Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial

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Summary

Background Two large trials have reported contradictory results at 1 year after thrombus aspiration in ST elevation myocardial infarction (STEMI). In a 1-year follow-up of the largest randomised trial of thrombus aspiration, we aimed to clarify the longer-term benefits, to help guide clinical practice.

Methods The trial of routine aspiration ThrOmbecTomy with PCI versus PCI ALone in Patients with STEMI (TOTAL) was a prospective, randomised, investigator-initiated trial of routine manual thrombectomy versus percutaneous coronary intervention (PCI) alone in 10 732 patients with STEMI. Eligible adult patients (aged ≥18 years) from 87 hospitals in 20 countries were enrolled and randomly assigned (1:1) within 12 h of symptom onset to receive routine manual thrombectomy with PCI or PCI alone. Permuted block randomisation (with variable block size) was done by a 24 h computerised central system, and was stratified by centre. Participants and investigators were not masked to treatment assignment. The trial did not show a difference at 180 days in the primary outcome of cardiovascular death, myocardial infarction, cardiogenic shock, or heart failure. However, the results showed improvements in the surrogate outcomes of ST segment resolution and distal embolisation, but whether or not this finding would translate into a longer term benefit remained unclear. In this longer-term follow-up of the TOTAL study, we report the results on the primary outcome (cardiovascular death, myocardial infarction, cardiogenic shock, or heart failure) and secondary outcomes at 1 year. Analyses of the primary outcome were by modified intention to treat and only included patients who underwent index PCI. This trial is registered with ClinicalTrials.gov, number NCT01149044.

Findings Between Aug 5, 2010, and July 25, 2014, 10 732 eligible patients were enrolled and randomly assigned to thrombectomy followed by PCI (n=5372) or to PCI alone (n=5360). After exclusions of patients who did not undergo PCI in each group (337 in the PCI and thrombectomy group and 331 in the PCI alone group), the final study population comprised 10 064 patients (5035 thrombectomy and 5029 PCI alone). The primary outcome at 1 year occurred in 395 (8%) of 5035 patients in the thrombectomy group compared with 394 (8%) of 5029 in the PCI alone group (hazard ratio [HR] 1·00 [95% CI 0·87–1·15], p=0·99). Cardiovascular death within 1 year occurred in 179 (4%) of the thrombectomy group and in 192 (4%) of 5029 in the PCI alone group (HR 0·93 [95% CI 0·76–1·14], p=0·48). The key safety outcome, stroke within 1 year, occurred in 60 patients (1·2%) in the thrombectomy group compared with 36 (0·7%) in the PCI alone group (HR 1·66 [95% CI 1·10–2·51], p=0·015).

Interpretation Routine thrombus aspiration during PCI for STEMI did not reduce longer-term clinical outcomes and might be associated with an increase in stroke. As a result, thrombus aspiration can no longer be recommended as a routine strategy in STEMI.

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Introduction

One of the hallmarks of ST elevation myocardial infarction (STEMI) is occlusion of the infarct vessel with a thrombus. Rapid primary percutaneous coronary intervention (PCI) has been shown to be beneficial in patients with STEMI.[1] However, a limitation of this intervention is distal embolisation of the thrombus after balloon dilatation or stenting, which can obstruct the distal microvasculature and impair tissue perfusion.[2] Both distal embolisation and reduced tissue perfusion (impaired ST segment resolution and angiographic myocardial blush grade) after primary PCI have been associated with substantial increases in mortality and morbidity.[2–4]

Thrombus aspiration during primary PCI has been thought to be an effective method for reducing distal embolisation and improving microvascular perfusion. The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study

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See Online for appendix

Research in context

Evidence before this study

We did a comprehensive systematic search of the MEDLINE, Embase, and Cochrane databases for randomised controlled trials that assessed the clinical utility of manual thrombectomy in patients presenting with ST elevation myocardial infarction (STEMI) only, published from any time up to Sept 3, 2015. We did not use any language restrictions in our search. Our search terms included "thrombectomy", "thrombus aspiration", "thromboaspiration", "myocardial infarction", "percutaneous coronary intervention", and "randomized" (appendix p 10). We identified 669 abstracts, from which we selected 20 randomised trials (n=21 173) for inclusion. Our search showed that before the TOTAL and TASTE trials were done, trials of manual thrombectomy were powered for surrogate outcomes and were quite small.

Added value of this study

TOTAL is the largest randomised trial so far to compare routine manual thrombectomy to PCI alone during STEMI PCI.

Implications of all the available evidence

In an updated meta-analysis, manual thrombectomy did not reduce all-cause mortality or recurrent myocardial infarction but was associated with an increased risk of stroke. Consequently, manual thrombectomy can no longer be recommended as a routine strategy during PCI for STEMI.

(TAPAS),[5] which enrolled 1071 patients, showed that routine thrombus aspiration improved the primary outcome of microvascular perfusion. At long-term follow-up at 1 year, the TAPAS trial also showed a significant reduction in mortality that was not apparent at 30 days.[6] By contrast, the larger Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial[7,8] of 7244 patients showed no significant reduction in mortality either at 30 days or at 1 year.

The trial of routine aspiration ThrOmbecTomy with PCI versus PCI ALone in Patients with STEMI (TOTAL)[9] showed no difference at 180 days in the primary outcome of cardiovascular death, myocardial infarction, cardiogenic shock, or class IV heart failure between patients who had received thrombectomy with PCI versus those who had PCI alone. Notably, the trial showed significant improvements in surrogate outcomes of distal embolisation and ST segment resolution in patients who received thrombectomy. However, whether or not the benefits of these surrogate outcomes will translate into a longer term clinical benefit at 1 year remains unclear. To address this unresolved question, we did a follow-up analysis of the 1-year outcomes of the TOTAL study.

