Safety and Efficacy of Aspiration Thrombectomy With Intracoronary Tirofiban in Patients Undergoing Primary Percutaneous Coronary Intervention: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Primary percutaneous coronary intervention (PPCI) may be complicated by heavy intracoronary thrombus burden leading to decrease in myocardial perfusion and increase in infarct size. The current meta-analysis aims to investigate the clinical outcomes of aspiration thrombectomy (AT) with intracoronary tirofiban during PPCI.

METHODS: A systematic search for randomized controlled trials that evaluate the safety and efficacy of AT with intracoronary tirofiban in ST-elevation myocardial infarction (STEMI) patients who underwent PPCI was done using PubMed, MEDLINE, EMBASE, Cochrane, ClinicalTrials.gov., and Herdin PH. Studies included those published between 2010 and 2023 and involved human subjects. Search terms included "aspiration thrombectomy," "intracoronary tirofiban," "primary percutaneous coronary intervention," and "STEMI patients."

RESULTS: Four randomized controlled trials (n = 490 participants) were included in this meta-analysis comparing AT with intracoronary tirofiban versus AT alone in STEMI patients undergoing PPCI. The results revealed no statistically significant difference in ST-segment resolution (risk ratio [RR], 1.02; 95% confidence interval [CI], 0.97–1.08; $P = 0.41$, $I^2 = 0\%$), myocardial blush grade 2–3, (RR, 1.04; 95% CI, 0.97–1.12; $P = 0.22$, $I^2 = 62\%$), and Thrombolysis In Myocardial Infarction 3 flow (RR, <1.0; 95% CI, 0.95–1.04; $P = 0.87$).

The occurrence of major adverse cardiovascular events did not significantly differ between the two groups (RR, 0.46; 95% CI, 0.19–1.09; $P = 0.08$, $I^2 = 0\%$). There was no statistically significant difference in terms of bleeding when combining intracoronary tirofiban to standard medical therapy (RR, 1.35; 95% CI, 0.64–2.84; $P = 0.78$, four trials [490 patients]).

CONCLUSION: In PPCI, major adverse cardiovascular event outcomes of AT with intracoronary tirofiban were similar to those for AT alone in terms of improving myocardial perfusion in STEMI patients without increasing the risk for bleeding. Our meta-analysis suggests that AT alone may be the more acceptable standard during PPCI when encountering heavy thrombus burden. Future validated studies may help further investigate the strategy of adding tirofiban during AT.

BACKGROUND

Despite the ability of primary percutaneous coronary intervention (PPCI) to rapidly restore myocardial flow in patients with ST-elevation myocardial infarction (STEMI), the presence of serious thrombus burden remains a persistent clinical challenge by exacerbating coronary artery obstruction and compromising myocardial flow. To address this issue, a range of strategies has been advocated to mitigate thrombus burden and improve outcomes.[1]

The utilization of aspiration thrombectomy and intracoronary tirofiban in STEMI patients undergoing PPCI holds clinical relevance by removal of thrombus burden, potentially reducing distal embolization and improving myocardial perfusion and by targeting platelet aggregation to mitigate thrombotic complications, respectively.[2] Given the paramount importance of achieving rapid and effective reperfusion in STEMI, the evaluation of these interventions is warranted to

assess overall impact on patient outcomes in terms of safety and efficacy.

Description of the Interventions

The use of aspiration thrombectomy in STEMI patients undergoing PPCI with significant thrombus burden is based on the premise that effective removal may potentially lead to a reduction in the thrombus load, a decrease in distal embolization rates, improvement in Thrombolysis In Myocardial Infarction 3 (TIMI 3) flow, a lowered occurrence of no-reflow phenomenon, enhanced microvascular perfusion, and subsequently better clinical outcomes.[3] However, it is important to note that a number of randomized trials comparing routine thrombus aspiration with PPCI alone in patients with ST-segment–elevation myocardial infarction (STEMI) have not consistently demonstrated a reduction in cardiovascular outcomes.[2,4]

Tirofiban, a glycoprotein IIb/IIIa receptor inhibitor used adjunctively in acute coronary syndromes as means of effective antiplatelet therapy, was introduced with the aim of further enhancing reperfusion therapy by providing rapid, localized inhibition of platelet aggregation at the site of thrombus.[5,6]

The objective of this comparative assessment is to evaluate these two strategies when used together in terms of procedural measures, including myocardial reperfusion, infarct size reduction, and the safety endpoints of major adverse cardiovascular events and bleeding.

Related Works and Importance of the Study

ST segment elevation myocardial infarction (STEMI) is a critical cardiovascular emergency demanding rapid and effective treatment to salvage myocardium and improve patient outcomes. Among evolving strategies for STEMI management, thrombus aspiration and intracoronary tirofiban administration have gained attention as potential interventions to enhance reperfusion and reduce adverse events during PPCI.

Aspiration Thrombectomy

Aspiration thrombectomy (AT), introduced in the early 2000s, emerged as a technique to mitigate distal embolization and improve coronary flow adjunctively to PPCI.[3] According to the TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trial in 2006, AT is superior in terms of clinical efficacy by improving myocardial reperfusion and reducing distal embolization when compared to percutaneous coronary intervention (PCI) alone.[7] The EXPIRA (Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention) trial in 2009 showcased significant enhancements in myocardial blush grade, ST-segment resolution, a reduction in microvascular obstruction (MVO), infarct size, and a lowered risk of cardiac death at both nine months[8] and two years.[9] The favorable outcomes were further substantiated by a meta-analysis by Kumbhani et al. showed improved rates of ST-segment resolution at 60 minutes, higher Thrombolysis In Myocardial Infarction blush grade 3 after the procedure, and a reduction in major adverse cardiovascular events, but more recent and substantial randomized trials have not been able to consistently demonstrate a significant reduction in terms of mortality. [10]

In 2013, the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial, involving 7,244 patients, found that routine AT did not lead to a reduction in 30-day or 1-year mortality or other cardiovascular events.[11] Subsequently, in 2015, the TOTAL (Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI) trial, which included 10,732 patients, also failed to demonstrate a reduction in cardiovascular events and mortality with an increased rate of stroke within 30 days and at 1 year. It did not demonstrate a significant reduction in adverse events with thrombectomy, challenging the previously established benefits.[12]

In 2017, Jolly et al further substantiated favorable outcomes by an individual patient-level meta-analysis of three trials, involving a total of 19,047 patients, indicating no discernible difference in clinical outcomes with routine thrombectomy.[13] However, when analyzing subgroups with a high thrombus burden, it revealed a lower incidence of cardiovascular deaths at the expense of an increased risk of stroke.[13] In another more recent meta-analysis of 25 randomized trials by Taglieri in 2019, employing thrombus aspiration alongside PPCI does not result in a decreased risk of death, myocardial infarction, or stent thrombosis with a relatively weak correlation of an elevated risk of stroke. [14]

In a 2022 study led by Inohara and colleagues, data from the J-PCI (Japanese PCI) registry assessing a large cohort of 282,606 patients with ACS, of which 53% had STEMI, AT had a higher rate of successful PPCI, defined as achieving TIMI 3 flow.[16] However, this benefit was counterbalanced by a significant increase in in-hospital deaths and procedural complications.

