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CLINICAL RESEARCH

CORONARY

Thrombus Aspiration in Patients With ST-Segment Elevation Myocardial Infarction Presenting Late After Symptom Onset

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ABSTRACT

OBJECTIVES The aim of this study was to examine whether manual thrombus aspiration reduces microvascular obstruction assessed by cardiac magnetic resonance imaging in patients with ST-segment elevation myocardial infarction (STEMI) presenting late after symptom onset.

BACKGROUND Thrombus aspiration is an established treatment option in patients with STEMI undergoing primary percutaneous coronary intervention (PCI). However, there are only limited data on the efficacy of thrombus aspiration in patients with STEMI presenting ≥12 h after symptom onset.

METHODS Patients with subacute STEMI presenting ≥12 and ≤48 h after symptom onset were randomized to primary PCI with or without manual thrombus aspiration in a 1:1 ratio. Patients underwent cardiac magnetic resonance imaging 1 to 4 days after randomization. The primary endpoint was the extent of microvascular obstruction.

RESULTS A total of 152 patients underwent randomization. The mean time between symptom onset and PCI was 28 ± 12 h. Baseline characteristics were comparable between groups. The majority of patients (60%) showed at least a moderate amount of viable myocardium in the affected region. Extent of microvascular obstruction was not significantly different between patients assigned to thrombus aspiration and the control group (2.5 ± 4.0% vs. 3.1 ± 4.4% of left ventricular mass, p = 0.47). There were also no significant differences in infarct size, myocardial salvage, left ventricular ejection fraction, and angiographic and clinical endpoints between groups.

CONCLUSIONS In this first randomized trial of thrombectomy in patients with STEMI presenting late after symptom onset, routine thrombus aspiration before PCI failed to show a benefit for markers of reperfusion success. (Effect of Thrombus Aspiration in Patients With Myocardial Infarction Presenting Late After Symptom Onset; NCT01379248) (J Am Coll Cardiol Intv 2016;9:113–22) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

LV = left ventricular

%LV = percentage of left ventricular mass

MSI = myocardial salvage index

MVO = microvascular obstruction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Thrombus aspiration is an established treatment option in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), although recent trials reported disappointing results, with no reduction in mortality and possibly an increase in stroke (1,2). Current evidence is restricted largely to patients presenting within the first hours after symptom onset. Nevertheless, patients presenting ≥12 h after the beginning of symptoms may display particularly high thrombus burden because of long dwelling times. Thus, thrombus aspiration might be a useful adjunct to conventional PCI in this subset of patients. A prior study suggested that thrombus aspiration may indeed be more effective in late-presenting patients (3). However, thrombectomy

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could also be detrimental in this situation because of mechanical thrombus dislodgment and distal embolization with subsequent microvascular injury and expansion of the necrotic zone. Thrombus composition may also play a role. Although in the initial stages of evolving infarction, thrombotic material is relatively soft (low fibrin content, high platelet content), it becomes more organized (high fibrin content, low platelet content) and possibly less suited for aspiration at later stages (4). However, data on the efficacy of thrombus aspiration in the subgroup of patients with STEMI presenting late after symptom onset are scarce.

In the present trial, we examined the effect of routine thrombus aspiration on microvascular obstruction (MVO) assessed by cardiac magnetic resonance imaging (CMR) in patients with subacute STEMI presenting between 12 and 48 h after symptom onset.

METHODS

DESIGN OVERVIEW. The trial's main objective was to study whether manual thrombus aspiration reduces MVO in patients with subacute STEMI. Eligible patients were randomized to primary PCI with or without manual thrombus aspiration. The main inclusion criteria were STEMI ≥12 and ≤48 h after symptom onset, irrespective of signs of ongoing ischemia, and age between 18 and 90 years. Exclusion criteria included prior thrombolysis, contraindications to CMR (known at the time of randomization), and severe comorbidities with limited life expectancy (<6 months). Patients underwent CMR 1 to 4 days after randomization. The primary efficacy endpoint was the extent of MVO on late gadolinium enhancement CMR. All patients were enrolled at a single institution (University of Leipzig-Heart Center). The study was approved by the local institutional review board and conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before randomization.

