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Thrombus Aspiration in ST Elevation Myocardial Infarction: An Individual Patient Meta-analysis

Running Title: *Jolly et al.;Thrombus Aspiration in STEMI*

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Abstract

***Background*—**Thrombus aspiration during percutaneous coronary intervention (PCI) for the treatment of ST 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 STEMI.

***Methods*—**Included were large (N≥1000) randomized controlled trials comparing manual thrombectomy vs. PCI alone in patients with STEMI. Individual patient data was provided by the leadership of each trial. The pre-specified primary efficacy outcome was cardiovascular (CV) mortality within 30 days and the primary safety outcome was stroke or transient ischemic attack (TIA) within 30 days.

***Results*—**The 3 eligible randomized trials (TAPAS, TASTE and TOTAL) enrolled 19,047 patients, of whom 18,306 underwent PCI and were included in the primary analysis. CV death at 30 days occurred in 221 (2.4%) of 9155 patients randomized to thrombus aspiration and 262 (2.9%) of 9151 randomized to PCI alone (hazard ratio (HR) 0.84; 95% CI 0.70-1.01, p=0.06). Stroke or TIA occurred in 66 (0.8%) randomized to thrombus aspiration and 46 (0.5%) randomized to PCI alone (odds ratio [OR] 1.43 95% CI 0.98-2.1, 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 thrombus grade ≥3) thrombus aspiration was associated with less CV death (170 [2.5%] vs. 205 [3.1%] HR 0.80; 95% CI 0.65-0.98, p =0.03), and with more stroke or TIA (55 [0.9%] vs. 34 [0.5%] OR 1.56; 95% CI 1.02-2.42, p=0.04). However, the interaction p-values were 0.32 and 0.34, respectively.

***Conclusions*—**Routine thrombus aspiration during STEMI PCI did not improve clinical outcomes. In the high thrombus burden subgroup the trends toward reduced CV death and increased stroke or TIA provide a rationale for future trials of improved thrombus aspiration technologies in this high-risk subgroup.

***Clinical Trial Registration*—**ClinicalTrials.gov identifier NCT02552407, PROSPERO CRD42015025936

Key words: meta-analysis; myocardial infarction; thrombectomy

Clinical Perspective

What is new?

- This is an individual patient meta-analysis of more than 18,000 patients with STEMI randomized to thrombus aspiration vs. PCI alone.
- As a routine strategy, thrombus aspiration did not reduce in cardiovascular mortality for STEMI patients undergoing primary PCI.
- An exploratory analysis of patients with high thrombus burden suggests that thrombus aspiration may improve CV mortality but at the price of an increased risk of stroke or TIA.

What are the clinical implications?

- Thrombus aspiration should not be used as a routine strategy in patients with STEMI.
- Further larger randomized trials are needed to determine if improved forms of thrombus aspiration can reduce CV mortality and to determine its safety with regards to stroke.

Introduction

The optimal treatment for ST 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 prior to stent deployment, thereby reducing distal embolization and improving outcomes.

Thrombus aspiration became part of routine practice based on the promising results of an early trial.[3, 4] However, the results of more 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 reduction in mortality (e.g. 20%) or of 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 at PROSPERO (international register of systematic reviews, CRD42015025936) and clinicaltrials.gov (NCT02552407) prior to unblinding or any data analysis. Large randomized trials (recruiting 1000 patients or more) that compared manual thrombus aspiration plus PCI and PCI alone in patients with STEMI were eligible. Large randomized trials were only included as 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 appendix).

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. Please refer to online supplement for details regarding outcomes variables. The TAPAS trial did not prospectively collect stroke or TIA data and was not included for this outcome. Outcomes were not adjudicated in TASTE and were from discharge diagnoses in administrative databases and death registry. The risk of bias was assessed as per the Cochrane Collaboration tool (figure S1).

The three individual trials (TASTE, TAPAS and TOTAL) 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 (UCR), Sweden and analyses were performed using 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 (PHRI), Canada using S-PLUS (TIBCO Software Inc, Palo Alto, Ca).

Statistical Analysis

For baseline characteristics, the Wilcoxon rank sum test was used for continuous variables and Pearson chi square test for categorical variables. The pre-specified primary efficacy outcome was cardiovascular death at 30 days. The pre-specified primary safety outcome was stroke or TIA at 30 days. The pre-specified 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 (i.e. normal coronary arteries) were not included in the primary analysis. A fixed effect model was used and study level was used as a covariate in analyses and study level interaction p values were reported.

