Thrombus Aspiration in ST-Segment–Elevation Myocardial Infarction

An Individual Patient Meta-Analysis: Thrombectomy Trialists Collaboration

BACKGROUND: Thrombus aspiration during percutaneous coronary intervention (PCI) for the treatment of ST-segment–elevation myocardial infarction (STEMI) has been widely used; however, recent trials have questioned its value and safety. In this meta-analysis, we, the trial investigators, aimed to pool the individual patient data from these trials to determine the benefits and risks of thrombus aspiration during PCI in patients with ST-segment–elevation myocardial infarction.

METHODS: Included were large (n≥1000), randomized, controlled trials comparing manual thrombectomy and PCI alone in patients with ST-segment–elevation myocardial infarction. Individual patient data were provided by the leadership of each trial. The prespecified primary efficacy outcome was cardiovascular mortality within 30 days, and the primary safety outcome was stroke or transient ischemic attack within 30 days.

RESULTS: The 3 eligible randomized trials (TAPAS [Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction], TASTE [Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia], and TOTAL [Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI]) enrolled 19 047 patients, of whom 18 306 underwent PCI and were included in the primary analysis. Cardiovascular death at 30 days occurred in 221 of 9155 patients (2.4%) randomized to thrombus aspiration and 262 of 9151 (2.9%) randomized to PCI alone (hazard ratio, 0.84; 95% confidence interval, 0.70–1.01; *P*=0.06). Stroke or transient ischemic attack occurred in 66 (0.8%) randomized to thrombus aspiration and 46 (0.5%) randomized to PCI alone (odds ratio, 1.43; 95% confidence interval, 0.98–2.10; *P*=0.06). There were no significant differences in recurrent myocardial infarction, stent thrombosis, heart failure, or target vessel revascularization. In the subgroup with high thrombus burden (TIMI [Thrombolysis in Myocardial Infarction] thrombus grade ≥3), thrombus aspiration was associated with fewer cardiovascular deaths (170 [2.5%] versus 205 [3.1%]; hazard ratio, 0.80; 95% confidence interval, 0.65–0.98; *P*=0.03) and with more strokes or transient ischemic attacks (55 [0.9%] versus 34 [0.5%]; odds ratio, 1.56; 95% confidence interval, 1.02–2.42, *P*=0.04). However, the interaction *P* values were 0.32 and 0.34, respectively.

CONCLUSIONS: Routine thrombus aspiration during PCI for ST-segment–elevation myocardial infarction did not improve clinical outcomes. In the high thrombus burden group, the trends toward reduced cardiovascular death and increased stroke or transient ischemic attack provide a rationale for future trials of improved thrombus aspiration technologies in this high-risk subgroup.

CLINICAL TRIAL REGISTRATION: URLs: http://www.ClinicalTrials.gov http://www.crd.york.ac.uk/prospero/. Unique identifiers: NCT02552407 and CRD42015025936.

Sanjit S. Jolly, MD, MSc
Stefan James, MD, PhD
Vladimír Džavík, MD
John A. Cairns, MD
Karim D. Mahmoud, MD, PhD
Felix Zijlstra, MD, PhD
Salim Yusuf, MBBS, DPhil
Goran K. Olivecrona, MD, PhD
Henrik Renlund, PhD
Peggy Gao, MSc
Bo Lagerqvist, MD, PhD
Ashraf Alazzoni, MD
Sasko Kedev, MD, PhD
Goran Stankovic, MD
Brandi Meeks, MEng
Ole Frøbert, MD, PhD

Correspondence to: Sanjit S. Jolly, MD, MSc, Room C3 118, CVSRI Bldg, Hamilton General Hospital, 237 Barton Street E, Hamilton, ON, Canada L8L 2X2. E-mail sanjit.jolly@phri.ca

Sources of Funding, see page 151

Key Words: meta-analysis [publication type] ■ myocardial infarction ■ thrombectomy

Clinical Perspective

What Is New?

- This is an individual patient meta-analysis of >18 000 patients with ST-segment–elevation myocardial infarction randomized to thrombus aspiration versus percutaneous coronary intervention alone.
- As a routine strategy, thrombus aspiration did not reduce cardiovascular mortality for patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention.
- An exploratory analysis of patients with high thrombus burden suggests that thrombus aspiration may improve cardiovascular mortality but at the price of an increased risk of stroke or transient ischemic attack.

What Are the Clinical Implications?

- Thrombus aspiration should not be used as a routine strategy in patients with ST-segment–elevation myocardial infarction.
- Further larger, randomized trials are needed to determine whether improved forms of thrombus aspiration can reduce cardiovascular mortality and to determine its safety with regard to stroke.

The optimal treatment for ST-segment–elevation myocardial infarction (STEMI) is rapid reperfusion with timely primary percutaneous coronary intervention (PCI) if available.[1] However, one of the limitations of primary PCI is embolization of thrombus distally and microvascular occlusion, associated with markedly increased mortality.[2] Thrombus aspiration was thought to be a simple method to remove thrombus before stent deployment, thereby reducing distal embolization and improving outcomes.

Thrombus aspiration became part of routine practice on the basis of the promising results of an early trial.[3,4] However, the results of recent, larger, multicenter trials have created uncertainty about the benefit of thrombus aspiration and suggested possible harm from increased stroke risk.[5–9] None of the individual trials were powered to detect a modest (eg, 20%) reduction in mortality or low-frequency events such as stroke. Accordingly, we undertook an individual patient–level meta-analysis to determine the effect of thrombus aspiration on 30-day cardiovascular mortality and stroke or transient ischemic attack (TIA).

