CKD (GFR <30 ml/min) – Left ventricular ejection fraction <30% – Inability to tolerate or comply with dual antiplatelet therapy for at least 1 year – Pregnancy or intention to become pregnant – Known intolerance to aspirin, heparin, zotarolimus, or contrast material – Life expectancy less than 1 year – Subject participating in other investigational drug or device studies that have not reached their primary endpoint

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; FFR: fractional flow reserve; GFR: glomerular filtration rate; IVUS: intravascular ultrasound; LM: left main; PCI: percutaneous coronary intervention

STUDY DEVICE AND PROCEDURE

The Resolute Onyx is the latest-generation zotarolimus-eluting stent built on the Resolute Integrity (a premounted composite of cobalt alloy and platinum-iridium alloy) platform. Resolute Onyx was the first drug-eluting stent available in 4.5 mm and 5.0 mm diameter sizes among major manufacturers, with a maximal expansion capability up to 6.0 mm. The 3.5-4.0 mm platform also has excellent expansion capability (up to 5.0 mm).

In case of LM bifurcation lesions, the technique selection was left to the operator's judgment. However, the following technical considerations were strongly suggested based on emergent best practices[2]: 1) a provisional technique was recommended whenever possible, followed by the proximal optimisation technique (POT), using a post-dilating balloon with a diameter selected 1:1 to the LM reference diameter; 2) if deemed necessary by the operator to appropriately treat complex LM bifurcation anatomies, an intentional double-stenting technique (T stenting, T and small

protrusion [TAP], double kissing [DK] mini crush, or culotte) could be adopted. Final kissing balloon inflation (preferably with non-compliant balloons) was strongly advised, as was final POT. Imaging-guided PCI (by either IVUS or optical coherence tomography [OCT]) to optimise stent sizing, expansion and apposition in the LM segment and for all complex non-LM lesions was not mandatory per protocol, yet strongly advised. Remaining non-LM lesions amenable for PCI could be treated at the time of the index intervention or staged. Antiplatelet therapy after PCI had to follow the latest guidelines[1]. An independent core laboratory analysed all procedural angiograms, both of the index and subsequent diagnostic or interventional coronary procedures during follow-up. Quantitative coronary angiography analyses were performed using the CAAS Workstation 8.4 (Pie Medical Imaging).

STUDY ENDPOINTS

The primary endpoint (EP) was target lesion failure (TLF): a composite of cardiac death, target vessel myocardial infarction (TVMI) and ischaemia-driven target lesion revascularisation (ID-TLR) at 1 year. Secondary EP were all-cause mortality, TVMI, ID-TLR, periprocedural MI, stroke rate and (definite or probable) stent thrombosis (ST). Follow-up was prospectively performed at 30 days (±7 days) and 1 year (±30 days) with outpatient visits or telephone interviews. Definitions of individual endpoints can be found in the study protocol **(Supplementary Appendix 1)**. Routine follow-up angiography was not recommended. All events were adjudicated by an independent clinical events committee, after review of original source documentation.

STATISTICAL ANALYSIS

For the ROLEX study, the sample size calculation was based on the primary EP at 1 year. An upper limit for primary EP incidence rates was set at 7%, consistent with reported event rates in the literature[6-8]. An overall sample size of 404 patients, increased to 450 to account for a 10% dropout rate, was expected to allow an estimation of the primary EP incidence rate of 7% with the precision of 2.5% and a confidence level (1-alpha) set at alpha=0.05.

According to the study protocol, several subanalyses were prespecified. In particular, subanalyses of patients with isolated LM CAD (with or without involvement of the proximal bifurcation main branch) receiving a 4.5/5.0 mm diameter stent and undergoing either IVUS or OCT imaging-guided LM PCI were planned. According to the study plan, a minimum of 150 patients with isolated LM CAD (with or without involvement of the proximal bifurcation main branch) was set in order to ensure that the EP incidence rate would be estimated in such subgroups with a precision of 3.5%, according to previous literature findings[6-8].

Descriptive statistics were reported as mean±standard deviation (SD) or median and 1st and 3rd interquartile ranges (IQR) for continuous variables and percentages for discrete variables. The Wilcoxon test was performed to compare the distribution of continuous variables. The chi-squared or Fisher's exact tests were performed to compare the distribution of categorical variables. P-values underwent the Benjamini-Hochberg procedure to control for false discovery rates. The incidence of the primary endpoint was evaluated using cumulative incidence functions (CIF) to account for competing risks. To adjust the results for possible confounders, a covariate balance propensity score (CBPS) was estimated, accounting for age, gender, diabetes, 3-vessel CAD (vs 1- or 2-vessel CAD), acute coronary syndrome (vs chronic coronary syndrome) and the use of intravascular imaging. The balancing performance for the CBPS was assessed via common support propensity score visualisation and reporting in a plot of the mean difference of the covariate before and after the adjustment. The covariates having a balanced mean difference within 0.1 in absolute variables were defined as well balanced after the propensity estimation procedure. Inverse probability of treatment weighted (IPTW) Cox regression models were estimated. A shared frailty random effect term was calculated to account for the cluster effect within the same centre. Results were reported as hazard ratios (HR), 95% confidence intervals [CI] and p-values. Computations were performed with the R 3.4.2 system and the CBPS and WeightIt packages (Microsoft).

Results

BASELINE CLINICAL CHARACTERISTICS

Between November 2017 and December 2020, a total of 450 patients with LM CAD were enrolled in the ROLEX study at 26 centres. Detailed demographics and clinical characteristics are described in **Table 2**. In summary, patients were aged 71.8±10.7 years, 83% were male, the mean European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was 2.7±3.3. Diabetes mellitus was present in one-third of the study population (9% insulin-dependent). Thirty-seven percent of subjects had a history of previous percutaneous coronary revascularisation, and baseline left ventricular ejection fraction (LVEF) was >50% in over two-thirds of patients. Clinical indications for LM PCI were acute coronary syndrome (ACS) in 53%, and 15% of patients had an NYHA Functional Class III-IV on admission.

ANGIOGRAPHIC CHARACTERISTICS

Details on baseline angiographic characteristics are reported in **Table 3**. The mean SYNTAX score of our study population was 24.5±7.2, with isolated LM CAD in 10% of patients. LM disease involved the ostium in 20% and the bifurcation in 78% of subjects. In 187 patients, the lesion involved either only the LM or the LM and the proximal part of its bifurcation main branch. Among the adverse lesion features, severe calcifications were present in 12%, LM thrombus was observed in 6% and severe tortuosity was found in 1% of patients. At quantitative coronary angiography analysis, baseline LM diameter stenosis was 61.9±16.9%, LM reference vessel diameter was 4.1±0.7 mm, and the angle of the LM bifurcation was 79.9±26.6 degrees.

PROCEDURAL DATA

LM PCI was performed in 77% of cases through the radial approach, mostly (82%) with a 6 Fr guiding catheter **(Table 4)**. By

Table 2. Baseline demographics and clinical characteristics.

Characteristic		N=450
Age		71.8±10.7
Female gender		75 (17%)
BMI (kg/m^2)		28.0±17.3
EuroSCORE II		2.7±3.3
Current smoker		95 (21%)
Diabetes mellitus		134 (30%)
Insulin-dependent		41 (9%)
Non-insulin-dependent		93 (21%)
Hypertension		355 (79%)
Hypercholesterolaemia		313 (70%)
Glomerular filtration rate (ml/min)		75 [57,90]
Previous stroke		27 (6%)
Previous MI		111 (25%)
Previous PCI		165 (37%)
Peripheral vascular disease		77 (17%)
COPD		30 (7%)
LVEF	Good (>50%)	292 (65%)
	Fair (30-50%)	158 (35%)
Chronic coronary syndrome		212 (47%)
CCS 0		238 (53%)
CCS 1		44 (10%)
CCS 2		66 (14%)
CCS 3		53 (12%)
CCS 4		49 (11%)
Acute coronary syndrome		238 (53%)
Unstable angina		63 (14%)
NSTEMI		175 (39%)
NYHA Class at admission	I	243 (54%)
	II	140 (31%)
	III	58 (13%)
	IV	9 (2%)
Dual antiplatelet therapy at the time of PCI		252 (56%)
Clopidogrel		150 (33%)
Ticagrelor		93 (21%)
Prasugrel		8 (2%)
Ticlopidine		1 (0.2%)
Oral anticoagulation		31 (7%)

Values are expressed as mean±SD, median [IQR] or n (%). BMI: body mass index; CCS: Canadian Cardiovascular Society Angina Score; COPD: chronic obstructive pulmonary disease; EuroSCORE: European System for Cardiac Operative Risk Evaluation; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SD: standard deviation

Table 3. Angiographic characteristics.

Characteristic		N=450
CAD distribution	Isolated LM disease	45 (10%)
	LM+single-vessel CAD	142 (31%)
	LM+dual-vessel CAD	152 (34%)
	LM+triple-vessel CAD	111 (25%)
SYNTAX score		24.5±7.2
<23		162 (36%)
23-32		288 (64%)
LM CAD distribution	Ostial LM disease	92 (20%)
	LM shaft disease	117 (26%)
	Distal LM disease	350 (78%)
	Medina 1,0,0	76 (17%)
	Medina 1,1,0	153 (34%)
	Medina 1,0,1	36 (8%)
	Medina 0,1,1	21 (5%)
	Medina 1,1,1	64 (14%)
LM calcifications	None	126 (28%)
	Mild/moderate	270 (60%)
	Severe	54 (12%)
LM thrombotic lesion		27 (6%)
Tortuosity	None	343 (76%)
	Mild/moderate	103 (23%)
	Severe	4 (1%)
Baseline QCA	LM diameter stenosis (%)	62±17
	LAD diameter stenosis (%)	56±30
	LCx diameter stenosis (%)	35±31
	LM RVD (mm)	3.7±0.7
	LAD RVD (mm)	3.2±0.8
	LCx RVD (mm)	2.9±0.6
	LM minimal lumen diameter (mm)	2.0±0.8
	LAD minimal lumen diameter (mm)	1.7±0.9
	LCx minimal lumen diameter (mm)	2.0±0.8
	LM lesion length (mm)	9.0±5.7
	LAD lesion length (mm)	11.1±9.7
	LCx lesion length (mm)	5.5±6.1
	Bifurcation angle (°)	79.9±26.6

Values are expressed as mean±SD or n (%). CAD: coronary artery disease; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main; QCA: quantitative coronary angiography; RVD: reference vessel diameter

intention, the stepwise provisional approach was applied in 79% of patients. Seventy-seven percent of LM PCI were completed with a single-stent strategy (without involving the LM bifurcation in 11% of cases), while 23% of cases required a 2-stent strategy. Double kissing (DK)-crush was the most commonly used 2-stent technique (8%), followed by culotte and TAP (both 6%) and, finally, T stenting (3%). The majority of LM PCI were performed with a 3.5 or 4.0 mm stent, and the extra-large DES platform (4.5-5.0 mm) was implanted in 17% of subjects. Final kissing balloon inflation was adopted in 64% of cases (93% in the cases of a 2-stent strategy), and final proximal optimisation technique (POT) was used in 87% of procedures. Over half of the patients underwent additional PCI not involving the LM, and the mean number

Table 4. Procedural characteristics.