A p-value of less than 0.05 was considered statistically significant. Hazard ratios and their 95% confidence intervals (CI) were estimated using a Cox proportional hazards regression model with treatment group as the predictor variable and p values were used from cox regression. For 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% CI 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, pre-specified subgroup analyses were performed comparing Thrombolysis In Myocardial Infarction (TIMI) thrombus grade <3 vs. ≥ 3 and <4 vs. ≥4. Additional pre-specified subgroup analyses were based on time from symptom onset (<6 vs. 6-12 hours vs. >12 hours), initial TIMI flow (0-1 vs. 2-3), lesion location (proximal vs. non-proximal 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 three randomized trials, 18,306 underwent PCI and were included in the primary analysis (figure 1). The individual trials (table S1, figures S2 and S3) included were the The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS, N=1,071)[4], Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE, N=7,244)[11] and routine aspiration ThrOmbecTomy with PCI versus PCI ALone in Patients with STEMI (TOTAL, N=10,732)[7]. These three large trials accounted for 19,047 patients out of 22,057 patients enrolled in manual thrombus aspiration trials.

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

In the thrombus aspiration group, direct stenting was more frequent (39.5% vs. 21.1%, p<0.001) and GP IIb/IIa use was slightly lower (32.3% vs. 35.1%, p<0.001). The rate of cross-over 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 min vs. 12.3 min, p<0.001, Table 1). Stent length, stent diameter and number of stents were not different between the groups.

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, 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 ratio 1.43; 95% CI 0.98-2.1, p=0.06), but with 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% vs. 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% vs. 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% vs. 2.2%, hazard ratio 1.00; 95% CI 0.68-1.47) or in stroke or TIA (0.5% vs. 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 TIMI thrombus grade ≥ 3 cut point were not statistically significant (p = 0.32 and 0.34, respectively, Table 3).

When a cut point of TIMI thrombus grade ≥4 rather than ≥ 3 was chosen, there were similar patterns for cardiovascular death (2.7% vs. 3.2%, hazard ratio 0.82; 95% 0.66-1.02, p =0.08, subgroup interaction p=0.67, study level interaction p=0.43) and stroke or TIA within 30 days (1.0% vs. 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).

There appeared to be a greater benefit for thrombus aspiration in patients receiving a GP IIb/IIIa 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 CV 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 which provided considerably greater power to examine important but low frequency events such as cardiovascular death and stroke and it allowed the evaluation of specific subgroups such as the one with a high thrombus burden. The protocol was finalized and registered prior to starting the analysis as per the PRISMA guidelines for individual patient data meta-analyses.[10]

At 30 days, there were no statistically significant differences for cardiovascular mortality, all-cause mortality between a strategy of routine manual thrombus aspiration vs 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 CV mortality and in

all-cause mortality but an increase in stroke or TIA at 30 days. It is biologically plausible that thrombus aspiration is only beneficial 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 while TOTAL and TAPAS did so pre-angiography and 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 due to 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 effect of thrombus aspiration on both CV death and stroke or TIA. However, these results should be interpreted cautiously, given this is a post hoc analysis. Furthermore, an important limitation is that TAPAS did not collect stroke or TIA and neurologic events were not adjudicated in TASTE.

Limitations of current manual thrombus aspiration technology include thrombus embolization downstream due to wire crossing (prior to 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 cohence 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 based on 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 GP IIb/IIIa inhibitors should be interpreted cautiously. First, GP IIb/IIIa inhibitors use is likely highly correlated to thrombus burden. Second, these were open label trials and GP IIb/IIIa use is a post randomization variable that may be impacted by knowledge of treatment assignment and procedural complications such as no reflow.

This individual patient meta-analysis is novel because it utilized cause-specific mortality (CV mortality) compared to all-cause mortality presented in the original TASTE and TAPAS publications.[3, 11] This is important as cause-specific mortality is more likely to be responsive to the intervention than all-cause mortality and thus increases study power. Furthermore, we pre-specified our primary outcome at 30 days instead of 180 days (primary outcome of TOTAL) as we hypothesized that the greatest benefit may be early for a one time intervention compared to

an ongoing therapy. Finally, we had detailed baseline data and were able to examine the effect of thrombus aspiration on important subgroups based on thrombus burden and time of symptom onset, both factors which may predict benefit of thrombus aspiration.

