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Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy

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ABSTRACT

BACKGROUND

During primary percutaneous coronary intervention (PCI), manual thrombectomy may reduce distal embolization and thus improve microvascular perfusion. Small trials have suggested that thrombectomy improves surrogate and clinical outcomes, but a larger trial has reported conflicting results.

METHODS

We randomly assigned 10,732 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI to a strategy of routine upfront manual thrombectomy versus PCI alone. The primary outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within 180 days. The key safety outcome was stroke within 30 days.

RESULTS

The primary outcome occurred in 347 of 5033 patients (6.9%) in the thrombectomy group versus 351 of 5030 patients (7.0%) in the PCI-alone group (hazard ratio in the thrombectomy group, 0.99; 95% confidence interval [CI], 0.85 to 1.15; P=0.86). The rates of cardiovascular death (3.1% with thrombectomy vs. 3.5% with PCI alone; hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P=0.34) and the primary outcome plus stent thrombosis or target-vessel revascularization (9.9% vs. 9.8%; hazard ratio, 1.00; 95% CI, 0.89 to 1.14; P=0.95) were also similar. Stroke within 30 days occurred in 33 patients (0.7%) in the thrombectomy group versus 16 patients (0.3%) in the PCI-alone group (hazard ratio, 2.06; 95% CI, 1.13 to 3.75; P=0.02).

CONCLUSIONS

In patients with STEMI who were undergoing primary PCI, routine manual thrombectomy, as compared with PCI alone, did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days. (Funded by Medtronic and the Canadian Institutes of Health Research; TOTAL ClinicalTrials.gov number, NCT01149044.)

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Primary percutaneous coronary intervention (PCI), when available, is the most effective method of achieving reperfusion in patients with ST-segment elevation myocardial infarction (STEMI).[1] However, a major limitation of primary PCI is the possibility of distal embolization of thrombus and failure to restore flow at the microvascular level. Measures of microvascular tissue reperfusion, such as the degree of ST-segment resolution or angiographic myocardial blush grade, have been shown to predict the rate of death after primary PCI.[2,3]

Removal of the thrombus by manual thrombectomy before stent deployment has the potential of reducing distal embolization and improving microvascular perfusion. Small, randomized trials of thrombectomy have shown improvements in markers of tissue reperfusion.[4] The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) showed improved myocardial blush grade (the primary outcome) and lower mortality with thrombectomy.[5,6] Practice guidelines were subsequently changed to recommend routine manual thrombectomy.[7,8] As a result, thrombectomy has become a part of clinical practice and its use has grown rapidly.

After the publication of the TAPAS findings, meta-analyses suggested that thrombectomy might increase the risk of stroke, but this finding was cautiously interpreted because it was based on small numbers of events.[9] Subsequently, the recent large Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial showed no reduction in mortality at 30 days or 1 year with routine thrombectomy.[10,11] Although an updated meta-analysis of thrombectomy that included the TASTE trial continued to suggest that a modest but clinically important benefit is possible,[12] the efficacy of this procedure remains uncertain.

Methods

Study Design

The Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) was an international, investigator-initiated, multicenter, prospective, randomized trial of upfront manual aspiration thrombectomy with the Export catheter (Medtronic) versus PCI alone. This was an open trial with blinded adjudication of outcomes. The trial design was published previously.[13]

The study was approved by the ethics committee at each participating center and by national regulatory authorities where required. The academic steering committee designed the trial protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring committee oversaw the safety of the trial. The Population Health Research Institute, a joint institute of McMaster University and Hamilton Health Sciences, conducted and coordinated the trial and also collected and held all trial data. The trial statisticians conducted all analyses (for details, see the Supplementary Appendix, available at NEJM.org). The trial's principal investigators vouch for the integrity and completeness of the data and analyses, as well as for the fidelity of this report to the trial protocol, and made the decision to submit the manuscript for publication. One of the principal investigators prepared the first draft of the manuscript, which was then reviewed and edited by the coauthors.

