



# Combined thrombectomy and intracoronary administration of glycoprotein IIb/IIIa inhibitors improves myocardial reperfusion in patients undergoing primary percutaneous coronary intervention: a meta-analysis

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## Abstract

**Background** Suboptimal myocardial reperfusion is common in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). Furthermore, it results in increased infarct size and mortality rates. We performed a meta-analysis to evaluate the role of aspiration thrombectomy (AT) combined with intracoronary administration of glycoprotein IIb/IIIa inhibitors (GPI) in the improvement of myocardial reperfusion and clinical outcomes. **Methods** PubMed, Embase, Web of Science, and CENTRAL databases were searched for randomized controlled trials (RCTs) investigating combined AT and intracoronary GPI treatment versus AT alone. Outcomes of interest were thrombolysis in myocardial infarction myocardial perfusion grade (TMPG), infarct size (IS) assessed by cardiac magnetic resonance imaging, left ventricular ejection fraction (LVEF), major adverse cardiac events (MACE) at short-term ( $\leq 1$  month) and long-term (6–12 months) follow-up, and bleeding complications during the hospital stay. **Results** Eight trials involving 923 patients were included. Compared with AT alone, combined AT and intracoronary GPI significantly increased TMPG 3 flow (RR: 1.15, 95% CI: 1.04 to 1.26), reduced IS [mean difference (MD):  $-3.46$ , 95% CI:  $-5.18$  to  $-1.73$ ], and improved LVEF (MD: 1.44, 95% CI: 0.54 to 2.33). Furthermore, GPI use decreased the risk of MACE at long-term follow-up (RR: 0.60, 95% CI: 0.37 to 0.98). There was no significant difference between the two groups in the incidence of minor and major bleeding complications. **Conclusions** Our findings showed that compared with AT alone, combined AT and intracoronary GPI treatment resulted in improved myocardial reperfusion, better cardiac function, and MACE-free survival benefits at the long-term follow-up for patients with STEMI undergoing PPCI.

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**Keywords:** Glycoprotein IIb/IIIa inhibitors; Meta-analysis; Myocardial reperfusion; Thrombectomy; Percutaneous coronary intervention

## 1 Introduction

Primary percutaneous coronary intervention (PPCI), if available, is widely accepted as the most effective reperfusion modality in patients with ST-segment elevation myocardial infarction (STEMI).<sup>[1]</sup> However, one of the limitations of PPCI is the possibility of distal embolization of the thrombus and microvascular obstruction (MVO), which results in suboptimal myocardial reperfusion and increased mortality.<sup>[2–4]</sup> Aspiration thrombectomy (AT) has been considered a simple way to remove the thrombus before stent

deployment, thereby improving myocardial reperfusion. However, recent trials have demonstrated a lack of benefit of thrombus aspiration on clinical outcomes and suggested possible harm from an increased risk of stroke.<sup>[5–7]</sup> Furthermore, studies have indicated that AT cannot remove the entire thrombotic mass and many small particles may remain in small arteries, leading to residual thrombus and microemboli in the microvasculature.<sup>[8]</sup> Glycoprotein IIb/IIIa inhibitors (GPI), such as abciximab, eptifibatide, and tirofiban, have been shown to be effective in lowering the thrombus burden and even disaggregating embolized platelet microaggregates; thus, they may play a role in counteracting the potential embolic effect of thrombectomy.<sup>[9,10]</sup> The preferred route of GPI administration is direct intracoronary injection into the infarct related artery as it has been shown to achieve a higher local concentration and further clinical efficacy than standard intravenous administration.<sup>[11–13]</sup>

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A number of clinical studies have been conducted to explore the effect of the combined strategy of AT and intracoronary GPI administration in patients with STEMI.<sup>[14–21]</sup> However, most of the randomized controlled trials (RCTs) have had relatively small sample sizes and reported conflicting results. A comprehensive evaluation of current clinical evidence about the role of this strategy in patients with STEMI has not been undertaken. Accordingly, we undertook a meta-analysis to evaluate the efficacy and safety of combined AT and intracoronary GPI versus AT alone in patients with STEMI undergoing PPCI.

## 2 Methods

### 2.1 Data sources

PubMed, Embase, Web of Science, and CENTRAL databases were searched systematically, as well as the references of eligible studies and recent reviews, for relevant studies published up until December 31, 2016. The keywords and corresponding Medical Subject Headings (Mesh) were as follows: “intracoronary”, “abciximab”, “tirofiban”, “eptifibatide”, “glycoprotein IIb/IIIa inhibitors”, “thrombectomy”, “myocardial infarction”, and “percutaneous coronary intervention”. No limits regarding language were applied.