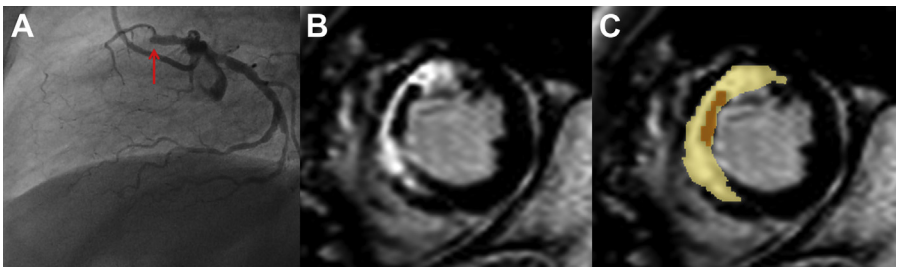
RANDOMIZATION AND BLINDING. Eligible patients willing to take part in the study were assigned in a 1:1 ratio to the treatment groups by permuted block randomization with randomly changing block sizes using an Internet-based system and a computer-generated list of random numbers. Randomization was performed before coronary angiography in the catheterization laboratory. The randomization list was generated and maintained by an information technology expert who was not involved in the clinical conduct of the study.

CMR and all other subsequent analyses were performed by readers blinded to treatment assignment. By design, physicians performing the invasive procedures were aware of randomization results. Patients were not informed about treatment allocation until completion of the study.

ENDPOINTS. The primary efficacy endpoint was the extent of MVO assessed by CMR in the modified intention-to-treat population. Secondary CMR endpoints included infarct size, myocardial salvage, and left ventricular (LV) volumes and ejection fraction. Furthermore, a central blinded analysis of angiographic markers of reperfusion success, such as the Thrombolysis In Myocardial Infarction (TIMI) flow post-PCI and myocardial blush grade, was performed. Coronary collateralization was graded according to the Rentrop classification (grade 0, no visible filling of any collateral channel; grade 1, filling of the side branches of the infarct-related artery; grade 2, partial filling of the epicardial vessel of the infarct-related artery; grade 3, complete collateral filling of the epicardial vessel) (5). For enzymatic infarct size determination, high-sensitivity troponin T after 24 and 48 h was evaluated. The clinical endpoints of all-cause and cardiovascular death, myocardial reinfarction, target vessel revascularization, stent thrombosis, and stroke were reported up to 30 days after randomization. Clinical endpoints were defined according to guidelines (6).

PCI. Thrombus aspiration had to be performed before the first balloon inflation using a 6-F manual aspiration catheter (Export AP; Medtronic, Minneapolis,

FIGURE 1 Cardiac Magnetic Resonance Imaging Analysis



Patient with subacute ST-segment elevation myocardial infarction (STEMI) presenting 21 h after symptom onset. **(A)** Proximal occlusion of left anterior descending coronary artery **(arrow)**. **(B)** Contrast-enhanced cardiac magnetic resonance imaging (CMR) showing transmural anteroseptal necrosis with a marked core of microvascular obstruction (MVO). **(C)** Computer-aided signal intensity analysis of MVO and infarct size. The **yellow overlay** (infarct size) indicates a signal intensity of >5 SDs compared with remote, healthy myocardium. The **yellow and brown overlay** within the infarct indicates the computer detected zone of MVO.

Minnesota). A minimum of 2 aspiration passages across the lesion was recommended. Otherwise, PCI was performed according to current best practice.

CMR. Patients underwent CMR 1 to 4 days after randomization for the evaluation of the primary endpoint MVO and selected secondary endpoints (infarct size, myocardial salvage, and LV ejection fraction and volumes). The scan protocol on a clinical 1.5-T scanner has been used in several other randomized trials and has been described in detail previously (7). In brief, infarct size and MVO were assessed in late gadolinium enhancement short-axis images covering the left ventricle approximately 15 min after the injection of gadolinium chelate. An inversion-recovery turbo gradient-echo sequence was used for image acquisition. A hypointense core within the hyperenhanced infarcted area was defined as MVO. For determination of infarct-related myocardial edema/area at risk, short-axis slices covering the left ventricle using a T2-weighted triple-inversion recovery turbo spin echo sequence before contrast administration were obtained. Assessment of LV function and volumes was performed in short-axis slices from base to apex acquired using a standard steady-state free precession technique.