Limitations of this analysis are related to limitations of the datasets of the individual trials. The 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 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 prior to 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 STEMI PCI 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 among patients with high thrombus burden.

Disclosures

During the conduct of the TOTAL trial, SSJ received an institutional research grant from Medtronic. During the conduct of the TASTE trial SJ received institutional research grants from Medtronic, Vascular Solutions and Terumo Inc. Thereafter he has received institutional research grants from Boston Scientific, Abbot Vascular, Astra Zeneca and The Medicines Company. He has received honoraria from Astra Zeneca, The Medicines Company, Bayer and Boston Scientific.

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Table 1. Baseline Characteristics and Procedural Variables

	Thrombus Aspiration N= 9155		PCI alone N= 9151	
Demographics				
Age, years (mean ±SD)	63.3	(12.0)	63.1	(12.1)
Age > 75 yr (%)	1620	(17.7)	1521	(16.6)
Male (%)	6930	(75.7)	7002	(76.5)
Killip class IV	72	(0.8)	71	(0.8)
History				
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)
	Thrombus Aspiration N= 9155		PCI alone N= 9151	
Initial PCI procedure				
Time from symptom onset to PCI start (min) [y]	190.0	(128–311)	185.5	(125-300)
Radial access (%)	5828	(67.4)	5843	(67.6)
Bivalirudin (%)	3846	(42)	3735	(40.8)
Enoxaparin (%)	572	(6.2)	572	(6.3)
Unfractionated intravenous Heparin (%)	7693 (84)		7761 (84.8)	
Glycoprotein IIb/IIIa inhibitor (%)‡‡	2957	(32.3)	3209	(35.1)
Contrast Volume (mL, SD)*	171 (98)		168 (100.3)	
Fluoroscopy time (min, SD)**	13.2 (19.2)		12.3 (25.4)	
TIMI thrombus grade (%) ***				
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 0/1 flow (%)	6808	(74.9)	6870	(75.5)
Direct Stenting (%)	3594	(39.5)	1916	(21.1)
Bare-metal stent	4783	(52.2)	4806	(52.5)
≥1 drug-eluting stent	4059	(44.3)	4038	(44.1)
Number of stents, mean (SD)	1.4	(0.7)	1.4	(0.7)
Total stent length mm, mean (SD)	28	(15.5)	28.1	(15.4)
Stent diameter mm, mean (SD)	3.2	(0.5)	3.1	(0.5)
Vessel treated at Index PCI				
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[z]				
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)
Beta Blocker	7161	(84.3)	7198	(84.9)
Oral anticoagulant	493 (5.8)		497 (5.9)	

† Current smoker P<0.001, [y] time from symptom onset to PCI P=0.025 ‡‡GP IIb/IIIa inhibitor P<0.001, *Contrast volume P<0.001, **Fluoroscopy time P<0.001 (TASTE and TOTAL only),*** TIMI thrombus grade P<0.001, [z] Medications at discharge only available from TASTE and TOTAL.

Table 2: Outcomes

Outcome	**Thrombus Aspiration N= 9155**	**PCI Alone N= 9151**	**HR**	**95% CI**	**P value**
Primary Outcome					
Cardiovascular death at 30 days	221 (2.4)	262 (2.9)	0.84	0.70-1.01	0.06
Key Safety Outcome					
Stroke or TIA at 30 days*	66/8518 (0.8)	46/8476 (0.5)	1.43	0.98-2.1	0.06
Other Outcomes at 30 days					
All Cause death	232 (2.5)	273 (3.0)	0.85	0.71-1.01	0.06
Myocardial infarction	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 year					
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 revascularisation	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

*Data only available from TASTE and TOTAL trials and OR reported not HR.
** Data only available from TASTE and TOTAL trials

Table 3: Outcomes by High and Low Thrombus Burden

Outcome	Thrombus Aspiration	PCI Alone	HR	95% CI	P value	Interaction P
Cardiovascular Death at 30 days						
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 days*						
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 days						
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 year						
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	

