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Efficacy and safety of thrombus aspiration in ST-segment elevation myocardial infarction: an updated systematic review and meta-analysis of randomised clinical trials

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Abstract

Background: The role of thrombus aspiration plus primary percutaneous coronary intervention in ST-segment elevation myocardial infarction remains controversial.

Methods: We performed a meta-analysis of 25 randomised controlled trials in which 21,740 ST-segment elevation myocardial infarction patients were randomly assigned to thrombus aspiration plus primary percutaneous coronary intervention or primary percutaneous coronary intervention. Study endpoints were: death, myocardial infarction, stent thrombosis and stroke.

Results: On pooled analysis, the risk of death (4.3% vs. 4.8%, odds ratio (OR) 0.90, 95% confidence interval (CI) 0.79–1.03; *P*=0.123), myocardial infarction (2.4% vs. 2.5%, OR 0.95, 95% CI 0.80–1.13; *P*=0.57) and stent thrombosis (1.3% vs. 1.6%, OR 0.80, 95% CI 0.63–1.01; *P*=0.066) was similar between thrombus aspiration plus primary percutaneous coronary intervention and primary percutaneous coronary intervention. The risk of stroke was higher in the thrombus aspiration plus primary percutaneous coronary intervention than the primary percutaneous coronary intervention group (0.84% vs. 0.59%, OR 1.401, 95% CI 1.004–1.954; *P*=0.047). However, on sensitivity analysis after removing the TOTAL trial, thrombus aspiration plus primary percutaneous coronary intervention was not associated with an increased risk of stroke (OR 1.01, 95% CI 0.58–1.78). The weak association between thrombus aspiration and stroke was also confirmed by the fact that the lower bound of the 95% CI was slightly below unity after removing either the study by Kaltoft or the ITTI trial. There was no interaction between the main study results and follow-up, evidence of coronary thrombus, or study sample size.

Conclusions: In patients with ST-segment elevation myocardial infarction, thrombus aspiration plus primary percutaneous coronary intervention does not reduce the risk of death, myocardial infarction or stent thrombosis. Thrombus aspiration plus primary percutaneous coronary intervention is associated with an increased risk of stroke; however, this latter finding appears weak.

Keywords

ST-segment elevation myocardial infarction, thrombus aspiration, primary percutaneous intervention, outcome

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Introduction

Primary percutaneous coronary intervention (PPCI) represents the treatment of choice for ST-segment elevation myocardial infarction (STEMI).[1,2] However, despite the achievement of infarct-related artery patency in most of the cases, myocardial tissue reperfusion may not occur because of microvascular damage that causes poor recovery of left

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ventricular function and poor prognosis.[3–5] In this process, known as the no-reflow phenomenon, several mechanisms are involved.[6]

During the past decade thrombus aspiration (TA), by means of thrombus removal, has been considered a simple way to reduce the risk of distal embolisation and ultimately to facilitate myocardial reperfusion. Indeed, early small to moderate sized randomised clinical trials (RCTs)[7–11] have consistently shown that adjunctive TA to PPCI improves indices of myocardial perfusion compared to PPCI. Furthermore, long-term data from the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS)[12] and early meta-analyses[13,14] suggested that the beneficial effect on indices of myocardial perfusion could translate into better clinical outcomes. However, these findings have been challenged by the results of both recent multicentre RCTs[15–18] and meta-analyses[19–21] showing no benefit in the use of routine TA plus PPCI compared to PPCI alone, while it might be associated with an increased risk of stroke.[17–21] However, these studies could still be underpowered to detect small differences in terms of both hard and rare clinical endpoints. Yet, since the publication of the most recent meta-analysis[21] additional studies and longer follow-ups are available.

Accordingly, we undertook an updated systematic review and meta-analysis including data at the longest follow-up available to determine whether in patients with STEMI a strategy of routine TA plus PPCI, compared to PPCI alone reduced the risk of clinical hard endpoints (all-cause mortality, myocardial infarction (MI), stent thrombosis) or may be associated with an increased risk of stroke. Of note, we performed a comprehensive sensitivity analysis to evaluate the possibility of interaction between final effect estimates and the following study characteristics: sample size, evidence of coronary thrombus as inclusion criteria and follow-up duration. Evaluation of study-level interaction was also performed.

Methods

Study selection and study endpoint

We carried out a systematic review of the available publications according to the current PRISMA guidelines to perform meta-analyses of RCTs.[22] We searched for relevant articles, published in MEDLINE and the Cochrane Library, using the following key words that were combined as follows: 'STEMI and thrombectomy', 'MI and thrombectomy', 'STEMI and aspiration', 'MI and aspiration', 'STEMI and thrombus aspiration', 'MI and thrombus aspiration' (Supplementary Table 1). No language restriction was used. We also checked the reference lists of reviews and relevant articles. Inclusion criteria were as follows: (a) RCT design; (b) full text article; (c) comparison between TA plus PPCI and PPCI alone in STEMI patients within 48 hours of symptoms onset, including rescue percutaneous coronary intervention (PCI) patients; (d) data on clinical outcome available.

We excluded trials that included patients treated with a fibrinolysis facilitated PPCI, trials performing mechanical thrombectomy, studies comparing different thrombectomy devices and those enrolling only patients treated on a saphenous vein coronary graft. Two investigators (NT and GG) independently reviewed the titles, abstracts and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were resolved by consensus.

The individual efficacy study endpoints were the rate of all-cause death, MI and stent thrombosis. The safety clinical endpoint was the rate of stroke. We used definitions applied in each study and data from the longest follow-up available. Data were extracted on the basis of the intention-to-treat populations. Risk of bias assessment was conducted according to the Cochrane criteria[23] (Supplementary Table 2).

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were used as the summary statistic. The pooled OR was calculated by using both fixed-effect (inverse variance weighted) and random-effect (DerSimonian and Laird) models. Between-study heterogeneity of effects was analysed using the χ^2 and inconsistency across study results quantified by I^2 statistics, with $I^2<25\%$, $25\%\leqslant I^2\leqslant 50\%$ and $I^2>50\%$, respectively, representing mild, moderate and severe inconsistency. Sensitivity analysis was performed by evaluating the influence of removing individual studies on the pooled OR. Sensitivity analysis was also performed with reference to the following study characteristics: sample size, evidence of coronary thrombus as inclusion criteria and duration of follow-up (short (in H–30 days) vs. mid follow-up (6–12 months)). The number needed to treat and the number treated to harm (NTH) for each outcome were calculated as previously described for meta-analysis.[24] We deemed P values less than 0.05 as significant (and all P values were two-sided). The possibility of publication bias was assessed both visually by funnel plot and Peter's test. Statistical analyses were performed using Stata/SE 12.0 (StataCorp LP, College Station, TX, USA).

Results

Figure 1 shows the flow chart for the study analysis. Of 632 potentially relevant articles initially screened, 25 met the inclusion criteria and were included in the meta-analysis, with a total of 21,740 patients.[7–11,15,17,25–42] Six studies presented extended follow-up in subsequent papers[12,16,18,43–45] and these data were used for the present meta-analysis. Supplementary Table 2 shows the risk of bias of studies included in the meta-analysis. Table 1 shows the main characteristics of the studies included. Patients were predominantly enrolled if they had

