ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2025) **26**, 197–206
https://doi.org/10.1093/ehjci/jeae289

ORIGINAL PAPER

High-risk plaques in non-culprit lesions and clinical outcome after NSTEMI vs. STEMI

Rick H.J.A. Volleberg [1†], Jan-Quinten Mol [1†], Anouar Belkacemi[2], Renicus S. Hermanides [3], Martijn Meuwissen [4], Alexey V. Protopopov [5,6], Peep Laanmets[7], Oleg V. Krestyaninov [8], Casper F. Laclé[9], Rohit M. Oemrawsingh [4,10], Jan-Peter van Kuijk [11], Karin Arkenbout [12], Dirk J. van der Heijden [3,13], Saman Rasoul [14,15], Erik Lipsic [16], Laura Rodwell [17], Cyril Camaro [1], Peter Damman [1], Tomasz Roleder [18], Elvin Kedhi [19], Maarten A.H. van Leeuwen [3], Robert-Jan M. van Geuns [1], and Niels van Royen [1]*

[1]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; [2]Department of Cardiology, AZ West Hospital, Veurne, Belgium; [3]Department of Cardiology, Isala Hospital, Zwolle, the Netherlands; [4]Department of Cardiology, Amphia Hospital, Breda, the Netherlands; [5]Department of Cardiology, Cardiovascular Center of Regional State Hospital, Krasnoyarsk, Russia; [6]Department of Cardiology, Krasnoyarsk State Medical University, Krasnoyarsk, Russia; [7]Cardiology Center, North Estonia Medical Center, Tallinn, Estonia; [8]Department of Cardiology, Meshalkin National Medical Research Center, Novosibirsk, Russia; [9]Department of Cardiology, Dr. Horacio E. Oduber Hospital, Oranjestad, Aruba; [10]Department of Cardiology, Albert Schweitzer Hospital, Dordrecht, the Netherlands; [11]Department of Cardiology, Sint Antonius Hospital, Nieuwegein, the Netherlands; [12]Department of Cardiology, Tergooi Hospital, Blaricum, the Netherlands; [13]Department of Cardiology, Haaglanden Medical Center, The Hague, the Netherlands; [14]Department of Cardiology, Zuyderland Medical Center, Heerlen, the Netherlands; [15]Department of Cardiology, MUMC+, Maastricht, the Netherlands; [16]Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; [17]Department of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Medical Center, Nijmegen, the Netherlands; [18]Faculty of Medicine, Wrocław University of Science and Technology, Wrocław, Poland; and [19]Department of Cardiology, McGill University Health Center, Royal Victoria Hospital, Montreal, Canada

Received 4 June 2024; revised 23 September 2024; accepted 27 October 2024; online publish-ahead-of-print 8 November 2024

Aims

Complete non-culprit (NC) revascularisation may help reduce recurrent events after non-ST-segment elevation myocardial infarction (NSTEMI), especially if NC lesions would harbour high-risk plaque (HRP) features similar to ST-segment elevation myocardial infarction (STEMI). This study aimed to assess differences in fractional flow reserve (FFR)-negative NC plaque morphology in patients presenting with NSTEMI vs. STEMI and assess the association of HRP morphology and clinical outcome.

Methods and results

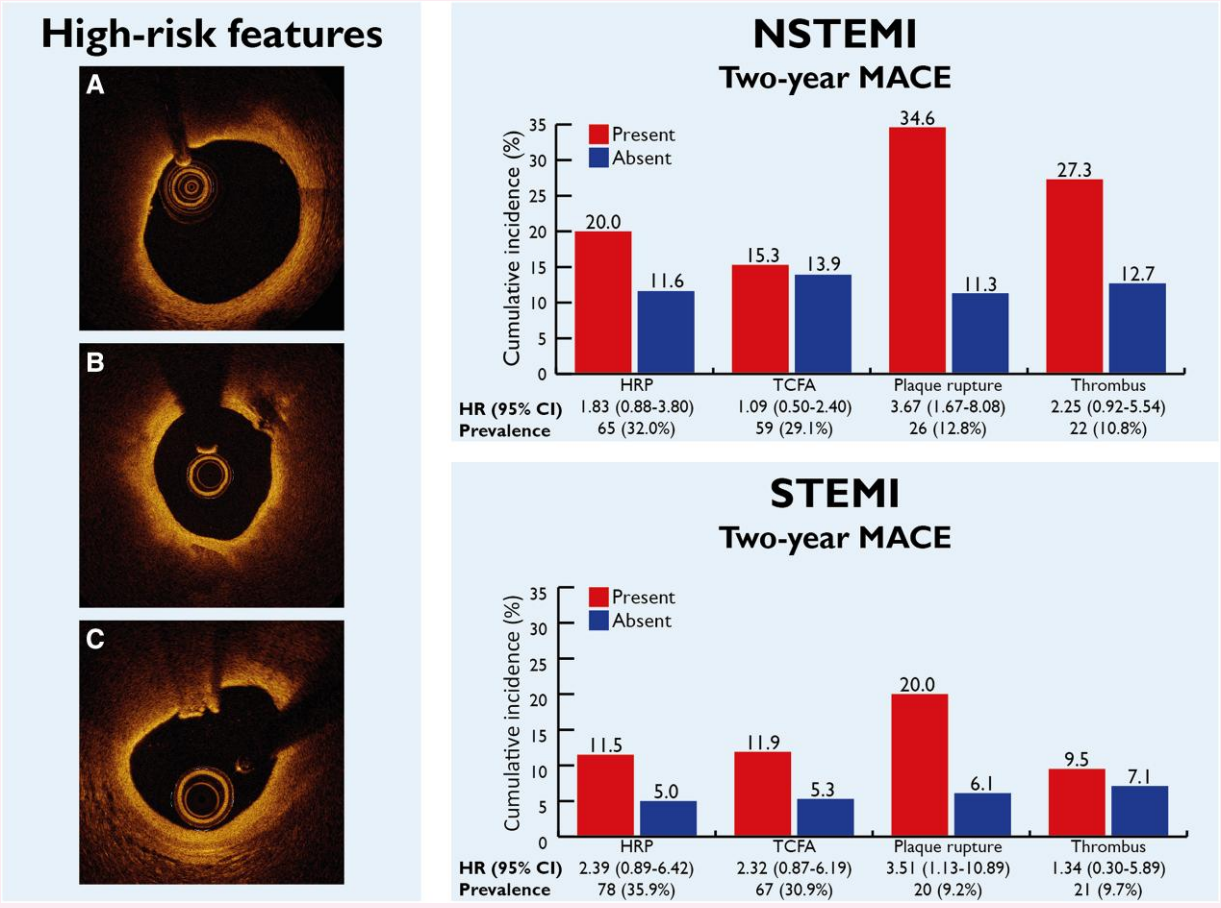
In the prospective PECTUS-obs study, 438 patients presenting with myocardial infarction (MI) underwent optical coherence tomography (OCT) of all FFR-negative intermediate NC lesions. The primary endpoint was the occurrence of major adverse cardiovascular events (MACE, composite of all-cause mortality, non-fatal MI or unplanned revascularisation) at 2-year follow-up. Four hundred and twenty patients had at least one analysable OCT, including 203 (48.3%) with NSTEMI and 217 (51.7%) with STEMI. The prevalence of HRPs, including thin-cap fibroatheromas, plaque rupture, and thrombus, was comparable between groups. MACE occurred in 29 (14.3%) NSTEMI patients and 16 (7.4%) STEMI patients ($P_{\text{uni-variable}} = 0.025$ and $P_{\text{multi-variable}} = 0.270$). Incidence of MACE was numerically higher among patients with HRP, irrespective of the clinical presentation at index ($P_{\text{interaction}} = 0.684$). Among HRP criteria, plaque rupture was associated with MACE in both NSTEMI ($P < 0.001$) and STEMI ($P = 0.020$).

