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FASTTRACK CLINICAL RESEARCH
Acute coronary syndromes

Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial

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Aims Patients with acute coronary syndrome who present initially with ST-elevation on the electrocardiogram but, subsequently, show complete normalization of the ST-segment and relief of symptoms before reperfusion therapy are referred to as transient ST-segment elevation myocardial infarction (STEMI) and pose a therapeutic challenge. It is unclear what the optimal timing of revascularization is for these patients and whether they should be treated with a STEMI-like or a non-ST-segment elevation myocardial infarction (NSTEMI)-like invasive approach. The aim of the study is to determine the effect of an immediate vs. a delayed invasive strategy on infarct size measured by cardiac magnetic resonance imaging (CMR).

Methods and results In a randomized clinical trial, 142 patients with transient STEMI with symptoms of any duration were randomized to an immediate (STEMI-like) [0.3 h; interquartile range (IQR) 0.2–0.7 h] or a delayed (NSTEMI-like) invasive strategy (22.7 h; IQR 18.2–27.3 h). Infarct size as percentage of the left ventricular myocardial mass measured by CMR at day four was generally small and not different between the immediate and the delayed invasive group (1.3%; IQR 0.0–3.5% vs. 1.5% IQR 0.0–4.1%, $P = 0.48$). By intention to treat, there was no difference in major adverse cardiac events (MACE), defined as death, reinfarction, or target vessel revascularization at 30 days (2.9% vs. 2.8%, $P = 1.00$). However, four additional patients (5.6%) in the delayed invasive strategy required urgent intervention due to signs and symptoms of reinfarction while awaiting angiography.

Conclusion Overall, infarct size in transient STEMI is small and is not influenced by an immediate or delayed invasive strategy. In addition, short-term MACE was low and not different between the treatment groups.

Keywords Transient STEMI • Timing • Coronary angiography • Percutaneous coronary intervention

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Introduction

An estimated 4–24% of patients with acute coronary syndrome (ACS) present with ST-segment elevation but show complete normalization of ST-segments and relief of symptoms before reperfusion therapy has been initiated.[1,2] This is commonly referred to as transient ST-segment elevation myocardial infarction (STEMI)[1] and poses a therapeutic challenge, because it is unclear whether this condition should be considered as STEMI or as non-ST-segment elevation myocardial infarction (NSTEMI). Current guidelines have no specific recommendations for the treatment of patients with transient STEMI.

The treatment strategies of STEMI and NSTEMI are clearly different. In patients with STEMI the preferred treatment is an immediate invasive strategy and percutaneous coronary intervention (PCI).[3] In NSTEMI a delayed invasive approach is recommended, with an invasive strategy within 24 h in high-risk patients and an invasive strategy within 72 h for intermediate risk patients.[4]

Patients with transient STEMI may benefit from an immediate invasive procedure by reducing infarct size in case of ongoing infarction or by preventing reinfarction. On the other hand a delayed approach may allow stabilization of the ruptured plaque and reduction of thrombus load. The latter was found by Meneveau *et al.*[5] in a small observational study, in which patients with transient STEMI who were treated with delayed PCI suffered less procedural complications. Therefore, we hypothesized that that delaying invasive strategy in patients with transient STEMI will reduce infarct size.

Here, we present the first randomized controlled clinical trial in patients with transient STEMI in which the outcomes of a STEMI-like approach (with an immediate invasive strategy) are compared with a NSTEMI-like approach (with a delayed invasive strategy).

Methods

Study design and participants

The primary objective of the trial was to evaluate whether a delayed invasive strategy is superior to an immediate invasive strategy, in patients presenting with a transient STEMI by reducing infarct size assessed by cardiac magnetic resonance imaging (CMR).

The TRANSIENT trial was a prospective, investigator-initiated randomized controlled clinical study, conducted in five high-volume PCI centres in the Netherlands. The complete study design has been published previously.[6]

The study protocol conforms to the international Conference on Harmonisation/Good Clinical Practice standards and the Declaration of Helsinki. Central ethics approval was obtained by the VU University Medical Center, Amsterdam, the Netherlands, and the respective local ethics committees.

The trial is registered with www.trialregister.nl, identifier: NTR4156.

