Systematic Review and Meta-Analysis

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Bleeding events associated with fibrinolytic therapy and primary percutaneous coronary intervention in patients with STEMI

A systematic review and meta-analysis of randomized controlled trials

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Abstract

From the year 1986 onwards, several studies have been published focusing on the comparison between fibrinolysis and primary percutaneous coronary intervention (PPCI) in patients with ST segment elevated myocardial infarction (STEMI). However, because antiplatelet and anticoagulating medications are used in approximation, before and during these procedures, bleeding events have been reported to be associated with both reperfusion therapies. This study aimed to compare the bleeding events associated with fibrinolytic therapy and primary angioplasty in patients with STEMI. Randomized controlled trials (RCTs) comparing fibrinolysis and primary angioplasty in patients with STEMI were searched from Medline, PubMed, EMBASE, and the Cochrane databases. Bleeding complications following 30 days from hospitalization were considered as the primary clinical endpoints in this study. Secondary endpoints included all-cause mortality, re-infarction, stroke, and shock. Antiplatelet and anticoagulating drugs used during these 2 different procedures were compared. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and the pooled analyses were performed with RevMan 5.3 software. Twelve studies involving 10 RCTs consisting of a total number of 5561 patients (2784 patients from the fibrinolysis group and 2777 patients from the PPCI group) were included in this meta-analysis. Our results showed no significant difference in the overall bleeding complications during a 30-day period between these 2 reperfusion therapies with OR 1.02; 95% CI 0.89 to 1.17, $P=0.78$. Nonintracranial bleeding was also not statistically significant with OR 0.85; 95% CI 0.70 to 1.04, $P=0.12$. However, fibrinolytic therapy was associated with a significantly higher rate of intracranial bleeding with OR 0.17; 95% CI 0.06 to 0.50, $P=0.001$ than PPCI. In addition, death, re-infarction, and stroke significantly favored primary angioplasty. According to the results of this study, even if the rate of nonintracranial bleeding was not statistically significant between these 2 reperfusion therapies, fibrinolytic therapy was associated with a significantly higher rate of intracranial bleeding than PPCI. In addition, PPCI was associated with a significantly lower rate of death, reinfarction, and stroke. Therefore, PPCI should be recommended in patients with STEMI, especially in PCI-capable hospitals.

Abbreviations: PPCI = primary percutaneous coronary intervention, STEMI = ST elevated myocardial infarction, RCTs = randomized controlled trials.

Keywords: bleeding complications, fibrinolysis, primary angioplasty, ST segment elevated myocardial infarction

1. Introduction

Guidelines normally recommend primary percutaneous coronary intervention (PPCI) as the main reperfusion therapy in patients with ST segment elevated myocardial infarction (STEMI) treated in PCI-capable hospitals, whereas if not contraindicated, fibrinolytic therapy has been the preferred reperfusion therapy for similar patients in non-PCI capable centers.[1]

Several studies have shown an increased risk of bleeding events associated with fibrinolytic therapy.[2] Unfortunately, PPCI is also not completely safe. Even if the risk of myocardial infarction (MI) is reduced in patients treated by PCI, platelet inhibition increases the risk of bleeding in these patients after primary angioplasty.[3]

From the year 1986 onwards, several studies have been published focusing on the comparison between fibrinolysis and PPCI in patients with STEMI. However, because antiplatelet and anticoagulating medications are used in approximation, before and during these procedures, for example, medications are often given according to weight and age, which are not often accurate, bleeding has been reported with both reperfusion therapies. As very few studies have assessed bleeding rates manifested between these 2 reperfusion therapies, this study aimed to compare the bleeding events associated with fibrinolytic therapy and primary angioplasty in patients with STEMI.

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2. Methods

2.1. Data sources and searched strategy

Medline, PubMed, EMBASE, and Cochrane databases were searched for RCTs comparing PPCI with fibrinolysis by typing the words or phrase "primary percutaneous coronary intervention and fibrinolysis and STEMI." The abbreviation "PPCI" was also used. To further enhance this search, PPCI was also replaced by the word "primary angioplasty." Relevant reference lists were also searched for suitable RCTs. Publications written in English were considered in this search strategy.

2.2. Inclusion and exclusion criteria

RCTs were included if:

1. They compared PPCI with fibrinolysis.
2. Bleeding complications were reported among their clinical outcomes.
3. They had a follow-up period of less than or equal to 30 days.

RCTs were excluded if:

1. They did not compare PPCI with fibrinolysis.
2. Outcomes related to bleeding were not reported.
3. They had a longer follow-up period.
4. They were duplicates.

2.3. Eligibility of the participants, the antiplatelet agents, and anticoagulating agents used in patients randomized to fibrinolysis and PPCI, respectively

Patients were eligible for enrollment if:

1. They arrived at the hospital within 3 hours after the onset of symptoms related to MI.
2. Results from their electrocardiogram showed evidence of acute STEMI represented by at least 2 mm elevation of the ST segment in 2 contiguous precordial leads.
3. PPCI could not be initiated within a period of about 1 hour after their first medical contact.

Patients were not eligible for enrollment if:

1. They had a history of hemorrhagic diathesis or any contraindication to fibrinolysis.
2. They had severe renal or hepatic insufficiency.
3. They had a history of previous aorto-femoral bypass or any condition that could hamper femoral artery access.
4. They had a history of cardiogenic shock or coronary artery bypass surgery (CABG).
5. They had previously been receiving oral anticoagulation therapy.