Methods

Study design and participants

The design of the TOTAL trial has been previously described.[10] TOTAL was a prospective, randomised, investigator-initiated trial of routine manual thrombectomy with the Export catheter (Medtronic Inc, Santa Rosa, CA, USA) with PCI versus PCI alone in patients with STEMI. The study was done in 87 hospitals in 20 countries (appendix p 3). An independent data and safety monitoring committee monitored the safety of the trial. The Population Health Research Institute at McMaster University (Hamilton, ON, Canada) undertook and coordinated the trial and also collected and held all trial data.

Adult patients (≥18 years of age) with STEMI were eligible for inclusion in the TOTAL study if they were referred for primary PCI within 12 h of symptom onset. Patients who had undergone previous coronary artery bypass surgery or had received fibrinolytic therapy were not eligible (see appendix p 4 for detailed inclusion and exclusion criteria). All participants provided written informed consent. Local research ethics boards approved the protocol.

Randomisation and masking

Enrolled patients were randomly assigned in a 1:1 ratio to either routine thrombus aspiration (manual thrombectomy) and PCI or PCI alone. Randomisation was done according to permuted blocks with variable block size, stratified by centre, through the use of a 24-h computerised central system located at the Population Health Research Institute (Hamilton, ON, Canada). Participants and investigators were not masked to treatment assignment.

Procedures

Detailed recommendations were provided to investigators regarding the thrombectomy procedure. The procedure was done by investigators who were interventional cardiologists. Aspiration was to be started before crossing the lesion. A minimum of two syringes (40 mL) of aspirate were recommended. Investigators were instructed to ensure that the guide catheter was engaged with the coronary ostia when removing the thrombectomy catheter. Finally, the guide catheter was to be aspirated after thrombectomy to avoid embolisation of air or thrombus from the guide catheter.

The PCI procedure was to be done without thrombectomy as per the investigator. Direct stenting was not mandated in either treatment group. Bailout thrombectomy was allowed after a failure of the initial PCI alone strategy, defined as a persistently occluded vessel (Thrombolysis In Myocardial Infarction [TIMI] grade 0 or 1 flow) with large thrombus after balloon pre-dilatation or a large thrombus after stent deployment irrespective of TIMI flow. The decision about bailout thrombectomy was made by the interventional cardiologist performing the initial PCI procedure.

Outcomes

The primary outcome of the TOTAL study was the composite of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or class IV heart failure within 180 days, and the key safety outcome was stroke within 30 days. These results have been published previously.[9] For the 1-year follow-up, we report the following prespecified outcomes: the primary outcome; components of the primary outcome (including cardiovascular death); the key net benefit outcome (cardiovascular death, recurrent myocardial infarction, cardiogenic shock, class IV heart failure, or stroke); and other outcomes including target vessel revascularisation, stent thrombosis, stroke, and transient ischaemic attack. All outcomes were analysed by modified intention to treat. Appendix p 5 provides a detailed list of outcome definitions. A central committee, masked to the treatment allocation, adjudicated all the primary outcome events, strokes, transient ischaemic attacks, major bleeding, and stent thrombosis.

Statistical analyses

The original sample size calculation of 4000 patients was based on a primary outcome rate of 14% at 180 days.[10] On the basis of a masked interim analysis that showed an overall event rate of 7%, we estimated that we would need to enrol 10 700 patients for 718 primary outcome events to have occurred, thus providing 80% power to detect a 20% reduction in risk.[10] The sample size was therefore increased without any knowledge of treatment effects.

Analyses were done by the trial statisticians. For the primary analysis, a modified intention-to-treat analysis was prespecified to include only randomly assigned patients who had undergone primary PCI. Patients were to be analysed in the treatment group to which they were originally allocated. Patients who had not undergone PCI for the index STEMI (eg, patients with normal coronary arteries) were not included in the primary analysis. Other prespecified sensitivity analyses included full intention-to-treat, on-treatment, and per-protocol analyses. In the full intention-to-treat analysis, all patients were analysed in the randomised treatment group to which they were assigned, irrespective of whether or not they underwent PCI. In the on-treatment analysis, all patients who received thrombectomy (upfront or bailout), irrespective of randomisation group, were compared with those who had PCI without thrombectomy. The per-protocol analysis included all patients who underwent PCI and did not cross over from their initial treatment allocation to the alternative therapy.

We used a two-sided, log-rank test to compare the two randomised groups for the primary and secondary outcomes at 1 year and a p value of less than 0·05 was judged to be significant. We estimated the hazard ratio (HR) and its 95% CI using a Cox proportional hazards regression model, with treatment group as the predictor variable. For subgroup analyses, we calculated HRs and 95% CIs and interaction p values. We assessed statistical interactions at a significance level of 0·05 and did not do any adjustments for multiple comparisons.

We did a post-hoc landmark analysis for stroke beyond 180 days to ascertain whether or not the late stroke rate was increased in the PCI and thrombectomy group compared with the PCI only group. For the on-treatment and per-protocol analyses, a multivariable analysis included adjustment for known predictors of outcome in STEMI and included age, sex, Killip class, diabetes, peripheral arterial disease, previous stroke, anterior myocardial infarction, time from symptom onset to first device crossing the lesion, heart rate, and blood pressure.

SAS version 9.1 was used for all statistical analyses.