Consequently, guideline committees, such as the 2021 American College of Cardiology/American Heart Association (ACC/AHA)[17] and the 2023 European Society of Cardiology guidelines on the management of acute coronary syndromes[18] have assigned routine thrombus aspiration during PPCI with a class III recommendation. However, in instances where a substantial thrombus remains after initial vessel opening using a guide wire or balloon, its may be considered emphasizing that the effectiveness of selective and bailout AT in patients undergoing PPCI is not firmly established.[18] In contrast, the Japanese Cardiological Society provides a class IIb recommendation for its selective or bailout use.[19]

However, despite recommendations, different responses in terms of utilization of AT is seen in the United States and Japan. In the US, there is a witnessed decline in AT adoption following larger clinical trials and updated guideline recommendations that by the second quarter of 2016 with manual AT employed in just 4.7% of all PPCI.[20] Contrary to the class III guideline recommendations, including those from Japan's own

guidelines, there was notably high utilization of thrombus aspiration, reaching 53% for their STEMI patients in Japan[4], suggesting a possibility of an ingrained practice that might be described as an "oculo-thrombotic reflex." coined by Eric Topol in 1988[21], defined as the "irresistible temptation among some invasive cardiologists to perform angioplasty on any significant residual stenosis after thrombolysis."[22]

Intracoronary Tirofiban

The presence of fibrin, red blood cells, and platelets contribute mainly in the induction and propagation of microvascular obstruction which is the target of the thrombolysis-based approach of using glycoprotein IIb/IIIa inhibitors by dissolving thrombi and inhibiting aggregation to enhance microvascular perfusion.[23]

The ACC/AHA 2021 guidelines advocate for the selective use of intravenous (IV) glycoprotein IIb/IIIa inhibitors (GPIs) in patients with STEMI.[17] However, these guidelines do not specifically address the effectiveness and safety of intracoronary GPIs when administered after passing a guidewire or balloon through the infarction-associated arteries. A study by Chen et al in 2013 concluded that intravenous GPI administration results in lower GPI concentration and suboptimal occupancy of the glycoprotein IIb/IIIa receptors. [24] Hence, it has been postulated that intracoronary administration offers better receptor occupancy, [25] anti-inflammatory effects, [24, 25] and improved endothelial function [24], in addition to lower rates of bleeding and immune responses. [25] Furthermore, intracoronary administration has been associated with successful thrombus dissolution[26] and a reduction in thrombus burden.

Several trials investigated the administration of tirofiban, a highly selective inhibitor of fibrinogen binding to platelet GP IIb/IIIa, during PPCI and highlighted its potential benefit in improving myocardial perfusion and reducing adverse events. Three pivotal trials include: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM)[27], Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS)[28], and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE)[29]. The PRISM trial, which included 3232 patients with unstable angina (UA), demonstrated a reduction in the composite endpoint of death, myocardial infarction (MI), or refractory ischemia at 48 hours with tirofiban infusion. However, this effect did not persist at the 30-day mark, and angiography was performed in 62% of cases within the first 30 days.[27] In the PRISM-PLUS trial, involving 1915 patients enrolled within 24 hours of UA or non–Q wave MI symptom onset, the tirofiban plus heparin dosing arm exhibited a statistically lower rate of the composite endpoint, including death, new MI, refractory ischemia within 7 days, or rehospitalization for UA with 60% of patients requiring revascularization procedures post-tirofiban therapy.[28] Lastly, the RESTORE trial, targeting patients undergoing coronary intervention within 72 hours of UA or acute MI, revealed no statistically significant difference in primary endpoints (death, MI, CABG surgery, or any revascularization procedure) within the first 30 days between the tirofiban and placebo groups. There were also no statistically significant increase in thrombocytopenia or major bleeding[29] which are the potential side effects of GP IIb/IIIa receptor antagonists. [30]

The "On-TIME 2" trial demonstrated that early administration of tirofiban during PCI in acute myocardial infarction, led to a significant reduction in infarct size and improvement in left ventricular function compared to late administration. However, no significant differences were observed in clinical endpoints such as mortality and reinfarction between the two groups.[31]

A meta-analysis of randomized controlled trials by Tian et al assessing the efficacy and safety of intracoronary versus intravenous tirofiban in STEMI patients undergoing PPCI, found that intracoronary tirofiban significantly improved the incidence of TIMI 3 in the high-dose group, in-hospital and 6-month LVEF, and reduced the 30-day major adverse cardiovascular event (MACE) incidence without increasing the risk of bleeding compared with IV. [32]

Combination AT and intracoronary tirofiban

The significance of the combined interventions lies in its impact on clinical practice and the ongoing debate regarding use in STEMI patients undergoing PPCI. While AT has demonstrated benefits in terms of improving myocardial reperfusion and reduction of thrombus burden, concerns about its universal utility are seen, as evidenced by studies like the TASTE[11] and TOTAL trial.[12]

Tirofiban, with its localized antiplatelet effects, presents a complementary approach, as suggested by the "On-TIME 2 trial".[31] When compared with the intravenous route, the intracoronary approach yields more potent platelet function inhibition [33], higher receptor occupancy [33, 34], improved microvascular perfusion[34, 35,] smaller infarct size [35], and decreased rates of adverse clinical outcomes such as death and MACE as evidenced by several randomized studies [36,37] and meta-analyses [38-41] however there are larger and more recent studies that have concluded conflicting results. [32, 33, 36]

The objective of this meta-analysis and systematic review is to validate current randomized trials that investigate the efficacy and safety of intracoronary-administered tirofiban with AT versus AT alone as an adjunct to PPCI among patients presenting with STEMI.