Antiplatelet and anticoagulating medications were used before and during these reperfusion procedures (PPCI and fibrinolysis, respectively). For example, an infusion of at least 5000 U heparin was required in the beginning in both groups.

Those patients randomized for primary angioplasty required at least another 5000 U intravenous infusion of heparin before catheterization. In the beginning, all patients were given at least 300 mg Aspirin. Clopidogrel 75 mg/day, ticlopidine 500 mg/day, and glycoprotein iib/iiia were also used before catheterization depending on the choice of the physician and the condition of the patients. These antiplatelets were continued orally for 1 month after reperfusion in certain trials.

For those patients who were randomized to fibrinolytic therapy, in addition to 5000 U heparin and 300 mg aspirin, tissue plasminogen activator such as alteplase, tenecteplase, activase, or streptokinase were also infused. Fifteen milligram alteplase followed by an alteplase infusion of 0.75 mg/kg (not exceeding 50 mg) over 30 minutes and then 0.5 mg/kg (not exceeding 35 mg) over the next 60 minutes up to a total dose of 100 mg were required in some trials. Other trials involved the use of 1,5 million U streptokinase intravenously over a period of 1 hour or activase given at a dose of 100 mg over 3 hours intravenously.

An additional heparin infusion was given for 3 to 5 days to patients from both groups. Medication dosage was given according to guidelines. Dosage could vary from 1 patient to another depending on their total weight and age. Detailed information about the blood thinners and anticoagulants have been provided in Table 1.

2.4. Data extraction and quality assessment

Two authors (P.K.B and G.J) independently reviewed and assessed the trials included in this study. Information and data regarding the type of study, the total number of participants randomized to fibrinolysis, the total number of participants randomized to PPCI, the patients' enrollment period, the antiplatelet and anticoagulants agents used before and during the reperfusion therapies, respectively, the bleeding events and other clinical outcomes reported, and the follow-up periods reported in each eligible trial were systematically extracted. If any of these 2 authors disagreed about including certain data, disagreements were discussed and finally a decision was reached. However, if they could not reach a consensus, a final decision was made by the third author (M.H.C). The 6 main components recommended by the Cochrane Collaboration were taken into consideration while assessing the risk of bias among the trials included in this study[4] whereby a score ranging from 0 to 12 points was allocated to each trial depending on whether each of the 6 components mentioned above corresponded to a low risk, moderate risk, or high risk of bias.

Three studies were allocated a score of 8, 5 studies were allocated a score of 10, and 4 studies were allocated a score of 11. These scores have been listed in Table 2.

3. Outcomes

General bleeding complications included major and minor bleeding, intracranial and nonintracranial hemorrhages, gastrointestinal bleeding, bleeding from other sites, and bleeding that required transfusion of red cells from the period of hospitalization to up to 30 days were considered as the primary clinical outcomes in this study. Intracranial and nonintracranial bleeding were also analyzed separately. Secondary outcomes included death, reinfarction, stroke, and shock. The primary clinical outcomes reported among all the trials have been listed in Table 3.

Five studies reported in-hospital bleeding, 1 study reported bleeding within 2 weeks, and the remaining 6 studies reported bleeding within or at 30 days.

4. Statistical analysis

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was considered for this systematic review and meta-analysis of RCTs.[5] All authors had full access

Table 1

Brief summary of the antiplatelet and antithrombotic medications used by patients randomized to fibrinolysis and primary angioplasty.

