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Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials

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Aims

The benefits of adjunctive mechanical devices to prevent distal embolization in patients with acute myocardial infarction (AMI) are still a matter of debate. Growing interests are on manual thrombectomy devices as compared with other mechanical devices. In fact, they are inexpensive and user-friendly devices, and thus represent an attractive strategy. The aim of the current study was to perform an updated meta-analysis of randomized trials conducted with adjunctive manual thrombectomy devices to prevent distal embolization in AMI.

Methods and results

The literature was scanned by formal searches of electronic databases [MEDLINE, CENTRAL, EMBASE, and The Cochrane Central Register of Controlled trials (http://www.mrw.interscience.wiley.com/cochrane/Cochrane_clcentral_articles_ fs.html)] from January 1990 to May 2008, the scientific session abstracts (from January 1990 to May 2008) and oral presentation and/or expert slide presentations (from January 2002 to May 2008) [on transcatheter coronary therapeutics (TCT), AHA (American Heart Association), ESC (European Society of Cardiology), ACC (American College of Cardiology) and EuroPCR websites]. We examined all randomized trials on adjunctive mechanical devices to prevent distal embolization in AMI. The following keywords were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, rescue angioplasty, thrombectomy, thrombus aspiration, manual thrombectomy, Diver catheter, Pronto catheter, Export catheter, thrombus vacuum aspiration catheter. Information on study design, type of device, inclusion and exclusion criteria, number of patients, and clinical outcome was extracted by two investigators. Disagreements were resolved by consensus. A total of nine trials with 2417 patients were included [1209 patients (50.0%) in the manual thrombectomy device group and 1208 (50%) in the control group]. Adjunctive manual thrombectomy was associated with significantly improved postprocedural TIMI (thrombolysis in myocardial infarction) 3 flow (87.1 vs. 81.2%, $P < 0.0001$), and postprocedural MBG 3 (myocardial blush grade 3) (52.1 vs. 31.7%, $P < 0.0001$), less distal embolization (7.9 vs. 19.5%, $P < 0.0001$), and significant benefits in terms of 30-day mortality (1.7 vs. 3.1%, $P = 0.04$).

Conclusion

This meta-analysis demonstrates that, among patients with AMI treated with percutaneous coronary intervention, the use of adjunctive manual thrombectomy devices is associated with better epicardial and myocardial perfusion, less distal embolization and significant reduction in 30-day mortality. Thus, adjunctive manual thrombectomy devices, if not anatomically contraindicated, should be routinely used among STEMI (ST-segment elevation myocardial infarction) patients undergoing primary angioplasty.

Keywords Primary angioplasty • Myocardial infarction • Distal embolization • Manual thrombectomy device

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Introduction

A significant improvement in survival has been observed in the last decades among patients with ST-segment elevation myocardial infarction (STEMI) due to the introduction and improvement of reperfusion strategies.[1–3] However, it has been shown that successful epicardial revascularization is associated with suboptimal myocardial reperfusion in a relatively large proportion of patients, resulting in unfavourable outcomes.[4–5] Mounting interest has emerged regarding the role of distal embolization as a major determinant of impaired myocardial perfusion after primary percutaneous coronary intervention (PCI). In fact, macroscopic distal embolization may occur in up to 16% of patients undergoing primary angioplasty.[6] Previous meta-analyses[7–8] of randomized trials[9–34] on adjunctive mechanical devices to prevent distal embolization did not show benefits in mortality, despite significant benefits in terms of myocardial perfusion and distal embolization. However, worse results were observed with mechanical thrombectomy devices. In the last years there has been increasing interest on manual thrombectomy devices, with several additional trials recently completed.[35–40] In fact, these devices are inexpensive and user-friendly, and thus represent a very attractive strategy. However, all the studies were powered for angiographic and electrocardiographic endpoints but not for hard clinical endpoints, such as mortality. Therefore, we performed a comprehensive meta-analysis of all randomized trials on adjunctive manual thrombectomy devices to prevent distal embolization in patients undergoing mechanical revascularization for STEMI.