MATERIALS AND METHODS

Search Strategy

We identified five references through electronic searches of Medline/PubMed, ClinicalTrials.gov, Cochrane Library and Herdin.ph from January 2015 up to October 2023. The reference list of articles were also included. Search was done using the following terms: "ST-elevation myocardial infarction," "aspiration thrombectomy," "percutaneous coronary intervention," "intracoronary tirofiban" and "randomized clinical trial." A total of 27 articles were identified and 4 were

▶ **Search Methods:**

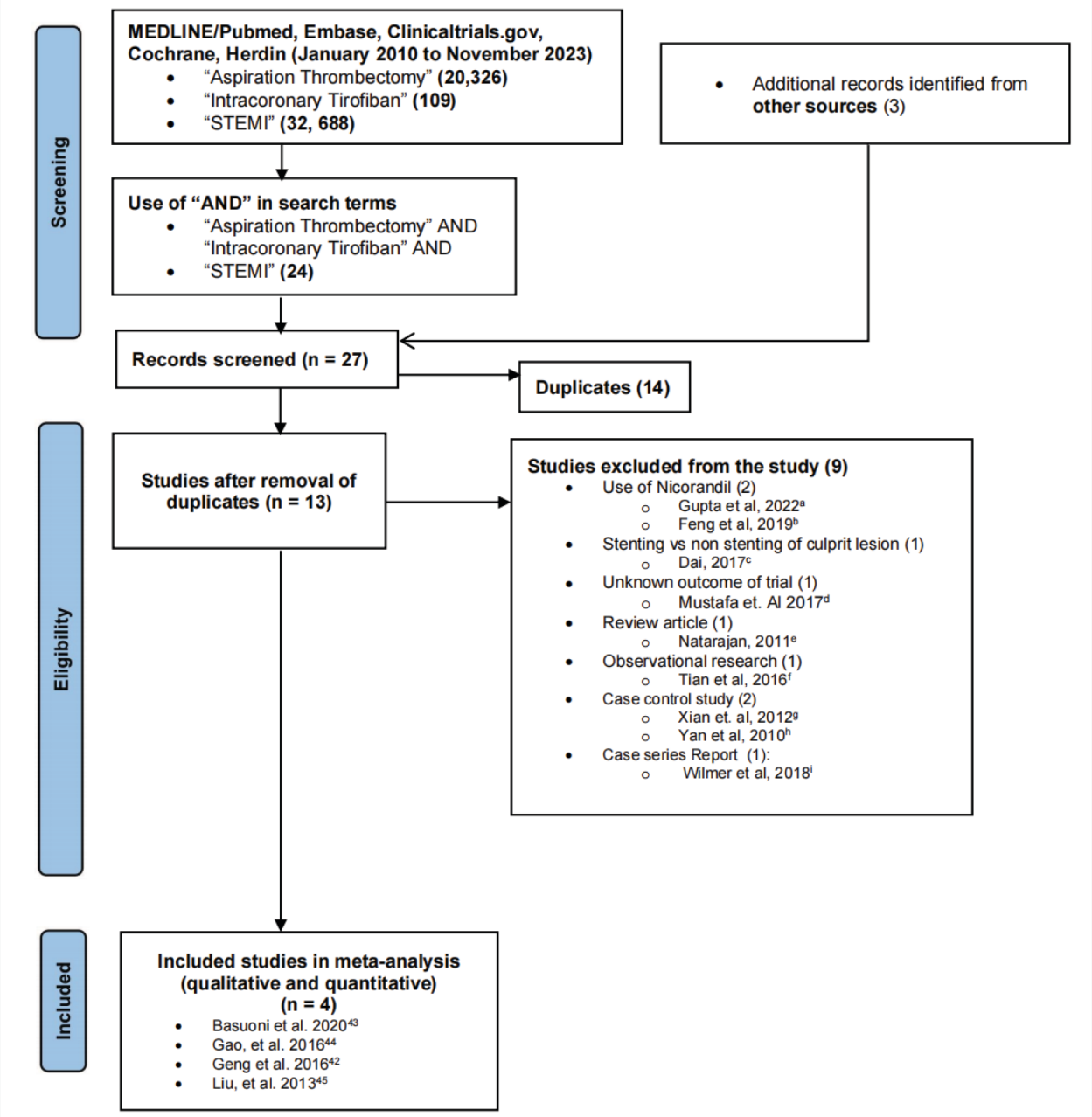


Figure 1. PRISMA flow diagram showing the included and excluded studies at each stage of the selection process. Abbreviation: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

included in the meta-analysis (Figure 1). The protocol for this systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews; Registration number: CRD42023431850). A systematic literature search was performed to identify studies evaluating the use of AT alone versus AT with intracoronary tirofiban in STEMI patients undergoing PPCI. The systematic literature review was performed independently by two investigators using the keywords and medical subject heading (MeSH) terms of "Aspiration Thrombectomy," "Intracoronary Tirofiban," "Aspiration and Intracoronary Tirofiban" and "STEMI patients."

Study Selection

Electronic literature searches for randomized controlled trials involving adult STEMI patients undergoing PPCI with AT and intracoronary tirofiban compared to AT alone. The primary study must address the procedural outcomes and coronary reperfusion indices (e.g., ST-segment resolution, TIMI flow grade, myocardial blush grade). Studies were excluded if they were (1) non-randomized studies, 2) duplicate studies or (3) animal studies.