METHODS

The meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines for individual patient data meta-analyses.[10] The protocol was finalized and registered with PROSPERO (international register of systematic reviews, CRD42015025936) and ClinicalTrials.gov (NCT02552407) before unblinding or any data analysis. Large, randomized trials (recruiting ≥1000 patients) that compared manual thrombus aspiration plus PCI and PCI alone in patients with STEMI were eligible. Only large, randomized trials were included because small trials are more susceptible to publication bias and tend to be lower quality. A comprehensive search strategy was used for Medline, EMBASE, and Cochrane Central Register of Controlled Trials on September 2, 2016, with no language restriction (online-only Data Supplement).

Authors of eligible trials collaboratively shared individual patient–level data. The databases from the individual trials were merged into a dedicated SAS file set up for the present study. Data sets were rigorously reviewed for completeness and consistency to ensure that no errors had occurred in reformatting of the data and to ensure agreement with the original publications. Any differences were resolved by queries within the collaborative group. Variables were not defined according to identical criteria in the studies, but common definitions were defined by consensus within the author group whenever possible. The online-only Data Supplement provides details on outcomes variables. The TAPAS trial [Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction] did not prospectively collect stroke or TIA data and was not included for this outcome. Outcomes were not adjudicated in TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and were obtained from discharge diagnoses in administrative databases and the death registry. The risk of bias was assessed with the Cochrane Collaboration tool (Figure I in the online-only Data Supplement).

The 3 individual trials (TASTE, TAPAS, and TOTAL [Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI) were each approved by an institutional review committee, and participants provided informed consent.

Study Organization

All data were merged at the Uppsala Clinical Research Center (Uppsala, Sweden), and analyses were performed with R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). Kaplan-Meier curves and forest plot figures were created at the Population Health Research Institute (Hamilton, ON, Canada) with S-PLUS (TIBCO Software Inc, Palo Alto, CA).

Statistical Analysis

For baseline characteristics, the Wilcoxon rank-sum test was used for continuous variables and the Pearson χ^2 test for categorical variables. The prespecified primary efficacy outcome was cardiovascular death at 30 days. The prespecified primary safety outcome was stroke or TIA at 30 days. The prespecified primary analysis was a modified intention-to-treat analysis that included all randomized patients who had undergone emergency PCI for STEMI, with all analyses conducted according to the originally allocated study group. Patients who did not undergo PCI for STEMI (ie, normal coronary arteries) were not included in the primary analysis. A fixed-effect model was used. Study level was used as a covariate in analyses, and study-level interaction *P* values were reported.

A value of $P<0.05$ was considered statistically significant. Hazard ratios and their 95% confidence intervals (CIs) were estimated with a Cox proportional hazards regression model

with treatment group as the predictor variable, and *P* values from Cox regression were used. For the outcome of stroke or TIA, the exact time of event was not available during initial hospitalization in the TASTE trial, so logistic regression was used for significance testing and to calculate odds ratios and 95% CIs with treatment group as the predictor variable.

Subgroup Analyses

We hypothesized that thrombus aspiration might be more effective in patients with higher thrombus burden. Accordingly, prespecified subgroup analyses were performed comparing TIMI (Thrombolysis in Myocardial Infarction) thrombus grade <3 with ≥3 and grade <4 with ≥4. Additional prespecified subgroup analyses were based on time from symptom onset (<6 versus 6–12 versus >12 hours), initial TIMI flow (grade 0–1 versus 2–3), lesion location (proximal versus nonproximal vessel), tertiles of site primary PCI volume, and use of a glycoprotein IIb/IIIa inhibitor. Statistical interactions were evaluated at a significance level of 0.05 with no adjustment made for multiple comparisons.

RESULTS

Of the 19 047 patients enrolled in the 3 randomized trials, 18 306 underwent PCI and were included in the primary analysis (Figure 1). The individual trials (Table I and Figures II and III in the online-only Data Supplement) included were the TAPAS (n=1071),[4] TASTE (n=7244),[11] and TOTAL (n=10 732).[7] These 3 large trials accounted for 19 047 patients of 22 057 patients enrolled in manual thrombus aspiration trials.

Baseline characteristics were well balanced except that the proportion of smokers was smaller in the thrombus aspiration group (39.9% versus 42.4%; *P*<0.001; Table 1) and the interval from symptom onset to hospital arrival was longer in the thrombus aspiration group (190 versus 185.5 minutes; *P*=0.025; Table 1). The majority of patients had TIMI grade 0 or 1 flow in the infarct artery at baseline.

In the thrombus aspiration group, direct stenting was more frequent (39.5% versus 21.1%; *P*<0.001) and glycoprotein IIb/IIa use was slightly lower (32.3% versus 35.1%; *P*<0.001). The rate of crossover from assigned thrombus aspiration to PCI alone was 5.5% and from PCI alone to thrombus aspiration was 6.8%. Fluoroscopy time was slightly longer with thrombus aspiration (13.2 versus 12.3 minutes; *P*<0.001; Table 1). Stent length, stent diameter, and number of stents were not different between the groups.

