European Heart Journal - Quality of Care and Clinical Outcomes (2023) **0**, 1–11
https://doi.org/10.1093/ehjqcco/qcad027

ORIGINAL ARTICLE

Occlusion of the infarct-related coronary artery presenting as acute coronary syndrome with and without ST-elevation: impact of inflammation and outcomes in a real-world prospective cohort

Francesco Bruno [1,2,†], Boris Adjibodou [3,†], Slayman Obeid [3,4], Simon C. Kraler [5], Florian A. Wenzl [5], M. Majid Akhtar [1], Andrea Denegri [6], Marco Roffi [7], Olivier Muller [8], Arnold von Eckardstein [9], Lorenz Räber [10], Christian Templin [11] and Thomas F. Lüscher [1,5,*], on behalf of the SPUM-ACS investigators

[1]Royal Brompton & Harefield Hospitals, Imperial College and King's College, Sydney Street, London SW3 6NP, UK; [2]Division of Cardiology, Cardiovascular and Thoracic Department, Città della Salute e della Scienza, Corso Bramante, 88, 10126, Turin, Italy; Cardiology, Department of Medical Sciences, University of Turin, Turin, Italy; [3]Division of Cardiology, Department of Medicine, Aarau Cantonal Hospital, Tellstrasse 25, 5001 Aarau, Switzerland; [4]Cardiology Liestal, Kantonsspital Baselland, Rheinstreet 26, CH-4410 Liestal, Switzerland; [5]Center for Molecular Cardiology, University of Zürich, Wagistrasse 12, 8952 Schlieren, Switzerland; [6]Division of Cardiology, Parma University Hospital, via Antonio Gramsci 14, 43126, Parma, Italy; [7]Division of Cardiology, Department of Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland; [8]Department of Cardiology, University Hospital of Lausanne, Rue du Bugnon46, 1011 Lausanne, Switzerland; [9]Clinical Chemistry, University Hospital, Raemistreet 100, 8091 Zurich, Switzerland; [10]Department of Cardiology, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; and [11]Department of Cardiology, University Heart Center, University Hospital Zurich, Raemistreet 100, 8091 Zurich, Switzerland

Received 21 January 2023; revised 18 April 2023; accepted 16 May 2023; online publish-ahead-of-print 17 May 2023

Background Patients with ST-segment elevation typically feature total coronary occlusion (TCO) of the infarct-related artery (IRA) on angiography, which may result in worse outcomes. Yet, relying solely on electrocardiogram (ECG) findings may be misleading and those presenting with non-ST-segment elevation acute coronary syndromes (NSTE-ACSs) may have TCO as well. Herein, we aimed to delineate clinical characteristics and outcomes of patients with ACS stratified by IRA location.

Methods A total of 4787 ACS patients were prospectively recruited between 2009 and 2017 in SPUM-ACS (ClinicalTrials.gov Identifier: NCT01000701). The primary endpoint was major adverse cardiovascular events (MACEs), a composite of all-cause death, non-fatal myocardial infarction and non-fatal stroke at 1 year. Multivariable-adjusted survival models were fitted using backward selection.

Results A total of 4412 ACS patients were included in this analysis, 56.0% ($n = 2469$) ST-elevation myocardial infarction (STEMI) and 44.0% ($n = 1943$) NSTE-ACS. The IRA was the right coronary artery (RCA) in 33.9% ($n = 1494$), the left-anterior descending coronary artery (LAD) in 45.6% ($n = 2013$), and the left circumflex (LCx) in 20.5% ($n = 905$) patients. In STEMI patients, TCO (defined as TIMI 0 flow at angiography) was observed in 55% of cases with LAD, in 63% with RCA, and in 55% with LCx. In those presenting with NSTE-ACS, TCO was more frequent in those with LCx and RCA as compared to the LAD (27 and 24%, respectively, vs. 9%, $P < 0.001$). Among patients with NSTE-ACS, occlusion of the LCx was associated with an increased risk of MACE during 1 year after the index ACS (fully adjusted hazard ratio 1.68, 95% confidence interval 1.10–2.59, $P = 0.02$; reference: RCA and LAD). Features of patients with NSTE-ACS

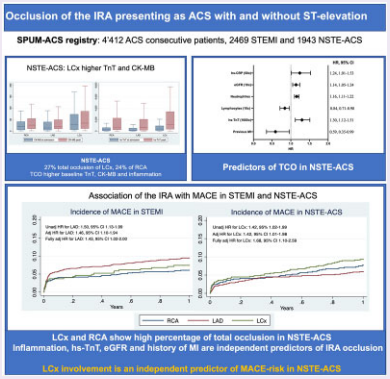
[†] Francesco Bruno and Boris Adjibodou equally contributed as first author.

* Corresponding author. Tel: +41 79 300 22 79, Email: cardio@tomluescher.ch

associated with TCO of the IRA included elevated lymphocyte and neutrophil counts, higher levels of high-sensitivity C reactive protein (hs-CRP) and high-sensitivity cardiac troponin T, lower eGFR, and notably a negative history of MI.

Conclusion In NSTE-ACS, both LCx and RCA involvement was associated with TCO at angiography despite the absence of ST-segment elevation. Involvement of the LCx, but not the LAD or RCA, as the IRA represented an independent predictor of MACE during 1-year follow-up. Hs-CRP, lymphocyte, and neutrophil counts were independent predictors of total IRA occlusion, suggesting a possible role of systemic inflammation in the detection of TCO irrespective of ECG presentation.

Graphical Abstract



Keywords Infarct size • Inflammation—left circumflex coronary artery • Infarct-related artery—non-ST-segment elevation myocardial infarction

Introduction

Identifying the infarct-related artery (IRA) in patients with acute coronary syndromes (ACSs) has profound diagnostic, therapeutic, and prognostic implications.[1,2] Although angiography is the gold standard to localize sites of coronary obstruction or occlusion, the 12-lead electrocardiogram (ECG) is considered the initial diagnostic test as it provides high diagnostic utility as a tool for rapid guidance of invasive treatment in ACS.[3,4] Indeed, while patients with ST-segment elevation myocardial infarction (STEMI) are rushed to the catheterization laboratory for immediate primary percutaneous coronary intervention (pPCI) as a total coronary occlusion (TCO) is suspected, those without ST-segment elevations (NSTE-ACS) are considered to present with a highly stenotic, but open IRA and scheduled for PCI immediately or up to 24 h for invasive management depending on the presence or absence of high-risk features and the GRACE 2.0 score.[1]

However, the ECG at presentation may be misleading and patients presenting as NSTE-ACS on a routine ECG may actually have TCO.[5,6] Limited data exist regarding the impact of the IRA location on major cardiovascular events (MACEs) in an unselected ACS population, especially in the NSTE-ACS subset.

In such patients, yet an acute TCO, typically of the left circumflex (LCx) or right coronary artery (RCA) as the IRA, might be at higher risk of MACE, mainly due to a delayed diagnosis and, consequently, an inappropriately prolonged time window to revascularization.[7,8]

Here, we aimed to study the impact of the IRA location in both STEMI and NSTE-ACS long-term outcomes in contemporary patients with ACS.

Methods

Study design

The study cohort is based on the investigator-initiated, prospective, multicenter SPUM-ACS study (ClinicalTrials.gov Identifier: NCT01000701) including patients aged 18 years or older who presented with ACS to one of the participating Swiss university hospitals (i.e. Zurich, Bern, Lausanne, and Geneva) between 2009 and 2017. Details on the study design of SPUM-ACS have been reported previously.[9–11] Briefly, comprehensive patient information on all patients presenting with ACS to study centers across Switzerland were collected in a centralized electronic database by dedicated study personnel with independent adjudication of diagnosis and outcome.

Inclusion and exclusion criteria

The diagnosis of ACS was made by treating physicians and verified independently by personnel at the local study site according to current guidelines at the time of study inclusion. ACS was defined as the presence of symptoms consistent with angina pectoris and at least one of the following characteristics: (i) ST-segment elevation or depression, T inversion or dynamic ECG changes, and new left bundle branch block (LBBB); (ii) evidence of positive troponin by local laboratory references values; and/or (iii) known coronary heart disease specified as status after myocardial infarction, PCI or bypass surgery, and $\geq$50% stenosis of an epicardial coronary artery. Patients were excluded if they presented a severe physical disability, were unable to consent to the study, or had a life expectancy of less than 1 year (for non-cardiac reasons). Patients without evidence of coronary atherosclerosis as a cause of the ACS were excluded from the present study.