* Corresponding author. E-mail: niels.vanroyen@radboudumc.nl, X: @NielsRoyen
† Contributed equally

Conclusion Presence of NC HRP is comparable between NSTEMI and STEMI and leads to numerically higher event rates in both. These results call for additional research on complete revascularisation in NSTEMI and treatment of HRP.

Clinical trial registration NCT03857971

Graphical Abstract



The presence of at least one optical coherence tomography-identified high-risk plaque (pre-defined in the presence of at least two characteristics: (i) lipid arc ≥90° (A-C), (ii) minimum fibrous cap thickness <65 μm (A, C), and/or (iii) presence of either plaque rupture (B) or thrombus (C)) in afractional flow reserve-negative intermediate non-culprit lesion leads to numerically higher incidences of major adverse cardiovascular events (composite endpoint of all-cause mortality, non-fatal myocardial infarction, or unplanned revascularisation) on a patient-level at 2-year follow-up after NSTEMI and STEMI (right panels). Among high-risk plaque features, plaque rupture was significantly associated with adverse outcome in both NSTEMI and STEMI. CI, confidence interval; HR, hazard ratio; HRP, high-risk plaque; MACE, major adverse cardiovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TCFA, thin-cap fibroatheroma

Keywords NSTEMI • STEMI • non-culprit • high-risk plaque • plaque rupture • TCFA • fractional flow reserve

Introduction

ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) are often considered different clinical entities. Patients presenting with STEMI are on average younger and have less traditional risk factors.[1–3] Furthermore, *in vivo* studies with optical coherence tomography (OCT) and intravascular ultrasound (IVUS) demonstrated a higher prevalence of plaque rupture and high-risk plaque (HRP) features at the culprit site in patients with STEMI.[4–6] Yet, patients with NSTEMI exhibit more recurrent MI.[7–9] Hypotheses regarding this excess number of events include the wrong identification of the culprit coronary artery, thereby leaving the culprit lesion untreated,[10] and the presence of high-risk non-culprit (NC) lesions that are prone to rupture.[11,12] Approximately half of recurrent events after MI are indeed related to NC lesions, that are often non-flow-limiting.[12] Complete revascularisation of NC disease in patients with STEMI now has a class I (level of evidence A) recommendation.[13,14] NC revascularisation in STEMI reduces cardiac mortality or recurrent myocardial infarction (MI) and need

for repeat revascularisation, which may partially be driven by sealing high-risk NC lesions.[15–17] Considering this hypothesis, and a diminished accuracy of the fractional flow reserve (FFR) in the acute setting of MI,[18,19] intracoronary imaging may provide adjunctive value on top of physiological evaluation of stenosis severity.

Evidence supporting complete revascularisation in NSTEMI is less robust.[20,21] However, complete revascularisation in NSTEMI could be a feasible option considering the excess in recurrent events, especially if NC lesions would harbour high-risk features similar to STEMI. Only limited evidence exists on differences in NC plaque morphology between NSTEMI and STEMI.[6,22] The aim of the present study is to assess differences in plaque characteristics of FFR-negative NC plaques in patients presenting with NSTEMI vs. STEMI and to assess the association of FFR-negative but high-risk NC plaques and clinical outcome in these patients.

Methods

Study design

This is a pre-planned sub-group analysis of the multi-centre (see supplementary methods S1) PECTUS-obs (NCT03857971) study, a prospective, observational study that was designed to assess the association between OCT-identified HRP in FFR-negative NC lesions and major adverse cardiovascular events (MACE) in patients presenting with MI. The design and primary results of this study were published previously.[23,24] Briefly, 438 patients with NSTEMI or STEMI underwent OCT of all FFR-negative intermediate NC lesions (defined as visually estimated stenosis 30–90% with an FFR > 0.80) after treatment of the infarct related artery. OCT acquisition was performed using the Dragonfly Optis catheter (Abbott Vascular, USA) under fluoroscopic guidance to ensure that OCT findings could be correlated to the coronary angiogram. Patients underwent structured clinical follow-up 1 and 2 years (± 30 days) after inclusion by means of telephone contact. The study was conducted in accordance with the 1964 declaration of Helsinki and was approved by the institutional review board and/or medical ethics committee of each participating centre. Written informed consent was obtained from all participants. For the present analysis, all patients with at least one analysable OCT pullback were included and were grouped according to the clinical syndrome at presentation (i.e. NSTEMI vs. STEMI).