Study protocol

Patients >18 years of age were eligible for the study if they had a clinical presentation of an acute STEMI, including symptoms of any duration and ST-segment elevation. Subsequently, patients must have complete relief of symptoms and complete normalization of ST-segments. Full inclusion and exclusion criteria are listed in Supplementary material online, *I*. All patients were routinely pretreated with aspirin, a $P2Y_{12}$ inhibitor and heparin, which was continued until coronary angiography. Patients were randomized in a 1:1 ratio to an immediate or a delayed invasive strategy. In patients randomized to the immediate invasive group, coronary angiography was initiated as soon as possible. Patients randomized to the delayed invasive group underwent coronary angiography pending on the GRACE risk score (>140 within 24 h or ≤140 within 72 h). Percutaneous coronary intervention was performed according to standard procedures and treatment was left to the discretion of the operator.

All CMR images were sent to a core laboratory for quality control and central analysis by two independent technicians, blinded to patient information and allocated group.

The primary endpoint of the study was myocardial infarct size (as percentage of the left ventricular myocardial mass) measured by CMR at four days. The secondary efficacy endpoints were area under the curve of creatine kinase-MB (CK-MB) and troponin T (Supplementary material online, *II*) and left ventricular ejection fraction (LVEF) and volumes measured by CMR. Major adverse cardiac events (MACE) was obtained at 30 days and was defined as death, reinfarction, or target vessel revascularization. The secondary safety endpoints included thrombolysis in myocardial infarction (TIMI) major bleeding[7] and the need for urgent revascularization due to signs of reinfarction before the planned procedure.

Statistical analysis

The study was powered for the primary endpoint of a difference in infarct size between the two treatment groups at baseline, measured by late gadolinium-enhanced CMR. We assumed that patients with transient STEMI are likely to show CMR characteristics similar to NSTEMI patients. A previous study reported a mean infarct size of 10% of the left ventricle.[8] We hypothesized that there would be a 25% reduction in infarct size in the delayed treatment group (a reduction in infarct size from 10% to 7.5% of the left ventricle).

It was desired to have a power of 80% to detect a difference in infarct size between the two treatment groups, assuming a standard deviation (SD) of 5%. Therefore, with 64 patients in each group, the study had 80% power to detect a 2.5% difference between early and delayed intervention (with a two-sided significance level of 5%). Based on the experience in previous studies, it was assumed that up to 10% of patients would be unavailable with respect to the infarct size measurements. The sample size was therefore increased to a total number of 142 patients. Statistical analysis is also described in Supplementary material online, *III*.

Results

Between 12 November 2013 and 31 August 2017, 142 patients with transient STEMI were enrolled in the five participating hospitals in the Netherlands. A total of 70 patients were randomized to the immediate intervention group and 72 to the delayed intervention group. One patient, allocated to the delayed intervention group, withdrew consent after randomization (*Figure 1*). The mean (SD) age of patients was 62.3 (11.6) years and 69.5% was male. Baseline characteristics are presented in *Table 1*. Patients in the immediate intervention group were more often treated with bivalirudin, while patients in the delayed intervention group received more often heparin or fondaparinux during hospitalization. Other medical therapy was similar in the two groups (*Table 2* and Supplementary material online, *IV*). All patients underwent coronary angiography. The median time of angiography after randomization in the immediate invasive group was 0.3 [interquartile range (IQR) 0.2–0.7] vs. 22.7 (IQR 18.2–27.3) h in the delayed group. In the delayed invasive group, four patients (5.6%)

Table 1 Baseline characteristics

Characteristic	Immediate invasive ($n = 70$)	Delayed invasive ($n = 71$)	*P*-value
Age (years), mean (SD)	62.0 (11.7)	62.6 (11.6)	0.74
Sex, male, *n* (%)	48 (68.6)	50 (70.4)	0.86
Hypertension, *n* (%)	20 (28.6)	33 (46.5)	0.04
Diabetes mellitus, *n* (%)	8 (11.4)	8 (11.3)	1.00
Smoking, *n* (%)			0.48
Current	34 (48.6)	30 (42.3)	
Previous	17 (24.3)	15 (21.1)	
Hypercholesterolaemia, *n* (%)	15 (21.4)	18 (25.4)	0.69
Family history of CAD, *n* (%)	30 (42.9)	32 (45.1)	0.87
Previous PCI, *n* (%)	4 (5.7)	4 (5.6)	1.00
Previous CABG, *n* (%)	2 (2.9)	1 (1.4)	0.62
CVA, *n* (%)	5 (7.1)	4 (5.6)	0.74
Peripheral artery disease, *n* (%)	6 (8.6)	6 (8.5)	1.00
ST-segment elevations ECG, *n* (%)			0.72
Pre-hospital	67 (95.7)	66 (93.0)	
Emergency Department	3 (4.3)	5 (7.0)	
Sum of ST-segment elevation (mm)[a], median (IQR)	7 (3–11)	5 (3–9)	0.10
Localization of ST-segment elevation on the ECG, *n* (%)			0.86
Anterior	25 (35.7)	25 (35.2)	
Lateral	3 (4.3)	5 (7.0)	
Inferior	40 (57.1)	38 (53.5)	
Posterior	2 (2.9)	3 (4.2)	
Killip Class I, *n* (%)	70 (100.0)	71 (100.0)	NA
GRACE risk score (for mortality at admission), *n* (%)			0.70
Low risk (≤108)	21 (30.0)	17 (23.9)	
Medium risk (109–140)	22 (31.4)	26 (36.6)	
High risk (>140)	27 (38.6)	28 (39.4)	

