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Paclitaxel-coated balloons for vulnerable lipid-rich plaques

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Acute coronary syndrome (ACS) predominantly arises from vulnerable lipid-rich plaques (LRPs). Despite contemporary systemic medical therapy, 30% of ACS patients have a recurrent event within 5 years, prompting interest in local prophylactic treatment options aimed at plaque stabilisation[1]. Near-infrared spectroscopy (NIRS) combined with intravascular ultrasound (IVUS) enables the identification of LRPs at risk for future coronary events[2]. Paclitaxel-coated balloons (PCBs) allow for targeted intracoronary pharmacological treatment without leaving behind a permanent implant. Preclinical studies have shown the potential of PCBs to serve as a local plaque-stabilising therapy[3]. We therefore investigated the safety and feasibility of using a PCB as a pre-emptive treatment for non-flow-limiting, non-culprit LRPs in patients presenting with non-ST-segment elevation ACS (NSTE-ACS).

The Intravascular Identification and Drug-Eluting Balloon Treatment of Vulnerable Lipid-Rich Plaques (DEBuT-LRP) study was an investigator-initiated, first-in-human proof-of-concept study conducted at the Amsterdam University Medical Centers (ClinicalTrials.gov: NCT04765956). The study design and rationale have been previously published[4]. Briefly, patients with NSTE-ACS underwent three-vessel IVUS-NIRS (Makoto TVC-MC10 imaging system, with a 50 MHz catheter [both Infraredx]) after successful percutaneous coronary intervention (PCI) of all flow-limiting culprit lesions, with confirmation through intracoronary functional testing in case of uncertainty. Complete inclusion and exclusion criteria are provided in **Supplementary Table 1**. An LRP was defined as a region with a maximum lipid core burden index (LCBI) in a 4 mm segment ($maxLCBI_{4mm}$) ≥325[2]. Patients with at least 1 LRP directly underwent PCB treatment under nominal pressure inflation (SeQuent Please NEO [B. Braun]) for the entire LRP length including 5 mm margins. In patients with multiple LRPs, only one was treated with the instruction to preferably target the one with the highest $maxLCBI_{4mm}$. LRPs in the left main or previously stented segments with 5 mm margins were excluded from PCB treatment. Repeat IVUS-NIRS was performed after PCB inflation. Clinical follow-up was performed at 1, 9 and 12 months. Repeat coronary angiography with three-vessel IVUS-NIRS was done at 9-month follow-up. All images were analysed at an independent core laboratory (MedStar Cardiovascular Research Network, Angiographic and Invasive Imaging Core Lab, Washington, D.C., USA). The primary endpoint was the change in $maxLCBI_{4mm}$ in the PCB-treated LRP from baseline to 9-month follow-up. Core laboratory methodology, secondary endpoints and endpoint definitions have been previously described[4]. Statistical analyses were performed using SPSS Statistics, version 28.0 (IBM). We used the Wilcoxon signed-rank test for the primary and secondary imaging endpoints. The absolute difference in units between baseline and follow-up imaging measurements was described as the median with interquartile range (IQR), and the relative risk in median with IQR as a percentage. The McNemar test was used for paired categorical data.

Between January 2021 and September 2022, 65 patients were screened for inclusion, of whom 45 patients underwent IVUS-NIRS imaging after successful PCI of flow-limiting lesions **(Supplementary Figure 1)**. Out of 26 patients with >1 LRP, 20 patients were enrolled in the study to undergo PCB treatment of 1 LRP. Six were excluded because of an unsuitable LRP location, as defined by the protocol. Baseline characteristics are displayed in **Supplementary Table 2** and **Supplementary Table 3**, and procedural and angiographic

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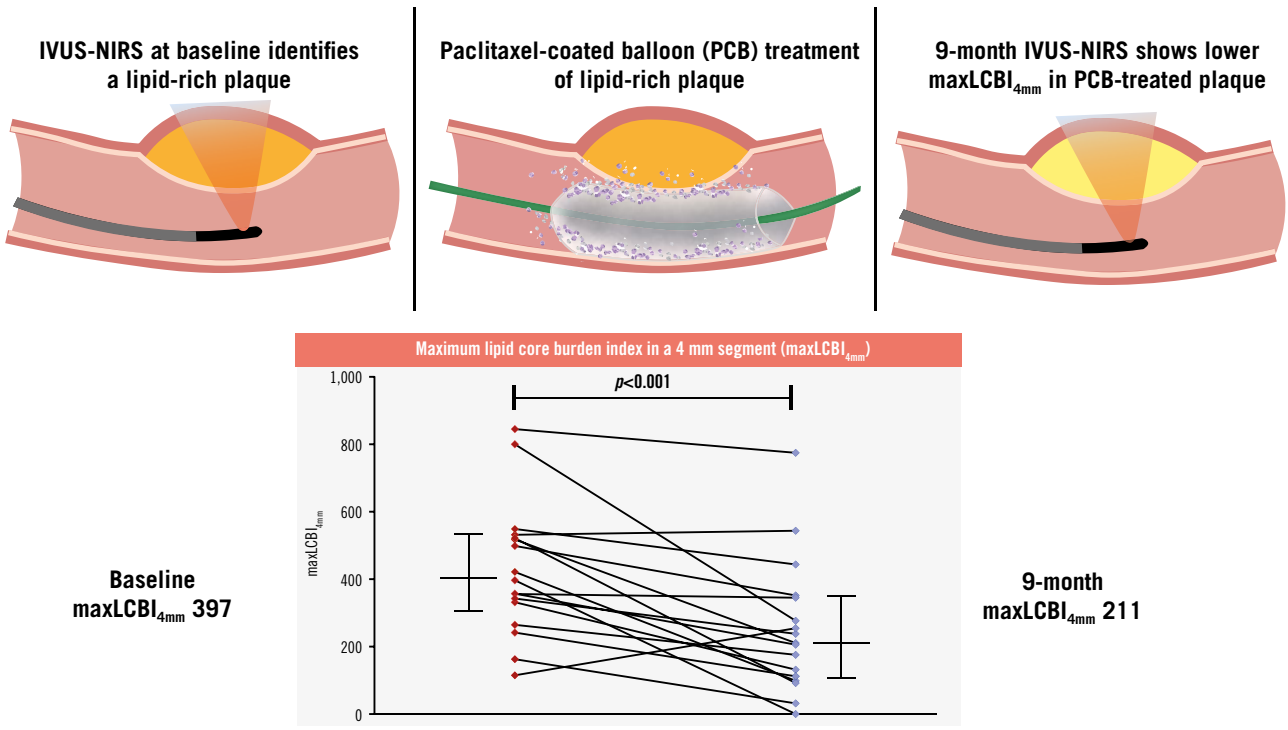
characteristics are shown in **Supplementary Table 4** and **Supplementary Table 5**. PCB treatment was performed under a median inflation pressure of 6 atmospheres (IQR 6 to 6) for 74 seconds (IQR 60 to 90). Three procedural complications occurred. One patient experienced distal embolisation after PCB treatment, which was resolved after intracoronary nitroglycerine and adenosine administration, resulting in swift restoration of Thrombolysis in Myocardial Infarction (TIMI)-3 flow. Alternatively, this could have been spasm **(Moving image 1-Moving image 4** demonstrate the case of this patient undergoing PCB treatment of an LRP in the left anterior descending artery, after successful treatment of a significant stenosis in the right coronary artery). No IVUS-NIRS-related complications occurred. Two patients experienced procedural complications due to PCI of significant lesions, not related to IVUS-NIRS or PCB treatment, with one wire dissection requiring bailout stenting and one distal embolisation of the culprit lesion only.