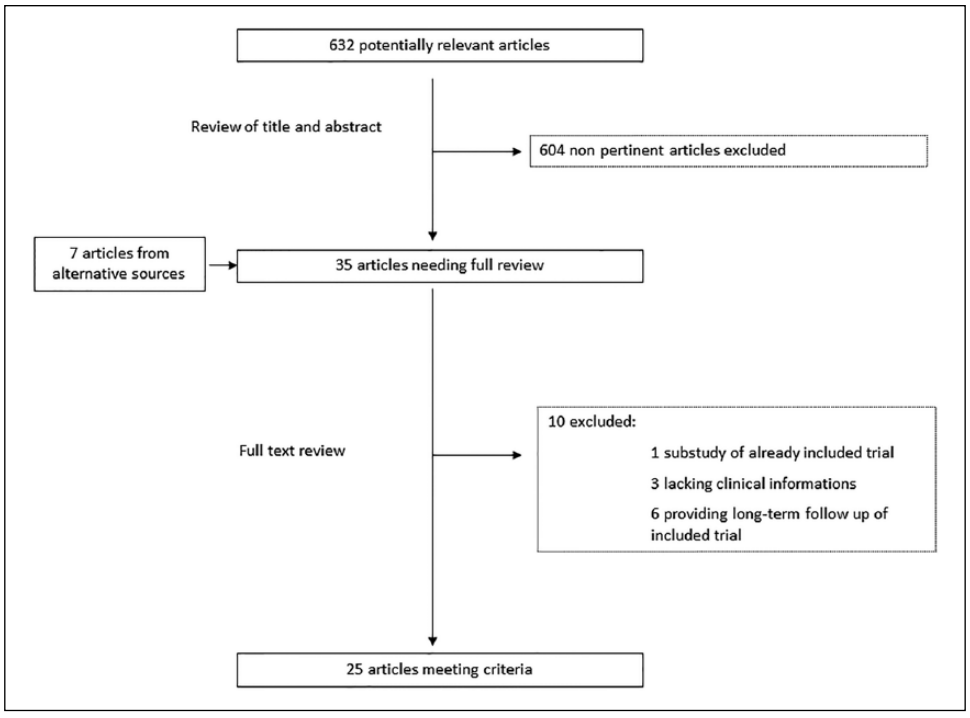

Figure 1. Study flow chart.

experienced STEMI within 12 hours of symptom onset. Patients with STEMI greater than 12 hours were enrolled in four studies.[15,26,28,41] Only TASTE[15] and TOTAL[17] trials had clinical events as the primary endpoint. Follow-up duration ranged from in-hospital to 12 months. Table 2 shows the main patients' baseline characteristics according to each study. The percentage of patients with high thrombus grade was much higher in the TOTAL trial as compared to the TASTE trial (89% vs. 31%).

All-cause mortality

Among the 21,740 patients included in the analysis, the rate of all-cause death was 4.5% at a weighted mean follow-up of 11.1 months. On pooled analysis, the risk of all-cause death was similar between patients undergoing TA plus PPCI and those undergoing PPCI alone (4.3% vs. 4.8%, OR on both fixed and random effect 0.90, 95% CI 0.79–1.03; P=0.123). There was no heterogeneity among the studies (I^2=0.0%, P=0.74) (Figure 2(a)). On sensitivity analyses studies' sample size (P for interaction 0.43, Figure 2(b)), evidence of thrombus as inclusion criteria (P for interaction 0.38, Figure 2(c)) and follow-up duration (P for interaction 0.42, Figure 2(d)) did not affect the relative risk of all-cause death in patients undergoing TA plus PPCI as compared to patients undergoing PPCI. Supplementary Figure 1 shows that after removing each individual study the pooled effect estimate remained substantially unchanged. The funnel plot was symmetric showing the lack of publication bias (Supplementary Figure 2). The Peter's test further supports this result (P value for small-study effect 0.22).

MI and stent thrombosis

Data on MI were available in 20 studies including 21,336 patients. The rate of MI was 2.5% at a weighted mean follow-up of 11.3 months. On pooled analysis, the risk of MI was similar between patients undergoing TA plus PPCI and those undergoing PPCI (2.4% vs. 2.5%, OR 0.95, 95% CI 0.80–1.13; P=0.57). There was no heterogeneity among the studies (I^2=0.0%, P=0.88) (Figure 3(a)). We noted no significant heterogeneity for MI between the effect estimate and studies grouped by sample size, evidence of thrombus as inclusion criteria and follow-up duration (Figure 3(b–d)). Supplementary Figure 3 shows that after removing each individual study the pooled effect estimate remained unchanged. Funnel plot (Supplementary Figure 4) and the Peter's test (P=0.26) showed the lack of publication bias.

Eleven studies reported data on stent thrombosis. Among 19,985 patients the rate of stent thrombosis at a weighted mean follow-up of 11.8 months was 1.4%. No studies had a follow-up time less than 6 months. Patients treated with TA plus PPCI showed a trend towards a lower risk of stent thrombosis compared to those undergoing only PPCI (1.3% vs. 1.6%, OR 0.80, 95% CI 0.63–1.01; P=0.066) (Figure 4(a)). We noted (Figure 4(b) and (c)) no significant heterogeneity for stent thrombosis between the effect estimate and both studies' sample size and evidence of thrombus as inclusion criteria. No individual study affected the effect

Table 1. Characteristics of included trials.

Trial name or first author	Year of publication	Design of the trial	Inclusion criteria	Exclusion criteria	Primary endpoint	Number of patients	Device	Follow-up, months
REMEDIA[7]	2005	Single RCT	STEMI <12 h referred for primary or rescue PCI	None	Rate of STR ⩾70%	99	Diver CE	1
De Luca et al.[9]	2006	Single RCT	Anterior STEMI + angiographically identifiable thrombus	Prior MI or CABG, 3VD, severe VHD, pre-TIMI flow grade ⩾2, unsuccessful I PCI	Rate of LV remodeling	76	Diver CE	6
DEAR-MI[10]	2006	Single RCT	STEMI <12 h undergoing primary angioplasty	Cardiogenic shock, prior MI or CABG, BBB, paced rhythm, contraindication to IIb/IIIa inhibitors	Rate of STR ⩾70%, and pos PPCI MBG 3	148	Pronto	1
Kaltoft et al.[42]	2006	Single RCT	STEMI <12 h	Left BBB, prior MI within 30 days, prior CABG, LMD, need for mechanical ventilation, severe HF requiring IABP	Myocardial salvage by 99mTC-sestamibi SPECT	215	Rescue	1
Chao et al.[8]	2007	Single RCT	STEMI <12 h	Killip class-IV, VT, prior CABG, LMD, culprit vessel <2 mm, TIMI flow grade 3	ΔTIMI and ΔMBG	74	Export	6
TAPAS[11,12]	2008	Single RCT	STEMI <12 h	Rescue PCI, Known disease resulting in a life expectancy of less 6 months	Rate of post-MBG 0 or 1	1071	Export	12
Chevalier et al.[25]	2008	Multicentre RCT	STEMI <12 h, visual reference VD ⩾2.5 mm, pre TIMI flow grade ⩽ 1	Cardiogenic shock, cardiac arrest, fibrinolysis, pre-intervention GP IIb/IIIa inhibitors, pacemaker	Rate of combined STR (<50 min) and MBG 3	249	Export	1
VAMPIRE[26]	2008	Multicentre RCT	STEMI <24 h	Primary thrombolysis, cardiogenic shock, history of cardiac arrest or CABG, CKD (cr >2.0 mg/dl), LMD target vessel diameter < 2.5 or > 5.0 mm	Rate of post-TIMI flow grade <3	355	Nipro (TVAC)	8
EXPIRA[27,43]	2009	Single RCT	First STEMI <9 h, IRA ⩾2.5 diameter, thrombus score ⩾3, TIMI flow grade ⩽1	Prior PCI on IRA, prior CABG, cardiogenic shock, 3 VD, LMA disease, severe VHD, thrombolysis, contraindication to GP IIb/IIIa inhibitors	Rate of MBG ⩾2 and STR	175	Export	9
Lipiecki et al.[28]	2009	Single RCT	First STEMI <48 h, baseline TIMI flow grade ⩽1	Killip class >2, previous MI or CABG, left BBB or paced rhythm, contraindication to SPECT or MRI	Infarct size as assessed by 99mTC-sestamibi SPECT	44	Export	H

Table 1. (Continued)