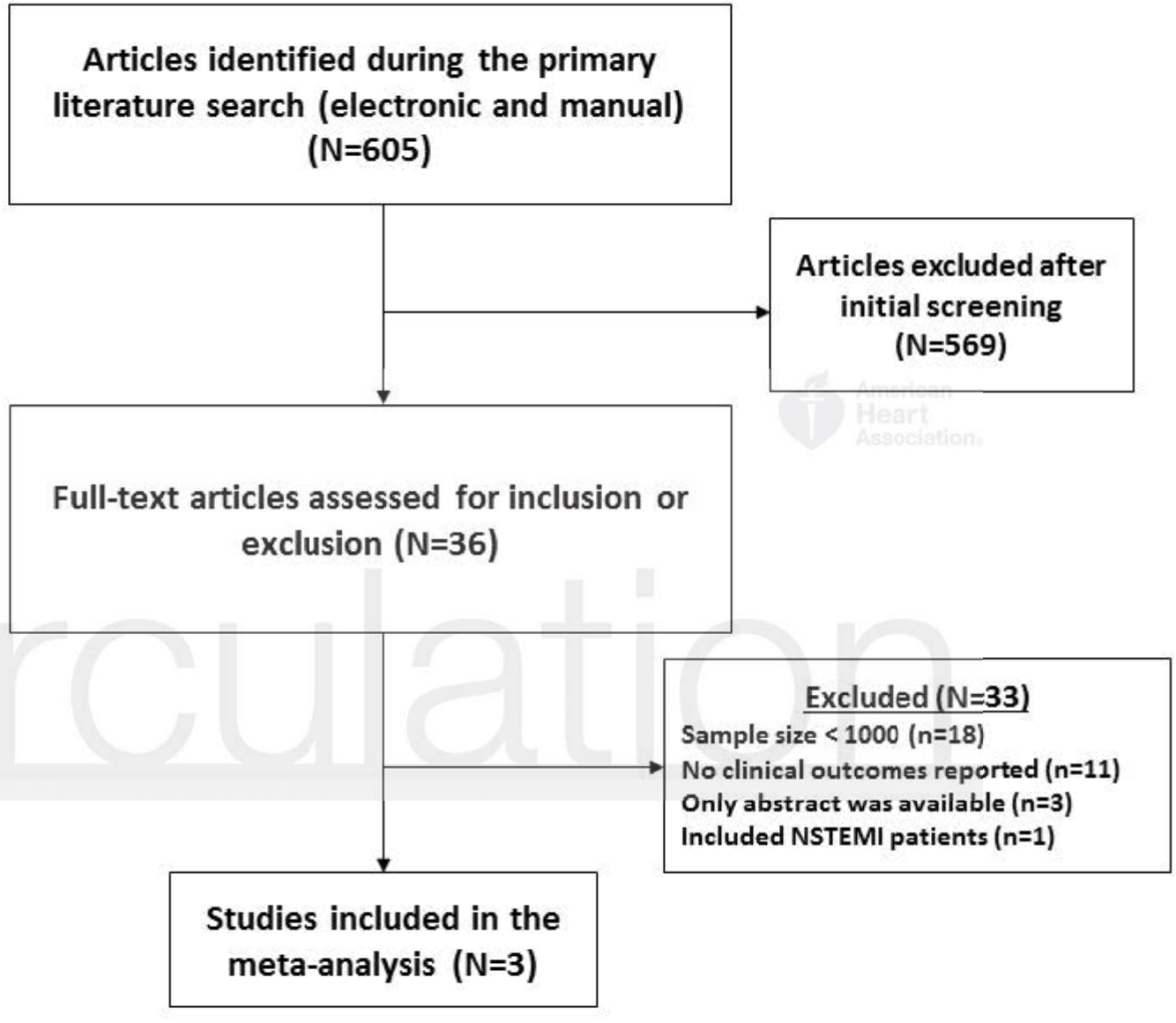
*Stroke or TIA outcomes have odds ratio reported instead of hazard ratio

