Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis

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Summary

Background Fibrinolytic therapy offers an alternative to mechanical reperfusion for ST-segment elevation myocardial infarction (STEMI) in settings where health-care resources are scarce. Comprehensive evidence comparing different agents is still unavailable. In this study, we examined the effects of various fibrinolytic drugs on clinical outcomes.

Methods We did a network meta-analysis based on a systematic review of randomised controlled trials comparing fibrinolytic drugs in patients with STEMI. Several databases were searched from inception up to Feb 28, 2017. We included only randomised controlled trials that compared fibrinolytic agents as a reperfusion therapy in adult patients with STEMI, whether given alone or in combination with adjunctive antithrombotic therapy, against other fibrinolytic agents, a placebo, or no treatment. Only trials investigating agents with an approved indication of reperfusion therapy in STEMI (streptokinase, tenecteplase, alteplase, and reteplase) were included. The primary efficacy outcome was all-cause mortality within 30–35 days and the primary safety outcome was major bleeding. This study is registered with PROSPERO (CRD42016042131).

Findings A total of 40 eligible studies involving 128 071 patients treated with 12 different fibrinolytic regimens were assessed. Compared with accelerated infusion of alteplase with parenteral anticoagulants as background therapy, streptokinase and non-accelerated infusion of alteplase were significantly associated with an increased risk of all-cause mortality (risk ratio [RR] 1·14 [95% CI 1·05–1·24] for streptokinase plus parenteral anticoagulants; RR 1·26 [1·10–1·45] for non-accelerated alteplase plus parenteral anticoagulants). No significant difference in mortality risk was recorded between accelerated infusion of alteplase, tenecteplase, and reteplase with parenteral anticoagulants as background therapy. For major bleeding, a tenecteplase-based regimen tended to be associated with lower risk of bleeding compared with other regimens (RR 0·79 [95% CI 0·63–1·00]). The addition of glycoprotein IIb or IIIa inhibitors to fibrinolytic therapy increased the risk of major bleeding by 1·27–8·82-times compared with accelerated infusion alteplase plus parenteral anticoagulants (RR 1·47 [95% CI 1·10–1·98] for tenecteplase plus parenteral anticoagulants plus glycoprotein inhibitors; RR 1·88 [1·24–2·86] for reteplase plus parenteral anticoagulants plus glycoprotein inhibitors).

Interpretation Significant differences exist among various fibrinolytic regimens as reperfusion therapy in STEMI and alteplase (accelerated infusion), tenecteplase, and reteplase should be considered over streptokinase and non-accelerated infusion of alteplase. The addition of glycoprotein IIb or IIIa inhibitors to fibrinolytic therapy should be discouraged.

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Introduction

The global incidence of acute myocardial infarction is estimated to have reached 8·5 million in 2013.[1] Although primary percutaneous coronary intervention is the preferred treatment option[2,3] for ST-segment elevation myocardial infarction (STEMI), the value of fibrinolytic therapy should not be overlooked in situations where primary percutaneous coronary intervention is not available or cannot be delivered in the appropriate time-frame. Several fibrinolytic agents have been shown to achieve a satisfactory infarct-related artery patency rate when delivered in a timely manner.[2–5]

The ACCESS registry[6] conducted in 19 developing countries reported that only 20% of patients with STEMI received primary percutaneous coronary intervention. Moreover, the pharmaco-invasive approach,[2] which has been become increasingly popular since 2010 in some logistically challenged settings in developed countries,[7–9] also relies on early fibrinolysis before accessing angiography and percutaneous coronary intervention. Thus, fibrinolytic therapy clearly remains an important part of modern STEMI management.

Despite the value of fibrinolytic therapy as an important alternative to mechanical reperfusion, comprehensive

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Research in context

Evidence before this study

Because of the low number of hospitals worldwide capable of providing percutaneous coronary intervention and the high cost of treatment, reperfusion therapy with fibrinolytic agents might be an optimum option for patients with ST-segment elevation myocardial infarction (STEMI) who cannot undergo percutaneous coronary intervention, especially those who live in remote areas or in low-income and middle-income countries. We searched PubMed from inception to June 30, 2016, for previously published systematic reviews and meta-analyses on reperfusion therapy with fibrinolytic agents in adult patients with STEMI by using the following search terms: "fibrinolytic", "thrombolytic", and "acute coronary syndrome". A previously published conventional pairwise meta-analysis by Dundar and colleagues in 2003 was not able to establish a clear hierarchy of efficacy and safety among available treatments because of an absence of direct comparison evidence.

