Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Comparison of Reperfusion Strategies for ST-Segment–Elevation Myocardial Infarction: A Multivariate Network Meta-analysis

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BACKGROUND: We systematically reviewed trials comparing different reperfusion strategies for ST-segment–elevation myocardial infarction and used multivariate network meta-analysis to compare outcomes across these strategies.

METHODS AND RESULTS: We identified 31 contemporary trials in which patients with ST-segment–elevation myocardial infarction were randomized to ≥2 of the following strategies: fibrinolytic therapy (n=4212), primary percutaneous coronary intervention (PCI) (n=6139), or fibrinolysis followed by routine early PCI (n=5006). We categorized the last approach as "facilitated PCI" when the median time interval between fibrinolysis to PCI was <2 hours (n=2259) and as a "pharmacoinvasive approach" when this interval was ≥2 hours (n=2747). We evaluated outcomes of death, nonfatal reinfarction, stroke, and major bleeding using a multivariate network meta-analysis and a Bayesian analysis. Among the strategies evaluated, primary PCI was associated with the lowest risk of mortality, nonfatal reinfarction, and stroke. For mortality, primary PCI had an odds ratio of 0.73 (95% CI, 0.61–0.89) when compared with fibrinolytic therapy. Of the remaining strategies, the pharmacoinvasive approach was the next most favorable with an odds ratio for death of 0.79 (95% CI, 0.59–1.08) compared with fibrinolytic therapy. The Bayesian model indicated that when the 2 strategies examining routine early invasive therapy following fibrinolysis were directly compared, the probability of adverse outcomes was lower for the pharmacoinvasive approach relative to facilitated PCI.

CONCLUSIONS: A pharmacoinvasive approach is safer and more effective than facilitated PCI and fibrinolytic therapy alone. This has significant implications for ST-segment–elevation myocardial infarction care in settings where timely access to primary PCI, the preferred treatment for ST-segment–elevation myocardial infarction, is not available.

Key Words: facilitated percutaneous coronary intervention ■ fibrinolytic therapy ■ pharmacoinvasive approach ■ primary percutaneous coronary intervention ■ ST-segment–elevation myocardial infarction

See Editorial by Mentias and Girotra

Primary percutaneous coronary intervention (PCI), when performed in a timely manner, is preferred to fibrinolytic therapy for reperfusion therapy during ST-segment–elevation myocardial infarction (STEMI).[1] However, logistical barriers limit the availability of primary PCI for most patients worldwide. In such situations, administering fibrinolytic therapy remains the customary approach, although this strategy is associated with higher rates of nonfatal reinfarction and worse mortality relative to primary PCI.[2] A more recent development has been the use of fibrinolysis followed by routine transfer for early invasive therapy with coronary angiography and possible PCI. This last strategy potentially leverages the strengths of both approaches

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015186

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Combining fibrinolytic therapy with immediate transfer for percutaneous coronary intervention (PCI) has been proposed as a management strategy for ST-segment–elevation myocardial infarction at centers without PCI capability; this approach is termed facilitated PCI when fibrinolytic to PCI time interval is shorter (<2 hours) and a pharmacoinvasive approach when this interval is longer (2–24 hours).
- To date no published trials of have directly compared a pharmacoinvasive approach and facilitated PCI for treatment of ST-segment–elevation myocardial infarction.
- We performed a multivariate network meta-analysis comparing 4 main strategies for treating ST-segment–elevation myocardial infarction: fibrinolytic therapy, primary PCI, a pharmacoinvasive approach, and facilitated PCI.

What Are the Clinical Implications?

- Primary PCI is the preferred treatment for ST-segment–elevation myocardial infarction.
- The key finding of this study is that, in settings where timely primary PCI is not available, a pharmacoinvasive approach is safer and more effective than facilitated PCI or fibrinolytic therapy alone.

Nonstandard Abbreviations and Acronyms

IQR	interquartile range
OR	odds ratio
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction

by combining the speed and ease of fibrinolytic therapy administration with the reliability and durability of PCI but has been studied to a more limited extent.

Thus, understanding the ideal approach to reperfusion therapy is complicated by a confusing landscape of clinical trials that have compared many but not all of these strategies head-to-head. For example, 2 different study designs have evaluated the combination of fibrinolysis with routine early invasive therapy: facilitated PCI and a pharmacoinvasive approach. The key distinction between these 2 designs relates to the time interval between the administration of fibrinolytics and performing PCI. The term *facilitated PCI* has been used when the time interval between fibrinolysis and PCI is shorter (eg, <2 hours), whereas the term *pharmacoinvasive approach* has implied an intentionally longer fibrinolysis to PCI interval (eg, 2–24 hours). Multiple trials comparing facilitated PCI with primary PCI have consistently found facilitated PCI to be inferior.[3–7] In contrast, trials have also consistently demonstrated that the pharmacoinvasive approach is superior to fibrinolytic therapy,[8–13] and multiple studies suggest equivalence to primary PCI when substantial delays are likely.[8,14–16] Importantly, no published trials to date have directly compared facilitated PCI with a pharmacoinvasive approach in patients who lack timely access to primary PCI.

As primary PCI is unavailable for a large proportion of the world's population, understanding the relative efficacy and safety of alternative reperfusion strategies is necessary for optimizing care for STEMI, which remains a leading cause of death and disability worldwide. Accordingly, we systematically reviewed the published literature and performed a multivariate network meta-analysis of randomized controlled trials for treatment of STEMI to summarize and compare various strategies for treatment, including primary PCI, fibrinolytic therapy, and facilitated PCI, and a pharmacoinvasive approach.

METHODS

Data Sources and Search Strategy

We gathered data from randomized controlled trials of patients with STEMI, presenting within 12 hours of symptom onset, in which any of the following treatments were compared: primary PCI, fibrinolytic therapy, and fibrinolysis followed by routine early (ie, within 24 hours) invasive therapy.

We searched MEDLINE, Embase, and the Cochrane Register of Controlled Trials, from January 1, 1999, to March 20, 2019, using the following key words: "primary angioplasty," "primary percutaneous coronary intervention," "facilitated angioplasty," "facilitated percutaneous coronary intervention," "pharmacoinvasive," "acute myocardial infarction," "ST elevation myocardial infarction," and "ST-segment–elevation myocardial infarction." We restricted our search to studies following 1999 to focus on those trials that used contemporary management strategies for PCI. We excluded trials that did not routinely use stenting during PCI (use of stents in <50% of coronary interventions) and those without follow-up beyond hospital discharge.

We only included reports published in English. We performed our search on March 20, 2019, and identified 62 reports that were reviewed by 2 independent readers (R.F., T.I.J.), with any discrepancies resolved by a third reviewer (B.K.N.).

