

## The effects of fibrinolytic before referring STEMI patients: A systematic review and meta-analysis



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### ABSTRACT

**Background:** Accessibility of primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) in primary care settings is limited. Referring patients to PCI-capable hospitals might increase cardiac events. Hence, fibrinolytic injection before referring patients to PCI-capable settings decreases cardiac events, however, the effect of fibrinolytic injection before the referral has not been systematically evaluated. This study aimed to systematically review the effect of fibrinolytic injection before referring patients with STEMI to PCI-capable settings.

**Methods:** A systematic search with Embase, Cochrane CENTRAL, Google scholar, and PubMed was conducted. Studies conducted in patients with STEMI presented to non PCI-capable settings and compared fibrinolytic injection with no injection before referring patients to PCI-capable settings were included. The primary outcome was the composite outcomes of major adverse cardiac events (MACEs) at 30 days. Meta-analyses were performed using random-effect model.

**Results:** Of 912 articles, three RCTs and three non-RCTs were included. Based on RCTs, fibrinolytic injection before the referral has failed to decrease MACEs compared to non-fibrinolytic injection [relative risk (RR) 1.18; 95% confidence interval (CI), 0.89–1.57,  $p = 0.237$ ]. Fibrinolytic injection has also failed to decrease mortality, re-infarction, and ischemic stroke. On the other hand, fibrinolytic injection was associated with a higher risk of major bleeding.

**Conclusions:** In non PCI-capable settings, fibrinolytic injection before referring patients with STEMI to PCI-capable settings has no clinical benefit but could increase risk of major bleeding. Clinicians might more carefully consider whether fibrinolytic injection should be used in patients with STEMI before the referral.

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### 1. Introduction

ST-segment elevation myocardial infarction (STEMI) is a clinical symptom which can lead to hospitalization and sudden death [1]. It is a significant public health problem in both developed and developing countries. In the USA, STEMI accounts for approximately 30–45% of an estimated 1.5 million hospitalizations for acute coronary syndromes annually and is associated with a high mortality rate [2]. It is the most urgent conditions for patients with coronary artery disease and requires immediate and appropriate treatment [2].

Fibrinolytic therapy and primary percutaneous coronary intervention (PCI) are approved for STEMI [1]. To date, primary PCI has been

shown to be superior to fibrinolytic therapy for treating patients with STEMI. Primary PCI could decrease rates of death, re-infarction and stroke [3]. However, primary PCI is suboptimal when it is prolonged in delays for inter-hospital transfer or resource mobilization [4]. Hence, this has stimulated interests in combining pharmacological treatment and primary PCI in an attempt to minimize delays to reperfusion. An administration of fibrinolytic therapy and/or glycoprotein (GP) IIb/IIIa inhibitors is an option while waiting for PCI. The rationale is to open infarct related arteries (IRAs) and possibly earlier reperfusion [4].

Although, there are theoretical benefits of fibrinolytic injection in an addition to primary PCI, randomized controlled trial (RCT) has failed to support clinical benefits of this strategy [5]. Previous meta-analysis demonstrated no advantage of additional fibrinolytic injection to PCI compared to primary PCI [6]. The previous studies did not focus on referring patients from non PCI-capable settings to PCI-capable settings which usually happens in real world practice, especially in Low-Middle Income Countries (LMICs). However, there was no study to

