SUPPLEMENTAL MATERIAL

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Supplemental Methods

Supplemental Methods 1 Inclusion and exclusion criteria

COMBINE (OCT-FFR)
Inclusion criteria
≥18 years of age
History of diabetes mellitus with any indication for coronary angiography (chronic coronary syndrome or any type of acute coronary syndrome including ST-segment elevation myocardial infarction)
Coronary angiography, including FFR and OCT imaging of at least one target lesion with the following additional characteristics: - Native not-grafted vessel - Visually estimated diameter stenosis of 40-80% - Target lesion should be other than the culprit lesion(s) in patients presenting with myocardial infarction
Exclusion criteria
TIMI flow <3 in the target lesion(s)
Target lesion reference diameter (on visual estimation) <2.0mm
Known left ventricular ejection fraction <30%
Known malignancy
Life expectancy <2 years
Unwilling or unable to provide informed consent

PECTUS-obs
Inclusion criteria
Hospitalization for STEMI or NSTEMI (or have been in the last 6 weeks), for which invasive coronary angiography is performed.
Invasive coronary angiography demonstrates residual non-culprit coronary artery disease (target lesion(s)) with the following additional characteristics: - Visually estimated stenosis 30-90% - FFR > 0.80 - Not in-stent restenosis
Exclusion criteria
Refusal or inability to provide informed consent
<18 years of age
Hemodynamic instability, respiratory failure, or Killip class ≥3 at time of inclusion.
Previous coronary artery bypass grafting.
Indication for revascularization by coronary artery bypass grafting.
Anatomy of target lesion(s) unsuitable for OCT catheter crossing or imaging (e.g. aorta-ostial lesions, too small diameter segment, severe calcifications, chronic total occlusion, distal lesions).
Pregnancy
Estimated life expectance <3 years.

FFR fractional flow reserve; NSTEMI non-ST-segment elevation myocardial infarction; OCT optical coherence tomography; STEMI ST-segment elevation myocardial infarction

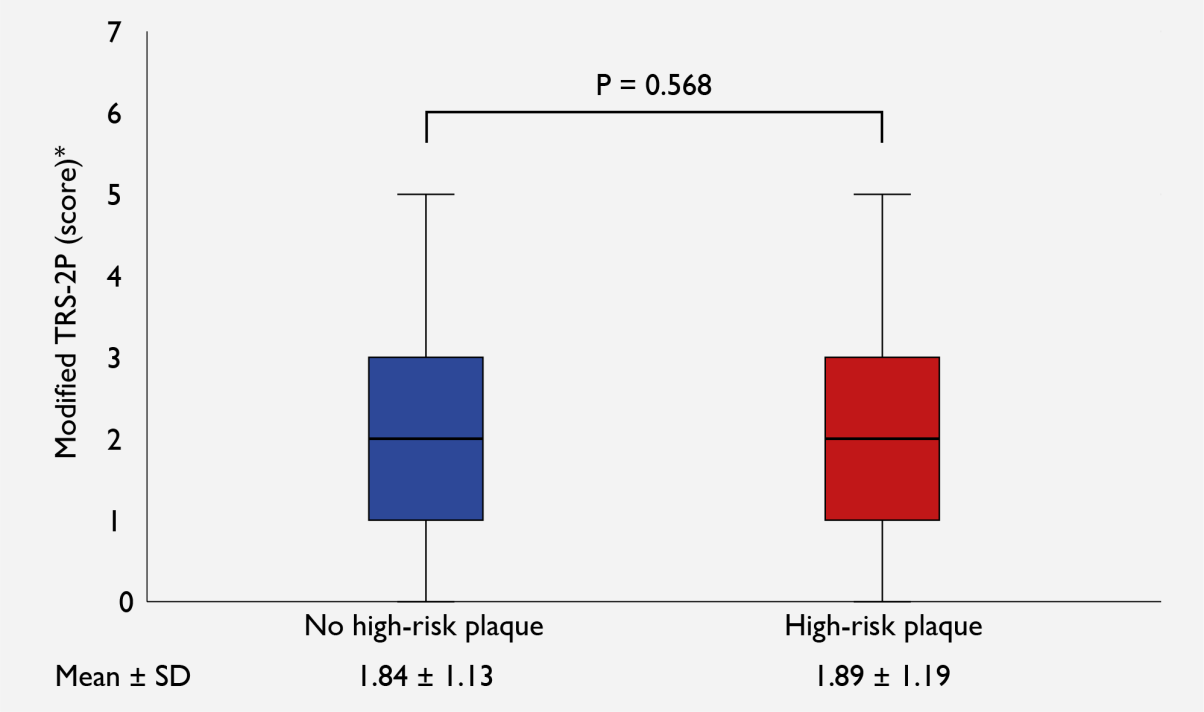
Supplemental Methods 2 Endpoint definitions