Table 1. Description of Included Studies

Studies/Trial	**Geng et al,[42] 2020**		**Basuoni et al,[43] 2016**		**Gao et al,[44] 2016**		**Liu et al,[45] 2013**	
Study Population	STEMI patients undergoing primary PCI		STEMI patients undergoing primary PCI		STEMI patients undergoing primary PCI		STEMI patients undergoing primary PCI	
Treatment	Primary PCI with aspiration thrombectomy and intracoronary tirofiban		Primary PCI with aspiration thrombectomy and intracoronary tirofiban		Primary PCI with aspiration thrombectomy and intracoronary tirofiban		Primary PCI with aspiration thrombectomy and intracoronary tirofiban	
Control	Primary PCI only with aspiration thrombectomy		Primary PCI only with aspiration thrombectomy		Primary PCI only with aspiration thrombectomy		Primary PCI only with aspiration thrombectomy	
Trial Characteristics								
Centers	1		2		1		1	
Enrollment period	November 2011–November 2013		August 2014–November 2015		September 2013–February 2015		July 2008–December 2009	
Treatment/follow-up	6 mo		30 d		6 mo		1 mo and 1 y	
Characteristics of the Patients at Baseline								
Studies/Trial	**Geng et al,[42] 2020**		**Basuoni et al,[43] 2016**		**Gao et al,[44] 2013**		**Liu et al,[45] 2013**	
	Control	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**
Patients, n	72	78	50	50	80	80	40	40
Mean age, y	59.7 ± 7.1	58.4 ± 5.8	47.32 ± 7.4	52.2 ± 6.9	64.1 ± 10.8	62.7 ± 11.9	64.5± 13.8	66.7± 15.9
Men, n (%)	40 (55.6)	43 (55.1)	42 (84%)	38 (76%)	40	33		
DM type 2	8 (11.1)	6 (76.9)	20 (40%)	22 (44%)	40.0 (32)	47.5 (38)		
HPN, n (%)	45 (62.5)	42 (53.8)	16 (32%)	8 (16%)	60.0 (48)	55.0 (44)		
Hyperlipidemia, n (%)	10 (13.9)	16 (20.9)	6 (12%)	6 (12%)	36.2 (29)	37.5 (30)		
FH of CAD	—	—	4 (16%)	4 (16%)	—	—		
Previous MI	2 (2.8)	1 (1.3)	0	0				
Anterior MI	—	—	50 (100%)	50 (100%)			24	23
Currently smoking, n (%)	2 (30.6)	31 (39.7)	34 (68%)	36 (72%)				
Obesity, n (%)	—	—	4 (8%)	10 (20%)	—	—		
Medication usage before myocardial infarction								
Aspirin					(14)	(10)		
ACEI/ARB (%, n)					46.2 (37)	40.0 (32)		
ACEI/ARB (%, n)					7.5 (6)	10.0 (8)		
CCB (%, n)					28.7 (19)	25.0 (20)		
Killip class, n (%)								
I	71 (98.6)	77 (98.7)	—	—	7	8	9	10
II	1 (1.4)	1 (1.3)	6 (12%)	6 (12%)	20	23	20	22
III					28	27	11	8
IV					25	22		
Symptom to hospital (h)	1.2 ± 1.8	1.1 ± 1.6	Median 4, IQR 2	Median 4, IQR 2				

Table 1. Description of Included Studies (Continued)

Studies/Trial	**Geng et al,[42] 2020**		**Basuoni et al,[43] 2016**		**Gao et al,[44] 2016**		**Liu et al,[45] 2013**	
ST-segment resolution post-PCI	68	76	50 (100%)	50 (100%)	68	70		
CR					*68*	*70*		
PR					*8*	*8*		
NR					*4*	*2*		
No reflow, % (n)					1.2 (1)	0.0 (0)		
Slow-reflow**, %** (n)					3.7 (3)	5.0 (2)**	**1 (2.5)***	**4 (10.0)**
Procedural Outcomes and Reperfusion Indices								
	Control	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**
PCI								
Symptom-to-door, h			Median 4, IQR 2	Median 4, IQR 2				
Door-to-balloon time, min	17.8 ± 9.1	19.2 ± 8.3	Median 30, IQR 15	Median 30, IQR 30				
Door-to-balloon time, h					1.8 ± 0.5	1.9 ± 0.3		
Onset-to-balloon time, h					5.0 ± 1.0	6.7 ± 0.8		
Intra-aortic balloon pump	0	0	—	—				
Left main					0	0		
LAD					30	38		
Proximal LAD, n (%)	42 (58.3)	46 (59)	28 (56%)	30 (60%)				
Mid-LAD, n (%)	30 (41.7)	32 (41)	22 (45.8%)	20 (41.7%)				
LCx					18	16		
RCA					32	36		
TIMI flow before PCI, n (%)								
0/1, n (%)	70 (97.2)	75 (96.2)						
0					46	52		
1					28	23		
2	2 (2.8)	3 (3.8)			6	5		
3					0	0		
Balloon dilatation, n					74	71		
TIMI flow after PCI, n (%)								
0/1	0	0						
0					1	0		
1					1	1		
2	2 (2.8)	0			2	1		
3	70 (97.2)	78 (100)	46 (92%)	44 (88%)	76	78	36 (90.0)*	33 (82.5)
Myocardial blush grade	—	—	50	50	—	—	36	33

Table 1. Description of Included Studies (Continued)

Studies/Trial	Geng et al,[42] 2020		Basuoni et al,[43] 2016		Gao et al,[44] 2016		Liu et al,[45] 2013	
TMP <3, n (%)	10 (13.9)	3 (3.8)					2.6±0.6* (mean)	1.6±0.3 (mean)
Multivessel lesions, n (%)					36	42		
Thrombus grade III			4 (8%)	8 (16%)				
Thrombus grade IV			0	0				
Thrombus grade V			46 (92%)	40 (80%)				
Drug-eluting stents			50 (100%)	50 (100%)				
No. of stents			Median 1, IQR 0	Median 1, IQR 0				
Stent length >30 mm			7 (29.2%)	10 (41.7%)				
Radial access			29 (58%)	30 (60%)				
Clinical Endpoints								
During hospitalization								
			90 d	90 d				
MACCE	—	—	6 (12%)	4 (8%)	1	0		
Heart failure	—	—	5	3				
Stroke	—	—	0	0				
Myocardial reinfarction	1 (1.4)	0	1	1				
CHD death, n (%)	1 (1.4)	0	0	0				
Re-PCI	0	0						
CABG	0	0						
Any of the above, n (%)	2 (2.8)	0						
Bleeding, n (%)	2 (2.8)	2 (2.6)	4 (8%)	6 (12%)	1	2	4	5
TIMI major								
TIMI minor			*4 (8%)*	*6 (12%)*				
Thrombocytopenia			0	0				
At the 6-mo follow-up								
Myocardial reinfarction, n (%)	3 (4.2)	1 (1.4)	—	—	4	1	0	0
Cardiac mortality, n (%)	2 (2.8)	1 (1.4)						
Re-PCI	0	0						
CABG	0	0						
Any of the above, n (%)	5 (6.9)	2 (2.6)			4	1	0	0
At 1-y follow-up								
MACE							0	0
Bleeding (minor)							4 (10)	5 (12.5)
Restenosis							1 (2.5)	0 (0)
Total events	5	2			4	1	0	0

Table 1. Description of Included Studies (Continued)