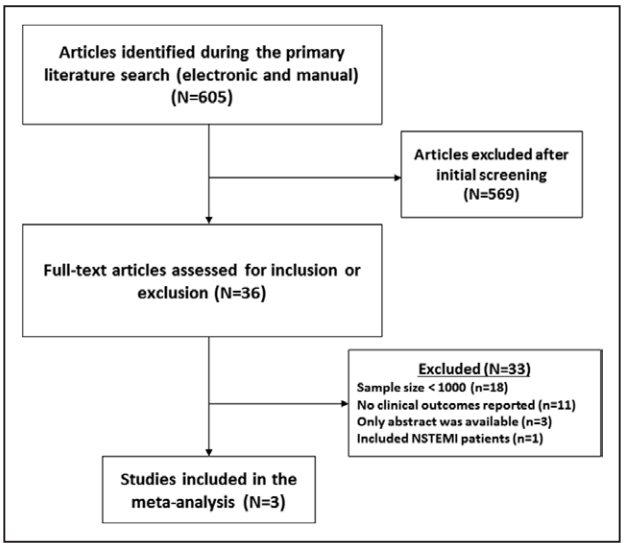


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.
NSTEMI indicates non–ST-segment–elevation myocardial infarction.

Efficacy and Safety

The primary efficacy outcome of cardiovascular death within 30 days in patients who had undergone PCI for STEMI was 2.4% in the thrombus aspiration group compared with 2.9% in the PCI alone group (hazard ratio, 0.84; 95% CI, 0.70–1.01; *P*=0.06; study-level interaction *P*=0.05; Figure 2 and Table 2). The primary safety outcome of stroke or TIA at 30 days was 0.8% in the thrombus aspiration group compared with 0.5% in the PCI alone group (odds ratio, 1.43; 95% CI, 0.98–2.10; *P*=0.06) but with a significant study-level interaction (*P*=0.02). There were no statistically significant differences in recurrent myocardial infarction, stent thrombosis, or target vessel revascularization (Table 2). At 1 year, the rate of cardiovascular death was 3.7% in the thrombus aspiration group compared with 4.2% in the PCI alone group (hazard ratio, 0.90; 95% CI, 0.78–1.04; *P*=0.15; Figure 2).

Subgroup Findings

In those with high thrombus burden (TIMI thrombus grade ≥3), thrombus aspiration was associated with reduced cardiovascular death (2.5% versus 3.1%; hazard ratio, 0.80; 95% CI, 0.65–0.98; *P*=0.03) with no significant heterogeneity across studies (study-level interaction *P*=0.22). However, this subgroup had an excess in stroke or TIA (0.9% versus 0.5%; odds ratio, 1.56; 95% CI, 1.02–2.42; *P*=0.04; Table 3) with no significant heterogeneity across studies (study-level interaction *P*=0.09). In the low thrombus burden subgroup (TIMI thrombus grade <3), there were no differences in cardiovascular death (2.2% versus 2.2%; hazard ratio, 1.00; 95% CI, 0.68–1.47) or in stroke or TIA (0.5% versus 0.5%; odds ratio, 0.99; 95% CI, 0.43–2.26). Interaction *P* values for differences in cardiovascular death and for stroke or TIA according to the cut point of TIMI thrombus grade ≥3 were not statistically significant (*P*=0.32 and 0.34, respectively; Table 3).

Table 1. Baseline Characteristics and Procedural Variables

	Thrombus Aspiration (n=9155)	PCI Alone (n=9151)
Demographics		
Age (mean±SD), y	63.3 (12.0)	63.1 (12.1)
Age >75 y, n (%)	1620 (17.7)	1521 (16.6)
Male, n (%)	6930 (75.7)	7002 (76.5)
Killip class IV, n (%)	72 (0.8)	71 (0.8)
History, n (%)		
Current smoker*	3535 (39.9)	3740 (42.4)
Hypertension	4239 (46.6)	4228 (46.5)
Diabetes mellitus	1419 (15.5)	1449 (15.9)
Prior myocardial infarction	907 (10.0)	940 (10.3)
Prior PCI	788 (8.6)	821 (9.0)
Initial PCI procedure		
Time from symptom onset to PCI start, min†	190.0 (128–311)	185.5 (125–300)
Radial access, n (%)	5828 (67.4)	5843 (67.6)
Bivalirudin, n (%)	3846 (42)	3735 (40.8)
Enoxaparin, n (%)	572 (6.2)	572 (6.3)
Unfractionated intravenous heparin, n (%)	7693 (84)	7761 (84.8)
Glycoprotein IIb/IIIa inhibitor, n (%)‡	2957 (32.3)	3209(35.1)
Contrast volume (SD), mL§	171 (98)	168 (100.3)
Fluoroscopy time (SD), min¶	13.2 (19.2)	12.3 (25.4)
TIMI thrombus grade, n (%)‖		
0, No thrombus present	728 (8.0)	803 (8.8)
1, Possible thrombus present	999 (11.0)	1112 (12.2)
2, Definite thrombus present, <0.5 vessel diameter	497 (5.5)	496 (5.5)
3, Definite thrombus present, 0.5–2.0 vessel diameters	1516 (16.6)	1321 (14.5)
4, Definite thrombus present, >2.0 vessel diameters	1658 (18.2)	1623 (17.8)
5, Total occlusion	3718 (40.8)	3740 (41.1)
Pre-PCI TIMI grade 0/1 flow, n (%)	6808 (74.9)	6870 (75.5)
Direct stenting, n (%)**	3594 (39.5)	1916 (21.1)
Bare-metal stent, n (%)	4783 (52.2)	4806 (52.5)
≥1 Drug-eluting stent, n (%)	4059 (44.3)	4038 (44.1)
No. of stents, mean (SD)	1.4 (0.7)	1.4 (0.7)
Total stent length, mean (SD), mm	28 (15.5)	28.1 (15.4)
Stent diameter, mean (SD), mm	3.2 (0.5)	3.1(0.5)
Vessel treated at index PCI, n (%)		
Left main coronary artery	79 (0.9)	86 (0.9)
Left anterior descending coronary artery	3945 (43.1)	4039 (44.1)
Left circumflex coronary artery	1404 (15.3)	1408 (15.4)
Right coronary artery	4129 (45.1)	4069 (44.5)
Coronary bypass graft	38 (0.4)	36 (0.4)
Medications at hospital discharge, n (%)#		
Aspirin	8238 (97.4)	8217 (97.3)
Ticagrelor	2043 (24)	2040 (24)
Prasugrel	966 (11.4)	961 (11.3)
Clopidogrel	5124 (60.3)	5085 (59.9)
Statin	8097 (95.3)	8086 (95.3)
Angiotensin-converting enzyme inhibitor or receptor blocker	6188 (72.8)	6251 (73.7)
β-Blocker	7161 (84.3)	7198 (84.9)
Oral anticoagulant	493 (5.8)	497 (5.9%)