Follow-up imaging was performed at 272 days (IQR 256 to 281) in 18 patients (2 patients refused). No complications occurred. A total of 17 patients had analysable IVUS-NIRS images prior to PCB treatment and after 9 months. The primary endpoint of the median maxLCBI$_{4mm}$ of the PCB-treated LRPs significantly decreased from 397 (IQR 299 to 527) at baseline to 211 (IQR 106 to 349) at follow-up (p<0.001), which was an absolute change of −131 (IQR −315 to −80) and a relative change of −42% (IQR −71 to −14) **(Central illustration, Table 1, Supplementary Figure 2)**. No significant differences were observed for the IVUS-derived area measurements. The minimum lumen area (MLA) increased numerically, but not significantly, from 6.7 mm^2 to 7.8 mm^2 within the maxLCBI$_{4mm}$ segment (p=0.23). A total of 14 patients had analysable IVUS-NIRS images at all 3 timepoints (before PCB treatment, after PCB treatment and after 9 months) and these outcomes are displayed in **Supplementary Table 6**. On a vessel basis, the maxLCBI$_{4mm}$ within the entire PCB-treated vessel significantly

EuroIntervention — Central **Illustration**

DEBuT-LRP study.



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Schematic overview of the DEBuT-LRP study with the primary outcome of change in maxLCBI$_{4mm}$ from baseline to 9-month follow-up in paclitaxel-treated lipid-rich plaques. In the DEBuT-LRP study, patients presenting with non-ST-segment elevation acute coronary syndromes underwent intravascular ultrasound combined with near-infrared spectroscopy (IVUS-NIRS). Lesions with a maxLCBI$_{4mm}$ ≥325 underwent additional paclitaxel-coated balloon treatment. Patients underwent repeat IVUS-NIRS after 9-month follow-up, and the maxLCBI$_{4mm}$ was significantly reduced compared with baseline. Red dots indicate the baseline measurement of maxLCBI$_{4mm}$ of the individual patients, and blue dots indicate the 9-month measurement. On both sides of the graph the median with interquartile range is displayed as horizontal lines. maxLCBI$_{4mm}$: maximum lipid-core burden index in a 4 mm segment

Table 1. Core laboratory-adjudicated 9-month imaging outcomes in PCB-treated LRPs.

	PCB (n=18)		Median absolute difference	Median relative difference, %	*p*-value[a]
	Baseline	9 months			
NIRS findings					
Within PCB segment[b]					
Maximum $LCBI_{4mm}$	397 (299 to 527)	211 (106 to 349)	–131 (–315 to –80)	–42 (–71 to –14)	<0.001
Maximum $LCBI_{4mm}$ ≥325	13 (77)	5 (29)	-	-	0.008[c]
LCBI of target lesion segment	178 (144 to 264)	87 (33 to 147)	–90 (–150 to –50)	–57 (–76 to –30)	<0.001
IVUS findings					
Within maximum $LCBI_{4mm}$[b]					
Plaque burden, %	47 (40 to 53)	44 (39 to 52)	–1.3 (–5.6 to 5.9)	–2.9 (–11.1 to 11.7)	0.71
Mean vessel area, mm^2	15.3 (10.9 to 18.9)	16.9 (12.7 to 19.8)	0.4 (–0.5 to 2.0)	3.0 (–2.6 to 17.4)	0.23
Minimal lumen area, mm^2	6.7 (5.1 to 8.6)	7.8 (4.9 to 9.9)	0.4 (–0.4 to 2.1)	9.4 (–7.2 to 21.5)	0.23
Mean plaque area, mm^2	6.7 (5.1 to 9.6)	6.9 (5.2 to 9.8)	0.5 (–0.3 to 0.9)	6.8 (–8.5 to 13.2)	0.30
Within PCB segment[b]					
Plaque burden, %	43 (36 to 49)	42 (37 to 45)	–1.2 (–4.7 to 1.7)	–2.8 (–9.8 to 5.3)	0.19
Mean vessel area, mm^2	15.4 (10.9 to 19.2)	15.5 (12.0 to 19.6)	0.3 (–0.7 to 1.0)	2.5 (–4.4 to 8.6)	0.38
Minimal lumen area, mm^2	5.3 (4.1 to 8.4)	5.8 (4.6 to 8.1)	0.1 (–0.9 to 1.1)	2.4 (–15.2 to 28.2)	0.82
Mean plaque area, mm^2	6.1 (4.5 to 8.7)	6.3 (5.2 to 8.4)	0.0 (–0.6 to 0.7)	0.3 (–9.4 to 14.7)	0.82
Angiographic findings					
Within PCB segment					
Minimum lumen diameter, mm	1.7 (1.3 to 2.2)	2.0 (1.6 to 2.4)	0.0 (–0.3 to 0.5)	2.7 (–15.0 to 32.3)	0.36
Reference vessel diameter, mm	2.7 (2.2 to 3.3)	2.7 (2.3 to 3.0)	0.0 (–0.4 to 0.3)	–1.0 (–12.7 to 13.4)	0.82
Diameter stenosis, %	35 (22 to 44)	26 (19 to 35)	–3.0 (–16.0 to 6.0)	–10.0 (–45.8 to 24.3)	0.28

Data are given as median (IQR) or number of patients (%). [a]p-value of difference from baseline to follow-up as derived from the Wilcoxon signed-rank test. [b]Data available in 17 patients. [c]p-value of difference as derived from the McNemar test. IQR: interquartile range; IVUS: intravascular ultrasound; LCBI: lipid-core burden index; LRP: lipid-rich plaque; NIRS: near-infrared spectroscopy; PCB: paclitaxel-coated balloon

decreased from 431 (IQR 362 to 519) at baseline to 331 (IQR 206 to 461) at follow-up (p=0.002), which was an absolute change of –111 (IQR –223 to –54) and a relative change of –24.6% **(Supplementary Table 7, Supplementary Figure 3)**. The $maxLCBI_{4mm}$ within the untreated vessels showed no significant difference between baseline (136 [IQR 98 to 243]) and 9-month follow-up (105 [IQR 61 to 217]; p=0.11). A case example is displayed in **Supplementary Figure 4**. Site-reported imaging outcomes are displayed in **Supplementary Table 8**.