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVA, cerebrovascular accident; ECG, electrocardiogram; IQR, interquartile range; NA, not applicable; PCI, percutaneous coronary intervention; SD, standard deviation.
[a]The sum of ST-segment elevation is the sum of ST-segment elevation in all 12 leads.

underwent urgent intervention due to signs and symptoms of reinfarction, while awaiting their procedure (Supplementary material online, *VI*). Two of those patients had TIMI 0–1 flow in the culprit vessel at the time of angiography. In the immediate group one patient had TIMI 0–1 flow in the culprit vessel. All were treated successfully with immediate PCI. All other patients showed spontaneous reperfusion at the time of angiography. There was no difference in the location of the culprit vessel or the extent of coronary artery disease between the two groups. The rate of PCI was higher in the immediate invasive group compared with the delayed invasive group (90% vs. 74.6%, $P = 0.03$). Patients in the delayed invasive group underwent coronary artery bypass grafting (CABG) more often compared with those in the immediate invasive group (11.3% vs. 0%, $P = 0.01$).

Cardiac magnetic resonance imaging was performed in 124 of the 142 patients (87%). The main reasons for not performing CMR included claustrophobia and refusal by the patient. In all patients CMR was performed after the invasive procedure and revascularization by PCI. In a subset of patients treated with CABG the CMR was performed before revascularization. The primary endpoint, left ventricular infarct size, was very small in general and not significantly different between the immediate invasive group and the delayed invasive group (1.3%; IQR 0.0–3.5% vs. 1.5%; IQR 0.0–4.1%, $P = 0.48$) (*Figure 2A*, *Take home figure*). Also, LVEF (58.0%; SD, 6.3% in the delayed group vs. 57.5%; SD 7.0% in the immediate group, $P = 0.66$) as well as all other CMR parameters did not differ between the groups (*Table 3*, Supplementary material online, *V*).

The CK-MB and/or troponin levels were available in 141 (99%) patients (*Table 4*). In the immediate group, the area under the curve of troponin T was in 10.56 (IQR 5.13–27.85) vs. 15.08 (IQR 3.85–24.17) in the delayed group ($P = 0.80$) (*Figure 2B*). Creatine kinase-MB release was also not different between groups (*Figure 2C*).

Major adverse cardiac events rate at 30 days was 2.9% in the immediate invasive group and 2.8% in the delayed invasive group, which was not significantly different (*Table 5*). For the principal analysis, the four patients with urgent unplanned procedures in the delayed invasive group were counted as crossovers, not adverse events. In a sensitivity analysis in which these were counted as MACE events