PCI indicates percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial infarction.

*Current smoker, $P<0.001$.

†Time from symptom onset to PCI, $P=0.025$.

‡Glycoprotein IIb/IIIa inhibitor, $P<0.001$.

§Contrast volume, $P<0.001$.

¶Fluoroscopy time, $P<0.001$ (TASTE [Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia] and TOTAL [Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI] only).

‖TIMI thrombus grade, $P<0.001$.

#Medications at discharge available only for TASTE and TOTAL.

**Direct stenting, $P<0.001$.

When a cut point of TIMI thrombus grade ≥4 rather than ≥3 was chosen, there were similar patterns for cardiovascular death (2.7% versus 3.2%; hazard ratio, 0.82; 95% CI, 0.66–1.02; $P=0.08$; subgroup interaction $P=0.67$; study-level interaction $P=0.43$) and stroke or TIA (1.0% versus 0.6%; odds ratio, 1.87; 95% CI, 1.18–3.02; $P=0.009$; subgroup interaction $P=0.04$; study-level interaction $P=0.41$; Table 3) within 30 days.

There appeared to be a greater benefit for thrombus aspiration in patients receiving a glycoprotein IIb/IIIa

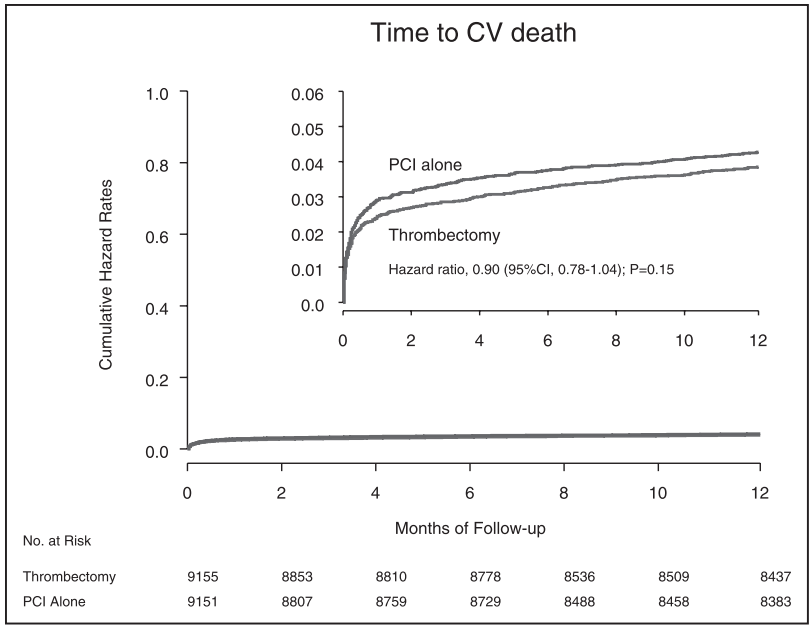


Figure 2. Kaplan-Meier curves for cardiovascular mortality.
CI indicates confidence interval; CV, cardiovascular; and PCI, percutaneous coronary intervention.

ORIGINAL RESEARCH ARTICLE

inhibitor for cardiovascular death within 30 days (interaction *P*=0.048), but there was also increased risk of stroke or TIA (interaction *P*=0.04; Figure 3A and 3B). There appeared to be a potential benefit in patients presenting within 6 hours for cardiovascular death but also harm in terms of stroke (Figure 3A and 3B).

DISCUSSION

In contrast to traditional meta-analyses summarizing group data, the present meta-analysis used individual patient data that provided considerably greater power to examine important but low-frequency events such as

Table 2. Outcomes for Thrombus Aspiration Versus PCI Alone

Outcome	Thrombus Aspiration (n=9155), n (%)	PCI Alone (n=9151), n (%)	HR	95% CI	*P* Value
Primary outcome					
Cardiovascular death at 30 d	221 (2.4)	262 (2.9)	0.84	0.70–1.01	0.06
Key safety outcome					
Stroke or TIA at 30 d*	66/8518 (0.8)	46/8476 (0.5)	1.43	0.98–2.1	0.06
Other outcomes at 30 d					
All-cause death	232 (2.5)	273 (3.0)	0.85	0.71–1.01	0.06
MI	96 (1.0)	104 (1.1)	0.92	0.70–1.21	0.55
Congestive heart failure†	141/8653 (1.6)	128/8648 (1.5)	1.10	0.87–1.40	0.44
Target vessel revascularization	215 (2.3)	239 (2.6)	0.90	0.74–1.08	0.24
Cardiovascular death, MI, cardiogenic shock, congestive heart failure, stent thrombosis, or target vessel revascularization†	604/8653 (7.0)	654/8648 (7.6)	0.92	0.82–1.03	0.14
Outcomes at 1 y					
Cardiovascular death	343 (3.7)	380 (4.2)	0.90	0.78–1.04	0.15
All-cause death	426 (4.7)	464 (5.1)	0.91	0.80–1.04	0.18
Myocardial infarction	233 (2.5)	239 (2.6)	0.97	0.81–1.16	0.73
Congestive heart failure†	268/8653 (3.1)	258/8648 (3.0)	1.04	0.87–1.23	0.68
Target vessel revascularization	495 (5.4)	504 (5.5)	0.97	0.86–1.10	0.68
Stroke or TIA*	128/8055 (1.6)	103/7990 (1.3)	1.24	0.95–1.61	0.11

CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; PCI indicates percutaneous coronary intervention; and TIA, transient ischemic attack.