Characteristic		N=450
Access	Femoral	104 (23%)
	Radial	346 (77%)
Guiding catheter	6 Fr	369 (82%)
	7 Fr	81 (18%)
Balloon predilation		333 (74%)
Intravascular imaging	IVUS	188 (42%)
	OCT	12 (3%)
FFR/iFR		28 (6%)
Rotational atherectomy		19 (4%)
Initial treatment strategy	Provisional	356 (79%)
	Two-stent strategy	94 (21%)
Final treatment strategy	One-stent	347 (77%)
	LM only	49 (11%)
	LM-LAD	278 (62%)
	LM-LCx	20 (4%)
	Two-stent	103 (23%)
	T stenting	12 (3%)
	TAP stenting	27 (6%)
	DK crush	36 (8%)
	Culotte	27 (6%)
	Kissing stenting	1 (0.2%)
Nominal LM stent diameter	≤3.0 mm	53 (12%)
	3.5-4.0 mm	319 (71%)
	4.5-5.0 mm	78 (17%)
LM stent length (mm)		22 [18,26]
Side branch stent length (mm)		18 [15,22]
POT		391 (87%)
POT balloon diameter (mm)		4.5 [4.0,5.0]
Final kissing balloon		288 (64%)
After two-stent strategy		95 (93%)
Additional PCI (not involving LM)		249 (55%)
LAD		152 (34%)
LCx		72 (16%)
RCA		25 (5%)
Number of implanted stents		2.2±1.2
Total stent length (mm)		46.1±25.5
Fluoroscopy time (min)		22 [16,30]
Contrast volume (cc)		220 [170,282]
Number of guidewires used		2 [2,3]
Final TIMI flow	0-1	2 (0.4%)
	2	4 (0.9%)
	3	444 (99%)
Any remaining coronary dissection		10 (2%)
Acute side branch occlusion		4 (0.8%)
Post-PCI QCA	LM diameter stenosis (%)	3±7
	LAD diameter stenosis (%)	5±11
	LCx diameter stenosis (%)	11±19
	LM minimal lumen diameter (mm)	4.0±0.6
	LAD minimal lumen diameter (mm)	3.3±0.7
	LCx minimal lumen diameter (mm)	2.8±2.2
Residual SYNTAX score		3.4±5.6
Gp IIb/IIIA inhibitors		9 (2%)
Mechanical circulatory support		58 (13%)
Planned		49 (11%)
Unplanned		9 (2%)
Clinical device success		444 (99%)
Procedural success		446 (99%)
Intraprocedural death		3 (0.7%)

Values are expressed as mean±SD, median [IQR] or n (%). DK: double kissing; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; Gp: glycoprotein; IVUS: intravascular imaging; LAD: left anterior descending artery; LCx: left circumflex; LM: left main; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; POT: proximal optimisaton technique; QCA: quantitative coronary analysis. RCA: right coronary artery; TAP: T and small protrusion

of implanted stents was 2.2±1.2. Intraprocedural death occurred in 3 (0.7%) patients.

At the time of PCI, 7% of patients were taking an oral anticoagulant (OAC), while 56% were already on dual antiplatelet therapy (DAPT). The time prescription for DAPT at discharge was 1-3 months for 20 patients (all with an indication for OAC), 6 months for 45 subjects, and ≥12 months for the rest of the study population. At 1-year follow-up, 77% of patients were taking 2 antiplatelet drugs.

OUTCOMES

The rates of primary and secondary EP are reported in **Table 5** and **Supplementary Table 1**. At 1 year, the incidence of the primary EP was 5.1% **(Figure 1)**. Cardiac death occurred in 2.7% of patients **(Supplementary Table 2)**, 2.7% experienced a TVMI, while 2.0% underwent ID-TLR (PCI: 1.3% and coronary bypass grafting [CABG]: 0.7%). The rate of definite/probable ST was 1.1%. In particular, 1 acute, 2 subacute and 2 late ST were reported during follow-up. Significant bleeding was observed at 1 year in 4.2% of the study population. Follow-up was completed in all patients at 1 year.

ANGIO-GUIDED VERSUS INTRACORONARY IMAGING-GUIDED LM PCI

Intravascular imaging guidance was used in 200 patients (45% of the entire study population; IVUS: 42%, OCT: 3%). The baseline and procedural characteristics of patients undergoing angiography-guided versus intracoronary imaging-guided LM PCI are reported in **Supplementary Table 3-Supplementary Table 5**. As depicted in **Figure 2**, after CBPS weighting **(Supplementary Figure 1)** and

Table 5. 1-year outcomes.

Outcome		N=450
Primary endpoint		
Target lesion failure		23 (5.1%)
Cardiac death		12 (2.7%)
TVMI		12 (2.7%)
ID-TLR		9 (2.0%)
Secondary endpoints		
All-cause death		28 (6.2%)
Periprocedural MI		17 (3.8%)
Stroke		5 (1.1%)
Stent thrombosis (definite/probable)		5 (1.1%)
Definite		3 (0.7%)
Probable		2 (0.4%)
Acute		1 (0.2%)
Subacute		2 (0.4%)
Late		2 (0.4%)
Bleeding		19 (4.2%)
BARC 2		3 (0.6%)
BARC 3A		11 (2.4%)
BARC 3B		4 (0.8%)
BARC 3C		1 (0.2%)
CCS	0	347 (84%)
	1	44 (11%)
	2	14 (3.4%)
	3	4 (1.0%)
	4	2 (0.5%)

Values are expressed as n (%). BARC: Bleeding Academic Research Consortium; CCS: Canadian Cardiovascular Society Angina Score; ID-TLR: ischaemia-driven target lesion revascularisation; MI: myocardial infarction; TVMI: target vessel myocardial infarction

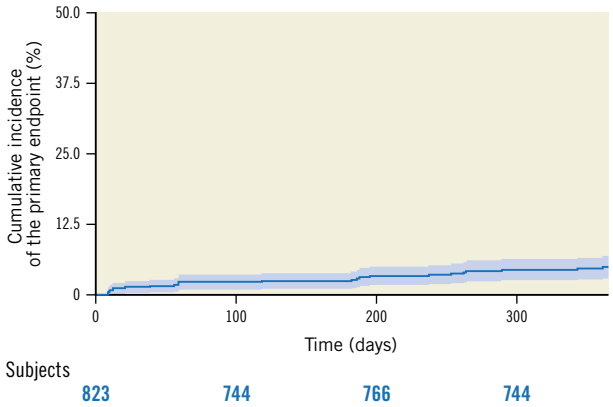


Figure 1. *Primary endpoint incidence estimated using the cumulative incidence function accounting for death as a competing risk.*

adjustment for the cluster effect within the same centre, the rate of the primary EP was significantly lower in patients undergoing intracoronary imaging-guided versus angio-guided PCI (2.0 vs 7.6%; HR 0.28, 95% CI: 0.13-0.58; p<0.001). Also, the 1-year incidence of cardiac death (1.0 vs 4.0%; HR 0.28, 95% CI: 0.10-0.78; p=0.015), TVMI (1.0 vs 4.0%; HR 0.25, 95% CI: 0.09-0.70, p=0.009), ID-TLR (1.0 vs 2.8%; HR 0.35, 95% CI: 0.11-1.14; p=0.081) and stent thrombosis (0.5 vs 1.6%, p=0.4) were lower in the study subgroup undergoing intracoronary imaging-guided PCI.

OTHER PRESPECIFIED SUBANALYSES

A total of 187 patients (41% of the study population) had isolated LM CAD (with or without involvement of the proximal main branch). As shown in **Figure 3**, these subjects had similar outcomes at follow-up, compared to patients with more diffused disease (HR 1.03, 95% CI: 0.58-1.86; p=0.91 for the primary

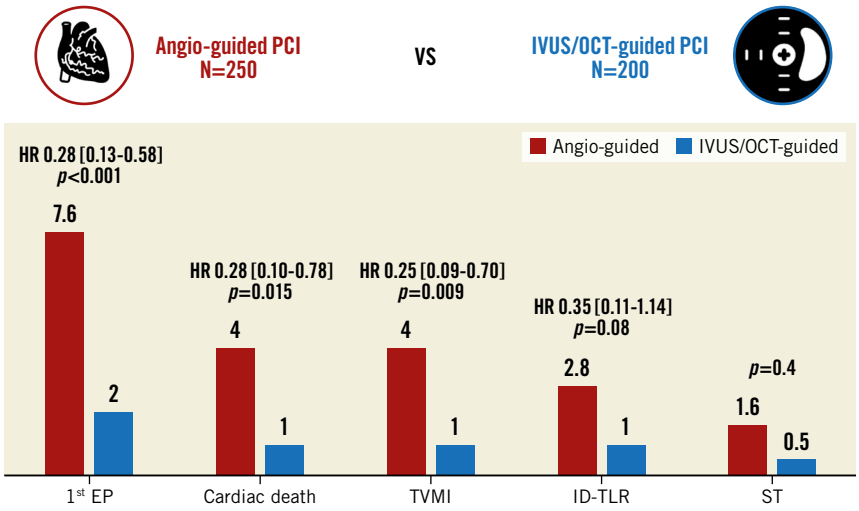


Figure 2. *One-year outcomes of patients undergoing angiography-guided vs intravascular imaging-guided left main percutaneous coronary interventions. Inverse probability treatment weighted Cox regression models. Propensity score has been estimated by considering as confounding factors age, gender, diabetes, 3-vessel CAD and ACS. ACS: acute coronary syndrome; CAD: coronary artery disease; EP: endpoint; HR: hazard ratio; ID-TLR: ischaemia driven target lesion revascularisation; IVUS: intravascular ultrasound; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; ST: stent thrombosis; TVMI: target vessel myocardial infarction*

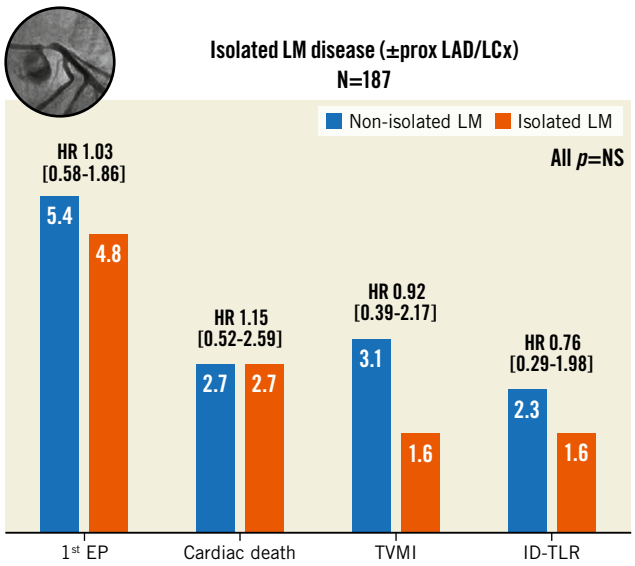


Figure 3. *Incidence of the composite primary endpoint and its single components in patients treated for isolated left coronary artery disease (with or without involvement of the proximal segment of the bifurcation main branch). Inverse probability treatment weighted Cox regression models. Propensity score has been estimated by considering as confounding factors age, gender, diabetes, ACS and use of intravascular imaging. ACS: acute coronary syndrome; DES: drug-eluting stent; EP: endpoint; HR: hazard ratio; ID-TLR: ischaemia driven target lesion revascularisation; LAD: left anterior descending; LCx: left circumflex; LM: left main; NS: nonsignificant; PCI: percutaneous coronary intervention; prox: proximal; TVMI: target vessel myocardial infarction*

EP). Baseline characteristics are reported in **Supplementary Table 6-Supplementary Table 8** (propensity score diagnostic plots in **Supplementary Figure 2**).