Table 2 Coronary angiography parameters and treatment

Variable	Immediate invasive (*n* = 70)	Delayed invasive (*n* = 71)	*P*-value
Symptoms—inclusion time (h), median (IQR)	2.7 (1.5–3.8)	2.3 (1.6–4.2)	0.89
Symptoms—CAG time (h), median (IQR)	3.1 (1.9–4.9)	25.8 (20.2–30.5)	<0.001
Inclusion—CAG time (h), median (IQR)	0.3 (0.2–0.7)	22.7 (18.2–27.3)	<0.001
CAD severity (≥70% stenosis), *n* (%)			0.61
1-Vessel disease	41 (58.6)	34 (47.9)	0.24
2-vessel disease	14 (20.0)	16 (22.5)	0.84
3-vessel disease	10 (14.3)	13 (18.3)	0.65
Left main disease	0 (0.0)	0 (0.0)	NA
No significant coronary stenosis	5 (7.1)	8 (11.3)	0.56
Culprit vessel, *n* (%)			0.76
LAD	24 (34.3)	24 (33.8)	1.00
LCX	9 (12.9)	9 (12.7)	1.00
RCA	31 (44.3)	27 (38.0)	0.50
Left main	0 (0.0)	0 (0.0)	NA
Graft	0 (0.0)	1 (1.4)	1.00
No culprit	6 (8.6)	10 (14.1)	0.43
TIMI-flow at CAG, *n* (%)			0.50
0–1	1 (1.4)	2 (2.8)[a]	
2	9 (12.9)	5 (7.0)	
3	60 (85.7)	64 (90.1)	
Treatment, *n* (%)			0.01
PCI	63 (90.0)	53 (74.6)	0.03
CABG	0 (0.0)	8 (11.3)	0.01
Conservative	7 (10.0)	10 (14.1)	0.61
TIMI-flow post-PCI, *n* (%), *n* = 116	(*n* = 63)	(*n* = 53)	0.34
0–1	0 (0.0)	0 (0.0)	
2	7 (11.1)	3 (5.7)	
3	56 (88.9)	50 (94.3)	
Medication during CAG, *n* (%)			
Unfractionated heparin	60 (85.7)	70 (98.6)	0.004
GpIIb/IIIa inhibitor	5 (7.1)	4 (5.6)	0.74
Bivalirudin	10 (14.3)	1 (1.4)	0.01
Medication during hospitalization, *n* (%)			
ASA	70 (100.0)	71 (100.0)	NA
Ticagrelor	50 (71.4)	55 (77.5)	0.44
Prasugrel	18 (25.7)	10 (14.1)	0.09
Clopidogrel	2 (2.9)	6 (8.5)	0.27
Bivalirudin	10 (14.3)	1 (1.4)	0.01
Unfractionated heparin/LMWH/fondaparinux	19 (27.1)	68 (95.8)	<0.001
GpIIb/IIIa inhibitor	7 (10.0)	6 (8.5)	0.78
Statin	69 (98.6)	71 (100.0)	0.50
ACE inhibitor or ARB	55 (78.6)	52 (73.2)	0.56
Beta-blocker	57 (81.4)	62 (87.3)	0.36
Nitroglycerine iv	13 (18.6)	24 (33.8)	0.06
Hospitalization duration (days), median (IQR)	4 (3–5)	3 (3–6)	0.91

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAG, coronary angiography; GpIIb/IIIa, glycoprotein IIb/IIIa; IQR, interquartile range; iv, intravenous; LAD, left anterior descending artery; LCX, left circumflex artery; LMWH, low molecular weight heparin; NA, not applicable; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.
[a]Urgent CAG due to recurrent signs and symptoms of reinfarction.

Table 3 CMR imaging

Outcome	Immediate invasive (*n* = 70)	Delayed invasive (*n* = 71)	*P*-value
CMR performed, *n* (%)	61 (87.1)	63 (88.7)	0.80
CMR analysed, *n* (%) (*n* = 123)	60 (85.7)	63 (88.7)	0.62
Inclusion—CMR time (days), mean (SD) (*n* = 124)	4.3 (1.4)	4.4 (1.7)	0.69
Infarct size (% of LV), median (IQR) (*n* = 119)[a,b]	1.3 (0.0–3.5)	1.5 (0.0–4.1)	0.48
Categorical infarct size, *n* (%) (*n* = 119)[a,b]			0.90
No infarction	23 (39.0)	20 (33.3)	
0.1–5.0%	26 (44.1)	28 (46.7)	
5.1–9.9%	6 (10.2)	8 (13.3)	
≥10.0%	4 (6.7)	4 (6.7)	
LVEF (%), mean (SD) (*n* = 123)	57.5 (7.0)	58.0 (6.3)	0.66
MVO present (%), *n* (%) (*n* = 120)[b]	2 (3.3)	3 (4.8)	1.00

CMR, cardiac magnetic resonance imaging; IQR, interquartile range; LV, left ventricle; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; SD, standard deviation.
[a]In one patient cine images were of insufficient quality for analysis.
[b]In three patients no late gadolinium enhancement images were available because CMR was aborted due to discomfort of the patient.

