Additional manual thrombus aspiration for ST-segment elevation myocardial infarction during percutaneous coronary intervention: an updated meta-analysis

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Abstract

Background  The clinical efficacy and safety of adjunctive thrombus aspiration (TA) in patients with ST-segment elevation myocardial infarction (STEMI) during percutaneous coronary intervention (PCI) remain controversial. Methods  Twenty five eligible randomized controlled trials were included to compare the use of thrombus aspiration (TA) with PCI and PCI-only for STEMI. The primary endpoint was all-cause mortality and death. The secondary endpoints were major adverse cardiac events (MACE), recurrent infarction (RI), target vessel revascularization (TVR), stent thrombosis (ST), perfusion surrogate markers and stroke. Results  TIMI flow grade 3 and MBG 2–3 were significantly increased in the TA plus PCI arm compared with the PCI-only arm (relative risk (RR): 1.05, 95% confidence intervals (CI): 1.02–1.09, \( P = 0.004 \)) and (RR: 1.68, 95% CI: 1.40–2.00, \( P < 0.001 \)), respectively. There were no significant differences in all-cause mortality, MACEs, TVR and ST rates between the two groups. The RI rate was lower in the TA plus PCI arm than that in the PCI-only arm with short-term follow-up duration (RR: 0.60, 95% CI: 0.38–0.96, \( P = 0.03 \)), but there was no significant difference in RI incidence over the medium- or long-term follow-up periods (RR: 1.00, 95% CI: 0.81–1.15, \( P = 0.69 \)), respectively. There were statistically significant differences in the rates of crude stroke and stroke over the medium- or long-term follow-up periods and the crude stroke rate in the TA plus PCI (RR: 1.60, 95% CI: 1.08–2.38, \( P = 0.02 \)) and (RR: 1.43, 95% CI: 1.03–1.98, \( P = 0.03 \)), respectively; this was not observed between the two arms during the short-term follow-up period (RR: 1.47, 95% CI: 0.97–2.21, \( P = 0.07 \)). Conclusions  Routine TA-assisted PCI in STEMI patients can improve myocardial reperfusion and get limited benefits related to the clinical endpoints, which may be associated with stroke risk.

Keywords: Manual thrombus aspiration; Meta-analysis percutaneous coronary intervention; Randomized controlled trials; ST-segment elevation myocardial infarction

1 Introduction

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) and is highly effective in improving epicardial coronary reperfusion. However, adequate myocardial reperfusion is not achieved in a significant proportion of patients despite successful restoration of coronary blood flow; this situation correlates closely with a poor prognosis in terms of mortality and morbidity and thrombectomy devices have been developed to improve clinical outcomes. Different trials of manual thrombus aspiration (TA) for STEMI have yielded conflicting results and the efficacy of TA therapy for improving surrogate reperfusion markers, which translate into favorable clinical outcomes remains controversial. It is hard to explain the disparity between post-procedural surrogate outcomes and long-term clinical outcomes. TA increased the risk of stroke in the TOTAL trial (trial of routine aspiration thrombectomy with PCI vs. PCI alone in patients with STEMI) regardless of the length of follow-up (30 days, 180 days or 1-year). In this updated meta-analysis, we assessed individual efficacy and safety outcomes between the TA plus PCI and PCI-only arms of randomized controlled trials (RCTs).

2 Methods

2.1 Search strategy

We performed a computerized literature search of Pub...
Med, Web of Science, Embase and Cochrane Library databases on December 31, 2015. To identify relevant original peer-reviewed reports of RCTs, the following MeSH terms and keywords were used: “aspiration thrombectomy”, “thrombectomy”, “thrombus aspiration”, “STEMI”, “ST-segment elevation myocardial infarction”, “myocardial infarction”, “randomized”, “percutaneous coronary intervention” and “PCI”. Abstracts from scientific meetings of the American Heart Association, the American College of Cardiology and the European Society were screened. We performed searches without any language restriction.