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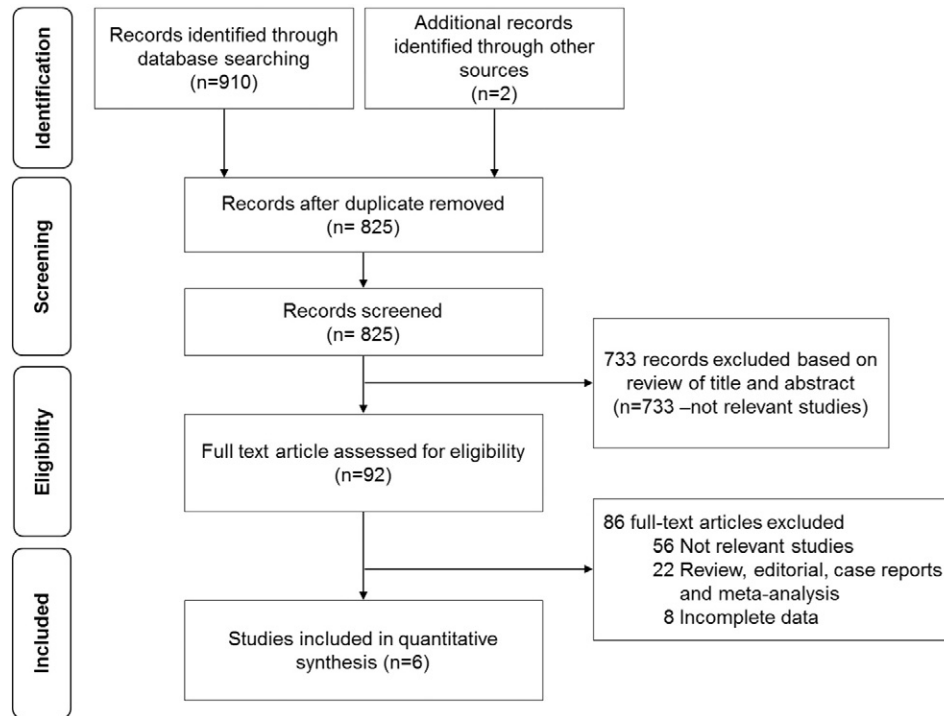


Fig. 1. A study selection flow diagram.

systematically evaluate the effect of fibrinolytic injection for patients with STEMI when waiting for referring to PCI-capable settings. This study aimed to systematically review the effect of fibrinolytic injection before referring patients with STEMI to PCI-capable settings.

## 2. Methods

### 2.1. Data source and search strategy

Several databases were systematically searched including EMBASE, Cochrane, Google scholar and PubMed. We collected published articles up to May 2016 with no language restriction. Key words were: 'st elevation myocardial infarction' or 'acute myocardial infarction' and

'fibrinolytic agents' or 'thrombolytic agents' or 'streptokinase' or 'tenecteplase' or 'tnk-tpa' or 'reteplase' or 'rpa' or 'facilitated pci' or 'facilitated percutaneous coronary intervention' and 'refer' or 'transfer' and 'mortality' or 'reinfarction' or 'ischemic stroke' or 'composite outcome' or 'major bleeding'. Reference lists of related articles were also reviewed to find unpublished articles.

### 2.2. Study selection

All clinical studies which met eligible criteria were included. Eligible criteria were (1) studies conducted in patients with STEMI (2) studies conducted in non-PCI capable settings, (3) studies compared the use of fibrinolytic agents before referral with no fibrinolytic use and (4) studies

**Table 1**  
Baseline characteristics.

Study (year)	Study design	Setting	Duration of study	Inclusion criteria	Intervention/comparator	
					Intervention	Comparator
Widimsky P et al. (2000)	Multicenter randomized trial	Czech Republic	1997–1999	STEMI or new LBBB symptom onset within 6 h	Streptokinase + PCI (after the referral)	Primary PCI (No fibrinolytic use before the referral)
Thiele H et al. (2011)	Multicenter randomized trial	Germany	2006–2009	STEMI symptom onset within 3 h	Tenecteplase + PCI (after the referral)	Primary PCI (No fibrinolytic use before the referral)
Armstrong PW et al. (2013)	Open-label, prospective, randomized, parallel-group, multicenter trial	Belgium	2008–2012	STEMI symptom onset within 3 h	Tenecteplase + PCI (after the referral)	Primary PCI (No fibrinolytic use before the referral)
Coleman CI et al. (2006)	Prospective cohort study	United States	2000–2003	STEMI symptom onset within 12 h	Fibrinolytic with GP IIb/IIIa inhibitor + PCI (after the referral)	Primary PCI (No fibrinolytic use before the referral)
Dudek D et al. (2010)	Prospective cohort study	Poland	2001–2003	STEMI symptom onset within 12 h, <75 years	Reduced-dose fibrinolytic + PCI (after the referral)	Primary PCI (No fibrinolytic use before the referral)
Larson DM et al. (2011)	Prospective cohort study	United States	2003–2009	STEMI or new LBBB symptom onset within 24 h	Half dose fibrinolytic + PCI (after the referral)	Primary PCI (No fibrinolytic use before the referral)

**Abbreviations:** PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; LBBB: left bundle branch block; GP IIb/IIIa: glycoprotein IIb/IIIa.