Studies/Trial	Geng et al,[42] 2020		Basuoni et al,[43] 2016		Gao et al,[44] 2016		Liu et al,[45] 2013	
Variables								
CK-MB (time to peak)			Median 12, IQR 8	Median 13.5, IQR 7				
CK-MB, U/L					215.1 ± 40.9	225.9 ± 34.5		
Troponin I, ng/mL					5.6 ± 3.0	5.8 ± 3.7		
ECHO (EF%)			Median 40.5, IQR 16	Median 46, IQR 13	39.1 ± 6.2	40.1 ± 5.5		
Myocardial Blush grade 2/3	76	68	46 (92%)	42 (84%)			39	36
cMR infarction size, g	18.1 ± 8.5	15.2 ± 7.6	Median 43.828, IQR 49.599	Median 15.451, IQR 17.404				
% Reduction of infarct size			Median 25.45, IQR 24.4	Median 13.3, IQR 8.7				

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CCB, calcium-channel blocker; CHD, congenital heart disease; CK-MB, creatine kinase-MB; DM, diabetes mellitus; EF, ejection fraction; FH, family history; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TMP, TIMI myocardial perfusion.

Data Collection And Analysis

Data extraction and quality assessment

After a systematic search of related literature, studies included were assessed individually based on its inclusion and exclusion criteria. Critical analysis of the primary and secondary outcomes, intervention, study population and comorbidities of participants were performed. Risk of bias assessment was done for each included study. Quality assessment was done using the evaluation instrument recommended by Cochrane Collaboration for bias risk assessment.

Measures of treatment effect

Outcomes whether dichotomous or continuous were used to describe both primary and secondary outcomes between the groups. Analysis was conducted using the statistical package Review Manager Version 5.4.

Assessment of heterogeneity and reporting biases

Cochran's Q-test and I^2 statistics were used to assess the statistical heterogeneity across the studies. As a guide, I2 values <25% indicates low, 25% to 50% moderate, >50% high heterogeneity. For categorical variables, Mantel-Haenszel effect model was used to calculate the pooled odds ratio for the studies and associated 95% confidence intervals. A p value of less than 0.05 was considered significant.

Overview of the Included Randomized Control Trials

As shown in Table 1, the four studies [42-45] included adult patients diagnosed with STEMI undergoing PPCI with adjunctive AT and intracoronary tirofiban in the treatment arm. The control arms consisted of AT only. A total of five centers involving 490 patients were included, with the largest population of 160 patients and the smallest population of 80 patients. Treatment and follow-up periods lasted between 30 days to one year.

Geng et al. included patients with STEMI who met specific inclusion criteria, including chest discomfort lasting at least 30 minutes, ST-segment elevation in certain leads, and timely hospital arrival. PPCI outcomes were assessed based on coronary angiography findings in the left anterior descending artery. Exclusion criteria comprised various pre-existing conditions and prior medical procedures.[42]

Basuoni et al. included patients aged 18 and above, regardless of gender, exhibiting symptoms consistent with STEMI lasting longer than 30 minutes and meeting specific electrocardiographic criteria. Eligible patients had ST-segment elevation in two or more contiguous leads in V1-V4 or a new left bundle-branch block, with a symptom-onset-to-device time of 6 hours or less. They were required to have a large acute

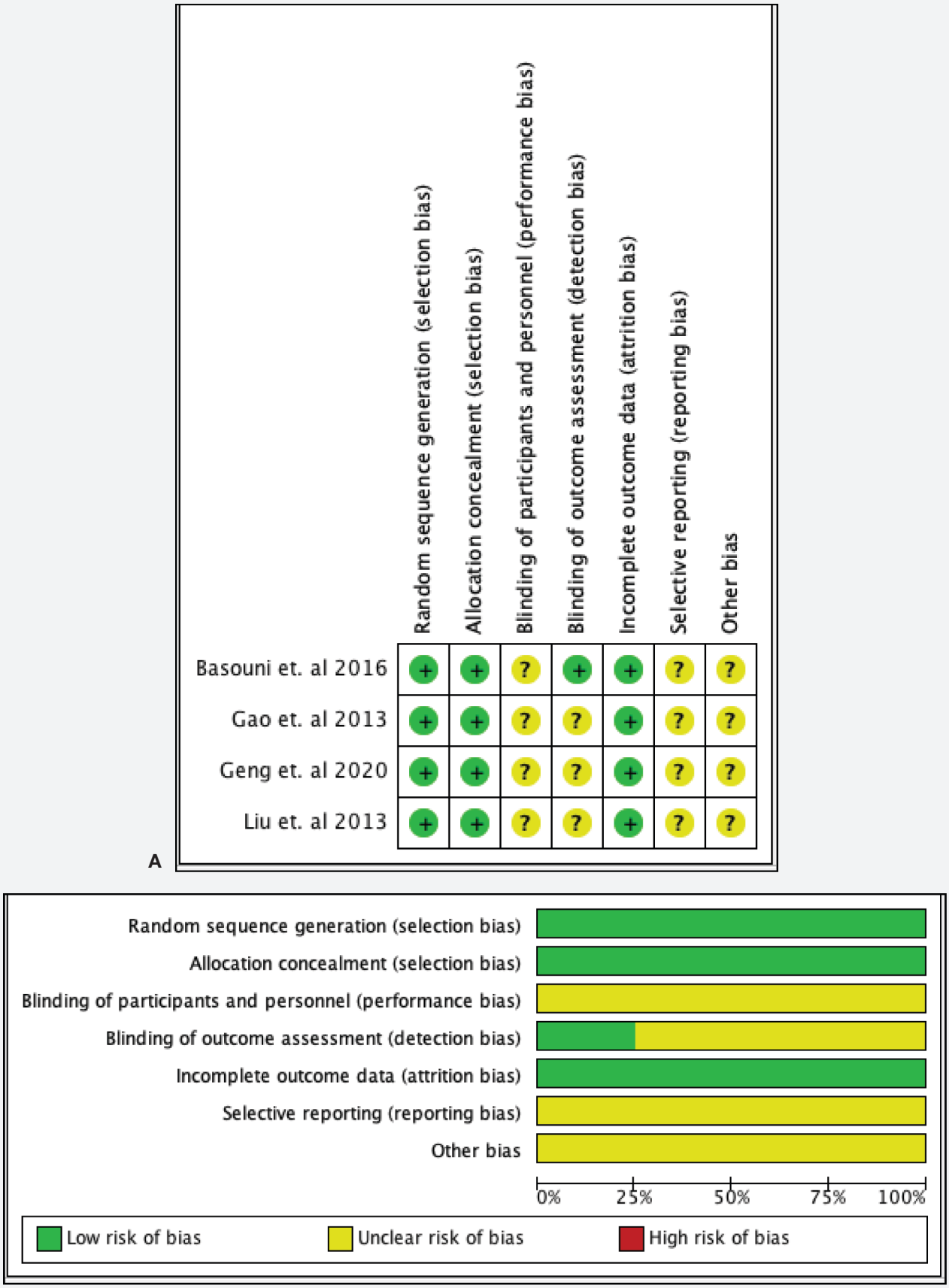


Figure 2. **A**. Risk-of-bias summary of the included studies. **B**. Risk-of-bias graph: review of author's judgments across different studies.