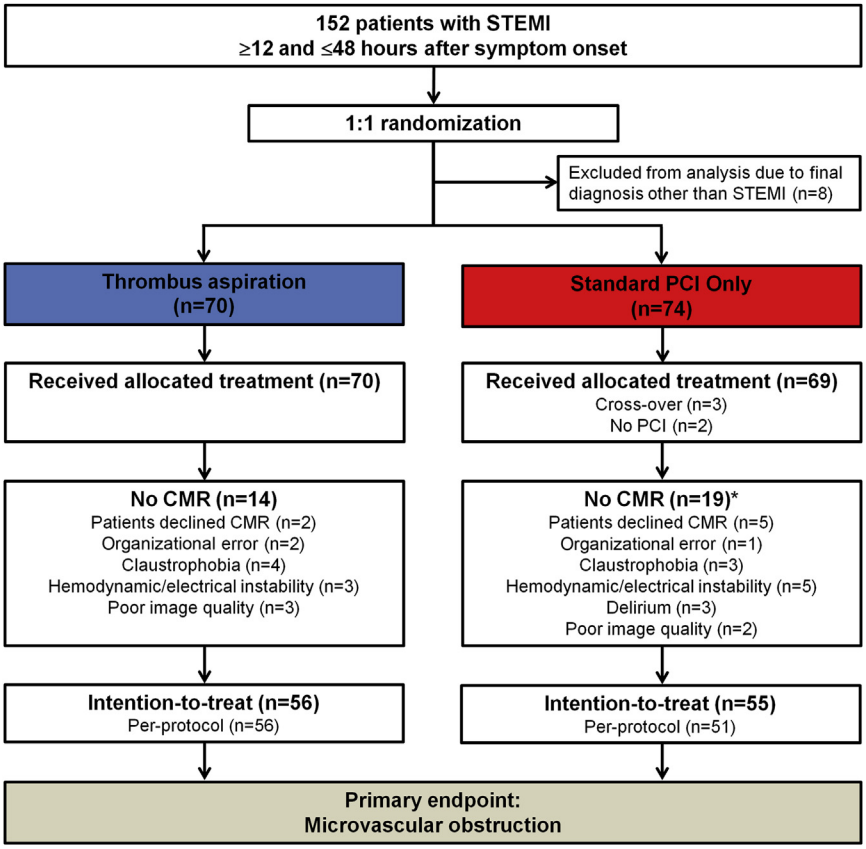
CMR images were sent on storable media to the CMR core laboratory at the University Heart Center Lübeck for assessment by fully blinded operators. For all quantitative analyses, certified CMR evaluation software was used (cmr42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Semiautomated computer-aided threshold detection was used to identify regions of edema, MVO, and infarcted myocardium. A myocardial region was regarded as affected if at least 10 adjacent myocardial pixels revealed a signal intensity of >2 SDs of remote healthy myocardium for edema and >5 SDs in late gadolinium enhancement images (**Figure 1**). MVO and infarct size were expressed as percentage of LV mass (%LV), given by the sum of the mass of MVO and late gadolinium enhancement regions for all slices divided by the overall mass of the LV myocardial cross-sectional slices. If present, MVO was included in the overall infarct size and was quantified separately. Myocardial salvage index (MSI) was calculated as area at risk minus infarct size divided by area at risk multiplied by 100, as previously described (8).

The core laboratory has vast experience in CMR image acquisition and post-processing (9,10).

SAMPLE SIZE. Sample size was calculated for the between-group comparison with regard to the primary endpoint. From the results of a previous study and internal data, we expected a mean difference of 2.0% LV in the extent of MVO between the treatment arms, with an SD of 3.5 (11). On the basis of these assumptions, a total of 132 patients needed to be analyzed to reject the null hypothesis of equal means between the 2 groups with statistical power of 90% (2-tailed Student t test, $\alpha = 0.05$). To account for a presumed rate of 15% of patients not undergoing CMR or without analyzable examinations, a total of 152 patients were randomized. Sample size was calculated using SiZ (Cytel, Cambridge, Massachusetts).

STATISTICAL ANALYSIS. Categorical variables are expressed as number and percentage of patients. Continuous data are reported as mean ± SD as well as 95% confidence intervals when appropriate. Correlations were investigated using Spearman's correlation coefficient. Patient characteristics were compared using the Fisher exact test for categorical

FIGURE 2 Study Flow



Study flowchart showing the number of randomized patients and patients with primary endpoint assessment. CMR = cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction. *Of the 69 patients who received the allocated treatment, 18 did not undergo CMR.

variables and independent-samples Student *t* tests as well as analysis of variance for continuous data. Data were analyzed for both a modified intention-to-treat (cohort for primary endpoint analysis) and a per protocol population. The modified intention-to-treat cohort comprised all patients with subacute STEMI who underwent randomization irrespective of treatment actually received or protocol adherence. On the basis of angiographic, laboratory, and CMR imaging results (normal coronary arteries, no elevation of cardiac enzymes, no edema), patients with final diagnoses other than STEMI were excluded (n = 8). The per-protocol analysis included all patients with subacute STEMI who received treatment according to the initial allocation.

Two-tailed p values <0.05 were considered to indicate statistical significance. Statistical analyses were performed with SPSS version 17.0 (SPSS, Chicago, Illinois).

RESULTS

BASELINE CHARACTERISTICS. From March 2011 through November 2014, a total of 152 patients underwent randomization (Figure 2). Eight patients were excluded from the analysis because of final diagnoses other than STEMI.