OCT image analysis

OCT image analysis was performed offline using Caas IntraVascular (Pie Medical Imaging B.V., the Netherlands) by an independent OCT core laboratory (Real Solution Sp. Z o.o., Poland) blinded to patient characteristics and clinical outcome. Pullbacks with insufficient image quality for assessment of the target region were excluded. Quantitative and qualitative image analyses were performed in accordance with contemporary consensus documents.[25,26] Calcification was defined as a sharply delineated signal-poor or heterogeneous region. A lipid plaque was defined as a poorly delineated signal-poor region with a fast signal drop-off that is separated from the lumen by a signal-rich band, the fibrous cap. Thin cap fibroatheroma (TCFA) was defined according to the original pathological criteria[11] as a lipid plaque with a lipid arc ≥90° and a minimum fibrous cap thickness <65 µm. Plaque rupture was defined as a discontinuity of the fibrous cap with or without thrombus. Thrombus was defined as an intraluminal mass either homogeneous with low backscattering or highly backscattering with high attenuation. Healed plaques were defined as regions with one or more layers of different optical densities and a clear demarcation from underlying components. Macrophage accumulation was defined as signal-rich, distinct or confluent punctuate regions with a cast shadow behind. Cholesterol clefts were characterized by a thin, linear high-intensity region and neovascularisation as signal-poor voids that can be followed in multiple consecutive frames. A plaque was considered a HRP in the presence of at least two of the following three pre-specified criteria: (i) a lipid arc ≥90°, (ii) a minimum fibrous cap thickness <65 µm, and/or (iii) presence of either plaque rupture or thrombus.

Clinical endpoints

The primary clinical endpoint was defined as the occurrence of MACE, a composite endpoint of all-cause mortality, any non-fatal MI or unplanned revascularisation, at 2 year (± 30 days) follow-up. Secondary clinical endpoints include the individual components of the primary endpoint, cardiac death, target-vessel failure and revascularisation, and target-lesion failure and revascularisation. Endpoints definitions are provided in Supplementary methods S2. All potential clinical events were adjudicated by an independent event adjudication committee, of which the members were blinded to the results of the OCT analyses. Endpoints were adjudicated using medical records from participating centres, primary care clinicians, or other medical centres.

Statistical analysis

Baseline demographics, procedural characteristics, OCT characteristics, and clinical outcome were compared between patients with NSTEMI and STEMI. Normally distributed continuous variables are expressed as means ± standard deviation (SD) and analysed using the Student's independent samples *t*-test, whereas non-normally distributed variables are expressed as medians with interquartile range and analysed using the Mann–Whitney *U* test. Categorical data are expressed as numbers and percentages and compared using the χ^2 test or Fisher's exact test, whenever appropriate. Lesion-level OCT characteristics were compared between groups using generalized estimating equations with an exchangeable correlation structure to account for potential within-patient clustering. The primary clinical endpoint was compared between groups using the log-rank test and is presented using cumulative incidence curves. Patients were censored at their last known moment of follow-up with a maximum of 2 years (+30 days) after inclusion. Uni-variable and multi-variable (correcting for all baseline clinical characteristics with a *P*-value <0.10 when compared between groups) Cox proportional hazards regression models were fitted to estimate the hazard ratio (HR) of NSTEMI at presentation for the primary clinical endpoint. HR for the secondary clinical endpoints were estimated using the Fine–Gray model with non-cardiac death and all-cause mortality as competing risk factors for cardiac death and all other secondary clinical endpoints, respectively. Multi-variable analyses were only performed for the secondary endpoints that differed significantly between groups in uni-variable analysis. The association between HRP or its individual components and the primary clinical outcome were evaluated in the complete cohort using interaction terms and separately within the sub-groups using the log-rank test and uni-variable Cox proportional hazards regression model to estimate the HR. For this analysis, all patients with at least one HRP were considered high-risk and patients without any HRP were considered non-high-risk. Event rates for the secondary endpoints within the sub-groups according to the presence or absence of HRP were only provided descriptively. Statistical significance was considered at two-sided *P*-values <0.05. Data were analysed using IBM SPSS Statistics software version 27.0 (IBM Corp., USA) and State, release 17 (Stata-Corp LCC, USA).

Results

Baseline and angiographic characteristics and clinical outcome

At least one OCT was analysable in 420 patients, of whom 203 (48.3%) presented with NSTEMI and 217 (51.7%) with STEMI (*Figure 1*). Baseline and angiographic characteristics are presented in *Table 1*. Patients with NSTEMI were on average older than patients with STEMI (mean age 65 ± 11 vs. 62 ± 10 years, $P = 0.004$). Patients with NSTEMI more frequently had a history of diabetes (18.2 vs. 11.1%, $P = 0.037$), hypercholesterolemia (41.6 vs. 31.8%, $P = 0.038$), and a family history for pre-mature atherosclerotic disease (38.7 vs. 23.5%, $P < 0.001$), resulting in an overall higher cardiovascular risk profile (see Supplementary data online, *Figure S1*). Moreover, NSTEMI patients