### 2.2 Selection criteria

The inclusion criteria were as follows: (1) RCTs involving patients with STEMI undergoing PPCI; (2) trials that compared combined AT and intracoronary GPI (abciximab, tirofiban, or eptifibatide) with AT alone (control); and (3) studies that reported data on any of the outcomes of interest (reported below). The exclusion criteria were: (1) trials using intracoronary administration of GPI combined with other drugs and (2) duplicate reports.

### 2.3 Data collection and quality assessment

Two independent investigators assessed the studies for eligibility and extracted the following information: the study characteristics, the patient characteristics at baseline, features of the interventions, and the outcomes. Data were managed according to the intention-to-treat principle. In the case of missing or unclear information, we attempted to contact the authors of the original studies by e-mail.

The methodological quality of eligible trials was assessed by two independent reviewers using the criteria of the Cochrane Handbook.<sup>[22]</sup> All divergences were resolved by discussion with a third reviewer.

### 2.4 Outcomes and definitions

The outcomes chosen for this meta-analysis were major

adverse cardiac events (MACE) at short-term ( $\leq 1$  month) and long-term (6–12 months) follow-up, thrombolysis in myocardial infarction (TIMI) myocardial perfusion grade (TMPG),<sup>[3]</sup> infarct size (IS) determined by cardiac magnetic resonance, left ventricular ejection fraction (LVEF), and bleeding complications during the hospital stay.

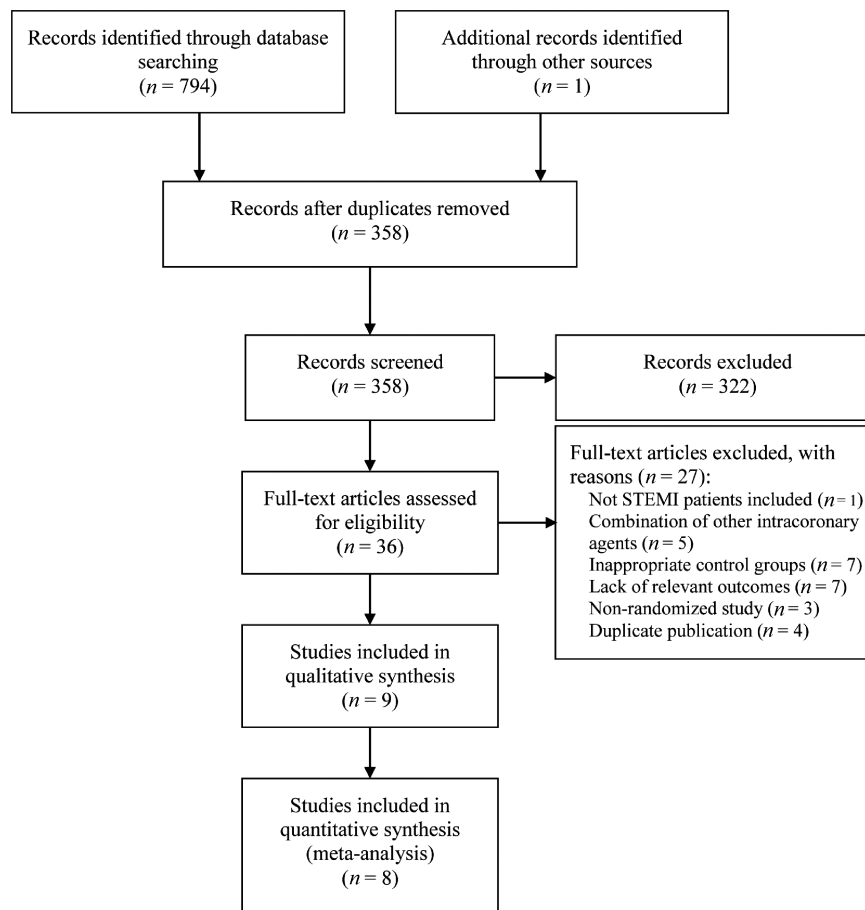
### 2.5 Statistical analysis

Two investigators cross-checked the data from all the identified studies. The risk ratio (RR) and mean difference (MD), and their corresponding 95% CIs, were calculated for dichotomous or continuous outcome data, respectively. A fixed-effect or random-effects model was chosen according to the presence of statistically significant heterogeneity between studies. Heterogeneity was assessed with the Cochrane Q test and the  $I^2$  statistic ( $P$  values  $< 0.1$  and  $I^2$  values  $> 50\%$  were considered statistically significant). If the continuous data were reported as the median and interquartile range (IQR), the mean and standard deviation (SD) were estimated using the median and the estimated SD ( $SD = IQR/1.35$ ).<sup>[22]</sup> We conducted sensitivity analyses by determining the influence of individual studies on the pooled estimates. A study was considered significantly influential if its exclusion changed the effect estimate by at least 20%.<sup>[23]</sup> Subgroup analyses for each outcome were performed according to the following criteria: type of GPI (abciximab vs. small-molecule GPI), median ischemic time (symptom onset to catheterization), baseline TIMI flow grade 0/1, left anterior descending occlusion ( $\leq 50\%$  or  $> 50\%$ ). Funnel plots were used to examine potential publication bias when the number of studies was sufficient.<sup>[22]</sup> A two-sided  $P < 0.05$  was considered statistically significant. All analyses were conducted using the statistical software RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata 11.0 (Stata Corp., College Station, Texas, USA). We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>[24]</sup>