Funding was provided by Medtronic and the Canadian Institutes of Health Research (CIHR) and the Canadian Network and Centre for Trials Internationally, an initiative funded by the CIHR. Medtronic agreed to provide funding on the basis of a review of the protocol developed by the steering committee and to increase funding on the basis of the steering committee's justifications for an increased sample size; company representatives also reviewed the analyses conducted by the trial statisticians and had the right to review but not to provide or deny approval of the final manuscript.

Patients and Randomization

Patients with STEMI who were referred for primary PCI within 12 hours after the onset of symptoms were eligible to participate in the trial. Patients who had undergone previous coronary-artery bypass grafting or those who had received fibrinolytic therapy were not eligible. (See Table S1 in the Supplementary Appendix for detailed inclusion and exclusion criteria.) All patients provided written informed consent.

Eligible patients were randomly assigned in a 1:1 ratio to undergo either thrombus aspiration

followed by PCI or PCI alone. Randomization was performed with the use of permuted blocks with stratification according to study center with the use of a 24-hour computerized central system located at the Population Health Research Institute. All patients and investigators were aware of study-group assignments.

THROMBECTOMY PROCEDURE

The study protocol and investigator guidance documents specified standard procedures for thrombectomy. After the lesion was crossed with a guidewire, the thrombectomy device was to be advanced and suction started before it crossed the lesion. If the operator was unable to cross the lesion with the thrombectomy catheter, predilation with a small-diameter balloon was to be performed, followed by another attempt at thrombectomy. It was recommended that the guide catheter be fully engaged with the coronary ostium during removal of the thrombectomy catheter in order to avoid embolizing thrombus to the systemic vasculature. After thrombectomy, the guide catheter was to be aspirated to ensure removal of air or thrombus. Locally approved Export aspiration catheters (6 or 7 French), including the XT, AP, and ADVANCE, were to be used for the thrombectomy procedure. The PCI procedure was performed after thrombus aspiration was completed.

PCI ALONE

The PCI-alone group underwent the procedure according to the operator's usual technique without thrombectomy. Bailout thrombectomy was allowed if there was failure of the initial PCI-alone strategy, defined as either Thrombolysis in Myocardial Infarction (TIMI) flow of 0 or 1 (on a scale of 0 to 3, with a higher grade indicating better flow) with a large thrombus after balloon predilation or the persistence of a large thrombus after stent deployment.

STUDY OUTCOMES

The primary efficacy outcome was death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or new or worsening New York Heart Association (NYHA) class IV heart failure within 180 days. Key secondary outcomes were the primary efficacy outcome plus stent thrombosis or target-vessel revascularization within 180 days and cardiovascular death within 180 days. The key safety outcome was stroke within 30 days, and the key net-benefit outcome was the occurrence of the primary outcome or stroke within 180 days.

A central committee whose members were unaware of study-group assignments adjudicated all the primary-outcome events, strokes, transient ischemic attacks, major bleeding, target-vessel revascularization, and stent thromboses. Detailed outcome definitions have been reported previously[13] (Table S2 in the Supplementary Appendix).

ST-segment resolution and angiographic outcomes were reported by investigators. Core laboratory analyses of electrocardiographic and angiographic data are ongoing and not yet available. The angiographic core laboratory assessed thrombus grade in a subgroup of patients for quality assurance; details of this process are available in the Supplementary Appendix.

SUBGROUP ANALYSES

Since we had hypothesized that thrombectomy would be more beneficial among patients with a high thrombus burden, the main subgroup analysis was based on the TIMI thrombus grade (grade <3 vs. grade ≥3), which was determined after the first injection of contrast material in the infarct-related artery before wire crossing. Other prespecified subgroups included TIMI thrombus grade (grade <4 vs. grade ≥4), symptom onset (<6 hours vs. 6 to 12 hours), initial TIMI flow (0 to 1 vs. 2 to 3), age (≤65 years vs. >65 years), centers divided into three groups of volume of primary PCI procedures, and type of myocardial infarction (anterior vs. nonanterior).

STATISTICAL ANALYSIS

According to the original sample-size calculations, which were based on a rate of the primary outcome of 14% at 180 days, we estimated that 4000 patients would be required for the study to have a power of 80% to detect a relative reduction of 25% in risk. On the basis of a blinded interim analysis showing an overall event rate of 7%, we estimated that 10,700 patients would be needed for 718 primary outcome events to occur, which would provide a power of 80% to detect a relative reduction of 20% in risk. The sample size was increased without knowledge of any treatment effects.