Added value of this study

Our findings provide the most comprehensive evidence of reperfusion therapy with fibrinolytic agents in patients with STEMI and include new data from a study in three Asian countries. Heterogeneity of the bleeding definition between each trial was matched according to the Bleeding Academic Research Consortium bleeding criteria, which is a current standardised hierarchical bleeding classification system. Our results clearly show that the use of fibrin-specific fibrinolytics (accelerated infusion of alteplase, tenecteplase, and reteplase) with parenteral anticoagulants was the most effective regimen with an acceptable risk of major bleeding compared with streptokinase and non-accelerated infusion of alteplase. The addition of glycoprotein IIb or IIIa inhibitors might be undesirable in view of the significant increase in bleeding risk despite the potential added benefit of mortality reduction.

Implications of all the available evidence

Our findings have several potential implications for clinical practice. First, our results suggest that reperfusion therapy with fibrin-specific fibrinolytics (accelerated infusion of alteplase, tenecteplase, and reteplase) in combination with parenteral anticoagulants is the optimum treatment regimen for patients who cannot access a hospital capable of percutaneous coronary intervention in a timely fashion. Streptokinase seems to be slightly less effective in terms of mortality outcome. However, additional information such as cost-effectiveness and consideration of antigenicity will need to be taken into account when formulating a treatment strategy. Second, the addition of glycoprotein IIb or IIIa inhibitors to a standard fibrinolytic regimen should be discouraged because the associated major bleeding risk outweighs any possible mortality benefit. Existing clinical practice guidelines do not support the use of this additional treatment. For patients who plan to undergo a pharmacoinvasive strategy (administration of fibrinolytic therapy either in the prehospital setting or at a hospital not able to provide percutanous coronary intervention, followed by immediate transfer to a percutanous coronary intervention-capable hospital for early coronary angiography and percutanous coronary intervention when appropriate), routine administration of glycoprotein inhibitors before percutanous coronary intervention should be considered carefully in view of the increased risk of major bleeding. Finally, it is important to note that reduced doses of fibrinolytic agents and agents associated with a lower bleeding risk, such as tenecteplase, were used in most of the trials investigating a pharmacoinvasive strategy. Findings derived from this study might not be directly inferable to the treatment strategy for these patients without extrapolating beyond the original data.

evidence comparing different fibrinolytic agents is still scarce. Previous reviews and meta-analyses have focused only on pairwise comparison of various fibrinolytic agents.[10,11] This study uses the available data in a network meta-analysis approach to examine the effects of various fibrinolytic agents on clinical outcomes in patients with STEMI.

Methods

Search strategy and selection criteria

See Online for appendix

This study is registered with PROSPERO[12] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis.[13]

We searched PubMed, Embase, the Cochrane Library, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) from inception of each of these databases up until Feb 28, 2017. We included only randomised controlled trials that compared fibrinolytic agents as a reperfusion therapy in adult patients with STEMI, whether given alone or in combination with adjunctive antithrombotic therapy, against other fibrinolytic agents, a placebo, or no treatment. Only trials investigating agents with an approved indication of reperfusion therapy in STEMI (streptokinase, tenecteplase, alteplase, and reteplase) were included. Studies assessing facilitated percutaneous coronary intervention (percutaneous coronary intervention after fibrinolysis) or primary percutaneous coronary intervention versus fibrinolytic therapy were excluded. Reference lists of relevant studies were also screened. Details of methods and the search strategies are described in the appendix (pp 4–10).

Data extraction and quality assessment

Two authors (PJ and JK) independently screened the titles and abstracts of retrieved citations to identify potentially relevant studies. The full articles were evaluated if a decision could not be made based on the titles and abstracts. Relevant data were abstracted by the same two reviewers (PJ and JK) using a standardised extraction form. The extracted data included study characteristics, patient characteristics, interventions, outcomes, and other

relevant findings. The Cochrane Collaboration's risk of bias assessment tool[14] was used to assess risk of bias. All extracted data were cross-checked by two other reviewers (CYF and NC) and any discrepancies were resolved by consensus.

Type of interventions

Fibrinolytic agents were streptokinase, tenecteplase, reteplase, and alteplase. Since two alteplase regimens are approved by the US Food and Drug Administration,[15] we categorised them into two groups: accelerated and non-accelerated infusion of alteplase. Other adjunctive antithrombotic therapies were parenteral anticoagulants (unfractionated heparin, low-molecular-weight heparin, anti Xa inhibitors, and direct thrombin inhibitors), glycoprotein IIb or IIIa inhibitors (abciximab, tirofiban, and eptifibatide), and antiplatelets (aspirin, clopidogrel, and ticlopidine). Details of interventions are described in the appendix (pp 12–53).

Outcomes

The primary efficacy outcome of interest was all-cause mortality within 30–35 days and the primary safety outcome of interest was major bleeding. Major bleeding was defined according to Bleeding Academic Research Consortium (BARC) type 3a, 3b, or 3c (appendix pp 4–7).[16] Secondary outcomes were recurrent infarction, stroke, haemorrhagic stroke, death from cardiovascular causes, and combined cardiovascular outcomes.