## 3 Results

### 3.1 Eligible studies

From an initial total of 795 publications (Figure 1), eight RCTs (923 patients) fulfilled the inclusion criteria.<sup>[14–21]</sup> Abciximab, eptifibatide, and tirofiban were the study drugs in two,<sup>[14,19]</sup> one,<sup>[17]</sup> and five studies,<sup>[15,16,18,20,21]</sup> respectively. The patients were administered with aspirin and clopidogrel in all studies except one in which a small number of patients was given prasugrel instead of clopidogrel.<sup>[19]</sup> The patients received procedural anticoagulation with unfractionated



**Figure 1.** Flow diagram of the review process, according to the PRISMA statement. STEMI: ST-segment elevation myocardial infarction.

heparin in all studies but one in which bivalirudin was used as the anticoagulant.<sup>[19]</sup> The mean age of patients in the individual trials ranged from 52 to 64 years. The majority of the patients were male (68%). The follow-up time reported among trials varied with seven trials reporting short-term outcomes (in-hospital to one month),<sup>[14–17,19–21]</sup> and four reporting only long-term results (6–12 months).<sup>[15,16,18,19]</sup> Detailed information regarding the identified trials is provided in Table 1.

According to the Cochrane Collaboration's risk of bias evaluation tool (Figure 2), six RCTs included in this meta-analysis reported detailed descriptions of appropriate randomization. Only one trial described the allocation concealments in detail. Five studies used blinding of outcome assessment to ensure that observers analyzed the data independently. Most trials had a low risk of bias in incomplete outcome data and selective reporting. No other obvious potential sources of bias were found in any trial.

### 3.2 Effects of interventions

The incidence of MACE at the longest available fol-

low-up was reported in eight studies (Figure 3). No study demonstrated a statistically significant difference in the risk of short-term MACE between GPI and control groups (RR: 0.75, 95% CI 0.38 to 1.50,  $P = 0.42$ ; heterogeneity:  $P_{\text{het}} = 0.54$ ,  $I^2 = 0$ ). However, intracoronary use of GPI was associated with a significantly reduced risk of MACE at long-term follow-up (RR: 0.60, 95% CI: 0.37 to 0.98,  $P = 0.04$ ; heterogeneity:  $P_{\text{het}} = 0.47$ ,  $I^2 = 0$ ).

Four studies assessed myocardial reperfusion assessed by TMPG (Figure 4). The pooling analysis showed that intracoronary GPI injection significantly increased the incidence of TMPG 3 compared to controls (RR: 1.15, 95% CI: 1.04 to 1.26,  $P = 0.005$ ; heterogeneity:  $P_{\text{het}} = 0.93$ ,  $I^2 = 0$ ).

Three studies reported IS assessed by cardiac imaging (Figure 5). Intracoronary GPI was associated with significant reduction in IS compared to controls (MD:  $-3.46$ , 95% CI:  $-5.18$  to  $-1.73$ ,  $P < 0.001$ ; heterogeneity:  $P_{\text{het}} = 0.85$ ,  $I^2 = 0$ ).

Eight studies assessed LVEF (Figure 6) and results showed that GPI significantly improved LVEF compared to the control group (MD: 1.44, 95% CI: 0.54 to 2.33,  $P = 0.002$ ; heterogeneity:  $P_{\text{het}} = 0.16$ ,  $I^2 = 34\%$ ).