Over a median follow-up period of 398 days (IQR 394 to 439), a total of 5 patients (25%) had a cardiovascular event **(Supplementary Table 9)**. There were no deaths. No index LRP-related events occurred. One patient had a type 1 myocardial infarction attributable to a definite stent thrombosis of the culprit NSTE-ACS lesion, occurring 6 days after index PCI due to antiplatelet therapy non-adherence. Three patients had unplanned visits to the emergency department due to angina. Two of them were discharged the same day after ruling out myocardial infarction. The third patient stayed overnight and underwent repeat coronary angiography, 34 days after the index PCI, where no significant stenosis was observed. However, at 9-month follow-up this same patient underwent repeat revascularisation for significant in-stent restenosis of the culprit NSTE-ACS lesion. Two patients experienced a bleeding event requiring medical intervention (one epistaxis, i.e., Bleeding Academic Research Consortium [BARC] 2 bleeding, and one gastrointestinal bleed with a haemoglobin drop of 2.2 mmol/L requiring endoscopic intervention, i.e., BARC 3b bleeding).

In summary, we demonstrated that prophylactic PCB-treatment of LRPs was safe and feasible and resulted in a significant reduction of the $maxLCBI_{4mm}$ at 9-month

follow-up, with no reduction of the maxLCBI$_{4mm}$ in plaques that were not PCB-treated. No PCB-treated LRP-related events occurred during 1 year of follow-up.

Even in the current era of potent systemic antithrombotic, lipid-lowering and anti-inflammatory therapies, recurrent ischaemic cardiovascular events occur in >30% of patients within 5 years after ACS[1]. Approximately half of patients presenting with ACS have additional vulnerable plaques, increasing the risk for recurrent coronary events[5]. Therefore, local treatment of a vulnerable plaque on top of systemic medical therapy deserves further study in an effort to reduce future adverse events. Prophylactic PCI of vulnerable non-culprit plaques with bioresorbable vascular scaffolds (BVS) was shown to improve intracoronary imaging outcomes in the PROSPECT ABSORB Trial[6]. No significant reduction of clinical events was found, although the study was not powered for clinical outcomes. The PREVENT trial (ClinicalTrials.gov: NCT02316886) is evaluating preventive stenting with either BVS or drug-eluting stents in patients with vulnerable plaques. Nonetheless, ethical concerns arise regarding stent-related complications for non-flow-limiting lesions. Therefore, drug-coated balloons may be a safe and effective alternative, allowing local pharmacological treatment of vulnerable plaques without leaving behind a permanent implant.

Paclitaxel is an antiproliferative and anti-inflammatory drug that reduces plaque burden and inflammation when locally delivered onto atherosclerotic lesions, based on preclinical data[3]. We studied, for the first time, the safety and efficacy of PCB treatment in LRPs and found that PCB treatment led to a significant decrease of the maxLCBI$_{4mm}$ after 9 months of follow-up, which appeared safe with no treatment-related complications. No significant change in IVUS measurements was seen, which could indicate that PCB treatment changes plaque composition but not plaque size. To address possible microembolisations overestimating the treatment effect, we compared the maxLCBI$_{4mm}$ before and after PCB treatment and found no significant difference, while the observed treatment effect of PCB mainly occurred up to 9-month follow-up **(Supplementary Table 6)**. While these findings might indicate a possible role for pre-emptive PCB treatment in plaque stabilisation, further randomised studies are essential to investigate the impact of this prophylactic treatment on clinical outcome and to compare the results with a control group receiving guideline-directed medical therapy alone to assess whether there is an additional effect of PCB treatment on top of lipid-lowering medication.

Several limitations must be acknowledged. First, the sample size is small and there was no control arm. However, patients can be considered their own control with LRPs that were not PCB treated. Second, at 1-year follow-up, 15% were not taking any lipid-lowering medication, and no routine cholesterol measurements were performed during follow-up. Lastly, only 10% of patients were female, which may be a result of the small sample size.

In conclusion, in this first-in-human proof-of-concept study, pre-emptive treatment of non-flow-limiting, non-culprit vulnerable lipid-rich plaques with a paclitaxel-coated balloon resulted in a significant reduction of the lipid burden (maxLCBI$_{4mm}$) without overt safety concerns. Future randomised controlled trials are warranted to investigate the potential prognostic impact of this novel treatment strategy to improve clinical outcomes.

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Conflict of interest statement

R. Delewi has received educational grants from Edwards Lifesciences and Boston Scientific, outside the submitted work. H.M. Garcia-Garcia has received research grants from Philips, Abbott, Boston Scientific, Corflow, Neovasc, MedAlliance, Medis, and Biotronik; speaker fees from ACIST, Medis, and Boston Scientific; and honoraria for participation in the Abbott Advisory Board. J.P.S. Henriques has received research grants from Health~Holland, B. Braun, and Infraredx/Nipro to conduct the current study; and research grants from ZonMw, AstraZeneca, and Abbott, outside the submitted work. B.E.P.M Claessen has received speaker fees from Abiomed; and consultancy fees from Amgen, Sanofi, Boston Scientific, and Philips, outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

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Moving image 4. Case example: End result after intracoronary nitroglycerine and adenosine injections.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-01073

Supplementary data

Supplementary Table 1. Full inclusion and exclusion criteria.