Data Extraction and Definition of the Reperfusion Strategies

We extracted data regarding study design, inclusion and exclusion criteria, clinical short-term outcomes, number of patients enrolled, and time delay intervals. The primary clinical end points we abstracted were death, nonfatal reinfarction, stroke, and major bleeding at 30 to 90 days. In all cases, we used the definitions utilized within the individual trials to define these outcomes. These definitions as well as details of protocols for each trial are outlined in Table S1.

We defined primary PCI as immediate PCI without prior administration of fibrinolytics. For our primary analysis, in accordance with time thresholds discussed in the 2017 European Society of Cardiology Guidelines for STEMI management, we categorized routine early PCI after fibrinolysis as facilitated PCI when the average time interval between administration of fibrinolytics and PCI was <2 hours and as a pharmacoinvasive approach when this interval was ≥2 hours. We did not consider pretreatment of STEMI before PCI with glycoprotein IIb/IIIa receptor inhibitors without fibrinolysis as either facilitated PCI or a pharmacoinvasive approach.

Statistical Analysis

We used multivariate network meta-analysis, as described by White and colleagues,[17–19] to compare treatment strategies. This method involves the simultaneous analysis of both direct and indirect comparisons among multiple treatment strategies and across multiple studies, thus allowing for competing interventions (ie, reperfusion strategies in this case) to be ranked based on the likelihood of outcomes. As such, this approach is clinically more useful than simple pairwise comparison of treatments and can provide a deeper understanding of the relative effectiveness and safety of strategies utilized in patients with STEMI even though some of these have not been directly compared in existing trials. We examined the heterogeneity among trials for each outcome using the multivariate R statistic.[20]

We also estimated the probability that each treatment strategy was associated with maximum risk for each of the individual outcomes of death, myocardial reinfarction, stroke, or major bleeding under a Bayesian model with flat priors.

As many of the trials included subsequent reports with longer follow-up times, we performed a sensitivity analysis by repeating our primary analysis using outcomes reported at longest reported follow-up. In order to assess the impact of the thrombolysis to PCI interval time threshold on our study results, we performed another sensitivity analysis in which we used a thrombolysis to PCI interval threshold of 180 minutes (instead of 120 minutes) to define facilitated PCI (<180 minutes) versus a pharmacoinvasive approach (≥180 minutes).

Finally, given their potential influence on study findings, we performed sensitivity analyses excluding the 2 largest trials (STREAM [Strategic Reperfusion Early After Myocardial Infarction][14] and ASSENT-4 [Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention][4]) one at a time in order to assess their impact on study results.

Role of the Funding Source

No sponsor of any of the individual trials had any role in the study design, data collection, data interpretation, drafting, or review of the report.

RESULTS

We screened the titles and abstracts of 1767 potentially eligible reports, reviewed the full text of 64 articles reporting on 38 separate trials, and identified 31 trials that met our inclusion criteria (Figure 1). The characteristics of the included trials are outlined in Table 1,[21–37] and Figure 2 shows the evidence network constructed from the 31 trials. A total of 15 357 patients were randomized in the included trials: 4212 to fibrinolytic therapy, 6139 to primary PCI, 2190 to a pharmacoinvasive approach, and 2816 to facilitated PCI. Among trials that included an arm with routine early PCI after fibrinolytic therapy, the weighted median time interval between administration of fibrinolytics to PCI was 90 minutes for facilitated PCI and 234 minutes for a pharmacoinvasive approach.

Unadjusted Mortality

All 31 trials provided information on the end point of death, with a median follow-up period of 30 days. An examination of unadjusted mortality revealed

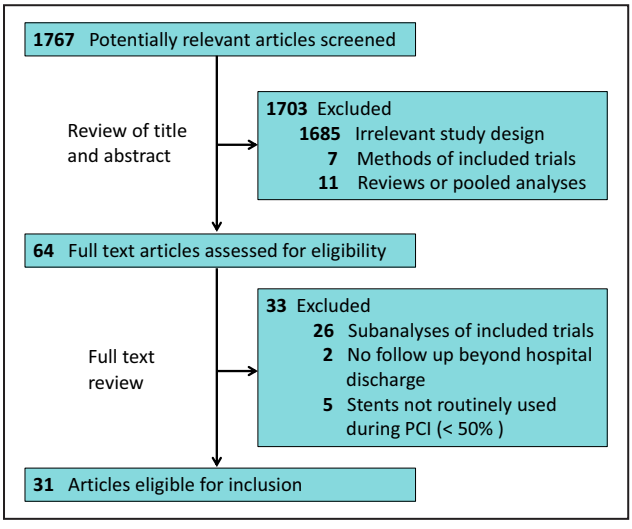

Figure 1. Study selection.
PCI indicates percutaneous coronary intervention.

Table 1. Characteristics of Included Studies

Source (Publication Year)	No. of Subjects	Treatment	Fibrinolysis to PCI Interval, min	Short-Term Follow-Up, d	Death	Myocardial Reinfarction	Stroke	Major Bleeding
PRAGUE[7] (2000)	99	Fibrinolytic therapy	···	30	14	10	1	N/A
	101	Primary PCI	···		7	1	0	
	100	Facilitated PCI	68		12	7	3	
STOPAMI[21] (2000)	69	Fibrinolytic therapy	···	30	5	4	0	2
	71	Primary PCI	···		3	2	0	3
STAT[22] (2001)	61	Fibrinolytic therapy	···	42	2	8	2	7
	62	Primary PCI	···		3	3	1	4
STOPAMI-2[23] (2002)	81	Fibrinolytic therapy	···	30	5	4	1	1
	81	Primary PCI	···		2	0	1	1
C-PORT[24] (2002)	226	Fibrinolytic therapy	···	42	16	20	8	15
	225	Primary PCI	···		12	11	3	29
Zwolle[25] (2002)	41	Fibrinolytic therapy	···	30	9	6	3	3
	46	Primary PCI	···		3	1	1	5
CAPTIM[26] (2002)	419	Fibrinolytic therapy	···	30	16	15	4	2
	421	Primary PCI	···		20	7	0	8
SIAM-III[10] (2003)	81	Fibrinolytic therapy	···	30	8	2	2	6
	82	Pharmacoinvasive	210		4	2	1	8
DANAMI-2[27] (2003)	782	Fibrinolytic therapy	···	30	61	49	16	N/A
	790	Primary PCI	···		52	13	9	
PRAGUE-2[28] (2003)	421	Fibrinolytic therapy	···	30	42	13	9	N/A
	429	Primary PCI	···		29	6	1	
BRAVE[16] (2004)	128	Primary PCI	···	30	2	1	0	2
	125	Pharmacoinvasive	125		2	2	1	7
GRACIA-1[9] (2004)	251	Fibrinolytic therapy	···	30	6	4	1	4
	248	Pharmacoinvasive	1002		6	3	0	4
APAMIT[29] (2004)	36	Primary PCI	···	30	1	1	1	2
	34	Facilitated PCI	60		1	0	0	1
CAPITAL AMI[30] (2005)	84	Fibrinolytic therapy	···	30	3	11	1	6
	86	Facilitated PCI	90		2	4	1	7
Leipzig[31] (2005)	82	Fibrinolytic therapy	···	30	4	7	1	5
	82	Facilitated PCI	84		2	3	0	4
ADVANCE MI[5] (2005)	77	Primary PCI	···	30	0	2	N/A	8
	69	Facilitated PCI	84		5	1		17
ASSENT-4[4] (2006)	838	Primary PCI	···	90	41	30	1	37
	829	Facilitated PCI	104		55	49	22	46
WEST[8] (2006)	100	Fibrinolytic therapy	···	30	4	9	0	1
	100	Primary PCI	···		1	3	1	1
	104	Pharmacoinvasive	295		1	6	1	2
SWEDES[32] (2006)	104	Fibrinolytic therapy	···	30	4	2	3	N/A
	101	Primary PCI	···		3	0	0	
HIS[33] (2006)	23	Fibrinolytic therapy	···	30	3	1	0	N/A
	25	Primary PCI	···		1	0	0	
Bialystok[34] (2007)	200	Fibrinolytic therapy	···	30	18	11	3	4
	201	Primary PCI	···		10	5	1	4
GRACIA-2[15] (2007)	108	Primary PCI	···	30	5	1	0	3
	104	Pharmacoinvasive	276		3	1	1	2