**Table 2**  
Study description and outcome measurement.

Study (year)	Sample size			Age (SD)		Male (%)		Composite outcomes of MACE	
	Total	Fibrinolytic	No fibrinolytic	Fibrinolytic	No fibrinolytic	Fibrinolytic	No fibrinolytic	Fibrinolytic	No fibrinolytic
<i>Randomized studies</i>									
Widimsky P et al. (2000)	201	100	101	62 (11)	61 (12)	73	72	15/100	8/101
Thiele H et al. (2011)	162	81	81	63 (54–73)	61 (53–72)	76	82	11/81	9/81
Armstrong PW et al. (2013)	1892	944	948	59.7 (12.4)	59.6 (12.5)	79.4	78.1	72/944	66/948
<i>Non-randomized studies</i>									
Coleman CI et al. (2006)	254	127	127	63.2 (13.1)	64.5 (13.6)	74.8	69.3	8/127	14/127
Dudek D et al. (2010)	1980	669	1311	57.1 (8.9)	58.0 (9.8)	77.4	73.8	26/669	55/1311
Larson DM et al. (2011)	2034	692	1342	63.2 (13.5)	61.2 (14.6), 65.4 (14.5)	73.8	73.2, 64.8	56/692	106/1342

**Abbreviations:** MACE: major adverse cardiac event.

reporting the number of mortality, re-infarction, ischemic stroke, the composite outcomes of major adverse cardiac events (MACEs), or major bleeding. Studies that were not original articles were excluded.

### 2.3. Outcome measures

Primary outcome was MACE at 30-days which was defined as one or more of following: mortality, re-infarction, and ischemic stroke. Secondary outcomes were mortality, re-infarction, ischemic stroke, and major bleeding. Mortality was defined as death from any cause, death from re-infarction, and death from ischemic stroke. Major bleeding was defined according to the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards. The clinical outcomes assessed at 30-days instead of over longer time periods (such as 90 days) was used because the outcomes in the longer time period may be impacted by several factors outside hospitals' control such as other complicating illnesses, patients' own behavior, or care provided to patients after discharge. It is well-documented that the appropriate timing for outcome measurement is within 30 days of PCI procedure [7]. If studies assessed clinical outcomes longer than 30 days, we converted it to 30-day outcomes using the following formula:  $tp_1 = 1 - (1 - tp_t)^{1/t}$  where  $tp_1$  is the yearly transition probability of outcome and  $tp_t$  is overall probability of outcome over time period  $t$  [8].

### 2.4. Data extraction and quality assessment

All articles were extracted independently by two investigators (K.T. and C.S.), and discrepancies were resolved through discussion. Data extracted from each study were study design, eligibility criteria, type of fibrinolytic, the number of patients, complications and other necessary information.

The quality of each study was assessed using Jadad scale [9] and Risk of Bias [10] for randomized controlled trials, while ACROBAT-NRSI was used for assessing the quality of non-randomized controlled trials [11].

**Table 3**  
Treatment duration.

Study (year)	Total ischemic time (minutes)		D2N (minutes)	PCI hospital D2B (minutes)		First medical contact to primary PCI (minutes)		Door-in-door out (minutes)	
	Fibrinolytic	No fibrinolytic	Fibrinolytic	Fibrinolytic	No fibrinolytic	Fibrinolytic	No fibrinolytic	Fibrinolytic	No fibrinolytic
<i>Randomized studies</i>									
Widimsky P et al. (2000)	112	120	40	30	28	106	96	32	40
Thiele H et al. (2011)	55	45	15	23	25	103	86	<80	<61
Armstrong PW et al. (2013)	62	61	38	433	29	521	108	NA	NA
<i>Non-randomized studies</i>									
Coleman CI et al. (2006)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dudek D et al. (2010)	NA	NA	36	26	17	168	NA	NA	NA
Larson DM et al. (2011)	NA	NA	NA	121	NA	NA	NA	NA	NA

**Abbreviations:** D2N: door to needle time; D2B: door to balloon time; PCI: percutaneous coronary intervention; NA: not applicable.