Definition and location of IRA

The IRA was defined based on clinical judgement of the interventional cardiologist, considering clinical presentation, ECG features, and wall motion abnormalities evident from left ventricular angiography and/or echocardiography, as reported previously.[1,2,12–14] Specifically, the identification of the IRA was based on the presence of at least two of the following morphological angiographic features suggestive of acute plaque rupture and/or coronary occlusion: (i) intraluminal filling defect consistent with a thrombus leading to an acute occlusion abruptly ending and with a squared-off

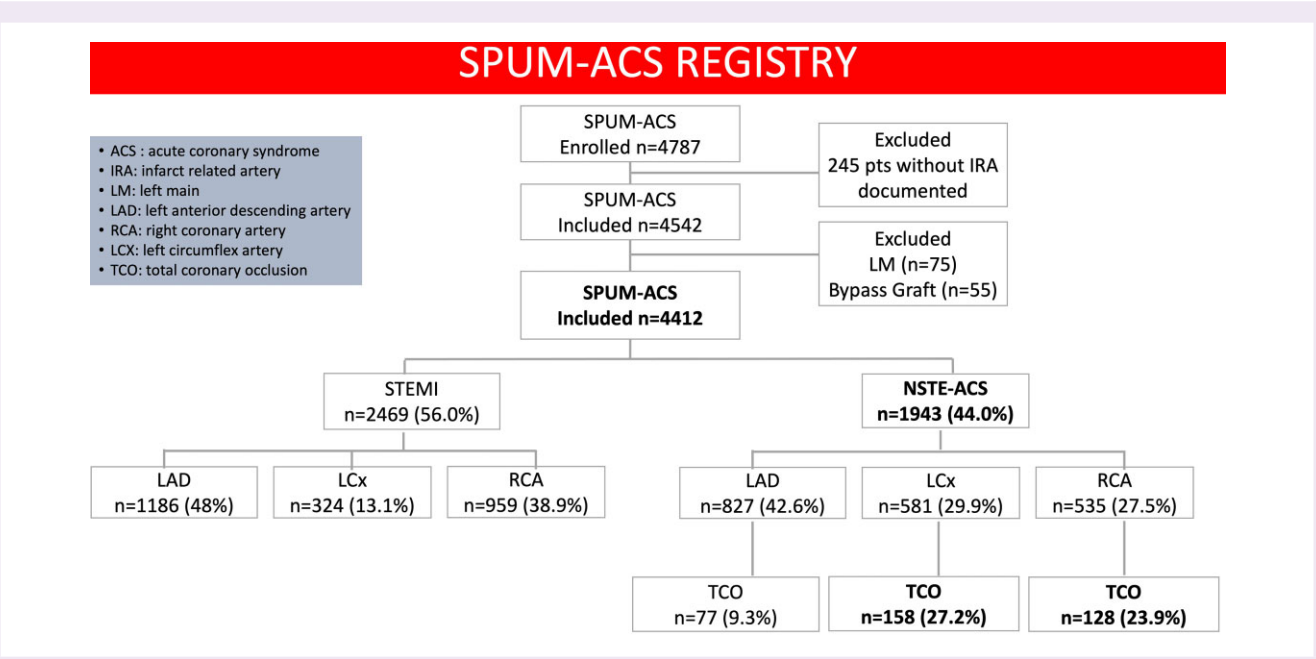


Figure 1 Flow chart of the SPUM-ACS registry and patients included in the analysis.

or convex upstream termination of the ST tract on ECG (i.e. ST, STEMI), (ii) intraluminal filling defect in a patent vessel within or adjacent to a stenotic region with surrounding homogeneous contrast opacification, (iii) plaque ulceration described as presence of contrast and hazy contour beyond the vessel lumen, (iv) plaque irregularity characterized by irregular margins or overhanging edges, (v) dissection, and (vi) impaired flow (TIMI 0 or I).[1,2] In patients with multiple lesions and more than one IRA, but without coronary occlusion, the artery showing a lesion consistent with ECG changes and/or wall motion abnormalities as detected by left ventricular angiography or echocardiography was considered the IRA. Intracoronary imaging was also used if needed at the discretion of the operator to detect the culprit lesion. Diagnostic workup included standard 12-leads ECG and, if clinically indicated, posterior (V7–V9) and right precordial leads were additionally placed, as appropriate and recommended by current guidelines at the time of study inclusion.[1,2]

Patient stratification

Included patients are reported in *Figure 1* and were stratified by IRA (RCA, left-anterior descending coronary artery [LAD], or LCx). Patients with unprotected left main or coronary artery bypass graft (CABG) as IRA were excluded from the current analysis due to their low sample size (75 and 55 patients, respectively), and differences in baseline characteristics and treatment strategy, preventing from direct comparison with the other three groups of patients.

Central biomarker measurements

Clinical biomarkers (i.e. high-sensitivity cardiac troponin T [hs-TnT]; high-sensitivity C-reactive protein [hs-CRP]; N-terminal pro-brain natriuretic peptide [NT-proBNP]) have been measured in the centralized core laboratory (Clinical Chemistry, University Hospital Zurich).[9] Briefly, frozen EDTA plasma aliquots were thawed on ice and immediately processed thereafter measured using high-sensitivity assays, as previously reported.[9] Electrochemilumines cence (NT-proBNP, hs-TnT) or particle-enhanced turbidimetric immunoassays (hs-CRP) were employed (all obtained from Roche Diagnostics, Boehringer Mannheim, Rotkreuz, Switzerland).

Follow-up and event adjudication

Follow-up visits were performed at 30 days (phone call) and 1 year (clinical visit) with independent event adjudication. At each study site, baseline and event data were documented by a trained study nurse using a web-based centralized data entry system (CARDIOBASE, Clinical Trial Unit and Department of Cardiology, University Hospital Bern, Bern, Switzerland, and Webspirit Systems GmbH, Ulm, Germany). All events were adjudicated by an independent clinical endpoint committee comprising three certified external expert cardiologists blinded to patient's baseline characteristics using pre-specified adjudication forms. When patients could not be reached for the 1 year follow-up visit, medical information was obtained from primary care physicians, trusted family members, hospital records, or registry offices.

Clinical outcomes

The primary outcome measure was MACEs defined as a composite of death, non-fatal myocardial infarction, or non-fatal stroke at 365 days after presentation. Secondary endpoints comprised individual components of the primary outcome measure, in-stent thrombosis, bleeds (all BARC type 1, 2, 3a, 3b, 3c, and 5), target vessel revascularization, and the composite of MACE and target vessel revascularization at 30 days and 1 year, respectively.[15] Cardiac biomarkers were used to assess the extent of ischemia (hs-TnT), inflammation (hs-CRP, neutrophil-to-lymphocyte ratio, NLR), and increased ventricular filling pressures (NT-proBNP). All analyses were performed in the whole cohort and stratified by type of ACS (i.e. final diagnosis of STEMI and NSTE-ACS, respectively).