2.2 Selection criteria

The studies meeting the following criteria were included: (1) RCTs; (2) the intervention group comprised patients with STEMI during PCI; and (3) the control group comprised STEMI patients treated with PCI-only. Observational studies, uncontrolled trials, review articles and case reports were excluded. We also excluded the studies of mechanical thrombectomy devices.

2.3 Definition of endpoints

The primary endpoint of this study was all-cause mortality, which was defined as death from any cause in most included trials. Deaths over different follow-up periods were also regarded as the primary endpoint. The secondary endpoints were major adverse cardiac events (MACE), recurrent infarction (RI), target vessel revascularization (TVR), stent thrombosis (ST), stroke and perfusion surrogate markers including post-procedural thrombolysis in myocardial infarction (TIMI) flow grade 3 and myocardial blush grade (MBG) 2–3.

2.4 Data extraction

Data extracted from each study included study population, study name, baseline patient characteristics, intervention, study design, inclusion and exclusion criteria, and methodologic quality criteria. Discrepancies were resolved by discussion.

2.5 Statistical analysis

The individual risk of bias of each study was assessed using the Cochrane risk of bias tool. An intention-to-treat analysis was applied in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. All analyses were performed using Review Manager (RevMan) 5.3. Statistically significant heterogeneity was considered to exist in cases where $\chi^2$ test $P$-values were less than 0.05 or the $I^2$ statistic exceeded 50%.[5] In the absence of heterogeneity, pooled estimates of relative risk (RR) with 95% confidence intervals (CI) were calculated using the Mantel–Haenszel (M–H) method. A random effects model for risk ratio (RR) estimation of all outcomes was employed when heterogeneity existed. Reported values are two tailed, and hypothesis testing results were considered statistically significant at $P < 0.05$. Funnel plots and Egger’s tests were used to assess small study effects, such as publication bias.[6]

3 Results

3.1 Study selection and characteristics

A total of 25 RCTs of 21,708 patients were included in the meta-analysis, with 10,829 patients randomized to the manual TA arm and 10,902 patients randomized to the PCI-only arm. Characteristics of the included studies are listed in Table 1.

We performed clinical outcome analyses based on different follow-up periods defined as short-term (from hospital admission to 1 month), medium-term (6–9 months) and long-term (≥1 year). Based on different follow-up periods, we calculated the RR for clinical endpoints.

3.2 Post-procedural perfusion markers

A significant increase in the frequency of post-procedural TIMI flow grade 3 was observed between the two groups (RR: 1.05, 95% CI: 1.02–1.09, $P = 0.004$; $P$ for heterogeneity $[P_{het}] = 0.02$, $I^2 = 49%$; Figure 2A). The post-procedural MBG 2–3 frequency was significantly higher in the TA plus PCI group compared with that in the PCI-only group (RR: 1.68, 95% CI: 1.40–2.00, $P < 0.001$; $P_{het} = 0.003$, $I^2 = 68%$; Figure 3A). No obvious publication bias was revealed in visual funnel plots of the included studies in this updated meta-analysis of TIMI flow grade 3 and MBG 2–3 (Figure 2B, Figure 3B).

3.3 Mortality

There were no reductions in the incidences of all-cause mortality (RR: 0.91, 95% CI: 0.80–1.02, $P = 0.11$; $P_{het}= 0.67$, $I^2 = 0$; Figure 4A) or death over the short-term (RR: 0.85, 95% CI: 0.72–1.00, $P = 0.06$; $P_{het} = 0.93$, $I^2 = 0$; Figure 4B), medium-term (RR: 0.90, 95% CI: 0.73–1.10, $P = 0.30$; $P_{het} = 0.69$, $I^2 = 0$; Figure 4C), and long-term (RR: 0.90, 95% CI: 0.80–1.02, $P = 0.12$; $P_{het} = 0.33$, $I^2 = 13%$; Figure 4D) follow-up periods.