**Table 1. Description of included studies.**

Study	Year	N	GPI protocol	Inclusion criteria	Primary outcome	Definition of MACE	Definition of bleeding	Follow-up, month	*Age, yrs	Men (%)	*Mean or median ischemic time, h	*Baseline TIMI flow grade 0/1, %	*LAD culprit artery, %
Ahn, <i>et al.</i> <sup>[14]</sup>	2014	20/10	IC bolus of abciximab (0.25 mg/kg)	STEMI < 6 h	Index of micro-circulatory resistance	Cardiac mortality or nonfatal MI	NR	1	57/63	90%/60%	4.1/5.8	90/100	75/70
Gao, <i>et al.</i> <sup>[15]</sup>	2016	80/80	IC bolus of tirofiban (10 µg/kg) with a subsequent 48-h IV infusion (0.15 µg/kg per minute)	STEMI < 12 h	MACE	Cardiac mortality, nonfatal MI, or revascularization	Hemorrhagia and stool occult blood	6	63/64	41%/50%	6.7/5.0	94/93	48/38
Geng, <i>et al.</i> <sup>[16]</sup>	2016	78/72	IC bolus of tirofiban (25 µg/kg)	STEMI < 12 h	MACE	Cardiac mortality, nonfatal MI, or revascularization	Bleeding gums, microscopic hematuria, and epistaxis	6	58/60	55%/56%	1.1/1.2 <sup>&amp;</sup>	96/97	100/100
Iancu, <i>et al.</i> <sup>[17]</sup>	2012	25/25	IC bolus of eptifibatid (180 µg/kg) with a subsequent 12-h IV infusion (2.0 µg/kg per minute)	STEMI < 12 h	Microvascular reperfusion	Mortality, nonfatal MI, or revascularization	NR	1	55/55	80%/88%	4.5/4.7	100/100	100/100
Ji, <i>et al.</i> <sup>[18]</sup>	2015	64/61	IC bolus of tirofiban (10 µg/kg) with a subsequent IV infusion (0.15 µg/kg per minute) for 12–36 h	STEMI < 12 h	Microvascular reperfusion	Cardiac mortality or nonfatal MI	TIMI criteria	6	58/59	38%/43%	2.0/1.9 <sup>&amp;</sup>	100/100	47/31
Stone, <i>et al.</i> <sup>[19]</sup>	2012	118/111	IC bolus of abciximab (0.25 mg/kg)	STEMI < 4 h	Infarct size	Mortality, nonfatal MI, stroke, or revascularization	TIMI criteria	12	60/62	71%/77%	2.4/2.5	75/72	100/100
Wang, <i>et al.</i> <sup>[20]</sup>	2015	72/47	IC bolus of tirofiban (10 µg/kg) with a subsequent 48-h IV infusion (0.15 µg/kg per minute)	STEMI < 12 h	Markers of platelet activation and endothelial dysfunction	Mortality, nonfatal MI, or revascularization	Gastrointestinal bleeding	In-hospital	57/58	71%/75%	NR	100/100	49/47
Zhang, <i>et al.</i> <sup>[21]</sup>	2014	30/30	IC bolus of tirofiban (25 µg/kg)	STEMI < 12 h	Micro-vascular reperfusion	Mortality, nonfatal MI, or revascularization	Bleeding gums, microscopic hematuria, gastrointestinal bleeding, hemoptysis, and epistaxis	1	57/60	80%/77%	4.9/5.9	100/100	100/100

\*Data are reported as thrombectomy and GPI/ thrombectomy alone; <sup>&</sup>Time from Symptom to hospital arrival; GPI: glycoprotein IIb/IIIa inhibitors; IC: intracoronary; IV: intravenous; LAD: left anterior descending coronary artery; MACE: major adverse cardiac events; MI: myocardial infarction; NR: not reported; STEMI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction.

Six studies reported periprocedural bleeding complications (Figure 7). There was no significant difference in minor bleeding complications between GPI and control groups (RR: 1.11, 95% CI: 0.62 to 1.99,  $P = 0.71$ ; heterogeneity:

$P_{het} = 0.91, I^2 = 0$ ). The risk of TIMI-defined major bleeding was similar in the GPI group and the control group (RR: 5.69, 95% CI: 0.69 to 49.67,  $P = 0.11$ ; heterogeneity:  $P_{het} = 0.87, I^2 = 0$ ).

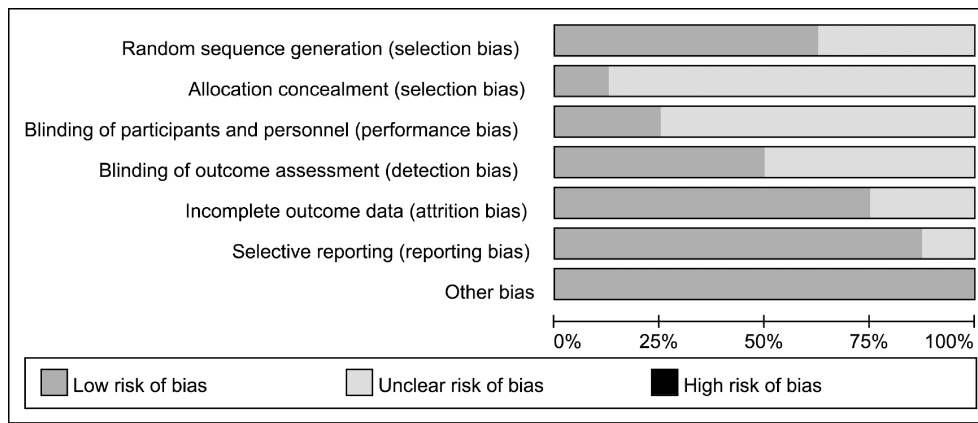


Figure 2. Risk of bias assessment according to the Cochrane Collaboration's bias tool.