Trial name or first author	Year of publication	Design of the trial	Inclusion criteria	Exclusion criteria	Primary endpoint	Number of patients	Device	Follow-up, months
Liistro et al.[29]	2009	Single RCT	First SEMI <12 h	Contraindication to GP IIb/IIIa inhibitors, rescue PCI, previous MI, absence of optimal echocardiographic view	STR ⩾70%	111	Export	6
PIHRATE[30]	2010	Multicentre RCT	First STEMI <6 h, baseline TIMI flow grade ⩽1	Prior MI, PCI or CABG, cardiogenic shock, fibrinolysis	Rate of STR >70%	196	Diver CE	6
ITTI[31]	2010	2 × 2 Factorial single RCT	STEMI <12 h	Cardiogenic shock, history of bleeding tendency, major operation <6 weeks, hepatic or renal insufficiency, contraindication to tirofiban	Rate of MBG 3	100	Thrombuster II	6
Ciszewski et al.[32]	2011	Single RCT	STEMI <12 h, LAD or RCA as IRA, baseline TIMI flow grade ⩽2, presence of thrombus	Cardiogenic shock, LCA as IRA, previous PCI or CABG, History of previous MI or CTO of any non-IRA	Myocardial salvage index by 99mTc-sestamibi SPECT	137	Rescue, Diver CE	H
Bulum et al. [33]	2012	Single RCT	STEMI <12 h	Rescue PCI, cardiogenic shock, triple vessel disease, significant LMD, prior PCI of IRA, previous CABG, limited life expectancy	In-stent restenosis	60	Export	6
MUSTELA[34]	2012	Multicentre RCT	STEMI <12 h, TIMI thrombus grade >3, Reference VD ⩾ 3 mm	Previous MI in the same ventricular wall, contraindications to abciximab, severe renal/liver failure, contraindication to MRI	Rate of STR at 60 min, Infarct size at 3 months by MRI	208	Export	12
INFUSE-AMI[35,44]	2012	2 × 2 Factorial single RCT	Anterior STEMI + anticipate symptoms-to-device time ⩽5 h	Contraindication to abciximab or contrast. Prior MI, CABG or LAD stenting, planned surgery requiring antiplatelet therapy interruption, contraindication to MRI, cardiogenic shock,	30-Day infarct size	452	Export	12
TROFI[36,45]	2013	Multicentre RCT	STEMI <12 h + angiographically visible stenosis (>30%) or baseline TIMI flow grade ⩽2	None	Minimum flow area after PPCI assessed by OFDI	141	Eliminate	H
TASTE[15,16]	2013	Multicentre registry-based RCT	STEMI <24 h	Need for emergency CABG	Overall mortality	7244	Eliminate, export, pronto	12

(Continued)

Table 1. (Continued)

Trial name or first author	Year of publication	Design of the trial	Inclusion criteria	Exclusion criteria	Primary endpoint	Number of patients	Device	Follow-up, months
Sim et al.[37]	2013	Single RCT	STEMI <12 h, visible thrombus, Killip class I–II	Previous MI or CABG, cardiogenic shock, LMD, rescue or facilitated PCI, contraindications to GP IIb/IIIa inhibitors	Infarct size assessed by CCT on a delayed enhancement scanning	86	Thrombuster II	12
TOTAL[17,18]	2014	Multicentre RCT	STEMI <12 h	Prior CABG, fibrinolysis, life expectancy less than 6 months due to non-cardiac condition	Composite of: cardiovascular causes, recurrent MI	10,064*	Export	12
Woo et al.[38]	2014	Single RCT	First STEMI <12 h	Cardiogenic shock, prior MI, contraindications to adenosine	Index of microcirculatory resistance	63	Export	6
Shehata et al. [39]	2014	Single RCT	Diabetic patients with STEMI <12 h	Rescue PCI, prior ACS, prior PCI or CABG, known cardiovascular disease, limited life expectancy	In-stent restenosis	100	Export	8
COCTAIL II[40]	2015	2 × 2 Factorial multicentre RCT	STEMI <6 h, culprit lesion in native coronary, evidence of thrombus with TIMI <3	Technical or clinical contraindication to OCT	OCT-assessed intrastent residual atherothrombotic area	128	Not reported	9
Desch et al.[41]	2016	Single RCT	STEMI ⩾12 h and STEMI ⩽48 h	Prior thrombolysis, contraindication to CMR, limited life expectancy	Extent of microvasculature obtruction as assessed by CMR	144	Export	1

ACS: acute coronary syndrome; ARF: acute renal failure; BBB: bundle brunch block; CABG: coronary artery bypass graftin; CCT: cardiac computed tomography; CKD: chronic kidney disease; CMR: cardiac magnetic resonance; HF: heart failure; IABP: intra-aortic balloon pump; IRA: infarct-related artery; LCA: left coronary artery; LMD: left main disease; LV: left ventricular; MBG: myocardial blush grade; MI: myocardial infarction; MRI: magnetic resonance imaging; OCT: optical coherence tomography; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; PPCI: primary percutaneous coronary intervention; RCA: right coronary artery; RCT: randomised control trial; SPECT: single-photon emission computed tomography; STEMI: ST-segment elevation myocardial infarction; STR: stent thrombosis resolution; TIMI: thrombolysis in myocardial infarction; TVAC: thrombus vacuum aspiration catheter; VD: vessel disease; VHD: valvular heart disease; VT: ventricular tachycardia.

*In TOTAL 10,732 STEMI patients were enrolled but the primary analysis was performed only in 10,064 patients who actually underwent PPCI.[18]

Table 2. Characteristics of patients.

	Age (years)		Male (%)		Diabetes (%)		Symptoms-to-angiography (min)		Advance Killip class (%)		Pre-TIMI <= 1 (%)		LAD involvment (%)		High thrombus grade (%)		GP IIb/IIIa inhibitors (%)	
	TA	C	TA	C	TA	C	TA	C	TA	C	TA	C	TA	C	TA	C	TA	C
REMEDIA[7]	61	60	90	78	22	18	274	300	30	29	86	89	40	51	58	55	68	63
De Luca et al.[9]	67	65	71	55	24	18	432	456	29	25	100	100	100	99	na	na	100	100
DEAR-MI[10]	57	59	84	76	21	15	206	199	11	5	81	73	43	51	na	na	100	100
Kaltoft et al.[42]	65	63	76	80	8	6	242	208	6	4	68	69	46	43	na	na	96	93
Chao et al.[8]	60	62	84	86	32	22	312	331	na	na	na	na	56	59	81	73	19	32
TAPAS[11,12]	63	63	68	73	11	12	190	185	na	na	55	60	43	43	48	44	93	90
Chevalier et al.[25]	50	61	81	81	17	13	225	219	12	11	99.2	100	48	52	na	na	3	11
VAMPIRE[26]	63	64	81	78	23	30	270	312	11	8	75	75	50	52	na	na	0	0
EXPIRA[27,43]	68	67	65	55	24	18	366	366	19	29	100	100	43	44	100	100	100	100
Lipiecki et al.[28]	59	59	60	75	5	8	426	444	0	0	100	96	35	46	na	na	30	74
Liistro et al.[29]	64	65	78	77	20	12	189	209	8	4	69	76	38	46	na	na	100	100
PIHRATE[30]	61	59	80	82	13	10	na	na	2	1	97	98	39	40	0	0	8	11
ITTI[31]	61	57	90	81	27	25	274	245	0	8	82	92	50	52	88	94	54	52
Ciszewski et al.[32]	64	64	48	50	10	17	37	34	na	na	90	91	37	34	100	99	84	80
Bulum et al.[33]	54	59	83	73	10	10	234	293	na	na	na	na	47	37	na	na	97	83
MUSTELA[34]	62	63	88	76	19	20	230	208	4	9	91	78	na	na	100	100	100	100
INFUSE-AMI[35,44]	61	59	74	74	15	8	146	163	1	2	51	50	na	na	na	na	51	50
TROFI[36,45]	61	61	76	69	8	13	na	na	1	1	48	46	45	43	86	83	48	63
TASTE[15,16]	67	66	75	75	12	13	185	182	6	5	78	78	41	40	31	30	15	17
Sim et al.[37]	63	60	67	70	28	33	180	120	0	0	77	77	63	49	na	na	30	47
TOTAL[17,18]	61	61	77	78	18	19	128	120	4	4	74	74	na	na	91	89	37	31
Woo et al. [38]	55	53	85	100	21	17	266	281	na	na	79	83	73	53	88	93	0	0
Shehata et al.[39]	60	59	62	66	100	100	78	74	12	8	na	na	29	25	na	na	100	100
COCTAIL II[40]	62	62	81	86	14	15	175	175	22	16	64	56	40	45	na	na	100	100
Desch et al.[41]	66	66	69	80	31	34	1560	1740	13	18	67	65	54	44	89	79	25	28

C: control; LAD: left anterior descending artery; na: not available; TA: thrombus aspiration.

estimate for stent thrombosis (Supplementary Figure 5). Funnel plot (Supplementary Figure 6) and the Peter's test (P=0.33) showed the lack of publication bias.