Statistical analysis

Continuous data are reported as mean and standard deviation or median and interquartile range (IQR) if skewed and categorical variables as frequencies and percentages, as appropriate. Differences in clinical and procedural characteristics according to the location of the IRA were examined using the two-tailed Kruskal–Wallis test for continuous data and by applying the Chi-squared test for categorical data, with *P*-values below 0.05 (two-tailed) considered significant. The correlation between

Table 1 Baseline lab values in the NSTE-ACS cohorts according to IRA and TCO

	NSTE–ACS						
	RCA (*n* = 535)	LAD (*n* = 827)	LCx (*n* = 581)	*P* value	TCO (*n* = 363)	Non-TCO (*n* = 1554)	*P* value
Hemoglobin	13.5 (12.3–14.6)	13.5 (12.3–14.6)	13.7 (12.7–14.7)	**0.03**	13.7 (12.8–14.7)	13.5 (12.4–14.7)	0.05
Hematocrit	39.9 (36.1–42.6)	40.2 (37.2–43.3)	40.4 (37–43.1)	**0.02**	40.1 (37.6–43)	40.1 (36.9–43)	0.46
White blood cells	8.3 (6.8–10.3)	8.3 (6.5–10.4)	8.6 (7.0–10.8)	0.06	9.9 (7.3–11.7)	8.7 (6.6–10.1)	**<0.001**
Red blood cells	4.4 (4.0–4.8)	4.5 (4.1–4.9)	4.5 (4.1–4.8)	**0.03**	4.5 (4.2–4.9)	4.4 (4.1–4.8)	0.28
Lymphocytes	1.9 (1.3–2.8)	1.9 (1.3–2.9)	1.8 (1.2–2.7)	0.11	1.9 (1.3–2.6)	1.9 (1.3–2.9)	0.41
Neutrophiles	5.7 (4.2–7.6)	5.4 (4.0–7.6)	5.9 (4.3–8.0)	**0.03**	6.9 (5.1–8.8)	5.4 (4.0–7.3)	**<0.001**
NLR	3.0 (1.8–4.6)	2.7 (1.5–4.6)	3.0 (1.9–5.5)	**0.007**	3.5 (2.2–6.1)	2.7 (1.6–4.5)	**<0.001**
Monocytes	0.7 (0.5–1.1)	0.7 (0.6–1.3)	0.7 (0.5–1.2)	0.77	0.7 (0.5–1.2)	0.7 (0.50–1.2)	0.26
Basophiles	0.03 (0.02–0.06)	0.03 (0.02–0.08)	0.03 (0.02–0.06)	0.16	0.03 (0.02–0.05)	0.03 (0.02–0.07)	**<0.001**
Eosinophiles	0.11 (0.05–0.3)	0.11 (0.05–0.3)	0.11 (0.04–0.3)	0.79	0.12 (0.02–0.19)	0.08 (0.05–0.3)	**<0.001**
Platelets	212 (181–253)	216 (184–253)	213 (179–255)	0.64	221 (184–256)	212 (181–253)	**0.15**
Glucose	5.9 (5.2–6.8)	5.9 (5.3–7.0)	6.0 (5.3–7.1)	0.08	6.0 (5.4–7)	5.9 (5.2–6.9)	0.06
Creatinine	0.84 (0.72–1.00)	0.85 (0.74–1.00)	0.87 (0.74–1.01)	0.17	0.89 (0.72–0.96)	0.93 (0.74–1.02)	0.05
eGFR	90.0 (73.1–99.9)	88.7 (72.7–99.5)	87.9 (72.7–98.9)	0.43	89.2 (79.7–102.80)	83 (71–98.74)	**<0.001**
Total cholesterol	4.7 (3.8–5.6)	4.8 (4.1–5.6)	4.7 (4.0–5.5)	0.07	4.8 (4.1–5.5)	4.8 (3.9–5.6)	0.40
HDL	1.1 (0.9–1.3)	1.1 (1.0–1.4)	1.1 (0.9–1.4)	**0.004**	1.2 (0.9–1.3)	1.2 (0.9–1.4)	0.48
LDL	2.9 (2.1–3.8)	3.0 (2.3–3.7)	2.9 (2.3–3.6)	0.18	3.0 (2.4–3.8)	2.9 (2.2–3.7)	0.05
Triglycerides	1.2 (0.8–1.7)	1.1 (0.8–1.7)	1.2 (0.7–1.7)	0.17	1.3 (0.7–1.6)	1.4 (0.8–1.7)	**0.003**
CK	192 (101–390)	161 (87–344)	308 (129–720)	**<0.001**	478 (212–956)	167 (91–353)	**<0.001**
CK–MB	19 (5.2–40.7)	13.7 (4.4–39.5)	27.2(6.3–72.9)	**<0.001**	48 (19–103)	14 (4–35)	**<0.001**
hsTroponin	234 (57–586)	171 (56–497)	370 (112–907)	**<0.001**	536 (228–1012)	179 (54–521)	**<0.001**
NT–ProBNP	437 (195–1319)	497 (154–1459)	481 (210–1231)	0.89	531 (255–1327)	445 (174–1331)	0.07
hsCRP	3.5 (1.4–10.2)	2.8 (1.3–7.4)	3.2 (1.4–9.6)	**0.03**	3.6 (1.8–11.7)	2.9 (1.2–8)	**<0.001**
CK peak	283 (139–634)	269 (130–608)	504 (196–1132)	**<0.001**	820 (357–1531)	265 (130–563)	**<0.001**
CK–MB peak	26 (10–54)	21 (10–49)	35 (11–86)	**<0.001**	65 (28–140)	21 (9–47)	**<0.001**
Hs TnT peak	507 (161–1460)	426 (131–1227)	959 (255–2320)	**<0.001**	1750 (800–3353)	419 (125–1130)	**<0.001**
Hemoglobin nadir	12.9 (11.5–13.9)	13.0 (11.5–14.1)	13.0 (11.8–14.0)	0.43	13.0 (12.0–13.9)	13.0 (11.6–14.0)	0.58
Platelets nadir	197 (166–235)	202 (166–239)	198 (163–236)	0.87	201 (166–235)	200 (166–239)	0.90
eGFR nadir	80.4 (64.2–94.4)	80.1 (61.9–92.7)	79.1 (63.3–92.2)	0.36	84.5 (70.5–92.3)	78.5 (62.0–92.3)	**<0.001**

In bold statistically significant results.
CK, creatinine kinase; CRP, C-reactive protein; NLR, neutrophile-lymphocyte ratio; eGFR, estimated glomerular filtration ratio; HDL, high-density lipoprotein; LAD, left anterior descending; LCx, left circumflex; LDL, low-density lipoprotein; RCA, right coronary artery; TCO, total coronary occlusion.

logarithm to the base 2 transformed (log2) hs-TnT and log2 hs-CRP, lymphocytes and neutrophils was assessed by calculating Pearson's correlations. Survival curves and the related cumulative incidence curves were obtained using the Kaplan–Meier (KM) method. Crude and multivariable-adjusted survival analyses were performed using a proportional hazard regression model of Cox, with a calculation of their respective hazard ratio (HR) and their confidence interval (CI) at 95%. All the baseline and procedural characteristics associated with the primary endpoint in univariable analysis (at $P \leq 0.10$) were entered into a Cox regression model in a step-wise fashion. To identify predictors of TCO in the NSTE-ACS population, univariable and multivariable logistic regression models were fitted. All variables associated with TCO (at $P \leq 0.10$) were included into a corresponding Cox regression model in a step-wise fashion (backward) as specified in detail in the respective figure legend. A receiver operating characteristic was fitted to assess the performance of the model. All analyses were performed on complete cases with STATA v17 (StataCorp, College Station, TX); see Supplementary material online, *Table S8*).

Results

A total sample of 4412 patients from the prospective SPUM-ACS registry were included. The RCA was the IRA in 33.9% ($n = 1494$), the LAD in 45.6% ($n = 2013$), and the LCx in 20.5% ($n = 905$) of the patients, respectively (*Figure 1*).

Baseline characteristics

Patient baseline characteristics in STEMI and NSTE-ACS according to IRA location and TCO of the IRA are reported in *Tables 1* and *2* and Supplementary material online, *Tables S1–S6*.