anterior STEMI, and PPCI was indicated for those with a TIMI 0/1/2 flow in the proximal or mid left anterior descending artery. Exclusion criteria encompassed previous heart conditions, severe vessel issues, and contraindications to cardiac magnetic resonance. [43]

Gao et al. included patients experiencing their first episode of STEMI and receiving emergency PPCI. The patients were randomly assigned to one of three groups: Group A received thrombectomy along with intracoronary tirofiban injection before PPCI, Group B received thrombectomy before PPCI, and Group C underwent PPCI only, with balloon dilatation performed as needed. Eligible participants were aged 18-80, able to comprehend the study's details, consent to participation, and agree to follow-up and necessary examinations. Exclusion criteria covered patients with non-ST elevation myocardial infarction, renal or severe liver disease, limited life expectancy, pregnancy or lactation, inability to provide consent, or concurrent participation in other medical studies. STEMI diagnosis adhered to World Health Organization criteria, including chest pain suggestive of myocardial ischemia for at least 30 minutes, specific ST-segment elevation patterns on the electrocardiogram, and relevant clinical indicators. [44]

Liu et al included patients who had their first episode of STEMI and received emergency PPCI were included. Eligible participants were aged 18-80, capable of comprehending the study's details, providing consent, and agreeing to follow-up and necessary examinations. Exclusion criteria included non-ST elevation myocardial infarction, renal or severe liver disease, limited life expectancy, pregnancy or lactation, inability to consent, or concurrent participation in other medical studies. The study was ethically approved, and all patients provided written informed consent. [41]

Characteristics of studies

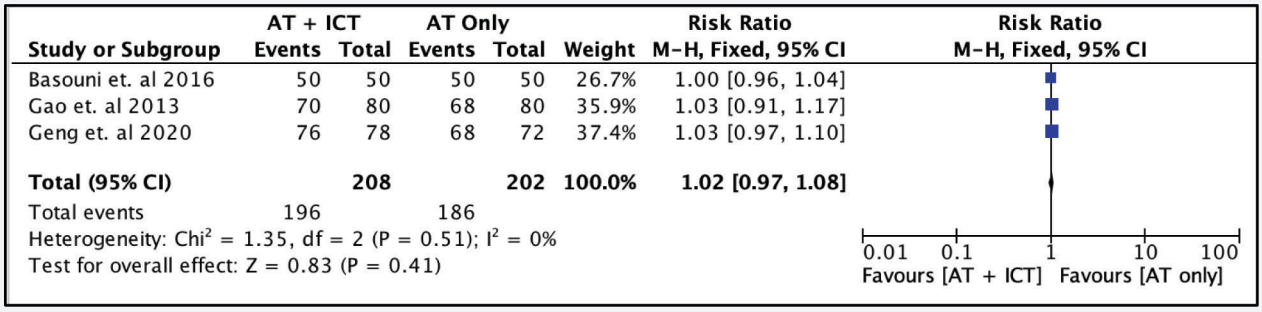
Risk of bias analysis was done on all four studies (Figures 2A, B). Random sequence generation was utilized for all the studies. Only one study (Basuoni et al, 2016)[43] was single-blinded where the operating physician was aware of the randomization assignment giving it an unclear risk for performance and reporting bias. The patients, the follow-up staff and clinical outcomes committee remained blinded of the treatment assignment.

The study by Geng et al [42] and Gao et al [43] had no mention regarding blinding of both the participants and the investigators, posing an unclear risk of performance and reporting bias. Liu et al[45] evaluated both TIMI flow grade and TIMI myocardial perfusion grade in an unblinded approach however for the purpose of statistical analysis, the statistician was kept unaware of the study group allocations giving it an unclear risk for performance and reporting bias. Attrition bias was low for all studies as all participants were followed up adequately with proper documentation of their primary and secondary endpoints.

DATA ANALYSIS

Primary outcomes

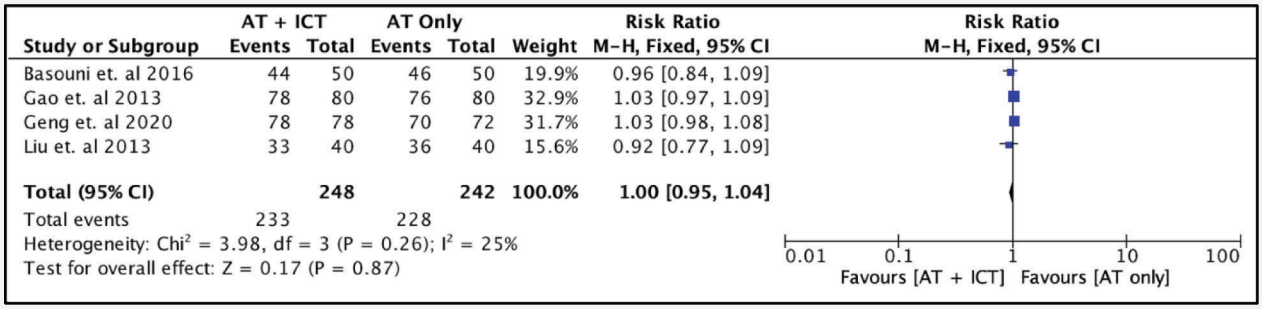
ST Segment Resolution



Forest plot of comparison: 1. Procedural Outcomes, outcome: 1.1 ST Segment Resolution.

