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Transient ST-elevation myocardial infarction versus persistent ST-elevation myocardial infarction. An appraisal of patient characteristics and functional outcome

Gladys N. Janssens [a], Jorrit S. Lemkes [a], Nina W. van der Hoeven [a], Maarten A.H. van Leeuwen [a,b], Henk Everaars [a], Peter M. van de Ven [c], Stijn L. Brinckman [d], Jorik R. Timmer [b], Martijn Meuwissen [e], Joost C.M. Meijers [f,g], Arno P. van der Weerdt [h], Tim J.F. ten Cate [i], Jan J. Piek [j], Clemens von Birgelen [k], Roberto Diletti [l], Javier Escaned [m], Albert C. van Rossum [a], Robin Nijveldt [a,i], Niels van Royen [a,i,*]

[a] Department of Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, the Netherlands
[b] Department of Cardiology, Isala Heart Center, Dokter van Heesweg 2, 8025AB Zwolle, the Netherlands
[c] Department of Epidemiology and Biostatistics, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1089a, 1081HV Amsterdam, the Netherlands
[d] Department of Cardiology, Tergooi Hospital, Rijksstraatweg 1, 1261AN Blaricum, the Netherlands
[e] Department of Cardiology, Amphia Hospital, Molengracht 21, 4818CK Breda, the Netherlands
[f] Department of Experimental Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, the Netherlands
[g] Department of Molecular and Cellular Hemostasis, Sanquin Research, Plesmanlaan 125, 1066CX Amsterdam, the Netherlands
[h] Department of Cardiology, Medical Center Leeuwarden, Henri Dunantweg 2, 8934AD Leeuwarden, the Netherlands
[i] Department of Cardiology, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525GA Nijmegen, the Netherlands
[j] Department of Cardiology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, the Netherlands
[k] Department of Cardiology, Medisch Spectrum Twente, Koningsplein 1, 7512KZ Enschede, the Netherlands
[l] Department of Cardiology, Erasmus MC, 's Gravendijkwal 230, 3015CE Rotterdam, the Netherlands
[m] Cardiovascular Institute, Hospital Clínico San Carlos IDISSC, Calle del Profesor Martín Lagos, S/N, 28040 Madrid, Spain

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ABSTRACT

Background: Up to 24% of patients presenting with ST-elevation myocardial infarction (STEMI) show resolution of ST-elevation and symptoms before revascularization. The mechanisms of spontaneous reperfusion are unclear. Given the more favorable outcome of transient STEMI, it is important to obtain further insights in differential aspects.

Methods: We compared 251 patients who presented with transient STEMI ($n = 141$) or persistent STEMI ($n = 110$). Clinical angiographic and laboratory data were collected at admission and in subset of patients additional index hemostatic data and at steady-state follow-up. Cardiac magnetic resonance imaging (CMR) was performed at 2–8 days to assess myocardial injury.

Results: Transient STEMI patients had more cardiovascular risk factors than STEMI patients, including more arterial disease and higher cholesterol values. Transient STEMI patients showed angiographically more often no intracoronary thrombus (41.1% vs. 2.7%, $P < 0.001$) and less often a high thrombus burden (9.2% vs. 40.0%, $P < 0.001$). CMR revealed microvascular obstruction less frequently (4.2% vs. 34.6%, $P < 0.001$) and smaller infarct size [1.4%; interquartile range (IQR), 0.0–3.7% vs. 8.8%; IQR, 3.9–17.1% of the left ventricle, $P < 0.001$] with a better preserved left ventricular ejection fraction (57.8 ± 6.7% vs. 52.5 ± 7.6%, $P < 0.001$). At steady state, fibrinolysis was higher in transient STEMI, as demonstrated with a reduced clot lysis time (89 ± 20% vs. 99 ± 25%, $P = 0.03$).

Conclusions: Transient STEMI is a syndrome with less angiographic thrombus burden and spontaneous infarct artery reperfusion, resulting in less myocardial injury than STEMI. The presence of a more effective fibrinolysis in transient STEMI patients may explain these differences and might provide clues for future treatment of STEMI.

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1. Introduction

Up to one out of four patients who initially present with a ST-elevation myocardial infarction (STEMI) may subsequently show

* Corresponding author at: Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, the Netherlands.
E-mail address: niels.vanroyen@radboudumc.nl (N. van Royen).

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complete resolution of symptoms and ST-elevation before revascularization therapy is initiated [1]. This condition is called 'transient STEMI'.