Methods

Eligibility and search strategy

We obtained results from all randomized trials on adjunctive manual thrombectomy devices to prevent distal embolization in primary angioplasty for STEMI. The literature was scanned by formal searches of electronic databases [MEDLINE, CENTRAL, EMBASE, and The Cochrane Central Register of Controlled trials (http://www.mrw.interscience.wiley.com/cochrane/Cochrane_clcentral_articles_fs.html)] from January 1990 to May 2008, the scientific session abstracts in Circulation, Journal of College of Cardiology, European Heart Journal and American Journal of Cardiology from January 1990 to May 2008. Furthermore, oral presentations and/or expert slide presentations were included [searched on the transcatheter coronary therapeutics (TCT) (www.tctmd.com), EuroPCR (www.europcr.com), ACC (American College of Cardiology; www.acc.org), AHA (American Heart Association; www.aha.org), and ESC (European Society of Cardiology; www.escardio.org) websites from January 2002 to May 2008]. The reference list of relevant studies was additionally scanned. Various combinations of the following keywords were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, rescue angioplasty, thrombectomy, thrombus aspiration, manual thrombectomy, Diver catheter, Pronto catheter, Export catheter, thrombus vacuum aspiration catheter. No language restrictions were enforced.

Inclusion criteria were: (i) randomized treatment allocation and (ii) availability of complete clinical data. Exclusion criteria: (i) follow-up data in $<$90% of patients; (ii) ongoing studies or irretrievable data; and (iii) trials including $<$50 patients.

Data extraction and validity assessment

Data were independently abstracted by two investigators. Agreement between investigators was evaluated by Kappa statistics. In case of disagreements, a third investigator was additionally involved to obtain a consensus In case of incomplete or unclear data, authors, where possible, were contacted. The study quality was evaluated by the same two investigators according to a score, modified from Jadad *et al*.[41] and Biondi-Zoccai *et al*.,[42] expressed on an ordinal scale, allocating one point for the presence of each of the following: (i) statement of objectives; (ii) explicit inclusion and exclusion criteria; (iii) description of interventions; (iv) objective means of follow-up; (v) description of adverse events; (vi) power analysis; (vii) description of statistical methods; (viii) multicenter design; (ix) discussion of withdrawals; and (x) details on medical therapy (e.g. antithrombotic regimens) during and after coronary procedures. Data were managed according to the intention-to-treat principle.

Outcome measures

Primary endpoint was 30-day mortality. Secondary endpoints were postprocedural thrombolysis in myocardial infarction (TIMI) 3 flow, myocardial blush grade (MBG) 3 and distal embolization.

Data analysis

Statistical analysis was performed using the Review Manager 4.27 freeware package, SPSS 11.5 statistical package. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. The pooled OR was calculated by using a random effect model (The DerSimonian and Laird method). The Breslow–Day test was used to examine the statistical evidence of heterogeneity across the studies ($P < 0.1$).

Potential publication bias was examined by constructing a 'funnel plot', in which sample size was plotted against ORs (for postprocedural TIMI 3 flow, angiographic endpoint available from all studies). In addition, a linear regression approach to measure funnel plot asymmetry was used.[43] A sensitivity analysis was performed according the type of publication (abstract only vs. full-length manuscript), population size ($<$150 vs. $>$150 patients) and study quality (higher than median and median vs. lower than median quality studies).[44]

The study was performed in compliance with the quality of reporting of meta-analyses (QUOROM) guidelines.[45]

Results

Eligible studies

Among 458 potentially relevant publications, a total of 20 randomized trials were initially identified.[9–21,32–33,35–39] Ten trials were excluded because of evaluation of mechanical thrombectomy devices,[9–15,18,32–33] whereas one trial because of comparison between two manual thrombectomy devices[38] (*Figure 1*). Therefore, a total of nine trials were finally included,[16–17,19–21,35–37,39] enrolling 2417 patients [1209 patients (50.0%) randomized to manual thrombectomy device and 1208 (50%) to conventional primary PCI]. Kappa statistics showed a good agreement between investigators in the selection, validity assessment, and data extraction (Kappa = 0.7). Trials characteristics are shown in *Table 1*.