Baseline characteristics in the STEMI population ($N = 2469$) according to the IRA are reported in Supplementary material online, *Tables S1–S3*. Patients with LAD ($N = 1186$) as the IRA had higher hs-TnT$_{Peak}$ (4514, IQR 1630–8981 ng/L vs. 3021, IQR 1290–5618 ng/L vs. 3930, IQR 1960–6818 ng/L, $P < 0.001$) and CK-MB$_{Peak}$ (155, IQR 65–330 ng/L vs. 112, IQR 55–220 ng/L vs. 174, IQR 82–

Table 2 Procedural characteristics in the NSTE-ACS cohorts according to IRA and TCO

	NSTE-ACS						
	RCA (*n* = 535)	LAD (*n* = 827)	LCx (*n* = 581)	*P* value	TCO (*n* = 363)	Non-TCO (*n* = 1554)	*P* value
PCI duration	27 (17–44)	30 (19–46)	28 (17–44)	0.05	32 (20–49)	28 (17–43)	**0.002**
Vasopressor use	2 (0.4)	6 (0.7)	8 (1)	0.17	6 (2)	9 (0.6)	**0.04**
IABP	5 (1)	13 (2)	4 (1)	0.27	4 (1)	17 (1)	0.99
L-VAD	1 (0.2)	5 (0.6)	2 (0.3)	0.48	0 (0)	8 (0.5)	0.17
Unfractioned Heparin	519 (97)	789 (96)	565 (97)	0.10	354 (98)	1496 (96)	**0.03**
Fondaparinux	21 (4)	61 (7)	43 (7)	0.02	32 (9)	90 (6)	**0.03**
Enoxaparin	22 (4)	26 (3)	20 (3)	0.63	10 (3)	56 (4)	0.43
Bivalirudin	4 (1)	14 (2)	9 (2)	0.32	6 (2)	21 (1)	0.66
GPIIbIIIa ihibitors	83 (16)	123 (15)	95 (16)	0.75	97 (27)	202 (13)	**<0.001**
Contrast administered	184.5 ± 69.2	205.8 ± 85.1	208.9 ± 84.8	**<0.001**			
Multivessel disease	212 (40)	381 (46)	209 (36)	**0.001**	119 (33)	663 (43)	**0.001**
Lesion location				**<0.001**			**<0.001**
Proximal	178 (33)	332 (40)	203 (35)		124 (34)	574 (37)	
Medial	203 (38)	338 (41)	–		72 (20)	463 (30)	
Distal/branches	154 (29)	157 (19)	378 (65)		167 (46)	517 (33)	
Intra-stent restenosis	26 (5)	38 (5)	26 (4)	0.95	15 (4)	74 (5)	0.61
TIMI Flow pre				**<0.001**	–	–	
0	128 (24)	77 (9)	158 (27)				
1	29 (6)	40 (5)	38 (7)				
2	84 (16)	149 (18)	88 (15)				
3	280 (53)	550 (67)	296 (51)				
Thrombus	136 (25)	101 (12)	134 (23)	**<0.001**	198 (55)	172 (11)	**<0.001**
Lesion classification (AHA/ACC)				**0.006**			**<0.001**
Type A	117 (23)	208 (26)	106 (19)		45 (13)	383 (26)	
Type B1	228 (44)	359 (45)	302 (54)		157 (45)	729 (49)	
Type B2	83 (16)	113 (14)	88 (14)		72 (20)	202 (13)	
Type C	90 (17)	118 (15)	76 (13)		79 (22)	188 (13)	
Controlateral Collaterals	110 (21)	43 (5)	26 (5)	**<0.001**	92 (26)	74 (5)	**<0.001**
Treatment of culprit lesion				**<0.001**			**0.002**
PCI + stent	488 (91)	721 (87)	534 (92)		322 (89)	1418 (91)	
PCI + balloon	21 (5)	49 (5)	34 (6)		31 (9)	67 (4)	
CABG	22 (4)	65 (8)	11 (2)		10 (3)	67 (4)	
Predilatation	396 (81)	564 (79)	450 (84)	**0.04**	277 (86)	1130 (80)	**0.009**
Direct stenting	91 (19)	153 (21)	83 (16)	**0.04**	44 (14)	283 (20)	**0.009**
Number of stents	1.3 ± 0.61	1.2 ± 0.53	1.2 ± 0.45	0.05	1.27 ± 0.54	1.22 ± 0.53	0.10
DES	419 (84)	639 (88)	458 (85)	0.21	310 (84)	1301 (84)	0.86
Bifurcation treatment	13 (3)	90 (12)	50 (9)	**<0.001**	20 (6)	133 (9)	0.05
TIMI flow post III	497 (98)	740 (98)	548 (97)	0.51	328 (94)	1454 (99)	**<0.001**

In bold statistically significant results. The location of the lesion was classified during angiography according to the latest guidelines and documented according to the Syntax Score (ie, proximal part, medial part (except from LCx) and distal part).
CABG, coronary artery bypass graft; DES, drug-eluting stent; IABP, intra-aortic balloon pump; LAD, left anterior descending; LCx, left circumflex; L-VAD, left ventricular assist device; RCA, right coronary artery; PCI, percutaneous coronary intervention; TCO, total coronary occlusion.

322 ng/L, $P < 0.001$) (see *Figure 2*, and Supplementary material online, *Table S2*).

In the NSTE-ACS population ($N = 1943$), patients with LCx ($N = 581$), or RCA ($N = 535$) as IRA had, compared to those with LAD ($N = 827$), more often TCO (27% and 24%, respectively vs. 9%, $P < 0.001$), and evidence of intracoronary thrombus formation at angiography (25% vs. 23% vs. 12%, respectively; $P < 0.001$; *Table 2*). Compared to RCA and LAD, patients with LCx as IRA had higher baseline hs-TnT (370 ng/L, IQR 112–907 vs. 234 ng/L, IQR 57–586 vs. 171 ng/L, IQR 56–497; $P < 0.001$), higher $CK\text{-}MB_{Peak}$ (35 U/L, IQR 11–86 vs. 26 U/L, IQR 10–54 vs. 21 U/L, IQR 10–49; $P < 0.001$) and $hs\text{-}TnT_{Peak}$ (959 ng/L, IQR 255–2320 vs. 507 ng/L, IQR 161–1460 vs. 426 ng/L, IQR 131–1227; $P < 0.001$; *Table 1*). These results were similarly observed in patients with NSTE-ACS and IRA–TCO compared to those without TCO, *Table 1*. ECG alterations and localization according to the IRA in the STEMI and

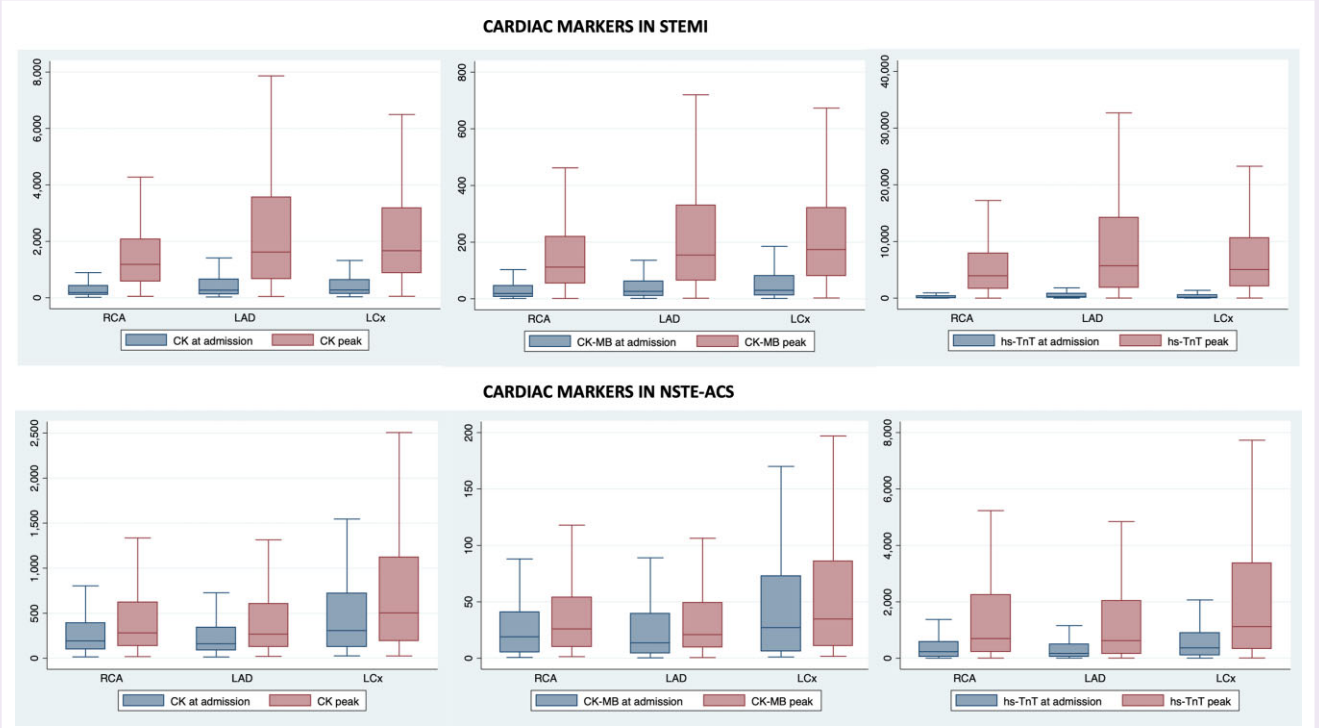


Figure 2 Cardiac markers according to IRA in the STEMI and NSTE-ACS cohorts. LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery.