Studies	Fibrinolysis	Primary angioplasty
O'Neill et al[6]	Aspirin 325 mg given every 8 hours, Streptokinase administered according to guidelines, 5000 U heparin administered in the beginning. Heparin started again 12 hours after streptokinase infusion and continued for 7–10 days.	Aspirin 325 mg every 8 hours, 5000 U heparin administered intravenously. Additional 5000 U infused and continued for 7–10 days.
Grines et al[7]	325 mg aspirin orally in the beginning and also given daily, Activase given at a dose of 100 mg over 3 hours intravenously, Intravenous heparin given as a 10,000 U bolus. Additional Heparin infusion given for 3–5 days.	325 mg aspirin orally in the beginning and continued daily, Iv heparin given as a 10,000 U bolus. Additional heparin administered 5000–10000 U. Heparin infusion given for 3 to 5 days.
Zijlstra et al[8]	300 mg aspirin iv in the beginning and 300 mg aspirin orally daily, 1.5 million U streptokinase intravenously over a period of 1 hour, Intravenous heparin given according to guidelines.	300 mg aspirin iv at the time of procedure and 300 mg aspirin orally daily, Intravenous heparin given according to guidelines.
Gusto[9]	Aspirin provided orally according to guidelines, 15 mg alteplase followed by an alteplase infusion of 0.75 mg/kg (not exceeding 50 mg) over 30 minutes and then 0.5 mg/kg (not exceeding 35 mg) over the next 60 minutes up to a total dose of 100 mg, heparin, or hirudin intravenously given for 3–5 days.	Aspirin given orally according to guidelines, Heparin or hirudin intravenously for 3–5 days. 3000 U of heparin or 30 mg hirudin at procedure.
Ribichini et al[10]	Aspirin 300 mg given intravenously, rt-PA infused according to guidelines, Heparin was administered immediately as a 5000 U IV bolus, followed by an initial infusion of 1000 U/h.	Aspirin 300 mg intravenously, ticlopidine 500 mg/day; for 1 month, Bolus of 10,000 U of heparin was administered intravenously.
García et al[11]	300 mg aspirin intravenously, 15 mg alteplase followed by an alteplase infusion of 0.75 mg/kg (not exceeding 50 mg) over 30 minutes and then 0.5 mg/kg (not exceeding 35 mg) over the next 60 minutes, iv bolus of 5000 IU heparin. Administered for at least 58 hours.	300 mg aspirin intravenously at procedure, 10,000 IU heparin. Later administered for at least 58 hours
Ross et al[12]	325 mg of aspirin in the beginning. Daily oral aspirin was continued throughout the hospitalization, IV bolus of rt-PA 50 mg (Activase given over 3 minutes, Unfractionated heparin, a 5000 IU bolus followed by an infusion of 1000 IU/h (1200 IU/h for patients 80 kg). IV heparin was maintained for a minimum of 48 hours.	325 mg of aspirin orally administered. Daily aspirin was continued throughout the hospitalization, Unfractionated heparin, a 5000-IU bolus followed by an infusion of 1000 IU/h (1200 IU/h for patients 80 kg). IV heparin was maintained for a minimum of 48 hours.
Bonnefoy et al[13]	All the patients received a 250–500 mg aspirin orally or intravenously, 15 mg alteplase followed by an alteplase infusion of 0.75 mg/kg (not exceeding 50 mg) over 30 minutes, and then 0.5 mg/kg (not exceeding 35 mg) over the next 60 minutes up to a maximum total dose of 100 mg. All the patients received a bolus of 5000 U heparin intravenously.	250–500 mg aspirin orally or intravenously before procedure, Thienopyridine for 1 month. All the patients received a bolus of 5000 U heparin intravenously.
Kastrati et al[14]	500 mg aspirin in the beginning and 100 mg aspirin twice a day indefinitely. 75 mg/day clopidogrel for 4 weeks (without a loading dose), Bolus dose of 15 mg alteplase followed by an infusion of 35 mg over the next 60 minutes, 60 U/kg heparin (up to a maximum of 5000 U) as well as abciximab given as a bolus of 0.25 mg/kg bodyweight followed by a continuous infusion of 0.125 μg/kg/ min (up to a maximum of 10 μg/min) for 12 hours, Intravenous injection of technetium-99m sestamibi and also abciximab	500 mg aspirin before procedure and 100 mg aspirin twice a day indefinitely, 75 mg/day clopidogrel for 4 weeks (without a loading dose), 60 U/kg heparin (up to a maximum of 5000 U) as well as abciximab given as a bolus of 0.25 mg/kg bodyweight followed by a continuous infusion of 0.125 μg/kg/ min (up to a maximum of 10 μg/min) for 12 hours. Received an additional dose of 2500 U heparin, intra-arterially, intravenous injection of technetium-99m sestamibi, and abciximab.
Bonnefoy et al[15]	250–500 mg aspirin orally or intravenously in the beginning, 15 mg alteplase followed by an alteplase infusion of 0.75 mg/kg (not exceeding 50 mg) over 30 minutes and then 0.5 mg/kg (not exceeding 35 mg) over the next 60 minutes up to a maximum total dose of 100 mg, 5000 U intravenous bolus heparin.	250–500 mg aspirin orally or iv. All the patients received a bolus of 5000 U heparin iv.
Armstrong et al[16]	Tenecteplase 30 mg if weight between 55 and 60 kg, Enoxaparin 30 mg iv + 1 mg/kg and 0.75 mg/kg for patients ≥75 years and subcutaneous every 12 hours.	150–325 mg at time of procedure followed by 75 to 325 mg daily, 300 mg loading dose of clopidogrel followed by 75 mg daily. Omitted in patients ≥75 years.
Sinnaeve et al[17]	Aspirin and clopidogrel as per guideline. Tenecteplase was administered in a weight-based dose, Enoxaparin as per guideline	Aspirin given according to guidelines, Clopidogrel given according to guidelines, Enoxaparin infused according to guidelines, Glycoprotein IIb/IIIa antagonists.

iv, intravenous route.

to and take full responsibility for the integrity of the data. Assessment of heterogeneity during the subgroup analysis was based on the Cochrane Q-statistic whereby a P value of ≤ 0.05 was considered statistically significant, whereas a P value of >0.05 was considered statistically insignificant. Moreover, the I^2-statistic test was also considered during the assessment of heterogeneity across the subgroups whereby an I^2 value of 0% indicated no or very low heterogeneity, and an increasing percentage of I^2 indicated increasing heterogeneity. For a better analysis, a fixed effect model was used if I^2 was $<50\%$ and a random effect model was used if I^2 was $>50\%$. Funnel plots were used to visually assess publication bias. OR with 95% CIs were calculated for categorical variables and the pooled analyses were performed using the latest version of RevMan 5.3 software. Ethical approval was not required for this type of study.

5. Results

5.1. Search strategy and analyzed studies

Two thousand eight hundred forty-two articles were obtained from Medline, PubMed, EMBASE, and the Cochrane databases. Two thousand seven hundred twenty-six articles were eliminated,

Table 2

The baseline features of the included studies.