Stroke

Data on stroke were available in 13 studies including 20,195 STEMI patients. At a weighted mean follow-up of 7.5 months the rate of stroke was 0.63%. Figure 5(a) shows that on pooled analysis, the risk of stroke was higher in patients undergoing TA plus PPCI as compared to those undergoing only PPCI (0.84% vs. 0.59%, OR 1.401, 95% CI 1.004–1.954; P=0.047). The NTH was 423. After removing the Trial of Routine Aspiration Thrombectomy with PCI versus PCI alone (TOTAL)[17,18] TA plus PCCI was no longer associated with an increased risk of stroke (OR 1.01, 95% CI 0.58–1.78; Supplementary Figure 7). The weak association between TA and stroke was also confirmed by the fact that the lower bound of the 95% CI was slightly below unity after removing either the study by Kaltoft et al.[42](OR 1.38, 95% CI 0.99–1.93) or the ITTI trial[31] (OR 1.39, 95% CI 0.99–1.94) (Supplementary Figure 7). On further sensitivity analyses (Figure 5(b) and (c)) studies' sample size (P for interaction 0.42) and follow-up duration (P for interaction 0.31) did not affect the relative increase in the risk of stroke in patients undergoing TA plus PPCI as compared to patients undergoing only PPCI (the only study[34] that required visible thrombus as inclusion criteria did not have cases of stroke). However, among studies that enrolled more than 1000 patients a moderate inconsistency was noted (I^2=27.3%, P=0.21). In this group of studies (mainly the Thrombus Aspiration during ST-segment Elevation Myocardial Infarction (TASTE) and TOTAL, as the TAPAS trial did not have events) the increased risk of stroke associated with TA plus PPCI was not statistically significant on random effect (0.86% vs. 0.60%, OR 1.43, 95% CI 0.93–2.19).

The funnel plot was symmetric showing the lack of publication bias (Supplementary Figure 8). The Peter's test further supports this result (P value for small-study effect 0.63).

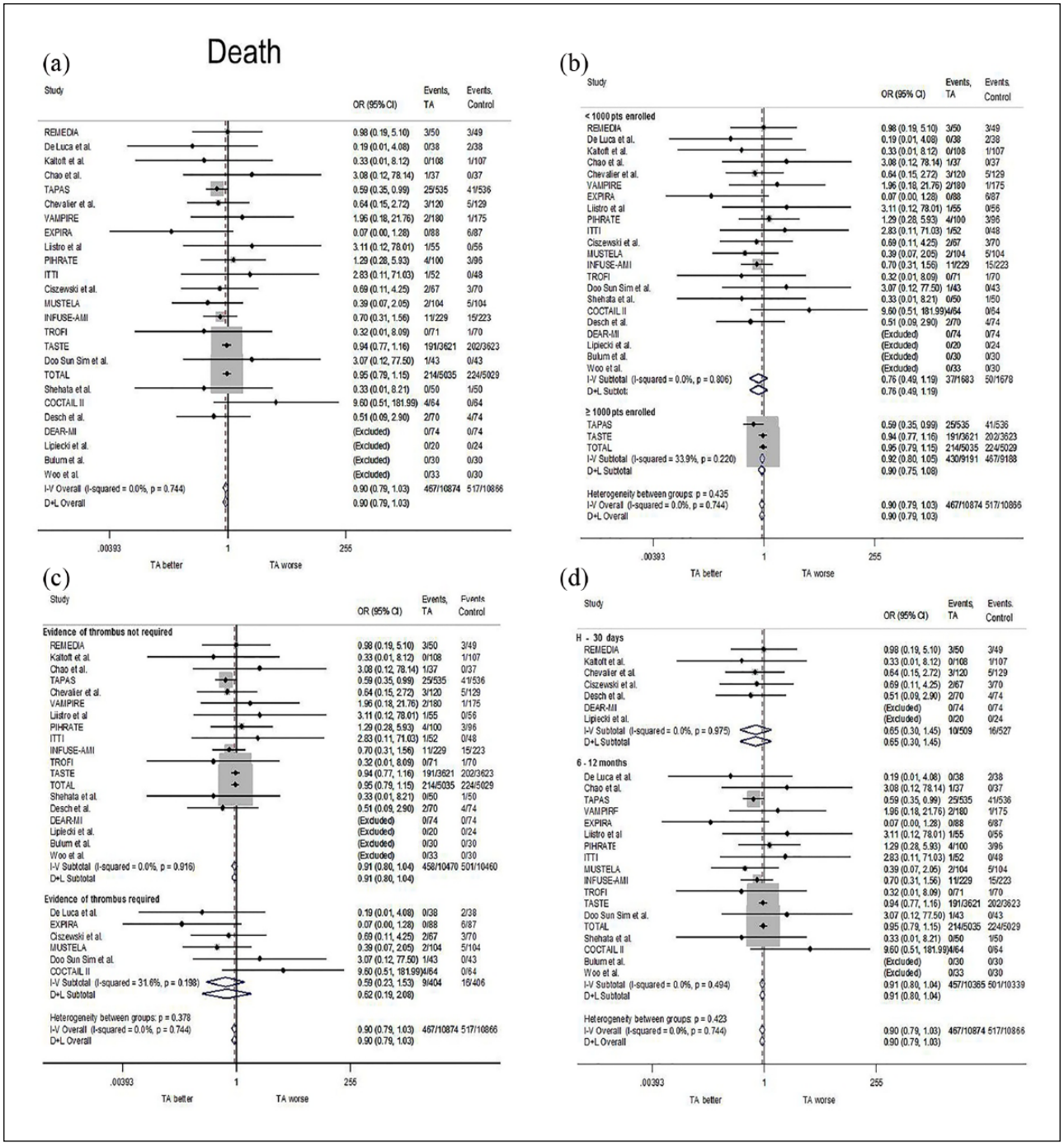

Figure 2. Risk of all-cause death (a) in STEMI patients treated with TA plus PPCI versus patients treated with PPCI alone. (b–d) Sensitivity analysis: studies are grouped by (b) sample size, (c) visible thrombus as inclusion criteria, (d) follow-up duration.
CIs: confidence intervals; D+L: DerSimonian and Laird; I−V: inverse variance weighted; OR: odds ratio; PPCI: primary percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration.

Discussion

The main results of the present study, drawn from data at the longest follow-up available of 25 RCTs including 21,740 STEMI patients, are as follows: (a) TA associated with PPCI does not reduce the risk of all-cause death, MI or stent thrombosis; (b) TA plus PPCI is associated with an increased risk of stroke; however, this finding is mainly driven by the results of the TOTAL trial; (c) follow-up duration (short (in H–30 days) vs. mid follow-up (6–12 months)), angiographic evidence of coronary thrombus or study sample size do not affect the main study results.