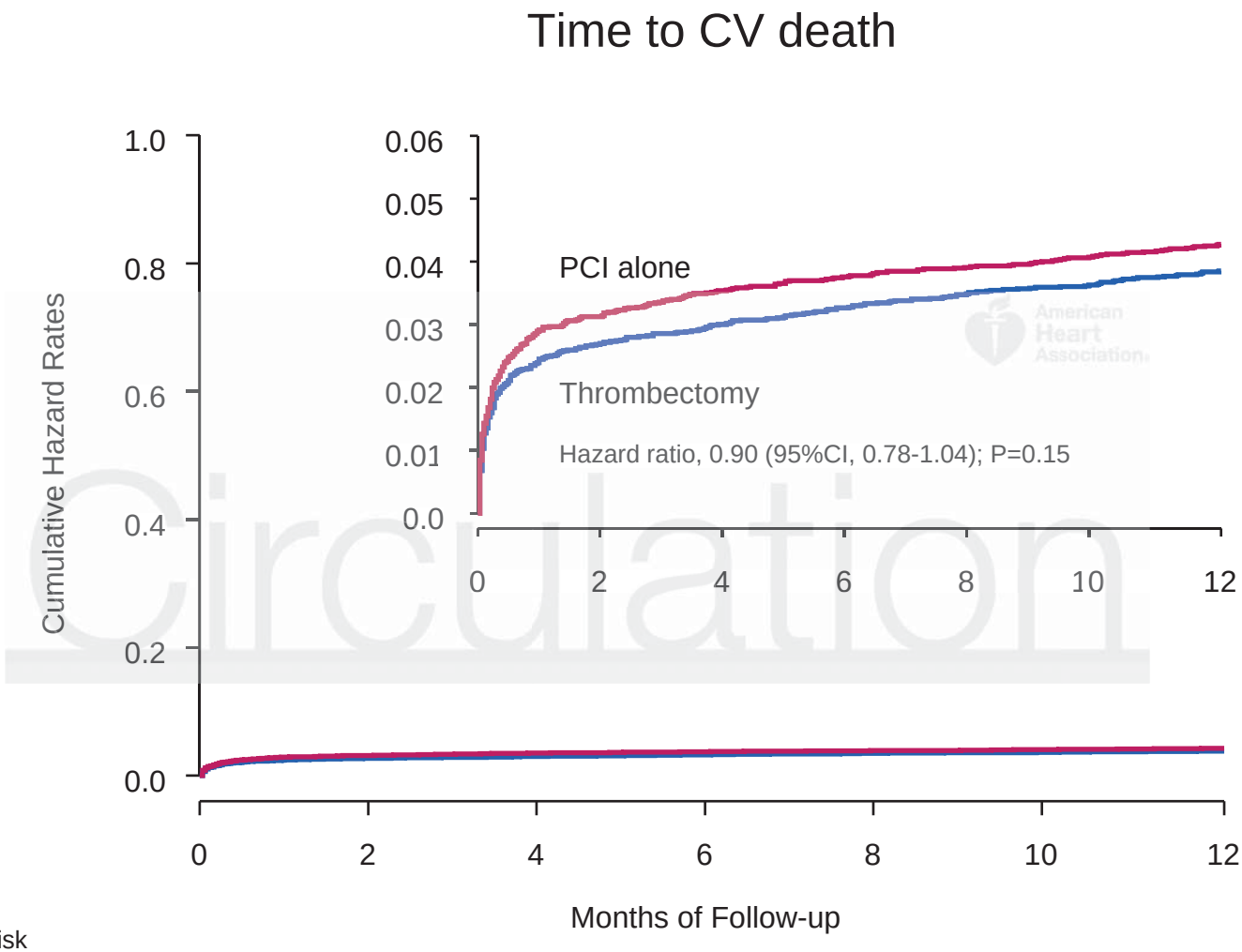
Figure Legends

Figure 1. PRISMA flowchart

Figure 2. Kaplan Meier Curves for cardiovascular mortality

Figure 3. A. Subgroup analysis for cardiovascular mortality at 30 days. B. Subgroup analysis for stroke or TIA within 30 days