*Data available only from TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and TOTAL (Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI), and odds ratios, not HRs, were reported.

†Data only available from TASTE and TOTAL trials.

Table 3. Outcomes by High and Low Thrombus Burden

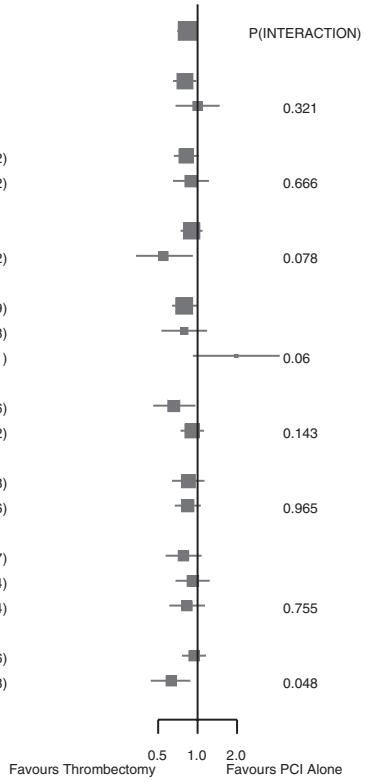
Outcome	Thrombus Aspiration, n (%)	PCI Alone, n (%)	HR	95% CI	*P* Value	Interaction *P*
Cardiovascular death at 30 d						
TIMI thrombus grade ≥3	170 (2.5)	205 (3.1)	0.80	0.65–0.98	0.03	0.32
TIMI thrombus grade <3	49 (2.2)	53 (2.2)	1.00	0.68–1.47	0.99	
TIMI thrombus grade ≥4	144 (2.7)	174 (3.2)	0.82	0.66–1.02	0.08	0.67
TIMI thrombus grade <4	75 (2.0)	84 (2.3)	0.89	0.65–1.22	0.48	
Stroke or TIA at 30 d*						
TIMI thrombus grade ≥3	55 (0.9)	34 (0.5)	1.56	1.02–2.42	0.04	0.34
TIMI thrombus grade <3	11 (0.5)	12 (0.5)	0.99	0.43–2.26	0.98	
TIMI thrombus grade ≥4	51 (1.0)	27 (0.6)	1.87	1.18–3.02	0.009	0.04
TIMI thrombus grade <4	15 (0.4)	19 (0.5)	0.80	0.40–1.57	0.512	
Other outcomes at 30 d						
All-cause death						
TIMI thrombus grade ≥3	176 (2.6)	210 (3.1)	0.81	0.66–0.99	0.04	0.31
TIMI thrombus grade <3	54 (2.4)	58 (2.4)	1.00	0.69–1.45	0.99	
TIMI thrombus grade ≥4	150 (2.8)	179 (3.3)	0.83	0.67–1.03	0.10	0.68
TIMI thrombus grade <4	80 (2.1)	89 (2.4)	0.90	0.66–1.22	0.49	
Myocardial infarction						
TIMI thrombus grade ≥3	78 (1.1)	84 (1.3)	0.90	0.66–1.23	0.52	0.95
TIMI thrombus grade <3	17 (0.76)	20 (0.83)	0.93	0.49–1.77	0.82	
TIMI thrombus grade ≥4	65 (1.2)	68 (1.3)	0.96	0.68–1.35	0.80	0.61
TIMI thrombus grade <4	30 (0.8)	36 (0.96)	0.82	0.51–1.33	0.43	
Outcomes at 1 y						
Cardiovascular death						
TIMI thrombus grade ≥3	261 (3.8)	298 (4.5)	0.84	0.72–1.0	0.05	0.17
TIMI thrombus grade <3	78 (3.5)	78 (3.2)	1.08	0.79–1.47	0.64	
TIMI thrombus grade ≥4	219 (4.1)	249 (4.6)	0.87	0.73–1.04	0.14	0.61
TIMI thrombus grade <4	120 (3.2)	127 (3.4)	0.94	0.73–1.21	0.64	
All-cause death						
TIMI thrombus grade ≥3	318 (4.6)	353 (5.3)	0.87	0.75–1.01	0.07	0.20
TIMI thrombus grade <3	104 (4.7)	106 (4.4)	1.06	0.81–1.39	0.69	
TIMI thrombus grade ≥4	262 (4.9)	289 (5.4)	0.90	0.76–1.06	0.20	0.74
TIMI thrombus grade <4	160 (4.3)	170 (4.6)	0.94	0.76–1.16	0.56	
Stroke or TIA*						
TIMI thrombus grade ≥3	98 (1.6)	76 (1.3)	1.24	0.92–1.68	0.17	0.94
TIMI thrombus grade <3	30 (1.6)	27 (1.3)	1.20	0.71–2.05	0.49	
TIMI thrombus grade ≥4	81 (1.7)	54 (1.2)	1.48	1.05–2.10	0.03	0.11
TIMI thrombus grade <4	47 (1.4)	49 (1.5)	0.96	0.64–1.44	0.85	

CI indicates confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and TIMI, Thrombolysis in Myocardial infarction.