Little is known about the etiology and optimal treatment of transient STEMI and therefore current guidelines do not provide specific recommendations for the treatment of these patients. It is unclear whether transient STEMI, apart from STEMI or non-ST-elevation myocardial infarction (NSTEMI), should be considered as a separate entity of acute coronary syndrome (ACS) and whether it might require a different treatment strategy [2,3].

Patients with transient STEMI appear to have a more favorable prognosis than patients with persistent STEMI. Previous studies demonstrated a smaller infarct size in transient STEMI and the recently published randomized TRANSIENT trial found similar outcomes for an immediate, STEMI-like, and a delayed, NSTEMI-like, invasive approach [4–6]. Spontaneous early reperfusion in transient STEMI is most likely the cause of the limited infarct size.

Transient STEMI patients appear to differ from other patients with myocardial infarction in that they are characterized by a younger age at presentation, more smoking and less arterial hypertension [1,5]. In addition, an augmented thrombogenic activity has been found in patients with intermittent reperfusion during acute myocardial infarction [7]. Therefore, it remains plausible that patient-specific characteristics account for spontaneous reopening of the occluded culprit artery. The profile of the respective patients may provide clues to differences in the pathophysiology, that subsequently might lead to alternative therapeutic approaches.

The purpose of this study was to assess patient characteristics, hemostatic and angiographic findings and functional outcome in prospectively enrolled patients with transient STEMI vs. STEMI, in order to reveal specific characteristics and potential clues for differences in etiology.

2. Methods

2.1. Study participants

For the current study we included patients from two prospective multicentre studies, the TRANSIENT trial ($n = 142$) and the REDUCE-MVI trial ($n = 110$). The study design and main results of both studies have been published previously [6,8–10]. Both study protocols conform to the Declaration of Helsinki and ethics approval was obtained by the respective institutional review boards (local medical ethics committees). The inclusion period of the two studies fell in the same time frame (between November 2013 and September 2017) and the majority of patients of both studies was included in the same hospital (VU University Medical Center, Amsterdam, the Netherlands). Both studies enrolled patients >18 years, presenting with an acute STEMI with ST-elevation on the ECG in at least two contiguous leads. Patients in the TRANSIENT trial subsequently had to show complete resolution of ST-elevations and symptoms before revascularization therapy was initiated. Exclusion criteria for both trials were a history of myocardial infarction, congestive heart failure, a left ventricular ejection fraction of <35%, haemodynamic instability, a creatinine clearance of <30 mL/min, contraindications for cardiovascular resonance imaging (CMR) or a life expectancy of <1 year (Supplementary material I). All patients provided written informed consent for study participation.

2.2. Study design and outcomes

All included patients were routinely pre-treated in the ambulance with aspirin, a $P2Y_{12}$ inhibitor and heparin according to standard protocol. Patients with STEMI were treated with immediate percutaneous coronary intervention (PCI) of the culprit lesion and thereafter randomized 1:1 to treatment with ticagrelor or prasugrel for 1 year. According to the study protocol, transient STEMI patients were randomly assigned 1:1 to an immediate or delayed invasive approach, depending on the Global Registry of Acute Coronary Events bureau (GRACE) risk score (>140 within 24 h or ≤140 within 72 h). Accordingly, transient STEMI patients received a $P2Y_{12}$-inhibitor as oral anticoagulant for 1 year. In both studies PCI was performed according to standard procedures and treatment was left to the discretion of the operator. In both studies all other standard medical treatment for acute coronary syndrome was administrated at the discretion of the treating physician and according to the guidelines. Detailed demographics, clinical, angiographic and laboratory data (e.g., blood cell counts, renal function tests, cardiac biomarkers, lipid profile) were recorded and used for the present analysis.

In both studies patients underwent CMR using a clinical 1.5 or 3.0 Tesla scanner at 2 to 8 days after acute myocardial infarction. Left ventricular function and volumes were assessed using cine imaging and late gadolinium enhancement was performed to assess infarct size (expressed as percentage of the left ventricular myocardial mass) and presence of microvascular obstruction.

Besides clinical laboratory data, in a subset of patients blood samples in citrate anticoagulant were collected at admission and steady-state follow-up (transient STEMI patients at 4 months and STEMI patients at 1 year). Platelet-poor plasma was processed by centrifugation and stored in cryovials at −80 °C. In a matched subset of 60 patients thrombogenic and fibrinolytic activity at admission was measured. The measured coagulation factors were prothrombin fragment F1 + 2, von Willebrand factor antigen, plasmin-alpha(2)-antiplasmin (PAP) and D-dimer. With the steady-state blood samples, clot lysis tests were performed by an assessor blinded to clinical presentation. To assess clot lysis, optical density of clotting plasma, triggered with tissue factor, was measured in the presence of tissue plasminogen activator to induce fibrinolysis. This technique has previously been described [11]. Clot lysis time is defined as the time between the maximal rate of fibrin generation and the maximal rate of clot lysis. To correct for differences in clot lysis times between the test series, clot lysis times were expressed as percentage of the normal pooled plasma.