(*Continued*)

Table 1. Continued

Source (Publication Year)	No. of Subjects	Treatment	Fibrinolysis to PCI Interval, min	Short-Term Follow-Up, d	Death	Myocardial Reinfarction	Stroke	Major Bleeding
CARESS-in-AMI[13] (2008)	300	Fibrinolytic therapy	···	30	14	6	4	7
	298	Pharmacoinvasive	135		9	4	2	10
ATAMI[35] (2008)	162	Primary PCI	···	30	9	3	1	0
	151	Facilitated PCI	92		1	2	0	0
FINESSE[3] (2008)	806	Primary PCI	···	90	36	15	8	21
	828	Facilitated PCI	90		43	17	9	39
TRANSFER-AMI[11] (2009)	522	Fibrinolytic therapy	···	30	18	30	6	47
	537	Pharmacoinvasive	234		24	18	3	40
NORDISTEMI[12] (2010)	132	Fibrinolytic therapy	···	30	3	7	5	3
	134	Pharmacoinvasive	163		3	2	3	2
TRIANA[36] (2011)	134	Fibrinolytic therapy	···	30	23	11	4	6
	132	Primary PCI	···		18	7	1	5
LIPSIA-STEMI[6] (2011)	78	Primary PCI	···	30	4	4	1	2
	80	Facilitated PCI	85		5	5	1	2
STREAM[14] (2013)	948	Primary PCI	···	30	42	21	5	45
	944	Pharmacoinvasive	483		43	23	15	61
EARLY-MYO[37] (2017)	173	Primary PCI	···	30	2	1	0	0
	171	Pharmacoinvasive	464		1	1	0	1

ASSENT-4 indicates Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention; ATAMI, Alteplase and Tirofiban in Acute Myocardial Infarction; BRAVE, Bavarian Reperfusion Alternatives Evaluation; CAPTIM, Comparison of Angioplasty and Prehospital Thromboysis in Acute Myocardial Infarction; CARESS-in-AMI, Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction; C-PORT, Atlantic Cardiovascular Patient Outcomes Research Team; DANAMI-2, Danish Trial in Acute Myocardial Infarction-2; EARLY-MYO, Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction; FINESSE, Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events; GRACIA, Grupo de Análisis de la Cardiopatía Isquémica Aguda; LIPSIA-STEMI, Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction; NORDISTEMI, Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction; PCI, percutaneous coronary intervention; PRAGUE, Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis; SIAM-III, Southwest German Interventional Study in Acute Myocardial Infarction; STOPAMI, Stent Versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction; STREAM, Strategic Reperfusion Early after Myocardial Infarction; TRANSFER-AMI, Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; TRIANA, Tratamiento del Infarto Agudo de Miocardio en Ancianos; and WEST, Which Early ST-Elevation Myocardial Infarction Therapy.

that 806 patients in the included studies died: 278 patients randomized to fibrinolytic therapy (median 6.2%, range 2.3–22.0%; interquartile range [IQR], 3.8–9.9%), 306 (5.0%) patients randomized to primary PCI (median 4.7%, range 0.0–13.6%; IQR, 2.9–5.4%), 96 (3.5%) patients randomized to a pharmacoinvasive approach (median 2.7%, range 0.6–4.9%; IQR, 1.8–4.1%), and 126 (5.6%) patients randomized to facilitated PCI (median 5.2%, range 0.7–12.0%; IQR, 2.4–6.6%).

Nonfatal Reinfarction

All 31 trials also provided information on the end point of nonfatal reinfarction, with a median follow-up of 30 days. In unadjusted analyses, a total of 516 patients experienced nonfatal myocardial reinfarction: 230 (5.5%) patients randomized to fibrinolytic therapy (median 5.7%, range 1.6–14.6%; IQR, 3.6–8.8%), 137 (2.2%) patients randomized to primary PCI (median 2.0%, range 0.0–5.3%; IQR, 1.0–2.9%), 61 (2.8%) patients randomized to a pharmacoinvasive approach (median 1.4%, range 0.6–5.8%; IQR, 1.0–2.4%), and 88 (3.1%) patients randomized to facilitated PCI (median 3.7%, range 0.0–7.0%; IQR, 1.4–5.9%).

Stroke

We found that 30 trials provided data on stroke, with a median follow-up period of 30 days. In unadjusted analyses, a total of 173 patients experienced a stroke: 74 (1.8%) patients randomized to fibrinolytic therapy (median 1.3%, range 0.0–7.3%; IQR, 1.0–2.9%), 36 (0.6%) patients randomized to primary PCI (median 0.5%, range 0.0–2.8%; IQR, 0.0–1.2%), 27 (1.0%) patients randomized to a pharmacoinvasive approach (median 0.9%, range 0.0–2.2%; IQR, 0.6–1.2%), and 36 (1.6%) patients randomized to facilitated PCI (median 1.1%, range 0.0–1.6%; IQR, 0.0–1.6%).