Only 78 patients received a 4.5 or 5.0 mm DES. There was no significant difference in the rates of the primary EP between patients receiving a 4.5 or 5.0 mm versus a ≤4.0 mm DES (HR 1.6, 95% CI: 0.88-2.90; p=0.12 for the primary EP) **(Supplementary Figure 3, Supplementary Figure 4, Supplementary Table 9-Supplementary Table 11)**.

Discussion

The improvement of LM PCI represents a hot topic in interventional cardiology and large, prospective, multicentre studies may integrate the randomised trial findings and provide important insights. In the present manuscript, we reported the final results of the largest prospective study on LM PCI with the latest-generation Resolute Onyx DES (covering all LM sizes). The main findings of the ROLEX study can be summarised as follows: 1) adverse events noticed up to 1 year were low (5.1% combined primary composite EP of cardiac death and/or TVMI and/or ID-TLR); 2) after adjustment for possible confounders, the use of intracoronary-imaging was associated with a lower incidence of adverse events at 1 year **(Central illustration)**.

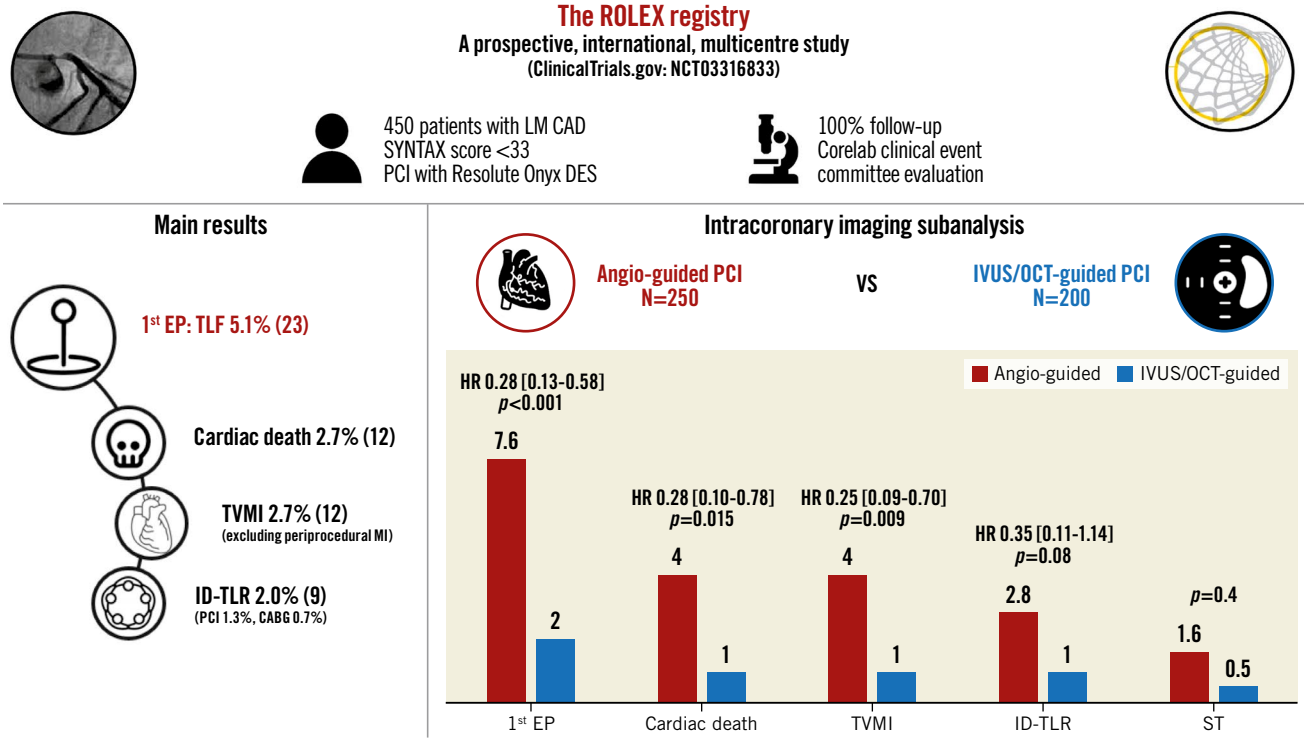
Left main CAD represents a high-risk subset with significant morbidity and mortality if not treated in a timely manner, as it supplies over 80% of the left ventricular myocardium[9]. PCI is an accepted treatment option in selected patients with unprotected LM CAD based on available clinical evidence from prospective registries and randomised trials[5-8]. Nevertheless, most LM PCI observational registries included subjects treated with previous-generation DES without a specific design for the treatment of larger vessels[3-5].

In the ROLEX study, we observed low rates of adverse events at mid-term follow-up with LM PCI performed with a latest-generation zotarolimus-eluting stent. At 1 year, the primary study EP, TLF, occurred in 5.1% of the patients, so the study hypothesis was met. As expected, outcomes compared favourably with those reported in the LM subgroup of the SYNTAX trial (15.8% incidence of major cardiovascular events at 1 year)[10], in which first-generation DES were implanted. Observed TLF rates were also in line with those described in more recent LM PCI trials, as well as in an individual patient data meta-analysis of LM randomised controlled studies[11] whose study population had similar baseline and procedural features compared to the ROLEX registry. In particular, 1-year TLF rates of 6-7% were reported in the PCI arm of the Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)[6] and the Nordic-Baltic-British Left Main Revascularization Study (NOBLE)[7] trials, where other new-generation DES lacking dedicated large vessel platforms were implanted. Notably, patients in the ROLEX registry reported significant symptomatic relief at 1-year follow-up, with a Canadian Cardiovascular Society (CCS) Angina Score of 0-1 in 95% of cases, as well as a higher rate of complete revascularisation (mean residual SYNTAX score 3.4), as compared to previous trials[12].

Since stent thrombosis is a dreadful complication especially when the LM represents the target lesion, it is important to note that the ST rate at 1 year was as low as 1.1%, similar to that of the European Bifurcation Club (EBC) main study (1.5%), which tested a provisional versus 2-stent strategy in LM bifurcation lesions with the same DES platform[13]. Notably, our incidence of definite/probable ST is just slightly higher than that reported in the EXCEL trial (0.8% at 1 year) with a thin-strut everolimus-eluting stent, and lower than that observed in the NOBLE trial, where a thicker-strut stainless steel biolimus-eluting stent was implanted in about 90% of patients[6,7]. Importantly, in these 2 randomised trials, the use of intravascular imaging was as high as 77%.

Improved LM PCI outcomes observed in our study and other recent studies can be explained by the advancements in stent technology, technical refinements and adjunctive drug therapy[14-16]. Latest-generation DES adopt thinner-strut platforms, improved delivery systems, and more biocompatible polymers than their predecessors. Stent design may impact expansion capability, an important attribute in the setting of LM PCI, where proximal post-dilation of the stent is normally necessary to match the proximal reference diameter and optimise stent apposition, as large diameter

CENTRAL ILLUSTRATION Summary of the ROLEX registry main results, including findings of the intravascular imaging-guided LM PCI subanalysis.



ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug-eluting stent; EP: endpoint; HR: hazard ratio; ID-TLR: ischaemia-driven target lesion revascularisation; IVUS: intravascular ultrasound; LM: left main; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; ST: stent thrombosis; TLF: target lesion failure; TVMI: target vessel myocardial infarction

mismatches increase the risk of over-stretching or underexpansion with malapposition. In fact, according to a large observational IVUS study, the mean LM diameter is 5 mm and ranges between 3.5 and 6.5 mm[17]. Bench tests have confirmed the ability of different DES platforms with a nominal size of 3-4 mm to maintain structural integrity when expanded to higher diameters[18-20], but major concerns exist regarding specific expansion limits, suboptimal plaque coverage (secondary to reduced metal-artery ratio) and the preservation of drug-elution kinetics. Only a few manufacturers provide large-diameter stents whose nominal range falls within the typical LM size (4.5-5.0 mm). The Resolute Onyx DES was among the first with an extra-large vessel platform (4.5-5.0 mm nominal diameter with a maximal expansion capability of 6.0 mm with minimum foreshortening), thus presenting an advantage in the treatment of the LM.

Beyond DES technical advances, PCI result optimisation and improved bifurcation stenting techniques might concur to explain the low rate of events observed in the ROLEX study. Despite the involvement of many centres and operators, slightly less than half of the enrolled patients received intravascular imaging-guidance (42% IVUS, 3% OCT). Such rates of intravascular imaging use look quite high (considering the observational nature of our study) and are superior to that reported in the recent EBC[13] and DKCRUSH-V[21] randomised controlled trials (38% and 41%, respectively), where mainly high-volume centres were enrolled. Intravascular imaging provides unique insights into the extent and distribution of coronary atherosclerosis, lesion morphology, stent sizing and technique, and mechanisms and complications of stent implantation at the LM. In keeping with this, in the ROLEX registry the use of intravascular imaging increased the use of larger stent platforms and prompted further interventions to optimise the final result in one-third of cases. In our prespecified subanalysis, angiography-guided LM PCI was associated with significantly higher rates of the composite endpoint (7.6 vs 2.0%), as compared to IVUS/OCT-guided intervention, and a similar trend was noticed for all secondary endpoints **(Figure 2)**. While the non-randomised design of the ROLEX study suggests caution in the interpretation of these results, the lower rates of adverse events in the intravascular imaging-guided LM PCI group were confirmed after propensity score analysis adjustment for potential confounders.

Importantly, the rate of definite/probable ST numerically increased 3-fold when intravascular imaging was not performed.

These findings add to the previous body of evidence suggesting that IVUS-guided LM stenting is associated with a clinically detectable benefit, with reduction of long-term mortality and improvement in clinical outcomes as compared with angiographic guidance alone[22,23] and extend them also to the latest-generation dedicated large-vessel stent platforms, reinforcing current guideline recommendations[1]. As a final remark, the more frequent use of IVUS as compared to OCT in our study is likely due to the challenges of OCT in the setting of LM, where, due to the need to create a blood-free space by dye, artefacts in the proximal LM segment are known to be common[24].

The other relevant technical issue which is potentially able to affect clinical outcomes in LM interventions is bifurcation stenting techniques[2]. In the ROLEX study, LM bifurcation involvement was frequent and similar to other recent large randomised trials[7,25]. As expected in a study where operators were free to select the stenting strategy according to the individual yield, the ROLEX investigators often adopted the stepwise provisional strategy and reserved an upfront 2-stent strategy mainly to treat the subgroup of patients with more extensive, true LM bifurcation lesions. Of note, the techniques were selected according to the operator's preference and were in agreement (as underlined by the 87% of POT and 93% of kissing with non-compliant balloons in 2-stent implantation) with best practices[2], which were indeed recommended according to the study protocol. Such a "tailored" approach was associated with a low procedural complication rate and resulted in excellent angiographic results as described by quantitative coronary angiography analysis. The latter showed single-digit percent diameter stenosis values in the LM-LAD axis and as low as 11±19% in the left circumflex artery (LCx).