NSTE-ACS cohort are shown in Supplementary material online, *Figure S1*.

Inflammatory markers

In the STEMI population, no difference between RCA, LAD and LCx was observed at baseline as regards lymphocytes, neutrophils counts, NLR, or hs-CRP, Supplementary material online, *Figure S2* and *Table S2*.

In contrast, in the NSTE-ACS population, baseline neutrophils counts and NLR were higher in the LCx group compared to both RCA and LAD, while hs-CRP was higher in the RCA and LCx group compared to LAD, Supplementary material online, *Figure S2* and *Table 1*. Inflammation markers in the NSTE-ACS population according to IRA–TCO are reported in *Table 1*.

Correlation between logarithm to the base 2 transformed (log2) hs-CRP, log2 lymphocytes, and log2 neutrophils at admission with log2 hs-TnT at admission are reported in Supplementary material online, *Figure S3*. Hs-CRP ($R = 0.34$, 0.38 in STEMI and 0.28 in NSTE-ACS) and neutrophils ($R = 0.32$ in NSTE-ACS) showed a modest positive correlation with hs-TnT at admission, Supplementary material online, *Figure S3*.

Primary endpoint

In the STEMI population, the primary endpoint occurred in 9.5% ($n = 113$) patients with LAD, in 6.1% ($n = 58$) in those with RCA, and 7.4% ($n = 24$) in those with LCx involvement ($P = 0.01$ vs. RCA and LCx; Supplementary material online, *Table S7*). In the KMtime-to-event curves of the STEMI population, patients with LAD as IRA had a significantly higher incidence of the primary endpoint (log rank $P = 0.01$; *Figure 3*). After multivariable adjustment, patients with LAD as IRA had an increased risk of MACE (1.43, 95% CI 1.02–2.00, $P = 0.04$) as compared to those with RCA and LCx (*Figure 3* and Supplementary material online, *Figure S4*).

In the NSTE-ACS population, the primary endpoint occurred in 5.9% ($n = 49$) of the patients with LAD, in 7.7% ($n = 41$) in those with RCA, and in 9.3% ($n = 54$) in those with LCx involvement ($P = 0.057$; Supplementary material online, *Table S7*). In the KM time-to-event curves, patients with LCx or RCA as IRA had a higher incidence of the primary endpoint (log rank $P = 0.06$; *Figure 3*). After multivariable adjustment, LCx as IRA was associated with an increased risk of MACE at follow-up (fully adjusted HR 1.68, 95% CI 1.10–2.59, $P = 0.02$) compared to RCA and LAD. (*Figure 3* and Supplementary material online, *Figure S4*).

Subanalyses

In the KM curves stratified for TCO at angiography, LCx and LAD with TCO had a higher incidence of the primary endpoint during follow-up ($p_{trend} = 0.04$) in the whole population and in the STEMI and NSTE-ACS population, *Figure 4*.

KM curves stratified by the presence or absence of collateral vessels both in the STEMI and NSTE-ACS population are reported in Supplementary material online, *Figure S5*. LCx with collateral vessels showed a higher incidence of the primary endpoint both in STEMI ($p_{trend} = 0.005$) and NSTE-ACS ($p_{trend} = 0.006$), followed by LAD with collaterals.

Secondary endpoints

Secondary endpoints at 30 days and 1 year in the overall, STEMI and NSTE-ACS population, are reported in Supplementary material online, *Table S7*.

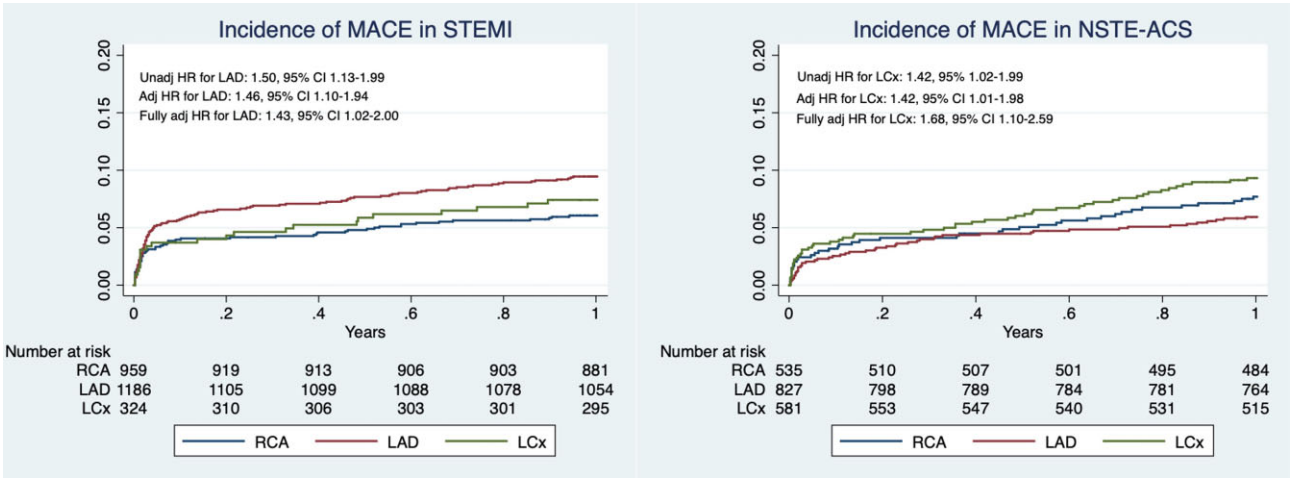


Figure 3 Incidence of primary endpoint in the STEMI and NSTE-ACS cohort. Adjusted model included sex and age, fully adjusted model included all the baseline and procedural variable associated with the primary endpoint with $P < 0.10$ in a step-wise manner. LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery.

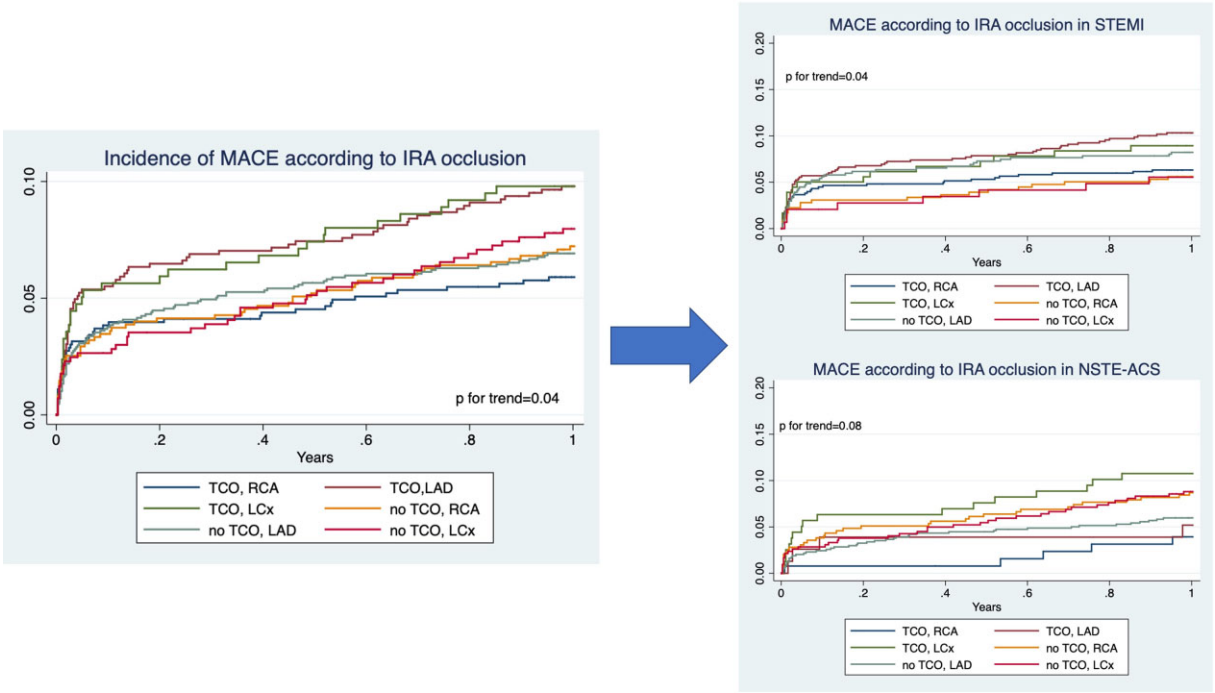


Figure 4 Incidence of primary endpoint according to TCO of the IRA in the whole population, in STEMI and NSTE-ACS. LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery, TCO = total coronary occlusion.