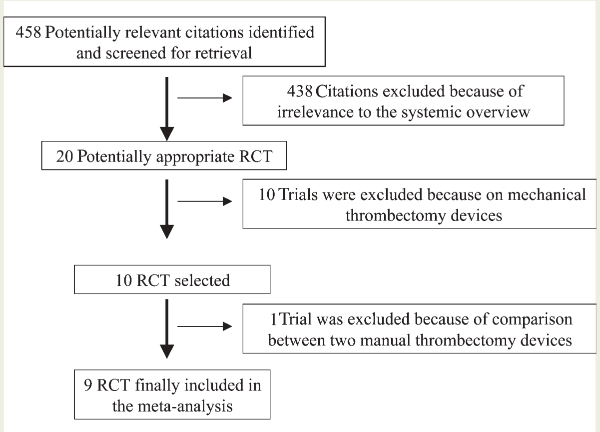

Figure 1 Flow diagram of the systematic overview process (RCT, randomized controlled trials).

Primary endpoint

Data on mortality were available in 2401 (99.4%) out of 2417 patients. As shown in *Figure 2*, a total of 58 patients (2.4%) died at 30-day follow-up. Adjunctive manual thrombectomy devices were associated with significant benefits in terms of 30-day mortality [1.7 vs. 3.1%, OR (95% CI) = 0.58 (0.34–0.98), $P = 0.04$, $P_{het} = 0.97$]. No potential publication bias was observed by visual analysis of the funnel plot (*Figure 3*), and by the mathematical estimate of the asymmetry of this plot provided by a linear regression approach. In fact, the intercept of the regression line did not deviate significantly from zero ($\alpha = -0.24$, 95% CI −0.58 to 0.33, $P = 0.86$).

Sensitivity analyses (*Table 2*) showed that the results were not influenced by the status of publication, sample size, and study quality.

Secondary endpoints

Postprocedural thrombolysis in myocardial infarction 3 flow

Data on postprocedural TIMI 3 flow were available in 2235 (92.5%) patients. As depicted in *Figure 4*, adjunctive manual thrombectomy devices were associated with a significantly higher rate of postprocedural TIMI 3 flow [87.2 vs. 81.2%, OR (95% CI) = 1.59 (1.26–2.0), $P < 0.0001$, $P_{het} = 0.8$].

Postprocedural myocardial blush grade 3 perfusion

Data on MBG were available in 2172 patients (89.9%). As depicted in *Figure 5*, adjunctive mechanical devices were associated with a significantly higher rate of postprocedural MBG 3 [52.1 vs. 31.7%, OR = (95% CI) = 2.44 (2.04–2.92), $P < 0.0001$, $P_{het} = 0.0003$].

Distal embolization

Data on angiographic distal embolization were available in 1207 patients (49.9%). As shown in *Figure 6*, adjunctive mechanical devices were associated with a significant reduction in distal embolization [7.9 vs. 19.5%, OR (95% CI) = 0.30 (0.20–0.44), $P < 0.0001$, $P_{het} = 0.24$].

Discussion

The main finding of this meta-analysis is that adjunctive manual thrombectomy devices are associated with a significant reduction in 30-day mortality, explained by the significant benefits in epicardial and myocardial perfusion, and less distal embolization.

Several randomized trials and a large meta-analysis have shown that primary PCI provides mortality benefits in comparison with thrombolysis, mainly due to better and sustained optimal epicardial perfusion. However, despite epicardial recanalization with TIMI 3 flow, suboptimal myocardial perfusion may be observed in up to 20–40% of patients, with a negative impact on long-term survival.[4–5]

In addition to microvascular damage, increasing interest, in the last years, is on distal embolization,[6,46] with several adjunctive and mechanical therapies being proposed to prevent this complication. A recent meta-analysis of randomized trials has shown that adjunctive abciximab administration is associated with a significant mortality reduction in primary angioplasty for STEMI.[3]

Several mechanical devices have been proposed, including distal or proximal protection devices and thrombectomy catheters.[9–40] Recent meta-analyses on these devices[7–8] have shown no benefits in survival, despite significant benefits in myocardial perfusion and distal embolization. However, a trend in mortality benefits was observed with distal protection devices, whereas a paradoxically larger mortality was observed with thrombectomy devices, mainly due to the negative results of the AIMI trial conducted with AngioJet.[15]