### 2.5. Data analysis

Meta-analyses under random-effects model were performed. Randomized controlled trials (RCTs) and non-RCTs were analyzed separately given the inherent differences between these types of study design. All comparisons were based on intention-to-treat analysis.  $I^2$ -statistic was used to assess statistical heterogeneity.  $I^2$ -statistic of 25%, 50%, and 75% indicates low, medium, and high heterogeneity, respectively.

In order to evaluate the robustness of our analysis, a number of subgroup/sensitivity analyses were performed. Those analyses included treatment regimen (streptokinase vs tenecteplase), study size ( $n < 1000$  vs  $n \geq 1000$ ) and first medication contact (FMC) to balloon time ( $> 120$  min vs  $\leq 120$  min).

## 3. Results

### 3.1. Study characteristics

A total of 912 studies were identified but only six articles [12–17] met eligible criteria (Fig. 1). Of six included studies, three studies were RCTs [12–14], while the rest were non-RCTs [15–17] with a total of 6523 patients.

The characteristics of included studies are shown in Tables 1 and 2. Briefly, patients with STEMI participated in all studies presented within 24 h after onset of myocardial infarction symptoms. The average age was between 57.1 and 65.4 years and approximately 72 to 82% of patients were men. Fibrinolytics were streptokinase [12], tenecteplase [13,14], reteplase [15] and alteplase [16]. One study conducted by Larson DM was no specific fibrinolytic [17].

### 3.2. Treatment duration

The total ischemic time in fibrinolytic injection group ranged from 55 to 112 min, while the time in no fibrinolytic group ranged from 45 to 120 min. Door to needle (D2N) time was 15 to 40 min. Door to balloon (D2B) time at PCI-capable hospital was 23 to 433 min and 25

**Table 4**

Risk of bias proposed by the Cochrane Collaboration and Jadad scale of the methodological quality of included studies in the systematic review.

Study (year)	Random generation of allocation sequence	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting of outcomes	Jadad scale
Widimsky P et al. (2000)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Thiele H et al. (2011)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Armstrong PW et al. (2013)	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	3

to 29 min in fibrinolytic injection group and no fibrinolytic group, respectively. In addition, the duration of first medication contact (FMC) to primary PCI was 103 to 521 min in fibrinolytic injection group and 96 to 108 min in no fibrinolytic group (Table 3).

### 3.3. Quality assessment

For the three included RCTs, two were low risk of bias, while one was high risk of bias (Table 4). All studies had clearly definition for eligibility criteria. The reason of patients' exclusion and clinical outcomes were reported appropriately. All of the included RCTs were open-label trials but it may not affect the number of outcomes because the outcomes were objective outcomes which were not affected by open-label design. For three non-RCT studies [15–17], two studies were at serious risk of bias [16,17], while one was moderate risk of bias [15].

### 3.4. Clinical outcomes

Our meta-analysis based on RCTs revealed that fibrinolytic injection before referring patients to PCI-capable settings was not associated with MACE compared to no fibrinolytic use (RR = 1.18, 95% CI 0.89 to 1.57,  $I^2 = 0.0\%$ ). In the three non-RCTs, fibrinolytic injection before the referral was not associated with MACE (RR = 0.95, 95% CI 0.74 to 1.21,  $I^2 = 0.0\%$ ) (Fig. 2).

Similar to MACE outcome, fibrinolytic injection before the referral was not associated with mortality, ischemic stroke, and re-infarction (Fig. 3). However, it was associated with an increased risk of major bleeding compared to no fibrinolytic use (RR = 1.41, 95% CI 1.06 to 1.87,  $I^2 = 0.0\%$ ).