For the primary analysis, a modified inten-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Thrombectomy (N=5033)	PCI alone (N=5030)
Age		
Mean ±SD — yr	61.0±11.8	61.0±11.9
Older than 75 yr — no. (%)	666 (13.2)	630 (12.5)
Male sex — no. (%)	3864 (76.8)	3933 (78.2)
Killip heart failure ≥2 at entry — no. (%)	219 (4.4)	210 (4.2)
Location of myocardial infarction — no./total no. (%)		
Anterior	1961/5027 (39.0)	2055/5026 (40.9)
Inferior	2807/5027 (55.8)	2710/5026 (53.9)
Lateral or other	259/5027 (5.2)	261/5026 (5.2)
Medical history — no. (%)		
Current smoker	2245 (44.6)	2353 (46.8)
Hypertension	2533 (50.3)	2516 (50.0)
Diabetes mellitus	919 (18.3)	936 (18.6)
Previous myocardial infarction	463 (9.2)	446 (8.9)
Previous percutaneous coronary intervention	416 (8.3)	423 (8.4)

* There were no significant differences between the groups in the listed categories except for smoking (P=0.03). PCI denotes percutaneous coronary intervention.

tion-to-treat analysis was prespecified to include only patients who had undergone randomization and primary PCI. Data were to be analyzed in the treatment group to which patients were originally assigned. Patients who had not undergone PCI for the index STEMI (e.g., those with normal coronary arteries) were not included in the primary analysis. Other prespecified sensitivity analyses included full intention-to-treat, as-treated, and per-protocol analyses. In the as-treated analysis, all patients who underwent thrombectomy (either upfront or bailout), regardless of their study-group assignment, were compared with patients who had undergone PCI without thrombectomy. The per-protocol analysis included all patients who had undergone PCI and did not cross over from their initial study-group assignment to the alternative therapy.

We used a two-sided, log-rank test to compare the two groups; a P value of less than 0.05 was considered to indicate statistical significance. We used a Cox proportional-hazards regression model with the treatment group as the predictor variable to estimate hazard ratios and 95% confidence intervals.

RESULTS

PATIENT AND PROCEDURE CHARACTERISTICS

From August 2010 through July 2014, a total of 10,732 patients were enrolled at 87 hospitals in 20 countries; 5372 patients were assigned to undergo thrombectomy followed by PCI, and 5360 were assigned to undergo PCI alone (Fig. S1 in the Supplementary Appendix). Of these patients, 10,063 (93.8%) underwent PCI for the index STEMI (5033 in the thrombectomy group and 5030 in the PCI-alone group) and were included in the primary analysis. The rate of crossover was 4.6% (230 patients) from thrombectomy to PCI alone and 1.4% (69 patients) from PCI alone to thrombectomy. Bailout thrombectomy was performed in 355 patients (7.1%) in the PCI-alone group.

Baseline characteristics were well balanced between the two groups except for the proportion of smokers, which was lower in the thrombectomy group (44.6% vs. 46.8%, P=0.03) (Table 1) and the interval from symptom onset to hospital arrival, which was longer in the thrombectomy group (128 vs. 120 minutes, P=0.02) (Table 2). The majority of patients (78.4%) had a high thrombus burden, as defined by TIMI thrombus grade 4 or 5, with similar proportions in the two groups.

The rate of use of glycoprotein IIb/IIIa inhibitors was lower in the thrombectomy group than in the PCI-alone group (37.4 vs. 41.4%, P<0.001). Direct stenting was performed more frequently in the thrombectomy group (38.3% vs. 21.3%, P<0.001). The PCI procedure time was longer in the thrombectomy group (39 minutes vs. 35 minutes, P<0.001). In the thrombectomy group, success in crossing the target lesion with the Export catheter at first attempt was observed in 82.5% of patients and in an additional 5.9% after balloon predilation. The use of evidence-based therapies at discharge was similar in the two groups (Table S3 in the Supplementary Appendix).