Endpoint	COMBINE (OCT-FFR)	PECTUS-obs
All-cause mortality	Death from any cause	Death from any cause
Cardiac death	Sudden death, death related to acute myocardial infarction, arrhythmia or congestive heart failure, death secondary to a cerebrovascular accident or death directly related to PCI or CABG, even if the ultimate cause of death is not clearly a cardiac event (e.g. infection)	Death due to an immediate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia) or any unwitnessed death or death of unknown cause, even in patients with co-existing and potentially fatal non-cardiac disease (e.g. cancer or infection)
Myocardial infarction	Detection of rise/and or fall of cardiac biomarkers (CKMB or troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: 1. Symptoms of ischemia 2. ECG changes indicative of new ischemia (new STT-changes or new, persistent, non-rate related left bundle branch block) 3. Development of pathological Q-waves (≥0.03 seconds in duration or ≥1mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads of the ECG 4. Imaging evidence of new loss of viable myocardial or regional wall motion abnormality	Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following: 1. Symptoms of ischemia 2. New ECG changes suggestive of ischemia (ST-elevation, ST-depression or T-wave abnormalities) 3. Development of new pathologic Q-waves on the ECG Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event. Pathological findings of an acute myocardial infarction during autopsy.
Unplanned revascularization	Clinically indicated: 1. Diameter stenosis ≥50% (QCA) and if one of the following occurs: a. A positive history of recurrent angina presumably related to the target vessel. b. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel. 2. Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve) independently from symptoms and degree of angiographic stenosis. 3. Presence of ruptured coronary atherosclerotic lesion with or without adjacent thrombus during OCT/IVUS evaluation on follow-up in presence of clinical symptoms that can be judged related to an acute coronary syndrome Not clinically indicated: Any revascularization for: 1. All-stenoses <50% (diameter stenos by QCA) in the presence or absence of ischemic signs or symptoms that no not fulfil criteria in point 2 and 3 of clinically indicated revascularization. 2. All-stenoses ≥50% (diameter stenosis by QCA) without ischemic signs or symptoms and do not fulfil criteria in point 2 and 3 of clinically indicated revascularization.	Any revascularization (PCI or CABG) that is performed during follow-up and has not been planned at time of inclusion. These included both elective and urgent revascularizations (any revascularization in a non-elective setting).

CABG coronary artery bypass grafting; ECG electrocardiogram; PCI percutaneous coronary intervention; QCA quantitative coronary angiography.