Predictors of TCO in the NSTE-ACS population

In the NSTE-ACS population, no previous myocardial infarction (MI) (odds ratio [OR] 0.59, 95% CI 0.35–0.99, $P = 0.04$), hs-TnT (10^3-fold increase OR 1.30, 95% CI 1.12–1.51, $P < 0.001$), hs-CRP (50-fold increase OR 1.24, 95% CI 1.01–1.53, $P = 0.04$), eGFR (10-fold increase OR 1.14, 95% CI 1.05–1.24, $P = 0.002$), lymphocyte (10-fold increase OR 0.84, 0.71–0.98, $P = 0.04$), and neutrophil count (OR 1.16, 95% CI 1.11–1.22, $P < 0.001$) at admission were independent predictors of IRA–TCO at angiography, *Tables 3*. The model including all these variables showed good performance to predict IRA occlusion (AUC 0.70), Supplementary material online, *Figure S6*.

Table 3 Univariable and multivariable independent predictors of total coronary occlusion (TCO) in the NSTE-ACS population

	Univariable OR 95% CI	*P* value	Multivariable OR 95% CI	*P* value
Age	0.97, 0.96–0.98	<0.001	0.99, 0.97–1.01	0.19
Women	0.67, 0.49–0.91	0.01	0.71, 0.47–1.06	0.10
Diabetes	0.71, 0.52–0.96	0.03	1.04, 0.72–1.48	0.87
Smoking	0.88, 0.76–1.00	0.06	1.04, 0.87–1.23	0.69
Hypertension	0.60, 0.48–0.76	<0.001	0.77, 0.57–1.05	0.10
Hypercholesterolemia	0.74, 0.58–0.94	0.01	0.79, 0.59–1.06	0.11
Previous MI	0.50, 0.34–0.74	0.001	**0.59, 0.35–0.99**	**0.04**
Previous PCI	0.50, 0.35–0.71	<0.001	0.73, 0.41–1.32	0.30
hs-TnT ng/l (1000x)	1.35, 1.19–1.02	<0.001	**1.30, 1.12–1.51**	**<0.001**
Leucocytes G/l	1.08, 1.05–1.52	<0.001	1.03, 0.97–1.08	0.35
Lymphocytes G/l (10x)	0.84, 0.72–0.97	0.02	**0.84, 0.71–0.98**	**0.04**
Neutrophiles G/l	1.13, 1.08–1.17	<0.001	**1.16, 1.11–1.22**	**<0.001**
Erythrocytes G/l	1.20, 0.99–1.45	0.07	0.97, 0.76–1.23	0.79
LDL mmol/l	1.10, 0.99–1.22	0.08	0.95, 0.83–1.09	0.49
eGFR ml/min/m2 (10x)	1.15, 1.08–1.23	<0.001	**1.14, 1.05–1.24**	**0.002**
hs-CRP mg/l (50x)	1.31, 1.09–1.57	0.004	**1.24, 1.01–1.53**	**0.04**
Ischemic alterations on ECG	1.27, 0.99–1.63	0.06	1.22, 0.90–1.64	0.20
Systolic BP mmHg	0.99, 0.98–0.99	<0.001	0.99, 0.99–1.00	0.10
Vasopressor	2.89, 1.02–8.18	0.05	2.13, 0.57–7.93	0.26

In bold statistically significant results.
BP, blood pressure; eGFR, estimated glomerular filtration ratio; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; CRP, C-reactive protein.

Discussion

Here, we show in a multicentre cohort of 4412 prospectively recruited patients with ACS and central biomarker measurement and external event adjudication, that (1) nearly a quarter of patients with NSTE-ACS on the initial ECG and LCx or RCA as culprit artery eventually had TCO at angiography, (2) in NSTE-ACS, LCx as IRA was an independent predictor of MACE at 1 year and (3) lymphocyte and neutrophil counts, hs-CRP, hs-TnT, eGFR, and absence of history of MI at admission were independent predictors of TCO at angiography in those presenting as NSTE-ACS. Finally, we confirm that in STEMI patients, LAD as IRA was an independent predictor of MACE during follow-up.

In the SPUM–ACS study, 56% of patients presented with STEMI of which more than half with the LAD as the IRA. These findings are consistent with recent registry data and underline the high incidence of LAD occlusion in patients with STEMI, in spite of the wide use of high-intensity statins in the primary prevention coronary artery disease.[16–19] Patients with STEMI in which the LAD was the IRA showed an unfavourable risk profile at presentation, including higher TnT peak and NT-ProBNP plasma levels and a lower LVEF confirming the a larger myocardial damage leading to adverse left ventricular remodelling and a higher incidence of heart failure and death.[20–22] Accordingly in our analysis, LAD as IRA in STEMI indeed had higher 1-year MACE rate and higher 1-year all-cause mortality. However, our follow-up was restricted at 1 year and an even stronger association with adverse events at longer term follow-up cannot be excluded, especially regarding heart failure.[23–25]

While in patients presenting with a STEMI, the decision for primary PCI is straight forward, in those presenting without ST-segment elevation an early interventional management is reserved to a minority of patients with high-risk features (e.g. cardiogenic shock, resuscitation, dynamic ST-changes, and/or a high GRACE risk score).[1] Although sometimes accurate identification of the IRA by invasive angiography may be challenging in patients with multivessel disease especially without the use of intravascular imaging, it is assumed that patients with a NSTE-ACS will present at angiography with a non-complete occlusion of the IRA and that hence delayed angiography is considered be appropriate based on current guidelines.[26–28] However, in clinical practice, a subset of patients with a total occlusion of the IRA at coronary angiography presented earlier as ACS without classic ST-elevation on the ECG, but elevated cardiac biomarkers. Such a mismatch between the ECG and angiographic findings may lead to inappropriate management decisions and as such may be associated with a higher risk of mortality and MACE during follow-up[8–29] In fact, due to lack of classic ECG findings, these patients, despite a complete occlusion of the IRA, may be underdiagnosed causing a delay in or, sometimes, even an exclusion from an invasive strategy.[8,30]

Such an ECG-angiographic mismatch has been commonly reported in patients presenting with the RCA and especially the LCx as the IRA.[6–8,26,31] In this large prospective real-world study in patients receiving guideline-based management and independent event adjudication, NSTE-ACS patients with RCA and LCx infarctions had more often TCO in the IRA (24% and 27 vs. 9% for LAD infarction, respectively), confirming the previously results reported by Wang et al.[5–7,28,32] Thus, the ECG has a very low sensitivity to detect acute ischemia in the infero-lateral and posterior myocardial segments causing delays in revascularization and consequently an unfavourable clinical course.[6,33] Although not commonly done in the emergency situation, posterior and right precordial leads may be useful as recommended by current ESC guidelines when an involvement of the posterior wall or right ventricle is suspected.

Interestingly, we found that in the NSTE-ACS baseline neutrophils and NLR were higher in the LCx group, while hs-CRP was higher in both the RCA and LCx group compared to those with LAD lesions, suggesting the presence of a more pronounced baseline inflammation, possibly as a reflection of prolonged acute IRA occlusion and an higher infarct size as we can observe from the positive correlation between hs-CRP and neutrophils with hs-TnT at admission. However, only patients with LCx as IRA had higher baseline and peak hs-TnT and CK-MB, indicating a greater area at risk and more pronounced myocardial necrosis due to untimely primary PCI, which is known to be associated with a higher risk of MACE at follow-up.[6] Similar findings were also observed in patients with NSTE-ACS and TCO.