ELECTROCARDIOGRAPHIC AND ANGIOGRAPHIC OUTCOMES

The rate of incomplete ST-segment resolution (less than 70%) was 27.0% in the thrombectomy group versus 30.2% in PCI-alone group (P<0.001). Rates of TIMI 3 flow after PCI were the same (93.1%) in the two groups (P=0.12), and were similar for no-reflow rates on angiography (2.4% vs. 2.8%, P=0.28). The rate of distal embolization was reduced with thrombectomy (1.6% vs. 3.0%,

Table 2. Study Procedures.*

Procedure	Thrombectomy (N=5033)	PCI Alone (N=5030)
Transported by ambulance — no. (%)†	3247 (64.5)	3388 (67.4)
Initial PCI procedure		
Time from symptom onset to hospital arrival — min‡	128	120
Time from hospital door to procedure — min	53.0	53.0
Radial access — no. (%)	3435 (68.2)	3430 (68.2)
Sheath size — no./total no. (%)		
≤5 French§	42/5022 (0.8)	124/5022 (2.5)
6 French¶	4857/5022 (96.7)	4793/5022 (95.4)
7 French	123/5022 (2.4)	105/5022 (2.1)
Medication use — no. (%)		
Unfractionated heparin	4065 (80.8)	4105 (81.6)
Bivalirudin	940 (18.7)	871 (17.3)
Enoxaparin	415 (8.2)	425 (8.4)
Glycoprotein IIb/IIIa inhibitor		
Upfront¶	1140 (22.7)	1274 (25.3)
Bailout (%)	741 (14.7)	806 (16.0)
Initial TIMI thrombus grade — no. (%)‖		
0: no thrombus present	115 (2.3)	145 (2.9)
1: possible thrombus present	219 (4.4)	264 (5.2)
2: definite thrombus present, <0.5× vessel diameter	126 (2.5)	129 (2.6)
3: definite thrombus present, 0.5–2.0× vessel diameter	611 (12.1)	498 (9.9)
4: definite thrombus present, >2.0× vessel diameter	690 (13.7)	685 (13.6)
5: total occlusion	3270 (65.0)	3298 (65.6)
Missing data	2 (<0.1)	7 (0.1)
TIMI 0 flow before PCI — no./total no. (%)**	3299/4973 (66.3)	3371/4969 (67.8)
Upfront manual thrombectomy — no. (%)	4803 (95.4)	69 (1.4)
Bailout thrombectomy — no. (%)	0	355 (7.1)
Use of stenting		
Direct stenting — no. (%)§	1928 (38.3)	1071 (21.3)
Type of stent — no. (%)		
Bare-metal	2636 (52.4)	2626 (52.2)
Drug-eluting	2248 (44.7)	2264 (45.0)
No. of stents	1.4±0.7	1.4±0.7
Total stent length — mm	21.5±6.6	21.4±6.4
Stent diameter — mm	3.1±0.5	3.1±0.5
Median PCI procedure time (IQR) — min§	39 (29–53)	35 (26–50)
Other surgical procedure — no. (%)		
Coronary-artery bypass grafting	136 (2.7)	139 (2.8)
Intraaortic balloon pump	96 (1.9)	110 (2.2)

* Plus–minus values are means ±SD. IQR denotes interquartile range, and TIMI Thrombolysis in Myocardial Infarction.
† P=0.003.
‡ P=0.02.
§ P<0.001.
¶ P=0.001.
‖ The thrombus grade is measured as the largest dimension of the thrombus as compared with the diameter of the vessel in which it occurs.
** TIMI flow is graded on a scale of 0 to 3, with a higher grade indicating better flow.

Table 3. Primary and Secondary Outcomes.