*Stroke or TIA outcomes have odds ratio reported instead of HR.

A

		Thrombectomy	PCI Alone	Hazard Ratio(95%CI)	P(INTERACTION)
		no. of events/total no. (%)			
OVERALL	18306	221/9155 (2.4)	262/9151 (2.9)	0.84(0.7-1.01)	
TIMI Thrombus Grade:					
>=3	13576	170/6892 (2.47)	205/6684 (3.07)	0.8(0.65-0.98)	
<3	4635	49/2224 (2.2)	53/2411 (2.2)	1(0.68-1.47)	0.321
TIMI Thrombus Grade:					
>=4	10739	144/5376 (2.68)	174/5363 (3.24)	0.82(0.66-1.02)	
<4	7472	75/3740 (2.01)	84/3732 (2.25)	0.89(0.65-1.22)	0.666
Initial TIMI Flow:					
0-1	13678	195/6808 (2.86)	219/6870 (3.19)	0.9(0.74-1.09)	
2-3	4515	24/2286 (1.05)	42/2229 (1.88)	0.55(0.34-0.92)	0.078
Symptom onset (h):					
<6	14016	142/6958 (2.04)	181/7058 (2.56)	0.79(0.64-0.99)	
6-12	2615	44/1359 (3.24)	51/1256 (4.06)	0.79(0.53-1.18)	
>12	629	20/317 (6.31)	10/312 (3.21)	1.97(0.92-4.21)	0.06
Vessel:					
Non-proximal	7234	48/3618 (1.33)	72/3616 (1.99)	0.66(0.46-0.96)	
Proximal	11072	173/5537 (3.12)	190/5535 (3.43)	0.91(0.74-1.12)	0.143
Lesion:					
Non LAD lesion	10322	91/5210 (1.75)	105/5112 (2.05)	0.85(0.64-1.13)	
LAD lesion	7984	130/3945 (3.30)	157/4039 (3.89)	0.84(0.67-1.06)	0.965
Site PCI Volume:					
Tertile 1	5879	67/2952 (2.27)	85/2927 (2.9)	0.78(0.57-1.07)	
Tertile 2	6861	81/3417 (2.37)	89/3444 (2.58)	0.92(0.68-1.24)	
Tertile 3	5514	73/2759 (2.65)	87/2755 (3.16)	0.83(0.61-1.14)	0.755
Glycoprotein inhib:					
No	12137	170/6198 (2.74)	174/5939 (2.93)	0.94(0.76-1.16)	
Yes	6166	51/2957 (1.72)	88/3209 (2.74)	0.63(0.44-0.88)	0.048



B

		Thrombectomy	PCI Alone	0dds Ratio(95%CI)	P(INTERACTION)
		no. of events/total no. (%)			
OVERALL	16994	66/8518 (0.77)	46/8476 (0.54)	1.43(0.98-2.1)	
TIMI Thrombus Grade:					
>=3	12619	55/6430 (0.86)	34/6189 (0.55)	1.56(1.02-2.42)	
<3	4291	11/2055 (0.54)	12/2236 (0.54)	0.99(0.43-2.26)	0.342
TIMI Thrombus Grade:					
>=4	9872	51/4969 (1.03)	27/4903 (0.55)	1.87(1.18-3.02)	
<4	7038	15/3516 (0.43)	19/3522 (0.54)	0.8(0.4-1.57)	0.041
Initial TIMI Flow:					
0-1	12819	57/6408 (0.89)	41/6411 (0.64)	1.39(0.94-2.1)	
2-3	4078	9/2057 (0.44)	5/2021 (0.25)	1.76(0.61-5.74)	0.683
Symptom onset (h):					
<6	12963	48/6452 (0.74)	30/6511 (0.46)	1.62(1.03-2.59)	
6-12	2427	10/1258 (0.79)	10/1169 (0.86)	0.92(0.38-2.26)	
>12	589	3/299 (1)	2/290 (0.69)	1.41(0.23-10.8)	0.549
Vessel:					
Non-proximal	6610	23/3310 (0.69)	13/3300 (0.39)	1.77(0.91-3.6)	
Proximal	10384	43/5208 (0.83)	33/5176 (0.64)	1.3(0.83-2.06)	0.457
Lesion:					
Non LAD lesion	9600	29/4856 (0.60)	20/4744 (0.42)	1.42(0.81-2.55)	
LAD lesion	7394	37/3662 (1.01)	26/3732 (0.70)	1.45(0.88-2.43)	0.953
Site PCI Volume:					
Tertile 1	5696	25/2875 (0.87)	12/2821 (0.43)	2.05(1.05-4.24)	
Tertile 2	6765	24/3373 (0.71)	21/3392 (0.62)	1.15(0.64-2.09)	
Tertile 3	4482	17/2243 (0.76)	13/2239 (0.58)	1.31(0.64-2.75)	0.432
Glycoprotein inhib:					
No	11854	45/6072 (0.74)	38/5782 (0.66)	1.13(0.73-1.75)	
Yes	5137	21/2446 (0.86)	8/2691 (0.3)	2.9(1.33-6.98)	0.038