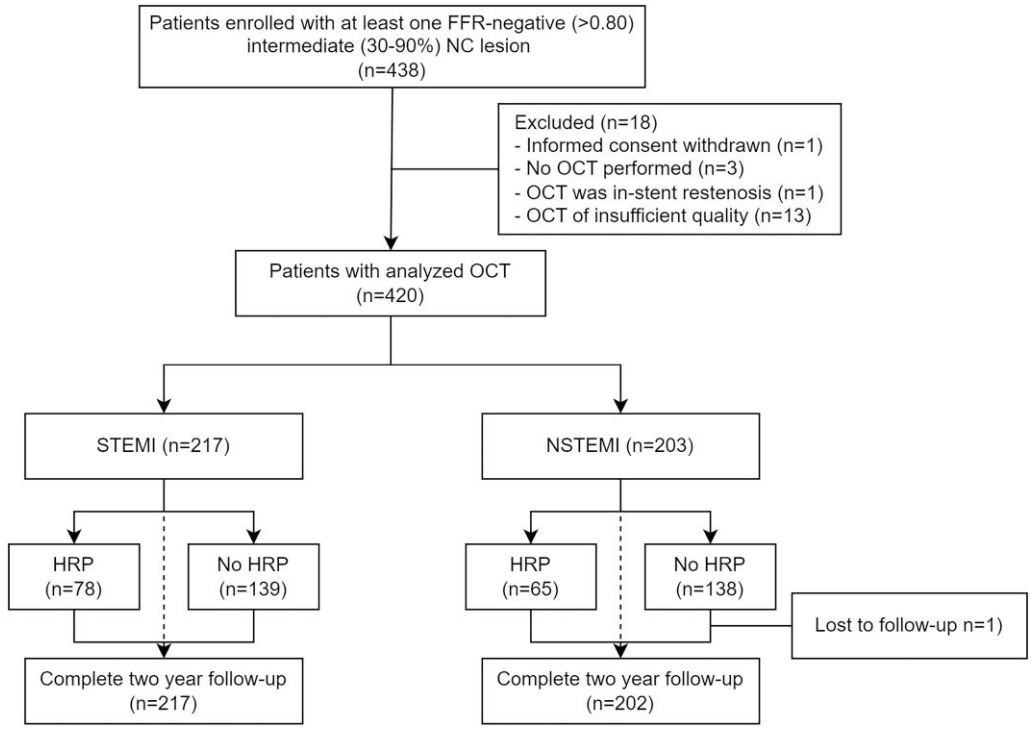


Figure 1 Study flowchart. Flowchart of subjects included in the study. FFR, fractional flow reserve; HRP, high-risk plaque; NSTEMI, non-ST-segment elevation myocardial infarction; NC, non-culprit; OCT, optical coherence tomography; STEMI, ST-segment elevation myocardial infarction.

more frequently had a history of PCI (19.2 vs. 10.6%, $P = 0.013$). Prescription of lipid lowering therapy at baseline was higher among patients with NSTEMI (33.0 vs. 18.9%, $P < 0.001$) and baseline LDL-cholesterol levels were lower (2.9 ± 1.2 vs. 3.2 ± 1.2 mmol/L, $P = 0.010$). Whilst the circumflex coronary artery was more frequently identified as the culprit artery in patients with NSTEMI (32.5 vs. 19.4%, $P = 0.002$), the right coronary artery was more frequently identified as culprit in patients with STEMI (29.1 vs. 45.2%, $P < 0.001$). No difference was observed in the number of FFR-negative NC lesions ($P = 0.450$) or in the mean FFR measurement ($P = 0.256$). Guideline directed medical therapy prescription at discharge and during follow-up was comparable between groups (see Supplementary data online, *Table S1*).

Only one patient was lost to follow-up in between 1- and 2-years follow-up. Primary and secondary clinical endpoints are summarized in *Table 2*. At 2-year follow-up, the primary clinical endpoint of MACE had occurred in 29 (14.3%) patients with NSTEMI compared with 16 (7.4%) patients with STEMI ($P = 0.025$) (*Figure 2*). Specifically, non-fatal MI had occurred more often in patients with NSTEMI (6.4 vs. 0.5%, $P = 0.011$). After correcting for baseline differences between groups, statistical significance was maintained for non-fatal MI ($P < 0.001$) but not for MACE ($P = 0.270$).

NC plaque characteristics

Luminal dimensions

A total of 494 FFR-negative NC lesions were analysable, 242 in patients with NSTEMI and 252 in patients with STEMI. Lesion-level OCT characteristics are presented in *Table 3*. The mean minimum lumen area and diameter were significantly larger in patients with NSTEMI (2.84 ± 1.58 vs. 2.56 ± 1.48 mm^2, $P = 0.048$ and 1.55 ± 0.45 vs. 1.47 ± 0.44 mm, $P = 0.045$, respectively). Accordingly, the percentage area stenosis was smaller in these patients (60.5 ± 16.6% vs. 64.0 ± 15.4%, $P = 0.016$).

HRP features

NC lesions in patients with NSTEMI less frequently had a lipid plaque (70.7 vs. 81.7%, $P = 0.004$) and lipid length was shorter (9.0 ± 6.7 vs. 10.6 ± 7.8 mm, $P = 0.026$). No difference was observed in the prevalence of HRP (29.3 vs. 32.9%, $P = 0.412$), but lesions in patients with NSTEMI less frequently had a lipid arc ≥90° (69.0 vs. 79.0%, $P = 0.015$). Plaque rupture was found in 27 (11.2%) lesions in patients with NSTEMI and in 21 (8.3%) lesions in patients with STEMI ($P = 0.288$). Thrombus was present in 22 (9.1%) and 21 (8.3%) lesions, respectively ($P = 0.744$). Macrophage accumulation was identified in 18.2% of lesions in NSTEMI compared with 27.8% in STEMI ($P = 0.014$).

