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ORIGINAL PAPER

Thrombus aspiration in patients with ST-elevation myocardial infarction presenting late after symptom onset: long-term clinical outcome of a randomized trial

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Abstract

Background In the largest randomized trial so far, thrombus aspiration failed to reduce the primary endpoint of microvascular obstruction (MVO) in patients with ST-elevation myocardial infarction (STEMI) presenting late after symptom onset. Long-term clinical outcome data of this trial have not been reported yet.

Methods and results A total of 144 patients with STEMI presenting ≥ 12 and ≤ 48 h after symptom onset were randomized to primary percutaneous coronary intervention (PCI) with or without manual thrombus aspiration in a 1:1 fashion. The primary efficacy endpoint was the extent of MVO assessed by cardiac magnetic resonance imaging and showed no significant difference between groups. Long-term clinical follow-up was performed at 4 years. Overall mortality at 4 years reached 18%. There was no significant difference between groups with respect to mortality and major adverse cardiac events defined as the composite of death, myocardial reinfarction and target vessel revascularization. In a multivariate Cox regression model glomerular filtration rate on admission, left ventricular ejection fraction, and cardiogenic shock were independently associated with time-dependent occurrence of death.

Conclusion Routine thrombus aspiration in STEMI patients presenting late after symptom onset showed no significant difference with respect to long-term clinical endpoints compared to conventional PCI only.

Keywords Thrombus aspiration · ST-elevation myocardial infarction · Late presenting · Clinical outcome

Introduction

Until recently, manual thrombus aspiration (TA) was an established treatment option in patients with ST-elevation myocardial infarction (STEMI). The idea of TA is to remove thrombotic material before it enters the microcirculation and consequently reduce microvascular injury and infarct size, which are independent predictors of adverse clinical events in STEMI patients [1–3].

Its use in STEMI patients was downgraded to bail-out situations after two well-powered randomized trials and a related meta-analysis showed no mortality benefit and even suggested a higher risk of stroke [4–7].

However, these large randomized trials enrolled almost exclusively patients within 12 h after symptom onset, whereas patients presenting thereafter were excluded. Late presenting patients display larger thrombus burden and differing thrombus characteristics compared to those presenting early due to a longer dwelling time [8]. Conceivably, this might impact the efficacy of TA due to larger and more organized thrombi. While such long dwelling thrombi might be more difficult to aspirate, the absolute aspiration volume might be higher. There might also be a greater chance to shift large amounts of thrombotic material downstream into the microcirculation increasing the risk of the procedure.

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We previously presented the results of the first randomized trial of TA in subacute STEMI patients presenting between 12 and 48 h after symptom onset. The study found no benefit of routine TA on the primary efficacy end point MVO assessed by cardiac magnetic resonance (CMR) imaging and early clinical outcome after 30 days [9].

In the present analysis we report the clinical long-term follow-up of the patients enrolled in this randomized trial. Next to comparing the two treatment groups, the aim of the analysis was to collect prospective long-term clinical outcome data in late presenting STEMI patients.

Methods

Study design and overview

The present analysis represents the long-term clinical follow-up of a randomized trial of TA in STEMI patients presenting late after symptom onset. Design and results have been published previously [9]. In brief, a total of 152 patients between the age of 18 and 90 years with STEMI presenting between 12 and 48 h after symptom onset were randomized in a 1:1 fashion to primary PCI with or without manual TA. Exclusion criteria included prior thrombolysis, contraindications to CMR (known at the time of randomization), and severe comorbidities with limited life expectancy (< 6 months). TA had to be performed before the first balloon inflation using a 6-F manual aspiration catheter (Export AP; Medtronic, Minneapolis, Minnesota). A minimum of 2 aspiration passages across the lesion were recommended. Otherwise, PCI was performed according to current best practice. The primary efficacy endpoint was the extent of MVO on late gadolinium enhancement CMR performed 1–4 days after PCI. Eight patients were excluded from the analysis because of final diagnoses other than STEMI. All patients were enrolled between March 2011 and November 2014 at a single institution (Heart Center Leipzig at University of Leipzig, Leipzig, Germany). Figure 1 displays the study flowchart including the long-term follow-up. The study was approved by the local institutional review board. All patients provided written informed consent before randomization.