Supplemental Figures

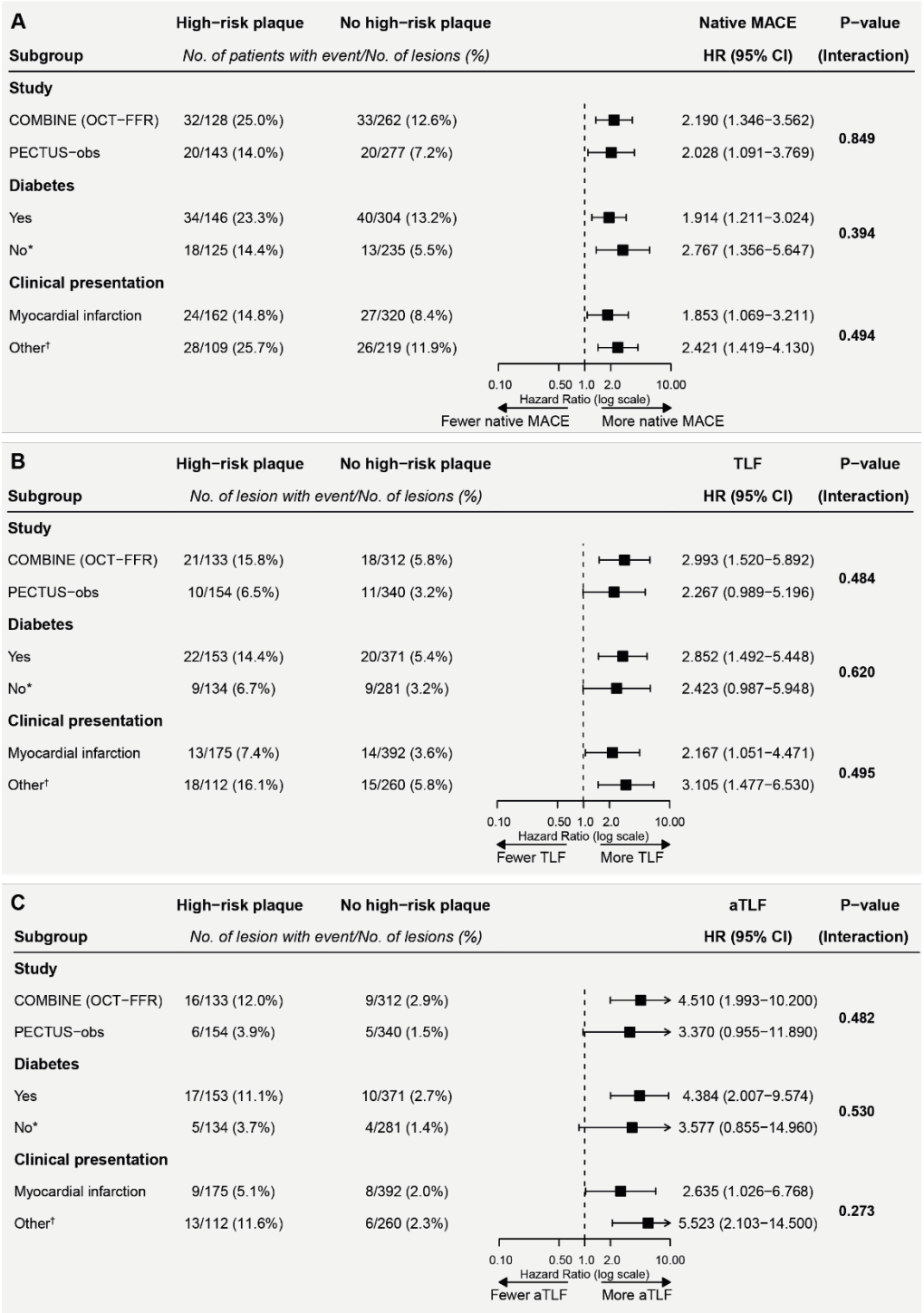
Figure S1 Baseline risk profile



* Modified version of the TIMI Risk Score for Secondary Prevention (TRS-2P).[28] Some adaptations were made to the original score, i.e. 'congestive heart failure' and 'other vascular disease (peripheral)' were left out as these variables were not collected systematically in both studies. Consequently, the modified score ranged from 0 to 7, with higher values indicating more risk factors. For categorical variables, missing values were imputed using the most prevalent class. Specifically, hypertension was considered present and smoking was considered non-smoking status. For continuous variables, missing values were imputed using the mean across the total population. The glomerular filtration rate was estimated using the 2021 CKD-EPI creatinine formula.[29]

SD standard deviation; TRS-2P TIMI Risk Score for Secondary Prevention.

Figure S2 Subgroup analyses



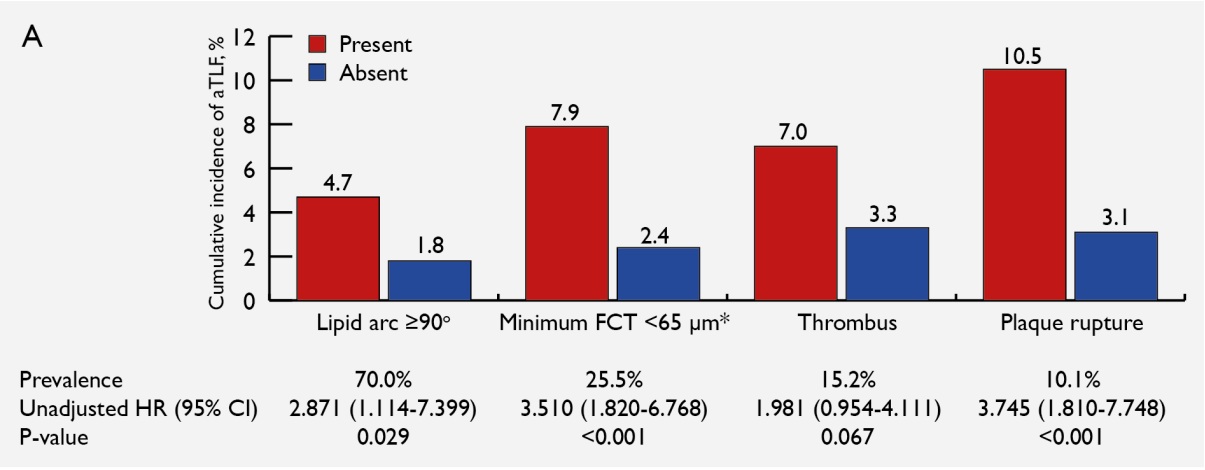
(A) Subgroup analyses for the primary endpoint of native MACE. (B) Subgroup analyses for the primary endpoint of TLF. (C) Subgroup analyses for the composite endpoint of aTLF.