Association between clinical outcome and OCT characteristics

Sixty-five (32.0%) patients with NSTEMI and 78 (35.9%) patients with STEMI had at least one HRP. The incidence of MACE at 2-year follow-up was numerically higher in patients with at least one HRP compared with patients without a HRP, both in patients with NSTEMI [20.0 vs. 11.6%, $P = 0.102$, HR 1.83 (95% CI 0.88–3.80)] and with STEMI [11.5 vs. 5.0%, $P = 0.075$, HR 2.39 (95% CI 0.89–6.42)] ($P_{interaction} = 0.684$)(*Figure 3*). All clinical endpoints according to the presence of HRPs within both groups are presented in Supplementary data online, *Table S2*. The association between the individual components of a HRP and MACE are presented in the Graphical Abstract. Among these, plaque rupture was significantly associated with MACE in patients with STEMI [$P = 0.020$, HR 3.51 (95% CI 1.13–10.89)] and NSTEMI [$P < 0.001$, HR 3.67 (95% CI 1.67–8.08)].

Table 1 Baseline and procedural characteristics

	NSTEMI $n = 203$	STEMI $n = 217$	*P* value
Age (years)	65 ± 11	62 ± 10	0.004
BMI (kg/m^2)	27.8 ± 5.0	27.7 ± 4.1	0.828
Female sex	44 (21.7%)	36 (16.6%)	0.185
Smoking status			0.221
Current	64 (32.0%)	59 (27.2%)	
Previous	65 (32.5%)	63 (29.0%)	
Hypertension	109 (53.7%)	113 (52.1%)	0.739
Diabetes	37 (18.2%)	24 (11.1%)	0.037
Hypercholesterolemia	84 (41.6%)	69 (31.8%)	0.038
Family history of pre-mature atherosclerosis	77 (38.7%)	51 (23.5%)	<0.001
Previous MI	36 (17.7%)	27 (12.4%)	0.129
Previous PCI	39 (19.2%)	23 (10.6%)	0.013
Previous CVA	5 (2.5%)	3 (1.4%)	0.491
History of carotid artery disease	7 (3.4%)	6 (2.8%)	0.686
History of PAD	9 (4.4%)	8 (3.7%)	0.698
Total cholesterol (mmol/L)	4.9 ± 1.3	5.1 ± 1.4	0.139
LDL-cholesterol (mmol/L)	2.9 ± 1.2	3.2 ± 1.2	0.010
Triglycerides (mmol/L)	2.1 ± 1.5	1.8 ± 1.4	0.037
eGFR (mL/min)	75.4 ± 18.8	83.9 ± 18.6	<0.001
CRP (mg/L)	6.8 ± 16.9	7.0 ± 27.3	0.933
Leukocytes (×10^9/L)	8.9 ± 2.8	10.5 ± 3.4	<0.001
Lipid lowering therapy at presentation	67 (33.0%)	41 (18.9%)	<0.001
Infarct related artery			
LM	3 (1.5%)	2 (0.9%)	0.676
LAD	83 (40.9%)	84 (38.7%)	0.649
Cx	66 (32.5%)	42 (19.4%)	0.002
RCA	59 (29.1%)	98 (45.2%)	<0.001
NC lesion assessment			
Immediate	114 (56.2%)	42 (19.4%)	<0.001
Staged	89 (43.8%)	175 (80.6%)	<0.001
Time to staged procedure (days)	16 ± 14	17 ± 16	0.598
Number of NC lesions	1.19 ± 0.44	1.16 ± 0.39	0.450
NC lesion distribution			
LM	3 (1.5%)	1 (0.5%)	0.357
LAD	86 (42.4%)	89 (41.0%)	0.779
Cx	69 (34.0%)	85 (39.2%)	0.271
RCA	63 (31.0%)	59 (27.2%)	0.386
Targeted NC FFR	0.89 ± 0.05	0.89 ± 0.05	0.256

BMI, body mass index; CRP, c-reactive protein; CVA, cerebrovascular accident; Cx, circumflex artery; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; LAD, left anterior descending artery; LDL, low-density lipoprotein; LM, left main coronary artery; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction

Discussion

In this prospective contemporary cohort of patients with NSTEMI or STEMI, we found a higher incidence of MACE in NSTEMI patients. We also observed an equal prevalence of plaque features that could indicate 'left-behind' culprit lesions in NSTEMI and STEMI. There was no interaction between the clinical presentation and the association between presence of HRP and MACE. Among high-risk criteria, plaque rupture was significantly associated with MACE in both groups. These data call for additional research on NC revascularisation in NSTEMI patients similar to STEMI patients and on treatment of HRP.

Table 2 Two-year clinical outcome

	NSTEMI $n = 203$	STEMI $n = 217$	Uni-variable HR (95% CI)	*P* value	Multi-variable HR (95% CI)[a]	*P* value
Primary endpoint	29 (14.3%)	16 (7.4%)	1.99 (1.08–3.66)	0.025	1.51 (0.72–3.16)	0.270
Death (any)	8 (3.9%)	6 (2.8%)	1.40 (0.49–4.04)	0.531		
Cardiac Death	5 (2.5%)	5 (2.3%)	1.03 (0.30–3.50)[b]	0.960		
Non-fatal MI	13 (6.4%)	1 (0.5%)	13.87 (1.82–105.81)[c]	0.011	14.09 (1.62–122.48)	<0.001
Unplanned revascularisation	16 (7.9%)	10 (4.6%)	1.70 (0.78–3.74)[c]	0.185		
Target vessel failure[d]	7 (3.4%)	4 (1.8%)	1.79 (0.53–6.06)[c]	0.347		
Target vessel revascularisation[d]	7 (3.4%)	4 (1.8%)	1.79 (0.53–6.06)[c]	0.347		
Target lesion failure[d]	4 (2.0%)	4 (1.8%)	1.07 (0.27–4.27)[c]	0.925		
Target lesion revascularisation[d]	4 (2.0%)	4 (1.8%)	1.07 (0.27–4.27)[c]	0.925		