Studies	Age (years)	Men (%)	HT (%)	Cs (%)	DM (%)	Cochrane Bias score
	F/A	F/A	F/A	F/A	F/A	
O'Neill et al[6]	53.8/56.8	92.6/79.3	37.0/48.3	—	—	11
Grines et al[7]	60.0/60.0	72.0/74.0	39.0/47.0	—	12.0/13.0	8
Zijlstra et al[8]	61.0/59.0	82.0/89.0	—	—	—	11
Gusto[9]	61.9/63.5	78.5/75.4	38.0/39.8	60.9/63.7	13.4/17.7	11
Ribichini et al[10]	60.2/63.4	85.0/82.0	45.5/40.0	54.5/63.6	10.9/16.3	10
García et al[11]	60.0/63.0	80.0/84.0	39.0/32.0	70.0/62.0	17.0/12.0	10
Ross et al[12]	57.6/58.4	79.1/78.3	40.1/43.8	43.7/43.8	15.9/16.8	8
Bonnefoy et al[13]	58.0/58.0	82.5/81.5	33.9/34.8	52.6/49.2	11.1/13.5	10
Kastrati et al[14]	61.1/61.4	75.0/75.0	—	44.0/57.0	21.0/16.0	10
Bonnefoy et al[15]	60.0/60.0	78.6/78.6	43.0/43.0	43.0/43.0	12.8/12.8	10
Armstrong et al[16]	59.7/59.6	79.4/78.1	46.7/44.4	—	12.1/13.1	10
Sinnaeve et al[17]	59.7/59.6	79.4/78.1	—	—	12.1/13.1	10

A, primary angioplasty group; Cs, current smoker; DM, diabetes mellitus; F, fibrinolytic group; HT, hypertension.

as they were either not related to our topic or they were duplicates. Among the remaining 116 articles, another 76 articles were eliminated, as they were meta-analyses, case studies, or observational studies. A further 4 articles were eliminated, as they involved facilitated PPCI. When screening studies for inclusion, 36 studies met the pre-defined inclusion criteria of having a randomized comparator group (comparing fibrinolytic therapy with primary angioplasty) between these patients with STEMI. However, because 24 among these 36 studies did not report bleeding complication as one of their clinical outcomes, these studies were strictly excluded. Finally, 12 studies were included in this meta-analysis. The flow diagram for the study selection has been represented in Fig. 1.

The 12 studies included in this meta-analysis reported bleeding complications (primary outcomes) from the period of hospitalization to up to 30 days after reperfusion therapy. Secondary clinical endpoints included all-cause mortality, reinfarction, stroke, and shock. The oldest trial included in this study was published in the year 1986, while the most recent trial included was published in the year 2014. One study was published in the year 1986,[6] 2 in the year 1993,[7,8] 1 in the year 1997,[9] 1 in the year 1998,[10] 2 in the year 1999,[11,12] 2 in the year 2002,[13,14] 1 in the year 2005,[15] 1 in the year 2013,[16] and another one in the year 2014.[17] The general features of the trials included in this study have been represented in Table 4.

Patient enrollments started from the year 1983 in certain trials until the year 2012 in other trials. Randomization of the patients to either fibrinolytic therapy or primary angioplasty was performed in several medical centers mainly from European countries such as Spain, France, Germany, Belgium, and Netherland.

A total number of 5561 patients (2784 patients from the fibrinolysis group and 2777 patients from the PPCI group) were included in this meta-analysis. All patients provided signed consents. The general features of these trials have been listed in Table 4.

5.2. Baseline characteristics

Table 2 reports the demographic features, including mean age, percentage of males, percentage of patients suffering from hypertension, diabetes, and those patients who are heavy smokers. Patients had an average age of 60 years in both the fibrinolytic and angioplasty groups. Except from 1 study, the percentage of males in the 2 reperfusion groups were almost similar. The percentages of patients suffering from hypertension, diabetes mellitus, and those patients who had a history of smoking were almost indifferent between these 2 groups. Overall, there was no significant difference in the baseline features between the fibrinolytic and angioplasty groups. These characteristics have been summarized in Table 2.

Table 3

Types of bleeding reported.

Trials	Bleeding reported
O'Neill et al[6]	Bleeding complications including blood loss that required transfusion of at least 2 units of red cells
Grines et al[7]	Overall bleeding, including intracranial, gastrointestinal, access site, retroperitoneal, CABG, bleeding at other sites, and transfusion given for decreased hematocrit
Zijlstra et al[8]	Inter-cerebral bleeding and bleeding necessitating a blood transfusion
Gusto[9]	Any type of bleeding including severe or life-threatening, moderate or worse bleeding, and bleeding requiring transfusion
Ribichini et al[10]	Intracerebral bleeding and bleeding requiring transfusion
García et al[11]	Bleeding requiring transfusion
Ross et al[12]	Major hemorrhage including intracerebral bleeding and blood loss that required transfusion of at least 2 units of red cells
Bonnefoy et al[13]	Severe bleeding
Kastrati et al[14]	Moderate and severe bleeding
Bonnefoy et al[15]	Severe bleeding complications
Armstrong et al[16]	Intracranial and nonintracranial hemorrhages.
Sinnaeve et al[17]	Intracranial hemorrhage and major nonintracranial bleeding

CABG, coronary artery bypass surgery.