3.4 MACE

There was no statistically significant difference in the
Records identified through database searching Pubmed, EMBASE, Web of Science and The Cochrane library, \(n = 813\)

Additional records identified through Other sources \(n = 1\)

Records after duplicates removed \(n = 343\)

Records based on review of title and abstract \(n = 343\)

Full-text articles assessed for eligibility \(n = 62\)

Studies included in qualitative synthesis \(n = 25\)

Studies included in the meta-analysis \(n = 25\)

Records excluded \(n = 281\)
- irrelevant studies \(n = 142\)
- observational studies \(n = 76\)
- uncontrolled trials \(n = 18\)
- cases reports \(n = 21\)
- review articles \(n = 24\)

Full-text articles excluded \(n = 37\)
- mechanical thrombectomy \(n = 11\)
- comparing one thrombectomy device to another \(n = 10\)
- distal protection devices \(n = 3\)
- no clinical outcomes reported \(n = 4\)
- subgroup analysis \(n = 9\)

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**Figure 1.** Flow diagram depicting the selection of studies included in the meta-analysis.

**Table 1.** Characteristics of the included studies.

| Study       | Year | Number | Design             | Device       | Follow-up duration |
|-------------|------|--------|--------------------|--------------|-------------------|
| REMEDIA[7]  | 2005 | 50/49  | Single center      | Diver CE     | 1 mon             |
| DEAR-MI[9]  | 2006 | 74/74  | Single center      | Pronto       | Hospital          |
| De Luca, et al[10] | 2006 | 38/38  | Single center      | Diver CE     | 6 mon             |
| Kaltoft, et al[10] | 2006 | 108/107| Single center      | Rescue       | 1 mon             |
| TAPAS[11,12] | 2008 | 535/536| Single center      | EXPORT       | 1mon, 12 mon      |
| Chao, et al[13] | 2008 | 37/37  | Single center      | EXPORT       | 6 mon             |
| EXPORT[14]  | 2008 | 120/129| Multicenter        | EXPORT       | 1 mon             |
| VAMPIRE[15–18] | 2008 | 180/175| Multicenter        | TAVC         | 1 mon, 8 mon, 2 yrs, 3 yrs, 5 yrs |
| EXPIRA[19,20] | 2009 | 88/87  | Single center      | EXPORT       | 9 mon, 24 mon     |
| Liistro, et al[21] | 2009 | 55/56  | Single center      | EXPORT       | 6 mon             |
| PHRARE[22]  | 2010 | 100/96 | Multicenter        | Diver CE     | 6 mon             |
| Ciszewski, et al[23] | 2011 | 67/70  | Single center      | Rescue/Diver CE | Hospital |
| INFUSE-AMF[24,25] | 2012 | 229/223| Multicenter        | EXPORT       | 1 mon, 12 mon     |
| MUSTELA[26] | 2012 | 50/104 | Multicenter        | EXPORT       | 12 mon            |
| TASTE[27,28] | 2014 | 3,621/3,623| Multicenter        | Eliminate/Pronto /EXPORT | 1 mon, 12 mon |
| TOTAL[29,30] | 2015 | 5,033/5,030| Multicenter        | EXPORT       | 6 mon, 12 mon     |
| Noel, et al[31] | 2005 | 24/26  | Single center      | EXPORT       | Hospital          |
| Lipiecki[32] | 2009 | 20/24  | Single center      | EXPORT       | Hospital          |
| TROPH[33]  | 2013 | 71/70  | Multicenter        | Eliminate    | Hospital          |
| NONSTOP[34] | 2004 | 129/129| Multicenter        | Rescue       | Hospital          |
| Balum, et al[35] | 2012 | 30/30  | Single center      | EXPORT       | 6 mon             |
| ITT[36]    | 2012 | 52/48  | Multicenter        | Thrombuster II | 6 mon          |
| Sim, et al[37] | 2013 | 43/43  | Single center      | Thrombuster II | 12 mon         |
| Hamza, et al[38] | 2013 | 25/25  | Single center      | Diver CE     | Hospital          |
| Shehata, et al[39] | 2013 | 50/50  | Single center      | EXPORT       | 8 mon             |
ZHANG Y, et al. Meta-analysis of adjunctive thrombectomy for STEMI during PCI

Figure 2. Forest plot for TIMI flow grade 3 and funnel plot for the endpoint of TIMI flow grade 3. PCI: percutaneous coronary in-tervention; RR: risk ratio; TA: thrombus aspiration; TIMI: thrombolysis in myocardial infarction.