2.3. Statistical analysis

Statistical analysis was performed using SPSS Statistics, version 26 (IBM Corp, Armonk, New York). Continuous variables were compared using the independent-samples *t*-test for normally distributed data and expressed as mean ± standard deviation. Skewed data were compared with the Mann-Whitney *U* test and expressed by median and interquartile range (IQR). Categorical variables were compared using the χ^2 test for binary variables or Fisher's exact test in case of multiple options and expressed as percentages. To account for potential confounding, adjusted analyses were performed using nominal regression and linear regression. Regression models included the grouping variable STEMI and transient STEMI as predictor together with the potential confounders. Statistical significance was assumed when two-sided *p*-value was <0.05.

3. Results

3.1. Patient characteristics

A total of 141 patients with transient STEMI and 110 patients with STEMI, prospectively enrolled between November 2013 and September 2017, was included in the study. Age of the total population was 62 ± 11 years. There were relatively more female patients in the transient STEMI population (30.5% vs. 14.5%, $P = 0.004$). Transient STEMI patients had more frequently a history of peripheral artery disease and previous PCI ($P = 0.001$ and $P < 0.001$, respectively). Other cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia and a positive family history for coronary artery disease did not differ between the groups. Median time from onset of symptoms to presentation was shorter in the transient STEMI group than in the STEMI group (1.0; IQR, 0.5–2.2 vs. 1.4; IQR, 0.7–3.6 h, $P = 0.02$). Upon arrival at the

hospital, the STEMI group showed a lower mean systolic blood pressure and a higher heart rate (both $P = 0.03$) as compared to the transient STEMI group (Table 1).

3.2. Angiographic characteristics and treatment

In the transient STEMI group 72 patients were randomly assigned to a delayed coronary angiography with a median time interval between onset of symptoms and invasive procedure of 25.8 h (IQR, 20.2–30.5) h and 70 patients to immediate angiography (3.1 h; IQR, 1.9–4.9 h). One patient, allocated to the delayed intervention group, withdrew consent after randomization. STEMI patients were all treated with immediate coronary angiography. The location of the culprit artery differed between the groups ($P < 0.001$), with less frequently involvement of the left circumflex artery in transient STEMI than in STEMI patients (12.8% vs. 26.4%), while there was no difference in the involvement of the left anterior descending artery and right coronary artery. Furthermore, no culprit was found in 11.3% of the patients with a transient STEMI. The vast majority of transient STEMI patients had a coronary flow of Thrombolysis In Myocardial Infarction (TIMI) grade 2–3 before PCI, and a TIMI flow grade 0–1 was seen in only 3 (2.1%) patients, which was accompanied by signs of reinfarction. In the STEMI group more than half of the patients had TIMI 0–1 flow (overall $P < 0.001$) (Fig. 1a). Accordingly, the thrombus burden scores were higher ($P < 0.001$) in STEMI patients (Fig. 1b). The difference in thrombus burden was also observed when only looking at the patients that underwent immediate coronary angiography in both patient groups (no thrombus in transient STEMI 31.4% vs. STEMI 2.7%, moderate thrombus burden 54.3% vs. 57.3% and high thrombus burden 14.3% vs. 40.0%, $P < 0.001$). As transient STEMI patients had more frequently a history of PCI and peripheral artery disease, it could be speculated that the use of antiplatelet therapy, as well as the shorter time to presentation, was of influence on pre-PCI TIMI flow grade and thrombus burden. Therefore additional adjustment for these parameters was performed, which did not change the results (Supplementary Table S1).

All STEMI patients were treated with subsequent primary PCI, while 5.7% of the transient STEMI patients were treated with coronary artery bypass grafting and 12.1% received conservative medical treatment (overall $P < 0.001$). The number of stents for the culprit lesion did not differ between the groups (both median 1, IQR 1–1, $P = 0.30$), but the median total stent length was 10 mm longer in STEMI patients ($P < 0.001$) (Table 2).

Table 1
Baseline characteristics.