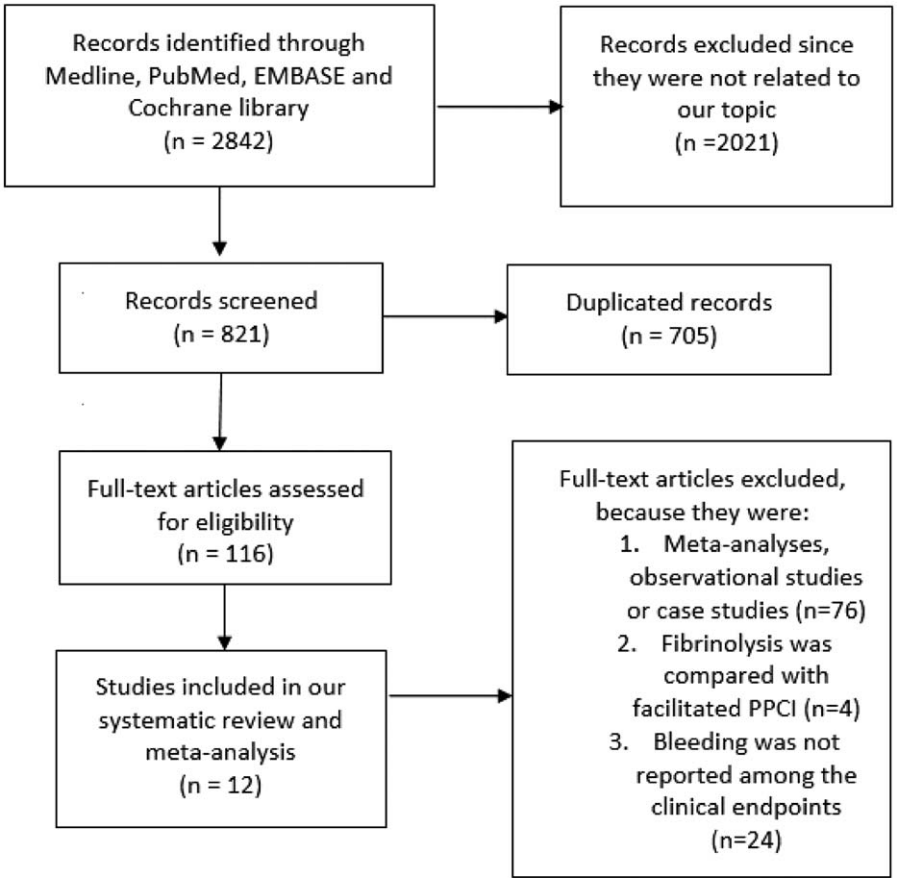

Figure 1. Flow diagram for the study selection.

5.3. Bleeding risk: analysis of the 5561 patients

The pooling analysis showed no significant difference in the general bleeding complications between patients who underwent reperfusion with fibrinolytic therapy and primary angioplasty with OR 1.02; 95% CI 0.89 to 1.17, $P=0.78$. This result has been represented in Fig. 2.

When intracranial and extracranial bleeding were analyzed separately, PPCI was associated with a significantly lower rate of intracranial bleeding than fibrinolysis with OR 0.17; 95% CI

Table 4

General features of the included studies.

Studies	No. of patients treated by fibrinolytic therapy (n)	No of patients treated by primary angioplasty (n)	Total no. of patients (n)	Region	Patients' enrollment period	Journal in which these RCTs were published	Type of study
O'Neill et al[6]	27	29	56	Ann arbor	1983–1984	NEJM	RCT
Grines et al[7]	200	195	395	Michigan	1990–1992	NEJM	RCT
Zijlstra et al[8]	72	70	142	Netherland	1990–1992	NEJM	RCT
Gusto[9]	573	565	1138	Cleveland	1994–1996	NEJM	RCT
Ribichini et al[10]	55	55	110	Italy	1993–1996	JACC	RCT
García et al[11]	111	109	220	Spain	1991–1996	JACC	RCT
Ross et al[12]	302	304	606	New York	—	JACC	RCT
Bonnefoy et al[13]	419	421	840	France	1997–2000	LANCET	RCT
Kastrati et al[14]	81	81	162	Germany	1999–2001	LANCET	RCT
Bonnefoy et al[15]	416	418	834	France	1997–2000	AHJ	RCT
Armstrong et al[16]	939	946	1885	Belgium	2008–2012	NEJM	RCT
Sinnaeve et al[17]	944	948	1892	Belgium	2008–2012	Circulation	RCT
Total	2784	2777	5561				

AHJ, *American Heart Journal*; JACC, *Journal of American College of Cardiology*; NEJM, *New England Journal of Medicine*; RCT, randomized controlled trial.Armstrong et al[16] and Sinnaeve et al[17] included patients from the same STREAM Trial and therefore the number of patients has been included only once in the final count for the total number of patients. This was similarly done for studies Bonnefoy et al[13] and Bonnefoy et al[15].