Inclusion Criteria
(1) Presence of NSTE-ACS (including non-ST-segment elevation MI and unstable angina);
(2) An invasive revascularization strategy with PCI is chosen.
Exclusion Criteria
Angiographic exclusion criteria
(1) Previous coronary artery bypass grafting;
(2) Presence of a chronic total occlusion;
(3) Too many (complex) coronary lesions requiring staged PCI procedure(s);
(4) Procedural complication of the index PCI.
Clinical exclusion criteria
(1) Unstable patients (cardiogenic shock, need for intubation, need for inotropes);
(2) ST-segment elevations on the ECG requiring immediate primary PCI;
(3) Body weight > 250 kg;
(4) Known renal insufficiency (eGFR <30 mL/min/1.73m^2 or subject on dialysis);
(5) Hypersensitivity or allergy to contrast with inability to properly pre-hydrate;
(6) Presence of a comorbid condition with a life expectancy of less than one year;
(7) Participation in another trial;
(8) Subject belongs to a vulnerable population (per the investigator's judgment, e.g., subordinate hospital staff);
(9) Subject is unable to read or write.

MI = myocardial infarction, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, PCI = percutaneous coronary intervention.

Supplementary Table 2. Baseline characteristics.

	PCB (n = 20)
Patient characteristics	
Age, years	66 (55 – 73)
Male	18 (90%)
Body mass index, kg/m^2	26.4 (23.3 – 36.4) [a]
Previous or current smoking	10 (67%) [b]
Chronic obstructive pulmonary disease	1 (5%)
Diabetes mellitus	1 (5%) [c]
Hypertension	11 (55%)
Hypercholesterolemia	12 (60%)
Family history of cardiovascular disease	5 (25%) [d]
Prior myocardial infarction	3 (15%)
Prior percutaneous coronary intervention	3 (15%)
Prior stroke	1 (5%)
Laboratory measures	
Hemoglobin, mmol/L	9.3 (8.7 – 10.1)
Thrombocytes, x10^9/L	204 (188 – 221)
Leucocytes, x10^9/L	7.7 (6.2 – 11.4) [e]
eGFR, mL/min/1.73 m^2	90 (67 – 94)
Total cholesterol, mmol/L	5.0 (4.2 – 6.4) [f]
High-density cholesterol, mmol/L	1.1 (1.0 – 1.3) [g]
Low-density cholesterol, mmol/L	2.8 (2.2 – 4.0) [g]
Triglycerides, mmol/L	1.9 (1.2 – 2.6) [g]
Maximum hs-TnT prior to PCI, ng/L	78 (20 – 150) [h]

Data are medians with interquartile ranges, or number of patients with percentages. Hs-TnT = high-sensitive troponin T, MI = myocardial infarction, PCI = percutaneous coronary intervention, PCSK9 = proprotein convertase subtilisin–kexin type 9, PCB = paclitaxel-coated balloon. a Data available in 11 patients. b Data available in 15 patients. c One patient with non-insulin-dependent diabetes mellitus. d Data available in 13 patients. e Data available in 19 patients. f Data available in 7 patients. g Data available in 6 patients. h Normal value hs-TnT < 14 ng/L and available in 19 patients.

Supplementary Table 3. Statin therapy during follow-up.

PCB (n = 20)	Baseline	1 month	9 month	1 year
Lipid-lowering medication	9 (45%)	18 (90%)	17 (85%)	17 (85%)
Statin	9 (45%)	17 (85%)	15 (75%)	15 (75%)
Rosuvastatin	4 (20%)	5 (25%)	5 (25%)	4 (20%)
Atorvastatin	3 (15%)	10 (50%)	9 (45%)	9 (45%)
Simvastatin	2 (10%)	2 (10%)	2 (10%)	2 (10%)
Ezetimib	0 (0%)	1 (5%)	2 (10%)	5 (25%)
PCSK9-inhibitor	0 (0%)	1 (5%)	1 (5%)	2 (10%)

Data are number of patients with percentages. PCB = paclitaxel-coated balloon. PCSK9 = proprotein convertase subtilisin/kexin type 9.

Supplementary Table 4. Baseline and follow-up procedural characteristics.

Baseline imaging	**N = 20**
Total procedure duration, min	58 (46 – 80)
Fluoroscopy duration, min	16 (11 – 22)
Contrast use, ml	100 (85 – 115) *
Follow-up imaging	**N = 18** †
Time to follow-up imaging, days	272 (256 – 281)
Additional PCI performed	1 (6%) ‡
Total procedure duration, min	33 (27 – 39)
Fluoroscopy duration, min	6 (4 – 9)
Contrast use, ml	66 (50 – 100)
Number of arteries scanned with IVUS-NIRS	3 (2 – 3)
Complications	0 (0%)

Data are medians with interquartile ranges, or number of patients with percentages. NIRS = near-infrared spectroscopy, PCB = paclitaxel-coated balloon. * Data available in 12 patients. † Two patients refused follow-up imaging. ‡ Significant in-stent restenosis of culprit lesion treated for non-ST-segment elevation acute coronary syndrome.

Supplementary Table 5. Baseline imaging characteristics.

	PCB (n = 20)
PCI of culprit lesion	
Total number of treated vessels	26
Left anterior descending artery	12 (46%)
Left circumflex artery	6 (23%)
Right coronary artery	8 (21%)
Number of treated vessels per patient	1 (1 – 2)
PCI successful	20 (100%)
TIMI flow pre	3 (2 – 3)
TIMI flow post	3 (3 – 3)
Number of stents used	1 (1 – 2)
Angiographic findings of target LRP	
Coronary artery lesion location	
Left anterior descending artery	9 (45%)
Left circumflex artery	8 (40%)
Right coronary artery	3 (15%)
Lesion location	
Proximal	9 (45%)
Mid	9 (45%)
Distal	2 (10%)
Lesion type B2/C	13 (65%)
Diameter stenosis, %	35 (22 – 44)
Reference vessel diameter, mm	2.7 (2.2 – 3.3)
Minimal lumen diameter, mm	1.7 (1.3 – 2.2)
Lesion length, mm	12 (7 – 15)
TIMI flow pre-PCB	3 (3 – 3)
PCB treatment of target LRP	
Inflation pressure, atmospheres	6 (6 – 6)
Inflation duration, sec	74 (60 – 90)
Balloon diameter, mm	3.5 (3.0 – 3.9)
Balloon length, mm	18 (15 – 20)
Procedural complications	
Total procedural complications	3 (15%)
Dissection	1 (5%)
Distal embolization	2 (10%) [a]
Culprit lesion	1 (5%)
Target LRP	1 (5%)
Tamponade	0 (0%)
Peri-procedural MI	0 (0%)
Occlusion side branch	0 (0%)
Device failure	0 (0%)
Access site related	0 (0%)

Data are medians with interquartile ranges, or number of patients with percentages. [a] One patient experienced distal embolization of the culprit vessel, and one patient experienced distal embolization of the target LRP, which resolved after intracoronary nitroglycerin and adenosine administration, without further sequelae. IVUS = intravascular ultrasound, LRP = lipid-rich plaque, $maxLCBI_{4mm}$ = maximum lipid-core burden index in a 4 mm segment, MI = myocardial infarction, NIRS = near-infrared spectroscopy, PCI = percutaneous coronary intervention, PCB = paclitaxel-coated balloon.