For our subgroup analyses, we postulated that thrombectomy would be more effective in patients with greater thrombus burden. Consequently, the main subgroup analysis was based on TIMI thrombus grade

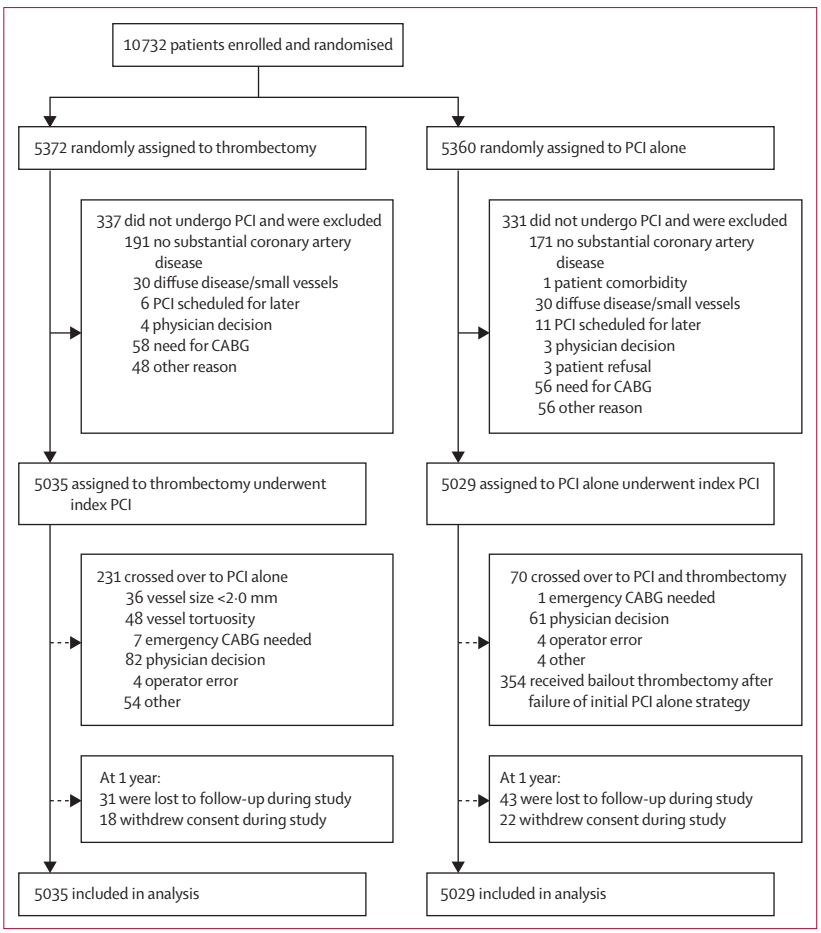

Figure 1: **Trial profile**
Information for two additional patients in the thrombectomy group was obtained (missing from previous publication) and identified them as having had index PCI so they are now included in the modified intention-to-treat analysis. Similarly, one patient from the PCI alone group was identified since the previous publication to have undergone PCI and is now included in the modified intention-to-treat analysis. PCI status was corrected in two patients who did not undergo index PCI and so have now been excluded from the modified intention-to-treat analysis. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft.

less than 3 versus 3 or higher. Other prespecified subgroup analyses were TIMI thrombus grade (<4 *vs* ≥4), symptom onset (<6 h *vs* 6–12 h), initial TIMI flow (0–1 *vs* 2–3), age (≤65 years *vs* >65 years), centres divided into tertiles of primary PCI volume (centres reported annual primary PCI volume and were then ranked and divided by thirds for subgroup analysis by centre volume), and myocardial infarction type (anterior *vs* non-anterior). Exploratory post-hoc subgroups were diabetes, smoking, bivalirudin use, glycoprotein IIb/IIIa inhibitor use, proximal lesions, or a combination of three criteria—initial TIMI 0–2 flow, proximal or mid-left anterior descending culprit lesion, and symptom onset to device ≤5 h—to identify patients who might benefit most from thrombectomy.

We did an exploratory post-hoc analysis to ascertain whether or not successful crossing of lesion with thrombectomy catheter or thrombus retrieval were associated with benefit from thrombectomy treatment. We used a multivariable Cox regression model for primary outcome to compare these subsets in the thrombectomy group versus the PCI alone group and adjustment was made for variables known to predict outcome in STEMI, including age, sex, Killip class, diabetes, peripheral arterial disease, previous stroke, anterior myocardial infarction, time from symptom onset to first device crossing the lesion, heart rate, and blood pressure.

We did a meta-analysis of previously published studies, for which we used the Mantel-Haenszel method for fixed effects to calculate the pooled odds ratios and 95% CI. Statistical analyses for this were done with Review Manager (RevMan) software version 5.

	Thrombectomy and PCI (n=5035)	PCI alone (n=5029)
Age, years	61·1 (11·8)	60·9 (11·9)
Age >75 years	667 (13%)	629 (13%)
Male sex	3864 (77%)	3934 (78%)
Killip class ≥2	221 (4%)	210 (4%)
Location of myocardial infarction*		
Anterior	1962/5031 (39%)	2055/5025 (41%)
Inferior	2809/5031 (56%)	2710/5025 (54%)
Lateral or other	260/5031 (5%)	260/5025 (5%)
History		
Previous stroke	158 (3%)	151 (3%)
Previous myocardial infarction	463 (9%)	446 (9%)
Previous PCI	416 (8%)	423 (8%)
Diabetes	921 (18%)	935 (19%)
Initial PCI procedure		
Symptom onset to hospital arrival time, min†	128 (75–225)	120 (71–217)
Hospital to device time, min	68 (38–107)	68 (38–107)
Radial access	3437 (68%)	3429 (68%)
Initial TIMI 0 or 1 flow	3705 (74%)	3748 (75%)
TIMI thrombus grade		
0: no visible thrombus	127 (3%)	149 (3%)
1: possible thrombus present	238 (5%)	277 (6%)
2: definite thrombus present, <0·5 vessel diameter	139 (3%)	143 (3%)
3: definite thrombus present, 0·5–2·0 vessel diameter	584 (12%)	480 (10%)
4: definite thrombus present, >2·0 vessel diameters	705 (14%)	713 (14%)
5: total occlusion	3240 (64%)	3261 (65%)
Upfront glycoprotein IIb/IIIa inhibitor‡	1143 (23%)	1276 (25%)
Bailout glycoprotein IIb/IIIa inhibitor	743 (15%)	808 (16%)
Drug-eluting stent	2250 (45%)	2266 (45%)
Bare metal stent	2638 (52%)	2626 (52%)
Coronary bypass surgery after randomisation	157 (3%)	165 (3%)
Therapies at 1 year		
Aspirin	4576/4795 (95%)	4527/4745 (95%)
Clopidogrel	2133/4796 (45%)	2060/4744 (43%)
Prasugrel	377/4795 (8%)	371/4744 (8%)
Ticagrelor	642/4795 (13%)	694/4744 (15%)
β blocker	3852/4795 (80%)	3800/4745 (80%)
Oral anticoagulants	225/4795 (5%)	236/4747 (5%)
ACE inhibitor or angiotensin receptor blocker	3798/4795 (79%)	3800/4745 (80%)
Statin	4492/4796 (94%)	4466/4748 (94%)