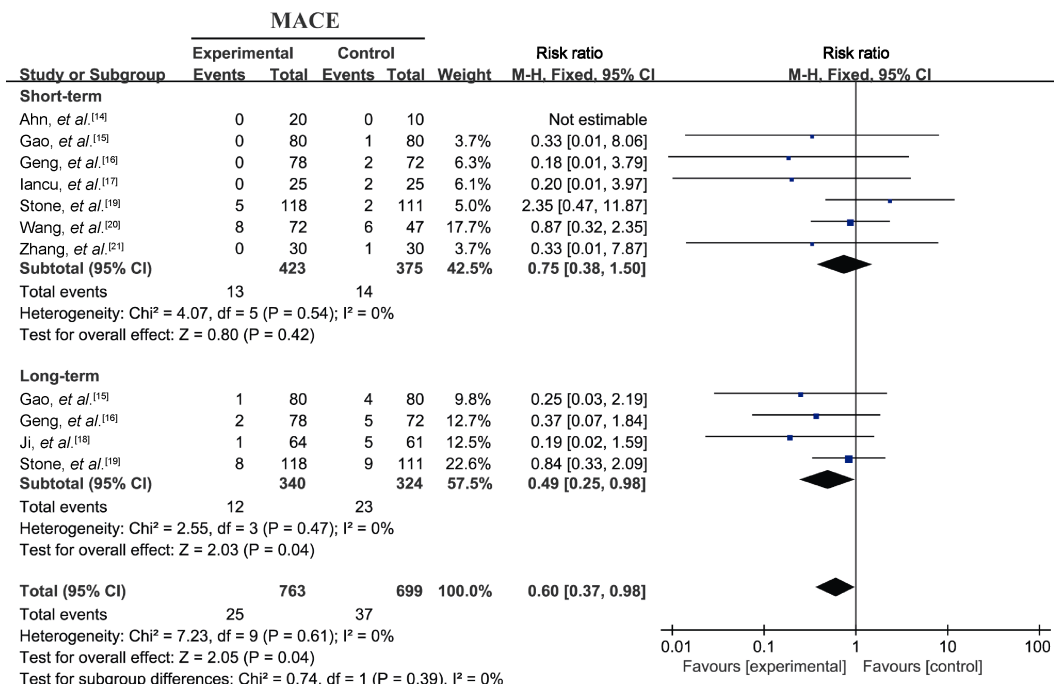


Figure 3. Relative risk of MACE for the combined thrombectomy and intracoronary GPI group versus the thrombectomy alone group at short- and long-term follow-up. MACE: major adverse cardiac events; GPI: glycoprotein IIb/IIIa inhibitors.

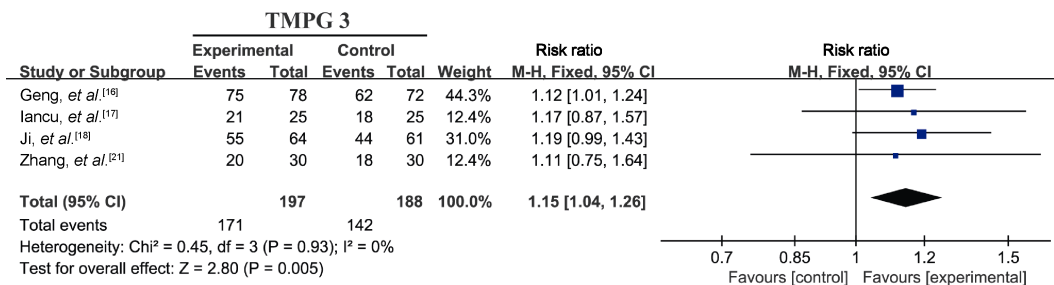
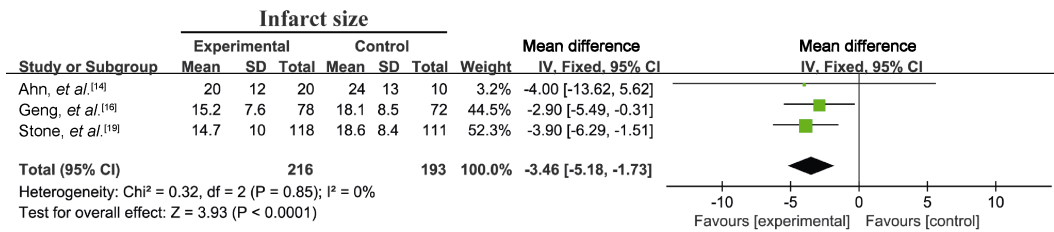
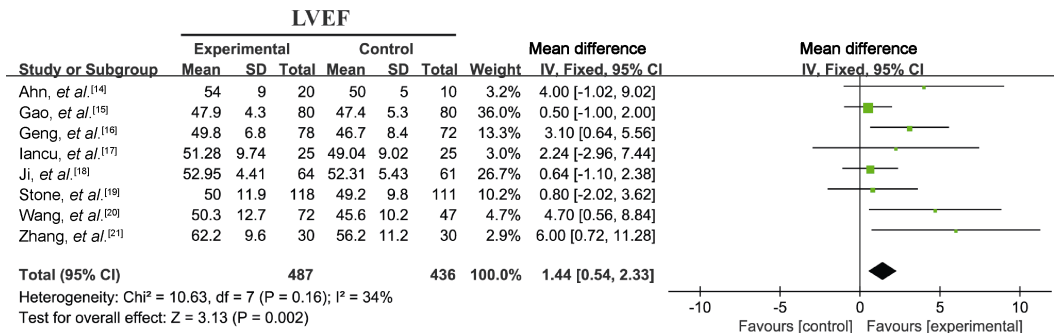