Characteristics	Transient STEMI (n = 141)	STEMI (n = 110)	*P*-value
Sex, male	98 (69.5)	94 (85.5)	0.004
Age, y	62 ± 12	61 ± 9	0.20
Weight, kg	82 ± 15	88 ± 14	0.001
Hypertension	53 (37.6)	33 (46.5)	0.23
Diabetes mellitus	16 (11.3)	11 (10.0)	0.84
Smoking			0.39
Current	64 (45.4)	47 (43.1)	0.72
Previous	32 (22.7)	19 (17.4)	0.31
Hypercholesterolemia	33 (23.4)	23 (20.9)	0.65
Family history of CAD	62 (44.0)	42 (38.2)	0.37
Previous PCI	8 (5.7)	4 (3.6)	<0.001
Peripheral artery disease	12 (8.5)	0 (0.0)	0.001
Prior antiplatelet therapy	19 (13.5)	9 (8.2)	0.26
Time symptoms-presentation STEMI, hours	1.0 (0.5–2.2)	1.4 (0.7–3.6)	0.02
Systolic blood pressure at admission, mmHg	132 ± 24	127 ± 16	0.03
Diastolic blood pressure at admission, mmHg	77 ± 14	79 ± 12	0.26
Heart rate at admission, bpm	72 ± 14	76 ± 15	0.03

Values are n (%), median (interquartile range), or mean ± SD. CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

3.3. Myocardial injury

Myocardial injury, based on peak creatine kinase-MB (CK-MB) and troponin T levels, was limited in the transient STEMI group with approximately five times lower values than in the STEMI group (CK-MB 20.0 μg/L [IQR, 9.8–38.7 μg/L] vs. 97.9 μg/L [IQR, 35.8–211.0 μg/L] and troponin 0.357 μg/L [IQR, 0.133–0.791 μg/L] vs. 1.872 μg/L [IQR, 0.506–4.253 μg/L], respectively) (Table 3). In accordance, median infarct size measured by CMR was only 1.4% (IQR, 0.0–3.7%) of the left ventricle in transient STEMI patients compared to 8.8% (IQR, 3.9–17.1%) in STEMI patients. Similarly, left ventricular ejection fraction was more preserved in transient STEMI patients (57.8 ± 6.7% vs. 52.5 ± 7.6%, both $P < 0.001$) and microvascular obstruction (MVO) was less frequently observed in patients with transient STEMI than with STEMI (4.2% vs. 34.6%, $P < 0.001$) (Fig. 2a-c). Adjustment of the left ventricular ejection fraction for prior antiplatelet therapy and final TIMI flow did not change the difference between the transient STEMI and STEMI group (Supplementary Table S2). In the subgroup of patients with transient STEMI without a culprit lesion median infarct size was even limited to 0.0% (IQR, 0.0–2.3%) of the left ventricle compared to transient STEMI patients with an identifiable culprit lesion (1.5, IQR, 0.0–4.2%, $P = 0.01$) (Supplementary Table S3). Coronary spasm was most frequently (37.5%) the reported clinical cause of transient STEMI in these patients (Supplementary Table S4).

Major bleeding did not occur significantly more in patients with transient STEMI compared to STEMI.

3.4. Laboratory measures

Several differences in laboratory values were found between the groups (Table 3). Both after admission and on day 3 platelet count was higher in transient STEMI patients (Fig. 3a), but regarding coagulation parameters at baseline only prothrombin fragment F1 + 2 showed a trend towards higher plasma levels in transient STEMI patients (238 ± 171 vs. 179 ± 68 pmol/L, $P = 0.09$) (Fig. 3b). The fibrinolytic measures PAP and D-dimer showed no between-group difference.

Furthermore, total cholesterol, high-density-lipoprotein and triglycerides were higher in transient STEMI patients. At steady state, there was a higher fibrinolytic activity as demonstrated by reduced clot lysis times in transient STEMI vs. STEMI patients (Fig. 3c). Also after adjustment of the analyses of hemostatic parameters for the use of prior anti-platelet therapy, the differences between transient STEMI and STEMI patients persisted (Supplementary Table S5).

4. Discussion

This merged analysis of the TRANSIENT and REDUCE-MVI randomized clinical trials provides new evidence supporting that transient STEMI is a clinical entity with specific characteristics and spontaneous infarct artery reperfusion, associated to less myocardial damage and better clinical outcomes compared to persistent STEMI. We also found that transient STEMI patients have a higher fibrinolytic activity. The implications of these findings are discussed in the next paragraphs.