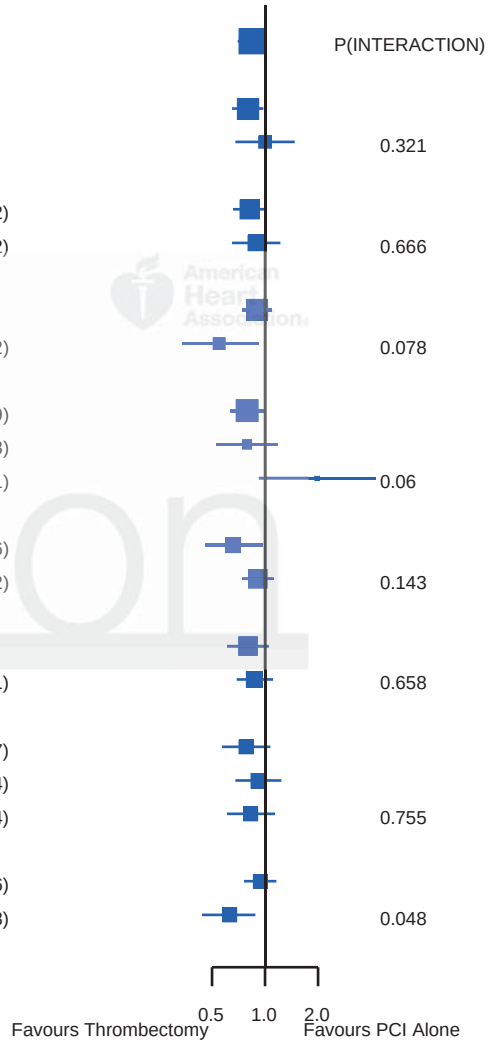




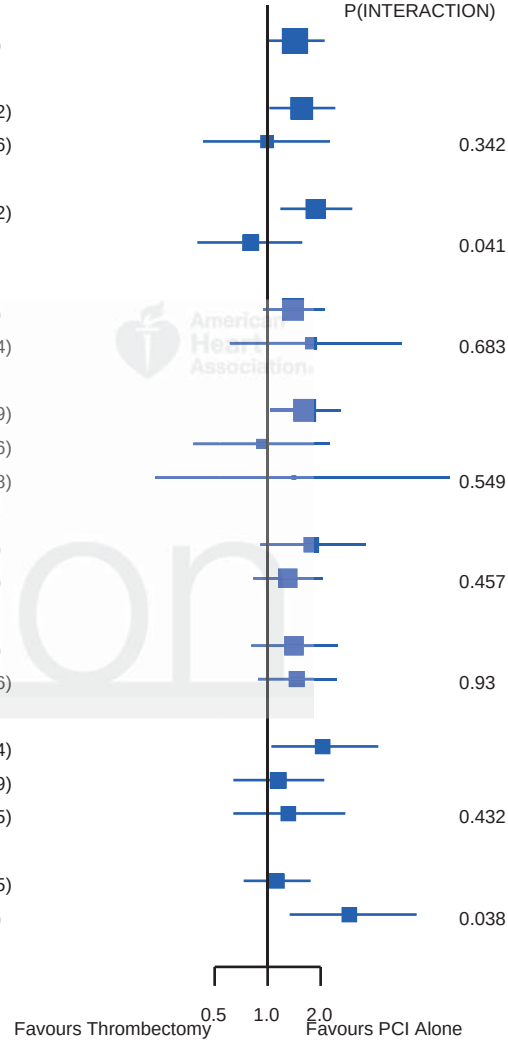
No. at Risk

Thrombectomy	9155	8853	8810	8778	8536	8509	8437
PCI Alone	9151	8807	8759	8729	8488	8458	8383

		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	10856	95/5455 (1.74)	117/5401 (2.17)	0.8(0.61-1.05)	
LAD lesion	7407	125/3674 (3.4)	145/3733 (3.88)	0.87(0.69-1.11)	0.658
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



		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	10125	30/5100 (0.59)	21/5025 (0.42)	1.41(0.81-2.5)	
LAD lesion	6828	36/3393 (1.06)	25/3435 (0.73)	1.46(0.88-2.46)	0.93
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



Thrombus Aspiration in ST Elevation Myocardial Infarction: An Individual Patient Meta-analysis

Sanjit S. Jolly, Stefan K. James, Vladimír Dzavík, John A. Cairns, Karim D. Mahmoud, Felix Zijlstra, Salim Yusuf, Göran K. Olivecrona, Henrik Renlund, Peggy Gao, Bo Lagerqvist, Ashraf Alazzoni, Sasko Kedev, Goran Stankovic, Brandi Meeks and Ole Frøbert

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SUPPLEMENTAL MATERIAL

Supplemental Methods: Search Strategy for Ovid MEDLINE and EMBASE as of September 2, 2016