Supplementary Table 6. Core laboratory-adjudicated imaging outcomes per PCB segment with direct post-IVUS-NIRS outcome.

PCB (n = 18)	Baseline Pre-PCB	Baseline Post-PCB	9 months	Median absolute difference (IQR) Baseline to post-PCB	Median absolute difference (IQR) Post-PCB to 9 months	P-value Baseline to post-PCB	P-value Post-PCB to 9 months
NIRS findings							
Within PCB segment *							
Maximum $LCBI_{4mm}$	397 (299 to 527)	400 (286 to 516)	211 (106 to 349)	-36 (-109 to 74)	-137 (-234 to -62)	0.57	0.008
LCBI of target lesion segment †	178 (144 to 264)	149 (107 to 194)	87 (33 to 148)	-32 (-140 to 44)	-66 (-115 to -2.5)	0.15	0.040
IVUS findings							
Within maximum $LCBI_{4mm}$ *							
Plaque burden, %	47 (40 to 53)	53 (46 to 58)	42 (37 to 45)	3.6 (0.6 to 7.3)	-4.4 (-10.2 to 1.1)	0.021	0.06
Mean vessel area, mm^2	15.3 (10.9 to 18.9)	16.7 (11.6 to 21.5)	16.9 (12.7 to 19.8)	0.0 (-1.5 to 1.4)	0.3 (-1.7 to 1.6)	0.95	0.72
Minimal lumen area, mm^2	6.7 (5.1 to 8.6)	7.4 (4.7 to 9.7)	7.8 (4.9 to 9.9)	-0.3 (-1.7 to 1.0)	0.3 (-0.6 to 2.3)	0.54	0.36
Mean plaque area, mm^2	6.7 (5.1 to 9.6)	8.0 (6.1 to 11.2)	6.9 (5.2 to 9.8)	0.9 (0.2 to 1.5)	-0.8 (-1.5 to 0.7)	0.02	0.24
Within PCB segment *							
Plaque burden, %	43 (36 to 49)	47 (44 to 54)	42 (37 to 45)	4.0 (0.5 to 8.5)	-4.5 (-8.6 to -2.1)	0.011	<0.001
Mean vessel area, mm^2	15.4 (10.9 to 19.2)	15.7 (11.2 to 20.9)	15.5 (12.0 to 19.6)	0.0 (-0.7 to 0.8)	0.2 (-1.0 to 0.8)	1.00	0.95
Minimal lumen area, mm^2	5.3 (4.1 to 8.4)	5.3 (3.8 to 6.9)	5.8 (4.6 to 8.1)	-0.8 (-1.6 to 0.2)	0.5 (-0.2 to 1.3)	0.08	0.06
Mean plaque area, mm^2	6.1 (4.5 to 8.7)	7.4 (5.2 to 10.3)	6.3 (5.2 to 8.4)	0.8 (0.1 to 1.2)	-0.5 (-1.3 to 0.1)	<0.001	0.007
Angiographic findings within segment							
Minimum lumen diameter, mm	1.7 (1.3 to 2.2)	1.8 (1.6 to 2.4)	2.0 (1.6 to 2.4)	0.2 (-0.1 to 0.4)	0.1 (-0.3 to 0.3)	0.08	0.82
Reference vessel diameter, mm	2.7 (2.2 to 3.3)	2.7 (2.2 to 3.2)	2.7 (2.3 to 3.0)	-0.1 (-0.2 to 0.2)	-0.1 (-0.3 to 0.3)	1.00	0.64
Diameter stenosis, %	35 (22 to 44)	28 (19 to 36)	26 (19 to 35)	-2.5 (-16.5 to 4.8)	-1.0 (-11.5 to 5.0)	0.16	0.41

Data are medians with interquartile ranges, or number of patients with percentages. * Data available in 14 patients. † Target lesion segment is defined as the region that was PCB-treated plus 5 mm margin. IVUS = intravascular ultrasound, LCBI = lipid-core burden index, NIRS = near-infrared spectroscopy, PCB = paclitaxel-coated balloon.

Supplementary Table 7. Core laboratory-adjudicated 9-month IVUS-NIRS outcomes per vessel.

PCB (n = 18)	Baseline	9 months	Median absolute difference (IQR)	Median relative difference (IQR)	p-value *
NIRS findings					
Within PCB-treated vessel					
Maximum $LCBI_{4mm}$	431 (362 – 519)	331 (206 – 461)	-111 (-223 to -54)	-24.6% (-49.1 to -11,0)	0.002
Total LCBI of entire pullback	120 (93 – 193)	91 (52 – 126)	-48 (-89 to -14)	-41.9% (-60.1 to -8.1)	0.012
Within untreated vessel					
Maximum $LCBI_{4mm}$	136 (98 – 243)	105 (61 – 217)	-17 (-59 to 22)	-17.6% (-41.5 to 26.6)	0.11
Total LCBI of entire pullback	51 (18 - 107)	28 (7 - 63)	-11 (-38 to 5)	-38.0% (-72.2 to 13.0)	0.028
IVUS findings					
Within PCB-treated vessel					
Plaque burden, %	42 (34 – 49)	39 (36 – 46)	-1.6 (-2.7 to 1.3)	-3.6% (-7.6 to 3.2)	0.17
Mean vessel area, mm^2	15.4 (12.8 – 19.8)	16.0 (12.8 – 20.3)	0.1 (-0.3 to 0.7)	0.9% (-2.0 to 3.8)	0.37
Minimal lumen area, mm^2	5.2 (3.3 – 6.8)	5.5 (3.6 – 8.1)	0.2 (-0.2 to 1.1)	5.8% (-5.0 to 18.2)	0.047
Mean plaque area, mm^2	6.7 (4.6 – 8.3)	7.0 (4.7 – 8.7)	-0.1 (-0.5 to 0.2)	-1.1% (-6.8 to 6.0)	0.80
Within maximum $LCBI_{4mm}$ in PCB-treated vessel					
Plaque burden, %	47 (38 – 56)	48 (39 – 56)	0.0 (-12.6 to 6.6)	-0.2% (-20.0 to 15.6)	0.77
Mean vessel area, mm^2	14.9 (12.0 – 20.3)	17.5 (14.6 – 20.2)	2.5 (-0.4 to 4.9)	18.4% (-2.1 to 33.1)	0.02
Minimal lumen area, mm^2	6.4 (4.6 – 9.0)	8.2 (5.7 – 10.2)	0.3 (-1.8 to 3.8)	5.1% (-20.3 to 65.3)	0.37
Mean plaque area, mm^2	7.2 (5.2 – 10.0)	8.3 (6.9 – 9.3)	0.2 (-0.8 to 2.1)	1.7% (-12.2 to 37.0)	0.28
Within untreated vessel					
Plaque burden, %	39 (32 – 45)	39 (36 – 46)	-0.4 (-3.5 to 3.1)	-0.9% (-8.3 to 9.6)	0.58
Mean vessel area, mm^2	16.2 (11.8 – 23.8)	16.9 (12.1 – 21.7)	-0.5 (-1.9 to 0.7)	-5.1% (-10.2 to 3.3)	0.11
Minimal lumen area, mm^2	6.2 (4.6 – 9.5)	6.9 (4.8 – 8.9)	-0.2 (-1.3 to 0.8)	-5.4% (-16.3 to 11.4)	0.21
Mean plaque area, mm^2	6.3 (4.4 – 9.6)	5.6 (4.4 – 9.0)	-0.2 (-10.2 to 3.3)	-5.7% (-17.3 to 8.7)	0.10