Up to a quarter of patients who present with acute myocardial infarction show transient ST-elevation with subsequent complete resolution [1]. Only few studies have compared the differences between transient STEMI and STEMI. In the current study, we have compared two cohorts of prospectively enrolled transient STEMI and STEMI patients in terms of their clinical characteristics and outcomes. Patients

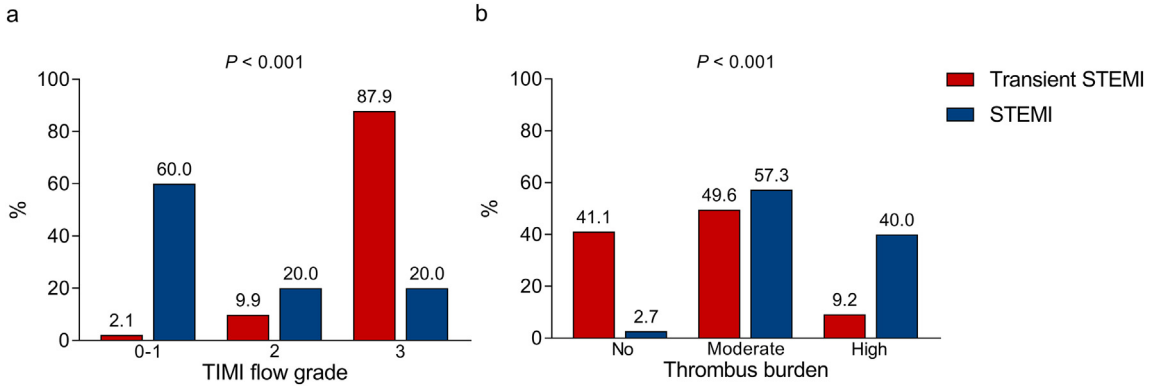

Fig. 1. a Pre-PCI TIMI flow grade and b thrombus burden in transient STEMI vs. STEMI patients.
Abbreviations as in Tables 1 and 2.

were enrolled during the same time period, using similar clinical protocols and the majority of patients were enrolled at the same hospital. The strength of the current study is that in prospectively enrolled patients a combination of hemostatic characteristics and functional outcomes were assessed. Several hemostatic factors were measured at baseline, and fibrinolytic activity was additionally assessed at steady state to rule out influence of acute coronary thrombosis. Functional outcome was measured accurately by CMR.

In accordance with other studies, transient STEMI patients had less frequently occluded coronary arteries compared to STEMI patients [12,13]. In fact, only 3 patients in the transient STEMI group had TIMI 0–1 flow and all 3 patients had signs of reinfarction with chest pain and recurrence of ST-elevation before coronary angiography. Of note, no culprit lesion was identified in 11.3% of the transient STEMI patients. In transient STEMI patients the thrombus burden was lower, which resulted in fewer thrombectomy procedures than in STEMI patients (2.1% vs. 10.0%, $P = 0.01$). Furthermore, the stent length for culprit lesions was shorter in transient STEMI patients. The clinical and angiographic differences might indicate another etiology of transient STEMI. For instance in patients without an identifiable culprit lesion, referred to as MINOCA, mostly no infarcted myocardium at all was observed, and coronary spasm and passed thromboembolism were most frequently reported as underlying cause of the clinical manifestation [14]. But also in patients with a culprit lesion, several differences in characteristics of transient STEMI vs. STEMI point to differences in pathophysiological mechanism, such as plaque erosion instead of plaque rupture as cause of a temporary coronary occlusion [15]. It may be of interest to further investigate this in future clinical studies with optical coherence tomography to compare lesion characteristics.

Similar to previous studies, infarct size was smaller in transient STEMI vs. STEMI patients as assessed by CMR and measured with cardiac biomarkers [4,5]. The shorter time from onset of symptoms to medical presentation in the transient STEMI group is likely to have contributed to the smaller infarct size in addition to earlier restoration of coronary patency. An alternative mechanism to explain lesser myocardial damage in transient STEMI may be more frequent prodromal angina inducing myocardial preconditioning. The extent of myocardial damage and residual left ventricular function are strong predictors for prognosis in patients with ACS [16].

Interestingly, as inconsistently found in previous research, patients with transient STEMI presented earlier after the onset of symptoms than STEMI patients (median, 1.0 vs. 1.4 h) [7,13]. Transient STEMI may represent a precursor of STEMI and the intermittency of the coronary occlusion may identify a group of patients in whom the evolution of myocardial infarction is relatively slow, while their sensitivity for antithrombotic medication may be above average. It is well-known that many patients may have ST-elevation resolution after antithrombotic therapy, particularly when they present early [17]. Unfortunately we do not have information whether ST elevation resolution occurred before or after the initiation of this therapy in our cohort.

Interestingly, transient STEMI patients were more frequently female and had more cardiovascular risk factors than STEMI patients, including more peripheral artery disease, previous PCI and higher cholesterol values. The latter might be in relation to correspondingly higher levels

Table 2
Coronary angiography parameters and treatment.