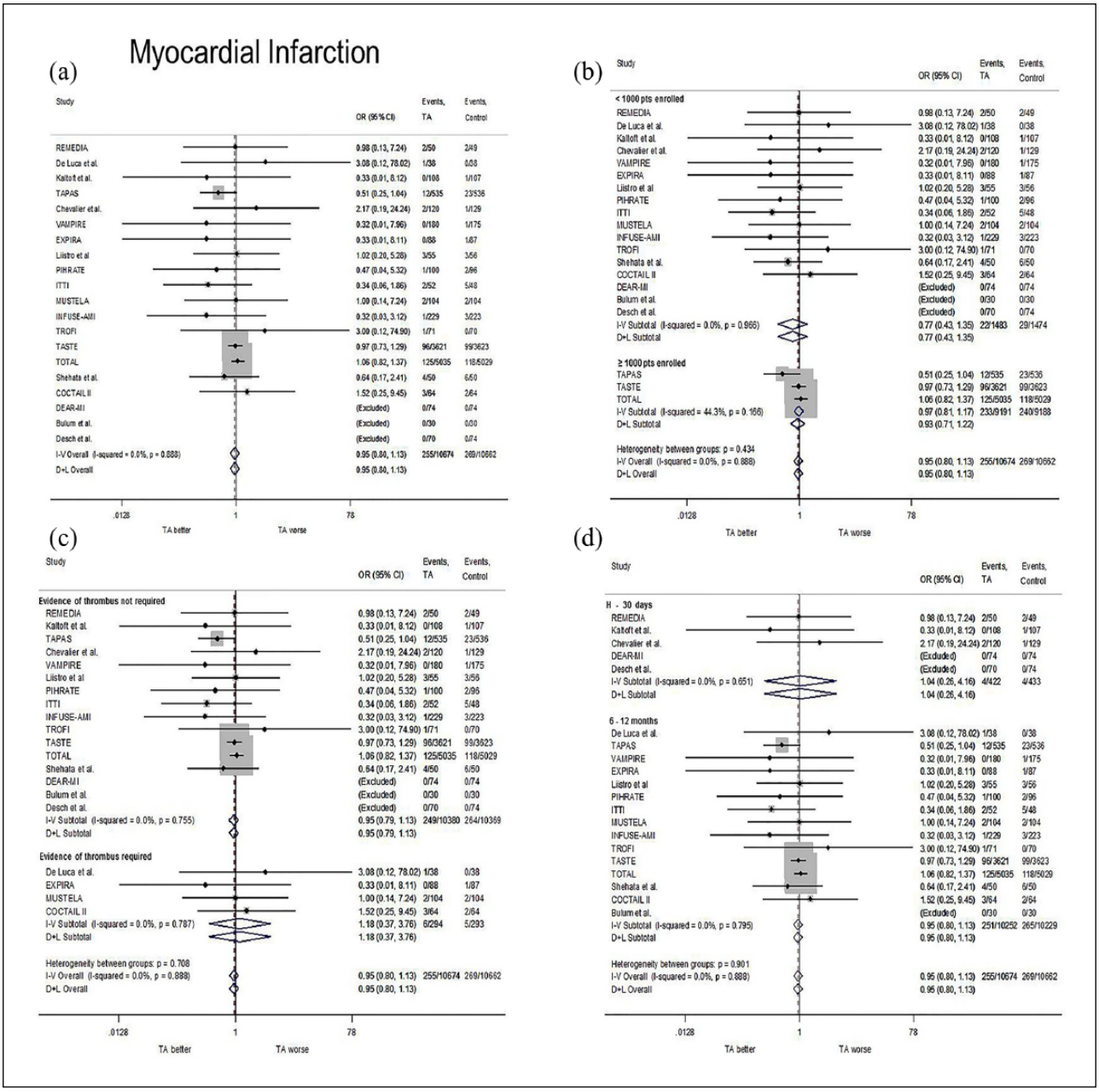

Figure 3. Risk of myocardial infarction (a) in STEMI patients treated with TA plus PPCI versus patients treated with PPCI alone. (b–d) Sensitivity analysis: studies are grouped by (b) sample size, (c) visible thrombus as inclusion criteria, (d) follow-up duration. CIs: confidence intervals; D+L: DerSimonian and Laird; I−V: inverse variance weighted; OR: odds ratio; PPCI: primary percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration.

PPCI performed in a timely fashion represents the treatment of choice in STEMI patients.[1,2] However, despite obtaining a high rate of epicardial coronary flow restoration an effective myocardial perfusion may still not occur, because of microvasculature obstruction, affecting short and long-term prognosis.[3–5] During the past decade TA has gained great popularity thanks to its intuitive pathophysiological basis and easy use to limit distal microembolisation to the microvasculature. Its utilisation has been initially supported by small to medium sized studies[7–12] and early meta-analyses[13,14] showing an improvement of both markers of myocardial perfusion and clinical outcome.

However, in the most recent 2017 European Society of Cardiology (ESC) guidelines for the management of STEMI patients[2] the role of routine TA during PPCI has been downgraded to a class III recommendation, with level A of evidence, based on the results of two large randomised trials[15–18] and meta-analyses.[18,20,21]

In the TASTE[15,16] study, a registry-based RCT enrolling 7244 STEMI patients, TA plus PPCI did not reduce either