It must be recognized that manual thrombectomy devices, by being inexpensive and user-friendly, represent a very attractive strategy. This explains the growing interests on these devices observed in the last years, with several additional randomized trials being conducted and recently completed. Three trials have been recently presented at last TCT 2007 held in Washington, DC, USA, showing benefits in myocardial perfusion and distal embolization.[35–37] Data from the large Thrombus Aspiration during Primary coronary intervention in Acute myocardial infarction Study (TAPAS) trial have recently been published.[39] In this trial 1072 STEMI patients were randomized before angiography to manual thrombectomy (Export catheter) or conventional primary PCI. The vast majority of patients received Gp IIb–IIIa inhibitors. This study showed significant benefits in myocardial perfusion (evaluated by myocardial blush and ST-segment resolution) and a trend in benefits in 30-day survival. The benefits in myocardial perfusion were confirmed in almost all the analysed subgroups, even though larger benefits were intuitively observed especially in patients revascularized within the first 3 h from symptom onset, when the amount of myocardial salvage is relatively high. One-year follow-up data have recently been presented at ACC 2008 meeting,[40] showing significant benefits in survival with manual thrombectomy.

In our meta-analysis, including nine randomized trials and 2417 patients, we observed that manual thrombectomy devices were associated with significant benefits in 30-day survival, explained by the improvement of epicardial and myocardial perfusion and reduction in distal embolization.

Randomized trials conducted so far on mechanical thrombectomy devices have failed to show benefits in terms on infarct size and myocardial perfusion. Whether the observed benefits in

Table 1 Characteristics of randomized trials included in the meta-analysis

Study	Period	Study device and design (number of patients)	Exclusion criteria	TCL	Primary endpoints	FU (months)
REMEDIA	2004	Diver ($n = 50$) vs. control ($n = 49$)	Ischaemia time > 12 h	No	MBG/STSR	1
De Luca *et al*.	2004	Diver ($n = 38$) vs. control ($n = 38$)	Thrombolytic therapy or Gp IIb–IIIa receptor inhibitor; IRA < 2.5 mm; TIMI 2–3 without large thrombus; CS	Yes	LV remodelling	6
DEAR MI	2004–2005	Pronto catheter ($n = 74$) vs. control ($n = 74$)	Shock; previous MI; recent thrombolitic therapy; previous bypass surgery; LBBB, severe renal and hepatic dysfunction; contraindication to glycoprotein IIb–IIIa inhibitors	No	STSR/MBG	1
Export	2004–2005	Export catheter ($n = 24$) vs. control ($n = 26$)	Preprocedural TIMI 3 flow	No	STSR	1
VAMPIRE	2004–2005	TVAC ($n = 180$) vs. control ($n = 175$)	Prior thrombolysis, cardiogenic shock, cardiac arrest or survivors of cardiac arrest, previous CABG, chronic renal failure, left main disease, vessel size <2.5 or >5.0 mm	No	MBG	1
Export study	2005–2006	Export catheter ($n = 120$) vs. control ($n = 129$)	Pre-cathlab use of thrombolytic therapy or IIb–IIIa antagonist; patients presenting with a cardiogenic shock (blood pressure <90 mmHg); patients presenting with cardiac arrest at any time before intervention; patients previously treated with a pacemaker or with left/right bundle branch block; any planned use of distal protection device; multi vessel coronary artery disease with planned non-target artery PCI or treated with emergent coronary artery bypass surgery	No	STSR/MBG	1
EXPIRA	2005–2006	Export catheter ($n = 88$) vs. control ($n = 87$)	Age < 18 years previous AMI or CABG; cardiogenic shock; 3-vessel/left main CAD; severe valvular heart disease; unsuccessful PCI (no antegrade flow or 50% residual stenosis in the IRA); rescue/facilitated PCI; contraindication to Gp IIb–IIIa inhibitors; STEMI > 9 h from symptoms onset; native IRA < 2.5 mm diameter; TS grade < 3; TIMI 2–3 at time of initial angiography	Yes	STR	9
PIHRATE	2005–2006	Diver ($n = 100$) vs. control ($n = 94$)	Contraindications to PCI (contrast allergy, no possibility to stent implantation); contraindications to ASA, thienopirydins or GP IIb/IIIa inhibitors; active bleeding or coagutopathy; prior CABG or PCI; known ejection fraction EF <35%; cardiogenic shock/SBP <90 mmHg, IABP and/or catheloamins usage; LBBB, pacemaker rhythm; severe calcifications; previous myocardial infarction; stroke history; no future patient cooperation expected; fibrinolysis directly administered before PCI	No	STR	1
TAPAS	2005–2006	Export catheter ($n = 535$) vs. control ($n = 536$)	Performance of a rescue PCI after thrombolysis, the known existence of a disease resulting in a life expectancy of less than 6 months	No	MBG	12