Major Bleeding

A total of 26 trials contributed to the end point of major bleeding, with a median follow-up of 30 days. In unadjusted analyses, 552 patients developed a major bleeding complication: 119 (4.3%) patients randomized to

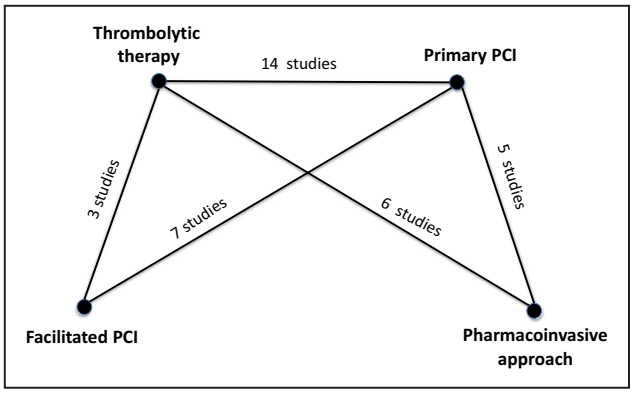

Figure 2. Evidence network for trials included in the meta-analysis.
The WEST (Which Early ST-Elevation Myocardial Infarction Therapy)[8] and PRAGUE (Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis)[7,28] trials each included 3 treatment arms, which is the reason the tally of studies in the diagram is 34 rather than 30 (which was the total number of studies in our analysis). PCI indicates percutaneous coronary intervention.

fibrinolytic therapy (median 3.7%, range 0.5–11.5%; IQR, 1.9–7.2%), 180 (3.8%) patients randomized to primary PCI (median 2.8%, range 0.3–12.9%; IQR, 1.7–5.2%), 137 (4.9%) patients randomized to a pharmacoinvasive approach (median 2.6%, range 0.6–9.8%; IQR, 1.7–6.2%), and 116 (5.4%) patients randomized to facilitated PCI (median 4.8%, range 0.3–24.6%; IQR, 2.8–6.2%).

Multivariate Network Meta-Analysis Results

The results of the multivariate network meta-analysis are listed in Table 2. Among the 4 strategies evaluated, primary PCI was associated with the lowest odds of death (odds ratio [OR], 0.73; 95% CI, 0.61–0.89) and nonfatal reinfarction (OR, 0.38; 95% CI, 0.29–0.50), as well as the lowest odds of stroke (OR, 0.38; 95% CI, 0.24–0.60). Among the remaining strategies, the pharmacoinvasive approach was associated with the lowest odds of mortality (OR, 0.79; 95% CI, 0.59–1.08). There was no statistically significant difference in the risk of major bleeding among the strategies evaluated; however, there was a trend for higher odds of major bleeding with facilitated PCI (OR, 1.51; 95% CI, 0.93–2.46). The multivariate R statistic calculated for each of the 4 outcomes revealed no evidence of significant heterogeneity among the trials (Table 2). The Bayesian model indicated that the probability of being the worst of the 4 treatment strategies was highest for fibrinolytic therapy and lowest for primary PCI in regards to the risk of death, nonfatal reinfarction, and stroke (Table 3).

Furthermore, the results of the Bayesian model suggested that the efficacy and safety of a pharmacoinvasive approach is superior to facilitated PCI when compared head-to-head. For example, the overall probability of facilitated PCI having the highest mortality rate among the compared treatments was estimated at 24.2% (second only to fibrinolytic therapy at 69.8%) and only 6.0% for a pharmacoinvasive approach. The probability of having the highest rates of stroke and major bleeding were also higher for facilitated PCI as compared with a pharmacoinvasive approach (16.3% versus 11.1%, and 77.4% versus 19.8%, respectively).

The results of the sensitivity analysis using the longest published follow-up of included studies revealed no significant difference from the primary analysis using short-term follow-up (Tables S2 and S3). In the sensitivity analysis in which a thrombolysis to PCI time interval of 180 minutes was used as the threshold to define facilitated PCI versus a pharmacoinvasive approach, the treatment arms of 3 trials––BRAVE (Bavarian Reperfusion Alternatives Evaluation),[16] CARESS-in-AMI (Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction),[13] and NORDISTEMI (Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction)[12]––were recategorized from a pharmacoinvasive approach to facilitated PCI. This resulted in a slightly higher stroke risk for pharmacoinvasive approach compared with facilitated PCI in the Bayesian analysis but no other significant changes in our findings (Tables S4 and S5). Sensitivity analyses excluding the ASSENT-4 and STREAM trials from the analysis

Table 2. Multivariate Network Meta-Analysis Results

Outcome	Fibrinolytic Therapy	Primary PCI		Pharmacoinvasive Approach		Faciliated PCI		Multivariate R Statistic	No. of Trials
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value		
Death	Reference	0.73 (0.61–0.89)	0.002	0.79 (0.59–1.08)	0.14	0.90 (0.66–1.24)	0.53	1.00	31
Reinfarction	Reference	0.38 (0.29–0.50)	<0.001	0.53 (0.37–0.75)	<0.001	0.52 (0.36–0.76)	0.001	1.00	31
Stroke	Reference	0.38 (0.24–0.60)	<0.001	0.70 (0.38–1.29)	0.25	0.71 (0.33–1.53)	0.38	1.00	30
Major bleeding	Reference	1.03 (0.72–1.49)	0.86	1.19 (0.81–1.74)	0.36	1.51 (0.93–2.46)	0.10	1.28	25

OR indicates odds ratio; and PCI, percutaneous coronary intervention.

Table 3. Results of the Bayesian Model to Estimate Probability of Maximum Risk

Outcome	Fibrinolytic Therapy, %	Primary PCI	Pharmacoinvasive Approach, %	Facilitated PCI, %	No. of Trials
Death	69.8	0.0%	6.0	24.2	31
Reinfarction	99.9	0.0%	0.1	0.0	31
Stroke	72.6	0.0%	11.1	16.3	29
Major bleeding	1.7	1.1%	19.8	77.4	26

These results estimate the probability that each treatment approach is associated with maximum risk of each adverse outcome relative to the other treatments. For example, these results suggest that there is a 69.8% probability that fibrinolytic therapy is associated with the highest risk of death as compared with the other 3 strategies. They also indicate that facilitated percutaneous coronary intervention (PCI) has the second highest probability (24.2%) of being associated with the highest mortality risk among the compared strategies and primary PCI has a >99.9% probability of having the lowest mortality risk among the treatments.

revealed no significant impact on the study findings (Tables S6 through S9).

DISCUSSION

Our study adds to the substantial body of evidence indicating that during STEMI, primary PCI, when performed in a timely manner, is the best strategy for reducing short-term major adverse cardiac events, including death. The key novel insights provided by our study, however, pertain to situations where timely primary PCI is not possible—scenarios in which the best approach to treatment of STEMI remains unclear and controversial. Our findings suggest that fibrinolysis followed by routine early invasive therapy is more effective in this setting as compared with standard fibrinolytic therapy alone. Importantly, our study also suggests that the time interval between fibrinolysis and PCI is a key determinant of the efficacy and safety of any approach combining fibrinolysis with routine early invasive therapy.