* All non-diabetic patients presented with myocardial infarction.

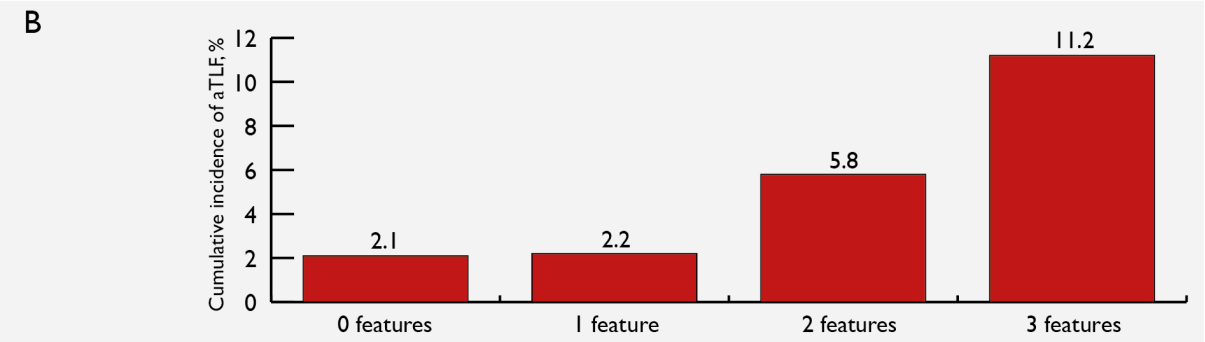
† Other refers to chronic coronary syndrome or unstable angina. All these patients originate from COMBINE (OCT-FFR) and have diabetes.

aTLF attributable target lesion failure; CI confidence interval; HR hazard ratio; MACE major adverse cardiovascular events; TLF target lesion failure.

Figure S3 High-risk plaque components and attributable target lesion failure



	Lipid arc ≥90°	Minimum FCT <65 µm*	Thrombus	Plaque rupture
Prevalence	70.0%	25.5%	15.2%	10.1%
Unadjusted HR (95% CI)	2.871 (1.114-7.399)	3.510 (1.820-6.768)	1.981 (0.954-4.111)	3.745 (1.810-7.748)
P-value	0.029	<0.001	0.067	<0.001



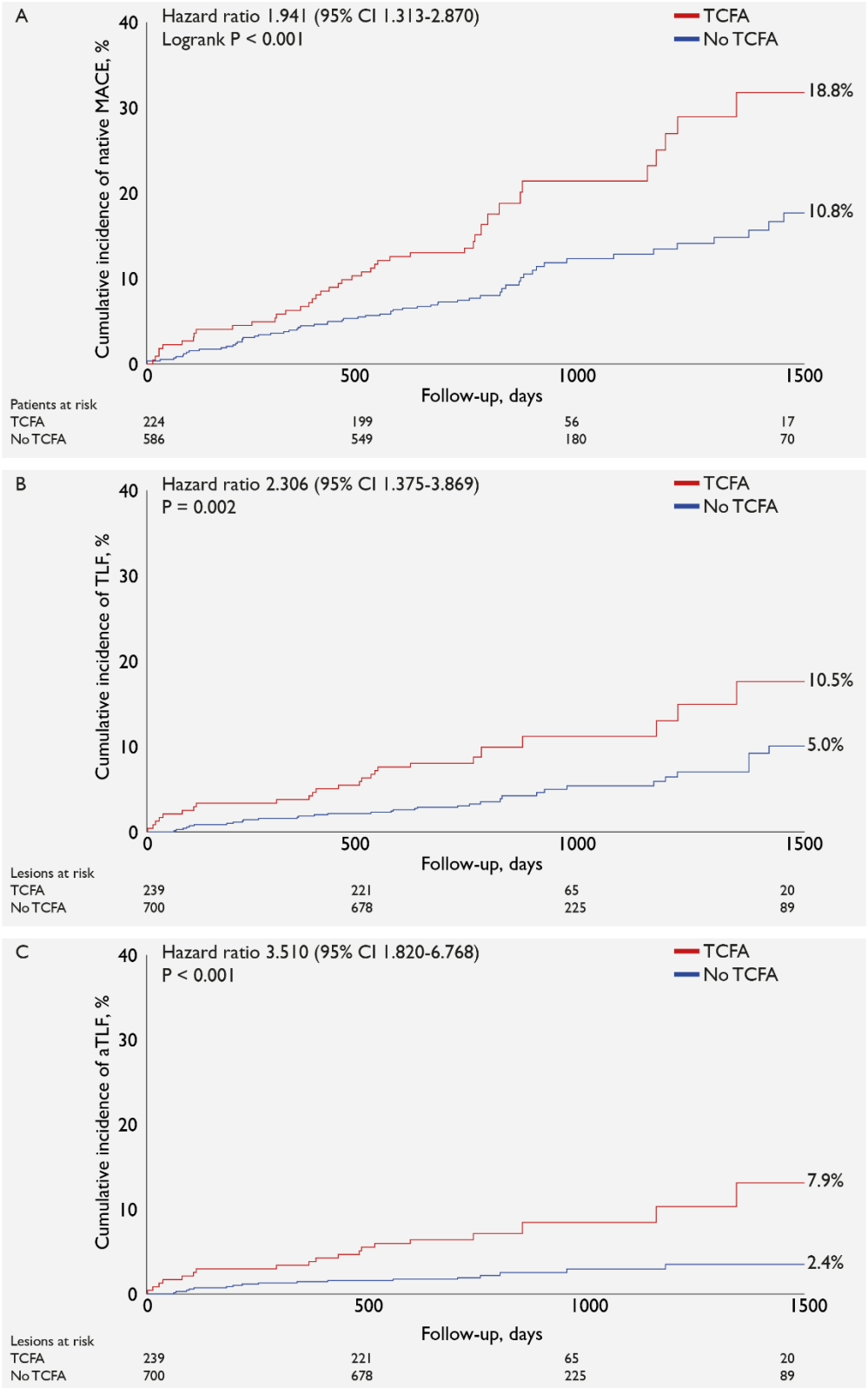
	0 features	1 feature	2 features	3 features
Prevalence	25.5%	43.9%	20.1%	10.4%
Unadjusted HR (95% CI)	*reference*	1.078 (0.361-3.222)	3.072 (1.065-8.862)	5.663 (1.986-16.150)
P-value	*reference*	0.893	0.038	0.001