Data are medians with interquartile ranges, or number of patients with percentages. * p-value of difference from baseline to follow-up as derived from Wilcoxon-signed ranked test. IVUS = intravascular ultrasound, LCBI = lipid-core burden index, NIRS = near-infrared spectroscopy, PCB = paclitaxel-coated balloon.

Supplementary Table 8. Site-reported NIRS outcomes.

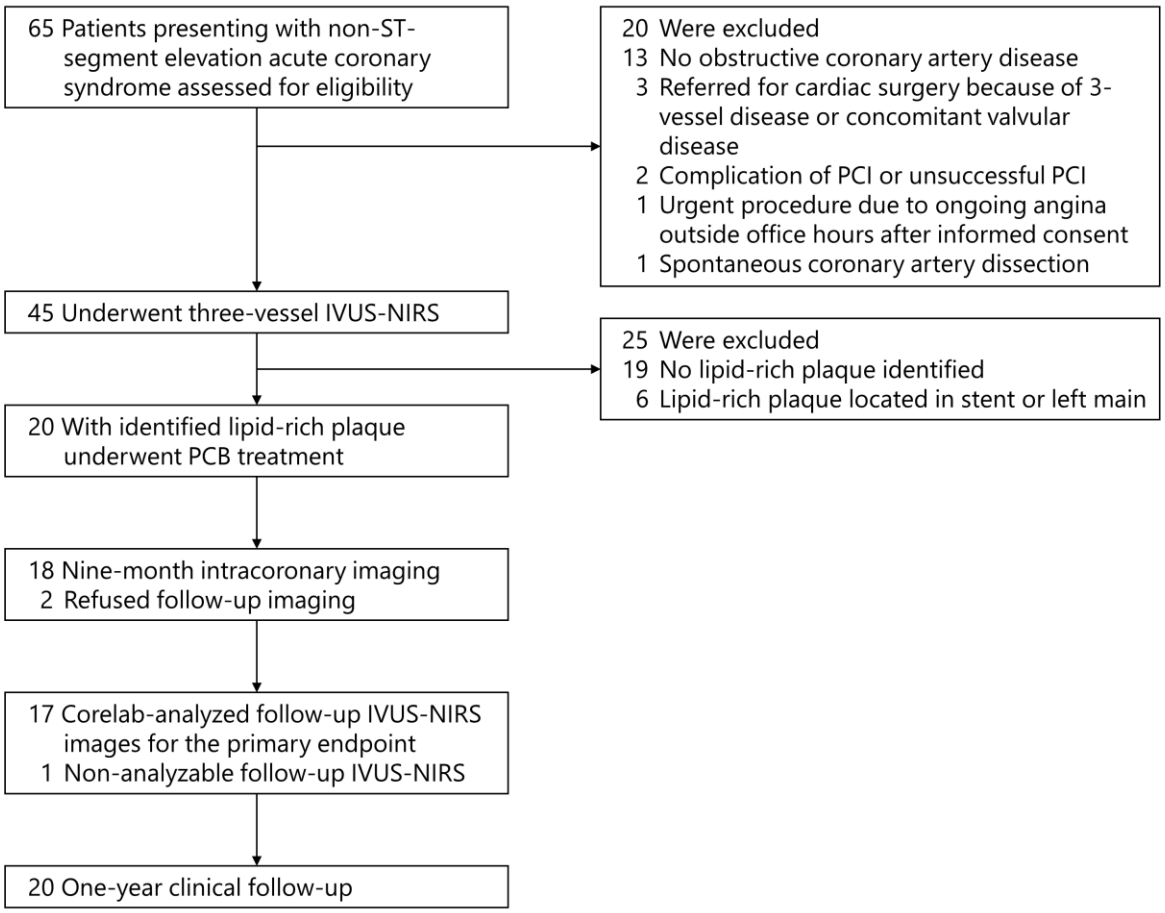
	PCB (n = 18)		
	Baseline	**9 months**	**p-value ***
NIRS findings			
Within lipid-rich plaque segment			
Maximum $LCBI_{4mm}$	455 (361 – 544)	206 (96 – 307)	<0.001
Maximum $LCBI_{4mm}$ > 325	18 (100%)	4 (22%)	<0.001 †
Total LCBI of segment	263 (220 – 339)	97 (38 – 169)	<0.001

Data are medians with interquartile ranges, or number of patients with percentages. * p-value of difference from baseline to follow-up as derived from Wilcoxon-signed ranked test. † p-value of difference as derived from McNemar test. LCBI = lipid-core burden index, NIRS = near-infrared spectroscopy, PCB = paclitaxel-coated balloon.

Supplementary Table 9. One-year clinical follow-up.