[a]Multi-variable Cox proportional hazard regression models with NSTEMI at presentation, age, history of diabetes, history of hypercholesterolemia, family history for pre-mature atherosclerosis, history of percutaneous coronary intervention, baseline LDL-cholesterol levels, baseline triglyceride levels, baseline estimated glomerular filtration rate, baseline leukocyte levels, right coronary artery as culprit artery, and circumflex artery as culprit artery as independent variables.
[b]HR estimated using the Fine-Gray method with non-cardiac death as competing risk factor.
[c]HR estimated using the Fine-Gray method with all-cause mortality as competing risk factor.
[d]'Target vessel/lesion' refers to the fractional flow reserve-negative NC vessel/lesion imaged by optical coherence tomography.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction

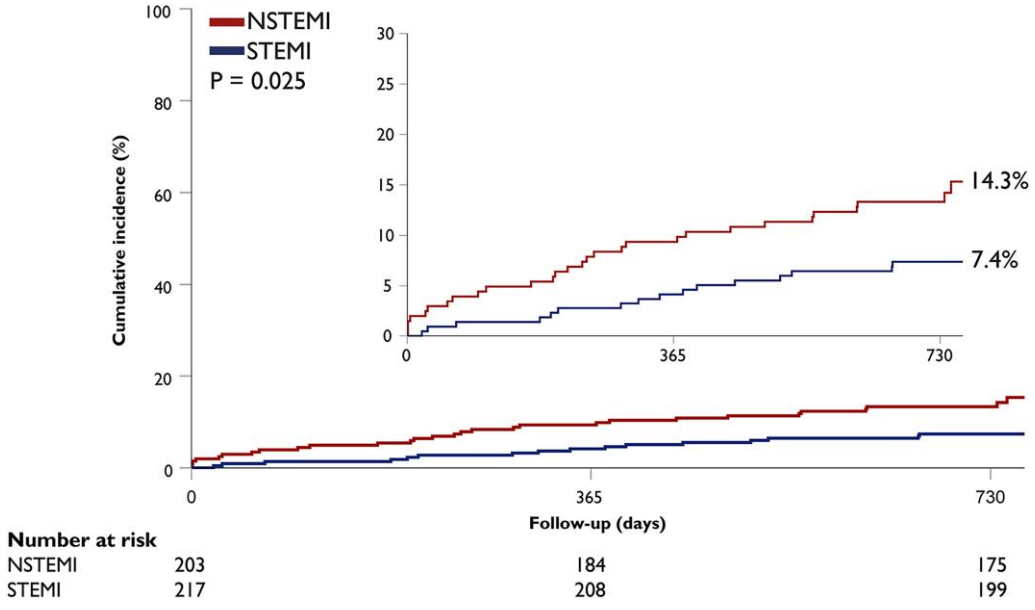


Figure 2 Two-year MACE. Kaplan–Meier curve for the primary clinical outcome of MACE (composite endpoint of all-cause mortality, non-fatal MI, or unplanned revascularisation) at 2 year follow. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

HRP features of NC lesions

A limited number of studies have assessed differences in NC plaque characteristics between NSTEMI and STEMI. In a sub-study of the PROSPECT study, including 668 patients (457 NSTEMI and 211 STEMI) who underwent 3-vessel greyscale and virtual histology-IVUS, no differences in NC plaque characteristics were identified on a patient-level, including an equal presence of TCFA.[22] Fang *et al.* performed three-vessel OCT and found that the percentage area stenosis and prevalence of plaque rupture, calcification and neovascularisation were higher in NC plaques of patients with STEMI. The prevalence of TCFA and calcified plaques were 17.2 and 37.3%, respectively.[6] In contrast, we observed a prevalence of 27.5 and 63.6%, respectively. This disparity may be related to the type of lesions included (i.e. three-vessel imaging versus targeted NC lesion imaging). The median minimum lumen area in the cohort of Fang *et al.* was 4.5 mm^2 (IQR 4.2–4.8) for NSTEMI and 4.2 mm^2 (IQR 4.0–4.4) for STEMI,[6] whereas we found a mean minimum lumen area of 2.84 ± 1.58 mm^2 and 2.56 ± 1.48 mm^2, respectively. Indeed, relative prevalence of TCFA and calcification increases with the degree of stenosis.[27,28]

Table 3 Lesion-level OCT characteristics according to clinical presentation

	NSTEMI *n* = 242	STEMI *n* = 252	*P* value
Minimum lumen area (mm^2)	2.84 ± 1.58	2.56 ± 1.48	0.048
Minimum lumen diameter (mm)	1.55 ± 0.45	1.47 ± 0.44	0.045
Percentage area stenosis	60.5 ± 16.6	64.0 ± 15.4	0.016
Lesion length (mm)	18.2 ± 8.6	19.2 ± 9.0	0.221
Calcification	162 (66.9%)	152 (60.3%)	0.128
Maximum calcification arc (°)	151 ± 99	138 ± 86	0.215
Maximum calcification thickness (μm)	860 ± 270	838 ± 244	0.455
Calcification length (mm)	9.3 ± 8.1	8.6 ± 7.9	0.459
Protruding calcification	35 (14.5%)	24 (9.5%)	0.102
Lipid	171 (70.7%)	206 (81.7%)	0.004
Lipid length (mm)	9.0 ± 6.7	10.6 ± 7.8	0.026
Maximum lipid arc (°)	226 ± 83	224 ± 84	0.996
Lipid arc ≥ 90°	167 (69.0%)	199 (79.0%)	0.015
Minimum fibrous cap thickness (μm)	106 ± 70	112 ± 68	0.444
Minimum cap thickness < 65 μm	65 (26.9%)	71 (28.2%)	0.748
TCFA	65 (26.9%)	71 (28.2%)	0.748
Plaque rupture	27 (11.2%)	21 (8.3%)	0.288
Thrombus	22 (9.1%)	21 (8.3%)	0.744
Macrophage accumulation	44 (18.2%)	70 (27.8%)	0.014
Neovascularisation	41 (16.9%)	37 (14.7%)	0.502
Healed plaque	48 (19.8%)	52 (20.6%)	0.781
Cholesterol clefts	21 (8.7%)	14 (5.6%)	0.187
High-risk plaque	71 (29.3%)	83 (32.9%)	0.412

NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TCFA, thin cap fibroatheroma.