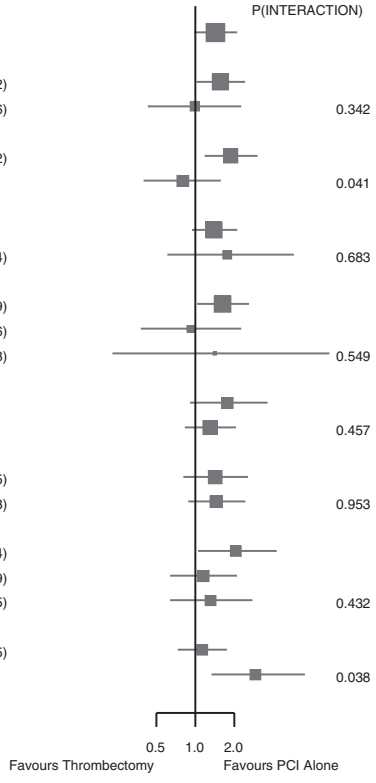


Figure 3. Subgroup analyses.
A, Subgroup analysis for cardiovascular mortality at 30 days. **B,** Subgroup analysis for stroke or TIA within 30 days. CI indicates confidence interval; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

cardiovascular death and stroke and allowed the evaluation of specific subgroups such as the one with a high thrombus burden. The protocol was finalized and registered before the analysis was started as per the PRISMA guidelines for individual patient data meta-analyses.[10]

At 30 days, there were no statistically significant differences for cardiovascular mortality and all-cause mortality between a strategy of routine manual thrombus aspiration and PCI alone overall.

Although there were no statistically significant subgroup interactions, in the subgroup of patients with high thrombus burden, there was a nominal reduction in cardiovascular mortality and all-cause mortality but an increase in stroke or TIA at 30 days. It is biologically plausible that thrombus aspiration is beneficial only in patients with moderate to high thrombus burden. On the other hand, if the mechanism of stroke is embolization of thrombus from the coronary artery to systemic circulation, it is logical that the risk would be higher in patients with high thrombus burden. Finally, in patients with high thrombus burden, the increase in stroke could counterbalance an early benefit such that the effect on all-cause mortality at 1 year was neutral.

For stroke or TIA, there was a significant study-level interaction. One potential reason is that the TASTE trial randomized patients after angiography, whereas TOTAL and TAPAS randomized patients before angiography, so it is possible that angiographic anatomy varied between the studies. Thrombus burden has been linked to stroke risk, and one hypothesis is that TOTAL had a higher stroke risk with thrombus aspiration as a result of the inclusion of patients with a higher thrombus burden.[8] To support this hypothesis, in the subgroup of patients with high thrombus burden, we found consistency at the study level for the effect of thrombus aspiration on both cardiovascular death and stroke or TIA. However, these results should be interpreted cautiously, given that this is a post hoc analysis. Furthermore, other important limitations are that TAPAS did not collect data on stroke or TIA and neurological events were not adjudicated in TASTE.

Limitations of current manual thrombus aspiration technology include thrombus embolization downstream as a result of wire crossing (before aspiration); limited ability to deal with large, organized thrombi; and embolization of thrombus to other vascular territories during removal of the aspiration catheter. These limitations are consistent with the TOTAL optical coherence tomography substudy, which showed a similar residual thrombus volume after routine thrombus aspiration and after balloon angioplasty.[12]

Innovations in device technology should focus on reducing the risk of systemic embolization of thrombus during thrombus aspiration, in addition to improving efficacy. It is conceivable that improved forms of thrombus aspiration that mitigate stroke risk could reduce cardiovascular mortality in patients with high thrombus burden. The effects on cardiovascular mortality and stroke or TIA observed in this meta-analysis in the high thrombus burden subgroup should be considered exploratory, given that the subgroup interactions were not statistically significant and that there was no adjustment for multiple testing. These findings could serve as a basis for much larger trials with new devices that reduce the risk of systemic embolization. Such trials would need to enroll 26 000 patients with a high thrombus burden to be powered for a 20% reduction in cardiovascular mortality on the basis of the event rates observed in this data set. The feasibility of such a trial may be questioned; however, the large fibrinolytic trials enrolled similar numbers of patients.

The finding that thrombus aspiration may reduce cardiovascular mortality but increase stroke or TIA in those treated with glycoprotein IIb/IIIa inhibitors should be interpreted cautiously. First, glycoprotein IIb/IIIa inhibitor use is likely highly correlated to thrombus burden. Second, these were open-label trials, and glycoprotein IIb/IIIa use is a postrandomization variable that may be affected by knowledge of treatment assignment and procedural complications such as no reflow.

This individual-patient meta-analysis is novel because it used cause-specific mortality (cardiovascular mortality) compared with all-cause mortality presented in the original TASTE and TAPAS publications.[3,11] This is important because cause-specific mortality is more likely to be responsive to the intervention than all-cause mortality and thus increases study power. Furthermore, we prespecified our primary outcome at 30 days instead of 180 days (primary outcome of TOTAL) because we hypothesized that the greatest benefit may be early for a one-time intervention compared with an ongoing therapy. Finally, we had detailed baseline data and were able to examine the effect of thrombus aspiration on important subgroups on the basis of thrombus burden and time of symptom onset, both factors that may predict benefit of thrombus aspiration.

Limitations of this analysis are related to limitations of the data sets of the individual trials. TAPAS did not prospectively collect the outcome of nonfatal stroke and was not included in the stroke analyses.[3] Direct stenting was recommended in TAPAS but not in the other trials. TASTE collected the composite outcome of stroke or TIA but not stroke alone, necessitating the composite of stroke or TIA as a safety outcome in our meta-analysis.[11] The time of stroke or TIA during the initial hospitalization was not collected in TASTE, so a time-to-event analysis was not possible for this outcome. Outcomes in the TASTE trial were from administrative databases, clinical registries, and death certificates and were not adjudicated. Another limitation is that thrombus grade was assessed before wire crossing in both TAPAS and TOTAL and after wire crossing in TASTE. There was no adjustment for multiple comparisons, so all secondary analyses should be considered hypothesis generating. Another limitation is that no

adjustment for clustering was performed. Finally, despite nearly 20 000 patients randomized, this analysis still was relatively underpowered to detect a modest but clinically important 20% relative risk reduction in cardiovascular mortality within 30 days.