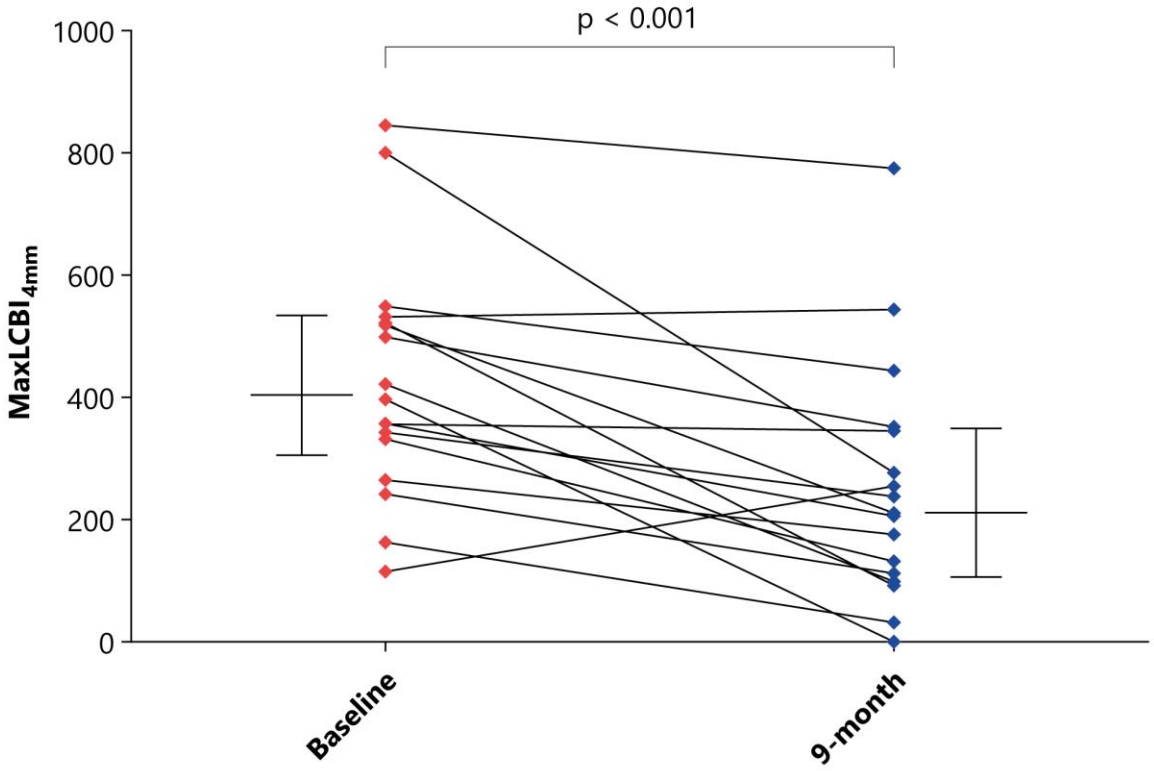
	PCB (n = 20)
Follow-up duration, days	398 (394 – 439)
Number of patients with any cardiovascular event	5 (25%)
Death	0 (0%)
Myocardial infarction	1 (5%)
Stent thrombosis	1 (5%)
Major arrhythmia	0 (0%)
Unexpected ED visit for angina, no MI	3 (15%)
Extra-cranial bleeding [a]	2 (10%)
BARC 2 bleeding	1 (5%)
BARC 3 bleeding	1 (5%)
Stroke	0 (0%)
Repeat unplanned coronary angiography	2 (10%)
Repeat revascularization	2 (10%)
Composite safety endpoint [b]	0 (0%)
Composite LRP lesion failure endpoint [c]	0 (0%)
Composite patient-oriented endpoint [d]	2 (10%)
Symptoms	
NYHA Class for dyspnea	
Class I	19 (95%)
Class II	1 (5%)
CCS Class for angina	
Class 0/no angina	16 (80%)
Class I	3 (15%)
Class II	1 (5%)

Data are median with interquartile range, or number of patients with percentages. a One patient with epistaxis without hemoglobin drop requiring non-surgical intervention (BARC 2), and one patient with gastrointestinal bleed with hemoglobin drop of 2.2 mmol/L requiring endoscopic intervention (BARC 3b). b Safety endpoint defined as the occurrence of bail-out stenting due to flow-limiting dissections or peri-procedural myocardial infarction. c LRP lesion failure defined as cardiac death, myocardial infarction, or ischemia-driven revascularization related to an identified non-culprit LRP lesion. d Patient-oriented composite outcome defined as all-cause mortality, myocardial infarction, or any repeat revascularization up to one-year follow-up. BARC = Bleeding Academic Research Consortium, CCS = Canadian Cardiovascular Society, ED = emergency department, LRP = lipid-rich plaque, MI = myocardial infarction, NYHA = New-York Heart Association, PCB = paclitaxel-coated balloon.



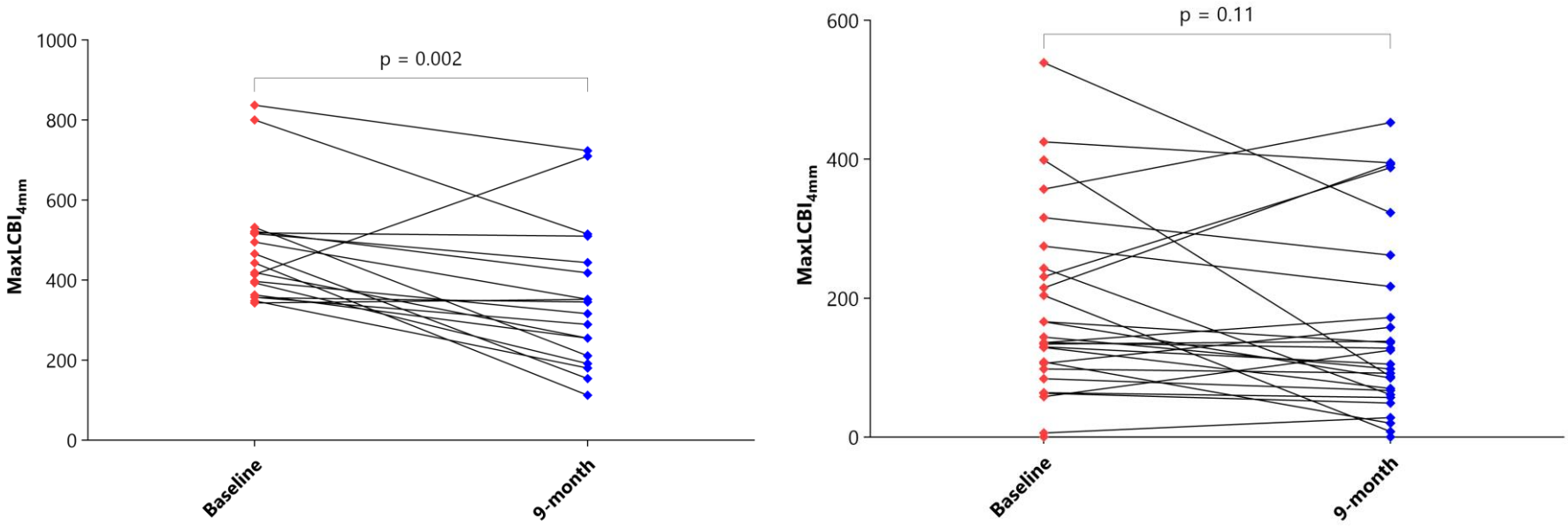
Supplementary Figure 1. Flowchart of patient enrolment and follow-up.