A key advantage of our study is that it incorporates data from trials involving all 4 reperfusion strategies that are currently utilized in contemporary practice, synthesizing them in a manner that allows for comparison and ranking. A single model leverages both direct and indirect comparisons between reperfusion strategies, which is useful for clinicians taking care of these patients as well as policy makers who design STEMI systems of care. This approach also allowed us to directly examine heterogeneity among trials in the time interval between fibrinolysis and PCI in those studies that examined routine early invasive therapy following fibrinolysis. For this issue, our results suggest that when the time interval between fibrinolysis and PCI is <2 hours (facilitated PCI), there is an increased risk of major bleeding and possibly death as compared with when the interval is 2 to 24 hours (pharmacoinvasive approach).

These findings have implications for a large number of patients worldwide. It is estimated that over 7 million people die annually from acute myocardial infarction and this number is projected to increase to over 9 million by 2030.[38] Approximately 80% of these deaths occur in low- and middle-income countries, where resources such as PCI-capable hospitals are scarce.[38] Fibrinolytic therapy remains the most widely used reperfusion strategy in the world.[39] In many developing countries, cardiac catheterization laboratories are only available in larger cities, making the use of primary PCI impossible for a large proportion of the population. A pharmacoinvasive approach is an attractive option in this setting as it expands access to PCI once patients are stabilized. Even in the United States, it is estimated that as many as 20% of individuals live more than 60 minutes away from a PCI-capable hospital,[40,41] and recent increases in PCI capacity among hospitals has mostly occurred in areas where neighboring facilities already have this capability rather than in areas of new geographic coverage.[42] These facts highlight the crucial importance of understanding the potential role of alternative reperfusion strategies to primary PCI for treating STEMI.

It is important to note that PCI-related delays in trials included in our study were relatively short: median randomization to balloon time in the primary PCI arms of the included trials was 80 minutes (IQR, 76–105 minutes) overall and 77 minutes (IQR, 76–80 minutes) for trials that compared primary PCI with a pharmacoinvasive approach. In other words, the strategy of primary PCI studied in trials included in our meta-analysis was ideally delivered without prolonged delays beyond guideline recommendations. In a recent post hoc analysis of the STREAM trial it was shown that the longer the delay to revascularization with primary PCI, the more favorably the pharmacoinvasive approach compared with it.[43] Thus, the pharmacoinvasive approach may be an even more attractive option than our results suggest in real-world settings where delays may be more prolonged.

STUDY LIMITATIONS

Our study should be interpreted in the context of the following limitations. First, there are potential sources of heterogeneity between studies that need to be

considered. However, formal evaluation of heterogeneity using the multivariate R did not reveal evidence of significant heterogeneity in our analyses, suggesting that our results are reasonably robust. Second, as with any meta-analysis, we were limited by the quality of the data collected at the level of the individual study. Finally, the limited number of studies between a few of the key reperfusion strategies (eg, no studies compared pharmacoinvasive therapy with facilitated PCI) limited the evidence available from direct comparisons. That said, it is unlikely that such studies will be performed, which makes the explicit comparisons we performed through this meta-analysis even more valuable.

CONCLUSIONS

Primary PCI is the preferred treatment for STEMI. Our findings suggest that when primary PCI is unavailable as a reperfusion therapy, a pharmacoinvasive approach is superior to facilitated PCI or standard fibrinolytic therapy in terms of mortality, stroke, and major bleeding. This information will help guide better design of STEMI systems of care across diverse healthcare systems for this important disease condition.

ARTICLE INFORMATION

Received November 15, 2019; accepted March 11, 2020.

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Sources of Funding

None.

Disclosures

Dr Yeh receives grant support from Abbott Vascular, AstraZeneca, Boston Scientific, and Medtronic and has served as a consultant to Abbott Vascular, AstraZeneca, Boston Scientific and Medtronic.

Supplementary Materials

Tables S1–S9

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of trials included in the meta-analysis.

Trial	Year	n	Trial design	Longest follow up	Fibrinolysis to PCI interval (minutes)	Fibrinolytic*	Glycoprotein IIb/IIIa (as part of treatment protocol)	Endpoint definitions and comments
Primary PCI versus Fibrinolytic Therapy								
PRAGUE**	2000	200	Multicenter, superiority	30	-	SK	Provisional	-**Reinfarction** was defined as recurrence of ischemic symptoms with a rise of at least 2x of CK-MB and/or new ECG changes **Major bleeding** was defined as a fatal bleeding event. -**Stroke** was defined as any new neurological deficit lasting >24 hours.
CAPTIM	2002	840	Multicenter, superiority	30	-	tPA	Provisional	-**Reinfarction** was defined as recurrent chest pain with a rise in CK-MB or troponin over the previous trough value. -**Stroke** had to be confirmed with CT or MRI of the brain. -**Major bleeding** was defined as intracranial hemorrhage, or a bleed causing hemodynamic compromise or requiring transfusion
DANAMI-2	2003	1572	Multicenter, superiority	30	-	tPA	Provisional	-**Reinfarction** was defined as a rise in CK-MB above reference level in patients whose CK-MB had normalized or 50% increase from last non-normalized CK-MB value. -**Major bleeding** was not reported. -**Stroke** was defined as fatal stroke or a stroke causing a clinically significant mental or physicial handicap at 30 days of follow up.
PRAGUE 2	2003	850	Multicenter, superiority	30	-	SK	Provisional	-**Reinfarction** was defined as recurrence of ischemic symptoms with new ECG changes and a rise in CK-MB. -**Major bleeding** was not reported. -**Stroke** was defined as any new neurological deficit lasting >24 hrs.
CPORT	2002	451	Multicenter, superiority	180	-	tPA	Provisional	-**Reinfarction**, within 18 hours of index MI, was defined as recurrence of ischemic symptoms with recurrent ST-segment elevation in at least 2 contiguous leads lasting at ≥30 minutes; and after 18 hours, as appearance of new Q waves, new LBBB, or elevated CK-MB ≥50% greater than the immediately previous value. -**Major bleeding** was defined as any bleed requiring transfusion. -**Stroke** was defined as any new, permanent neurological deficit.
STAT	2001	123	Single center, superiority	42	-	tPA	Provisional	-**Reinfarction** was defined as recurrent ischemic symptoms at rest lasting at least 30 minutes with new or recurrent ST-segment elevation, new LBBB, or re-elevation of CK-MB to at least 2x the upper limit of normal. -**Major bleeding** was defined as a drop of at least 5gm/dL in hemoglobin. -**Stroke** was defined as a focal neurological deficit lasting >24 hours.
TRIANA	2011	266	Multicenter, superiority	365	-	TNK	Provisional	-This trial only included patients ≥75 years of age. -**Reinfarction** was defined, in the first 24 hours after randomization, as recurrence of ischemic symptoms with ST elevation in ≥2 contiguous leads for ≥30 minutes. After the first 24 hours, re-elevation of cardiac enzymes was also required. -**Major bleeding** was defined as intracranial hemorrhage or a drop of >=5gm/dL in hemoglobin or >=15% in hematocrit. -**Stroke** was defined as new permanent focal or generalized neurologic symptoms affecting the normal life of a patient associated with abnormal CT or MRI of the brain.
Zwolle-elderly	2002	87	Single center, superiority	30	-	SK	Provisional	-This trial only included patients ≥75 years of age. -**Reinfarction** was defined as chest pain, changes in the ST-segment and a second increase in CK to >2x upper limit of normal or an increase of >200 U/l over previous value if it had not normalized. -**Stroke** and **major bleeding** definitions were not specified.
STOPAMI	2000	140	Multicenter, superiority	30	-	tPA	Abciximab (PPCI)	-**Reinfarction** was defined as typical chest pain, new ST-segment changes, and an increase in CK of ≥50% over the trough level measured in at least 2 samples in which levels were ≥240 U/l -**Major bleeding** was defined as any bleeding causing hemodynamic compromise or requiring transfusion. -**Stroke** had to be confirmed with CT or MRI of brain.
STOPAMI-2	2002	162	Multicenter, superiority	30	-	tPA	Abciximab (all)	-**Reinfarction** was defined as typical chest pain, new ST-segment changes, and a rise in CK of at least 50% previous trough value in at least 2 samples reaching ≥240 U/l.