(A) Association between individual high-risk plaque features and aTLF. (B) Association between the number of high-risk plaque features and aTLF, in which presence of plaque rupture and/or thrombus are considered 1 high-risk plaque feature.

* Considering that all lesions with a minimum FCT <65 µm had a lipid arc ≥90°, all these lesions qualified as a thin-cap fibroatheroma.

aTLF attributable target lesion failure; CI confidence interval; FCT fibrous cap thickness; HR hazard ratio.

Figure S4 Cumulative incidence of the cumulative endpoints according to the presence of thin-cap fibroatheroma



Cumulative incidence curve for the cumulative endpoints of native MACE (A), TLF (B) and aTLF (C) truncated at 1,500 days.

aTLF attributable target lesion failure; CI confidence interval; MACE major adverse cardiovascular events; TLF target lesion failure.

Supplemental Tables

Table S1 Serious adverse events during OCT image acquisition

Case	Serious adverse event	Description
1	Ventricular fibrillation	R-on-T extrasystole causing ventricular fibrillation during removal of OCT catheter, resolved after defibrillation
2	Air embolism	Air embolus during contrast injection for OCT causing temporary repolarization abnormalities which resolved spontaneously
3	Sidebranch occlusion	Occlusion of right descending posterior branch after OCT of middle segment of right coronary artery, which was left untreated considering gracile aspect and in absence of regional wall motion abnormalities and repolarization abnormalities. Etiology unknown, potentially air embolism.

OCT optical coherence tomography.

Table S2 Medical therapy during follow-up

Variables	High-risk plaque			TCFA		
	Present n=271	Absent n=539	P-value	Present n=224	Absent n=586	P-value
Medication at discharge (n=810)						
Statin	240 (88.6)	495 (91.8)	0.129	198 (88.4)	537 (91.6)	0.154
Acetylsalicylic acid	248 (91.5)	499 (92.6)	0.593	210 (93.8)	537 (91.6)	0.315
P2Y12-inhibitor	215 (79.3)	396 (73.5)	0.067	186 (83.0)	425 (72.5)	0.002
Dual antiplatelet therapy	206 (76.0)	385 (71.4)	0.166	180 (80.4)	411 (70.1)	0.003
Anticoagulation	43 (15.9)	62 (11.5)	0.081	27 (12.1)	78 (13.3)	0.634
Betablocker	230 (84.9)	435 (80.7)	0.114	191 (85.3)	474 (80.9)	0.146
ACE-inhibitor	180 (66.4)	358 (66.4)	1.000	151 (67.4)	387 (66.0)	0.712
Last-known medication after discharge (n=777)						
Statin	197 (77.0)	420 (80.6)	0.236	163 (76.2)	454 (80.6)	0.169
Acetylsalicylic acid	199 (77.7)	397 (76.2)	0.634	172 (80.4)	424 (75.3)	0.136
P2Y12-inhibitor	41 (16.0)	56 (10.7)	0.037	37 (17.3)	60 (10.7)	0.012
Dual antiplatelet therapy	26 (10.2)	33 (6.3)	0.059	26 (12.1)	33 (5.9)	0.003
Anticoagulation	44 (17.2)	76 (14.6)	0.346	33 (15.4)	87 (15.5)	0.991
Betablocker	160 (62.5)	336 (64.5)	0.587	131 (61.2)	365 (64.8)	0.349
ACE-inhibitor	144 (56.3)	318 (61.0)	0.202	126 (58.9)	336 (59.7)	0.839