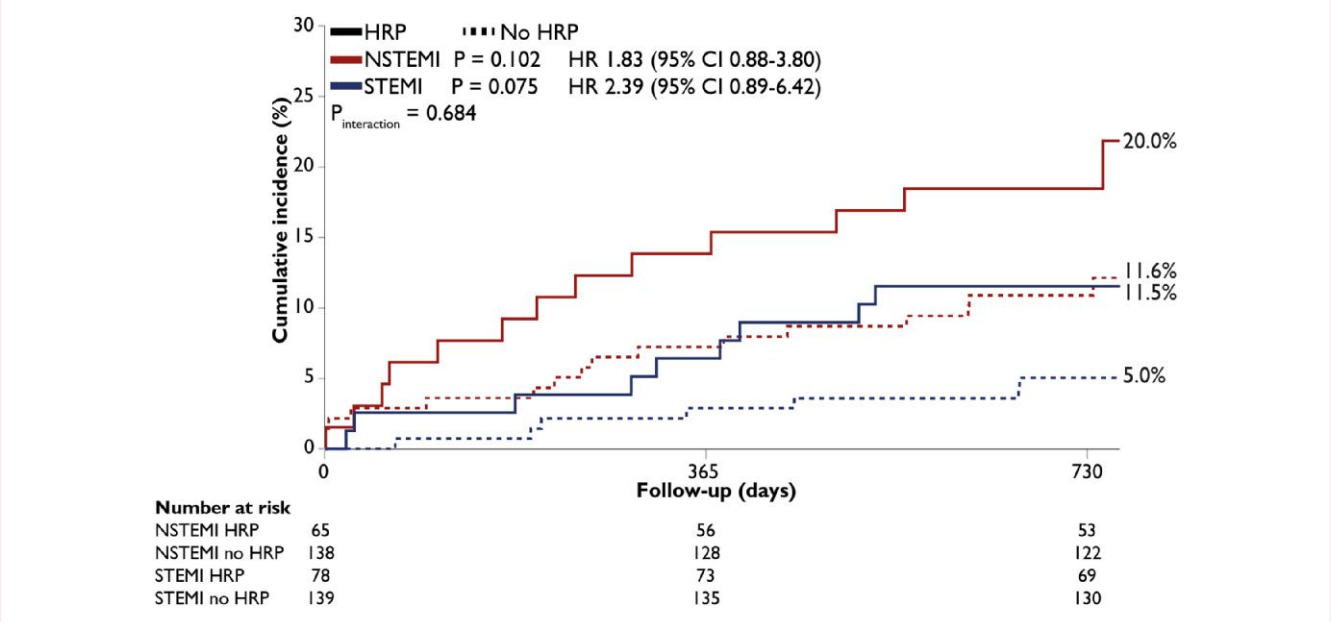


Figure 3 Two-year MACE and presence of HRP. Kaplan–Meier curve for the primary clinical outcome of MACE (composite endpoint of all-cause mortality, non-fatal MI, or unplanned revascularisation) at 2 year follow according to the presence of a HRP in NSTEMI and STEMI. CI, confidence interval; HRP, high-risk plaque; HR, hazard ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Clinical outcome

Despite an equal presence of HRPs in the present cohort, we observed a higher incidence of MACE, and non-fatal MI in particular, in patients with NSTEMI, which was partially attributable to more traditional risk factors in these patients. This observed higher incidence of events during follow-up in patients with NSTEMI is in accordance with large-scale registry data in which this effect was also partly attributable to more cardiovascular comorbidities among these patients.[8,9] Such comorbidities have been associated with rapid lesion progression and future MI.[29,30]

Association between clinical outcome and OCT characteristics

In the primary analysis of the PECTUS-obs, we demonstrated a significant association between OCT-identified HRP and 2-year MACE after MI.[24] These observations suggest incremental value of intracoronary imaging on top of physiological lesion assessment, also considering a diminished accuracy of the FFR in the acute setting of MI due to a temporary increased microvascular resistance,[18] and higher recurrent event rates among STEMI patients after FFR-guided deferral of NC revascularisation compared with those patients undergoing revascularisation with a positive FFR.[19] Although the present analysis was not powered to demonstrate statistically significant associations within sub-groups, we report no significant interaction between the primary outcome and the clinical syndrome at presentation. Presence of a HRP led to numerically higher incidence of MACE both in NSTEMI and STEMI compared with absence of HRP, irrespective of the more adverse clinical profile of patients with NSTEMI. STEMI patients without a HRP were at low risk for subsequent events (2-year incidence of MACE 5.0%). On the contrary, especially patients with NSTEMI and HRP were at very high risk for recurrent events with a 2-year incidence of MACE of 20.0%. Likewise, in a multi-national registry, encompassing 1474 patients (5.1% NSTEMI and 7.1% STEMI), patients with lipid rich plaques and NC related MACE during follow-up were more likely to have presented with NSTEMI at baseline.[31] These results challenge the hypothesis of reduced impact of HRP in NSTEMI and support ongoing research on complete revascularisation of NC plaques in these patients as well as studies on intensified medical treatment or focal treatment for HRP after MI.[32–35] Recently, the PREVENT trial demonstrated for the first time a potential benefit with regards to the latter, but included a very small proportion of patient with MI and OCT-identified HRPs drove revascularisation in a minority of cases.[36] Future studies assessing the clinical value of preventive treatment of HRP, ideally in more high-risk populations, are warranted for more definitive conclusions. It should however be acknowledged that recurrent events also occur in absence of HRP in the imaged segments. In this study, a strategy of targeted imaging of intermediate NC lesions was adopted rather than three-vessel imaging. We therefore cannot rule out that HRP phenotypes were present in other segments without intermediate obstruction. Additionally, other plaque phenotypes other than the pre-defined PECTUS-obs criteria may be related to adverse outcome, calling for a retrospective evaluation of lesions progressing to cause events. Finally, OCT imaging was performed at a single point in time, which precluded assessment of plaque evolution over time.