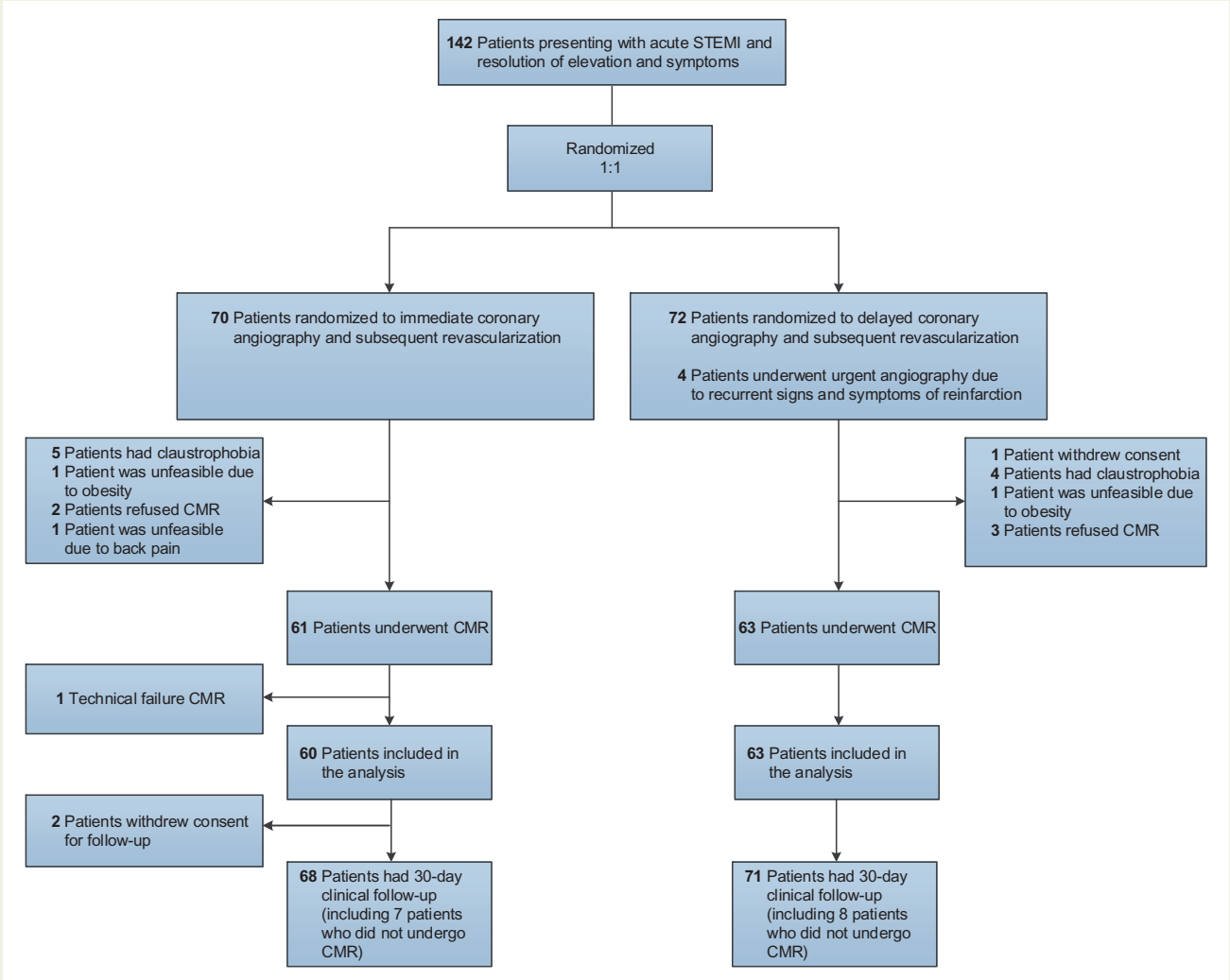


Figure 1 Enrolment flow diagram. CMR, cardiac magnetic resonance imaging; STEMI, ST-segment elevation myocardial infarction.