Table 1 Characteristics of randomized trials included in the meta-analysis (continued)

Study	Age (years)		Male gender (%)		Diabetes (%)		Killip > 1 (%)		Ischaemia time (min)		Gp IIb–IIIa inhibitors (%)		Stenting (%)		Quality score
	TAS	Cont	TAS	Cont	TAS	Cont	TAS	Cont	TAS	Cont	TAS	Cont	TAS	Cont	
REMEDIA	61 ± 13	60 ± 13	90	77.6	22	18.4	30	28.6	274 ± 137	300 ± 202	68	63.3	100	100	8
De Luca *et al.*	67 ± 14	65 ± 12	71	55.3	23.7	18.4	21[a]	28.9[a]	456 ± 108	432 ± 114	100	100	100	100	7
DEAR MI	57 ± 13	59 ± 14	84	76	21	15	11	5	206 ± 115	199 ± 124	100	100	99	97	8
Export	58	62	n.r	n.r	13	12	25	12	312 ± 180	252 ± 132	n.r	n.r	n.r	n.r	2
VAMPIRE	n.r	n.r	n.r	n.r	n.r	n.r	n.r	n.r	294	294	0	0	92.9	94.7	5
Export study	59 ± 13	61 ± 13	80.8	81.4	16.7	13.2	11.7	10.9	322 ± 413	271 ± 198	57.1	73.5	100	100	8
EXPIRA	67 ± 14	65 ± 12	64.7	55.1	22.7	18.4	19.3[a]	28.7[a]	408 ± 54	456 ± 108	100	100	100	100	7
PIHRATE	61 ± 10	58 ± 10	79.4	81.3	11.8	9.8	16.7	8.8	220 ± 122	210 ± 115	62.2	63.4	99	96.8	6
TAPAS	63 ± 13	63 ± 13	67.9	73.1	10.6	12.6	9.8	9.4	190	185	93.4	89.9	92.3	92	9

TCL, thrombus containing lesion (as inclusion criteria); TIMI, thrombolysis in myocardial infarction; SBP, systolic blood pressure; MBG, myocardial blush grade; STSR, ST-segment resolution; LBBB, left bundle branch block; LM, left main stenosis; IRA , infarct related artery; PCI, percutaneous coronary Intervention; CABG, coronary artery bypass graft; EF, ejection fraction; CS, cardiogenic shock; RD, reference diameter; TVAC, thrombus vacuum aspiration catheter; TS, thrombus score; TAS, thrombus aspiration; Cont, Control; n.r., not reported.

[a]Killip class > 3.