Interestingly, plaque rupture was associated with recurrent events both in NSTEMI and STEMI. (Sub)clinical plaque rupture is a sign of pan-coronary vulnerability and can lead to acute manifestations when resulting in acute thrombotic occlusion or to rapid lesion progression after subclinical healing.[37–39] Plaque rupture could therefore be a potential target for pre-emptive treatment both in NSTEMI and STEMI. However, considering that presence of plaque rupture and/or thrombus were only included in the pre-defined high-risk criteria of PECTUS-obs and not in earlier natural history studies, confirmation of the prognostic impact in additional studies is warranted. Nevertheless, the FORZA trial demonstrated that indication for revascularisation based on OCT-criteria, among which was plaque rupture, appeared to be a safe alternative to FFR-guided revascularisation.[40,41] However, this population consisted predominantly of patients with chronic coronary syndrome and was not powered to demonstrate differences in clinical outcome. Additional evidence may arise from the ongoing COMBINE-INTERVENE and INTERCLIMA trials, in which plaque rupture and thrombus are incorporated in the HRP criteria, respectively.[42,43]

Potential culprit lesion misidentification

The culprit lesion is generally easily identifiable in STEMI. In contrast, no culprit lesion can be identified by coronary angiography in one-third of NSTEMI patients, 60% of whom have evidence of focal MI on cardiac magnetic resonance. Furthermore, among the two-third of patients in whom a lesion is designated as culprit based on the coronary angiogram, cardiac magnetic resonance identifies another artery as culprit in one in seven cases.[10] The strong association between plaque rupture and future MACE in NSTEMI (2 year incidence of MACE 34.6%) and the observed trend towards higher MACE in the presence of thrombus could indicate that some of the NC lesions imaged may have in fact been the culprit lesion. However, in accordance with the findings of the PROSPECT study,[22] we report equal proportions of NC lesions with presence of plaque rupture or thrombus in NSTEMI and STEMI, contradicting the potential of missed culprit lesions. It is however unknown how true culprit lesions are distributed among FFR-positive and FFR-negative lesions. Irrespectively, pursuing complete angiographic NC revascularisation would imply treatment of all potential culprit lesions.

The present study has some limitations. First, OCT was performed of FFR-negative intermediate NC lesions only rather than three-vessel OCT. The results therefore only apply to FFR-negative lesions and it remains uncertain whether the imaged lesions were indeed all NC lesions, especially in NSTEMI. Furthermore, the latest ESC guidelines on acute coronary syndrome advocates complete angiography-guided revascularisation rather than FFR-guided revascularisation of NC lesions.[14] Although the present study is not in line with this recommendation, no recommendations on guidance of NC revascularisation were made in the prevailing guidelines during the conduct of the study. Additionally, although medical prescription rates were largely comparable between groups, only few patients were on PCSK9-inhibitors and effectiveness of prescribed lipid lowering therapy could not be assessed in absence of cholesterol levels during follow-up. Last, the study was not powered to demonstrate differences in secondary endpoints in the complete cohort or in clinical outcome within the sub-groups and results on the association between HRP components and clinical outcome should therefore be considered hypothesis generating and require confirmation in larger studies.

Conclusion

FFR-negative NC lesions in patients with NSTEMI have a lower degree of stenosis and less frequently harbour lipid plaques compared with patients with STEMI, but prevalence of HRP is comparable. NC HRP leads to numerically higher event rates in both clinical scenarios. These results call for additional research on complete revascularisation in NSTEMI as well as on treatment of HRP after MI.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Acknowledgements

PECTUS-obs was financially supported by Abbott and Health~Holland (grant number LSHM19102). Funding parties were not involved in the

design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review and approval of the manuscript; and decision to submit the manuscript for publication.

Consent

Written informed consent was obtained from all participants.

Funding

PECTUS-obs was financially supported by Abbott and Health~Holland (grant number LSHM19102). Funding parties were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review and approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest: R.H.J.A.V. reported receiving grant funding from Abbott Vascular and Health~Holland during the conduct of the study. J.-Q.M. reported receiving grant funding from Abbott Vascular and Health~Holland during the conduct of the study. A.B. reported receiving speaker's fees from Daiichi Sankyo Inc, travel fees from Novo Nordisk and Daiichi Sankyo, and is shareholder of Pfizer, outside the submitted work. R.S.H. reported receiving speaker fees from Amgen Inc, Angiocare, Edwards Lifesciences and Novartis AG outside the submitted work. R.M.O. reported receiving speaker fees from Abbott Vascular outside the submitted work. E.L. reported receiving grant funding from Abbott Laboratories outside the submitted work. C.C. reported receiving honorarium for organizing regional meetings from AstraZeneca outside the submitted work. P.D. reported receiving grant funding from Abbott Laboratories, AstraZeneca and Philips, ans consulting fees from Abbott Laboratories outside the submitted work. E.K. reported receiving grant funding from Abbott Laboratories and Medtronic, and proctorship honoraria from Abbott laboratories outside the submitted work. M.A.H.v.L. reported receiving grant funding from AstraZeneca, Top Sector Life Sciences & Health, Terumo Corporation, TOP Medical BV, and Abbott Laboratories and speakers' fees and consulting from Terumo Corporation, Daiichi Sankyo Inc, and Abbott Laboratories outside the submitted work. R.-J.M.v.G. reported receiving grant funding from InfraRedx, and speaker fees from Amgen and Sanofi outside the submitted work. N.v.R. reported receiving grant funding and personal fees from Abbott Vascular and Health~Holland during the conduct of the study and grants from Philips, Biotronik, and Medtronic Inc, and speaker fees from Bayer AG, MicroPort, and RainMed Medical outside the submitted work.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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