Outcome	Thrombectomy (N=5033)	PCI Alone (N=5030)	Hazard Ratio (95% CI)*	P Value
	no. (%)			
Primary outcome within 180 days: cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure	347 (6.9)	351 (7.0)	0.99 (0.85–1.15)	0.86
Cardiovascular death within 180 days	157 (3.1)	174 (3.5)	0.90 (0.73–1.12)	0.34
Recurrent myocardial infarction within 180 days	99 (2.0)	92 (1.8)	1.07 (0.81–1.43)	0.62
Cardiogenic shock within 180 days	92 (1.8)	100 (2.0)	0.92 (0.69–1.22)	0.56
NYHA class IV heart failure within 180 days	98 (1.9)	90 (1.8)	1.09 (0.82–1.45)	0.57
Cardiovascular death, recurrent myocardial infarction, cardiogenic shock, NYHA class IV heart failure, stent thrombosis, or target-vessel revascularization within 180 days	497 (9.9)	494 (9.8)	1.00 (0.89–1.14)	0.95
Stent thrombosis within 180 days	77 (1.5)	87 (1.7)	0.88 (0.65–1.20)	0.42
Definite stent thrombosis within 180 days	64 (1.3)	68 (1.4)	0.94 (0.67–1.32)	0.72
Target-vessel revascularization within 180 days	225 (4.5)	218 (4.3)	1.03 (0.85–1.24)	0.77
Major bleeding within 180 days	79 (1.6)	77 (1.5)	1.02 (0.75–1.40)	0.89
Key safety outcome: stroke within 30 days	33 (0.7)	16 (0.3)	2.06 (1.13–3.75)	0.02
Net-benefit outcome within 180 days: cardiovascular death, recurrent myocardial infarction, cardiogenic shock, NYHA class IV heart failure, or stroke	377 (7.5)	364 (7.2)	1.04 (0.90–1.20)	0.64

* Hazard ratios are for the thrombectomy group as compared with the PCI-alone group. NYHA denotes New York Heart Association.

P<0.001). There were no significant between-group differences in target-vessel dissection, left main coronary-artery dissection, or thrombus embolization to the left main coronary artery.

EFFICACY AND SAFETY

The rate of the primary outcome of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days in patients who underwent PCI for index STEMI was 6.9% in the thrombectomy group versus 7.0% in the PCI-alone group (hazard ratio in the thrombectomy group, 0.99; 95% confidence interval [CI], 0.85 to 1.15; P=0.86) (Table 3 and Fig. 1A). The secondary outcome of a combination of the primary outcome and stent thrombosis or target-vessel revascularization within 180 days occurred in 9.9% of patients in the thrombectomy group and 9.8% of patients in PCI-alone group (hazard ratio, 1.00; 95% CI, 0.89 to 1.14; P=0.95).

Cardiovascular mortality was similar in the two groups within 30 days (2.3% with thrombectomy vs. 2.8% with PCI alone; hazard ratio, 0.83; 95% CI, 0.65 to 1.06; P=0.13) and within 180 days (3.1% vs. 3.5%; hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P=0.34), as were the other components of the primary and secondary outcomes and major bleeding (Table 3, and Table S4 in the Supplementary Appendix).

Within 30 days, stroke occurred in 0.7% of patients in the thrombectomy group and 0.3% of the patients in the PCI-alone group (hazard ratio, 2.06; 95% CI, 1.13 to 3.75; P=0.02). Within 180 days, stroke occurred in 52 patients (1.0%) in the thrombectomy group and 25 patients (0.5%) in the PCI-alone group (hazard ratio, 2.08; 95% CI, 1.29 to 3.35; P=0.002) (Fig. 1B). The rate of the net-benefit outcome (the primary outcome plus stroke within 180 days) was similar in the two groups (Table 3).

The results of the intention-to-treat, as-treated, and per-protocol analyses were consistent