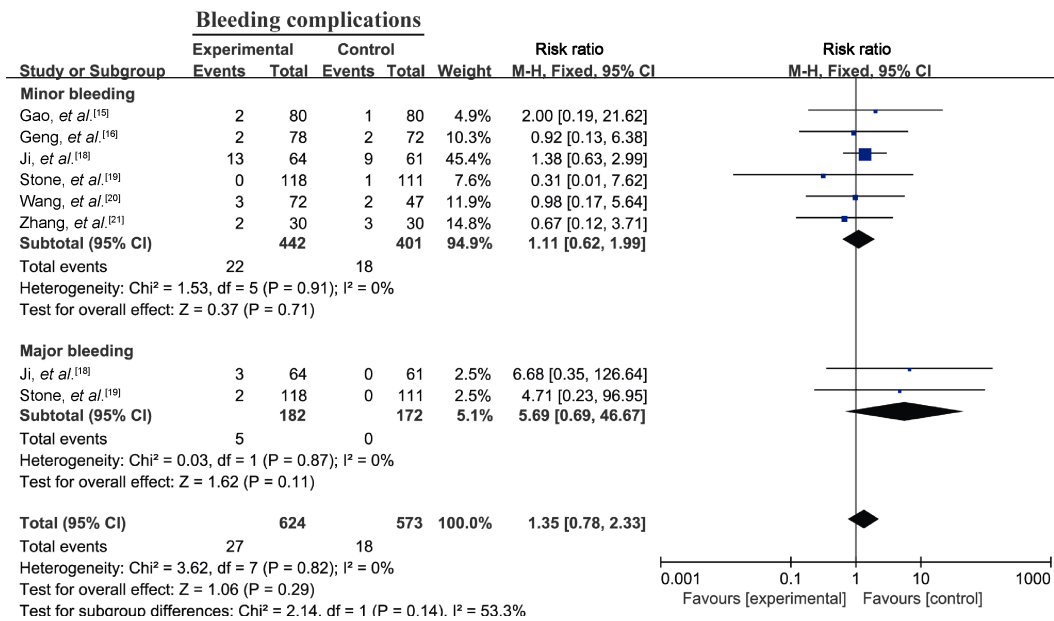
Figure 4. Relative risk of TMPG 3 for the combined thrombectomy and intracoronary GPI group versus the thrombectomy alone group. GPI: glycoprotein IIb/IIIa inhibitors; TIMI: thrombolysis in myocardial infarction; TMPG: TIMI myocardial perfusion grade.



**Figure 5. Mean difference of in infarct size for the combined thrombectomy and intracoronary GPI group versus the thrombectomy alone group.** GPI: glycoprotein IIb/IIIa inhibitors.



**Figure 6. Mean difference of LVEF for the combined thrombectomy and intracoronary GPI group versus the thrombectomy alone group.** GPI: glycoprotein IIb/IIIa inhibitors; LVEF: left ventricular ejection fraction.



**Figure 7. Relative risks of minor and major bleeding for the combined thrombectomy and intracoronary GPI group versus the thrombectomy alone group.** GPI: glycoprotein IIb/IIIa inhibitors.

**3.3 Sensitivity and subgroup analyses**

The sensitivity analyses demonstrated that no single study significantly altered the pooled RR of MACE, TMPG, IS, LVEF, and bleeding complications. The subgroup analy-

ses revealed that type of GPI, ischemic time, baseline TIMI flow grade, and infarct artery lesion location did not significantly influence the RR of the GPI or control group with respect to all of the outcomes mentioned above (all *P*<sub>interaction</sub> > 0.05) (Table 2).