TCFA thin-cap fibroatheroma.

Table S3 Baseline characteristics according to the occurrence of MACE

Variables	N=810	Native MACE n=104	No native MACE n=706	P-value
Age, years		66 ± 11	65 ± 10	0.286
Male sex		30 (28.8)	195 (27.6)	0.794
BMI, kg/m^2	780	29.0 ± 5.0	28.6 ± 4.8	0.467
Smoking status				
Current		29 (28.4)	169 (25.5)	
Previous	764	32 (31.4)	183 (37.6)	0.456
Never		41 (40.2)	310 (46.8)	
Diabetes		73 (70.2)	377 (53.4)	**0.001**
Hypertension	808	71 (68.3)	440 (62.5)	0.255
Hypercholesterolemia	808	52 (50.0)	333 (47.3)	0.607
Family history of premature CVD	796	34 (33.7)	234 (33.7)	0.999
Previous MI		34 (32.7)	157 (22.2)	**0.019**
Previous PCI		42 (40.4)	164 (23.2)	**<0.001**
Previous CVA		7 (6.7)	33 (4.7)	0.366
MI at presentation		51 (49.0)	431 (61.0)	**0.020**
STEMI		21 (41.2)	209 (48.5)	0.323
NSTEMI		30 (58.8)	222 (51.5)	
MINOCA		3 (5.9)	19 (4.4)	0.718
ST-elevation		0 (0.0)	3 (15.8)	1.000
Non-ST-elevation		3 (100)	16 (84.2)	
Medication at discharge				
Statin		87 (83.7)	648 (91.8)	**0.008**
Acetylsalicylic acid		93 (89.4)	654 (92.6)	0.254
P2Y12 inhibitor		73 (70.2)	538 (76.2)	0.184
Dual antiplatelet therapy		69 (66.3)	522 (73.9)	0.104
Oral anticoagulation		20 (19.2)	85 (12.0)	**0.042**
Betablocker		87 (83.7)	578 (81.9)	0.658
ACE inhibitor		70 (67.3)	468 (66.3)	0.837
Laboratory assessment				
Creatinine, µmol/L	743	89.5 ± 22.2	87.1 ± 25.6	0.382
C-reactive protein, mg/L	483	3.00 (1.50-6.00)	2.90 (1.00-5.60)	0.321
Total cholesterol, mmol/L	629	4.48 ± 1.19	4.69 ± 1.32	0.166
LDL-cholesterol, mmol/L	502	2.76 ± 1.12	2.83 ± 1.21	0.669
HDL-cholesterol, mmol/L	506	1.10 (0.92-1.27)	1.10 (0.93-1.38)	0.160
Triglycerides, mmol/L	521	1.75 (1.30-2.53)	1.60 (1.10-2.40)	0.076
Glycated hemoglobin, %	183	7.63 ± 1.60	7.50 ± 1.18	0.593
PCI of non-target lesion(s)		65 (62.5)	477 (67.6)	0.306
Number of target lesions		1.16 ± 0.40	1.19 ± 0.43	0.622
Target lesion distribution				
LM		1 (1.0)	11 (1.6)	1.000
LAD		36 (34.6)	353 (50.0)	**0.003**
LCx		47 (45.2)	241 (34.1)	**0.028**
RCA		36 (34.6)	213 (30.2)	0.359
Target lesion FFR		0.88 ± 0.05	0.89 ± 0.05	0.610

BMI body mass index; CVA cerebrovascular accident; CVD cardiovascular disease; FFR fractional flow reserve; LAD left anterior descending artery; LCx left circumflex artery; LDL low-density lipoprotein; LM left main coronary artery; MACE major adverse cardiovascular events; MI myocardial infarction; MINOCA myocardial infarction with nonobstructive coronary arteries; NSTEMI non-ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention; RCA right coronary artery; STEMI ST-segment elevation myocardial infarction; TLF target-lesion failure.