Briefly summarized, the results showed no significant difference in the extent of MVO between patients assigned to TA and the control group ($2.5 \pm 4.0\%$ vs. $3.1 \pm 4.4\%$ of left ventricular mass, $p = 0.47$). There were also no significant differences with respect to infarct size, myocardial salvage, left ventricular ejection fraction, angiographic endpoints and early clinical outcomes after 30 days.

Assessment and definition of clinical events

Long-term follow-up was performed 4 years after randomization of the last patient by telephone using a standardized questionnaire including death, recurrent myocardial infarction, recurrent coronary revascularization, stent thrombosis, stroke and quality of life assessed by EuroQol 5D questionnaire. All events were verified by hospital charts or direct contact with the treating physician. In patients where information could be obtained neither from the patient nor the treating physician, vital status was provided by the local government registration. All investigators involved in

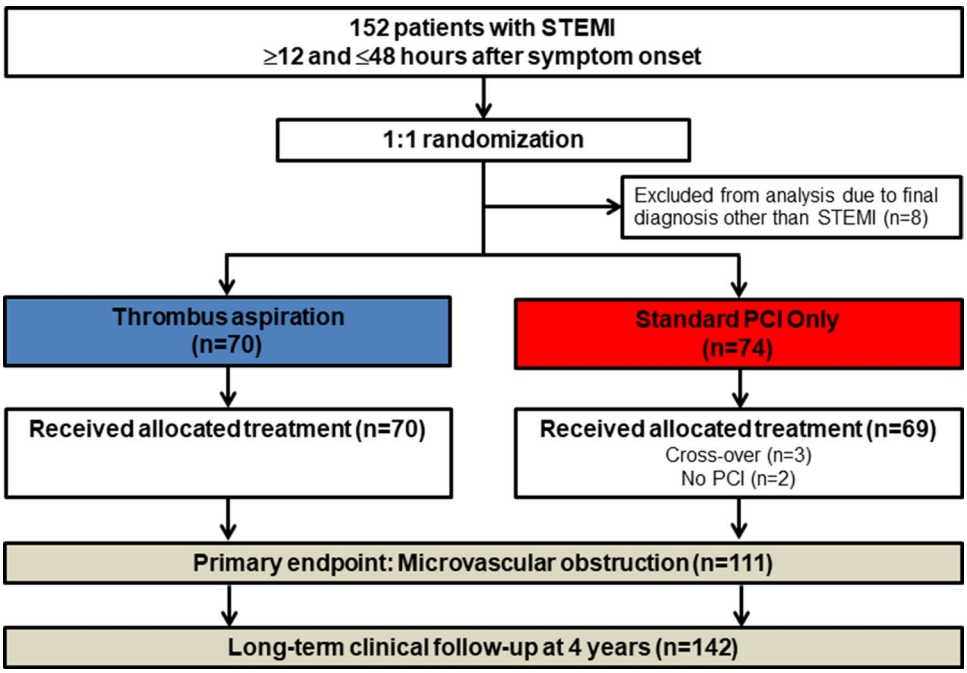


Fig. 1 Study flow. *STEMI* ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention

endpoint assessment were blinded to the patients' treatment allocation.

Death was defined as all-cause mortality. Myocardial reinfarction was determined according to current guidelines [10]. Target vessel revascularization (TVR) was defined as a repeated procedure, either PCI or bypass surgery, on the target vessel and target lesion revascularization (TLR) as any re-intervention inside the stent(s) implanted during the index procedure or within 5 mm proximal or distal to the stent. Stroke was characterized as any new focal neurological deficit of central origin lasting ≥ 24 h which resulted in irreversible brain damage or body impairment in association with signs of ischemia or hemorrhage in a cranial computed tomography or magnetic resonance scan. Major adverse cardiac events (MACE) were defined as the composite of death, myocardial reinfarction and TVR.