Moving from procedure to the broad issue of LM patient management, the high prevalence (77%) of patients on dual antiplatelet therapy at 1 year in our study population should be underlined, since it also likely contributed to the low rate of thrombotic events (in particular, ST) during follow-up. Of note, in the ROLEX registry there were 2 definite ST following premature DAPT discontinuation (1 because of major bleeding and 1 for urgent non-cardiac surgery). In fact, a recent analysis including over 5,000 patients undergoing bifurcation PCI showed that DAPT discontinuation before 6 months in stable CAD patients and before 12 months in ACS patients was associated with a higher risk of adverse events[26]. Moreover, two-thirds of patients on oral anticoagulation had a DAPT time prescription of 1-3 months. Yet, in our study, significant bleeding beyond 30 days from the index procedure was observed in 1.3% of patients. Accordingly, DAPT duration should be decided based on clinical presentation, baseline bleeding risk, stenting strategy and use of intracoronary imaging[27].

In another prespecified subanalysis, we failed to find a significant difference in the primary EP incidence between patients with isolated LM CAD (with or without involvement of the proximal bifurcation main branch) and those with 2- or 3-vessel involvement. This hypothesis was based on the observation of a meta-analysis of individual patient-level data of LM CAD patients included in the PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease)[15] and SYNTAX (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery)[8] trials, showing that in this subgroups of patients, PCI was associated with a 60% reduction in all-cause mortality and a 67% reduction in cardiac mortality when compared to CABG[28]. While this result might be explained by the low event rate in our study, it is noteworthy that in the 45 patients with isolated ostial or mid-shaft LM disease, no cardiac death and just 1 cardiovascular event (an ID-TLR at 8 months after the index procedure) was observed.

Finally, the results of the remaining subanalysis on patients receiving an extra-large vessel stent platform cannot be considered informative, given the low number of patients treated with a 4.5/5.0 mm DES. The higher number of patients (51% observed difference) receiving an extra-large vessel platform in the intravascular imaging-guided versus the angiography-guided LM PCI group, despite comparable reference vessel diameters at quantitative coronary angiography, suggests that the 4.5/5.0 mm DES might have been underutilised in our study (probably a result of the operators' tendency to routinely use 3.5-4.0 mm platforms as the other DES types lack larger sizes).

Limitations

The present prospective study has some limitations that should be acknowledged. It is not an all-comers registry and has some inclusion/exclusion criteria, including the type of stent used. Accordingly, the favourable results of LM PCI in our study cannot be generalised to all patients with LM CAD. In particular, they should not be extended to patients with a SYNTAX score >32, severe chronic kidney disease (CKD), severe left ventricular systolic dysfunction and those presenting with STEMI or cardiogenic shock. Nevertheless, patients with low-to-intermediate anatomical complexity excluded from the ROLEX study (e.g., those with severe CKD, STEMI or severe left ventricular dysfunction, etc.) represent fewer than 7% of LM patients in all-comers registries like the DELTA 1 and 2[5,29]. Moreover, the most important baseline characteristics in the ROLEX study are very similar to the ones reported in the individual patient data meta-analysis of the EXCEL, NOBLE, SYNTAX and PRECOMBAT trials[11].

The observational, non-randomised nature of the prespecified subanalyses, as well as the lower incidence of adverse events at follow-up, makes the results hypothesis-generating, with the need for confirmation in future studies. Notwithstanding, although the influence of confounders cannot be excluded, the lower incidence of the primary EP in the intravascular imaging-guided versus angio-guided LM PCI group also remained significant after adjustment for differences in age, sex, diabetes, the extent of CAD and clinical presentation by a propensity score weight analysis, and for the cluster effect within centres. Moreover, these results are consistent with those of previously published studies and reinforce current guideline recommendations[1]. Yet, further analysis

on intravascular imaging, such as on the impact of LM distal bifurcation calcification severity on PCI strategy or on stent strut malapposition on IVUS/OCT, was not performed, as the use of intracoronary imaging was not mandatory per protocol. Notably, the results of the other 2 prespecified subanalyses should also be considered exploratory, considering the small sample size and low number of events.

One-year follow-up alone is not adequate, and we are currently progressing to 2-year follow-up. To this regard, the study steering committee has considered extending the follow-up to 5 years, in order to investigate the long-term results of LM PCI with this new-generation DES. The favourable safety and efficacy profile of LM PCI observed in our study was obtained in high-volume centres with expert interventionalists (all performing >15 LM PCI/year); operator volume is a known predictor of better outcomes of LM PCI[30]. Again, we attempted to mitigate this potential confounder by accounting for the cluster effect within centres. Among procedural variables highlighting the specific study environment, it should be emphasised that as many as 13% of patients received mechanical circulatory support and that this was mainly not used as a bailout. Thus, these event rates might not be reproducible in catheterisation laboratories with less experienced PCI operators or different equipment availability. Finally, the results of this study cannot be extended to LM PCI with other DES not included in this analysis. To note, another DES with similar platform sizes (SYNERGY MEGATRON; Boston Scientific) became available after the present study was conceived.

Conclusions

In this large, prospective registry on LM PCI performed with the latest-generation Resolute Onyx DES, the 1-year incidence of TLF was low, suggesting a favourable safety and efficacy profile of the procedure when a dedicated large-vessel stent platform is also available. As compared with angiographic guidance, intracoronary imaging-guided LM stenting was found to be associated with a clinically detectable benefit, and its use during LM PCI with latest-generation DES should be strongly recommended. Yet, these findings need to be confirmed by future randomised studies.

Impact on daily practice

The ROLEX study showed good safety and efficacy of LM PCI with the Resolute Onyx DES, which has dedicated extra-large vessel platforms. As the use of IVUS/OCT was found to be associated with lower rates of target vessel myocardial infarction, ischaemia-driven target lesion revascularisation, and definite/probable stent thrombosis after adjustment for potential confounders, this study supports the use of intravascular imaging guidance during LM PCI with the latest-generation dedicated large-vessel DES. Whether the Resolute Onyx DES is superior in the setting of LM PCI to other DES platforms without a dedicated large-vessel design remains to be studied in future randomised trials.

Appendix. Authors' affiliations

1. Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy; 2. Rivoli Infermi Hospital ASL TO3, Rivoli, Turin, Italy; 3. Centro Cardiologico Monzino, IRCCS, Milan, Italy; 4. Ospedale San Giovanni di Dio, Agrigento, Italy; 5. Fondazione Policlinico Universitario A. Gemelli ICCS, Università Cattolica del Sacro Cuore, Rome, Italy; 6. Policlinico San Marco, Zingonia, Italy; 7. University of Naples Federico II, Naples, Italy; 8. Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; 9. Department of Cardiosciences, A.O. San Camillo-Forlanini Hospital, Rome, Italy; 10. Cardiovascular Department, Azienda USL Toscana SudEst, Misericordia Hospital, Grosseto, Italy; 11. Division of Cardiology, Peschiera del Garda Hospital, Verona, Italy; 12. Division of Cardiovascular Medicine, Department of Medicine, University of Verona, Verona, Italy; 13. Ospedale Civile di Mirano, Mirano, Italy; 14. Interventional Cardiology Unit, San Luigi Gonzaga University Hospital, Orbassano, Italy; 15. Unit of Biostatistics, Epidemiology and Public Health, University of Padova, Padova, Italy; 16. Division of Cardiology, University of Messina, Messina, Italy; 17. Mater Salutis Hospital Legnago, Legnago, Italy; 18. Division of Cardiology, University of Palermo, Palermo, Italy; 19. Division of Cardiology, ASST Papa Giovanni XXIII Hospital, Cuneo, Italy; 20. Division of Cardiology, Azienda Socio-Sanitaria Territoriale di Cremona, Cremona, Italy; 21. Hospital de Santa Cruz, CHLO, Nova Medical School, CEDOC, Lisbon, Portugal; 22. Sandro Pertini Hospital, Rome, Italy; 23. Cardiology, CAST-Policlinico Hospital, Cardio-Thorax-Vascular and Transplant Department, University of Catania, Catania, Italy; 24. Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.

Guest editor

This paper was guest edited by Franz-Josef Neumann, MD; *Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany*.

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Supplementary data

Supplementary Appendix 1. Study protocol.

Supplementary Table 1. Thirty-day outcomes.

Supplementary Table 2. Details about cardiac deaths.

Supplementary Table 3. Baseline demographics and clinical characteristics (angiography vs intravascular imaging-guided LM PCI).

Supplementary Table 4. Angiographic characteristics (angiography vs intravascular imaging-guided LM PCI).

Supplementary Table 5. Procedural characteristics (angiography vs intravascular imaging-guided LM PCI).

Supplementary Table 6. Baseline demographics and clinical characteristics (extension of CAD).

Supplementary Table 7. Angiographic characteristics (extension of CAD).

Supplementary Table 8. Procedural characteristics (extension of CAD).

Supplementary Table 9. Baseline demographics and clinical characteristics (LM stent diameter).

Supplementary Table 10. Angiographic characteristics (LM stent diameter).

Supplementary Table 11. Procedural characteristics (LM stent diameter).

Supplementary Figure 1. Propensity score diagnostic plots (angiography vs intravascular imaging-guided LM PCI subanalysis).

Supplementary Figure 2. Propensity score diagnostic plots (extension of CAD subanalysis).

Supplementary Figure 3. Propensity score diagnostic plots (LM stent diameter subanalysis).

Supplementary Figure 4. Incidence of the composite primary endpoint and its single components in patients receiving a 4.5/5.0 mm drug-eluting stent.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00454

Supplementary data

Supplementary Appendix 1. Study protocol.

APPENDIX I: DEFINITIONS

DEATH

The deaths will be adjudicated per the ARC definition (17). All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac death: Any death due to proximate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all study procedure related deaths including those related to concomitant treatment.

Vascular death: Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-cardiovascular death: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

MYOCARDIAL INFARCTION (MI)

Spontaneous MI is defined based on the third universal definition of myocardial infarction, while periprocedural MI is defined according to the SCAI definition.

Spontaneous MI (>48 hours after intervention, MI type I) (18)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB
- Development of new Q waves in the ECG evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a *target* or *non-target vessel or lesion* in most cases.

Periprocedural MI after PCI (within 48 hours after PCI, MI type 4a)

The occurrence within 72 hours after PCI of either:

- CK-MB above 10 x URL (*determined on a single measurement), OR
- CK-MB above 5 x URL (*determined on a single measurement), PLUS

ƒ new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, or angiographically documented new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

This definition is the same as that of the EXCEL trial (4).

Symptoms of cardiac ischemia are not required for the diagnosis of peri-procedural MI.

Target-vessel vs. non-target-vessel MI: Any MI not clearly attributable to a non-target vessel will be considered as target-vessel MI.

REVASCULARIZATION
The revascularizations will be adjudicated per the ARC definition (18).

Location of Revascularization:
Target Lesion Revascularization (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. All TLR should be classified prospectively as clinically indicated (CI) or not clinically indicated by the investigator prior to repeat angiography. 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 Revascularization (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 Revascularization (Non-TLR): Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

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

Ischemia-driven Revascularization (CI-TLR/TVR): A revascularization is considered clinically indicated if associated with any of the following:

- Positive functional ischemia study including positive FFR
- Ischemic symptoms and angiographic diameter stenosis ≥ 50% by QCA
- Angiographic diameter stenosis ≥ 70% without angina or positive functional study.

Coronary artery bypass grafting (CABG):

- Urgent CABG is defined as immediate transfer from the cath-lab to the operation room for urgent bypass surgery during the index procedure.
- CABG during follow-up is only considered as a clinically-indicated target lesion revascularization if coronary angiography indicates a diameter of stenosis ≥ 50% of the treated coronary segment associated with one of the following conditions:
  - A positive history of recurrent angina pectoris presumably related to the target vessel.
  - Objective signs of ischemia (12-lead ECG, exercise test or equivalent) presumably related to the target vessel.
  - Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve).
  - A TLR/TVR with a diameter stenosis ≥70% in the absence of the above mentioned ischemic signs or symptoms.