Data are mean (SD), n (%), n/N (%), or median (IQR). PCI=percutaneous coronary intervention. TIMI=Thrombolysis In Myocardial Infarction. ACE=angiotensin-converting enzyme. *Location of myocardial infarction is missing for four patients in the thrombectomy group and four patients in the PCI alone group. †For comparison of symptom onset to hospital arrival time between groups, p=0·0201. ‡For comparison of use of upfront glycoprotein IIb/IIIa inhibitors during PCI between groups, p=0·0017.

Table 1: **Baseline characteristics**

Role of the funding source

Medtronic approved funding based on the review of the protocol developed by the steering committee and also approved the increase in sample size. The trial was conducted by the Population Health Research Institute and Steering Committee, who designed the trial and were responsible for patient recruitment and data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 5, 2010, and July 25, 2014, 10732 eligible patients were enrolled from 87 hospitals in 20 countries, of whom 5372 were randomly assigned to thrombectomy followed by PCI and 5360 were assigned to PCI alone (figure 1). Of these patients, 10064 (94%) underwent primary PCI for (index) STEMI. Bailout thrombectomy after a failure of the PCI alone strategy was done in 354 (7%) of 5029 patients randomly assigned to PCI alone (figure 1).

Thrombectomy was attempted in 4804 (95%) of 5035 patients randomly assigned to thrombus aspiration who underwent PCI. The operator successfully crossed the culprit lesion with the thrombectomy catheter as first device in 4156 (83%) of 5035 patients and only after balloon predilatation in an additional 296 (6%) of 5035 patients. Of the 4452 (93%) of 4804 patients whose lesion was crossed with the thrombectomy catheter, 3124 (70%) had visible macroscopic material retrieved in the basket.

Table 1 shows the baseline and procedural characteristics and therapies at 1 year. Patients in the thrombectomy group had a slightly longer symptom onset to hospital arrival time than did those in the PCI alone group (table 1). Upfront use of glycoprotein IIb/IIIa inhibitors during PCI was more common in the PCI alone group (table 1). Follow-up was complete in 9950 (99%) of 10 064 participants at 1 year (figure 1).

The rate of incomplete ST segment resolution (<70% resolution) was 27% in the thrombectomy group versus 30% in the PCI alone group (p=0·0003). The rate of investigator-reported distal embolisation was reduced with thrombectomy (80 cases [1·6%] in the thrombectomy group *vs* 152 [3·0%] in the PCI alone group; p<0·0001).

The primary outcome (cardiovascular death, recurrent myocardial infarction, shock, or class IV heart failure) at 1 year occurred in 395 (8%) of 5035 patients randomly assigned to thrombectomy compared with 394 (8%) of 5029 randomly assigned to PCI alone (HR 1·00 [95% CI 0·87–1·15], p=0·99; figure 2, table 2). Cardiovascular death at 1 year occurred in 179 (4%) of 5035 patients in the thrombectomy group compared with 192 (4%) of 5029 assigned to PCI alone (HR 0·93 [95% CI 0·76–1·14], p=0·48). Recurrent myocardial infarction, cardiogenic shock, or heart failure at 1 year were similar between the groups (table 2), as were all-cause death, stent thrombosis, definite stent thrombosis, target vessel revascularisation, and major bleeding.

Stroke at 1 year occurred in 60 (1·2%) patients in the thrombectomy group compared with 36 (0·7%) in the PCI alone group (HR 1·66 [95% CI 1·10–2·51], p=0·015). A landmark analysis for strokes occurring beyond 180 days showed no difference in strokes between the groups (7 [0·1%] in the thrombectomy group *vs* 10 [0·2%] in the PCI alone group; HR 0·70 [95% CI 0·27–1·83], p=0·46).

Subgroup analyses showed consistent findings, with no difference at 1 year for the subgroup of patients with a high thrombus burden (figure 3). The other prespecified subgroups of age, symptom onset duration, location of the infarct, initial TIMI flow, and site primary PCI volume showed consistent findings with the overall analysis (figure 3), as did the exploratory post-hoc subgroups (figure 3).

The outcomes for the full intention-to-treat analysis, on-treatment analysis, and per-protocol analysis are shown in appendix p 8 and also show consistent findings with the main analysis.

An exploratory analysis showed that successful crossing of lesion with aspiration catheter (adjusted HR 0·95 [95% CI 0·81–1·11]) or actual thrombus retrieval (adjusted HR 0·93 [0·79–1·10]) were not predictors of benefit of thrombectomy for the primary outcome after adjustment for predictors of mortality after STEMI.