Figure 3. Forest plot for myocardial blush grade 2-3 and funnel plot for the endpoint of myocardial blush grade 2-3. PCI: percutaneous coronary intervention; RR: risk ratio; TA: thrombus aspiration; TIMI: thrombolysis in myocardial infarction.

3.5 RI

The RI rate was significantly lower in the TA plus PCI arm than that in the PCI-only arm over the short-term follow-up period (RR: 0.60, 95% CI: 0.38–0.96, P = 0.03; Phet = 0.86, $\hat{f} = 0$; Figure 6A), while there was no significant difference in RI incidence during the medium- and long-term follow-up periods (RR: 1.00, 95% CI: 0.77–1.29, P = 0.98; Phet = 0.66, $\hat{f} = 0$; Figure 6B), and (RR: 0.96, 95% CI: 0.81–1.15, P = 0.69; Phet = 0.36, $\hat{f} = 9$%; Figure 6C), respectively.

3.6 Target vessel revascularization

The incidence of target vessel revascularization (TVR) was not reduced by TA plus PCI therapy compared with PCI-only therapy during the short-term (RR: 0.82, 95% CI: 0.63–1.08, P = 0.16; Phet = 0.66, $\hat{f} = 0$; Figure 7A), medium-term (RR: 0.99, 95% CI: 0.84–1.18, P = 0.94; Phet = 0.88, $\hat{f} = 0$; Figure 7B), and long-term (RR: 0.98, 95% CI: 0.87–1.10, P = 0.70; Phet = 0.78, $\hat{f} = 0$; Figure 7C) follow-up periods.

3.7 ST

There was no reduction in the crude ST rate in the TA plus PCI arm compared to that in the PCI-only arm (RR: 0.80, 95% CI: 0.64–1.01, P = 0.06; Phet = 0.91, $\hat{f} = 0$; Figure 8).

3.8 Stroke

The risk of stroke significantly increased in the TA plus PCI arm over the medium- and long-term follow-up (RR: 1.60, 95% CI: 1.08–2.38, P = 0.02; Phet = 0.57, $\hat{f} = 0$; Figure 9B), while the crude stroke rate was higher in the TA plus PCI than that in the PCI-only arm (RR: 1.43, 95% CI: 1.03–1.98, P = 0.03; Phet = 0.70, $\hat{f} = 0$; Figure 9C). However, there was no difference between the two arms in the incidence of early stroke in the short-term follow-up period (RR: 1.47, 95% CI: 0.97–2.21, P = 0.07; Phet = 0.46, $\hat{f} = 0$; Figure 9A).
Figure 4. Forest plot results. (A): The endpoint of all-cause mortality; (B): mortality over short-term follow-up; (C): mortality over medium-term follow-up; and (D) mortality over long-term follow-up. PCI: percutaneous coronary intervention; RR: risk ratio; TA: thrombus aspiration; TIMI: thrombolysis in myocardial infarction.
Discussion

This meta-analysis was performed to further evaluate the efficacy and safety of manual TA for patients with STEMI undergoing PCI. Our main findings showed that manual TA reduces the incidence of short-term recurrent infarction and did not increase the risk of stroke risk over the short-term follow-up period; however, the rates of all-cause mortality and ST were not reduced. There were no statistically differences in the rates of mortality, MACE, and TVR over short-, medium- and long-term follow-up periods and in the incidence of RI over medium- and long-term follow-up periods. These findings were derived mainly from the TASTE and TOTAL trials.[27–30]