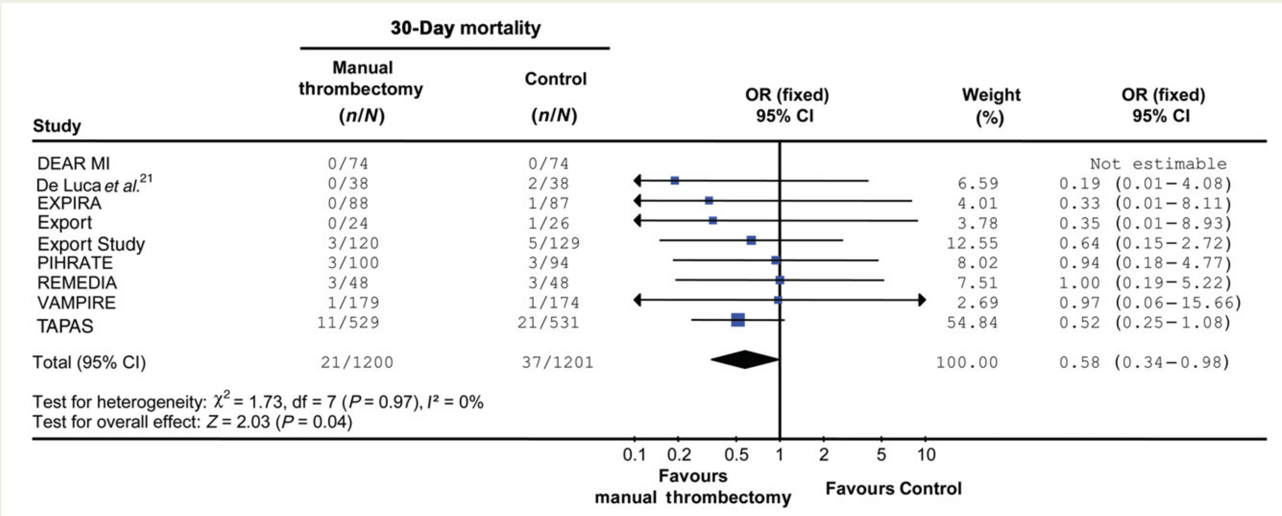

Figure 2 Adjunctive manual thrombectomy devices and 30-day mortality, with odds ratios (OR) and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

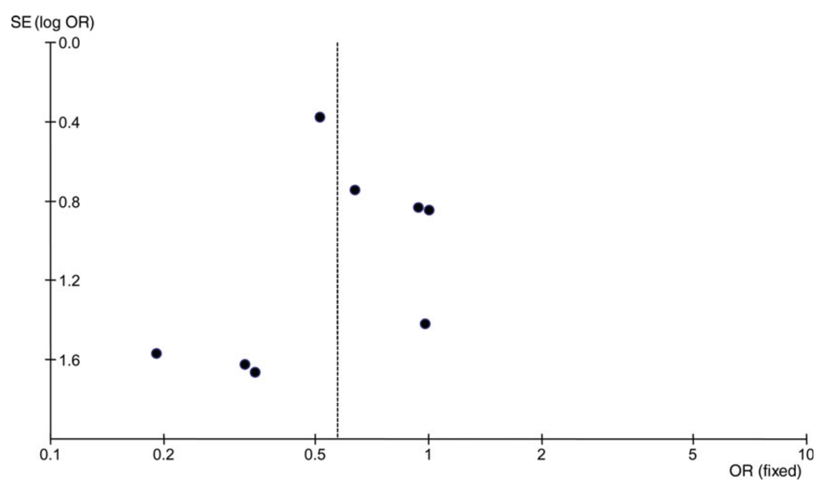

Figure 3 Funnel plot of all studies included in the meta-analysis. Sample size of each study was plotted against the odds ratio for 30-day mortality. No skewed distribution was observed, suggesting no publication bias.

survival with manual thrombectomy but not other mechanical devices are strictly depending on device features and performance or the availability of larger number of trials, is still unknown.

A large-scale controlled randomized trial with the AngioJet in thrombotic lesions in acute myocardial infarction (AMI) is currently underway in Europe, and will probably provide additional data on the benefits from mechanical thrombectomy devices.

Limitations

This meta-analysis was not performed on individual patient data, as complete data sets were not available. Caution should be exercised in the interpretation of the results, given the potential clinical heterogeneity among trials, due to varying inclusion criteria, definition of variables, and different manual thrombectomy devices. We could not include infarct size as endpoint of the current meta-analysis due to the unavailability of data and disparity in the measurement among studies [by enzymes, nuclear scintigraphy or MRI (magnetic resonance imaging)]. Even if several trials have not been published as full-length articles yet, a sensitivity analysis did not show any impact of the publication status on study results (*Table 2*). Finally, the large use of Gp IIb–IIIa inhibitors observed in the vast majority of trials (*Table 1*), has certainly minimized the risk of any potential overestimation of the benefits from thrombus aspiration.