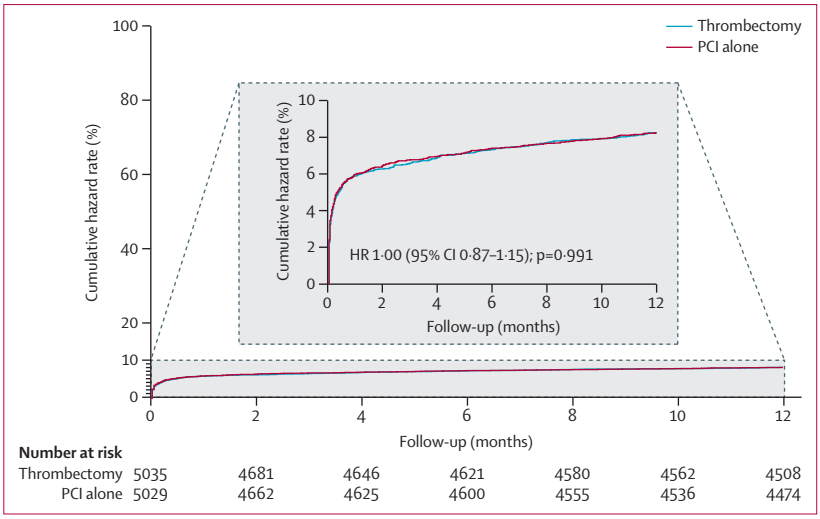

Figure 2: **Kaplan-Meier curves for the two treatment groups for the primary outcome (composite of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or class IV heart failure within 1 year)**
The smaller Kaplan–Meier graph is a scaled up version of the main graph, so that the lines for the two treatment groups are discernible. PCI=percutaneous coronary intervention.

	Thrombectomy and PCI (n=5035)	PCI alone (n=5029)	HR (95% CI)	p value
Primary outcome and components within 1 year				
Cardiovascular death, myocardial infarction, cardiogenic shock, or class IV heart failure	395 (7·8%)	394 (7·8%)	1·00 (0·87–1·15)	0·99
Cardiovascular death	179 (3·6%)	192 (3·8%)	0·93 (0·76–1·14)	0·48
Recurrent myocardial infarction	125 (2·5%)	118 (2·3%)	1·05 (0·82–1·36)	0·68
Cardiogenic shock	95 (1·9%)	105 (2·1%)	0·90 (0·68–1·19)	0·47
Class IV heart failure	106 (2·1%)	96 (1·9%)	1·10 (0·83–1·45)	0·50
Cardiovascular death, myocardial infarction, cardiogenic shock or class IV heart failure, stent thrombosis, or target vessel revascularisation	572 (11·4%)	563 (11·2%)	1·01 (0·90–1·14)	0·85
All-cause death	214 (4·3%)	224 (4·5%)	0·95 (0·79–1·15)	0·60
Stent thrombosis	87 (1·7%)	105 (2·1%)	0·82 (0·62–1·09)	0·18
Definite stent thrombosis	65 (1·3%)	73 (1·5%)	0·89 (0·63–1·24)	0·48
Target vessel revascularisation	275 (5·5%)	257 (5·1%)	1·06 (0·90–1·26)	0·48
Major bleeding	94 (1·9%)	88 (1·7%)	1·06 (0·79–1·42)	0·69
Safety outcomes within 1 year				
Stroke	60 (1·2%)	36 (0·7%)	1·66 (1·10–2·51)	0·015
Transient ischaemic attack	14 (0·3%)	8 (0·2%)	1·74 (0·73–4·15)	0·205
Stroke or transient ischaemic attack	73 (1·4%)	44 (0·9%)	1·65 (1·14–2·40)	0·008
Net risk-benefit risk outcome within 1 year				
Cardiovascular death, myocardial infarction, cardiogenic shock, class IV heart failure, or stroke	430 (8·5%)	415 (8·3%)	1·03 (0·90–1·18)	0·63

PCI=percutaneous coronary intervention. HR=hazard ratio.

Table 2: **Primary and secondary outcomes**

In our systematic review of previously published studies, we identified 669 abstracts in our search and selected 20 randomised trials (n=21 173) for inclusion. In these trials overall, all-cause death occurred in 452 (4%) of 10 250 patients in the thrombectomy group compared