Characteristics	Transient STEMI ($n = 141$)	STEMI (n = 110)	*P*-value
Access site			
Radial	135 (95.7)	105 (95.5)	0.91
Femoral	6 (4.3)	6 (5.5)	0.66
Culprit artery			<0.001
Left main	0 (0.0)	0 (0.0)	
LAD	47 (33.3)	34 (15.8)	
LCX	18 (12.8)	29 (26.4)	
RCA	59 (41.8)	47 (53.5)	
No culprit	16 (11.3)	0 (0.0)	
Treatment after angiography			<0.001
PCI	116 (82.3)	110 (100.0)	
CABG	8 (5.7)	0 (0.0)	
Conservative	17 (12.1)	0 (0.0)	
TIMI flow post-PCI	($n = 116$)	(n = 110)	0.90
0–1	0 (0.0)	1 (0.9)	
2	10 (8.6)	9 (8.2)	
3	106 (91.4)	100 (90.9)	
Total stent length, mm	22 (18–30)	32 (22–38)	<0.001
Maximal stent diameter culprit, mm	3.61 ± 0.62	3.61 ± 0.54	0.97
Procedure-related complications	7 (5.0)	1 (0.9)	0.08
Dissection	2 (1.4)	1 (0.9)	
No reflow	1 (0.7)	0 (0.0)	
Side branch occlusion	1 (0.7)	0 (0.0)	
Acute stent thrombosis	1 (0.7)	0 (0.0)	
Other	2 (1.4)	0 (0.0)	
Medication during CAG			
Unfractionated heparin	130 (92.2)	110 (100.0)	0.003
GpIIb/IIIa inhibitor	9 (6.4)	13 (11.9)	0.18
Bivalirudin	11 (7.8)	0 (0.0)	0.003
Medication prescribed during hospitalisation			
ASA	140 (100.0)	108 (99.1)	0.26
$P2Y_{12}$ inhibitor	139 (99.3)	109 (100.0)	1.00
Beta-blocker	118 (84.3)	99 (90.8)	0.18
Lipid lowering medication	139 (99.3)	108 (99.1)	1.00
ACE-inhibitor	106 (75.7)	95 (87.2)	0.03

Values are n (%), median (interquartile range), or mean ± SD. ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAG, coronary angiography; GpIIb/IIIa, glycoprotein IIb/IIIa; LAD, left anterior descending artery; LCX, left circumflex artery; NA, not applicable; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; other abbreviations as in Table 1.

Table 3
Laboratory values.

Characteristics	Transient STEMI (n = 141)	STEMI (n = 110)	*P*-value
vWF antigen (*n* = 60), %	172 ± 74	179 ± 68	0.72
PAP (n = 60), μg/L	766 ± 367	780 ± 752	0.31
D dimer (n = 60), mg/L	0.38 (0.26–0.60)	0.40 (0.23–0.59)	0.97
CRP (*n* = 237), mg/L	2.5 (2.5–5.5)	2.5 (2.5–5.0)	0.65
Hb (*n* = 249), mmol/L	9.0 ± 0.9	8.7 ± 0.9	0.01
Ht (n = 237), L/L	0.42 ± 0.04	0.41 ± 0.04	0.02
Total leukocyte count (*n* = 248), $\cdot 10^9$/L	10.8 ± 3.4	10.7 ± 3.3	0.79
Glucose (*n* = 243), mmol/L	7.3 (6.5–9.1)	7.6 (6.6–9.3)	0.26
Creatinin (*n* = 250), μmol/L	82.5 ± 17.9	80.6 ± 21.4	0.43
Total cholesterol (*n* = 210), mmol/L	5.3 ± 1.1	4.7 ± 1.1	<0.001
LDL (*n* = 163), mmol/L	3.4 ± 1.1	3.1 ± 1.0	0.08
Triglycerides (*n* = 167), mmol/L	1.2 (0.7–1.5)	0.8 (0.6–1.2)	0.01
Baseline CK-MB, μg/L	3.2 (0.0–11.0)	7.9 (2.5–24.7)	<0.001
Baseline troponin T, μg/L	0.045 (0.019–0.095)	0.093 (0.033–0.321)	<0.001
Peak troponin T, μg/L	0.357 (0.133–0.791)	1.872 (0.506–4.253)	<0.001
Peak CK-MB, μg/L	20.0 (9.8–38.7)	97.9 (35.8–211.0)	<0.001

Values are n (%), median (interquartile range), or mean ± SD. CK-MB, creatine kinase-MB; HDL, High-density-lipoprotein; LDL, low-density-lipoprotein; PAP, plasmin-alpha(2)-antiplasmin; vWF, von Willebrand factor; other abbreviations as in Table 1.

of lipoprotein(a), a low-density lipoprotein variant. The latter might be in relation with findings of Haider et al., who demonstrated that patients with intermittent occlusion of the infarct-related coronary artery have higher serum levels of lipoprotein(a) and that this is related to enhanced thrombin generation [18].