Table S4 Baseline characteristics according to the occurrence of TLF

Variables	N=939	TLF n=60	No TLF n=879	P-value
Age, years		69 ± 11	65 ± 10	0.131
Male sex		47 (78.3)	640 (72.8)	0.378
BMI, kg/m^2	907	28.0 ± 4.6	28.8 ± 4.8	0.336
Smoking status				
Current		16 (26.7)	209 (25.5)	
Previous	881	16 (26.7)	233 (28.4)	0.943
Never		28 (46.7)	379 (46.2)	
Diabetes		42 (70.0)	482 (54.8)	0.060
Hypertension	936	45 (75.0)	545 (62.2)	0.104
Hypercholesterolemia	935	31 (51.7)	417 (47.7)	0.448
Family history of premature CVD	923	20 (33.3)	296 (34.3)	0.699
Previous MI		18 (30.0)	204 (23.2)	0.121
Previous PCI		23 (38.3)	216 (24.6)	0.183
Previous CVA		5 (8.3)	39 (4.4)	0.118
MI at presentation		27 (45.0)	540 (61.4)	0.051
STEMI		13 (48.1)	252 (46.7)	0.847
NSTEMI		14 (51.9)	288 (53.3)	
MINOCA		1 (3.7)	30 (5.6)	0.848
ST-elevation		0 (0.0)	3 (10.0)	1.000
Non-ST-elevation		1 (100)	27 (90.0)	
Medication at discharge				
Statin		50 (83.3)	806 (91.7)	0.112
Acetylsalicylic acid		53 (88.3)	815 (92.7)	0.110
P2Y12 inhibitor		40 (66.7)	669 (76.1)	0.136
Dual antiplatelet therapy		38 (63.3)	649 (73.8)	0.097
Oral anticoagulation		16 (26.7)	102 (11.6)	**0.008**
Betablocker		49 (81.7)	730 (83.0)	0.584
ACE inhibitor		38 (63.3)	588 (66.9)	0.837
Laboratory assessment				
Creatinine, µmol/L	866	92.0 ± 22.6	87.9 ± 25.7	0.220
C-reactive protein, mg/L	565	3.15 (2.00-14.50)	2.90 (1.00-5.60)	0.385
Total cholesterol, mmol/L	737	4.35 ± 1.33	4.70 ± 1.31	0.187
LDL-cholesterol, mmol/L	583	2.67 ± 1.28	2.85 ± 1.21	0.499
HDL-cholesterol, mmol/L	589	1.10 (0.96-1.30)	1.10 (0.94-1.37)	0.146
Triglycerides, mmol/L	604	1.66 (1.20-2.23)	1.66 (1.13-2.45)	0.939
Glycated hemoglobin, %	253	7.59 ± 1.69	7.53 ± 1.19	0.942
PCI of non-target lesion(s)		37 (61.7)	582 (66.2)	0.563
Number of target lesions		1.30 ± 0.56	1.32 ± 0.54	0.807
Target lesion distribution				
LM		1 (1.7)	9 (1.0)	0.644
LAD		23 (38.3)	354 (40.3)	0.830
LCx		21 (35.0)	267 (30.4)	0.522
RCA		15 (25.0)	248 (28.2)	0.626
Target lesion FFR		0.87 ± 0.05	0.89 ± 0.05	**0.006**

BMI body mass index; CVA cerebrovascular accident; CVD cardiovascular disease; FFR fractional flow reserve; LAD left anterior descending artery; LCx left circumflex artery; LDL low-density lipoprotein; LM left main coronary artery; MACE major adverse cardiovascular events; MI myocardial infarction; MINOCA myocardial infarction with nonobstructive coronary arteries; NSTEMI non-ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention; RCA right coronary artery; STEMI ST-segment elevation myocardial infarction; TLF target-lesion failure.