Statistical analysis

Statistical analyses were performed according to the intention-to-treat principle. Categorical variables are presented as number and percentages, continuous data as mean ± standard deviation. For categorical variables, two-group comparisons were performed using Chi-square or Fisher's exact test when the expected cell value was less than five. For continuous variables, Student's *t* tests were applied for normally distributed and Wilcoxon rank-sum tests for non-normally distributed variables. To analyze the time-dependent occurrence of death or MACE, Kaplan–Meier curves with log-rank comparison were computed. To identify predictors of death, univariate and multivariate Cox regression analyses were performed. Variables assessed for inclusion in the model were gender, age, diabetes mellitus, hypertension, active smoking, prior myocardial infarction, symptom-onset-to-balloon time, treatment group, multivessel disease, cardiogenic shock, culprit lesion in left anterior descending artery, unsuccessful PCI, glomerular filtration rate (GFR) on admission, left ventricular ejection fraction (LVEF) on CMR and clinical events (recurrent myocardial infarction, stroke, stent thrombosis). Variables with a p value < 0.10 in univariate testing were entered in the multivariable model after testing for multicollinearity. A two-sided p value of 0.05 was considered statistically significant for all tests. Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, Illinois, USA).

Results

Baseline and procedural characteristics

A total of 144 patients were included in the final analysis (70 patients randomized to additional TA and 74 patients to standard PCI only). The mean age was 66 ± 15 years.

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. Three patients randomized to PCI alone underwent thrombus aspiration by operator's choice (bail-out situations due to unsatisfactory results after conventional PCI) and in five patients randomized to TA the aspiration catheter could not be advanced to the culprit lesion. Except for pre-dilation (39% in the TA group vs. 75% in the standard PCI only group, $p < 0.001$) angiographic and procedural characteristics did not differ significantly between groups.

Clinical events and quality of life at long-term follow-up

Clinical events at 4 years are displayed in Table 2. Overall mortality at 4 years was 18%. Twelve patients (17%) died in the TA group compared to 14 (19%) in the standard PCI only group ($p = 0.78$). MACE occurred in 31 patients (23% in the TA group vs. 26% in the standard PCI only group, $p = 0.68$). Similar to mortality and MACE, there were no significant differences between groups with respect to the individual components of MACE as well as TLR, nTVR, and stroke (Table 2).

Kaplan–Meier curves for all-cause mortality and MACE up to a maximum follow-up period of 7.2 years are displayed in Fig. 2a, b. There was no significant difference between the two groups with respect to the time-dependent occurrence of the respective endpoints.

Results of the Euro-QoL-5D questionnaire were available in 98 of 110 patients who were alive at long-term follow-up. The findings grouped according to the different dimensions are displayed in Fig. 3. Visual analogue scale classifying subjective quality of life was obtainable in 97 patients with a median of 70 of 100 achievable points (interquartile range 58–80). There were no significant differences in quality of life measures between groups.

Mortality predictors at long-term follow-up

Co-variates with a p value < 0.10 in univariate Cox regression analysis are displayed in Table 3. Stent thrombosis was excluded from multivariate testing due to an excessively high standard error in univariate analysis. In multivariate analysis GFR on admission, LVEF on CMR and cardiogenic shock were independently associated with the time-dependent occurrence of death (Table 3).