Baseline characteristics were well balanced between the 2 treatment groups (Table 1). The mean time between symptom onset and PCI was 28 ± 12 h for the overall cohort (p = 0.17 for between-group comparison). The aspiration catheter could not be advanced to the culprit site in 5 patients. Three patients randomized to PCI alone underwent thrombus aspiration by operator's choice (bailout situations due to unsatisfactory results after conventional PCI). Thrombectomy led to aspiration of macroscopic thrombus material in >60% of patients (Table 1). Administration of glycoprotein IIb/IIIa receptor

TABLE 1 Baseline and Procedural Characteristics

	Thrombus Aspiration (n = 70)	Standard PCI Only (n = 74)
Age, yrs	66 ± 12	66 ± 15
Men	48/70 (69)	59/74 (80)
Hypertension	55/70 (79)	48/74 (65)
Current smoking	25/70 (36)	31/72 (43)
Hyperlipoproteinemia	11/70 (16)	17/74 (23)
Diabetes mellitus	22/70 (31)	25/74 (34)
Cardiogenic shock	2/70 (3)	4/74 (5)
Prior myocardial infarction	2/70 (3)	4/74 (5)
Prior coronary artery bypass surgery	2/70 (3)	0
Body mass index, kg/m^2	28.9 ± 3.8	28.6 ± 4.7
Glomerular filtration rate, ml/min/1.73 m^2*	86 ± 27	79 ± 26
Ongoing signs of ischemia on admission	28/57 (49)	34/62 (55)
Door-to-balloon-time, min	78 ± 150	62 ± 105
Symptom-onset-to-balloon-time, h	26 ± 13	29 ± 12
Infarct-related coronary artery		
Left anterior descending	38/70 (54)	32/72 (44)
Left circumflex	11/70 (16)	9/72 (13)
Right	21/70 (30)	31/72 (43)
TIMI flow before PCI		
0	44/70 (63)	46/74 (62)
1	3/70 (4)	2/74 (3)
2	14/70 (20)	13/74 (18)
3	9/70 (13)	12/74 (18)
TIMI thrombus grade before wire crossing		
0 (no thrombus)	5/70 (7)	12/74 (16)
1 (possible thrombus)	1/70 (1)	1/74 (1)
2 (definite thrombus, <0.5 × vessel diameter)	2/70 (3)	0/74
3 (definite thrombus, 0.5–2 × vessel diameter)	8/70 (11)	4/74 (5)
4 (definite thrombus, >2 × vessel diameter)	9/70 (13)	11/74 (15)
5 (total occlusion)	44/70 (63)	46/74 (62)
Killip class at presentation		
I	61/70 (87)	61/74 (82)
II	5/70 (7)	8/74 (11)
III	2/70 (3)	1/74 (1)
IV	2/70 (3)	4/74 (5)
Cardiogenic shock	2/70 (3)	4/74 (5)
Myocardial blush grade before PCI		
0	52/70 (74)	53/74 (72)
1	5/70 (7)	4/74 (5)
2	4/70 (6)	6/74 (8)
3	9/70 (13)	11/74 (15)
Multivessel disease	38/70 (54)	44/74 (60)
Pre-dilation†	27/70 (39)	54/72 (75)
Post-dilation	7/69 (10)	14/72 (19)
Visible thrombus in aspirate‡	31/51 (61)	2/3 (67)
Drug-eluting stent	50/69 (73)	44/72 (61)
Number of stents	1.6 ± 0.9	1.8 ± 1.2
Long-term medication before hospital admission		
Aspirin	61/70 (87)	55/74 (74)
Thienopyridine	36/70 (51)	33/74 (45)
Statin	11/70 (16)	15/74 (20)
Beta-blocker§	38/70 (54)	27/74 (37)
ACE inhibitor/angiotensin receptor antagonist	36/70 (51)	37/74 (50)
Oral anticoagulant agent	2/70 (3)	4/74 (5)

Values are mean ± SD and n/N (%). *Estimated according to the MDRD (Modification of Diet in Renal Disease) formula. †p < 0.001. ‡3 patients randomized to PCI alone underwent bailout thrombus aspiration (crossover). §p = 0.04.

ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

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inhibitors was similar between groups (18 patients [25%] in the thrombus aspiration group vs. 21 [28%] in the control group, p = 0.85).

IMPACT OF THROMBECTOMY ON CMR PARAMETERS. MVO was present in 59% (n = 33) and 64% (n = 35) of patients after thrombectomy and conventional PCI, respectively (p = 0.69). The primary endpoint, extent of MVO, was 2.5 ± 4.0%LV in patients assigned to thrombus aspiration and 3.1 ± 4.4%LV in patients randomized to the control group (p = 0.47) (Table 2, Figure 3). There were also no significant differences in infarct size, MSI, and LV volumes or ejection fraction between groups (Table 2). The results were consistent across all subgroups (Figure 4) and did not change substantially when analyzing only the per protocol population.