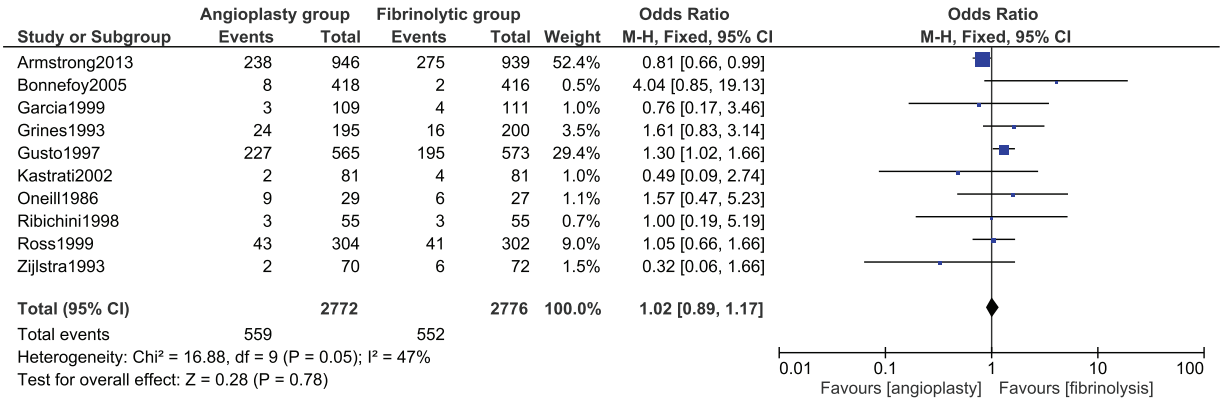

Figure 2. General bleeding complications between fibrinolysis and primary percutaneous coronary intervention.

0.06 to 0.50, $P=0.001$. Nonintracranial bleeding also favored PPCI with OR 0.85; 95% CI 0.70 to 1.04, $P=0.12$; however, this result was not statistically significant. Results assessing intracranial and nonintracranial bleeding have been illustrated in Fig. 3.

5.4. Secondary outcomes

According to the patients analyzed, mortality was significantly higher in the fibrinolysis group with OR 0.75; 95% CI 0.59 to 0.97, $P=0.03$. Reinfarction also significantly favored PPCI with OR 0.63; 95% CI 0.47 to 0.84, $P=0.001$. Stroke was significantly lower in the PPCI group with OR 0.35; 95% CI 0.19 to 0.62, $P=0.0003$. However, our results showed that shock significantly favored fibrinolysis with OR 1.44; 95% CI 1.07 to 1.95, $P=0.02$. Results reporting the secondary outcomes have been illustrated in Fig. 4.

For all of the above analyses, sensitivity analyses yielded consistent results. On the basis of a visual inspection of the funnel plots that assessed primary and secondary outcomes in this study, there has been no evidence of publication bias among the included studies. The funnel plots have been illustrated in Fig. 5A and B.

6. Discussion

Patients with STEMI often undergo reperfusion therapy by fibrinolysis or PPCI. However, both reperfusion therapies are associated with bleeding complications. Hence, we have conducted this meta-analysis including 5561 randomized patients in order to compare the bleeding events between these 2 reperfusion therapies so as to know which one is safer during a 30-day period after reperfusion.

Despite the differences in antiplatelet and anticoagulation regimens between these 2 groups, fibrinolytic therapy and primary angioplasty were associated with almost similar overall bleeding complications (including all types of bleeding combined together). However, when bleeding events were further classified into intracranial and nonintracranial bleeding, fibrinolysis was associated with a significantly higher rate of intracranial bleeding than PPCI. Other secondary outcomes including death, reinfarc-

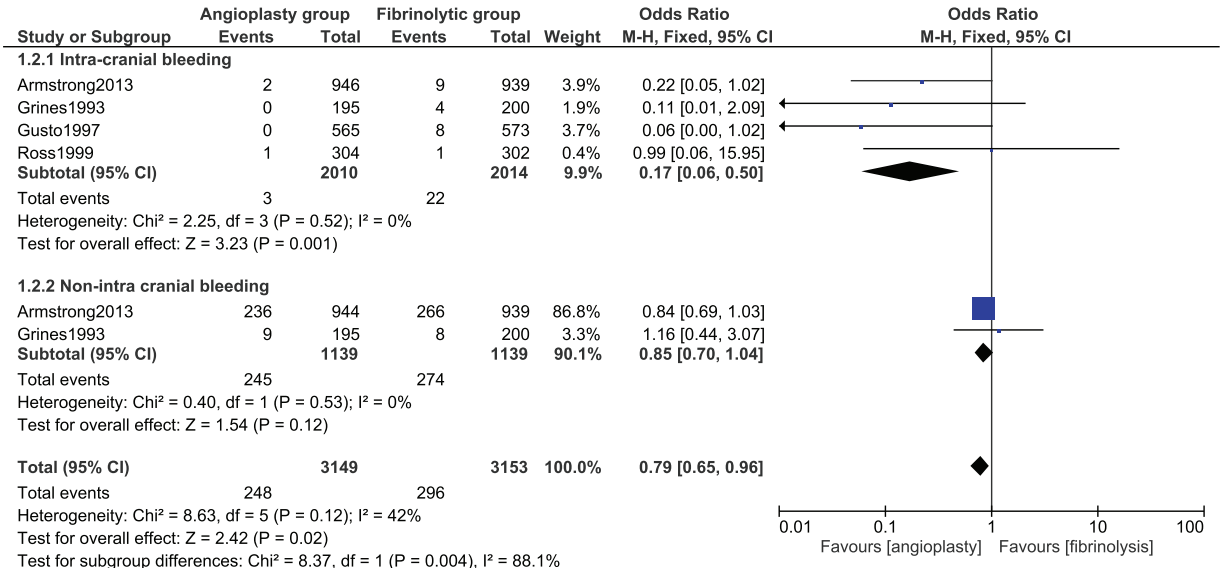

Figure 3. Intracranial and nonintra cranial bleeding between fibrinolytic therapy and primary percutaneous coronary intervention.