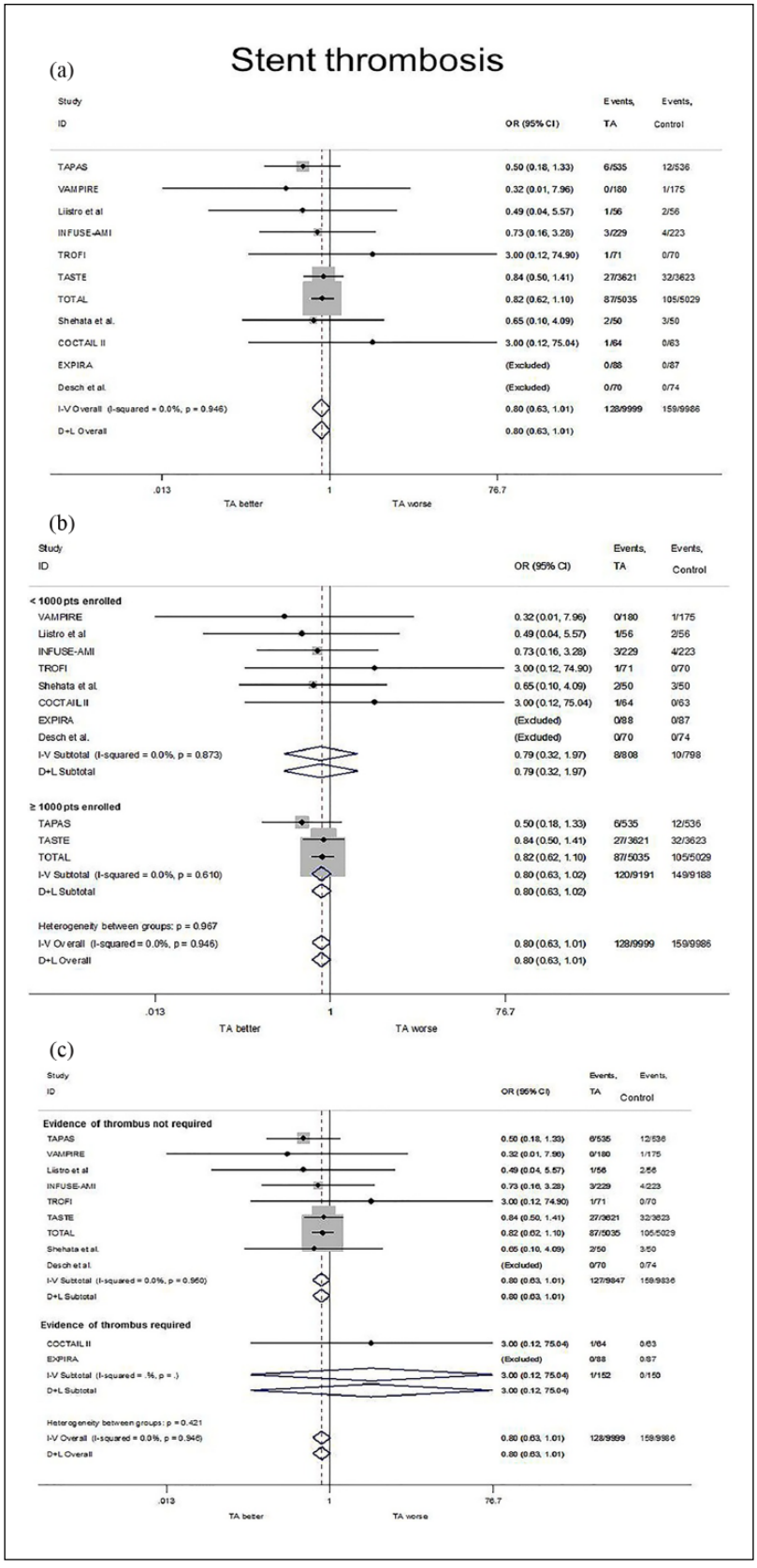

Figure 4. Risk of stent thrombosis (a) in STEMI patients treated with TA plus PPCI versus patients treated with PPCI alone. (b) and (c) Sensitivity analysis: studies are grouped by (b) sample size, (c) visible thrombus as inclusion criteria.
CIs: confidence intervals; D+L: DerSimonian and Laird; I−V: inverse variance weighted; OR: odds ratio; PPCI: primary percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration.

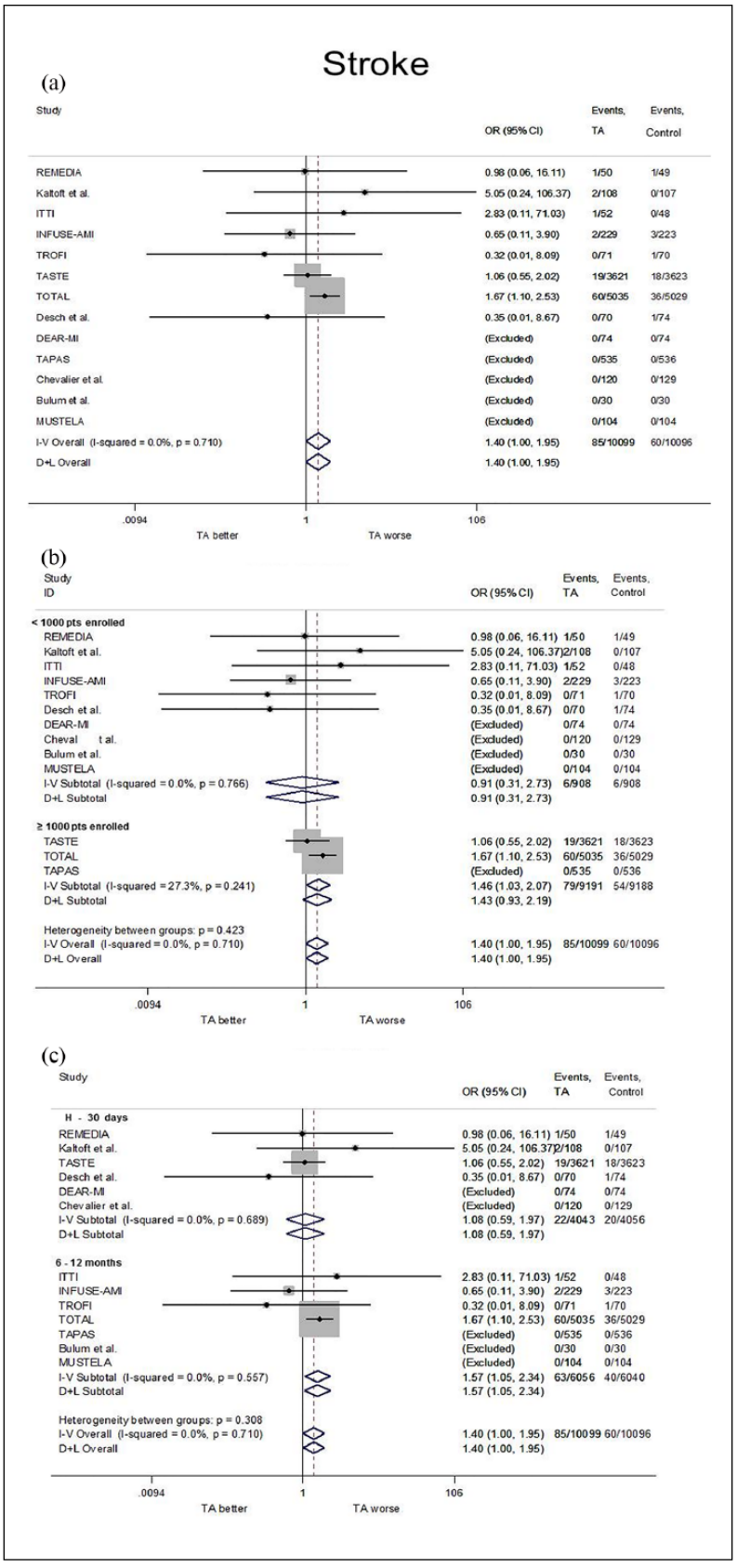

Figure 5. Risk of stroke (a) in STEMI patients treated with TA plus PPCI versus patients treated with PPCI alone. (b) and (c) Sensitivity analysis: studies are grouped by (b) sample size, (c) follow-up duration.
CIs: confidence intervals; D+L: DerSimonian and Laird; I−V: inverse variance weighted; OR: odds ratio; PPCI: primary percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration.

30-day or 1-year mortality compared to PPCI. In the TOTAL trial[17,18] enrolling 10,732 STEMI patients TA plus PPCI did not reduce the risk of the combined endpoint of cardiovascular death, re-MI, cardiogenic shock or New York Heart Association (NYHA) class IV heart failure at 6 months' follow-up. On the other hand, patients treated with TA had a higher risk of stroke both at 30 days and 6 months.[17] Two recent meta-analyses including TASTE and TOTAL trial, one[20] reporting data at the earliest follow-up for each trial and the other one[18] at the longest follow-up available have confirmed that TA plus PPCI does not reduce the risk of all-cause mortality as compared to PPCI alone, while it might be associated with an increased risk of stroke (*P*=0.08,[20] *P*=0.03,[18] respectively). The efficacy and the safety of TA have also been addressed by an individual patient meta-analysis including 18,306 STEMI patients undergoing PCI from the TAPAS, TASTE and TOTAL trial.[21] The authors showed that routine TA during PPCI did not reduce the rate of 30-day cardiovascular mortality (primary endpoint 2.4% TA plus PCI group, 2.6% PCI alone, hazard ratio 0.84, 95% CI 0.70–1.01; *P*=0.06). The rate of 30-day stroke or transient ischaemic attack was 0.8% in the TA plus PCI group and 0.5% in the PPCI alone group (OR 1.43, 95% CI 0.98–2.10; *P*=0.06), but with a significant study-level interaction (*P*=0.02).

Since the publication of this latter meta-analysis additional RCTs and longer follow-up have been reported. Therefore, we have performed the present meta-analysis, including the totality of data up to date, referring to 25 trials and 21,740 STEMI patients, aimed at determining whether in patients with STEMI a strategy of routine TA plus PPCI, compared to PPCI alone reduces the risk of clinical hard endpoints (all-cause mortality, MI, stent thrombosis) or may be associated with an increased risk of stroke.