ANGIOGRAPHIC AND PROCEDURAL OUTCOME. The majority of patients (n = 90 [62.5%]) displayed

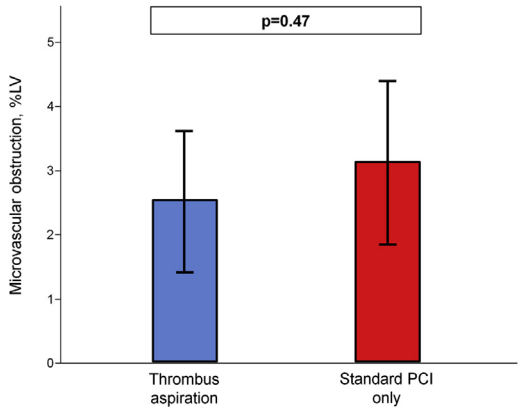
TABLE 2 Results of Cardiac Magnetic Resonance Imaging

	Thrombus Aspiration (n = 56)	Standard PCI Only (n = 55)	p Value
Time from PCI to CMR, days	2.2 ± 1.5	2.4 ± 2.4	0.66
LV mass, g	147 ± 45	140 ± 36	0.36
Microvascular obstruction, g	4.2 ± 7.8	4.7 ± 7.5	0.77
Microvascular obstruction, %LV	2.5 ± 4.0	3.1 ± 4.4	0.47
Infarct size, g	44.0 ± 28.0	38.6 ± 26.8	0.32
Infarct size, %LV	29.5 ± 16.6	27.2 ± 16.7	0.49
Area at risk, g	57.0 ± 28.6	49.6 ± 23.9	0.17
Area at risk, %LV	38.9 ± 16.1	37.1 ± 16.3	0.59
Myocardial salvage, g	12.5 ± 8.5	11.8 ± 12.7	0.77
Myocardial salvage index, % area at risk	26.2 ± 21.2	28.8 ± 30.8	0.63
LV ejection fraction, %	46.4 ± 10.7	44.8 ± 11.5	0.44
LV end-diastolic volume, ml	160 ± 52	157 ± 42	0.77
LV end-systolic volume, ml	88 ± 38	89 ± 34	0.89

Values are mean ± SD.

CMR = cardiac magnetic resonance imaging; LV = left ventricular; PCI = percutaneous coronary intervention; %LV = percentage of left ventricular mass.

FIGURE 3 Extent of Microvascular Obstruction With and Without Thrombus Aspiration



Shown is the mean extent of microvascular obstruction (MVO) between patients assigned to percutaneous coronary intervention (PCI) with and without thrombus aspiration. **Error bars** display 95% confidence intervals. %LV = percentage of left ventricular mass.

complete occlusion of the culprit vessel before PCI corresponding to thrombus grade 5 (Table 1). Coronary collateral vessels were present in 89 patients (62%), with no differences between the groups ($p = 0.23$). In the thrombectomy group, significantly more patients underwent primary stenting without pre-dilation of the lesion ($p < 0.001$; Table 1).

Post-interventional TIMI flow grade 3 was achieved in 54 patients (78%) in the thrombectomy group and 50 patients (69%) in the control group with conventional PCI only ($p = 0.44$). Myocardial blush grade after PCI was not significantly different between groups (grade 3, 70.0% vs. 64.9%; $p = 0.83$).

ENZYMATIC INFARCT SIZE. Enzymatic infarct size assessed by high-sensitivity troponin T values was similar between the thrombectomy and the standard PCI groups, with 3,031 ± 2,189 ng/l versus 2,588 ± 1,908 ng/l at 24 h ($p = 0.24$) and 2,995 ± 2,395 ng/l versus 3,150 ± 2,140 ng/l ($p = 0.75$) at 48 h.

CLINICAL OUTCOMES. Follow-up at 30 days was completed in all patients. The clinical event rate was low (Table 3). Overall, 16 events were recorded. One patient who did not undergo thrombus aspiration had a stroke several hours after catheterization.

With respect to early clinical outcomes, no significant differences between the groups could be observed (Table 3). The mortality rate at 30 days was 2.9% ($n = 2$) in patients undergoing thrombectomy versus 5.4% ($n = 4$) in those undergoing standard PCI only ($p = 0.68$).

REPERFUSION SUCCESS. CMR was performed a mean of 2.3 ± 2.0 days after PCI, with no significant difference between groups ($p = 0.66$). A total of 33 patients did not undergo CMR or had nonanalyzable images (Figure 2).