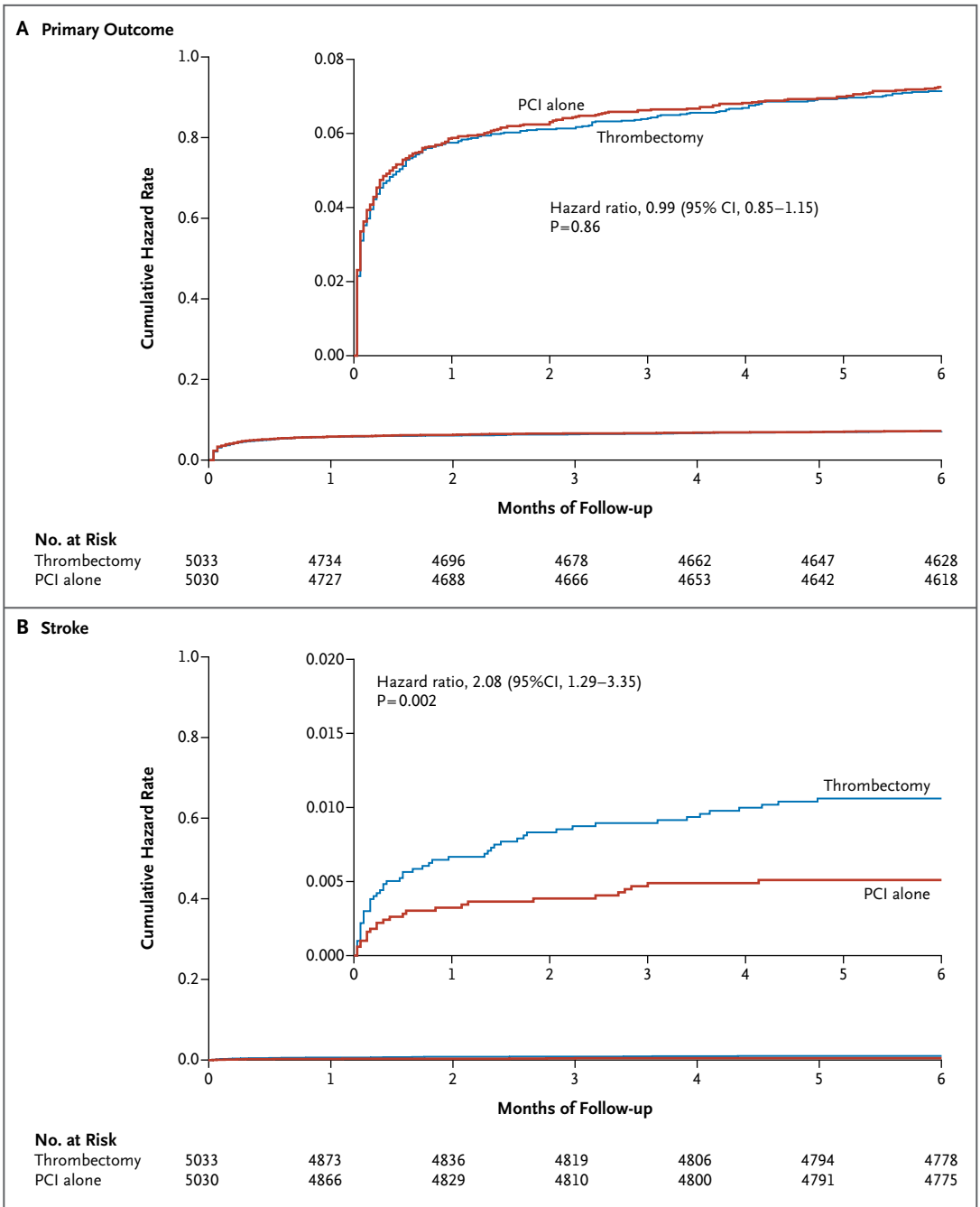

Figure 1. Kaplan–Meier Estimates for the Primary Outcome and Stroke at 180 Days.

Shown are the cumulative hazard rates of the primary outcome (death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV heart failure) (Panel A) and stroke (Panel B) in the thrombectomy group and the percutaneous coronary intervention (PCI)–alone group within 180 days after the procedure. In each panel, the inset shows a more detailed view of the same data up to a probability of 0.08 in Panel A and 0.020 in Panel B.