Similar to our meta-analyses of RCTs, our meta-analyses of non-RCTs indicated that fibrinolytic injection was not associated with mortality, re-infarction, ischemic stroke and major bleeding, RR was 0.86 (95% CI, 0.65 to 1.14,  $I^2 = 0.0\%$ ), 1.23 (95% CI, 0.64 to 2.34,  $I^2 = 0.0\%$ ), 1.51 (95% CI, 0.61 to 3.74,  $I^2 = 0.0\%$ ) and 1.76 (95% CI, 0.98 to 3.17,  $I^2 = 59.9\%$ ), retrospectively.

### 3.5. Subgroup/sensitivity analysis

Subgroup analysis was performed according to sample size, treatment regimen and FMC to balloon time. The results indicated that sample size more than one thousand, type of fibrinolytic and FMC to balloon time > 120 min, were not associated with all clinical outcomes except major bleeding (Table 5).

## 4. Discussion

Our meta-analysis findings indicated that there was no difference in clinical benefits between the use of fibrinolytic before referring patients with STEMI to PCI-capable settings compared to no fibrinolytic use including MACE, mortality, ischemic stroke, and re-infarction. Moreover, we observed that the use of fibrinolytic before the referral could increase risk of major bleeding.

This is the first systematic review and meta-analysis comparing the outcomes treated and untreated with fibrinolytic agents in STEMI patients before transferring for primary PCI. Our findings contradicted to previous meta-analysis which showed benefits of referral patients with STEMI for angioplasty over onsite fibrinolysis in terms of re-