Conclusions

The present meta-analysis has demonstrated that, among patients with STEMI undergoing primary PCI, the use of adjunctive

Table 2 Sensitivity analyses

Subgroup	Number of studies	Number of patients	30-Day mortality (manual thrombectomy)	30-day Mortality (Control)	30-day mortality [OR (95% CI)]	*P*-value	*P*-heterogeneity	*P*-interaction
Overall	9	2401	21/1200	37/1201	0.58 (0.34–0.98)	0.04	0.97	0.82
Published[a]	5	1629	17/809	31/820	0.55 (0.31–1.00)	0.05	0.79	
Unpublished	4	772	4/391	6/381	0.69 (0.22–2.21)	0.53	0.9	
Large size (>150 patients)	5	2031	18/1016	31/1015	0.58 (0.32–1.04)	0.07	0.95	0.86
Small size (≤150 patients)	4	370	3/184	6/186	0.56 (0.16–1.99)	0.37	0.6	
High study quality	4	1553	17/771	29/782	0.58 (0.32–1.07)	0.08	0.77	0.78
Low study quality	5	848	4/429	8/419	0.56 (0.19–1.62)	0.28	0.88	

[a]As full-length manuscript.

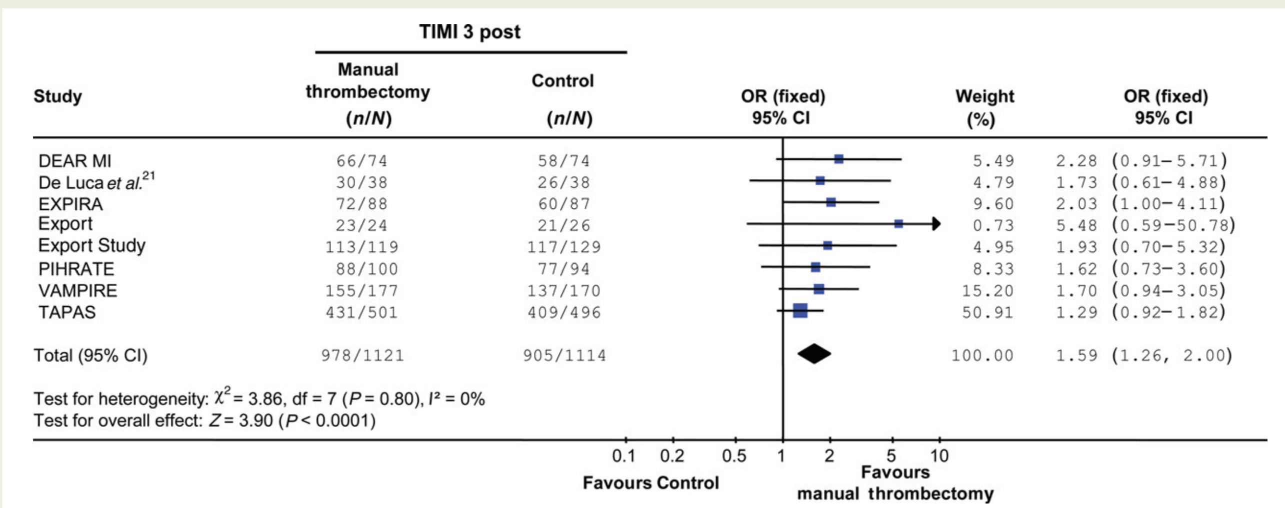

Figure 4 Adjunctive mechanical devices and postprocedural thrombolysis in myocardial infarction (TIMI) 3 flow, with odds ratios (OR) and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