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 subject left the catheterization lab.

Timing:

Acute stent thrombosis: 0 - 24 hours post stent implantation
Subacute 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

Categories:

Definite stent thrombosis: Confirmed either angiographically or pathologically.

Angiographic confirmation: 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 ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical elevation in cardiac biomarkers (refer to definition of spontaneous MI)
- Non-occlusive thrombosis
- Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified 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 embolization 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. 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: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis: Any unexplained death within the first 30 days, or, irrespective of the time after the index procedure, any MI that is related to documented acute ischemia 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 study follow up.

STROKE

Stroke is defined as a sudden onset of focal neurological deficits due to vascular lesions of the brain that persists >24 hours. Any neurological symptom that lasts < 24 hours is classified as transient ischemic attack (TIA). Stroke results from either of two types of cerebral vascular disturbance: ischemia or hemorrhage.

TRANSIENT ISCHEMIC ATTACK (TIA)

TIAs are focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours) that reflect dysfunction in the distribution of the affected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.

CORONARY LESION TYPE (ACC/AHA DEFINITION)

Type A Lesions (High success, >85%; Low Risk

Discrete (< 10 mm length); Concentric; Readily accessible; Nonangulated segment, < 45°; Smooth contour; Little or no calcification; Less than totally occlusive; Not ostial in location; No major branch involvement; Absence of thrombus

Type B Lesions (Moderate success, 60-85%; Moderate Risk

Tubular (10-20 mm length); Eccentric; Moderate tortuosity of proximal segment; Moderately angulated segment, > 45°, < 90°; Irregular contour;

* Type B1 lesions: One adverse characteristic
* Type B2 lesions: ≥ two adverse characteristics

Type C Lesions (Low success, <60%; High Risk

Diffuse (>20 mm length); Excessive tortuosity of proximal segment; Extremely angulated segments >90°; Total occlusions >3 months old; Inability to protect major side branches; Degenerated vein grafts with friable lesions

TIMI FLOW GRADES

0. No contrast flow through the stenosis.
1. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
2. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
3. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.

DISSECTION (by NHLBI dissection classification system)

A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.
B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.
C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.
D. Spiral luminal filling defects.
E. New persistent filling defects.
F. Non-A-E types that lead to impaired flow or total occlusion.

Note: Type E and F dissections may represent thrombus.

ANGINA PECTORIS

Braunwald Classification of Unstable Angina:

New onset of severe or accelerated angina. Patients with new onset (≤ 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not

experienced pain at rest during the preceding 2 months. Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours. Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Canadian Cardiovascular Society [CCS] Classification of Stable Angina:

Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation. Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace. Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

BLEEDING EVENT

Bleeding is defined per the Bleeding Academic Research Consortium (BARC) Classification (19).

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (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 Types 3, 4, or 5 but does meet at least one of the following criteria: Requiring non-surgical, medical intervention by a health care professional Leading to hospitalization of increased level of care Prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to <5** g/dL (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop ≥5** g/dL (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal) Subcategories: confirmed by autopsy or imaging or LP Intra-ocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period* Chest tube output ≥ 2 L within a 24 hour period
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

ACUTE SUCCESS

Clinical device success: Successful delivery and deployment of the stent at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of < 30% by QCA (by visual estimation if QCA unavailable) and TIMI 3 flow in main branch.

Clinical procedure success: Achievement of final in-stent residual stenosis of <30% by QCA (by visual estimation if QCA unavailable) with successful delivery and deployment of the stent at the intended target lesion and successful withdrawal of the delivery system without the occurrence of death, target lesion related MI or repeat ischemia-driven revascularization of the target lesion during the hospital stay (maximum of 7 days).

ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation when subject was treated with a study product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product whether or not related to the investigational device.

SERIOUS ADVERSE EVENT

If an adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE).

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization for treatment (diagnostic hospitalization is not regarded as a SAE)
- Requires intervention to prevent permanent impairment or injury
- Results in a persistent or significant disability/incapacity
- Results in a congenital disease or anomaly
- An important medical event that may not result 1) – 5) but may be considered serious based upon the investigators appropriate judgment

ADVERSE DEVICE EFFECT

Adverse device effects include issues related to its specifications, product experiences and device malfunctions, insufficient contents of instruction for use and adverse device effects. It also includes inevitable adverse events potentially occurs even if a device is properly used. This means that an adverse device effect is defined as any adverse event that is related to the study device, or whose relationship to the study device is unknown.

UNANATICIPATED ADVERSE DEVICE EFFECT (UADE)

An unanticipated adverse device effect is an adverse device effect (including infection that is suspected to relate to use of the device) of which occurrence and the occurrence trend such as number and frequency of the occurrences, and conditions on the occurrence cannot be predicted from the Investigator’s Brochure of the investigational device.

APPENDIX II: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post- trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a

research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.

32. For medical research using identifiable human material or data, such as research on material

or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Supplementary Table 1. Thirty-day outcomes.

Outcome	**N = 450**
All-cause death	11 (2.4%)
Cardiac Death	7 (1.6%)
TV-MI	5 (1.1%)
ID-TLR	3 (0.7%)
Stroke	2 (0.4%)
Stent-thrombosis	4 (0.9%)
Bleeding	13 (2.8%)
BARC 2	3 (0.6%)
BARC 3A	6 (1.3 %)
BARC 3B	3 (0.7%)
BARC 3C	1 (0.2%)

TV-MI: target vessel myocardial infarction; ID-TLR: ischemia-driven target lesion revascularisation; BARC: Bleeding Academic Research Consortium.

Supplementary Table 2. Details about cardiac deaths.

Patient	Outcome	Clinical information	Days after index procedure
1	Cardiac Death	Intraprocedural Death	0
2	Cardiac Death	Intraprocedural Death	0
3	Cardiac Death	Intraprocedural Death	0
4	Cardiac Death	Probable ST followed by large anterior myocardial infarction	5
5	Cardiac Death	Definite ST and cardiogenic shock following DAPT discontinuation because of major bleeding	7
6	Cardiac Death	Congestive heart fialure	12
7	Cardiac Death	Cardiogenic shock during in-hospital stay	18
8	Cardiac Death	Definite ST and cardiac arrest following DAPT discontinuation for urgent non-cardiac surgery	42
9	Cardiac Death	Sudden unexplained death	115
10	Cardiac Death	Sudden unexplained death	175
11	Cardiac Death	Congestive heart failure	227
12	Cardiac Death	Non-target vessel myocardial infarction	311

DAPT: dual antiplatelet therapy; ST: stent thrombosis

Supplementary Table 3. Baseline demographics and clinical characteristics (angiography vs intravascular imaging-guided LM PCI).

Characteristic	Angio-guided N = 250	Imaging-guided N = 200	p-value
Age	72±10	71±11	0.9
Gender: female	43 (17%)	32 (16%)	0.6
BMI (kg/m^2)	29.2±22.3	26.3±4.5	0.6
Euroscore II	3.1±3.8	2.2±2.2	0.004
Current smoker	56 (22%)	39 (20%)	0.9
Diabetes mellitus	75 (30%)	59 (30%)	0.9
Insulin dependent	26 (10%)	15 (7%)	0.6
Non-Insulin dependent	50 (20%)	43 (21%)	
Hypertension	203 (81%)	152 (76%)	0.6
Hypercholesterolemia	173 (69%)	140 (70%)	0.9
Glomerul filtration rate (ml/min)	72 [56; 90]	78 [58; 90]	0.3
Previous stroke	14 (6%)	13 (6%)	0.9
Previous MI	61 (24%)	50 (25%)	0.9
Previous PCI	87 (35%)	78 (39%)	0.6
Peripheral vascular disease	45 (18%)	32 (16%)	0.9
COPD	18 (7%)	12 (6%)	0.7
LVEF			0.4
Good (>50%)	153 (61%)	139 (69%)	
Fair (30-50%)	99 (40%)	59 (29%)	
Chronic coronary syndrome	105 (42%)	107 (53%)	0.9
CCS 0	145 (58%)	93 (47%)	
CCS 1	21 (8%)	23 (11%)	
CCS 2	33 (13%)	33 (16%)	
CCS 3	27 (11%)	26 (13%)	
CCS 4	24 (10%)	25 (13%)	
Acute coronary syndrome	145 (58%)	93 (47%)	0.015
Unstable angina	32 (13%)	34 (17%)	
NSTEMI	113 (45%)	59 (30%)	
NYHA class at admission			0.7
I	130 (52%)	113 (57%)	
II	80 (32%)	60 (30%)	
III	33 (13%)	25 (12%)	
IV	7 (3%)	2 (1%)	
Dual antiplatelet therapy	136 (54%)	116 (58%)	0.7
Clopidogrel	78 (31%)	72 (36%)	

Ticagrelor	52 (21%)	41 (20%)	
Prasugrel	5 (2%)	3 (2%)	
Ticlopidine	1 (0.4%)	0 (0.0%)	
Oral anticoagulation	16 (6%)	15 (7%)	0.6

MI: myocardial infarction; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulòmonary disease; LVEF: left ventricular ejection fraction; CCS: Canadian Cardiovascular Society Angina Score; NSTEMI: non-ST-elevation myocardial infarction; NYHA: New York Heart Association

Supplementary Table 4. Angiographic characteristics (angiography vs intravascular imaging-guided LM PCI).

Characteristic	Angio-guided N = 250	Imaging-guided N = 200	p-value
CAD distribution			0.2
Isolated LM disease	25 (10%)	21 (11%)	
LM+single vessel CAD	72 (29%)	69 (34%)	
LM+dual vessel CAD	80 (32%)	72 (36%)	
LM+triple vessel CAD	73 (29%)	38 (19%)	
SYNTAX score	25±7	23±7	0.2
<23	75 (30%)	87 (44%)	
23-32	175 (70%)	113 (56%)	
LM CAD distribution			
Ostial LM disease	52 (21%)	40 (20%)	0.9
LM shaft disease	64 (26%)	53 (27%)	0.9
Distal LM disease	189 (75%)	161 (80%)	0.4
Medina 1.0.0	40 (16%)	36 (18%)	
Medina 1.1.0	80 (32%)	73 (36%)	
Medina 1.0.1	15 (6%)	21 (11%)	
Medina 0.1.1	14 (6%)	7 (3%)	
Medina 1.1.1	40 (16%)	24 (12%)	
LM calcifications			0.8
None	64 (25%)	62 (31%)	
Mild/moderate	154 (62%)	116 (58%)	
Severe	32 (13%)	22 (11%)	
LM Thrombotic lesion	11 (4%)	16 (8%)	0.3
Tortuosity			0.5
None	183 (73%)	160 (80%)	
Mild/moderate	63 (25%)	40 (20%)	
Severe	4 (2%)	0 (0%)	
Baseline QCA			
LM diameter stenosis (%)	62±18	61±16	0.7
LAD diameter stenosis (%)	56±30	56±29	0.9
LCx diameter stenosis (%)	35±32	35±31	0.9
LM RVD (mm)	3.7±0.7	3.7±0.7	0.9
LAD RVD (mm)	3.0±0.8	3.3±0.8	0.2
LCx RVD (mm)	2.8±0.7	2.9±0.6	0.9
LM minimal lumen diameter (mm)	1.9±0.8	2.1±0.8	0.2
LAD minimal lumen diameter (mm)	1.6±0.9	1.9±0.9	0.056

LCx minimal lumen diameter (mm)	1.9±0.8	2.0±0.8	0.7
LM lesion length (mm)	8.9±5.3	9.0±6.2	0.9
LAD lesion length (mm)	12.0±11.0	10.0±8.0	0.9
LCx lesion length (mm)	5.8±6.5	5.3±5.7	0.9
Bifurcation angle (°)	80±27	79±25	0.9

CAD: coronary artery disease; LM: left main; QCA: quantitative coronary angiography; LAD: left anterior descending artery; LCX: left circumflex artery; RVD: reference vessel diameter

Supplementary Table 5. Procedural characteristics (angiography vs intravascular imaging-guided LM PCI).