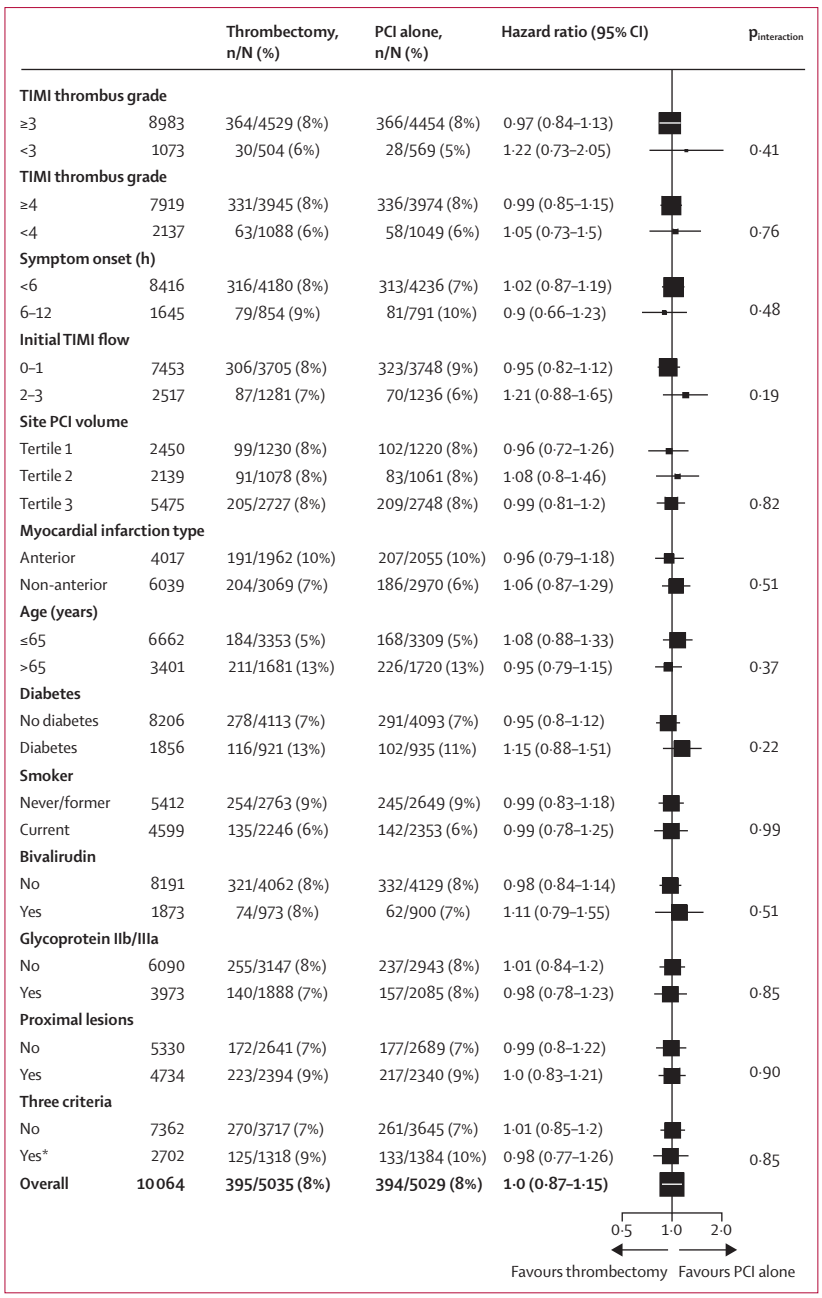

***Figure 3*: Subgroup analysis for primary outcome**
PCI=percutaneous coronary intervention. TIMI=Thrombolysis In Myocardial Infarction. *Three criteria: proximal or mid left anterior descending artery culprit lesion, TIMI 0–2 flow, and symptom onset to device use ≤5 h.

with 503 (5%) of 10 282 assigned to PCI alone group (odds ratio [OR] 0·90 [95% CI 0·79–1·02], p=0·10, I^2=0%; figure 4). Stroke occurred in 85 (0·9%) patients in the thrombectomy group compared with 59 (0·6%) patients in the PCI alone group (OR 1·43 [95% CI 1·03–1·99], p=0·03, I^2=0%; figure 5). The incidence of recurrent myocardial infarction did not differ between the groups (2·4% thrombectomy *vs* 2·5% PCI alone; OR 0·95 [95% CI 0·79–1·13], p=0·53, I^2=0%).

Discussion

The TOTAL trial is the largest trial so far to compare a strategy of routine thrombus aspiration and PCI versus PCI alone in patients with STEMI. Despite the early improvement in surrogate outcomes such as ST segment resolution, routine thrombus aspiration did not reduce the incidence of cardiovascular death, myocardial infarction, shock, or heart failure at 1 year. Moreover, routine thrombus aspiration was associated with a potentially increased rate of stroke. Additionally, the results showed that the procedure had no benefit in patients with a high thrombus burden.

One of the key questions arising from this trial is how to account for the discordance between the surrogate outcomes and longer-term clinical outcomes. Thrombus aspiration in the TOTAL trial improved ST segment resolution and reduced the occurrence of angiographic distal embolisation.[9] In the TOTAL angiographic substudy, distal embolisation and not blush grade was independently associated with worse prognosis.[24] However, distal embolisation occurred in only 10% of patients in the PCI alone group and this surrogate endpoint was only reduced by a third with thrombus aspiration compared with PCI alone.[24] Furthermore, we did not record an improvement in the other surrogate outcomes of TIMI flow, myocardial blush grade, or the incidence of no reflow. These findings suggest that thrombus aspiration has an only modest effect on some, but not all, surrogate outcomes in the TOTAL trial, which might explain the absence of clinical benefit.

The optical coherence tomography substudy of TOTAL showed no difference between the two groups in thrombus burden before stenting at the culprit lesion site.[25] Additionally, the thrombus burden was lower than expected, suggesting that either a balloon or thrombectomy catheter were an effective method of mitigating thrombus at the culprit lesion site.

The results of TOTAL differ from those of the TAPAS trial at 1 year, which showed a benefit of thrombus aspiration. The TOTAL study is about ten times larger than the TAPAS trial, which was not designed to detect a reduction in clinical events. The benefit of thrombus aspiration reported in TAPAS was unexpected and surprisingly large, which raises the issue that the apparent difference in TAPAS could have been caused by chance. This conclusion is confirmed by the neutral results of the TASTE (n=7244) and TOTAL (n=10732) trials, both of which were specifically designed to reliably detect differences in clinical outcomes.[7,8] The findings of TOTAL are also consistent with the Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE AMI) trial,[26] which showed no difference in infarct size with routine thrombus aspiration.

The previously reported finding of increased stroke with thrombus aspiration recorded at 30 and 180 days in the TOTAL study persisted at 1 year.[9,27] A previously