								-**Major bleeding** was defined as intracranial hemorrhage or bleeding causing hemodynamic compromise or requiring transfusion. -**Stroke** had to be confirmed with CT or MRI of brain
SWEDES	2006	205	Multicenter, superiority	30	-	rPA	Abciximab (PPCI)	-**Reinfarction** was defined as two of the following: typical chest pain, development of Q waves, and elevation of cardiac enzymes greater than normal. -**Stroke** was defined as a new neurological deficit with confirmation by CT or MRI of the brain.
Bialystok	2007	401	Multicenter, superiority	365	-	SK	Tirofiban (PPCI)	-**Reinfarction** was defined as a new increase in CK of at least 50% of the prior value or of more than 2x upper limit of normal, with new ECG changes and/or recurrence of chest pain. -**Major Bleeding** was defined based on TIMI criteria. Only in-hospital bleeding was reported (not 30 day). -**Stroke** was defined as any new neurological deficit lasting >24 hours with confirmation by CT imaging.
WEST**	2006	200	Multicenter, superiority	30	-	TNK	Abciximab (PPCI)	-**Reinfarction** was defined as follows: within first 18 hrs after randomization- recurrence of ischemic symptoms at rest with new or recurrent ST-segment elevations; after 18 hrs- new Q waves in ≥2 leads and/or increase in CK-MB or troponin above upper limit of normal and >50% over the previous value -**Major bleeding** was defined as bleeding causing hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or CPR to maintain sufficient cardiac output. -**Stroke** definition was not specified.
HIS	2006	48	Multicenter, superiority	365	-	Fibrin-specific	Abciximab (PPCI)	-Trial was stopped prematurely due to slow enrollment -**Reinfarction**, within 18 hours, was defined as recurrent ischemic discomfort ≥30 minutes and new or recurrent ST-segment elevation ≥0.1 mV. After 18 hours, a criterion of reelevation of CK-MB to above the upper limit of normal and increased by ≥50% over the previous value was also required. -**Major bleeding** was defined based on the TIMI criteria as overt bleeding associated with an absolute decrease in hematocrit ≥15% or a decrease in hemoglobin of ≥5 g/dL, or any intracranial or retroperitoneal bleed.
Pharmacoinvasive Approach and Facilitated PCI versus Fibrinolytic Therapy								
WEST**	2006	204	Multicenter, superiority	30	295	TNK		-**Reinfarction** was defined as follows: within first 18 hrs after randomization- recurrence of ischemic symptoms at rest with new or recurrent ST-segment elevations; after 18 hrs- new Q waves in ≥ 2 leads and/or increase in CK-MB or troponin above upper limit of normal and >50% over the previous value -**Major bleeding** was defined as bleeding causing hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or CPR to maintain sufficient cardiac output. -**Stroke** definition was not specified.
CAPITAL AMI	2005	170	Multicenter, superiority	180	90	TNK	Provisional	-**Reinfarction** was defined as recurrent ischemic symptoms at rest lasting ≥30 minutes with new or recurrent ST-segment changes, new LBBB, or re-elevation of CK level to more than 2x the upper limit of normal and ≥50% above the lowest level measured after infarction. -**Major bleeding** was defined based on TIMI criteria. In-hospital bleeding was reported only (not 30 day) -**Stroke** was defined as a focal neurological deficit lasting >24 hours
GRACIA 1	2004	499	Multicenter, superiority	365	1002	fibrin-specific	Provisional	-**Reinfarction** was defined as typical chest pain lasting >30 minutes with a new rise in CK-MB with or without new ECG abnormalities. Within 48 hrs of index MI, CK-MB had to rise during the descendent phase to at least 150% of last measurement. After 48 hours, CK-MB had to reach at least 3x the upper limit of normal. -**Major bleeding** was defined as bleeding causing death, need for surgery or transfusion, or extended time in hospital. -**Stroke** definition was not specified.
SIAM 3	2003	163	Multicenter, superiority	180	210	rPA	Provisional	-**Reinfarction** was defined as at least 2 of the following: chest pain for ≥30 minutes, new significant ST-elevation, and rise in CK level to >3x the upper limit of normal. -**Major bleeding** included need for transfusion, surgery, or intracerebral, ocular, retroperitoneal, abdominal, intestinal, urogenital, or drop of >4g% within 72 hours of treatment. -**Stroke** definition was not specified.
PRAGUE**	2000	199	Multicenter, superiority	365	68	SK	Provisional	-**Reinfarction** was defined as recurrence of ischemic symptoms with a rise of at least 2x of CK-MB and/or new ECG changes **Major bleeding** was defined as a fatal bleeding event. -**Stroke** was defined as any new neurological deficit lasting >24 hours.