All-cause mortality

We have confirmed that routine TA associated with PPCI does not reduce the risk of all-cause death during a mean weighted follow-up of 11.1 months as compared to PPCI. The strength of these findings rely on the satisfaction of all requirements for meta-analysis in term of low heterogeneity, no publication bias and sensitivity analyses. These findings open the question of why the consistently shown beneficial effect of TA on surrogate markers of myocardial perfusion[46] does not translate into a better survival rate. First, as a possible explanation, it may be speculated that improved myocardial perfusion could manifest clinically at a longer follow-up in terms of mortality reduction. This observation may be supported by the results of early meta-analyses[14,47] showing that the clinical benefit of TA depends on follow-up duration (although we did not find an interaction between effect estimates on mortality and follow-up duration), and by the fact that STEMI patients experiencing the no-reflow phenomenon have an increasingly higher risk of mortality over years compared to patients with successful myocardial perfusion.[48] Second, more than one decade had passed between the publication of the earliest RCTs on TA and the more recent ones. During this decade the adoption of new evidence-based therapies and strategies may have contributed to improved clinical outcomes making it difficult to achieve further improvements with additional interventions. Indeed, the rate of 1-year death in the control group was 7.6% in TAPAS, 5.5% in TASTE and 4.5% in TOTAL. Finally, it is possible that a theoretical benefit of TA on all-cause mortality could be partly offset by a real, although small (NTH 423) increased risk of stroke. This could be particularly relevant in those patients who would benefit the most from TA plus PPCI. Indeed, subgroup analysis of a recent individual-level meta-analysis including patients from TAPAS, TASTE and TOTAL[21] showed that in patients with high thrombus burden, TA was associated with both a reduced risk of 30-day cardiac mortality (2.5% vs. 3.1%, hazard ratio 0.80, 95% CI 0.65–0.98; *P*=0.03) and an increased risk of stroke or transient ischaemic attack (0.9% vs. 0.5%, 95% CI 1.02–2.42; *P*=0.04) compared to PPCI alone. At 1-year follow-up the difference between TA plus PPCI and PPCI alone in terms of all-cause mortality was not statistically significant (4.6% vs. 5.3%, *P*=0.20).

MI and stent thrombosis

It has been suggested that TA may facilitate some aspects of stent implantation in the context of STEMI patients.[49,50] Indeed, by reducing the thrombus burden it allows a better visualisation of the culprit lesion and vessel reference diameter with subsequent implantation of shorter and larger stents, thus minimising the risk of late malapposition and ultimately the risk of stent thrombosis and MI. In some cases, complete thrombus retrieval by TA may even reduce the need for stent implantation.[51] In the present study we observed on a large scale that patients treated with TA plus PPCI showed a trend towards a lower risk of stent thrombosis compared to patients treated with only PPCI (1.3% vs. 1.6%, OR 0.80, 95% CI 0.63–1.01; *P*=0.066), whereas the risk of recurrent MI was very similar between the two groups (2.4% vs. 2.5%, OR 0.95, 95% CI 0.80–1.13; *P*=0.57). These findings suggest that the above-mentioned theoretical beneficial effects of TA may reduce specifically the risk of stent thrombosis rather than the risk of spontaneous MI. However, despite the fact that we enrolled nearly 20,000 STEMI patients the present study was still relatively underpowered to detect a modest but clinically relevant relative reduction in stent thrombosis during follow-up. Indeed, assuming a stent thrombosis rate of 1.6% in the PPCI only arm, to detect a significant relative risk reduction of 20% in the TA plus PPCI arm, with a study power of 80% and an alfa level of 0.05, 22,377 STEMI patients should be recruited in a RCT.

Stroke

Safety concerns regarding the risk of stroke associated with TA have arisen in a previous meta-analysis[19] and were confirmed by the TOTAL trial[17,18] and recent meta-analyses.[20,21,52]

In the present meta-analysis of 13 trials enrolling a slightly higher number of patients (n=20,195) we confirmed that patients treated with TA plus PPCI have a higher risk of stroke compared to patients treated with PPCI alone (0.84% vs. 0.59%, OR 1.401, 95% CI 1.004–1.954; P=0.047). However, unlike previous meta-analyses[18,20,21] we performed a sensitivity analysis the main results of which are as follows: (a) the association between TA and the risk of stroke is driven by the result of the TOTAL trial because after removing that study it was no longer significant (OR 1.05, 95% CI 0.60–1.85); (b) the association of TA with the risk of stroke appears weaker than previously described[20] because the lower bound of the 95% CI was slightly below unity after removing either the study by Kaltoft et al.[42](OR 1.38, 95% CI 0.99–1.93) or the ITTI trial[31] including two and one case(s) of stroke in the TA group, respectively; (c) meta-analysis on the risk of stroke including only the largest two studies on TA in STEMI, namely TASTE (n=7244) and the TOTAL (n=10,732) trial, showed a moderate between-study heterogeneity leading to a non-significant difference in terms of stroke between TA plus PPCI and PPCI alone on random effect estimates (0.86% vs. 0.60%, OR 1.43, 95% CI 0.93–2.19).

These inter-study differences as suggested by the investigators of the TOTAL trial may be partly related to differences in terms of sample size and event adjudication. However, it should be noted that in the TASTE trial not even a trend towards an increased risk of stroke was noted in the TA group. Furthermore, although in the TASTE trial events were adjudicated on the basis of discharge diagnosis it is unlikely there was an underestimation of non-fatal events because data were monitored and adjudicated in the context of a validated national registry.[53]

On the other hand, data from our study underline that patients enrolled in the TOTAL trial had a higher degree of coronary thrombus (thrombolysis in myocardial infarction (TIMI) thrombus grade >2, 89% of cases) compared to patients enrolled in the TASTE trial (31%). In keeping with the theoretical mechanism of retrograde embolisation this could partly explain the higher risk of stroke related to TA observed in the former study. However, it should be underlined that the ascertainment of thrombus burden was performed before wire passage in the TOTAL and after wire passage in the TASTE trial. Although different definitions might have accentuated these findings the possibility of between-studies differences in baseline thrombus burden and its role in determining the increased risk of stroke observed in TOTAL may not be ruled out.

Alternatively, some authors[54] have suggested that the risk of stroke related to TA observed in TOTAL could be attributed to the between-group differences in terms of risk factors for stroke. However, this mechanism seems unlikely because such differences in terms of age, gender, previous stroke, peripheral artery disease, hypertension, diabetes and medications are numerically trivial and not statistically significant.

Study limitations

The results of the present study should be interpreted with caution given some limitations.

This meta-analysis was based on aggregate data of RCTs that traditionally enrol patients with low-risk clinical profiles, and generalisation of effect estimates should be undertaken with caution. Although we reported data at the longest follow-up available for each study, it was quite heterogeneous, ranging from in-hospital to 12 months' follow-up, limiting the number of events and ultimately reducing the power of the study. Yet, it is not possible to rule out a beneficial effect on long-term mortality as follow-up data longer than 12 months are not available to date.

Conclusions

In patients with STEMI, routine TA plus PPCI does not reduce the risk of all-cause death, MI or stent thrombosis during a mean weighted follow-up of 11.1 months. TA plus PPCI is associated with an increased risk of stroke; however, this finding appears weak and is mainly driven by the results of the TOTAL trial. Future investigations should test whether a selective use of TA plus PPCI may have a beneficial effect in patients at increased risk of no-reflow and stent thrombosis and focus on new techniques/devices to limit the risk of adverse events.