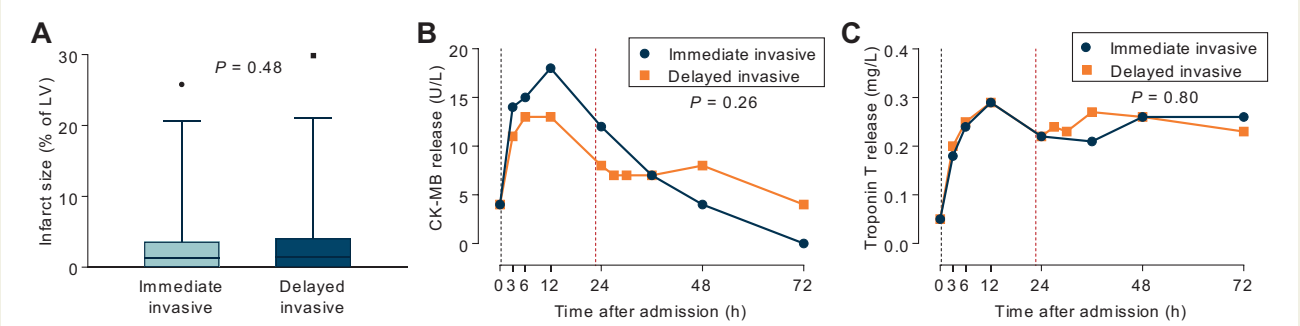


Figure 2 Infarct size by cardiac magnetic resonance imaging and cardiac biomarkers. (*A*) The ends of the boxes indicate the interquartile ranges; the middle lines indicate the medians; the whiskers indicate the 2.5–97.5 percentiles. (*B* and *C*) The black dashed lines demonstrate the median time to coronary angiography in the immediate invasive group, the red dashed lines demonstrate the median time to coronary angiography in the delayed invasive group. CK-MB, creatine kinase-MB; CMR, cardiac magnetic resonance imaging; LV, left ventricle.

Table 4 Cardiac biomarkers

Outcome	Immediate invasive (*n* = 70)	Delayed invasive (*n* = 71)	*P*-value
Baseline troponin T (μg/L), median (IQR)	0.047 (0.023–0.106)	0.043 (0.017–0.91)	0.58
Peak troponin T (μg/L), median (IQR)	0.309 (0.150–0.751)	0.397 (0.127–0.842)	0.75
AUC course troponin T, median (IQR)	10.56 (5.13–27.85)	15.08 (3.85–24.17)	0.80
Peak CK-MB (U/L), median (IQR), *n* = 133	20.6 (10.4–41.3)	20.0 (8.3–32.2)	0.83
AUC course CK-MB, median (IQR), *n* = 133	462.1 (219.5–921.4)	479.3 (200.9–937.7)	0.26

AUC, area under the curve; CK-MB, creatine kinase-MB; IQR, interquartile range.

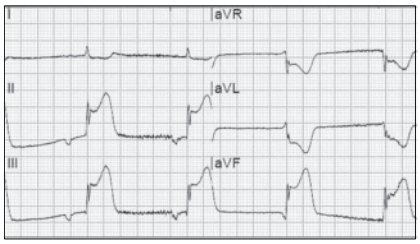
Table 5 Bleeding and adverse events

Outcome	Immediate invasive (*n* = 70)	Delayed invasive (*n* = 71)	*P*-value
Urgent intervention due to signs of reinfarction before the index procedure, *n* (%)	NA	4 (5.6)	NA
Major bleeding, *n* (%)	1 (1.4)	2 (2.8)	1.00
CAG-access site related	1 (1.4)	0 (0.0)	1.00
CABG-related	0 (0.0)	2 (2.8)	0.50
Events at 30 days, *n* (%)	(*n* = 68)	(*n* = 71)	
Reinfarction	1 (1.5)	1 (1.4)	1.00
Target vessel revascularization	2 (2.9)	1 (1.4)	0.61
Definite stent thrombosis	1 (1.5)	1 (1.4)	1.00
Death	0 (0.0)	1 (1.4)	1.00
Cardiac death	0 (0.0)	0 (0.0)	NA
MACE at 30 days	2 (2.9)	2 (2.8)	1.00
MACE at 30 days including urgent intervention due to signs of reinfarction	2 (2.9)	6 (8.5)	0.28

CABG, coronary artery bypass grafting; CAG, coronary angiography; MACE, major adverse cardiac events; NA, not applicable.
MACE consist of reinfarction, target vessel revascularization and death.

(including two of which were considered reinfarctions because of TIMI 0/1 flow at coronary angiography), the MACE rates were 2.9% in the immediate invasive group vs. 8.5% in the delayed invasive group ($P = 0.28$). However, these adverse events did not result in an increased infarct size in the delayed invasive arm (Supplementary material online, *VI*, *VII*). Mortality at 30 days was low and only one patient died due to pulmonary complications after CABG in the delayed invasive group. The timing of the intervention did not influence the incidence of TIMI major bleeds (1.4% in the immediate group vs. 2.8% in the delayed group).