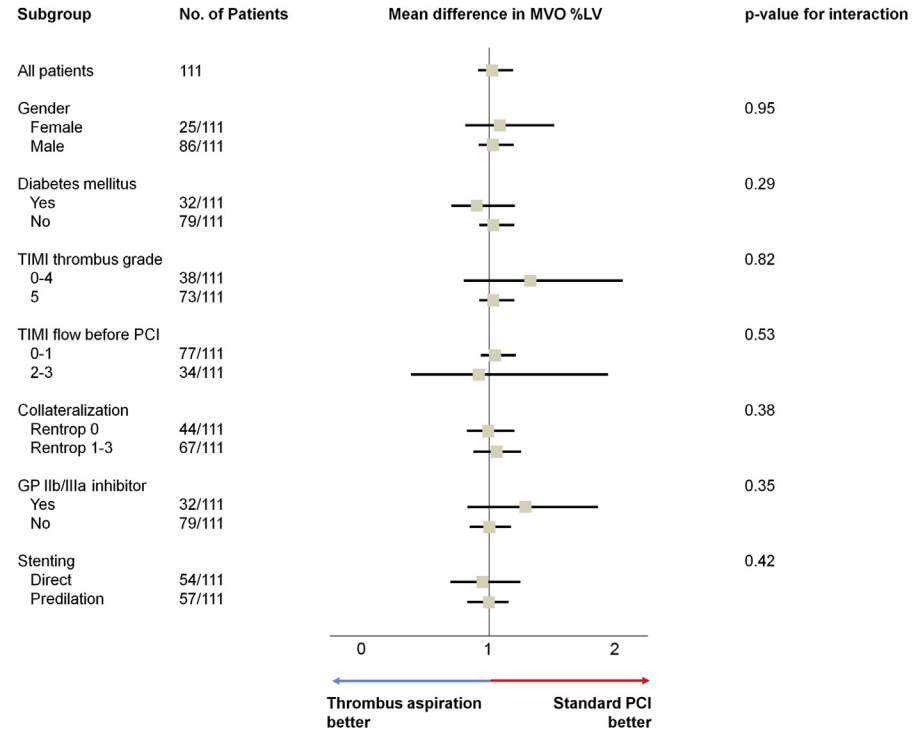
LV ejection fraction was moderately impaired (45 ± 11%). At an area at risk of 38 ± 16%LV and a final infarct size of 28 ± 17%LV, MSI was 27 ± 26. The majority of patients (60%) had MSIs >10. MSI did not differ between asymptomatic patients and those with ongoing ischemic symptoms (33 ± 29 vs. 26 ± 25; $p = 0.31$). MSI was higher in patients with preserved or residual epicardial flow of TIMI flow grades 3 and 2 before reperfusion compared with those with severely compromised or absent flow of TIMI flow grades 1 and 0 (43 ± 32 vs. 21 ± 20; $p < 0.001$). Patients with at least a minimum of angiographically visible collateral vessels (Rentrop grades 1 to 3) displayed higher MSI in comparison with those without (37 ± 30 vs. 21 ± 21; $p = 0.004$). MSI, infarct size, and MVO showed no significant difference between patients in the shortest, intermediate, and longest tertiles of symptom onset-to-PCI times (Figure 5). There were no correlations of MSI ($p = 0.30$), infarct size ($p = 0.80$), and MVO ($p = 0.41$) with symptom onset-to-balloon time.

DISCUSSION

This was the first randomized controlled study to examine a possible beneficial effect of routine manual thrombus aspiration exclusively in patients with subacute STEMI. Furthermore, we report on the largest cohort of late-presenting STEMI patients undergoing CMR imaging for the assessment of reperfusion success. The main findings can be summarized as follows: 1) aspiration thrombectomy did not reduce the extent of MVO compared with standard PCI without thrombectomy, which was corroborated by a lack of benefit in secondary endpoints; and 2) patients with STEMI with symptom onset-to-reperfusion times >12 h had only a moderate amount of salvageable myocardium.

THROMBUS ASPIRATION IN STEMI. Previous randomized trials evaluating the effects of thrombus aspiration in STEMI have focused mainly on patients within 12 h of symptom onset. A medium-sized study showed a reduction in the extent of MVO and reduced infarct size after thrombectomy (11). In line with these results, the single-center TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in

FIGURE 4 Subgroup Analysis for the Primary Endpoint, Extent of Microvascular Obstruction



Mean difference and 95% confidence intervals in the primary endpoint of microvascular obstruction (MVO) between the standard PCI (percutaneous coronary intervention) group and the thrombectomy group for pre-defined subgroups. GP = glycoprotein; TIMI = Thrombolysis In Myocardial Infarction.