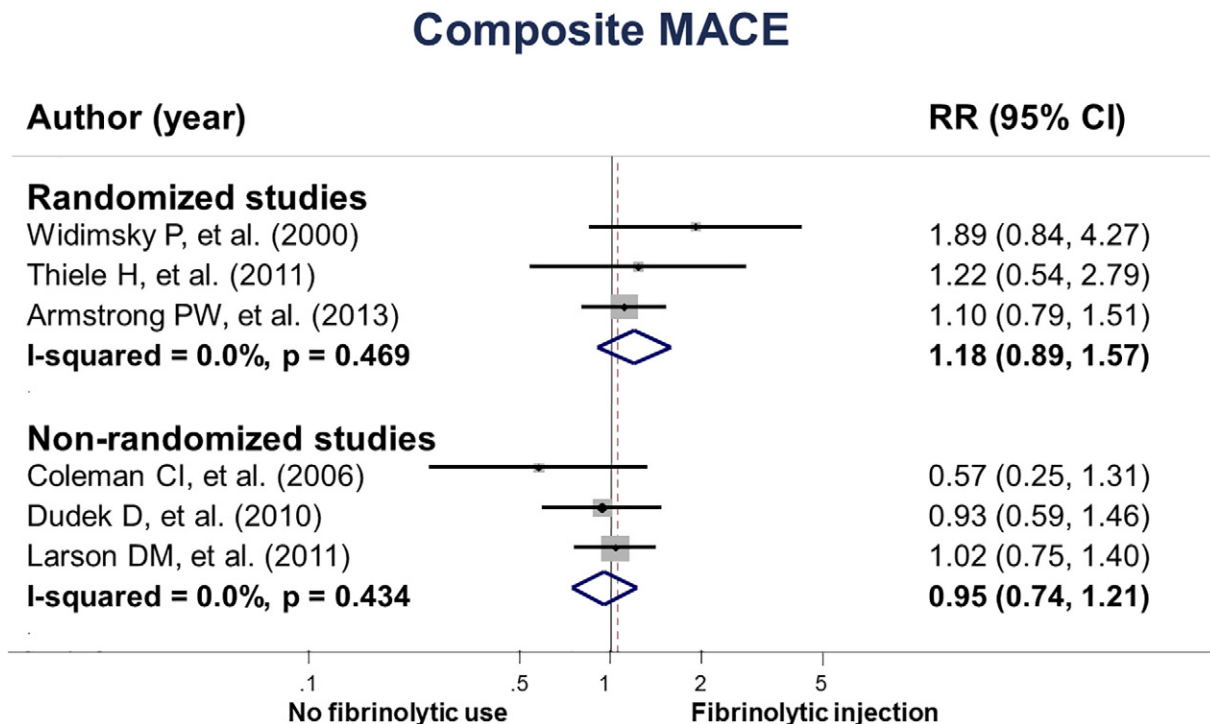
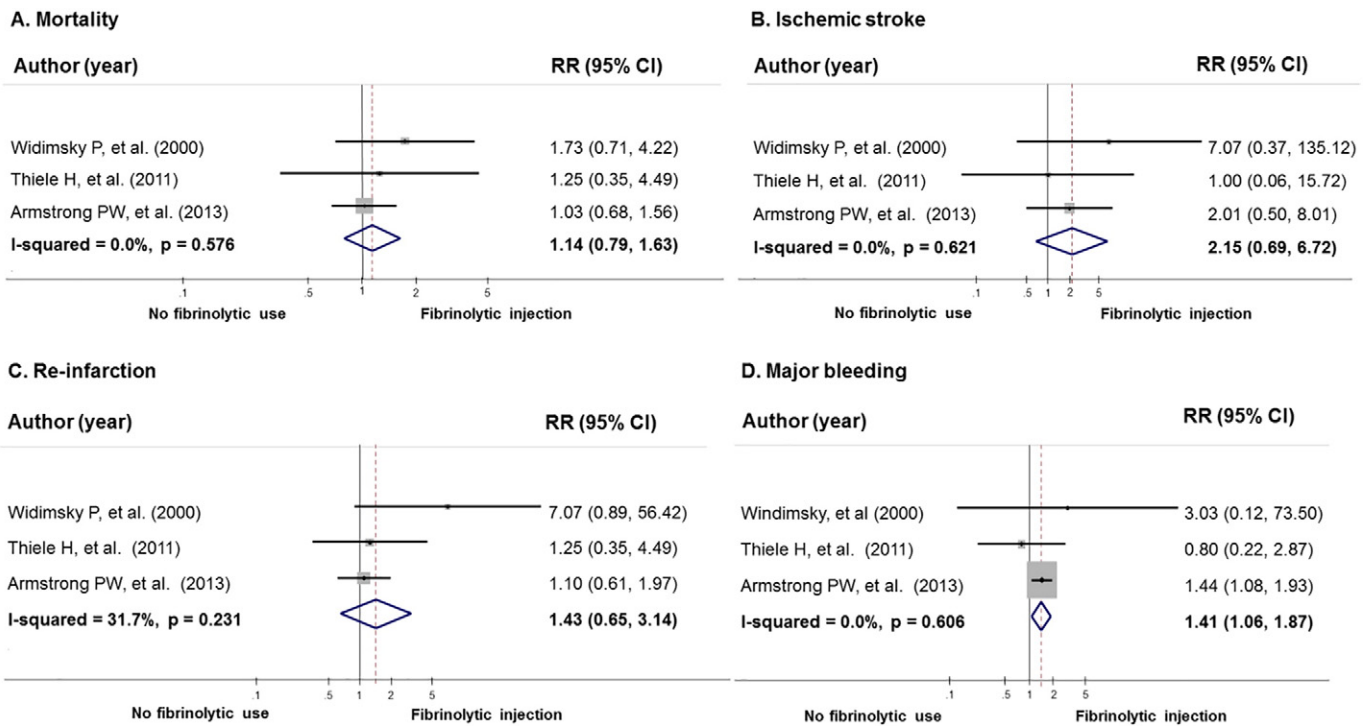


Fig. 2. The effect of fibrinolytic injection before referring patients with STEMI on MACE.



**Fig. 3.** The effect of fibrinolytic injection before referring patients with STEMI on mortality, ischemic stroke, re-infarction, and major bleeding in randomized studies. A) Mortality; B) ischemic stroke; C) re-infarction; D) major bleeding.

infarction, stroke and combined endpoint of death/re-infarction/stroke [18]. However, the previous systematic review [4] demonstrated that STEMI patients receiving fibrinolytic therapy while waiting for primary PCI were associated with increased intracranial hemorrhage, which was similar to our study.