A



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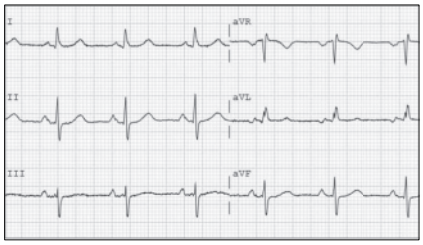

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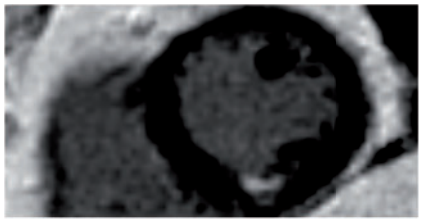

D

Outcome	Immediate invasive	Delayed invasive	*P-value*
LVEF, %	57.5 ± 7.0	58.0 ± 6.3	0.66
Infarct size, % of LV	1.3 (0.0-3.5)	1.5 (0.0-4.1)	0.48
MVO present *n* (%)	2 (3.3)	3 (4.8)	1.00
CK-MB AUC	462.1 (219.5-921.4)	479.3 (200.9-937.7)	0.26
Cardiac death *n* (%)	0 (0.0)	0 (0.0)	NA

Take home figure (*A* and *B*) Typical electrocardiograms of transient ST-segment elevation myocardial infarction. (*C*) cardiac magnetic resonance imaging of typical transient ST-segment elevation myocardial infarction patient. (*D*) Similar study outcomes between the treatment groups. AUC, area under the curve; CK-MB, creatine kinase-MB; LV, left ventricle; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; NA, not applicable.

Discussion

The TRANSIENT trial is the first prospective, randomized, controlled study assessing the effect of a STEMI-like approach vs. a NSTEMI-like approach in patients presenting with transient STEMI. We found no difference for the primary endpoint left ventricular infarct size as assessed by CMR between both groups. In general, we found infarct size in patients with transient STEMI to be very small. Also, we observed spontaneous reperfusion in all patients that remained free of symptoms or recurrent ST-segment elevation. Four patients (5.6%) in the delayed invasive strategy required urgent intervention due to signs and symptoms of reinfarction while waiting for their procedure. By intention to treat, MACE was low and equally distributed over the two treatment arms. A significant shift was observed from PCI to CABG-treatment in the delayed arm.

Current guidelines on STEMI or NSTEMI provide no specific recommendations for the treatment of transient STEMI except that in case of 'Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation', patients should be treated with an immediate invasive strategy.[4]

Overall, short-term clinical outcome was excellent in our study with very low mortality (0.7%) at 30-day follow-up. This is in line with a previous report by Rimar *et al.*[9] who found a 30-day mortality of 1% in patients with transient STEMI, which is significantly lower when compared with patients with STEMI. Furthermore, Blondheim *et al.*[10] found a favourable long-term outcome in transient STEMI patients compared with NSTEMI and STEMI patients.

Meneveau *et al.* investigated a matched comparison between a group of 39 patients with transient STEMI treated with immediate angioplasty, and a group of 39 patients with transient STEMI treated with delayed angioplasty (24 h). Patients in the delayed group, who were routinely treated with glycoprotein IIb/IIIa inhibitors, showed thrombus load reduction at the time of PCI, lower peak CK-MB levels and less procedural-related complications, without causing an increase in bleeding or MACE.[5] Therefore, the rationale of our study was based on the assumption that delaying angiography and PCI in patients with transient STEMI will reduce infarct size by reducing the chance of procedural-related complications such as slow or no-reflow, distal embolization, and microvascular plugging. Indeed we saw a peak in CK-MB levels shortly after PCI (*Figure 2B*). However, this was observed in both groups and did not result in a difference in infarct size measured by area under curve or CMR.

Badings *et al.* recently performed a *post hoc* analysis of the ELISA 3 trial. In this trial, high-risk NSTEMI patients were treated with an early (<12 h) vs. a late (>48 h) NSTEMI strategy. In a subgroup analysis of 129 patients with transient STEMI (24.2% of the total ELISA 3 cohort), they found no difference in enzymatic infarct size or the primary endpoint of death, reinfarction or recurrent ischaemia at 30 days.[2]

Our results are also in line with recent findings on deferred stenting in STEMI patients in whom TIMI III flow is restored in the acute phase and stenting is performed during hospitalization in a staged procedure. Although the randomized DEFER-STEMI trial showed that deferred stenting in primary PCI reduced no-reflow and increased myocardial salvage in high-risk STEMI patients,[11] the much larger DANAMI 3-DEFER trial found no significant difference in MACE at 2 years.[12] Furthermore, a CMR substudy of the DANAMI 3-DEFER showed no reduction in infarct size in the deferred arm.[13] This implies that as long as epicardial blood flow is restored, the timing of coronary intervention or stenting is less important for long-term outcome.