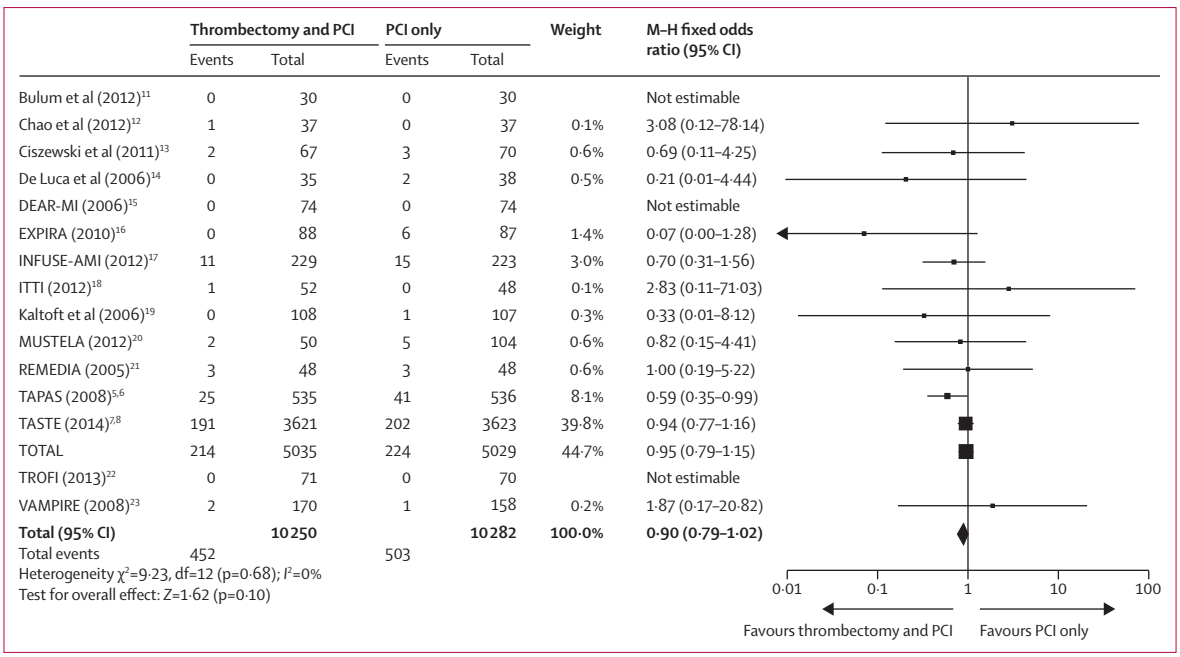

Figure 4: **All-cause death from meta-analysis of trials of manual thrombectomy**
PCI=percutaneous coronary intervention. M-H=Mantel-Haenszel. df=degrees of freedom.

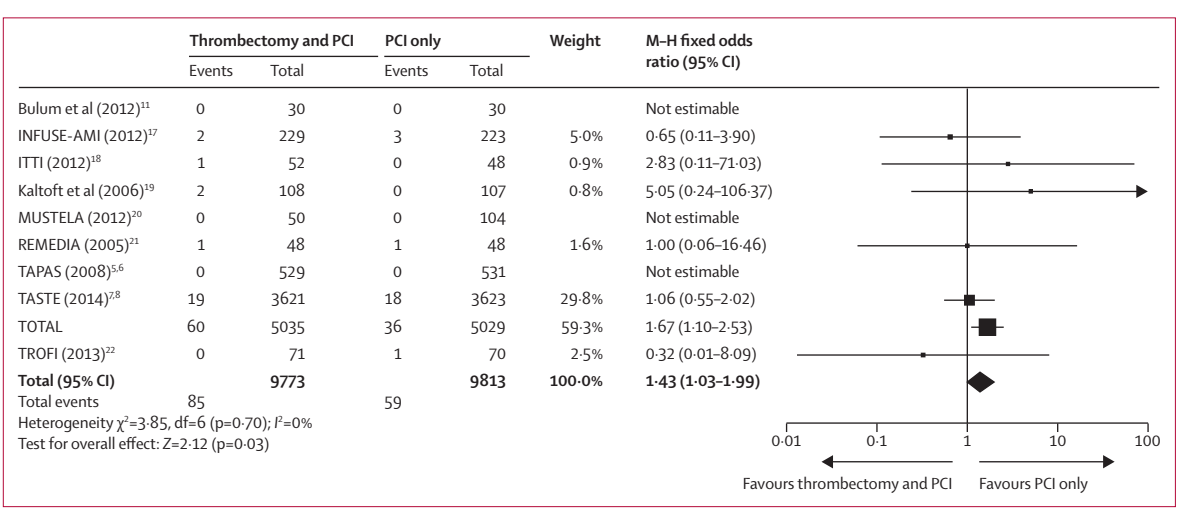

Figure 5: **Stroke from meta-analysis of trials of manual thrombectomy**
PCI=percutaneous coronary intervention. M-H=Mantel-Haenszel. df=degrees of freedom.

published detailed analysis of the strokes in the TOTAL trial showed a significant increase in strokes—mainly ischaemic—in the first 48 h.[27] A potential mechanism of stroke related to thrombectomy is embolisation of thrombus to systemic circulation during removal of the thrombectomy catheter. A landmark analysis showed no difference in late strokes beyond 180 days. Consequently, the significance at 1 year of the stroke findings are probably related to the events that accrued earlier. It could be postulated that the benefit of thrombus aspiration on surrogate outcomes did not translate into a mortality reduction in the longer term because any potential benefit was counterbalanced by the increased risk of stroke.

In the TASTE trial, stroke or neurological event rates during initial hospital admission did not differ with thrombus aspiration versus PCI alone.[7] However, TASTE was a registry-based trial that relied on discharge diagnosis codes without adjudication. Moreover, in the TAPAS trial, stroke was not a prespecified outcome and was not reported.[5,6] Conversely, the TOTAL trial is the largest trial of thrombus aspiration with significantly more power to detect differences, in which stroke was a prespecified safety outcome. In TOTAL, stroke outcomes

were recorded prospectively, with adjudication by neurologists who were masked to treatment assignment. Our updated meta-analysis of randomised trials showed a consistent significant increase in stroke with manual thrombectomy versus PCI alone (see figure 5).

In conclusion, in this large multicentre randomised trial, a strategy of routine thrombus aspiration did not reduce the composite of cardiovascular death, myocardial infarction, shock, or heart failure within 1 year compared with PCI alone. A strategy of routine thrombus aspiration might be associated with an increased rate of stroke. As a result, thrombus aspiration can no longer be recommended as a routine strategy in STEMI.

Contributors

SSJ wrote the report with critical revisions from all coauthors (JAC, SY, MJR, PG, BM, SKe, GS, RM, AG, SC, SL, KN, IB, WJC, ANC, PGS, RCW, TS, OFB, AA, RB, MKN, DH, RCML, SKa, SVR, ME-O, SRM, JLV, SP, and VD). PG did the data analysis. SSJ, VD, JAC, and SY designed the study.