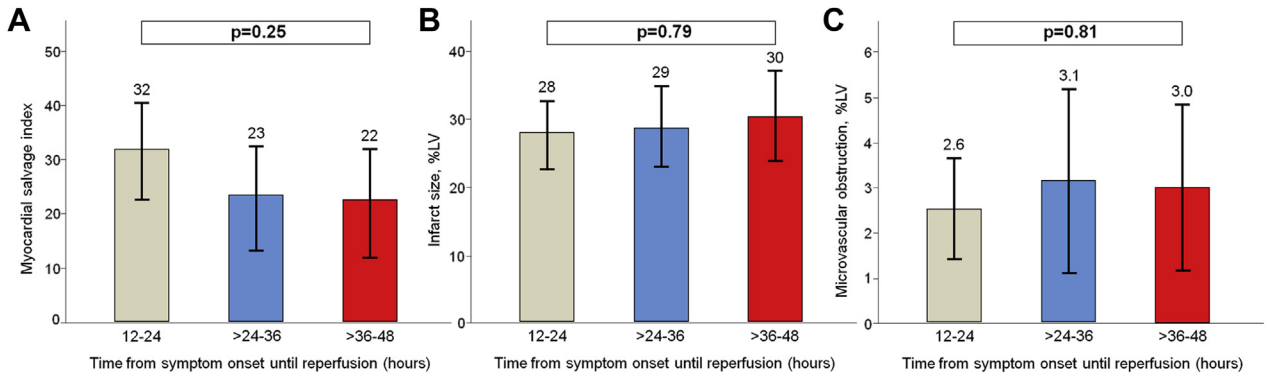
Acute Myocardial Infarction Study) found improvements in angiographic as well as electrocardiographic markers of reperfusion success and even reductions in all-cause and cardiac death at 1 year (12,13). These positive initial results were recently challenged by several large trials: the INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) study did not reveal a beneficial effect of thrombus aspiration on infarct size assessed by CMR in patients with anterior STEMI presenting very early after symptom onset (14). The multicenter TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) study randomized 7,244 patients to manual thrombus aspiration followed by PCI versus PCI only (1). There was a beneficial effect of thrombectomy neither on the primary endpoint of all-cause mortality nor on any other clinical endpoint. The largest trial to date (TOTAL [Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone]) in 10,732 patients with acute STEMI confirmed these neutral results on mortality but found an increased stroke rate at 30 days after thrombus aspiration (2). Consistent with these results, in a recent meta-analysis, the investigators concluded that in STEMI, aspiration thrombectomy before primary PCI is not associated

TABLE 3 Clinical Events at 30 Days

	Thrombus Aspiration (n = 70)	Standard PCI Only (n = 74)	p Value
All-cause death	2 (3)	4 (5)	0.68
Cardiovascular death	2 (3)	3 (4)	1.00
Reinfarction	0	0	–
Target vessel revascularization	2 (3)	0	0.24
Target lesion revascularization	2 (3)	0	0.24
Stent thrombosis	0	0	–
Stroke	0	1 (1)	0.24

Values are n (%).
PCI = percutaneous coronary intervention.

FIGURE 5 Cardiac Magnetic Resonance Imaging Parameters According to Time From Symptom Onset to Reperfusion



Shown is the mean extent of myocardial salvage index (MSI) **(A)**, infarct size **(B)**, and microvascular obstruction (MVO) **(C)** according to the time from symptom onset to reperfusion (12 to 24, >24 to 36, and >36 to 48 h). **Error bars** display 95% confidence intervals. %LV = percentage of left ventricular mass.

with any benefit on clinical endpoints and might increase the risk for stroke (15). The same likely holds true for patients with non-ST-segment elevation myocardial infarction (10). The results from TASTE and TOTAL have not yet found their way into treatment guidelines, which still express a moderate recommendation for routine manual thrombectomy in all patients with STEMI (16,17).

It is important to realize that there are only scarce data on the efficacy of thrombus aspiration in patients who present later than 12 h after symptom onset. Although the aforementioned TASTE trial had a liberal inclusion window of 24 h after initial symptoms, the vast majority of patients presented within the first hours (the median time between symptom onset and PCI was 3 h).

Several hypotheses might serve to explain why thrombus aspiration failed in the majority of recent trials, including ours, despite being a theoretically sound concept. First, aspiration will remove thrombotic material in many patients (as verified by analysis of the aspirate), but manipulation with the catheter might also dislodge thrombotic material, with subsequent embolization into the microcirculation. These opposing effects might balance each other, resulting in a neutral outcome.

Second, the magnitude of the presumed net effect of thrombus aspiration might not be enough to produce changes in the extent of MVO or other surrogate parameters of reperfusion success. This might be especially true in a late-presenting cohort in which, because of high thrombus burden, the potential for significant iatrogenic distal embolization is likely higher than in patients presenting early after symptom onset. However, thrombus aspiration in the first hours of infarction revealed equally sobering results. In the INFUSE-AMI trial, which randomized only patients with large anterior infarctions within 4 h of symptom onset, manual thrombus aspiration did not affect infarct size measured by CMR (14). Subgroup analyses from the TASTE and TOTAL trials also found no reductions in clinical events in patients with the shortest symptom onset-to-PCI times (1,2). Specific to subacute stages of STEMI, the amount of myocardium to be salvaged may also be too small for thrombus aspiration to effectively affect infarct size. In the present trial, we explored the unselected routine use of thrombus aspiration before PCI in patients with subacute STEMI. However, it is possible that thrombus aspiration might be advantageous only in specific subsets of patients, such as those with large thrombus burden, total occlusion, or reduced flow. However, almost 90% of patients in our trial displayed either complete vessel occlusion or high thrombus burden (thrombus grades 3-5), making this an unlikely explanation for the neutral results.