Characteristic	Angio-guided N = 250	Imaging-guided N = 200	p-value
Access			0.059
Femoral	70 (28%)	34 (17%)	
Radial	180 (72%)	166 (83%)	
Guiding catheter			0.9
6 F	207 (83%)	162 (81%)	
7 F	43 (17%)	38 (19%)	
Balloon predilation	182 (73%)	151 (76%)	0.8
Intravascular imaging			<0.001
IVUS	0 (0%)	188 (94%)	
OCT	0 (0%)	12 (6%)	
FFR/iFR	15 (6%)	13 (6%)	0.9
Rotational atherectomy	9 (4%)	10 (4%)	0.9
Initial treatment strategy			0.9
Provisional	195 (78%)	161 (81%)	
Two-stent strategy	55 (22%)	39 (19%)	
Final treatment strategy			0.8
One-stent	189 (76%)	158 (79%)	
LM only	31 (12%)	18 (9%)	
LM-LAD	146 (59%)	132 (66%)	
LM-LCx	12 (5%)	8 (4%)	
Two-stent	61 (24%)	42 (21%)	
T stenting	7 (3%)	5 (2%)	
TAP stenting	18 (7%)	9 (5%)	
DK crush	26 (10%)	10 (5%)	
Culotte	9 (4%)	18 (9%)	
Kissing stenting	1 (0.4%)	0 (0.0%)	
Nominal LM stent diameter			0.2
≤3.0 mm	37 (15%)	16 (8%)	
3.5-4.0 mm	177 (71%)	142 (71%)	
4.5-5.0 mm	36 (14%)	42 (21%)	
LM stent length (mm)	22 [18,26]	22 [16,26]	0.6
Side branch stent length (mm)	18 [12,22]	18 [15,22]	0.5
POT	210 (84%)	181 (91%)	0.2
POT balloon diameter (mm)	4.5 [4.0,4.5]	4.5 [4.0,5.0]	0.1

Final kissing balloon	152 (61%)	136 (68%)	0.3
After two-stent strategy	56 (92%)	39 (93%)	
Additional PCI (not involving LM)	150 (60%)	99 (50%)	0.2
LAD	93 (37%)	59 (30%)	
LCx	42 (17%)	30 (15%)	
RCA	15 (6%)	10 (5%)	
Number of implanted stent	1.9±1.2	2.3±1.0	0.9
Total stent length (mm)	48±26	44±24	0.4
Fluoroscopy time (min)	22 [15; 34]	22 [17; 28]	0.9
Contrast volume (cc)	230 [170; 300]	220 [160; 271]	0.4
Number of guidewires used	2 [2,3]	2 [1,3]	0.4
Final TIMI flow			0.6
0-1	0 (0.0%)	2 (1%)	
2	3 (1%)	1 (0.5%)	
3	247 (99%)	197 (98%)	
Any remaining coronary dissection	1 (0.4%)	9 (4%)	0.076
Acute side branch occlusion	3 (1%)	1 (0.5%)	0.9
Post-PCI QCA			
LM diameter stenosis (%)	3±7	3±7	0.9
LAD diameter stenosis (%)	5±12	4±10	0.8
LCx diameter stenosis (%)	11±18	12±19	0.9
LM minimal lumen diameter (mm)	4.0±0.6	3.9±0.6	0.9
LAD minimal lumen diameter (mm)	3.2±0.8	3.3±0.6	0.5
LCx minimal lumen diameter (mm)	2.8±2.9	2.6±0.7	0.6
Residual SYNTAX score	3.7±6.2	2.9±4.5	0.8
Gp IIb/IIIA inhibitors	6 (2%)	3 (2%)	0.9
Mechanical circulatory support	58 (13%)	58 (13%)	0.4
Planned	27 (12%)	22 (11%)	
Unplanned	2 (1%)	7 (2%)	
Clinical device success	248 (99%)	196 (98%)	0.9
Procedural success	248 (99%)	198 (99%)	0.9
Intraprocedural death	3 (1%)	0 (0.0%)	0.6

IVUS: intravascular imaging; OCT: optical coherence tomography; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; LM: left main; LAD: left anterior descending artery; LCx: left circumflex; TAP: T-and-protrusion; DK: double kissing; POT: proximal optimisation techniques; PCI: percutaneous coronary intervention; RCA: right coronary artery; QCA: quantitative coronary analysis

Supplementary Table 6. Baseline demographics and clinical characteristics (extension of CAD).

Characteristic	Other N = 263	Isolated LM/ LM + 1-vessel CAD N = 187	p-value
Age	73±11	70±11	0.058
Gender: female	42 (16%)	33 (18%)	0.6
BMI (kg/m^2)	27.9±15.4	28.0±19.9	0.5
Euroscore II	2.95±3.63	2.39±2.61	0.085
Current smoker	48 (18%)	47 (25%)	0.5
Diabetes mellitus	90 (34%)	44 (24%)	0.080
Insulin dependent	35 (13%)	6 (3%)	0.049
Non-Insulin dependent	55 (21%)	38 (20%)	
Hypertension	222 (84%)	133 (72%)	0.028
Hypercholesterolemia	190 (72%)	123 (67%)	0.5
Glomerul filtration rate (ml/min)	72 [55; 89]	77 [60; 90]	0.087
Previous stroke	18 (7%)	9 (5%)	0.6
Previous MI	76 (29%)	35 (19%)	0.068
Previous PCI	113 (43%)	52 (28%)	0.028
Peripheral vascular disease	49 (18%)	28 (15%)	0.5
COPD	19 (7%)	11 (6%)	0.7
LVEF			0.058
Good (>50%)	158 (60%)	134 (71%)	
Fair (30-50%)	105 (40%)	53 (29%)	
Chronic coronary syndrome	118 (45%)	94 (50%)	0.6
CCS 0	145 (55%)	93 (50%)	
CCS 1	24 (9%)	20 (11%)	
CCS 2	33 (13%)	33 (17%)	
CCS 3	31 (12%)	22 (12%)	
CCS 4	30 (11%)	19 (10%)	
Acute coronary syndrome	145 (55%)	93 (50%)	0.8
Unstable angina	37 (14%)	26 (14%)	
NSTEMI	108 (41%)	67 (36%)	
NYHA class at admission			0.9
I	141 (54%)	102 (54%)	
II	84 (32%)	56 (30%)	
III	33 (12%)	25 (13%)	
IV	5 (2%)	4 (3%)	
Dual antiplatelet therapy	151 (57%)	101 (55%)	0.7
Clopidogrel	88 (33%)	62 (33%)	

Ticagrelor	57 (22%)	36 (19%)	
Prasugrel	3 (1%)	5 (3%)	
Ticlopidine	1 (0.04%)	0 (0.0%)	
Oral anticoagulation	20 (7.7%)	11 (5.9%)	0.6

MI: myocardial infarction; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulòmonary disease; LVEF: left ventricular ejection fraction; CCS: Canadian Cardiovascular Society Angina Score; NSTEMI: non-ST-elevation myocardial infarction; NYHA: New York Heart Association

Supplementary Table 7. Angiographic characteristics (extension of CAD).

Characteristic	Other N = 263	Isolated LM/ LM + 1-vessel CAD N = 187	p-value
CAD distribution			<0.001
Isolated LM disease	0 (0.0%)	45 (24%)	
LM+single vessel CAD	0 (0.0%)	142 (76%)	
LM+dual vessel CAD	152 (59%)	0 (0.0%)	
LM+triple vessel CAD	111 (41%)	0 (0.0%)	
SYNTAX score	27±6	21±7	<0.001
<23	60 (23%)	109 (58%)	
23-32	203 (77%)	78 (42%)	
LM CAD distribution			
Ostial LM disease	39 (15%)	54 (29%)	0.002
LM shaft disease	63 (24%)	52 (28%)	0.6
Distal LM disease	218 (82%)	126 (67%)	<0.001
Medina 1.0.0	46 (17%)	30 (16%)	
Medina 1.1.0	86 (33%)	67 (36%)	
Medina 1.0.1	20 (8%)	16 (8%)	
Medina 0.1.1	15 (6%)	6 (3%)	
Medina 1.1.1	51 (19%)	13 (7%)	
LM calcifications			0.040
None	58 (22%)	68 (36%)	
Mild/moderate	169 (64%)	101 (54%)	
Severe	36 (14%)	18 (10%)	
LM Thrombotic lesion	15 (6%)	12 (6%)	0.8
Tortuosity			0.9
None	200 (76%)	143 (77%)	
Mild/moderate	60 (23%)	43 (23%)	
Severe	3 (1%)	1 (0.5%)	
Baseline QCA			
LM diameter stenosis (%)	62±16	61±18	0.9
LAD diameter stenosis (%)	62±27	48±32	<0.001
LCx diameter stenosis (%)	43±32	23±26	<0.001
LM RVD (mm)	3.7±0.7	3.7±0.7	0.9
LAD RVD (mm)	3.1±0.7	3.2±0.9	0.7
LCx RVD (mm)	2.9±0.6	2.8±0.7	0.9
LM minimal lumen diameter (mm)	2.0±0.8	2.0±0.9	0.9
LAD minimal lumen diameter (mm)	1.7±0.9	1.8±0.9	0.2

LCx minimal lumen diameter (mm)	1.9±0.8	2.1±0.8	0.001
LM lesion length (mm)	8.7±5.1	9.3±6.4	0.9
LAD lesion length (mm)	12.0±10.0	10.0±9.0	0.012
LCx lesion length (mm)	6.3±5.9	4.3±6.3	<0.001
Bifurcation angle (°)	81±27	77±25	0.2

CAD: coronary artery disease; LM: left main; QCA: quantitative coronary angiography; LAD: left anterior descending artery; LCx: left circumflex artery; RVD: reference vessel diameter

Supplementary Table 8. Procedural characteristics (extension of CAD).