Quality of evidence

The quality of evidence from direct and network meta-analysis was assessed by using GRADEpro GDT software online version (GRADE Working Group, McMaster University, Hamilton, ON, Canada).[17] There were four levels of quality of evidence: high, moderate, low, and very low.[18,19] Details about grading of the quality of evidence are presented in the appendix (pp 80–93). The quality of evidence for each outcome was based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Data synthesis and statistical analysis

The relative intervention effects (ie, risk ratio [RR]) were estimated for individual studies. A direct meta-analysis was used to pool RRs using a random-effects model.[20] Heterogeneity was assessed using the Cochran *Q* test and the I^2 statistic.[21] A network meta-analysis with consistency model was applied to compare all interventions using direct and indirect data.[22,23] Accelerated infusion alteplase with parenteral anticoagulants was used as the common comparator in the network model. Inconsistency assumption—the level of disagreement between direct and indirect estimates—was evaluated using global inconsistency test by fitting design-by-treatment in the inconsistency model.[24] To rank the intervention hierarchy in the network meta-analysis, the rankograms, surface under the cumulative ranking (SUCRA) curves,[25] and mean ranks were estimated. The comparison-adjusted funnel plot was used to analyse publication bias.[26]

Prespecified subgroup analyses were done for primary outcomes according to predictors of increased bleeding risk such as elderly age (age >65 years), Asian ethnicity, female sex, and patients with renal impairment (appendix pp 1–7). Prespecified sensitivity analyses were done for the primary outcomes by restricting analyses to trials with the following characteristics: inclusion of aspirin in treatment protocol, bleeding definition compatible with BARC type 3b or 3c,[16] and time to receive fibrinolytics within 4 h or within 6 h. Other sensitivity analyses included omission of small trials (<25th percentiles),[27] trials done in China (due to concerns about fabrication of data),[28] trials with inadequate allocation concealment, and trials with a high risk of bias. Additional sensitivity analyses of net clinical benefit were conducted by varying weighting factors from 0·15 to 0·6 (appendix pp 76–79).

We also did a net clinical benefit analysis of all fibrinolytic regimens in STEMI following the approach used in a previous meta-analysis.[29] We calculated the 30-day mortality prevented by fibrinolytic therapy subtracted by the additional risk of major bleeding, which was multiplied by a weighting factor of 0·15, implying that a single major bleeding event had 15% of the effect of a single mortality. The weighting factor was based on an analysis of six landmark randomised controlled trials[30–35] showing the proportion of deaths in patients with STEMI with major bleeding (appendix pp 76–79).[36]

All analyses were done in Stata version 14.0 using the self-programmed Stata routines for network meta-analysis described elsewhere.[26,37] A two-sided p value of less than 0·05 was regarded as statistically significant.

The study protocol is registered with PROSPERO, number CRD42016042131.[12]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 13728 records, in which 233 potentially eligible articles were reviewed in full text (appendix p 11). Of these articles, 157 were excluded, mostly because of the lack of reporting of the outcomes of interest (n=33 articles), being non-randomised controlled trials (n=24), being irrelevant post-hoc analyses or being a substudy of trials that have already been included (n=56), and other reasons (n=44), leaving 76 eligible studies for inclusion in our review. A total of 40 studies were included in our quantitative analysis since 36 of the 76 eligible studies either assessed fibrinolytic agents and other adjunctive antithrombotic therapies not indicated