Although 5.6% of patients in the delayed invasive group showed signs of reinfarction while awaiting their procedure, this did not significantly increase infarct size or MACE. Furthermore, the need for urgent intervention is also not uncommon in NSTEMI patients.[14] This percentage of reinfarction may be reduced with the routine use of glycoprotein IIb/IIIa inhibitors in transient STEMI, since Meneveau *et al.*[5] reported no reinfarction in their study.

Except for two patients in whom urgent intervention was performed due to reappearance of complaints and ST-segment elevation, no patients in the delayed group had an occluded culprit vessel at the time of angiography in our study. Furthermore, while we found an increased use of antithrombotic agents in the delayed group, this did not lead to an excess in major bleedings.

Interestingly, although the extent of coronary artery disease was similar in both groups, PCI was performed in a significantly higher proportion of patients in the immediate group (90% vs. 75%; $P = 0.03$), whereas CABG was exclusively performed in the delayed group (0% vs. 11.3%; $P = 0.01$). The delayed group represents a NSTEMI-like approach. Previous studies have shown that in NSTEMI patients PCI is less often reported and CABG is quite a common treatment strategy compared with STEMI patients.[14]

The incidence of microvascular obstruction (MVO) in the TRANSIENT trial was very small (4.2% of patients) compared with what has been reported in STEMI trials (43.6–50% of patients),[13,15] also pointing to a relatively benign course and good clinical outcome of transient STEMI. Given the small infarct size and the low MVO and MACE rates, these patients behave more like NSTEMI than STEMI, although it has been suggested that transient STEMI should be considered as a unique group of ACS-patients.[10]

Whether the aetiology of transient STEMI is different compared with STEMI is unknown. As reported previously, we found patients with transient STEMI to be of a younger age, predominantly male and consisting of a high percentage of smokers.[2] It has been suggested that the latter might play an important role in the aetiology of transient STEMI,[1,2] as cigarette smoking has been shown to be a major risk factor for coronary spasm. Hypercontractility of coronary smooth muscle cells can lead to transient coronary occlusion and transient ST-segment elevation.[16] Prolonged coronary spasm can trigger coronary thrombosis, while a thrombus forming over a plaque rupture plaque itself can cause coronary spasm due to the release of vasoactive agents by platelets.[17] Also, plaque erosion and temporary thrombotic occlusion could be the underlying aetiology of transient STEMI.[18]

Study limitations

The trial was powered for a 25% reduction in infarct size in the delayed treatment group, from an estimated 10% to 7.5% of the left ventricle. However, the actual observed infarct size was much smaller (1.4%; IQR 0.0–3.7%) than previously reported, which makes our trial inconclusive for superiority regarding infarct size. However, given the extreme low infarct size in both groups, it is questionable whether any potential difference in infarct size measured by CMR would have clinical impact.[19]

Our results only apply to similarly stable patients, as patients presenting with conditions such as heart failure and ventricular arrhythmias were not included in this study.

A number of eligible patients were not enrolled. This was either patient or operator preference. It carries the risk of selection bias. Furthermore, four centres were initiated during the enrolment phase of the study, which is one of the reasons of slow enrolment.

Also, due to the nature of the study we could not blind patients and physicians to the allocated treatment arm. The impact on the study outcome is probably small, since CMR analysis of the primary endpoint was performed in a blinded fashion. Cardiac magnetic resonance imaging was not performed in about 12% of patients. However, in 99% of patients laboratory values were available to estimate myocardial infarct size, showing similar results.

Conclusion

This is the first randomized study in patients with transient STEMI. In this specific cohort of ACS patients, there is no difference with regard to myocardial infarct size, between patients treated with an immediate vs. a delayed invasive strategy. In general, patients with transient STEMI have a very small infarct size and a relatively benign clinical course. Therefore, patients with transient STEMI can be treated with both an immediate or delayed invasive strategy with similar outcome. These data complement current guidelines for both STEMI and NSTEMI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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