Authors' note

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task

Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 61: e78–140.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. *Eur Heart J* 2018; 39: 119–177.
3. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 1996; 93: 223–228.
4. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. *Circulation* 2004; 109: 1121–1126.
5. Ito H. No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nat Clin Pract Cardiovasc Med* 2006; 3: 499–506.
6. Niccoli G, Burzotta F, Galiuto L, et al. Myocardial no-reflow in humans. *J Am Coll Cardiol* 2009; 54: 281–292.
7. Burzotta F, Trani C, Romagnoli E, et al. Manual thrombus-aspiration improves myocardial reperfusion: the randomized evaluation of the effect of mechanical reduction of distal embolization by thrombus-aspiration in primary and rescue angioplasty (REMEDIA) trial. *J Am Coll Cardiol* 2005; 46: 371–376.
8. Chao CL, Hung CS, Lin YH, et al. Time-dependent benefit of initial thrombosuction on myocardial reperfusion in primary percutaneous coronary intervention. *Int J Clin Pract* 2008; 62: 555–561.
9. De Luca L, Sardella G, Davidson CJ, et al. Impact of intracoronary aspiration thrombectomy during primary angioplasty on left ventricular remodelling in patients with anterior ST elevation myocardial infarction. *Heart* 2006; 92: 951–957.
10. Silva-Orrego P, Colombo P, Bigi R, et al. Thrombus aspiration before primary angioplasty improves myocardial reperfusion in acute myocardial infarction: the DEAR-MI (Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction) study. *J Am Coll Cardiol* 2006; 48: 1552–1559.
11. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; 358: 557–567.
12. 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: 1915–1920.
13. Burzotta F, De Vita M, Gu YL, et al. Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur Heart J* 2009; 30: 2193–2203.
14. Kumbhani DJ, Bavry AA, Desai MY, et al. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol* 2013; 62: 1409–1418.
15. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2014; 369: 1587–1597.
16. Lagerqvist B, Frobert O, Olivecrona GK, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014; 371: 1111–1120.
17. Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015; 372: 1389–1398.
18. Jolly SS, Cairns JA, Yusuf S, et al. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet* 2016; 387: 127–135.
19. Tamhane UU, Chetcuti S, Hameed I, et al. 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.
20. Elgendy IY, Huo T, Bhatt DL, et al. Is aspiration thrombectomy beneficial in patients undergoing primary percutaneous coronary intervention? Meta-analysis of randomized trials. *Circ Cardiovasc Interv* 2015; 8: e002258.
21. Jolly SS, James S, Dzavik V, et al. Thrombus aspiration in ST-segment-elevation myocardial infarction: an individual patient meta-analysis. Thrombectomy Trialists Collaboration. *Circulation* 2017; 135: 143–152.
22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.
23. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
24. Furukawa TA. From effect size into number needed to treat. *Lancet* 1999; 353: 1680.
25. Chevalier B, Gilard M, Lang I, et al. Systematic primary aspiration in acute myocardial percutaneous intervention: a multicentre randomised controlled trial of the export aspiration catheter. *EuroIntervention* 2008; 4: 222–228.
26. Ikari Y, Sakurada M, Kozuma K, et al. Upfront thrombus aspiration in primary coronary intervention for patients with ST-segment elevation acute myocardial infarction: report of the VAMPIRE (VAcuuM asPIration thrombus REmoval) trial. *JACC Cardiovasc Interv* 2008; 1: 424–431.
27. Sardella G, Mancone M, Bucciarelli-Ducci C, et al. Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. *J Am Coll Cardiol* 2009; 53: 309–315.
28. Lipiecki J, Monzy S, Durel N, et al. Effect of thrombus aspiration on infarct size and left ventricular function in high-risk patients with acute myocardial infarction treated by percutaneous coronary intervention. Results of a prospective controlled pilot study. *Am Heart J* 2009; 157: 583; e581–e587.
29. Liistro F, Grotti S, Angioli P, et al. Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circ Cardiovasc Interv* 2009; 2: 376–383.

30. Dudek D, Mielecki W, Burzotta F, et al. Thrombus aspiration followed by direct stenting: a novel strategy of primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. Results of the Polish–Italian–Hungarian RAndomized ThrombEctomy Trial (PIHRATE Trial). *Am Heart J* 2010; 160: 966–972.
31. Liu CP, Lin MS, Chiu YW, et al. Additive benefit of glycoprotein IIb/IIIa inhibition and adjunctive thrombus aspiration during primary coronary intervention: results of the Initial Thrombosuction and Tirofiban Infusion (ITTI) trial. *Int J Cardiol* 2012; 156: 174–179.
32. Ciszewski M, Pregowski J, Teresinska A, et al. Aspiration coronary thrombectomy for acute myocardial infarction increases myocardial salvage: single center randomized study. *Catheter Cardiovasc Interv* 2011; 78: 523–531.
33. Bulum J, Ernst A and Strozzi M. The impact of successful manual thrombus aspiration on in-stent restenosis after primary PCI: angiographic and clinical follow-up. *Coron Artery Dis* 2012; 23: 487–491.
34. De Carlo M, Aquaro GD, Palmieri C, et al. A prospective randomized trial of thrombectomy versus no thrombectomy in patients with ST-segment elevation myocardial infarction and thrombus-rich lesions: MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 2012; 5: 1223–1230.
35. 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: 1817–1826.
36. Onuma Y, Thuesen L, van Geuns RJ, et al. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study – TROFI trial. *Eur Heart J* 2013; 34: 1050–1060.
37. Sim DS, Ahn Y, Kim YH, et al. Effect of manual thrombus aspiration during primary percutaneous coronary intervention on infarct size: evaluation with cardiac computed tomography. *Int J Cardiol* 2013; 168: 4328–4330.
38. Woo SI, Park SD, Kim DH, et al. Thrombus aspiration during primary percutaneous coronary intervention for preserving the index of microcirculatory resistance: a randomised study. *EuroIntervention* 2014; 9: 1057–1062.
39. Shehata M. Angiographic and clinical impact of successful manual thrombus aspiration in diabetic patients undergoing primary PCI. *Int J Vasc Med* 2014; 2014: 263926.
40. Prati F, Romagnoli E, Limbruno U, et al. Randomized evaluation of intralesion versus intracoronary abciximab and aspiration thrombectomy in patients with ST-elevation myocardial infarction: the COCTAIL II trial. *Am Heart J* 2015; 170: 1116–1123.
41. Desch S, Stiermaier T, de Waha S, et al. Thrombus aspiration in patients with ST-segment elevation myocardial infarction presenting late after symptom onset. *JACC Cardiovasc Interv* 2016; 9: 113–122.
42. Kaltoft A, Bottcher M, Nielsen SS, et al. Routine thrombectomy in percutaneous coronary intervention for acute ST-segment-elevation myocardial infarction: a randomized, controlled trial. *Circulation* 2006; 114: 40–47.
43. Sardella G, Mancone M, Canali E, et al. Impact of thrombectomy with EXPort Catheter in Infarct-Related Artery during Primary Percutaneous Coronary Intervention (EXPIRA Trial) on cardiac death. *Am J Cardiol* 2010; 106: 624–629.
44. Stone GW, Witzenbichler B, Godlewski J, et al. Intralesional abciximab and thrombus aspiration in patients with large anterior myocardial infarction: one-year results from the INFUSE-AMI trial. *Circ Cardiovasc Interv* 2013; 6: 527–534.
45. Garcia-Garcia HM, Muramatsu T, Nakatani S, et al. Serial optical frequency domain imaging in STEMI patients: the follow-up report of TROFI study. *Eur Heart J Cardiovasc Imaging* 2014; 15: 987–995.
46. Sharma V, Jolly SS, Hamid T, et al. Myocardial blush and microvascular reperfusion following manual thrombectomy during percutaneous coronary intervention for ST elevation myocardial infarction: insights from the TOTAL trial. *Eur Heart J* 2016; 37: 1891–1898.
47. 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: 973–977.
48. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-Year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol* 2010; 55: 2383–2389.
49. Fernandez-Rodriguez D, Regueiro A, Brugaletta S, et al. Optimization in stent implantation by manual thrombus aspiration in ST-segment-elevation myocardial infarction: findings from the EXAMINATION trial. *Circ Cardiovasc Interv* 2014; 7: 294–300.
50. McCormick LM, Brown AJ, Ring LS, et al. Direct stenting is an independent predictor of improved survival in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2014; 3: 340–346.
51. Rechavia E, Brosh D, Dvir D, et al. Primary PCI: should we stent every single culprit artery? *Eur Heart J Acute Cardiovasc Care* 2014; 3: 126–131.
52. Jolly SS, Cairns JA, Yusuf S, et al. Stroke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. *Eur Heart J* 2015; 36: 2364–2372.
53. Sarno G, Lagerqvist B, Frobert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2012; 33: 606–613.
54. Shah R. Letter by Shah regarding article "Thrombus Aspiration in ST-Segment-Elevation Myocardial Infarction: An Individual Patient Meta-Analysis: Thrombectomy Trialists Collaboration". *Circulation* 2017; 135: e1101–e1102.