Results using Search Strategy

1 Myocardial Infarction.mp. (440266)
2 Thrombectomy.mp. (23156)
3 Thrombus Aspiration.mp. (3260)
4 Thromboaspiration.mp. (426)
5 2 or 3 or 4 (25178)
6 Randomized.mp. (1465727)
7 1 and 5 and 6 (818)
8 Remove duplicates from 7 (605)

Supplemental Table S1: Characteristics of Included Trials

Table S1. Trial overview

	TOTAL	TASTE	TAPAS
n	10,732	7,244	1,071
n screened	Not reported	12,005	1,161
% included	Not reported	60	92
No. of centers	87	31	1
Included symptom duration, hrs	0-12	0.5-24	0.5-12
Intervention	Routine Thrombus Aspiration	Routine Thrombus Aspiration	Routine Thrombus Aspiration with direct stenting when possible
Manual Aspiration device	Export®	Export®, Pronto®, Eliminate®	Export®
Primary Outcome	CV death, new MI, chock, or NYHA IV heart failure within 180 days	30 day all-cause death	Myocardial blush grade 0 or 1

CV, cardiovascular; NYHA, New York Heart Association; MI, myocardial infarction.

Supplemental Table S2: Outcome Definitions

Table S2.

<table>
<tr><th>Trial</th><th>CV Death</th><th colspan="2">Recurrent MI</th><th>Heart Failure</th></tr>
<tr><td rowspan="4">TOTAL</td><td rowspan="4">All deaths with a clear cardiovascular or unknown cause will be classified as cardiovascular.</td><td colspan="2">Recurrent myocardial infarction (MI) will be subdivided into MI within the first 24 hours of randomization, between 24 hours and 7 days after randomization and more than 7 days after randomization.</td><td rowspan="4">New or worsening NYHA Class IV heart failure is defined as a physician decision to treat HF with IV diuretic, inotropic agent or vasodilator plus at least one of the following: 1) presence of pulmonary edema or pulmonary vascular congestion on chest radiograph thought to be due to HF; 2) rales reaching above the lower 1/3 of the lung fields thought to be due to HF; or 3) PCWP or LVEDP ≥ 18 mm Hg.</td></tr>
<tr><td>MI occurring within 24 hours of randomization</td><td>Recurrent ischemic symptoms greater than 20 minutes with new ST elevation greater than 0.1 millivolt in at least 2 contiguous leads not due to changes from evolution of the index MI.</td></tr>
<tr><td>MI occurring between 24 hours and 7 days of randomization</td><td>Ischemic symptoms greater than 20 minutes and either i) elevation or re-elevation of cardiac biomarkers (CK-MB or troponin) greater than twice the upper limit of normal, and if already elevated then further elevations more than 50% above a previous value that was decreasing or, ii) new ST segment elevation or, new significant Q waves in at least 2 contiguous leads, which are separate from the baseline MI.</td></tr>
<tr><td>MI occurring after 7 days of randomization</td><td>Typical rise and fall of biochemical markers of myocardial necrosis to greater than twice the upper limit of normal or if markers were already elevated, further elevation of a marker to greater than 50% of a previous value that was decreasing and > 2X ULN, with at least one of: i) ischemic symptoms, ii) development of new pathological Q waves, iii) ECG changes of new ischemia, or Pathological evidence of MI.</td></tr>
</table>

Trial	CV Death	Recurrent MI		Heart Failure
		MI occurring within 24 hours following non-index PCI that is performed more than 24 hours after randomization	Cardiac biomarker (CK-MB or troponin) greater than 3 times the upper limit of normal (ULN) or increased by 50% from the pre-procedural valley level and greater than or equal to 3 times ULN in patients with already elevated enzymes, or new ST segment elevation or development of significant Q waves in 2 or more contiguous leads which are discrete from baseline MI.	
		Within 24 hours Post-CABG	CK-MB (or Total CK, if CK-MB is unavailable) greater than or equal to 5 times ULN and increased 50% from the pre-procedural valley level AND > 5 X ULN in patients with already elevated enzymes and development new pathological Q waves in 2 or more contiguous leads, or CK-MB value greater or equal to 10 times ULN without new pathological Q waves.	
TASTE	All deaths with a clear cardiovascular or unknown cause will be classified as cardiovascular by information from national death registry.	Rehospitalization for myocardial infarction defined as ICD codes I21 and I22 by the treating physician		ICD code I50 as judged by the treating physician.
TAPAS	Death was regarded as cardiac unless an unequivocal non-cardiac cause of death was established	Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of cardiac markers to at least twice the upper limit of normal. +NSTEMI.		Not available
Meta-analysis definition	All deaths with a clear cardiovascular or unknown cause will be classified as cardiovascular.	Recurrent MI as per study definition 30 days, 180 days, 1 year		Heart failure (TOTAL and TASTE only)