Table S5 Baseline characteristics according to the presence of TCFA

Variables	N=939	TCFA n=224	No TCFA n=586	P-value
Age, y		65 ± 11	66 ± 10	0.296
Male sex		158 (70.5)	427 (72.9)	0.508
BMI, kg/m^2	780	28.8 ± 4.9	28.6 ± 4.8	0.619
Smoking status				
Current		60 (28.2)	138 (25.0)	
Previous	764	68 (31.9)	147 (26.7)	0.110
Never		85 (39.9)	266 (488.3)	
Diabetes		115 (51.3)	335 (57.2)	0.135
Hypertension	808	138 (61.6)	373 (63.9)	0.550
Hypercholesterolemia	808	105 (47.1)	280 (47.9)	0.843
Family history of premature CVD	796	77 (35.2)	191 (33.1)	0.583
Previous MI		54 (24.1)	137 (23.4)	0.827
Previous PCI		53 (23.7)	153 (26.1)	0.474
Previous CVA		12 (5.4)	28 (4.8)	0.734
MI at presentation		138 (61.6)	344 (58.7)	0.451
STEMI		70 (50.7)	160 946.5)	0.403
NSTEMI		68 (49.3)	184 (53.5)	
MINOCA		1 (0.7)	21 (6.1)	0.011
ST-elevation		0 (0.0)	3 (14.3)	0.864
Non-ST-elevation		1 (100)	18 (85.7)	
Statin at presentation		95 (42.4)	317 (54.1)	0.003
Laboratory assessment				
Creatinine, µmol/L	743	86.7 ± 24.6	87.6 ± 25.4	0.641
C-reactive protein, mg/L	483	3.00 (1.10-6.40)	2.90 (1.10-5.53)	0.371
Total cholesterol, mmol/L	629	4.86 ± 1.29	4.58 ± 1.30	0.015
LDL-cholesterol, mmol/L	502	3.05 ± 1.20	2.72 ± 1.19	0.004
HDL-cholesterol, mmol/L	506	1.12 (0.95-1.39)	1.10 (0.92-1.34)	0.219
Triglycerides, mmol/L	521	1.60 (1.14-2.20)	1.67 (1.11-2.50)	0.637
Glycated hemoglobin, %	183	7.43 ± 1.07	7.56 ± 1.32	0.548
PCI of non-target lesion(s)		173 (77.2)	369 (63.0)	<0.001
Number of target lesions		1.28 ± 0.52	1.15 ± 0.38	<0.001
Target lesion distribution				
LM		2 (0.9)	10 (1.7)	0.311
LAD		98 (43.8)	291 (49.7)	0.132
LCx		80 (35.7)	208 (35.5)	0.953
RCA		90 (40.2)	159 (27.1)	<0.001
Target lesion FFR		0.88 ± 0.05	0.89 ± 0.05	0.222

BMI body mass index; CVA cerebrovascular accident; CVD cardiovascular disease; FFR fractional flow reserve; LAD left anterior descending artery; LCx left circumflex artery; LDL low-density lipoprotein; LM left main coronary artery; MI myocardial infarction; MINOCA myocardial infarction with nonobstructive coronary arteries; NSTEMI non-ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention; RCA right coronary artery; STEMI ST-segment elevation myocardial infarction; TCFA thin-cap fibroatheroma.

Table S6 Association between the presence of TCFA and clinical outcome

Variables	TCFA	No TCFA	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)*	P-value
Patient-level	**n=224**	**n=586**				
Native MACE	42 (18.8)	63 (10.8)	1.941 (1.313-2.870)	<0.001	1.968 (1.327-2.919)	<0.001
All-cause mortality	10 (4.5)	26 (4.4)	1.070 (0.516-2.219)	0.856		
Non-fatal MI	12 (5.4)	10 (1.7)	3.264 (1.410-7.559)	0.003	3.497 (1.496-8.173)	0.004
Unplanned revascularization	33 (14.7)	36 (6.1)	2.615 (1.630-4.197)	<0.001	2.659 (1.651-4.285)	<0.001
Lesion-level	**n=239**	**n=700**				
TLF	25 (10.5)	35 (5.0)	2.306 (1.375-3.869)	0.002	2.247 (1.344-3.755)	0.002
Cardiac death	6 (2.5)	19 (2.7)	0.983 (0.398-2.432)	0.971		
Target-vessel MI	7 (2.9)	3 (0.4)	7.028 (1.836-26.910)	0.004	6.726 (1.697-26.650)	0.007
Target-lesion revascularization	17 (7.1)	17 (2.4)	3.138 (1.597-6.167)	<0.001	2.940 (1.495-5.783)	0.002
aTLF	19 (7.9)	17 (2.4)	3.510 (1.820-6.768)	<0.001	3.291 (1.702-6.361)	<0.001

*Multivariable Cox proportional hazards regression models (patient level) or robust standard errors (lesion level) with the following independent and dependent variables: presence of a high-risk plaque, history of diabetes, history of percutaneous coronary intervention, presentation with myocardial infarction, statin therapy at discharge, oral anticoagulation therapy at discharge, target lesion in the left anterior descending artery and target lesion in the left circumflex artery as independent variable with MACE or its components as dependent variable. Presence of high-risk plaque, history of diabetes, presentation with myocardial infarction, statin therapy at discharge and oral anticoagulation therapy at discharge as independent variable with (a)TLF or its components as dependent variable.

aTLF attributable target lesion failure; CI confidence interval; HR hazard ratio; MACE major adverse cardiovascular events; MI myocardial infarction; TCFA thin-cap fibroatheroma; TLF target lesion failure.