Discussion

This long-term clinical follow-up of a randomized trial comparing primary PCI with and without manual TA in STEMI patients presenting late after symptom onset showed

Table 1 Baseline and procedural characteristics

Variable	Thrombus aspiration ($n=70$)	Standard PCI only ($n=74$)
Age (years)	66 ± 12	66 ± 15
Male	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/m²)	28.9 ± 3.8	28.6 ± 4.7
Glomerular filtration rate (ml/min/1.73 m^2)[a]	86 ± 27	79 ± 26
Door-to-balloon-time (min)	78 ± 150	62 ± 105
Symptom-onset-to-balloon-time (hours)	26 ± 13	29 ± 12
Infarct-related artery		
Left anterior descending	38/70 (54)	32/72 (44)
Left circumflex	11/70 (16)	9/72 (13)
Right coronary	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)
Multivessel disease	38/70 (54)	44/74 (60)
Predilation*	27/70 (39)	54/72 (75)
Postdilation	7/69 (10)	14/72 (19)
Visible thrombus in aspirate[b]	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

Categorical data are presented as frequencies (percentages), continuous data as means ± standard deviation

PCI percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

*p value < 0.001

[a]Estimated according to MDRD (modification of diet in renal disease) formula

[b]Three patients randomized to PCI alone underwent bailout thrombus aspiration (cross-over)

no significant difference in all-cause mortality or MACE between the groups. In multivariate regression analysis, GFR on admission, LVEF and cardiogenic shock were identified as independent risk factors of mortality in this dedicated subgroup of STEMI patients.

In 8.5–12.0% of patients with STEMI, time from symptom onset to presentation ranges between 12 and 48 h [11, 12]. To date, only a small number of studies dealt exclusively with these late-presenting patients mainly focusing on the question whether invasive treatment should be performed > 12 h after symptom onset [13, 14].

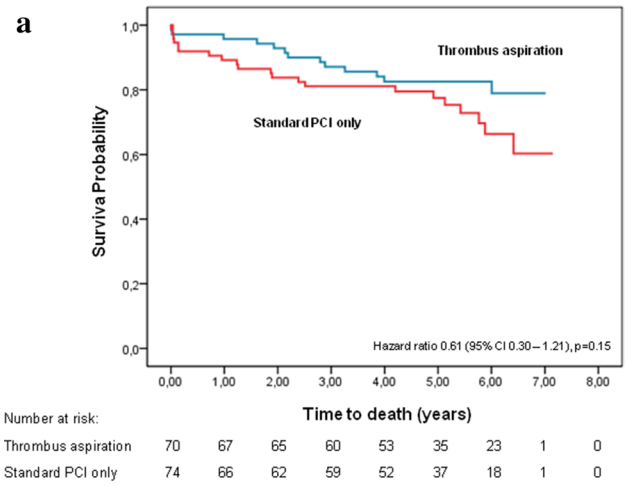
The only published long-term clinical outcome data in subacute STEMI patients (presenting ≥ 12 to ≤ 48 h after symptom onset) are from the Beyond 12 h Reperfusion Alternative Evaluation (BRAVE)-2 trial, which compared coronary angiography vs. conservative treatment in

Table 2 Clinical events at 4-year follow-up

Variable	Overall ($n=144$)	Thrombus aspiration ($n=70$)	Standard PCI only ($n=74$)	p	Odds ratio (95% confidence interval)
All-cause death	26/142 (18)	12/69 (17)	14/73 (19)	0.78	0.88 (0.37–2.08)
MACE	31/128 (24)	15/66 (23)	16/62 (26)	0.68	0.84 (0.38–1.90)
Reinfarction	11/128 (9)	7/66 (11)	4/62 (6)	0.53	1.72 (0.48–6.19)
Stent thrombosis	3/127 (2)	2/65 (3)	1/62 (2)	1.00	1.94 (0.17–21.91)
TVR	6/127 (5)	4/65 (6)	2/62 (3)	0.68	1.97 (0.35–11.15)
TLR	6/127 (5)	4/65 (6)	2/62 (3)	0.68	1.97 (0.35–11.15)
nTVR	36/131 (27)	18/66 (27)	18/65 (28)	0.89	0.98 (0.45–2.11)
Stroke	1/110 (1)	0/60 (0)	1/50 (2)	0.46	NA