CONCLUSIONS

Routine manual thrombus aspiration during PCI for STEMI did not improve clinical outcomes overall. Whether improved methods for thrombus aspiration could reduce the risk of stroke and enhance overall benefit is not known and warrants testing in future trials of patients with high thrombus burden.

SOURCES OF FUNDING

None.

DISCLOSURES

During the conduct of the TOTAL trial, Dr Jolly received an institutional research grant from Medtronic. During the conduct of the TASTE trial, Dr James received institutional research grants from Medtronic, Vascular Solutions, and Terumo Inc. Since then, he has received institutional research grants from Boston Scientific, Abbot Vascular, AstraZeneca, and The Medicines Company. He has received honoraria from AstraZeneca, The Medicines Company, Bayer, and Boston Scientific. The other authors report no conflicts.

AFFILIATIONS

From McMaster University and the Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada (S.S.J., S.Y., P.G., A.A., B.M.); Department of Medical Science, Uppsala University and Uppsala Clinical Research Centre, Uppsala, Sweden (S.J., H.R., B.L.); Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada (V.D.); University of British Columbia, Vancouver, BC, Canada (J.A.C.); Department of Cardiology, Thorax Center, Erasmus Medical Centre, Rotterdam, the Netherlands (K.D.M., F.Z.); Skåne University Hospital-Lund/Lund University, Lund, Sweden (G.K.O.); University Clinic of Cardiology, Sts. Cyril and Methodius University, Skopje, Macedonia (S.K.); Clinical Center of Serbia and Department of Cardiology, Medical Faculty, University of Belgrade, Belgrade, Serbia (G.S.); and Örebro University, Faculty of Health, Department of Cardiology, Södra Grev Rosengatan, Örebro, Sweden (O.F.).

FOOTNOTES

Received September 7, 2016; accepted October 28, 2016.

Guest Editor for this article was Eric Bates, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.025371/-/DC1.

Circulation is available at http://circ.ahajournals.org.

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. doi: 10.1016/S0140-6736(03)12113-7.
2. Henriques JP, Zijlstra F, Ottervanger JP, de Boer MJ, van 't Hof AW, Hoorntje JC, Suryapranata H. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J*. 2002;23:1112–1117. doi: 10.1053/euhj.2001.3035.
3. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer AJ, Zijlstra F. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med*. 2008;358:557–567. doi: 10.1056/NEJMoa0706416.
4. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer AJ, Zijlstra F. 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;371:1915–1920. doi: 10.1016/S0140-6736(08)60833-8.
5. Fröbert O, Lagerqvist B, Gudnason T, Thuesen L, Svensson R, Olivecrona GK, James SK. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial): a multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform: study design and rationale. *Am Heart J*. 2010;160:1042–1048. doi: 10.1016/j.ahj.2010.08.040.
6. Lagerqvist B, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, Andersson J, Calais F, Carlsson J, Collste O, Götberg M, Hårdhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskar V, Tödt T, Zelleroth E, Östlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med*. 2014;371:1111–1120. doi: 10.1056/NEJMoa1405707.
7. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemelä K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Naber CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, ten Berg JM, Shestakovska O, Gao P, Widimsky P, Džavík V; TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med*. 2015;372:1389–1398. doi: 10.1056/NEJMoa1415098.
8. Jolly SS, Cairns JA, Yusuf S, Meeks B, Gao P, Hart RG, Kedev S, Stankovic G, Moreno R, Horak D, Kassam S, Rokoss MJ, Leung RC, El-Omar M, Romppanen HO, Alazzoni A, Alak A, Fung A, Alexopoulos D, Schwalm JD, Valettas N, Džavík V; TOTAL Investigators. 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;36:2364–2372. doi: 10.1093/eurheartj/ehv296.
9. Jolly SS, Cairns JA, Yusuf S, Rokoss MJ, Gao P, Meeks B, Kedev S, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Bernat I, Cantor WJ, Cheema AN, Steg PG, Welsh RC, Sheth T, Bertrand OF, Avezum A, Bhindi R, Natarajan MK, Horak D, Leung RC, Kassam S, Rao SV, El-Omar M, Mehta SR, Velianou JL, Pancholy S, Džavík V; TOTAL Investigators. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet*. 2016;387:127–135. doi: 10.1016/S0140-6736(15)00448-1.
10. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF; PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of

Individual Participant Data: the PRISMA-IPD Statement. *JAMA*. 2015;313:1657–1665. doi: 10.1001/jama.2015.3656.

11. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angerås O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Kåregren A, Nilsson J, Robertson L, Sandhall L, Sjögren I, Ostlund O, Harnek J, James SK; TASTE Trial. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587–1597. doi: 10.1056/NEJMoa1308789.
12. Bhindi R, Kajander OA, Jolly SS, Kassam S, Lavi S, Niemelä K, Fung A, Cheema AN, Meeks B, Alexopoulos D, Kočka V, Cantor WJ, Kaivosoja TP, Shestakovska O, Gao P, Stankovic G, Džavík V, Sheth T. 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;36:1892–1900. doi: 10.1093/eurheartj/ehv176.