Subgroup	No. of Patients	Thrombectomy	PCI Alone	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Overall	10,063	347/5033 (6.9)	351/5030 (7.0)	0.99 (0.85–1.15)	
TIMI thrombus grade					0.26
≥3	9,052	322/4571 (7.0)	329/4481 (7.3)	0.96 (0.82–1.12)	
<3	998	24/460 (5.2)	21/538 (3.9)	1.35 (0.75–2.43)	
TIMI thrombus grade					0.52
≥4	7,943	289/3960 (7.3)	300/3983 (7.5)	0.97 (0.82–1.14)	
<4	2,107	57/1071 (5.3)	50/1036 (4.8)	1.11 (0.76–1.62)	
Symptom onset					0.66
<6 hr	8,375	274/4159 (6.6)	278/4216 (6.6)	1.00 (0.84–1.18)	
6–12 hr	1,665	70/862 (8.1)	71/803 (8.8)	0.92 (0.66–1.28)	
Initial TIMI flow					0.22
0–1	7,443	273/3699 (7.4)	291/3744 (7.8)	0.95 (0.80–1.12)	
2–3	2,519	72/1282 (5.6)	58/1237 (4.7)	1.21 (0.85–1.70)	
Site PCI volume					0.66
Lower third	2,450	90/1229 (7.3)	97/1221 (7.9)	0.92 (0.69–1.22)	
Middle third	2,139	78/1077 (7.2)	69/1062 (6.5)	1.12 (0.81–1.55)	
Upper third	5,474	179/2727 (6.6)	185/2747 (6.7)	0.97 (0.79–1.20)	
Myocardial infarction type					0.77
Anterior	4,016	176/1961 (9.0)	188/2055 (9.1)	0.98 (0.80–1.20)	
Nonanterior	6,037	171/3066 (5.6)	162/2971 (5.5)	1.02 (0.82–1.27)	
Age					0.36
≤65 yr	6,662	156/3354 (4.7)	143/3308 (4.3)	1.08 (0.86–1.35)	
>65 yr	3,401	191/1679 (11.4)	208/1722 (12.1)	0.94 (0.77–1.14)	

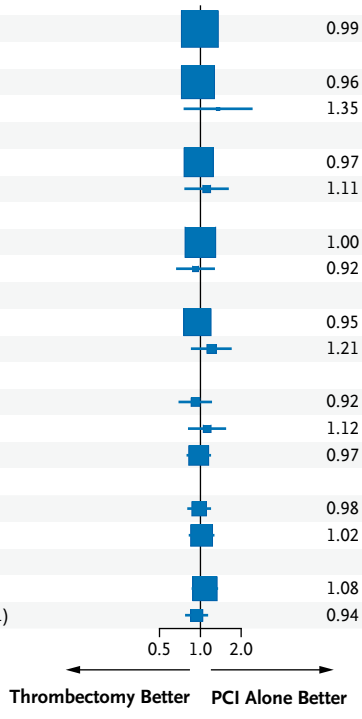

Figure 2. Forest Plot of the Primary Outcome in Prespecified Subgroups.

With the use of the Thrombolysis in Myocardial Infarction (TIMI) grading system, patients were categorized according whether the largest dimension of the thrombus was 0.5 to 2.0 times the diameter of the vessel (grade 3) or more than 2.0 times the diameter (grade 4). TIMI flow was graded on a scale of 0 to 3, with a higher grade indicating better flow. The size of the squares is proportional to the number of patients.

with those of the primary analysis (Table S5 in the Supplementary Appendix). The primary outcome within 180 days was consistent across all prespecified subgroups, including patients who had high thrombus burden (Fig. 2).

DISCUSSION

In our trial, a strategy of routine manual thrombectomy during primary PCI did not reduce the risk of the primary outcome of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days, as compared with a strategy of PCI alone with thrombectomy permitted only as bailout. This finding was consistent in patients with a high thrombus burden, the group that might be expected to have the most benefit from thrombus aspiration. Stroke rates were higher in patients who had undergone routine thrombectomy than in those who underwent PCI alone.

The findings of our trial with regard to the efficacy of thrombectomy are consistent with those of the TASTE trial and the Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial.[10,14] Our study was the largest of these three trials and thus had the most power to detect a benefit, since it was designed to detect a relative reduction of 20% in the risk of the composite primary outcome. In addition, our trial, unlike the TASTE trial, used detailed event definitions, and the outcomes were adjudicated in a blinded fashion by an independent central committee rather than relying on registry data.