Declaration of interests

SSJ has received grants from Medtronic during the conduct of the study. JAC has received grants from the Canadian Institutes of Health Research and Medtronic during the conduct of the study, and grants from Medtronic outside the submitted work. RM has received personal fees from Medtronic during the conduct of the study. AG has received personal fees and advisory board fees from AstraZeneca, and grants, meeting support, and research grants from Medronic, outside the submitted work. PGS has received personal fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck-Sharpe-Dohme, Novartis, Otsuka, Pfizer, Roche, Medtronic, Vivus, Janssen, Orexigen, and Regado; grants and personal fees from Sanofi and Servier; and personal fees and non-financial support from The Medicines Company, outside the submitted work. RCW has received personal fees from Medtronic; grants from Abbott Vascular and Edwards Lifesciences, grants and personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Jansen and BMS/Pfizer, outside the submitted work. SVR has received personal fees from Medtronic, outside the submitted work. SP has received personal fees from Medtronic, outside the submitted work. VD has received an institutional grant to conduct the trial from the TOTAL Coordinating Centre during the conduct of the study. All other coauthors declare no competing interests.

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References

1 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361:** 13–20.

2 Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J* 2002; **23:** 1112–17.

3 Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol* 2002; **39:** 591–97.

4 Buller CE, Fu Y, Mahaffey KW, et al. ST-segment recovery and outcome after primary percutaneous coronary intervention for ST-elevation myocardial infarction: insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. *Circulation* 2008; **118:** 1335–46.

5 Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; **358:** 557–67.

6 Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 2008; **371:** 1915–20.

7 Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **369:** 1587–97.

8 Lagerqvist B, Frobert O, Olivecrona GK, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014; **371:** 1111–20.

9 Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015; **372:** 1389–98.

10 Jolly SS, Cairns J, Yusuf S, et al. Design and rationale of the TOTAL trial: a randomized trial of routine aspiration ThrOmbecTomy with percutaneous coronary intervention (PCI) versus PCI ALone in patients with ST-elevation myocardial infarction undergoing primary PCI. *Am Heart J* 2014; **167:** 315–21.

11 Bulum J, Ernst A, Strozzi M. The impact of successful manual thrombus aspiration on in-stent restenosis after primary PCI: angiographic and clinical follow-up. *Coron Artery Dis* 2012; **23:** 487–91.

12 Chao CL, Hung CS, Lin YH, et al. Time-dependent benefit of initial thrombosuction on myocardial reperfusion in primary percutaneous coronary intervention. *Int J Clin Pract* 2008; **62:** 555–61.

13 Ciszewski M, Pregowski J, Teresinska A, et al. Aspiration coronary thrombectomy for acute myocardial infarction increases myocardial salvage: single center randomized study. *Catheter Cardiovasc Interv* 2011; **78:** 523–31.

14 De Luca L, Sardella G, Davidson CJ, et al. Impact of intracoronary aspiration thrombectomy during primary angioplasty on left ventricular remodelling in patients with anterior ST elevation myocardial infarction. *Heart* 2006; **92:** 951–57.

15 Silva-Orrego P, Colombo P, Bigi R, et al. Thrombus aspiration before primary angioplasty improves myocardial reperfusion in acute myocardial infarction: the DEAR-MI (Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction) study. *J Am Coll Cardiol* 2006; **48:** 1552–59.

16 Sardella G, Mancone M, Canali E, et al. Impact of thrombectomy with Export catheter in infarct-related artery during primary percutaneous coronary intervention (EXPIRA Trial) on cardiac death. *Am J Cardiol* 2010; **106:** 624–29.

17 Stone GW, Witzenbichler B, Godlewski J, et al. Intralesional abciximab and thrombus aspiration in patients with large anterior myocardial infarction: one-year results from the the INFUSE-AMI trial. *Circ Cardiovasc Interv* 2012; **6:** 527–34.

18 Liu C, Lin M, Chiu Y, et al. Additive benefit of glycoprotein IIb/IIIa inhibition and adjunctive thrombus aspiration during primary coronary intervention: results of the Initial Thrombosuction and Tirofiban Infusion (ITTI) trial. *Int J Cardiol* 2012; **156:** 174–79.

19 Kaltoft A, Bottcher M, Nielsen SS, et al. Routine thrombectomy in percutaneous coronary intervention for acute ST-segment-elevation myocardial infarction: a randomized, controlled trial. *Circulation* 2006; **114:** 40–47.

20 De Carlo M, Aquaro GD, Palmieri C, et al. A prospective randomized trial of thrombectomy versus no thrombectomy in patients with ST-segment elevation myocardial infarction and thrombus-rich lesions: MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) Trial. *JACC Cardiovasc Interv* 2012; **5:** 1223–30.

21 Burzotta F, Trani C, Romagnoli E, et al. Manual thrombus-aspiration improves myocardial reperfusion: the randomized evaluation of the effect of mechanical reduction of distal embolization by thrombus-aspiration in primary and rescue angioplasty (REMEDIA) trial. *J Am Coll Cardiol* 2005; **46:** 371–76.

22 Onuma Y, Thuesen L, van Geuns RJ, et al. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study-TROFI trial. *Eur Heart J* 2013; **34:** 1050–60.

23 Ikari Y, Sakurada M, Kozuma K, et al. Upfront thrombus aspiration in primary coronary intervention for patients with ST-segment elevation acute myocardial infarction: report of the VAMPIRE (VAcuuM asPIration thrombus REmoval) trial. *JACC Cardiovasc Interv* 2008; **1:** 424–31.

24 Overgaard CB, Sharma V, Chan W, et al. Myocardial blush and microvascular reperfusion following manual thrombectomy during PCI for STEMI: insights from the TOTAL trial. *EuroIntervention* 2015; **2015:** 15-A-OP006.

25 Bhindi R, Kajander OA, Jolly SS, et al. Culprit lesion thrombus burden after manual thrombectomy or percutaneous coronary intervention-alone in ST-segment elevation myocardial infarction: the optical coherence tomography sub-study of the TOTAL (ThrOmbecTomy versus PCI ALone) trial. *Eur Heart J* 2015; **36:** 1892–900.

26 Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 2012; **307:** 1817–26.

27 Jolly SS, Cairns JA, Yusuf S, et al. Stroke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. *Eur Heart J* 2015; **36:** 2364–72.