**Table 2. Overall and subgroup analyses for all outcome measures.**

	Short-term MACE	Long-term MACE	TMPG	IS	LVEF	Minor bleeding	Major bleeding
Overall analysis	0.75 (0.38–1.50)	0.49 (0.25–0.98)	1.15 (1.04–1.26)	–3.46 (–5.18, –1.73)	1.44 (0.54, 2.33)	1.11 (0.62–1.99)	5.69 (0.69–46.67)
Subgroup analysis							
Type of GP IIb/IIIa inhibitors							
Abciximab	2.35 (0.47–11.87)	0.84 (0.33–2.09)	NA	–3.91 (–6.22, –1.59)	1.57 (–0.89, 4.02)	0.31 (0.01–7.62)	4.71 (0.23–96.95)
Small-molecule	0.54 (0.24–1.21)	0.27 (0.09–0.81)	1.15 (1.04–1.26)	–2.90 (–5.49, –0.31)	1.42 (0.45, 2.38)	1.18 (0.65–2.15)	6.68 (0.35–126.64)
Ischemic time							
≤ 4 h	1.14 (0.33–3.91)	0.54 (0.26–1.12)	1.19 (0.99–1.43)	–3.44 (–5.20, –1.69)	1.33 (0.06, 2.59)	1.18 (0.59–2.35)	5.69 (0.69–46.67)
> 4 h	0.27 (0.05–1.62)	0.25 (0.03–2.19)	1.12 (1.01–1.25)	–4.00 (–13.62, 5.62)	1.22 (–0.12, 2.55)	1.00 (0.26–3.84)	NA
Proportion of patients with baseline TIMI flow grade 0/1							
≤ 90%	2.35 (0.47–11.87)	0.84 (0.33–2.09)	NA	–3.90 (–6.29, –1.51)	0.80 (–2.02, 3.62)	0.31 (0.01–7.62)	4.71 (0.23–96.95)
> 90%	0.54 (0.24–1.21)	0.27 (0.09–0.81)	1.15 (1.04–1.26)	–2.97 (–5.47, –0.47)	1.51 (0.56, 2.46)	1.18 (0.65–2.15)	6.68 (0.35–126.64)
Proportion of LAD occlusion							
≤ 50%	0.78 (0.30–1.99)	0.22 (0.05–0.98)	1.19 (0.99–1.43)	–2.90 (–5.49, –0.31)	0.85 (–0.24, 1.94)	1.35 (0.69–2.66)	6.68 (0.35–126.64)
> 50%	0.73 (0.27–2.01)	0.67 (0.30–1.46)	1.12 (1.01–1.25)	–3.91 (–6.22, –1.59)	2.65 (1.08, 4.22)	0.66 (0.21–2.15)	4.71 (0.23–96.95)

Treatment effects were expressed as the risk ratio and mean difference for the dichotomous or continuous outcome data, respectively. IS: infarct size; LAD: left anterior descending; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac events; NA: not applicable; TIMI: thrombolysis in myocardial infarction; TMPG: TIMI myocardial perfusion grade.

### 3.4 Publication bias

Visual inspection of the funnel plots did not reveal any asymmetry with regard to MACE, LVEF, or bleeding complications.

## 4 Discussion

In this meta-analysis of eight randomized trials involving 923 patients, we found that compared with aspiration thrombectomy alone, concomitant administration of intracoronary GPI enhanced myocardial perfusion, reduced infarct size, and improved LVEF in patients with STEMI undergoing PCI. Furthermore, GPI use may decrease the risk of long-term MACE. There was no significant difference between the two groups in the incidence of minor and major bleeding complications, suggesting comparable safety.

During PPCI, distal embolization of the thrombus and subsequent MVO limit effective myocardial reperfusion and further extend infarction, resulting in a poor prognosis.<sup>[2–4]</sup> Adjunctive mechanical and pharmacologic treatments have

been proposed to reduce distal embolization and achieve the best myocardial reperfusion after PPCI. By further reducing the risk of thrombotic debris embolization and subsequent MVO with myocardial injury, it has been postulated that the combination of mechanic and pharmacologic treatment will enhance myocardial salvage and may improve clinical outcomes in patients with STEMI.<sup>[10]</sup> A retrospective registry study of 644 patients with STEMI found that the combination of AT with intravenous GPI exerted a synergistic effect on improving myocardial perfusion and clinical outcomes compared with either treatment modality administered separately.<sup>[25]</sup> A previous meta-analysis pooling the individual data of 2686 patients enrolled in 11 RCTs indicated that the combination of AT and abciximab was associated with a significantly reduced rate of mortality at a median follow-up of one year compared to AT alone [hazard ratio (HR): 0.61, 95% CI: 0.38 to 0.90].<sup>[26]</sup> Similarly, in a recent individual patient meta-analysis of more than 18000 patients with STEMI, patients treated with both AT and GPI had a lower risk of cardiovascular death within 30 days compared to those receiving AT only (HR: 0.63, 95%CI: 0.44 to 0.88).<sup>[27]</sup>