Data are presented as frequencies (percentages)

PCI percutaneous coronary intervention, *MACE* major adverse cardiac events, *TVR* target vessel revascularization, *TLR* target lesion revascularization, *nTVR* non-target vessel revascularization



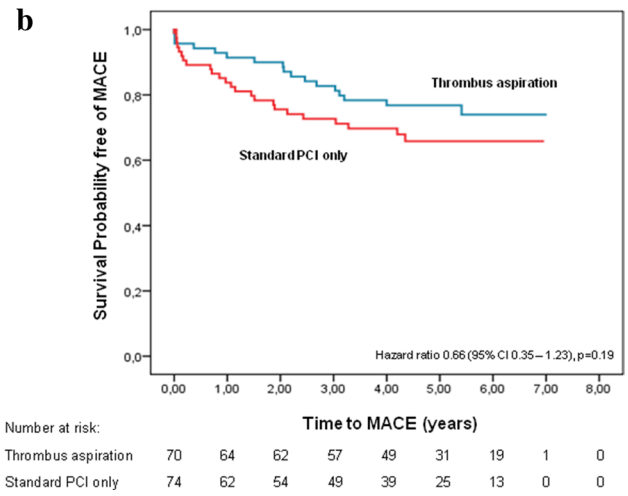


Fig. 2 **a** Kaplan–Meier curve survival probability. *CI* confidence interval, *PCI* percutaneous coronary intervention. **b** Kaplan–Meier curve survival probability free of MACE. *MACE* major cardiac events, *CI* confidence interval, *PCI* percutaneous coronary intervention

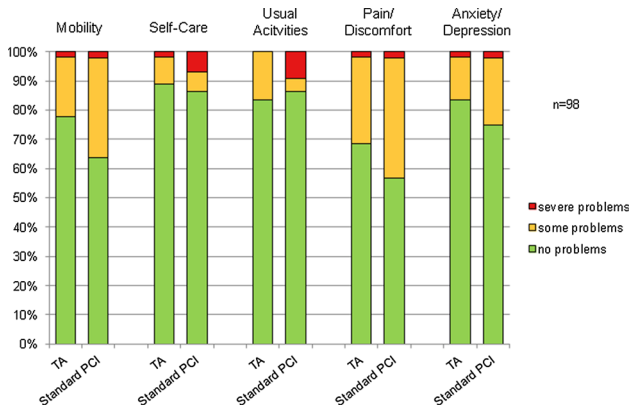


Fig. 3 Results of the EuroQol-5D questionnaire. *TA* thrombus aspiration

a randomized fashion [13, 15]. The incidence of clinical events in the present analysis is consistent with the results of the BRAVE-2 4-year follow-up, except for a slightly higher mortality, which might be driven by the exclusion of patients with cardiogenic shock in BRAVE-2. Furthermore, the rate of subsequent revascularization of the infarct-related artery was notably higher in the BRAVE 2 cohort (53% vs. 4% in the present analysis). This difference is likely caused by a significantly higher rate of TVR in the initially conservatively treated group (69%) in BRAVE-2, whereas in the current study almost all patients received PCI at the time of presentation.