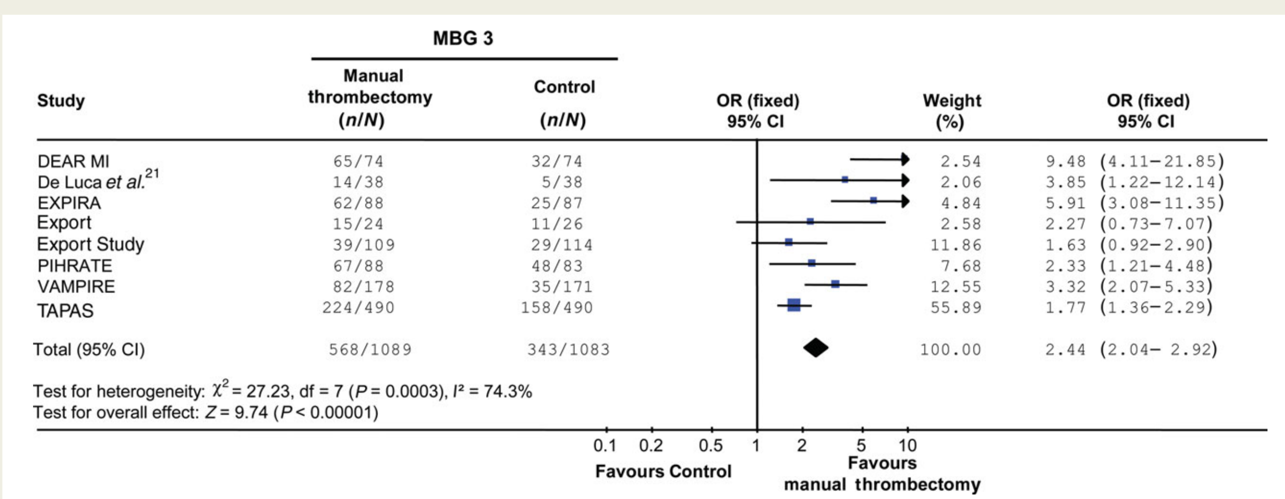

Figure 5 Adjunctive mechanical devices and postprocedural myocardial blush grade (MBG) 3, with odds ratios (OR) and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

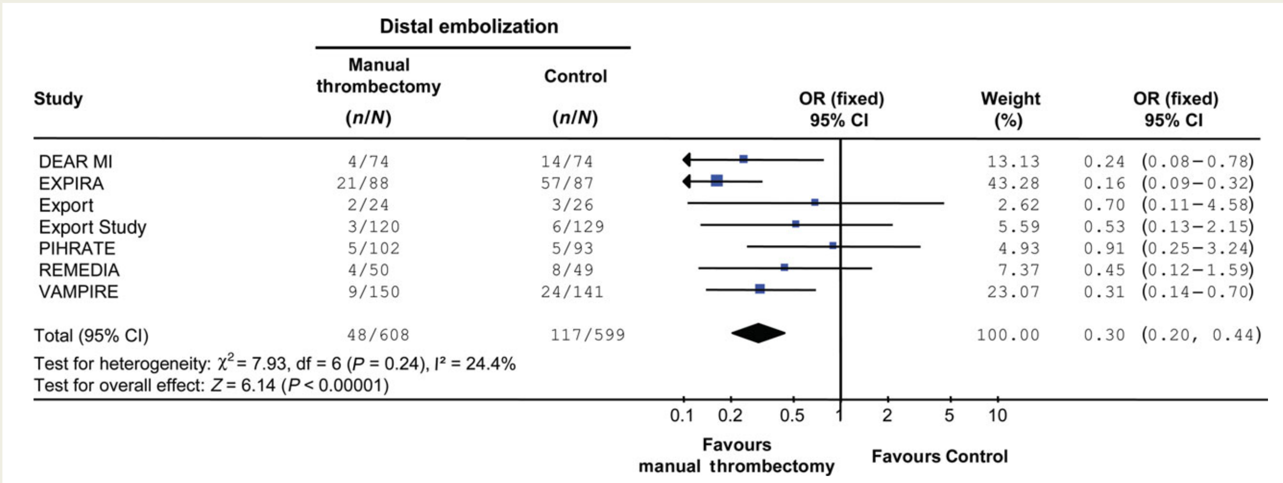

Figure 6 Adjunctive mechanical devices and distal embolization, with odds ratios (OR) and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

manual thrombectomy devices to prevent distal embolization is associated with better epicardial and myocardial perfusion and less distal embolization. These beneficial effects translated into significant benefits in 30-day survival. Thus, adjunctive manual thrombectomy devices, if not anatomically contraindicated, should be routinely used among STEMI patients undergoing primary angioplasty.

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All co-authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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