In accordance, the present study shows that patients with intermittent coronary occlusion have a higher level of thrombogenic activity. In transient STEMI patients, platelet count was higher and plasma levels of prothrombin fragment F1 + 2, a measure of the generation of the thrombogenic factor thrombin [19], showed a trend towards higher values. Tissue damage in myocardial infarction can be a cause of acute phase thrombocytosis, which suggests that intermittent reperfusion is an extra stimulus for coagulation and thrombosis. The thrombotic stimulus could either be the interaction between the restored blood flow and the residual thrombus [20] or the underlying collagen exposed by the disrupted atheroma [21]. Furthermore, the increased thrombogenic state may be a result of spontaneous lysis underlying the intermittency, increasing the possibility of reocclusion. On the other hand the augmented thrombogenic activity may indicate a fundamental difference between the groups, in a way that the patients with intermittent occlusion have a slow evolution of thrombus formation. A favorable endothelial function rapidly initiating fibrinolysis might be an underlying feature in these patients [22].

In the presence of a higher thrombotic activity in the transient STEMI group, one might also expect a greater fibrinolytic activity to explain the

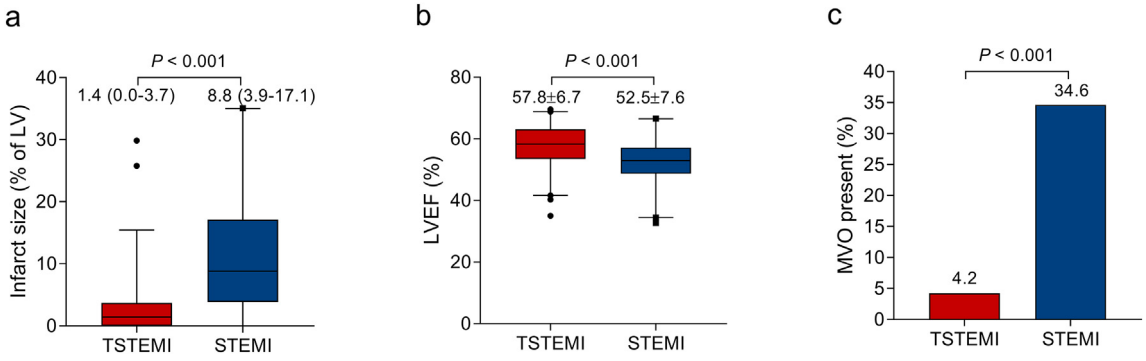

Fig. 2. a CMR-derived infarct size, b LVEF and c MVO.
Abbreviations: LV, left ventricle; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; STEMI, ST-elevation myocardial infarction; TSTEMI, transient ST-elevation myocardial infarction.

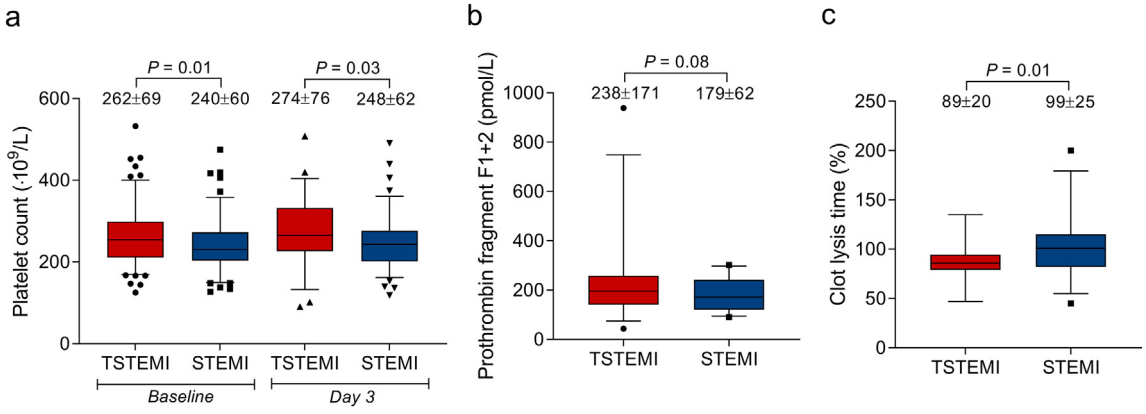

Fig. 3. a Platelet levels, b prothrombin fragment F1 + 2 and c clot lysis time at steady state.
Abbreviations as in Fig. 2.