The TOTAL trial, which is the largest trial conducted to date, involving 10,732 patients with STEMI during PCI, showed that manual TA improved ST-segment resolution effectively and reduced the incidence of angiographic distal embolization. However, only 10% of STEMI patients with PCI-only developed distal embolization. Other surrogate outcomes such as TIMI flow grade 3, MBG 2–3 and no reflow were not improved. Therefore, the clinical findings of the TOTAL trial suggested that TA has only a modest effect on some, but not all the surrogate post-procedural outcomes.[30]

In contrast, our meta-analysis including the TOTAL trial data showed that post-procedural TIMI flow grade 3 and MBG 2–3 were improved by manual TA, which is consistent with the findings of previous clinical trials and meta-analyses.[40–42] The statistically significant heterogeneity found in post-procedural myocardial reperfusion
Figure 6. Forest plot for RI follow-up. (A): Results are short-term follow-up; (B): medium-term follow-up; and (C): long-term follow-up. PCI: percutaneous coronary intervention; RI: recurrent infarction; RR: risk ratio; TA: thrombus aspiration; TIMI: thrombolysis in myocardial infarction.

markers is inevitable due to the different inclusion criteria and aspiration thrombectomy devices used in various clinical trials. Inverse funnel plots showed symmetrical distributions, indicating an absence of the small studies effect.

The registry-based TASTE trial showed no difference in the stroke or neurological event rates within 30 days between the TA and the PCI-only groups. Since the TOTAL trial is the largest-scale RCT of manual TA conducted to date, these data are the most robust available with respect to the effect of thrombectomy on stroke. The TOTAL trial showed that the stroke rates increased at 30 days, 180 days or 1 year; however, the current updated meta-analysis suggested additional TA for STEMI increases the stroke risk over the medium and long-term follow-up periods, while the effect on patients presenting with STEMI remains controversial during the short-term follow-up period (30 days). However, stroke is such an infrequent event that the relevance of the incidence at 30 days should be interpreted cautiously. Although, the high statistical power of the TOTAL trial allows detection of differences in the incidence of rare events, the registry-based TASTE trial that depended on discharge diagnosis codes might underestimate non-fatal events, particularly minor strokes. Therefore, further trials are required to clarify the effects of manual TA on the stroke rate within 30 days.

4.1 Study limitations

Some inherent limitations of this study should be noted. First, although a comprehensive search was conducted, publication bias may be unavoidable. Second, this meta-analysis may be influenced by differences between the included studies in individual patients, study designs, thrombectomy
devices, inclusion and exclusion criteria, follow-up periods, attrition rates, and even variable definitions of some clinical endpoints. Despite these limitations, this is the largest meta-analysis conducted to date that includes recently published data of late follow-up outcomes reported from the TASTE and TOTAL trials.

![Forest plot for TVR follow-up](image1)

Figure 7. Forest plot for TVR follow-up. (A): Results are short-term follow-up; (B): medium-term follow-up; and (C): long-term follow-up. PCI: percutaneous coronary intervention; RR: risk ratio; TA: thrombus aspiration; TIMI: thrombolysis in myocardial infarction; TVR: target vessel revascularization.

![Forest plot for ST](image2)

Figure 8. Forest plot for ST. PCI: percutaneous coronary intervention; RR: risk ratio; ST: stent thrombosis; TA: thrombus aspiration; TIMI: thrombolysis in myocardial infarction; TVR: target vessel revascularization.
In conclusion, among patients with STEMI, routine TA-assisted PCI can improve epicardial and myocardial parameters of reperfusion, such as TIMI flow grade 3 and MBG 2–3. Adjunctive TA for STEMI can increase the stroke risk over the medium and long-term follow-up periods, while the effects on patients presenting with STEMI remains controversial in the short-term. There is no statistically significant difference in clinical outcome endpoints of all-cause death, mortality, MACE, TVR, ST or medium- and long-term RI between in the TA plus PCI arm and the PCI-only arm; the effects of TA plus PCI might be associated with a reduction in recurrent myocardial infarction over the short-term follow-up period.

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