REPERFUSION SUCCESS AND PRIMARY PCI IN SUBACUTE STEMI. There is general consensus that primary PCI is the treatment of choice for patients with STEMI who present within 12 h of symptom onset. Data are much less clear for patients presenting thereafter. Recent treatment guidelines recommend considering reperfusion therapy with primary PCI in patients with STEMI with symptom duration of 12 to 48 h (18).

The theoretical consideration favoring reperfusion over medical therapy in subacute STEMI is the hypothesis that a significant amount of viable myocardium that can still be salvaged despite prolonged ischemia is present. Factors such as a stuttering course with intermittent occlusion and recanalization, ischemic preconditioning, persistence of minimal flow in the infarct-related artery, or recruitment of collateral vessels may prevent complete necrosis and preserve some degree of myocardial viability (19–23). The present study is the first to study the hypothesis by means of CMR demonstrating a moderate amount of viable myocardium in patients presenting between 12 and 48 h after symptom onset. However, these findings cannot be interpreted as being supportive of a beneficial effect of mechanical reperfusion, as all patients underwent PCI. Only a few prospective studies have investigated the value of late mechanical reperfusion. In the BRAVE 2 (Beyond 12 Hours Reperfusion Alternative Evaluation 2) trial, 335 asymptomatic patients with STEMI presenting 12 to 48 h after symptom onset were randomized to immediate invasive or conservative treatment (23). Infarct size by single-photon emission computed tomography was significantly smaller with the invasive strategy, which might translate into a reduction in mortality observed at long-term follow-up (24). The OAT (Occluded Artery Trial) randomized 2,166 late-presenting clinically stable post-STEMI patients with occluded infarct-related arteries to either PCI or medical treatment. PCI was not associated with a reduction in clinical events compared with conservative therapy (25). However, OAT is hardly comparable with the present trial because it differs in several key aspects. First, OAT enrolled patients presenting between 3 and 28 calendar days after symptom onset, with only a few patients enrolled in the very early period (26). In contrast, we randomized patients as soon as 12 and no later than 48 h after symptom onset. Second, OAT enrolled patients in stable condition without signs of ongoing ischemia on presentation, whereas in the present trial, more than 50% of patients had persistent ischemic symptoms. Third, OAT enrolled only patients with complete occlusion of the infarct-related artery, whereas this was not a prerequisite in our trial.

STUDY LIMITATIONS. Although a total of 132 patients were to be analyzed according to the a priori sample size calculation, only 111 patients ultimately entered the primary endpoint analysis. The study thus did not reach the planned statistical power of 90%. Second, the significantly lower percentage of pre-dilation in patients assigned to thrombus aspiration might have introduced a certain degree of bias. Upfront thrombus aspiration may have more frequently led to decreased local thrombus burden and adequate visualization of the culprit site to perform direct stenting. Although evidence is limited, direct stenting in suitable lesions may result in a reduction of microvascular injury (27). The trial did not study the effect of thrombectomy as bailout therapy. Large residual thrombus and slow or absent flow after unsuccessful conventional PCI should thus be considered a differing clinical scenario. Interventionalists were not blinded to treatment allocation. However, the potential for significant bias is limited because all endpoint analyses were performed by fully blinded investigators.

CONCLUSIONS

In patients with subacute STEMI presenting between 12 and 48 h after symptom onset, routine manual thrombus aspiration before PCI failed to show a significant reduction in the primary endpoint of MVO assessed by CMR compared with conventional PCI alone. These findings are supported by a lack of benefit in angiographic, enzymatic, and clinical secondary endpoints.

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PERSPECTIVES

WHAT IS KNOWN? Patients with STEMI presenting within 12 h after symptom onset do not benefit from routine manual thrombus aspiration in the infarct-related artery. It is unclear whether thrombectomy may be a treatment option in late-presenting patients between 12 and 48 h, who often display particularly high thrombus burden.

WHAT IS NEW? Patients with STEMI presenting late after symptom onset do not benefit from routine manual aspiration thrombectomy before PCI.

WHAT IS NEXT? Treatment modalities other than routine thrombus aspiration are needed to further reduce microvascular injury in patients with STEMI.

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