In this study, our findings revealed no significant difference. These findings could be explained as all included studies conducted in developed countries which provided a good quality in transferring system. The average duration of FMC to primary PCI of included studies was in the period recommended by ACCF/AHA guidelines [1]. Therefore, a short time to treatment may result in non-significant difference of both groups. However, subgroup analysis according to FMC to balloon time was performed. The result demonstrated that the time period > 120 min non-significantly increased risk of composite MACE, mortality, ischemic

stroke and re-infarction. In non-RCTs, there was a trend toward reduction in composite MACE with the use of fibrinolytic therapy before referral, which contrasted to the results from RCTs. This could be described as, in non-RCTs, patients received the combination of fibrinolytic agents and glycoprotein IIb/IIIa receptor inhibitors which could increase ST-segment resolution [15] and improve the efficacy of fibrinolytic administration [16,19].

Our analysis should be interpreted with limitations. Studies included in our review used different doses and types of fibrinolytic. They might have different effects on clinical outcomes. However, our subgroup analysis by treatment regimen indicated that each fibrinolytic was not associated with clinical outcomes including MACE, mortality, ischemic stroke and re-infarction. In addition, the current study presented time from FMC to balloon time because this was the parameter used for

**Table 5**  
Sensitivity analysis.

	Composite MACE		Mortality		Re-infarction		Ischemic stroke		Major bleeding	
	N	Risk ratio (95% CI)	N	Risk ratio (95% CI)	N	Risk ratio (95% CI)	N	Risk ratio (95% CI)	N	Risk ratio (95% CI)
<i>Sample size</i>										
<i>RCT</i>										
N < 1000	2	1.53 (0.86–2.72)	2	1.56 (0.75–3.23)	2	2.46 (0.45–13.45)	2	2.49 (0.33–18.62)	2	0.96 (0.29–3.15)
N ≥ 1000	1	1.10 (0.79–1.51)	1	1.03 (0.68–1.56)	1	1.10 (0.61–1.97)	1	2.01 (0.50–8.01)	1	1.44 (1.08–1.93)
<i>Non-RCT</i>										
N < 1000	1	0.57 (0.25–1.31)	1	0.58 (0.24–1.43)	1	1 (0.06–15.81)	1	0.33 (0.01–8.11)	1	1.27 (0.60–2.70)
N ≥ 1000	2	0.99 (0.77–1.28)	2	0.90 (0.67–1.21)	2	1.24 (0.64–2.42)	2	1.72 (0.67–4.45)	2	1.99 (0.91–4.35)
<i>Treatment regimen</i>										
<i>RCT</i>										
Streptokinase	1	1.89 (0.84–4.27)	1	1.73 (0.71–4.22)	1	7.07 (0.89–56.42)	1	7.07 (0.37–135.12)	1	3.03 (0.12–73.5)
Tenecteplase	2	1.11 (0.82–1.50)	2	1.05 (0.71–1.56)	2	1.12 (0.66–1.91)	2	1.75 (0.51–6.01)	2	1.40 (1.06–1.86)
<i>First medical contact to balloon time in fibrinolytic injection group</i>										
<i>RCT</i>										
<120 min	2	1.53 (0.86–2.72)	2	1.56 (0.75–3.23)	2	2.46 (0.45–13.45)	2	2.49 (0.33–18.62)	2	0.96 (0.29–3.15)
≥120 min	1	1.10 (0.79–1.51)	1	1.03 (0.68–1.56)	1	1.10 (0.61–1.97)	1	2.01 (0.50–8.01)	1	1.44 (1.08–1.93)

**Abbreviations:** MACE: major adverse cardiac event; RCT: randomized controlled trial.

making a decision when patients arrived at non-PCI capable hospital, and it has the complete information among studies. In order to make the results more interpretable, time to refer should be provided.

## 5. Conclusion

In non PCI-capable settings, fibrinolytic injection before referring patients with STEMI to PCI-capable settings has no clinical benefit but could increase risk of major bleeding. Clinicians might more carefully consider whether fibrinolytic injection should be used in patients with STEMI before the referral.

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## Declaration of conflicting interests

The authors report no relationships that could be construed as a conflict of interest.

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