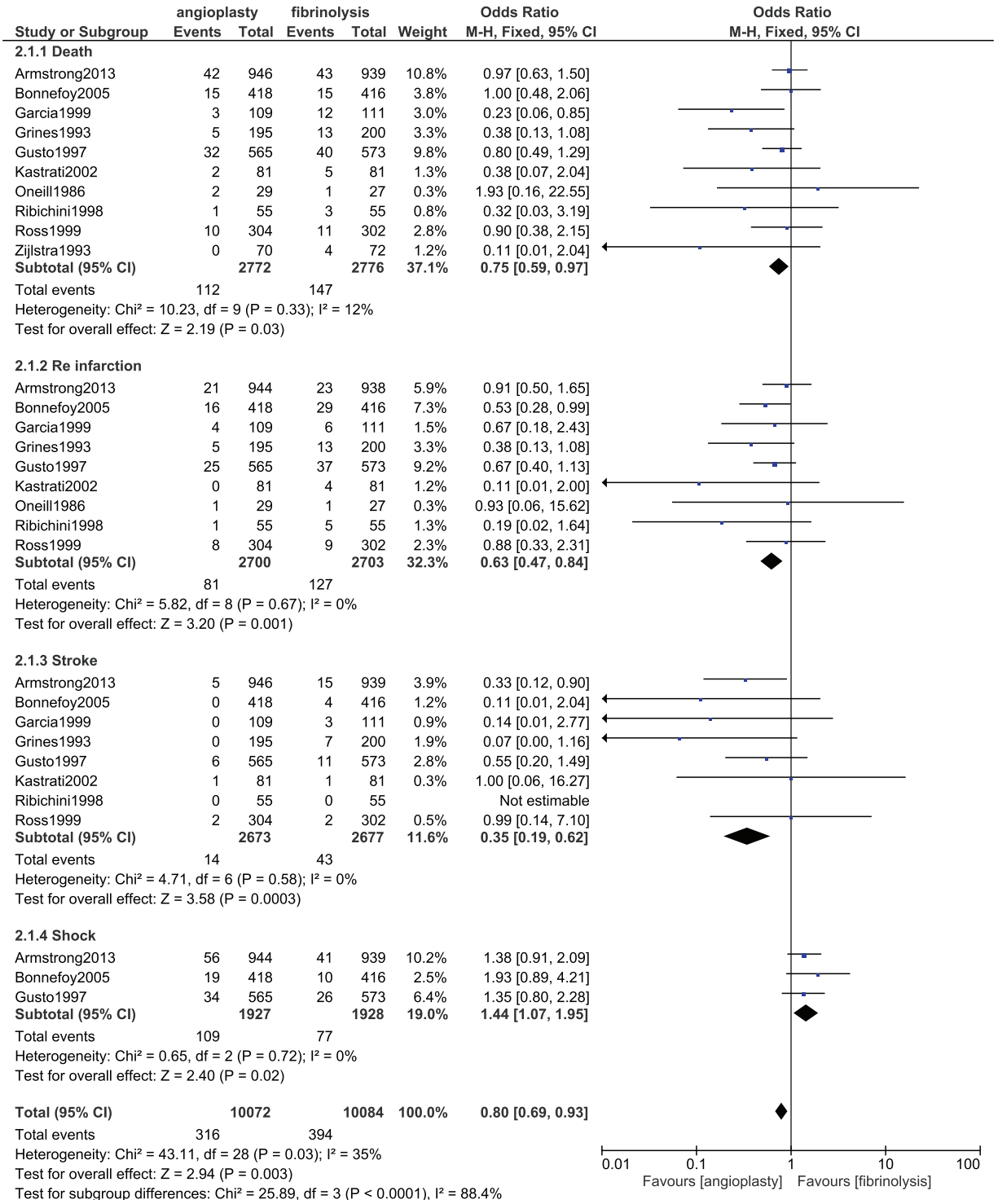

Figure 4. Secondary endpoints analyzed between fibrinolysis and primary percutaneous coronary intervention.

tion, and stroke significantly favored PPCI. However, shock significantly favored fibrinolysis.

Very few research reported bleeding events between these 2 reperfusion therapies. Most of the studies mainly focused on the impact of fibrinolytic therapy and primary angioplasty on mortality in patients with STEMI. The randomized trial of direct coronary angioplasty versus streptokinase in patients with acute MI conducted by Ribeiro et al[18] did not report any bleeding complication between these 2 reperfusion therapies and stated that not even a single patient in either group required blood transfusion during this in-hospital follow-up period. However, another study by Mehta et al[19] comparing fibrinolytic therapy with primary angioplasty showed a decreased in mortality and reinfarction in the angioplasty group with no change in other outcome measures, in elderly patients with STEMI.