Basuoni et al [43] and Geng et al [42] defined ST-segment resolution (STR) at 60 minutes which was defined as resolving of ST-segment more than 50% while Gao et .al further categorized STR as: 1) complete STR (CR): 70% resolution; 2) partial STR (PR): 30% but <70% resolution); or 3) no STR (NR): <30% resolution. There was no statistically significant difference in ST-segment resolution (risk ratio of 1.02, 95% confidence interval 0.97–1.08; $P = 0.41$, $I^2 = 0\%$, three trials [410 patients]) when combining AT with intracoronary tirofiban compared to AT alone. No significant heterogeneity was noted among the studies (X2=1.35, df=2, p=0.51, I2=0%).

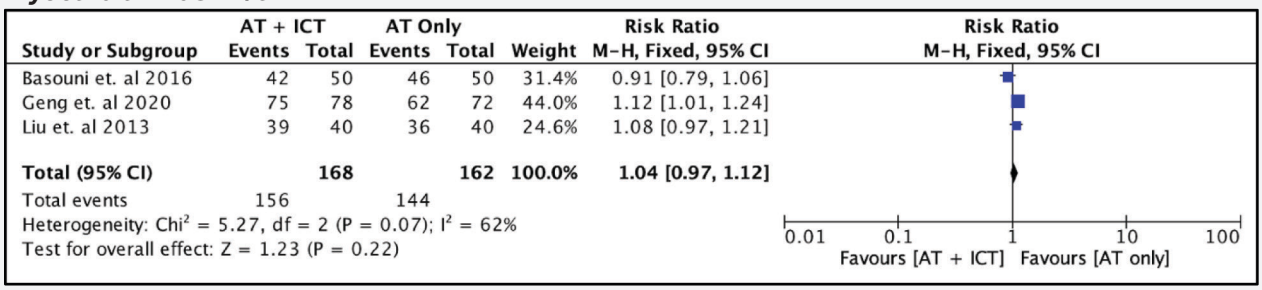
TIMI 3 Flow



Forest plot of comparison: 1. Procedural Outcomes, outcome: 1.2 TIMI 3 Flow.

Although two studies (Basuoni et al and Liu et al) [43,45] favored AT with intracoronary tirofiban and the two other studies (Gao et al and Geng et al) [42,44] favored AT only, there was no statistically significant difference in the TIMI 3 flow (risk ratio of 1.0, 95% confidence interval 0.95–1.04; *P* = 0.87, four trials [490 patients]). No significant heterogeneity was noted among the studies (X2=3.98, df=3, p=0.26, I2=25%).

Myocardial Blush 2/3

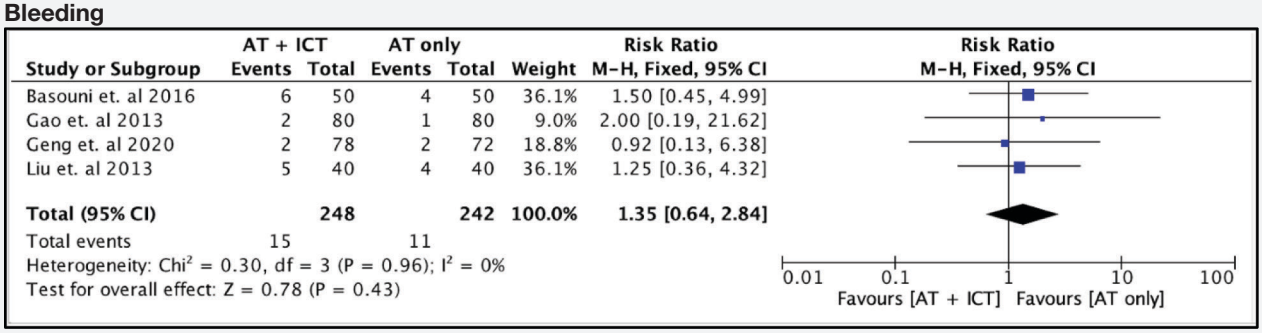


Forest plot of comparison: 1. Procedural Outcomes, outcome: 1.3 Myocardial Blush Grade 2-3.

Myocardial blush grade is an independent predictor for outcome in acute MI patients treated with reperfusion therapy. Although favoring AT only, the study by Geng et al [42] and Liu et al [45] as compared to the study by Basuoni et al[43] which favored AT with intracoronary tirofiban, there was no statistically significant difference in the said outcome (risk ratio of 1.04, 95% confidence interval 0.97–1.12; *P* = 0.22, I^2 = 62%, three trials [330 patients]). However moderate heterogeneity was noted between the studies (X2=5.27, df=2, p=0.07, I2=62%).

Secondary Outcomes:

Bleeding

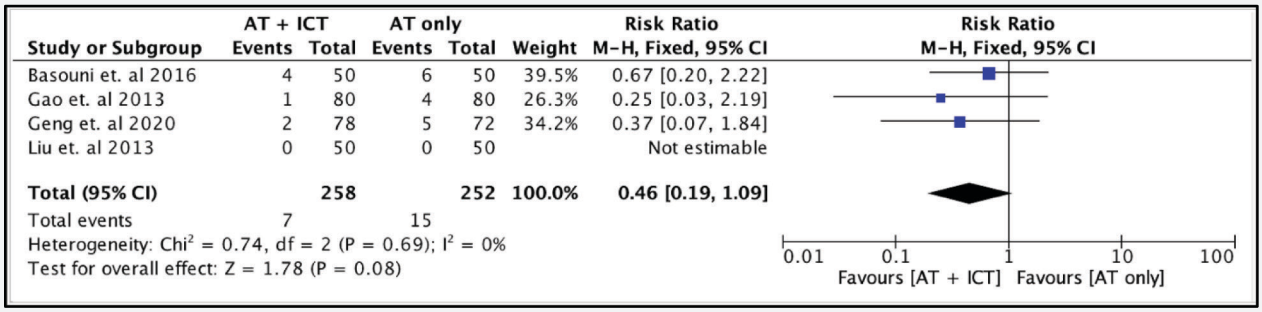


Forest plot of comparison: 2. Secondary/Safety Outcomes, outcome: 2.1 Bleeding

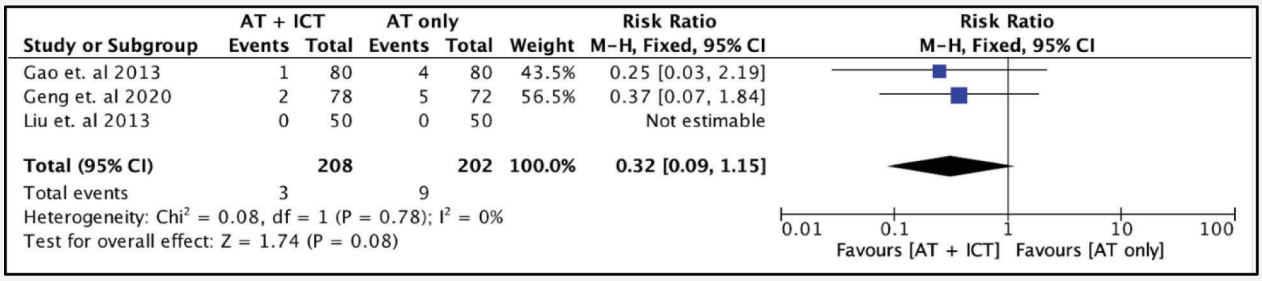
Basuoni et al. categorized bleeding risk using TIMI major and minor bleeding events.[43] Geng observed that two patients who underwent AT alone experienced mild bleeding, with one case involving bleeding gums and the other with epistaxis. Additionally, two patients who underwent AT with intracoronary tirofiban experienced mild bleeding, with one case showing microscopic hematuria and the other exhibiting epistaxis.[42] Gao reported one case of hemorrhagia and stool occult blood in group A, as well as one case of stool occult blood in group B.[44] Liu's findings from the intervention group revealed that five patients reported various bleeding events such as epistaxis, gum bleeding, hematuria, skin ecchymosis, or bleeding at puncture sites, all of which showed improvement following treatment.[45]

Although three out four studies favor the AT only arm, there was no statistically significant difference in terms of bleeding when combining intracoronary tirofiban to standard medical therapy (Risk ratio 1.35, 95% confidence interval 0.64–2.84; *P* = 0.78, four trials [490 patients]). No significant heterogeneity was noted among these studies (X2=0.30, df=3, P=0.96, I2=0%).

Major Adverse Cardiovascular Event



Forest plot of comparison: 2. Secondary/Safety Outcomes, outcome: 2.3 Overall MACE



Forest plot of comparison: 2 Secondary/Safety Outcomes, outcome: 2.3 MACE in 6 months

Although, all three studies trended towards favoring AT with intracoronary tirofiban, there was no statistically significant difference in MACE (risk ratio of 0.46, 95% confidence interval 0.19–1.09; *P* = 0.08, I^2 = 0%, four trials [490 patients]) compared to AT only therapy in both. No significant heterogeneity was noted among the studies (X2=0.74, df=2, p=0.08, I2=0%). A sensitivity analysis done for MACE in 6 months also yielded no statistically significant difference in outcomes.

DISCUSSION

Despite PPCI being the preferred treatment for acute STEMI, its effectiveness falls short even after successfully reopening the infarct-related epicardial artery and achieving optimal TIMI 3 flow due to inadequacy of the mechanical clearance of coronary occlusion, leading to the antegrade embolization of coronary thrombus debris causing microvascular obstruction. As a consequence, there is a resultant larger infarct size, reduced LV function and concomitant reduction in myocardial perfusion.

Evidence supports the understanding that unstable plaque rupture is a primary trigger for acute MI in cases of coronary atherosclerosis. Thrombus aspiration during emergency PCI has shown significant benefits, reducing no/slow reflow, distal-end thrombosis, and improving clinical outcomes.[1] Although it is commonly used in cases with a substantial thrombus burden, it may lead to clot formation and distal microvascular embolization. Previous studies have shown conflicting results on the benefits of mechanical clot aspiration such as the TAPAS[7] and EXPIRA.[12,13] Intracoronary tirofiban, a GP IIb/IIIa receptor antagonist, despite not being a class I indication, has shown potential benefits in improving myocardial reperfusion however concerns about increased bleeding risk limit their use.[23,24] Addressing these adverse processes may be optimally achieved through a combined approach involving intracoronary glycoprotein IIb/IIIa inhibitors (IC GPIs) and AT.

Individually, all the four trials included in this meta-analysis, investigated the combination of AT with intracoronary tirofiban revealing promising safety and efficacy outcomes in STEMI patients undergoing PPCI. Gao et al. observed a lower incidence of no/slow reflow and MACE compared to AT alone however on the background of a small sample size and short follow-up. Geng et al. focused on patients with a large angiographic thrombus burden, highlighting the combination's superiority in enhancing myocardial perfusion, leading to improved left ventricular reconstruction and reduced infarction

size without increased bleeding risk. While MACE rates did not significantly differ between groups, the combined-treatment group exhibited lower rates.

Basuoni et al. assessed infarct size in early-stage large evolving anterior STEMI, showing that combination therapy modestly reduced infarct size at 30 days compared to AT with no significant differences in ST-segment resolution (STR) and 30-day clinical event rates. According to Liu et al., the combination therapy demonstrated improved postoperative TIMI grade 3 flow, reduced no/slow reflow rates, and enhanced left ventricular ejection fraction. However, larger trials are needed to confirm whether this reduction translates into improved clinical outcomes without an increased bleeding risk.

In the meta-analysis performed, the combination did not show a significant advantage over AT alone in terms of ST-segment resolution, TIMI 3 flow, myocardial blush grade 2-3, bleeding events, or MACCE at 6 months.

The use of intracoronary tirofiban during AT for STEMI in the Philippines is a common but challenging practice, considering its significant cost of approximately 10,000 Php per box. In light of our observations, which indicate that MACE outcomes associated with the combination therapy are comparable to AT alone and offer no significant advantage in terms of enhancing myocardial perfusion or reducing MACE, an essential consideration is the economic impact. Importantly, the combination did not pose an increased risk of bleeding complications. These findings suggest that, at present, AT alone may be considered the more acceptable standard during PPCI, particularly when faced with a heavy thrombus burden.

Given the financial constraints and the economic burden associated with intracoronary tirofiban, the current evidence supports a reconsideration of its routine use during AT in the local context. The equivalence in MACE outcomes between the two strategies implies that the additional use of intracoronary tirofiban does not confer substantial benefits in terms of preventing MACE or improving myocardial perfusion.

However, it's crucial to acknowledge that our understanding is based on the available evidence, and future well-designed and validated studies are warranted to delve deeper into the strategy of incorporating tirofiban during AT in the PPCI setting. While this paper introduces a novel approach, it is essential to note that the participant pool remains relatively small. Consequently, we advocate for additional studies to broaden the sample size and await the outcomes of other upcoming trials.

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