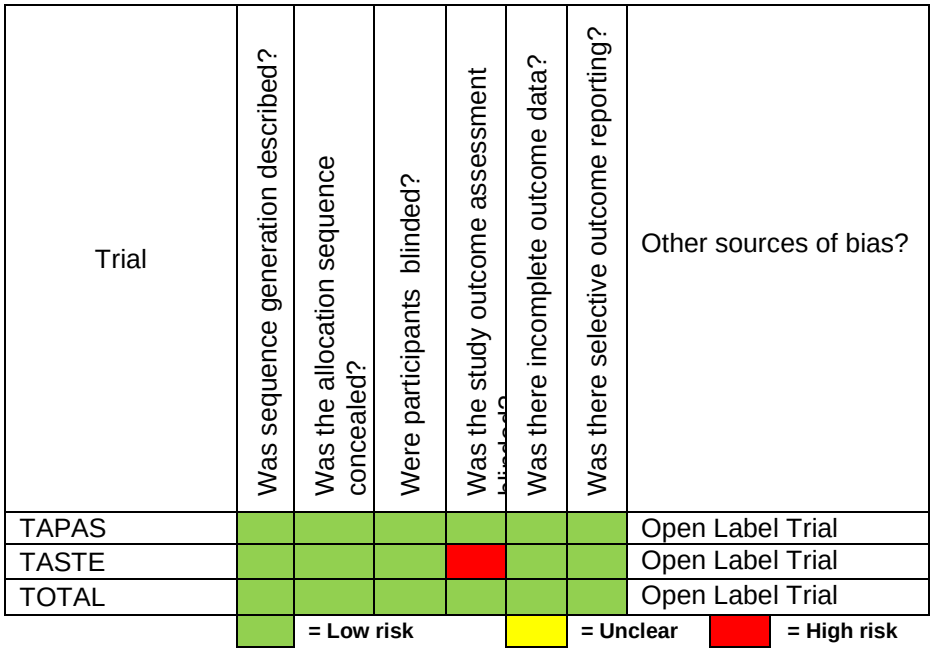
Trial	CV Death	Recurrent MI	Heart Failure
	30 days, 180 days, 1 year		

Table S2. Continued

Trial	Stroke/TIA	Definite Stent Thrombosis	TVR
TOTAL	Any stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours OR A transient episode of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting <24 hours.	Academic Research Consortium Definition	Any revascularization procedure (PCI or CABG) involving the vessel treated during the index PCI procedure for STEMI.
TASTE	Procedure-related stroke or neurologic complication as judged by the treating physician or in the ward.	Defined according to the Academic Research Consortium definition for "definite and confirmed stent thrombosis" i.e.: "symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis". In TASTE the diagnosis of stent thrombosis was confirmed by angiography in all cases.	A new therapeutic PCI in the same coronary artery as the index procedure or coronary artery bypass surgery after the index procedure.
TAPAS	No stroke or TIA collected.	Angiographically proven stent thrombosis was defined as a complete or partial occlusion within the stented segment, with evidence of thrombus and reduced	Ischemia driven target vessel revascularization by means of PCI or CABG

Trial	Stroke/TIA	Definite Stent Thrombosis	TVR
		antegrade flow (TIMI flow <3) with a concurrent acute clinical ischaemic event	
Meta-analysis definition	Stroke/TIA 30 days, 180 days, 1 year	Definite stent thrombosis 24 hours, 30 days, 180 days, 360 days	TVR 30 days, 180 days, 1 year

Supplemental Figure S1: Risk of bias as per the Cochrane Collaboration's tool



Supplemental Figure S2: CV Death at 30 days by Study

Supplemental Figure S3: Stroke or TIA at 30 days by Study