spontaneous reopening of the occluded culprit artery. Although the fibrinolytic measures PAP and D-dimer did not differ from the STEMI patients at admission, clot lysis testing revealed a higher fibrinolytic activity in transient STEMI patients at steady state. These results do not exclude a higher local fibrinolytic activity at the site of the epicardial coronary thrombus in patients with transient STEMI. Our findings corroborate the results of Farag et al. who found that patients with spontaneous ST-resolution had a more rapid fibrinolysis and clot lysis time did not change until 30 days after STEMI [23]. It is therefore presumed that patients who develop a transient STEMI have a more effective endogenous fibrinolysis.

Furthermore, according to the PLATO trial, rapid clot lysis is a strong independent predictor of favorable outcome in patients with ACS patients, independent of their antiplatelet therapy [24]. Therefore, an important question is whether endogenous fibrinolysis is a modifiable feature. Fibrinolysis is not affected by oral antiplatelet medication, but previous studies suggest that non-vitamin K antagonist oral anticoagulants (NOACs) or vorapaxar, a thrombin receptor antagonist, could modify clot lysis [25,26]. The ATLAS ACS 2–TIMI 51 trial demonstrated that the addition of a NOAC to dual antiplatelet therapy can reduce the risk of recurrent ischemic cardiovascular events in ACS patients, although with an increase in (nonfatal) bleedings on the counter side [27]. A point-of-care test, such as the global thrombosis test, could identify STEMI patients with slow clot lysis, who might profit from additional antithrombotic therapy. Whether selected persistent STEMI patients may benefit from acuminated care should be addressed in future research.

4.1. Study limitations

The current study was performed as a post-hoc analysis and findings are hypothesis generating and should be interpreted with caution. We compared data of patients included in two separate prospective clinical trials that were performed in the same period of time. The in- and exclusion criteria of the used trials were similar, but not identical. The transient STEMI patients were treated with either an immediate or delayed coronary intervention strategy and the STEMI patients were randomized 1:1 to the $P2Y_{12}$ inhibitors ticagrelor or prasugrel after admission, so for these aspects the population was not homogenous, but adequately treated according to current clinical knowledge. However, both clinical trials did not find differences in outcomes between the treatment strategies, so effects of the compared treatment strategies may be expected to be only limited. Furthermore, enrolment of the TRANSIENT trial (transient STEMI cohort) started one and a half year earlier than the REDUCE-MVI trial (STEMI cohort), and slight differences in treatment were seen. Furthermore, the sample size of this study was limited and did not allow the comparison of adverse clinical events. Lastly, as the first blood samples were drawn after the administration of aspirin, heparin and the $P2Y_{12}$-inhibitor ticagrelor in the ambulance, no clot lysis tests could be performed at baseline.

5. Conclusion

Transient STEMI is a syndrome with less angiographic thrombus burden and spontaneous infarct artery reperfusion, associated with smaller infarct size compared to STEMI. Therefore, our data strongly re-emphasize the benefits of early reperfusion. Transient STEMI patients appear to have a more effective fibrinolysis, which might provide clues for acuminating future treatment of STEMI. Future studies are necessary to assess whether endogenous fibrinolysis is a modifiable feature, targetable by pharmacotherapy, to reduce cardiovascular risk and improve prognosis in STEMI patients.

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Ethics approval

Ethics approval was obtained by the respective institutional review boards (local medical ethics committees).

Consent to participate

All patients provided written informed consent for study participation.

Consent for publication

All authors have participated in this work, have reviewed it and agree with the content of the article.

Availability of data

Study data is not publicly available.

Code availability

Statistical analysis was performed using SPSS Statistics, version 26 (IBM Corp, Armonk, New York).

Declaration of Competing Interest

Prof. dr. van Royen reports research grants from AstraZeneca, Abbott, Philips, Biotronik and a honorarium from Medtronic. Dr. Lemkes reports grants from Biotronik and Astrazeneca, during the conduct of the study. Prof. dr. Piek reports non-financial support from Abbott Vascular as member medical advisory board, personal fees and non-financial support from Philips/Volcano as Consultant, outside the submitted work. Prof. dr. von Birgelen reports institutional research grants from Abbott Vascular, Biotronik, Boston Scientific and Medtronic, outside the submitted work. Dr. van Leeuwen reports grants from AstraZeneca, grants from Top Sector Life Sciences & Health, during the conduct of the study. Dr. Escaned reports consultancies work for Philips, outside of the submitted work. All other authors declare no competing interests with regards to the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.05.018.

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