TRANSFER AMI	2009	1059	Multicenter, superiority	180	234	TNK	Provisional	-**Reinfarction** was defined as recurrence of ST-segment elevation and chest pain lasting for at least 30 minutes during the first 18 hours. After 18 hours, the diagnosis required a rise in CK-MB up to 3 times the upper limit of normal or new Q waves -**Major bleeding** was defined based on TIMI criteria -**Stroke**- only intracranial hemorrhage was reported.
Leipzig	2005	164	Multicenter, superiority	30	84	rPA (half-dose)	Abxiximab (all)	-**Reinfarction** was defined based on clinical symptoms, new ST-segment changes, and rise in CK-MB above reference level in patients with normalized values after index event or an increase of 50% or more from the last non-normalized measurement. -**Major bleeding** was defined as bleeding causing hemodynamic compromise or requiring transfusion. -**Stroke** was defined as a fatal stroke or stroke causing significant mental or physicial handicap.
NORDISTEMI	2009	266	Multicenter, superiority	365	163	TNK	Provisional	-**Reinfarction** was defined- during the first 18 hours- as recurrent symptoms at rest with new ST-segment elevations lasting at least 30 minutes. After 18 hours, it was defined as new Q waves in 2 or more leads or new increase in cardiac enzymes 3x above the upper limit of normal and >50% higher than the previous value. -**Major bleeding** was defined based on the GUSTO criteria. -**Stroke** was defined as a new focal, neurological deficit of vascular origin lasting more than 24 hours.
CARESS-in-AMI	2008	598	Multicenter, superiority	30	135	rPA (half-dose)	Abciximab (all)	-**Reinfarction** was defined as recurrent symptoms or signs of myocardial infarction lasting more than 30 minutes with new Q-wave or ST-segment changes, or new LBBB and significant rise in CK-MB (after at least a 25% decrease in CK-MB, a more than 2x the upper limit of normal in the absence of PCI or more than 3x the upper limit after PCI) -**Major bleeding** was defined as intracranial, retroperitoneal or ocular bleeds, requiring transfusion or >=50 g/L drop in hemoglobin. -**Stroke** definition was not specified.
Pharmacoinvasive Approach and Facilitated PCI versus Primary PCI								
WEST**	2006	204	Multicenter, superiority	30	295	TNK	Abciximab (PPCI)	-**Reinfarction** was defined as follows: within first 18 hrs after randomization- recurrence of ischemic symptoms at rest with new or recurrent ST-segment elevations; after 18 hrs- new Q waves in >= 2 leads and/or increase in CK-MB or troponin above upper limit of normal and >50% over the previous value -**Major bleeding** was defined as bleeding causing hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or CPR to maintain sufficient cardiac output. -**Stroke** definition not specified.
ASSENT-4	2006	1667	Multicenter, superiority	90	104	TNK	Provisional	-Study was terminated early due to evidence of harm with facilitated PCI. -**Reinfarction**, during the first 18 hours, was defined as recurrent ischemic symptoms with new or recurrent ST-segment elevations for at least 30 min. After 18 hours, the definition was new Q waves in ≥2 leads or further increases in cardiac enzymes above the upper limit of normal and higher than the previous value. -**Stroke** definition not specified. -**Major bleeding** defined as that requiring transfusion or intervention due to hemodynamic compromise
PRAGUE**	2000	201	Multicenter, superiority	30	68	SK		-**Reinfarction** was defined as recurrence of ischemic symptoms with a rise of ≥2x of CK-MB and/or new ECG changes **Major bleeding** was defined as a fatal bleeding event. -**Stroke** was defined as any new neurological deficit lasting >24 hours.
GRACIA-2	2007	212	Multicenter, superiority	180	276	TNK	Abciximab (PPCI)	-**Reinfarction** was defined as typical chest pain lasting >30 minutes with a new rise in CK-MB with or without new ECG abnormalities. Within 48 hrs of index MI, CK-MB had rise during the descendent phase to at least 150% of last measurement. After 48 hours, CK-MB had to reach at least 3x upper limit of normal. -**Major bleeding** was defined as bleeding causing death, need for surgery or transfusion, or extended time in hospital. -**Stroke** definition was not specified.
LIPSIA-STEMI	2011	158	Multicenter, superiority	30	85	TNK	Provisional	-**Reinfarction** and **stroke** definitions not specified. -**Major bleeding** was defined based on the GUSTO criteria. -gp IIB/IIIa inhibitor used in 29% of facilitated PCI and 88% of primary PCI
STREAM	2013	1892	Multicenter, superiority	30	483	TNK	Provisional	-**Reinfarction**, in the first 18 hours, was defined as recurrent signs and symptoms of ischemia at rest, accompanied by new or recurrent ST-segment elevations lasting ≥ 30 min. After 18 hours, new Q waves in two or more leads and/or enzyme/ biochemical evidence of reinfarction: re-elevation of CK-MB or troponin to above the upper limit of normal and increased by ≥ 50% over the previous value were required. -**Stroke** definition was not specified.

								-**Major bleeding** was defined as that causing hemodynamic compromise requiring intervention or life-threatening or fatal bleeds.
ADVANCE MI	2005	146	Multicenter, superiority	30	84	TNK	Eptifibitide (all)	-Study was terminated early due to slow enrollment -**Reinfarction** was defined as recurrent symptoms or signs of myocardial infarction lasting more than 30 minutes with new Q-wave or ST-segment changes, or new LBBB and significant rise in CK-MB (after at least a 25% decrease in CK-MB, a more than 2x the upper limit of normal in the absence of PCI or more than 3x the upper limit after PCI). -**Major bleeding** was defined based on TIMI criteria.
FINESSE	2008	1634	Multicenter, superiority	90	90	rPA	Abciximab (facilitated PCI)	-Study terminated early due to slow enrollment . -**Major bleeding** was defined based on TIMI criteria. Bleeding endpoint is in-hospital only (not 30 day).
BRAVE	2004	253	Multicenter, superiority	180	125	rPA	Abciximab (all)	-**Reinfarction** was defined based on the presence of at least two of the following: typical angina, new ST-segment changes, and a rise in CK-MB of at least 50% more than the previous trough level in at least two samples reaching at least 3x the upper limit of normal. -**Stroke**: the diagnosis of hemorrhagic stroke required confirmation by CT or MRI of the brain. -**Major bleeding** was defined as intracranial hemorrhage or clinically overt signs associated with >5g/dL drop in hemoglobin
APAMIT	2004	70	Two-center, superiority (pilot study)	180	30-60	tPA	Abciximab (all)	-**Major bleeding** was defined as intracranial hemorrhage or bleed requiring transfusion.
ATAMI	2008	313	Single center, superiority	30	121	tPA	Tirofiban (PPCI)	-**Major bleeding** was defined based on the GUSTO criteria.
EARLY MYO	2017	344	multicenter, randomized, noninferiority	30	464	tPA (half-dose)	Provisional	-**Major bleeding** was defined based on the GUSTO criteria.

***** SK denotes streptokinase, tPA alteplase, TNK tenecteplase, and rPA reteplase.
****** WEST and PRAGUE both had three treatment arms.

Results of sensitivity analysis using longest available follow up of trials

Table S2. Multivariate network meta-analysis results.