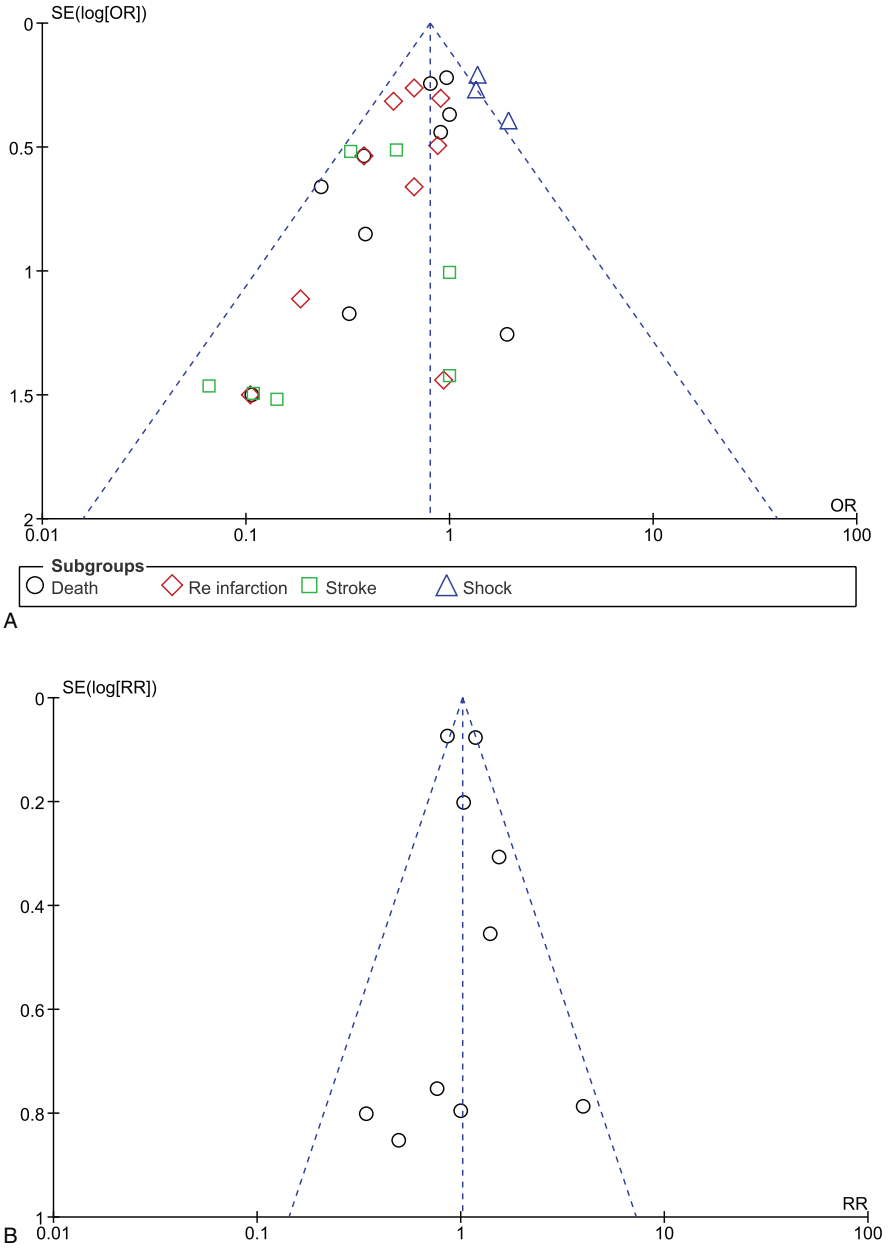

Figure 5. (A) and (B) Funnel plots representing sensitivity analysis.

This current study involved only published trials. However, results from an observational study showed a major bleeding (3.2%) associated with thrombolytic therapy and (4.2%) associated with primary angioplasty in low-volume primary angioplasty hospitals.[20] But, in intermediate and high volume hospitals, the major bleeding rates were 4.3% and 3.8%, and 4.0% and 3.6%, in the thrombolytic and angioplasty groups, respectively.

In addition, the comparison of tenecteplase with rt-PA also showed that tenecteplase did not increase intracranial hemorrhage but was associated with less noncerebral bleeding especially in high-risk patients.[2] However, as our study compared fibrinolytic therapy with primary angioplasty, our results were completely different. A meta-analysis conducted by Kwok et al[3] using data from 42 studies concluded that major bleeding after PCI was independently associated with a 3-fold increase in mortality and major adverse cardiac outcomes, which was also different from the results of this current study. But, however, their study was not comparing PCI with fibrinolytic therapy.

These 2 types of reperfusion therapies in patients with STEMI have their own particular advantages. Fibrinolytic therapy is a reperfusion therapy that is easier and does not require any type of surgery. This kind of reperfusion therapy is more common in PCI-noncapable centers.

On the contrary, PPCI is an invasive procedure that is not as easy as the fibrinolytic therapy, and requires skills and can only be performed by an experienced interventionist.

Because the resistance of cross-linked fibrin to fibrinolysis is time-dependent, fibrinolysis is most effective when given within

the first four hours after the onset of symptoms, particularly within the first 70 minutes.[21,22] Factors such as delayed to be transported to the hospital, an unclear or unknown patient history or, contraindication to fibrinolysis, could limit the use of this reperfusion therapy in many medical centers. Thus, guidelines recommend primary angioplasty as a better option even if both treatment regimens are almost similar.[1]

7. Limitations

Due to a smaller population size, the result of this study might be restricted to some extent. Moreover, 1 study did not report all-cause mortality, and therefore, data for cardiac mortality were used instead. This could have an effect on our results. Different follow-up periods ranging from in-hospital follow-up to a follow-up period of 30 days were reported. Combining and comparing studies with different follow-up periods altogether could also be a limitation in this study.

8. Conclusion

According to the results of this study, even if the rate of nonintracranial bleeding was not statistically significant between these 2 reperfusion therapies, fibrinolytic therapy was associated with a significantly higher rate of intracranial bleeding than PPCI. In addition, PPCI was associated with a significantly lower rate of death, reinfarction, and stroke. Therefore, PPCI should be recommended in patients with STEMI, especially in PCI-capable hospitals. Fibrinolysis should only be reserved for non-PCI capable hospitals.

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