Data on long-term outcomes in IRA occlusion in the NSTE-ACS population are scarce, and there are no large studies in the contemporary PCI era providing insight into the clinical consequences of LCx occlusion missed by the standard 12-lead ECG.[6,34,35] Previous published studies reported a longer time delay and worse results of PCI in the LCx artery in the context of NSTE-ACS, findings associated with worse short-term outcomes.[6,30,35,36] However, a possible impact on longer term outcomes is still being debated.[33] Here, we provide solid evidence that in the NSTE-ACS population, LCx as IRA was associated with an increased risk of the primary endpoint (a composite of all-cause death, MI, and stroke) compared to RCA and LAD. Furthermore, the LCx as IRA was an independent predictor of the primary endpoint in the multivariable analysis when adjusting for baseline, clinical, and procedural characteristics.

Thus, missing an LCx occlusion due to the absence of ST segment elevation has severe negative clinical implication compared to an RCA occlusion, probably due to a larger infarct size and worse post-MI left ventricular remodelling with a higher incidence of reinfarction and mortality. Patients with left coronary dominance might be more prone to adverse outcomes, although a previous published analysis showed that occlusion of a dominant LCx usually presents as STEMI, while it presents as NSTE-ACS when not dominant.[33] There is thus a strong clinical need of risk stratification tools to identify patients with NSTE-ACS with a total occlusion and to facilitate an early revascularization and, thus, improve longer term outcomes, especially when the LCx is involved.

Finally, our study is the first to report that in the NSTE-ACS population, no previous MI, eGFR increase, high baseline troponin and higher level of inflammation such as a higher hs-CRP, a high number of neutrophils, and a lower number of lymphocytes are independent predictors of total occlusion of the IRA at angiography. Although these results remain hypothesis generating and warrant confirmation in independent cohorts of NSTE-ACS patients, our results highlight that widely available variables have the potential to guide clinical decision-making to identify those patients who could possibly have a total coronary occlusion of the IRA and would clearly benefit from an early revascularization strategy to eventually improve long-term outcomes.

However, inflammatory markers such as neutrophils, NLR, and hs-CRP were found to be increased in the LCx group and correlated with hs-TnT at admission, suggesting a possible link between systemic inflammation, IRA total occlusion, and adverse cardiac events during follow-up in the NSTE-ACS patients. Inflammation, in fact, is a well-know mechanism triggering ACS and MACE and multiple studies targeting the inflammation cascade have been conducted, with some reporting promising results.[37–40] IL-6 has been identified as a specific marker in culprit plaque rupture and ACS, suggesting a possible important role in the identification of patients with IRA total occlusion in the context of a NSTE-ACS.[41–44] Future studies are needed to identify more specific inflammatory markers in this complex scenario, to better stratify NSTE-ACS patients and offer to high-risk patients an early invasive strategy, while current guidelines suggest a routine invasive strategy only in 24 h.[1]

Limitations

Our study has some limitations. First, as in any observational study, we cannot exclude the presence of residual confounding factors that may have affected the results. However, the SPUM study is a prospective multicenter registry, with extensive phenotypic patient documentation, a central biomarker core laboratory for baseline hs-TnT, NT-proBNP, and hs-CRP and independent event adjudication. Owed to the study design of SPUM-ACS, ECG traces at presentation and coronary angiograms were not reviewed by a central core lab, limiting our analysis to the herein reported variables for the prediction of total occlusion in NSTE-ACS patients. Intravascular imaging was used as needed at the discretion of the operator to detect culprit lesions in multivessel disease. However, this was not performed systematically and comprehensive imaging data were not documented according to the study protocol of SPUM-ACS due to financial restraints. Finally, coronary artery dominance (left or right) during angiography was not available, preventing us to provide any information of a potential impact of coronary dominance on outcomes in the NSTE-ACS population.

Conclusions

Among all ACS patients included in the SPUM-ACS, NSTE-ACS patients at initial ECG and RCA and LCx involvement had more often a TCO of the IRA at angiography, but only LCx as IRA was associated with a higher incidence of MACE at 1 year and was an independent predictor of MACE during follow-up. Hs-CRP, lymphocyte and neutrophil counts, hs-TnT, eGFR, and history of MI at admission were found to be independent predictors of IRA occlusion at angiography. Thus, NSTE-ACS patients showing such features should further be evaluated for timely PCI because they could possibly have a TCO of the IRA.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Acknowledgments

The authors would wish to thank the two adjudication committees (Cohort I: Profs. Lukas Kappenberger, Mathias Pfisterer, Tiziano Moccetti, Cohort II: David Carballo, Baris Gencer, Philippe Meyer) and the study nurses involved in the project. The authors are also grateful to Dr Diriek Heg, Institute of Social and Preventive Medicine, University of Bern, Switzerland, for handling the database and all other members of the SPUM-ACS consortium.

Funding

Swiss National Science Foundation (SPUM 33CM30-124112, 32473B_163271); the Swiss Heart Foundation (both Bern, Switzerland to T.F.L.); the Theodor-Ida Herzog Stiftung, Zurich, Switzerland, to S.K.; the Foundation for Cardiovascular Research—Zurich Heart House, Zurich, Switzerland, to T.F.L., S.K., and F.W. The SPUM consortium was further supported by unrestricted grants of Roche Diagnostics (Rotkreuz, Switzerland), Eli Lilly (Indianapolis, IN, USA, AstraZeneca Baar, Switzerland), Medtronic (Münchenbuchsee, Switzerland), and Merck Sharpe and Dome (Lucerne, Switzerland).

Author contributions

F.B, B.A., S.K, F.A.W., S.O., and T.F.L. conceived the study; F.B. performed the statistical analysis, F.B, B.A, S.O., and T.F.L. analysed and interpreted the data; F.B, B.A., and T.F.L. wrote the first draft of the manuscript. All co-authors revisited the work critically for important intellectual content and approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the integrity of any part of the work presented are appropriately investigated and resolved.

Conflict of interest: F.B., B.A., and S.O. have no conflicts of interest to declare. F.A.W. has no conflicts of interest related to this manuscript but has received support from the Foundation for Cardiovascular Research—Zurich Heart House, the Lindenhof Foundation, the Fonds zur Förderung des akademischen Nachwuchses of the University of Zurich, the SphingotecGmbH, the 4TEEN4 Pharmaceuticals GmbH, and the PAM Theragnostics GmbH outside this work. S.K. received funding from the Swiss Heart Foundation, the Lindenhof Foundation, the Novartis Foundation for Medical-biological Research, and the Theodor-Ida-Herzog-Egli Foundation, and equipment and materials from Roche Diagnostics outside the submitted work. L.R. received funding from Abbott, Biotronik, Boston Scientific, Heartflow, Sanofi, and Regeneron, and declares consulting fees from Abbott, Amgen, AstraZeneca, Canon, Medtronic, NovoNordisk, Occlutech, Sanofi, and Vifor, payment or honoraria from Abbott and Occlutech, and travel support from AstraZeneca. A.v.E. received speaker and/or consultant fees from Amgen, MSD, and Sanofi-Aventis. T.F.L. has no conflicts of interest related to this manuscript, but has received educational and research grants from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Daichi-Sankyo, Novartis, Sanofi, Servier, and Vifor and honoraria from Daiichi-Sankyo, DalCor, Inbeeo/Novo Nordisk, Menarini Foundation, Novartis, Pfizer, and Philips outside this work.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author subject to approval of institutional review boards.