Flowchart of patient enrolment and follow-up. IVUS-NIRS = intravascular ultrasound/near-infrared spectroscopy. PCI = percutaneous coronary intervention. PCB = paclitaxel -coated balloon.



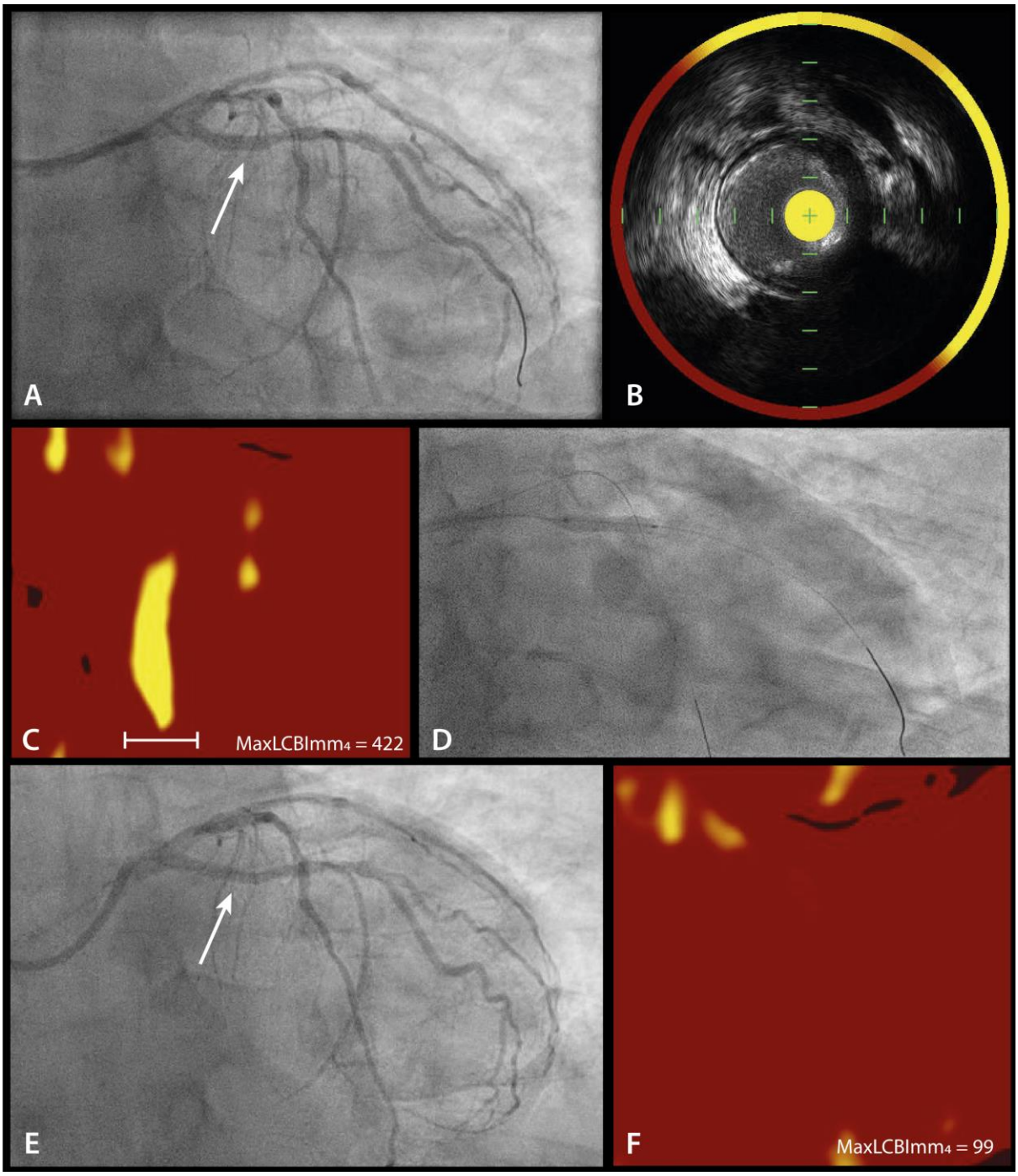
Supplementary Figure 2. Primary endpoint: change of maxLCBI$_{4mm}$ from baseline to 9-month follow-up.

The graphs present the per-patient change in maxLCBI4mm from baseline to 9 months follow-up after paclitaxel-coated balloon treatment, with median (long horizontal line) and 25th and 75th quartile (error bars).



Supplementary Figure 3. Regression of maxLCBI$_{4mm}$ from baseline to 9-month follow-up per vessel.

Regression of maxLCBI4mm from baseline to nine-month follow-up of lesions treated with PCB (left panel), and of lesions not treated with PCB (right). MaxLCBI4mm = maximum lipid-core burden index in a 4 mm segment.



Supplementary Figure 4. Case example.

Panel **A** demonstrates the angiogram of a patient presenting with non-ST-segment elevation acute coronary syndrome. The arrow points at the location of a lipid-rich plaque. Panel **B** demonstrates the transversal intravascular ultrasound image of the plaque, and panel **C** demonstrates the chemogram. The chemogram represents the lipid probability, where red denotes low lipid probability, while yellow signifies high lipid probability. The Lipid Core Burden Index (LCBI) is calculated as the fraction of yellow pixels by all analyzable pixels in the region of interest, multiplied by 1000. In this patient, a LRP with maxLCBImm$_4$ of 422 was found. According to study protocol, this lesion underwent paclitaxel-eluting drug-coated balloon (PCB) treatment as demonstrated in panel **D.** At 9-month follow-up imaging (panel **E**), the chemogram (in panel **F**), demonstrates a reduction of the maxLCBI$_{4mm}$ of the PCB-treated LRP from 422 to 99.