Characteristic	Other N = 263	Isolated LM/ LM + 1-vessel CAD N = 187	p-value
Access			0.026
Femoral	73 (28%)	31 (17%)	
Radial	190 (72%)	156 (83%)	
Guiding catheter			0.4
6 F	212 (81%)	157 (84%)	
7 F	51 (19%)	30 (16%)	
Balloon predilation	209 (79%)	124 (67%)	0.006
Intravascular imaging			
IVUS	104 (39%)	84 (45%)	0.4
OCT	5 (2%)	7 (4%)	0.4
FFR/iFR	11 (4%)	17 (9%)	0.1
Rotational atherectomy	16 (6%)	3 (2%)	0.2
Initial treatment strategy			<0.001
Provisional	181 (69%)	175 (94%)	
Two-stent strategy	82 (31%)	12 (6%)	
Final treatment strategy			<0.001
One-stent	175 (67%)	172 (92%)	
LM only	14 (5%)	35 (19%)	
LM-LAD	145 (56%)	133 (71%)	
LM-LCx	16 (6%)	4 (2%)	
Two-stent	88 (33%)	15 (8%)	
T stenting	11 (4%)	1 (0.5%)	
TAP stenting	23 (9%)	4 (2%)	
DK crush	30 (11%)	6 (3%)	
Culotte	23 (9%)	4 (2%)	
Kissing stenting	1 (0.3%)	0 (0.0%)	
Nominal LM stent diameter			0.4
≤3.0 mm	35 (13%)	18 (10%)	
3.5-4.0 mm	187 (71%)	132 (70%)	
4.5-5.0 mm	41 (16%)	37 (20%)	
LM stent length (mm)	22 [18,26]	22 [15,26]	0.3
Side branch stent length (mm)	18 [15,22]	18 [15,26]	0.6
POT	230 (87%)	161 (87%)	0.9
POT balloon diameter (mm)	4.5 [4.0,4.9]	4.5 [4.0,4.5]	0.048
Final kissing balloon	191 (72%)	97 (52%)	<0.001

After two-stent strategy	82 (93%)	13 (87%)	
Additional PCI (not involving LM)	167 (63%)	82 (44%)	<0.001
LAD	83 (31%)	69 (37%)	
LCx	58 (22%)	14 (8%)	
RCA	19 (7%)	6 (3%)	
Number of implanted stent	2.4±0.8	1.9±0.9	<0.001
Total stent length (mm)	51±25	39±23	<0.001
Fluoroscopy time (min)	23 [17; 31]	21 [15; 27]	0.041
Contrast volume (cc)	226 [170; 297]	220 [161; 280]	0.7
Number of guidewires used	2 [2,3]	2 [2,3]	0.010
Final TIMI flow			0.3
0-1	1 (0.4%)	1 (0.5%)	
2	4 (2%)	0 (0.0%)	
3	258 (98%)	186 (99%)	
Any remaining coronary dissection	3 (1%)	7 (4%)	0.2
Acute side branch occlusion	2 (0.7%)	2 (1%)	0.9
Post-PCI QCA			
LM diameter stenosis (%)	3±7	3±7	0.7
LAD diameter stenosis (%)	6±12	3±10	0.040
LCx diameter stenosis (%)	12±19	11±19	0.5
LM minimal lumen diameter (mm)	4.0±0.6	3.9±0.5	0.9
LAD minimal lumen diameter (mm)	3.2±0.7	3.3±0.7	0.7
LCx minimal lumen diameter (mm)	2.9±2.8	2.6±0.8	0.8
Residual SYNTAX score	4.4±6.0	2.0±4.6	<0.001
Gp IIb/IIIA inhibitors	2 (0.8%)	7 (4%)	0.1
Mechanical circulatory support	40 (15%)	18 (10%)	0.006
Planned	38 (14%)	11 (6%)	
Unplanned	2 (1%)	7 (4%)	
Clinical device success	260 (98%)	186 (99%)	0.9
Procedural success	262 (99%)	185 (99%)	0.9
Intraprocedural death	0 (0.0%)	3 (2%)	0.2

IVUS: intravascular imaging; OCT: optical coherence tomography; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; LM: left main; LAD: left anterior descending artery; LCx: left circumflex; TAP: T-and-protrusion; DK: double kissing; POT: proximal optimisation techniques; PCI: percutaneous coronary intervention; RCA: right coronary artery; QCA: quantitative coronary analysis

Supplementary Table 9. Baseline demographics and clinical characteristics (LM stent diameter).

Characteristic	< 4.5 mm N = 372	>= 4.5 mm N = 78	p-value
Age	72±11	73±9	0.8
Gender: female	62 (17%)	13 (17%)	0.9
BMI (kg/m^2)	28.1±18.8	27.3±4.3	0.8
Euroscore II	2.8±3.4	2.3±2.1	0.8
Current smoker	79 (21%)	16 (20%)	0.9
Diabetes mellitus	112 (30%)	22 (28%)	0.9
Insulin dependent	35 (9%)	6 (8%)	0.9
Non-Insulin dependent	77 (21%)	16 (21%)	
Hypertension	299 (80%)	56 (72%)	0.8
Hypercholesterolemia	260 (70%)	53 (68%)	0.9
Glomerul filtration rate (ml/min)	74 [56; 90]	78 [59; 90]	0.8
Previous stroke	21 (6%)	6 (8%)	0.8
Previous MI	89 (24%)	22 (28%)	0.8
Previous PCI	131 (35%)	34 (43%)	0.8
Peripheral vascular disease	64 (17%)	13 (16%)	0.9
COPD	24 (6%)	6 (8%)	0.9
LVEF			0.9
Good (>50%)	242 (65%)	50 (63%)	
Fair (30-50%)	130 (35%)	28 (37%)	
Chronic coronary syndrome	183 (49%)	29 (37%)	0.8
CCS 0	189 (51%)	49 (63%)	
CCS 1	37 (10%)	7 (9%)	
CCS 2	59 (16%)	7 (9%)	
CCS 3	45 (12%)	8 (10%)	
CCS 4	42 (11%)	7 (9%)	
Acute coronary syndrome	189 (51%)	49 (61%)	0.8
Unstable angina	45 (12%)	18 (23%)	
NSTEMI	144 (39%)	31 (40%)	
NYHA class at admission			0.9
I	197 (53%)	46 (60%)	
II	120 (32%)	20 (25%)	
III	48 (13%)	10 (12%)	
IV	7 (2%)	2 (3%)	
Dual antiplatelet therapy	202 (54%)	50 (64%)	0.8
Clopidogrel	122 (33%)	28 (35%)	
Ticagrelor	75 (20%)	18 (23%)	

Prasugrel	4 (1%)	4 (5%)	
Ticlopidine	1 (0.03%)	0 (0.0%)	
Oral anticoagulation	21 (6%)	10 (13%)	0.8

MI: myocardial infarction; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulòmonary disease; LVEF: left ventricular ejection fraction; CCS: Canadian Cardiovascular Society Angina Score; NSTEMI: non-ST-elevation myocardial infarction; NYHA: New York Heart Association

Supplementary Table 10. Angiographic characteristics (LM stent diameter).

Characteristic	< 4.5 mm N = 372	>= 4.5 mm N = 78	p-value
CAD distribution			0.11
Isolated LM disease	34 (9%)	12 (15%)	
LM+single vessel CAD	120 (32%)	21 (28%)	
LM+dual vessel CAD	122 (33%)	30 (38%)	
LM+triple vessel CAD	96 (26%)	15 (19%)	
SYNTAX score	25±7	24±9	0.9
<23	126 (34%)	34 (44%)	
23-32	246 (66%)	44 (56%)	
LM CAD distribution			
Ostial LM disease	78 (21%)	14 (18%)	0.9
LM shaft disease	96 (26%)	21 (27%)	0.9
Distal LM disease	287 (77%)	63 (80%)	0.9
Medina 1.0.0	61 (16%)	15 (19%)	
Medina 1.1.0	123 (33%)	30 (38%)	
Medina 1.0.1	28 (7%)	8 (10%)	
Medina 0.1.1	15 (4%)	6 (7%)	
Medina 1.1.1	60 (16%)	4 (5%)	
LM calcifications			0.9
None	106 (28%)	20 (27%)	
Mild/moderate	219 (59%)	51 (65%)	
Severe	47 (13%)	7 (8%)	
LM Thrombotic lesion	22 (6%)	6 (8%)	0.8
Tortuosity			0.9
None	287 (77%)	56 (72%)	
Mild/moderate	82 (22%)	21 (27%)	
Severe	3 (0.8%)	1 (1%)	
Baseline QCA			
LM diameter stenosis (%)	62±17	63±14	0.8
LAD diameter stenosis (%)	58±29	43±33	0.2
LCx diameter stenosis (%)	34±31	35±33	0.8
LM RVD (mm)	4.0±0.6	4.2±1.2	0.8
LAD RVD (mm)	3.1±0.8	3.5±0.8	0.8
LCx RVD (mm)	2.8±0.6	3.1±0.7	0.7
LM minimal lumen diameter (mm)	2.0±0.8	2.1±0.9	0.8
LAD minimal lumen diameter (mm)	1.7±0.9	2.2±0.8	0.8
LCx minimal lumen diameter (mm)	2.0±0.8	2.1±0.9	0.8

LM lesion length (mm)	9.0 ±5.7	8.7 ±4.2	0.9
LAD lesion length (mm)	11.0±10.0	10.0±11.0	0.9
LCx lesion length (mm)	5.5±6.0	5.8±6.3	0.8
Bifurcation angle (°)	80±26	82±26	0.8

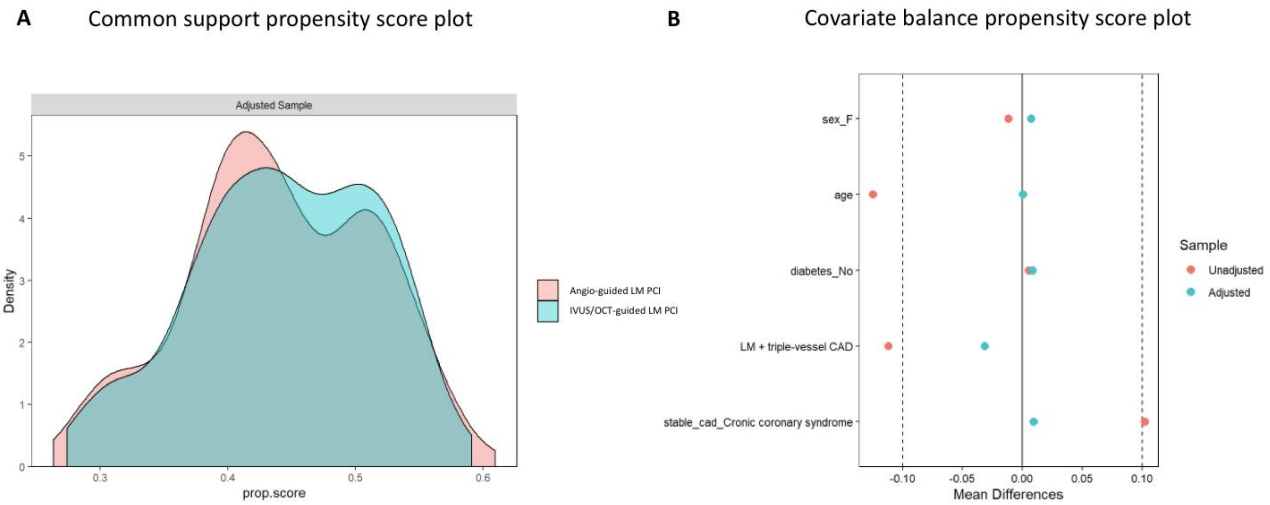
CAD: coronary artery disease; LM: left main; QCA: quantitative coronary angiography; LAD: left anterior descending artery; LCx: left circumflex artery; RVD: reference vessel diameter

Supplementary Table 11. Procedural characteristics (LM stent diameter).