Outcome	Fibrinolytic therapy	Primary PCI		Pharmacoinvasive approach		Faciliated PCI		Multivariate R Statistic	No. of trials
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value		
Death	Reference	0.75 (0.62 – 0.90)	0.003	0.76 (0.57 – 1.00)	0.05	0.91 (0.67 – 1.25)	0.57	1.00	31
Reinfarction	Reference	0.39 (0.31 – 0.51)	<0.001	0.54 (0.39 – 0.74)	<0.001	0·55 (0.38 – 0.79)	0.001	0.99	31
Stroke	Reference	0.39 (0.25 – 0.61)	<0.001	0.70 (0.39 – 1.26)	0.23	0.75 (0.35 – 1.60)	0.46	1.00	30
Major Bleeding	Reference	1.05 (0.73 – 1.50)	0.79	1.19 (0.83 – 1.73)	0.34	1.52 (0.95 – 2.45)	0.08	1.24	26

Table S3. Results of the Bayesian model to estimate probability of maximum risk.

Outcome	Fibrinolytic therapy	Primary PCI	Pharmacoinvasive approach	Facilitated PCI	No. of trials
Death	70.2 %	0.0 %	2.3 %	27.5 %	31
Reinfarction	99.9 %	0.0 %	0.1 %	0.0 %	31
Stroke	70.3 %	0.0 %	10.2 %	19.5 %	30
Major bleeding	1.1 %	0.9 %	17.6 %	80.1 %	26

These results estimate the probability that each treatment approach is associated with maximum risk of each adverse outcome relative to the other treatments.

Sensitivity analysis using 3 hour threshold for thrombolysis to PCI interval to define facilitated PCI versus a pharmacoinvasive approach.

Table S4. Multivariate network meta-analysis results.

Outcome	Fibrinolytic therapy	Primary PCI		Pharmacoinvasive approach		Faciliated PCI		Multivariate R Statistic	No. of trials
		OR (95% CI)	P-	OR (95% CI)	P-value	OR (95% CI)	P-value		
Death	Reference	0.73 (0.60 – 0.88)	0.001	0.81 (0.58 – 1.13)	0.22	0.87 (0.65 – 1.16)	0.35	1.00	31
Reinfarction	Reference	0.53 (0.36 – 0.78)	<0.001	0.52 (0.36 – 0.74)	0.001	0.51 (0.36 – 0.74)	<0.001	1.00	31
Stroke	Reference	0.38 (0.24 – 0.60)	<0.001	0.75 (0.36 – 1.57)	0.44	0.67 (0.36 – 1.26)	0.23	1.00	30
Major Bleeding	Reference	1.02 (0.72 – 1.46)	0.8	1.12 (0.74 – 1.68)	0.54	1.51 (0.98 – 2.31)	0.06	1.26	26

Table S5. Results of the Bayesian model to estimate probability of maximum risk. These results estimate the probability that each treatment approach is associated with maximum risk of each adverse outcome relative to the other treatments.

Outcome	Fibrinolytic therapy	Primary PCI	Pharmacoinvasive approach	Facilitated PCI	No. of trials
Death	75.0 %	0.0 %	10.2 %	14.8 %	31
Reinfarction	99.8 %	0.0 %	0.2 %	0.0 %	31
Stroke	71.4 %	0.0 %	20.6 %	8.0 %	30
Major bleeding	1.0 %	0.9 %	13.1 %	85.0 %	26

Sensitivity analysis removing the ASSENT4 Trial from the meta-analysis

Table S6. Multivariate network meta-analysis results.

Outcome	Fibrinolytic therapy	Primary PCI		Pharmacoinvasive approach		Faciliated PCI		Multivariate R Statistic	No. of trials
		OR (95% CI)	P-	OR (95% CI)	P-value	OR (95% CI)	P-value		
Death	Reference	0.74 (0.61 – 0.90)	0.003	0.80 (0.59 – 1.08)	0.147	0.84 (0.57 – 1.22)	0.35	1.00	30
Reinfarction	Reference	0.39 (0.30 – 0.51)	<0.001	0.53 (0.37 – 0.76)	0.001	0.44 (0.28 – 0.69)	<0.001	1.00	30
Stroke	Reference	0.39 (0.25 – 0.62)	<0.001	0.71 (0.39 – 1.30)	0.27	0.53 (0.24 – 1.18)	0.12	1.00	29
Major Bleeding	Reference	1.02 (0.70 – 1.49)	0.9	1.19 (0.80 – 1.77)	0.38	1.59 (0.91 – 2.79)	0.10	1.29	25

Table S7. Results of the Bayesian model to estimate probability of maximum risk.

Outcome	Fibrinolytic therapy	Primary PCI	Pharmacoinvasive approach	Facilitated PCI	No. of trials
Death	78.0 %	0.1 %	6.6 %	15.3 %	30
Reinfarction	99.9 %	0.0 %	0.1 %	0.0 %	30
Stroke	81.0 %	0.0 %	13.4 %	5.6 %	29
Major bleeding	1.5 %	1.8 %	16.9 %	79.8 %	25

These results estimate the probability that each treatment approach is associated with maximum risk of each adverse outcome relative to the other treatments.

Sensitivity analysis removing the STREAM Trial from the meta-analysis

Table S8. Multivariate network meta-analysis results.

Outcome	Fibrinolytic therapy	Primary PCI		Pharmacoinvasive approach		Faciliated PCI		Multivariate R Statistic	No. of trials
		OR (95% CI)	P-	OR (95% CI)	P-value	OR (95% CI)	P-value		
Death	Reference	0.73 (0.59 – 0.89)	0.002	0.83 (0.59 – 1.21)	0.33	0.90 (0.64 – 1.23)	0.50	1.00	30
Reinfarction	Reference	0.37 (0.28 – 0.49)	<0.001	0.58 (0.39 – 0.88)	0.011	0.50 (0.34 – 0.74)	<0.001	1.00	30
Stroke	Reference	0.42 (0.26 – 0.67)	<0.001	0.56 (0.28 – 1.13)	0.11	0.76 (0.35 – 1.65)	0.5	1.00	29
Major Bleeding	Reference	1.11 (0.74 – 1.67)	0.6	1.10 (0.71 – 1.71)	0.6	1.60 (0.96 – 2.66)	0.07	1.23	25

Table S9. Results of the Bayesian model to estimate probability of maximum risk.

Outcome	Fibrinolytic therapy	Primary PCI	Pharmacoinvasive approach	Facilitated PCI	No. of trials
Death	63.8 %	0.0 %	14.4 %	21.8 %	30
Reinfarction	99.2 %	0.0 %	0.8 %	0.0 %	30
Stroke	72.5 %	0.0 %	4.9 %	22.6 %	29
Major bleeding	0.8 %	1.6 %	12.8 %	84.8 %	25

These results estimate the probability that each treatment approach is associated with maximum risk of each adverse outcome relative to the other treatments.