References

1. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. *Eur Heart J* 2018;**39**:119–177.
3. Ijkema B.B.L.M, Bonnier J.J.R.M, Schoors D, Schalij M.J, Swenne C.A. Role of the ECG in initial acute coronary syndrome triage: primary PCI regardless presence of ST elevation or of non-ST elevation. *Neth Heart J* 2014;**22**:484–490.
4. Mazurek M, Kowalczyk J, Lenarczyk R, Swiatkowski A, Kowalski O, Sedkowska A *et al.* The impact of unsuccessful percutaneous coronary intervention on short-and long-term prognosis in STEMI and NSTEMI. *Catheter Cardiovasc Interv* 2011;**78**:514–522.
5. Poh KK, Chia BL, Tan HC, Yeo TC, Lim YT. Absence of ST-elevation in ECG leads V7, V8, V9 in ischemia of non-occlusive aetiologies. *Int J Cardiol* 2004, **97**:389–392.
6. Krishnaswamy A, Lincoff AM, Menon V. Magnitude and consequences of missing the acute infarct-related circumflex artery. *Am Heart J* 2009;**158**:706–712.
7. Wang TY, Zhang M, Fu Y, Armstrong PW, Newby LK, Gibson CM *et al.* Incidence, distribution and prognostic impact of occluded culprit arteries among patients with non-ST-elevation acute coronary syndromes undergoing diagnostic angiography. *Am Heart J* 2009;**157**:716–723.
8. Khan AR, Golwala H, Tripathi A, Bin Abdulhak AA, Bavishi C, Riaz H *et al.* Impact of total occlusion of culprit artery in acute non-ST elevation myocardial infarction: a systematic review and meta-analysis. *Eur Heart J* 2017;**38**:3082–3089.
9. Kraler S, Wenzl FA, Georgiopoulos G, Obeid S, Liberale L, von Eckardstein A *et al.* Soluble lectin-like oxidized low-density lipoprotein receptor-1 predicts premature death in acute coronary syndromes. *Eur Heart J* 2022;**43**:1849–1860.
10. Wenzl FA, Kraler S, Ambler G, Weston C, Herzog SA, Räber L *et al.* Sex-specific evaluation and redevelopment of the GRACE score in non-ST-segment elevation acute coronary syndromes in populations from the UK and Switzerland: a multinational analysis with external cohort validation. *Lancet* 2022;**400**:744–756.
11. Wenzl FA, Lüscher TF. Application of a sex-specific GRACE score in practice - Authors' reply. *Lancet* 2023;**401**:23.
12. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neil WW *et al.* Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000;**343**:915–922.
13. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ *et al.* For the Veterans Affairs non-Q-Wave infarction strategies in hospital (VANQWISH) trial investigators. *J Am Coll Cardiol* 2002;**39**:1456–1463.
14. Balbi MM, Scarparo P, Tovar MN, Masdjedi K, Daemen J, Den Dekker WD *et al.* Culprit lesion detection in patients presenting with non-ST elevation acute coronary syndrome and multivessel disease. *Cardiovasc Revasc Med* 2022;**35**:110–118.
15. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J *et al.* Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**:2736–2747.
16. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P *et al.* Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2005. *Circulation* 2017;**136**:1908–1919.
17. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM *et al.* Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 2008;**156**:1026–1034.
18. Stähli B, Roffi M, Eberli F, Rickli H, Erne P, Maggiorini M *et al.* Temporal trends in in-hospital complications of acute coronary syndromes: insights from the nationwide AMIS Plus registry. *Int J Cardiol* 2020;**313**:16–24.
19. Weidmann L, Obeid S, Mach F, Shahin M, Yousif N, Denegri A *et al.* Pre-existing treatment with aspirin or statins influences clinical presentation, infarct size and inflammation in patients with de novo acute coronary syndromes. *Int J Cardiol* 2019;**275**:171–178.
20. Reindl M, Holzknecht M, Tiller C, Lechner I, Schiestl M, Simma F *et al.* Impact of infarct location and size on clinical outcome after ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Int J Cardiol* 2020;**301**:14–20.
21. Kandzari DE, Tcheng JE, Gersh BJ, Cox DA, Stuckey T, Turco M *et al.* Relationship between infarct artery location, epicardial flow, and myocardial perfusion after primary percutaneous revascularization in acute myocardial infarction. *Am Heart J* 2006;**151**:1288–1295.
22. Bahit MC, Kochar A, Granger CB. Post-Myocardial infarction heart failure. *JACC Heart Fail* 2018;**6**:179–186.
23. Lewis EF, Moye LA, Rouleau JL, Sacks FM, Arnold JM, Warnica JW *et al.* Predictors of late development of heart failure in stable survivors of myocardial infarction: the CARE study. *J Am Coll Cardiol* 2003;**42**:1446–1453.
24. Sulo G, Igland J, Vollset SE, Nygård O, Ebbing M, Sulo E *et al.* Heart failure complicating acute myocardial infarction; burden and timing of occurrence: a nation-wide analysis including 86 771 patients from the cardiovascular disease in Norway(CVDNOR) project. *J Am Heart Assoc* 2016;**5**:e002667
25. De Filippo O, D'Ascenzo F, Wańha W, Leonardi S, Raposeiras Roubin S, Fabris E *et al.* Incidence and predictors of heart failure after acute coronary syndrome: the CORALYS registry. *Int J Cardiol* 2023;**370**:35–42.
26. Fang C, Yin Y, Jiang S, Zhang S, Wang J, Wang Y *et al.* Increased vulnerability and distinct layered phenotype at culprit and nonculprit lesions in STEMI versus NSTEMI. *JACC Cardiovasc Imaging* 2022;**15**:672–681.
27. Balbi MM, Scarparo P, Tovar MN, Masdjedi K, Daemen J, Den Dekker W *et al.* Culprit lesion detection in patients presenting with non-ST elevation acute coronary syndrome and multivessel disease. *Cardiovasc Revasc Med* 2022;**35**:110–118.
28. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med* 2002;**347**:5–12.
29. Masoumkhani F, Gohari S, Reshadmanesh T, Ahangar H, Faghihzadeh S. Association between ST-segment resolution after primary angioplasty and short-term outcomes in patients with acute myocardial infarction. *Minerva Cardiol Angiol* 2021;**69**:133–140.
30. Menon V, Ruzyllo W, Carvalho AC, Almeida de Sousa JM, Forman SA, Jaworska K *et al.* Infarct artery distribution and clinical outcomes in occluded artery trial subjects presenting with non-ST-segment elevation myocardial infarction (from the long-term follow-up of Occluded Artery Trial [OAT]). *Am J Cardiol* 2013;**111**:930–935.
31. Dixon WC 4th, Wang TY, Dai D, Shunk KA, Peterson ED, Roe MT; National Cardiovascular Data Registry. Anatomic distribution of the culprit lesion in patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: findings from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2008;**52**:1347–1348.
32. Wang TY, Zhang M, Fu Y, Armstrong PW, Newby LK, Gibson CM *et al.* Incidence, distribution, and prognostic impact of occluded culprit arteries among patients with

non-ST-elevation acute coronary syndromes undergoing diagnostic angiography. *Am Heart J* 2009;**157**:716–723.
33. Waziri H, Jørgensen E, Kelbæk H, Fosbøl EL, Pedersen F, Mogensen UM *et al.* Acute myocardial infarction and lesion location in the left circumflex artery: importance of coronary artery dominance. *EuroIntervention* 2016;**12**:441–448.
34. Kuno T, Kohsaka S, Numasawa Y, Ueda I, Suzuki M, Nakamura I *et al.* Location of the culprit coronary lesion and its association with delay in door-to-balloon time (from a multicenter registry of primary percutaneous coronary intervention). *Am J Cardiol* 2015;**115**:581–586.
35. Gibson CM, Pride YB, Mohanavelu S, Wiviott SD, Antman EM, Braunwald E *et al.* Angiographic and clinical outcomes among patients with acute coronary syndrome presenting with isolated anterior ST-segment depressions. *Critical Care* 2018;**22**:1–11.
36. Terlecki M, Wojciechowska W, Dudek D, Siudak Z, Plens K, Guzik TJ *et al.* Impact of acute total occlusion of the culprit artery on outcome in NSTEMI based on the results of a large national registry. *BMC Cardiovasc Disord* 2021;**21**:297.
37. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009;**54**:2129–2138.
38. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C *et al.*; CANTOS Trial Group. Antiinflammatory therapy with Canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–1131.
39. Kraler S, Wenzl FA, Lüscher TF. Repurposing colchicine to combat residual cardiovascular risk: the LoDoCo2 trial. *Eur J Clin Invest* 2020;**50**:e13424.
40. Fiolet ATL, Opstal TSJ, Mosterd A, Eikelboom JW, Jolly SS, Keech AC *et al.* Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. *Eur Heart J* 2021;**42**:2765–2775.
41. Maier W, Altwegg LA, Corti R, Gay S, Hersberger M, Maly FE *et al.* Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. *Circulation* 2005;**111**:1355–1361.
42. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F *et al.* Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab anti-inflammatory thrombosis outcomes study (CANTOS). *Eur Heart J* 2018;**39**:3499–3507.
43. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M *et al.*; RESCUE Investigators. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2021;**397**:2060–2069.
44. Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* 2012;**379**:1214–1224.