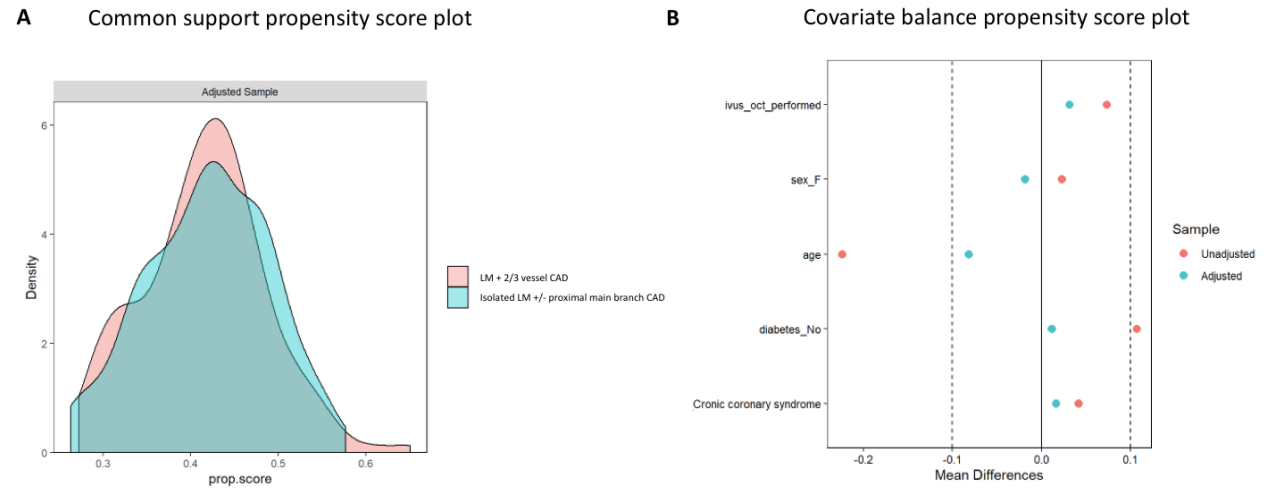
Characteristic	< 4.5 mm N = 372	>= 4.5 mm N = 78	p-value
Access			0.9
Femoral	86 (23%)	18 (23%)	
Radial	286 (77%)	60 (77%)	
Guiding catheter			0.044
6 F	316 (85%)	53 (68%)	
7 F	56 (15%)	25 (32%)	
Balloon predilation	277 (75%)	56 (71%)	0.5
Intravascular imaging			
IVUS	146 (39%)	42 (53%)	0.12
OCT	11 (3%)	1 (%)	0.9
FFR/iFR	26 (7%)	2 (3%)	0.9
Rotational atherectomy	16 (4%)	3 (4%)	0.7
Initial treatment strategy			0.9
Provisional	296 (80%)	60 (77%)	
Two-stent strategy	76 (20%)	18 (23%)	
Final treatment strategy			0.9
One-stent	287 (77%)	60 (77%)	
LM only	38 (10%)	11 (14%)	
LM-LAD	237 (64%)	41 (53%)	
LM-LCx	12 (3%)	8 (10%)	
Two-stent	85 (23%)	18 (23%)	
T stenting	7 (2%)	5 (6%)	
TAP stenting	24 (6%)	3 (4%)	
DK crush	30 (8%)	6 (8%)	
Culotte	23 (6%)	4 (5%)	
Kissing stenting	1 (0.2%)	0 (0.0%)	
Nominal LM stent diameter			<0.001
≤3.0 mm	53 (14%)	0 (0.0%)	
3.5-4.0 mm	319 (86%)	0 (0.0%)	
4.5-5.0 mm	0 (0.0%)	78 (100%)	
LM stent length (mm)	22 [18,26]	18 [12,23]	0.8
Side branch stent length (mm)	18 [15,22]	22 [16,24]	0.8
POT	325 (88%)	66 (83%)	0.9
POT balloon diameter (mm)	4.5 [4.0,4.5]	5.0 [4.5,5.0]	0.8
Final kissing balloon	236 (64%)	52 (66%)	0.9
After two-stent strategy	77 (91%)	17 (100%)	

Additional PCI (not involving LM)	204 (55%)	45 (57%)	0.4
LAD	127 (34%)	25 (32%)	
LCx	57 (15%)	15 (19%)	
RCA	20 (5%)	5 (6%)	
Number of implanted stent	1.8±1.2	2.3±1.2	0.8
Total stent length (mm)	47±25	37±24	0.3
Fluoroscopy time (min)	22 [16; 31]	20 [14; 23]	0.8
Contrast volume (cc)	225 [170; 290]	193 [130; 235]	0.8
Number of guidewires used	2 [2,3]	2 [2,4]	0.5
Final TIMI flow			0.8
0-1	1 (0.2%)	1 (1%)	
2	3 (1%)	1 (1%)	
3	368 (99%)	76 (97%)	
Any remaining coronary dissection	8 (2%)	2 (3%)	0.9
Acute side branch occlusion	3 (1%)	1 (1%)	0.9
Post-PCI QCA			
LM diameter stenosis (%)	3±7	3±7	0.9
LAD diameter stenosis (%)	5±12	5±11	0.9
LCx diameter stenosis (%)	11±18	13±18	0.8
LM minimal lumen diameter (mm)	3.9±0.6	4.3±0.6	0.8
LAD minimal lumen diameter (mm)	3.2±0.7	3.7±0.8	0.8
LCx minimal lumen diameter (mm)	2.8±2.4	2.8±0.9	0.8
Residual SYNTAX score	3.2±4.9	4.5±6.7	0.2
Gp IIb/IIIA inhibitors	6 (2%)	3 (4%)	0.8
Mechanical circulatory support	45 (12%)	13 (16%)	0.9
Planned	37 (10%)	12 (15%)	
Unplanned	8 (2%)	1 (1%)	
Clinical device success	365 (98%)	78 (100%)	0.9
Procedural success	367 (99%)	78 (100%)	0.9
Intraprocedural death	3 (0.8%)	0 (0.0%)	0.9

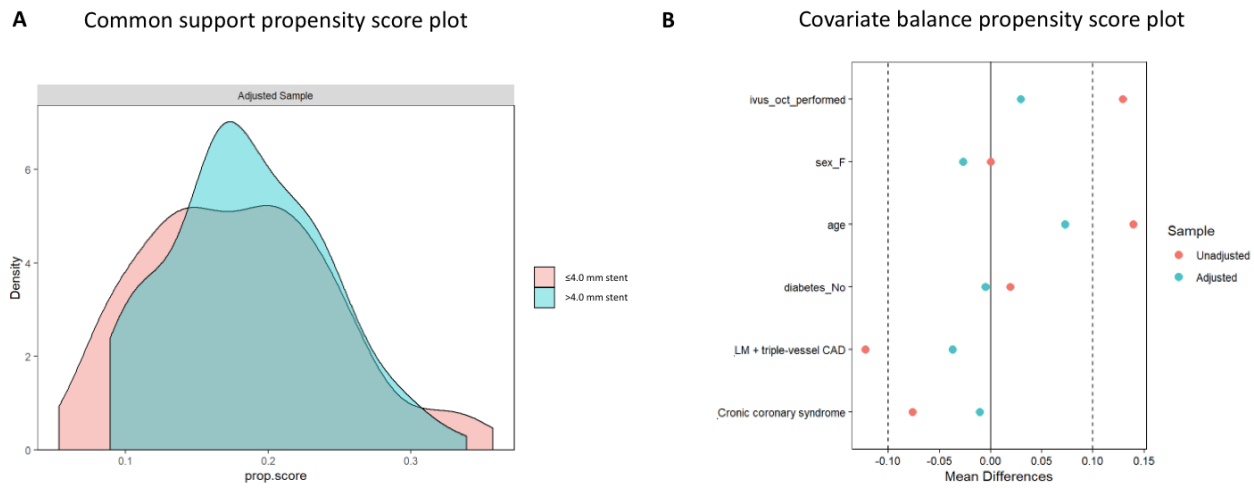
IVUS: intravascular imaging; OCT: optical coherence tomography; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; LM: left main; LAD: left anterior descending artery; LCx: left circumflex; TAP: T-and-protrusion; DK: double kissing; POT: proximal optimisation techniques; PCI: percutaneous coronary intervention; RCA: right coronary artery; QCA: quantitative coronary analysis



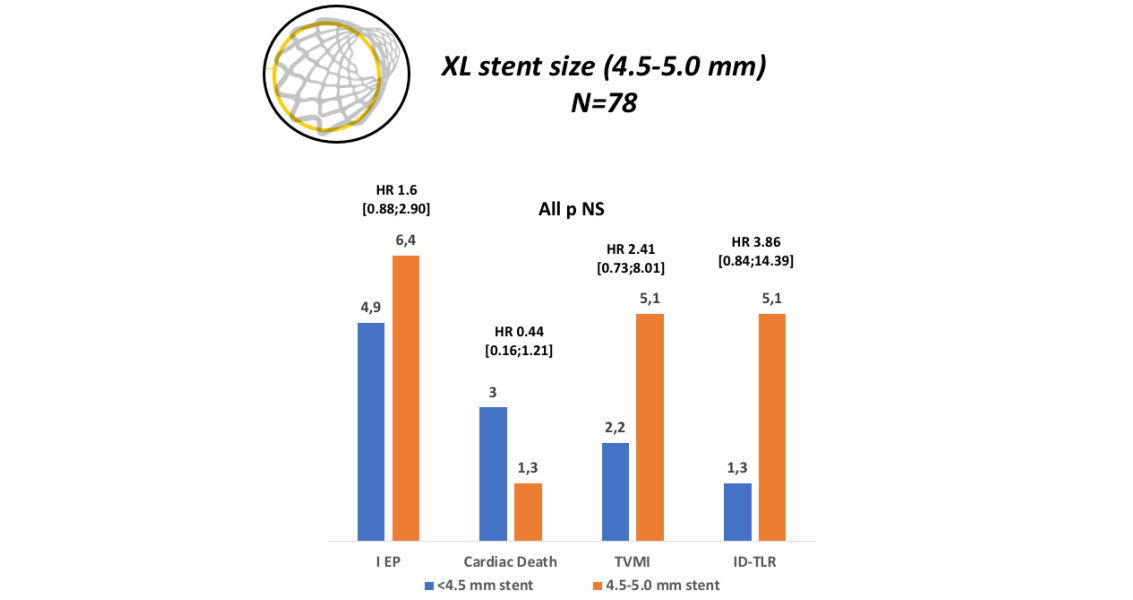
Supplementary Figure 1. Propensity score diagnostic plots (angiography vs intravascular imaging-guided LM PCI subanalysis).
The overlap of the propensity scores distributions across groups was found to be satisfactory (the differences between the propensity-adjusted means are within the limit of 0.1, indicating a good balance of the propensity score concerning the covariates.



Supplementary Figure 2. Propensity score diagnostic plots (extension of CAD subanalysis).
The overlap of the propensity scores distributions across groups was found to be satisfactory (the differences between the propensity-adjusted means are within the limit of 0.1, indicating a good balance of the propensity score concerning the covariates.



Supplementary Figure 3. Propensity score diagnostic plots (LM stent diameter subanalysis).
The overlap of the propensity scores distributions across groups was found to be satisfactory (the differences between the propensity-adjusted means are within the limit of 0.1, indicating a good balance of the propensity score concerning the covariates.



EP:Endpoint; TV-MI: Target vessel myocardial infarction ; ID-TLR: Ischemia driven target lesion revascularization

Inverse Probability Treatment Weight Cox regression models.
Propensity score has been estimated by considering as confounding factors age, gender, diabetes, 3-vessel CAD, ACS and use of intravascular imaging

Supplementary Figure 4. Incidence of the composite primary endpoint and its single components in patients receiving a 4.5/5.0 mm drug-eluting stent.