Long-term mortality at 3–5 years in STEMI patients presenting within the first 12 h after symptom onset ranges between 7% and 12% [16, 17]. Compared to these data, death rate in the present analysis is considerably higher. This might be explained by the extended time between symptom onset and hospitalization as symptom onset-to-balloon-time exceeding 3 h, respectively, 4 h represents an independent risk factor for mortality [12, 18]. CMR data

Table 3 Predictors of long-term mortality on univariate and multivariate Cox regression analysis

Variable	Univariate Cox regression			Multivariate Cox regression		
	Coefficient B	Hazard ratio (95% confidence interval)	*p*	Coefficient B	Hazard ratio (95% confidence interval)	*p*
Age (per year)	0.04	1.04 (1.01–1.08)	0.01	0.002	1.00 (0.97–1.03)	0.91
Symptom-onset-to-balloon time (per hour)	0.03	1.03 (1.00-1.06)	0.04	0.002	1.00 (0.95–1.05)	0.94
Cardiogenic shock	2.89	17.97 (6.67–48.39)	< 0.001	3.18	23.04 (2.14–248.7)	0.01
Multivessel disease	0.92	2.50 (1.13–5.52)	0.02	1.10	3.00 (0.74–12.17)	0.12
Glomerular filtration rate on admission (per 1 ml/kg/m²)	− 0.03	0.97 (0.95–0.98)	< 0.001	-0.03	0.976 (0.95–0.997)	0.03
Left ventricular ejection fraction (per 1%)	− 0.09	0.92 (0.87–0.96)	0.001	-0.07	0.94 (0.89–0.99)	0.01
Myocardial reinfarction	1.69	5.43 (2.52–11.67)	< 0.001	1.17	3.23 (0.94–11.12)	0.06
Stent thrombosis	1.53	4.63 (1.10–19.46)	0.04	N/A	N/A	N/A

N/A not available

comparing early and late presenting STEMI patients (cut-off 12 h) in matched cohorts confirmed a significantly larger infarct size and decreased myocardial salvage in late presenting patients [19]. However, a further delay in hospitalization after exceeding 12 h does not seem to be independently associated with a higher mortality according to the present Cox regression model.

A recent individual patient meta-analysis of the 3 largest randomized trials comprising over 18,000 early presenting STEMI patients displayed no significant difference in clinical outcomes between patients treated with or without TA [4–6]. In subgroup analyses, TA in patients with high thrombus burden was nominally associated with fewer cardiovascular deaths but with a higher risk of stroke or transient ischemic attack (TIA). However, analyses by interaction terms revealed a significant difference between the groups only for the risk of stroke or TIA. Follow-ups exceeding 1 year of the above mentioned randomized controlled trials are not published to date. In summary, the findings are largely consistent and do not support a beneficial effect of TA in early presenting patients. However, there was justified hope that TA might be more beneficial in late presenting STEMI patients given the larger thrombus burden and modified composition with increasing ischemic time [8, 20] Of note, thrombus composition is an independent predictor of major adverse cardiovascular events and long-term mortality in patients with STEMI [20, 21].

Nevertheless, neither CMR parameters nor clinical endpoints were significantly different between TA and standard PCI in the present study supporting no beneficial or detrimental effect of TA also in late-presenting patients. Potential dwelling times and organization of thrombus in late-presenting patients do not seem to play a role on the effect of TA.

Several hypotheses have been postulated concerning the question why thrombus aspiration does not lead to an improvement of clinical outcome. First, TA might not generate a sufficient effect to change the extent of MVO and other parameters of reperfusion success, especially in patients with low thrombus burden. Additionally, outcome might be dominated by additional factors other than removal of thrombus material. Second, a positive effect of removing thrombotic material might be outweighed by dislodging the same, potentially leading to coronary or peripheral embolization [6, 9].

Strength and limitations

This is the first study reporting on long-term clinical outcome in patients presenting late after STEMI treated with or without thrombus aspiration. Furthermore, it is one of the scarce long-term reports in STEMI patients presenting after 12 h of symptom onset.

There are several limitations. The randomized trial was not powered for outcome analysis and is thus only hypothesis-generating. Second, aside from vital status, follow-up of clinical events was not available for all patients leading to a potential bias in group comparison.

Conclusion

Thrombus aspiration in STEMI patients presenting late after symptom onset (≥ 12 h to ≤ 48 h) showed no significant difference with respect to long-term clinical events compared to conventional PCI only.

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