The improvements in ST-segment resolution and distal embolization that were observed with

manual thrombectomy in our trial did not translate into clinical benefits. This finding cautions against changing practice on the basis of trials showing an improvement in surrogate outcomes. In addition, although our results for ST-segment resolution are consistent with those of the substantially smaller TAPAS trial,[5] we did not confirm their finding of a reduction in cardiac mortality,[6] a result that emphasizes the importance of conducting large, multicenter trials to verify findings of smaller trials.

In TOTAL, stroke was a prespecified safety outcome because previous meta-analyses had suggested an increased risk of stroke with thrombectomy,[9] and we indeed found a higher rate of stroke among patients in the thrombectomy group. It may be hypothesized that if the primary mechanism of stroke were embolization of thrombus or air to the brain during the procedure, then the excess strokes would have occurred predominantly within 24 hours after the procedure or at least during the initial hospitalization. Therefore, our finding of a continued increase in the rate of stroke between 30 and 180 days cannot be easily explained. We cannot completely rule out the play of chance as the explanation for our findings with respect to stroke, given the relatively small number of events.

The TASTE trial showed no difference in stroke rates (0.5% vs. 0.5%), but strokes were reported only during the initial hospitalization.[10] Further data from the TASTE trial regarding stroke rates at 30 and 180 days will be important. In our study, the rates of stroke in both groups (1.0% in the thrombectomy group and 0.5% in the PCI-alone group at 180 days) are consistent with those observed in previous studies (ranging from 1.3 to 2.0%).[15,16]

Several limitations of our study should be taken into account. First of all, the treating interventional cardiologists were aware of study-group assignments, which could have led to biases in management. For example, the lack of blinding may account for the lower rate of use of glycoprotein IIb/IIIa inhibitors in the thrombectomy group; however, this difference is quite modest and unlikely to have had an effect on the outcomes of the trial.

Second, the inclusion of some patients with a low thrombus burden may have resulted in a patient population that would be less responsive to thrombectomy. However, we observed similar outcomes regardless of the initial thrombus burden. We did not reclassify the TIMI thrombus grade after wire crossing or small-diameter balloon inflation. We therefore cannot exclude a benefit of thrombectomy in patients with a persistent thrombus burden after wire crossing. However, in the TASTE trial, investigators graded the thrombus burden after wire crossing and did not observe a benefit for manual thrombectomy in such patients.[10]

Third, our trial evaluated a strategy of routine upfront thrombectomy versus PCI alone with thrombectomy reserved as bailout; it did not study the effect of selective use of thrombectomy versus no thrombectomy. Finally, there was no systematic collection of screening logs, so we cannot provide the number or characteristics of patients who were screened for inclusion as compared with those who underwent randomization.

In conclusion, in patients with STEMI who were undergoing PCI, a strategy of routine manual thrombectomy did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or class IV heart failure within 180 days, as compared with a strategy of PCI alone with only bailout thrombectomy. Routine thrombectomy was associated with an increased rate of stroke within 30 days.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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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. 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.
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; 39:591-7.
4. De Luca G, Dudek D, Sardella G, Marino P, Chevalier B, Zijlstra F. Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. Eur Heart J 2008;29: 3002-10.
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. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205-41. [Erratum, J Am Coll Cardiol 2009;54:2464.]
8. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.
9. Tamhane UU, Chetcuti S, Hameed I, Grossman PM, Moscucci M, Gurm HS. Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for acute ST elevation MI: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2010;10:10.
10. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587-97. [Erratum, N Engl J Med 2014;371:786.]
11. Lagerqvist B, Fröbert O, Olivecrona GK, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. N Engl J Med 2014;371:1111-20.
12. Kumbhani DJ, Bavry AA, Desai MY, et al. Aspiration thrombectomy in patients undergoing primary angioplasty: totality of data to 2013. Catheter Cardiovasc Interv 2014;84:973-7.
13. 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.
14. 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.
15. Guptill JT, Mehta RH, Armstrong PW, et al. Stroke after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction: timing, characteristics, and clinical outcomes. Circ Cardiovasc Interv 2013;6:176-83.
16. Budaj A, Flasinska K, Gore JM, et al. Magnitude of and risk factors for in-hospital and postdischarge stroke in patients with acute coronary syndromes: findings from a Global Registry of Acute Coronary Events. Circulation 2005;111:3242-7.