These two meta-analyses suggested that concomitant administration of intravenous GPI could enhance the clinical benefits observed with AT.<sup>[26,27]</sup> In contrast, in a meta-regression analysis including 17 trials with 20,960 patients, Elgendy, *et al.*<sup>[28]</sup> found that GPI administration did not modify any association between AT and adverse cardiovascular outcomes (mortality, reinfarction, and the combined outcome of mortality or reinfarction). However, the conflicting results of three meta-analyses<sup>[26–28]</sup> may not be definitive given that these were subgroup or meta-regression analyses. Further studies are needed to evaluate whether combined thrombectomy and GPI can exert a synergistic cardioprotection effect during PPCI. For the administration of GPI, intracoronary injection could offer increased local drug concentrations resulting in a more pronounced inhibition of platelet clot aggregation compared to the intravenous route.<sup>[11]</sup> Furthermore, the locally administered GPI would reach the cellular and molecular target more efficiently after mechanical removal of the thrombus.<sup>[25]</sup> Indeed, the CICERO trial, which randomized 534 patients with STEMI undergoing primary PCI with AT, has demonstrated that intracoronary administration of abciximab was superior to intravenous administration in improving myocardial reperfusion (reflected by myocardial blush grade) and reducing IS.<sup>[12]</sup> In a retrospective study exploring the role of AT combined with intracoronary administration of GPI in patients with STEMI, Yan, *et al.*<sup>[29]</sup> reported that the combination treatment was related with improved myocardial perfusion, saved more myocardium, and resulted in better clinical prognoses. The present study summarized the current available RCTs comparing the combination of AT with intracoronary GPI treatment with AT alone in patients with STEMI undergoing PPCI, with a view to providing more explicit information for use in the clinical setting. TMPG is an angiographic marker of myocardial perfusion.<sup>[3]</sup> Achievement of TMPG 3 is the important goal of reperfusion therapy, and has shown to be associated with improved clinical outcomes at long-term follow-up.<sup>[30]</sup> Our meta-analysis found that the improvement in microvascular perfusion in response to the combination treatment was paralleled by an improvement in myocardial salvage, as assessed by IS and LVEF. Additionally, these beneficial effects on surrogate endpoints could translate into a reduced rate of long-term MACE.

Although there were no statistically significant subgroup interactions, we cannot state with certainty whether these specified factors impacted the intervention effect. Our study included the trials of three types of GPI (abciximab, eptifibatide and tirofiban). The different pharmacokinetic and pharmacodynamic features of these drugs may have produced different clinical effects. However, a previous meta-

analysis demonstrated that there was no difference in angiographic, electrocardiographic, and clinical outcomes in patients with STEMI using abciximab and small molecule GPI.<sup>[31]</sup> The ischemic time, preprocedural TIMI flow grade, and location of occlusion are known factors affecting myocardial infarct size. It is plausible that combined intracoronary GPI and thrombectomy treatment would be more effective in patients with the greatest potential for infarct size reduction.<sup>[32]</sup> However, the small sample size in our meta-analysis did not allow us to draw any definite conclusions. More large-scale RCTs with greater statistical power are required to confirm these observations.

In the 2015 ACC/AHA/SCAI guideline update on PPCI, routine use of AT as an adjunct to PPCI is not recommended because AT use did not bring clinical benefit to patients with STEMI but could increase stroke risk.<sup>[33]</sup> However, there is still a role for AT in selective conditions with heavy thrombus burden or procedural-related thrombotic complications.<sup>[27,33]</sup> In the clinical setting, physicians should consider the use of intracoronary GPI to obtain the best myocardial reperfusion for patients with STEMI undergoing PCI with AT.

A major strength of the present study was that this is the first meta-analysis to exclusively compare combined AT and intracoronary GPI treatment with AT alone in a contemporary cohort of patients with STEMI. Our findings offer positive evidence for the improvement of myocardial perfusion after primary PCI, and pave the way for further RCTs to confirm the beneficial role of combined AT and intracoronary GPI treatment in patients with STEMI.

#### 4.1 Study limitations

Our study had several limitations. First, this is a study-level meta-analysis based on the published aggregate patient data. Second, the definition of MACE was not fully consistent across the trials. However, the MACE endpoint usually consisted of mortality, myocardial infarction, and repeat revascularization. In support of this, our analysis of MACE outcomes did not show any evidence of statistical heterogeneity ( $I^2 = 0$ ). Additionally, we did not evaluate the individual components of the MACE endpoint because they were reported in a minority of studies only. Third, dose and method of GPI administration were heterogeneous among the included studies. Fourth, some outcomes were applicable for evaluation in only a portion of included studies, which led to wider 95% CI and less conclusive results.

#### 4.2 Conclusions

Our findings showed that thrombectomy combined with



intracoronary GPI treatment could result in improved myocardial reperfusion, smaller infarcts, and better cardiac function compared to thrombectomy alone. Furthermore, these cardioprotective effects may translate into a MACE-free survival benefit at long-term follow-up for patients with STEMI undergoing PPCI. However, additional evidence from large RCTs is warranted to further substantiate these findings, given the limitations of the current available evidence.

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