	Year	Sample size (n)	Treatment groups (patients, n)	Participants' age, years	ECG findings	Duration from onset of symptoms (h)	Aspirin use	TIMI 3 flow* at 60–90 min after thrombolytics (%)
AMI-SK[38]	2002	496	Streptokinase (n=243) *vs* streptokinase + parenteral anticoagulants (n=253)	≥18	ST elevation	≤12	Yes	Not reported
ASSENT-2[33]	1999	16 949	Tenecteplase + parenteral anticoagulants (n=8461) *vs* alteplase (accelerated) + parenteral anticoagulants (n=8488)	≥18	ST elevation, left bundle branch block	≤6	Yes	Not reported
ASSENT-3[34]	2001	6095	Tenecteplase + parenteral anticoagulants (n=4078) *vs* tenecteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=2017)	≥18	ST elevation, left bundle branch block	≤6	Yes	Not reported
Bleich et al[39]	1990	84	Alteplase (n=42) *vs* alteplase + parenteral anticoagulants (n=42)	NS	ST elevation	≤6	Yes	Not reported
Central Illinois[40]	1993	253	Streptokinase + parenteral anticoagulants (n=130) *vs* alteplase + parenteral anticoagulants (n=123)	≤75	ST elevation	≤4	Yes	Not reported
Cherng et al[41]	1992	122	Streptokinase + parenteral anticoagulants (n=63) *vs* alteplase + parenteral anticoagulants (n=59)	<70	ST elevation	≤6	Yes	Not reported
CORRETA[42]	2004	266	Tenecteplase + parenteral anticoagulants (n=132) *vs* alteplase (accelerated) + parenteral anticoagulants (n=134)	≥18	ST elevation, left bundle branch block	≤6	Yes	Not reported
ECSG-6[43]	1992	644	Alteplase (n=320) *vs* alteplase + parenteral anticoagulants (n=324)	21–70	ST elevation	≤6	Yes	71·0%
ECSG-tPA[44]	1988	721	Parenteral anticoagulants (n=366) *vs* alteplase + parenteral anticoagulants (n=355)	21–71	ST elevation	≤5	Yes	Not reported
ENTIRE-TIMI-23[45]	2002	483	Tenecteplase + parenteral anticoagulants (n=242) *vs* tenecteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=241)	21–75	ST elevation	≤6	Yes	50·7%
GISSI-2/ISG[46,53]	1990	20 768	Streptokinase (n=5205) *vs* streptokinase + parenteral anticoagulants (n=5191) *vs* alteplase (n=5202) *vs* alteplase + parenteral anticoagulants (n=5170)	NS	ST elevation	≤6	Yes	Not reported
GUSTO-I[30]	1993	41 021	Streptokinase + parenteral anticoagulants (n=20 251) *vs* streptokinase + alteplase + parenteral anticoagulants (n= 10 374) *vs* alteplase (accelerated) + parenteral anticoagulants (n=10 396)	NS	ST elevation	<6	Yes	Not reported
GUSTO-III[32]	1997	15 059	Reteplase + parenteral anticoagulants (n=10 138) *vs* alteplase (accelerated) + parenteral anticoagulants (n=4921)	NS	ST elevation, bundle branch block	≤6	Yes	Not reported
GUSTO-V[47]	2001	16 588	Reteplase + parenteral anticoagulants (n=8260) *vs* reteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=8328)	≥18	ST elevation, left bundle branch block	≤6	Yes	Not reported
IMPACT-AMI[48]	1997	48	Alteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=35) *vs* alteplase (accelerated) + parenteral anticoagulants (n=13)	18–75	ST elevation, left bundle branch block	≤6	Yes	67·5%
INJECT[49]	1995	6010	Reteplase + parenteral anticoagulants (n=3004) *vs* streptokinase + parenteral anticoagulants (n=3006)	≥18	ST elevation, bundle branch block	≤12	Yes	Not reported
INTEGRITI[50]	2003	237	Tenecteplase + parenteral anticoagulants (n=118) *vs* tenecteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=119)	18–75	ST elevation	≤6	Yes	54·0%
INTRO AMI[51]	2002	299	Alteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=199) *vs* accelerated alteplase + parenteral anticoagulants (n=100)	>18	ST elevation	≤6	Yes	50·7%
ISAM[52]	1986	1741	Parenteral anticoagulants (n=882) *vs* streptokinase + parenteral anticoagulants (n=859)	≤75	ST elevation	≤6	Yes	Not reported
Janousek et al[54]	1988	57	Parenteral anticoagulants (n=26) *vs* streptokinase + parenteral anticoagulants (n=31)	≤65	ST elevation	≤4	Not reported	Not reported

(Table continues on next page)

by clinical practice guidelines[2,3] or compared treatment regimens regarded as the same in our network meta-analysis. The details of our literature search are reported in the appendix (pp 8–10). The PRISMA flow diagram demonstrating processes of electronic searching is presented in the appendix (p 11).

The 40 studies involving 128 071 patients[30,32–34,38–72] (Boehringer Ingelheim, personal communication) were assessed in the network meta-analysis (table); of these, 20 studies[32–34,38,42,45,47–51,61–65,68–70] (Boehringer Ingelheim, personal communication) were done during 1995–2009 and were mainly done in Europe and North America.

	Year	Sample size (n)	Treatment groups (patients, n)	Participants' age, years	ECG findings	Duration from onset of symptoms (h)	Aspirin use	TIMI 3 flow* at 60–90 min after thrombolytics (%)
(Continued from previous page)								
Kennedy et al[55]	1988	368	Parenteral anticoagulants (n=177) *vs* streptokinase + parenteral anticoagulants (n=191)	≤75	ST elevation	≤6	Not reported	49·4%
LATE[56]	1993	5711	Parenteral anticoagulants (n=2875) *vs* alteplase + parenteral anticoagulants (n=2836)	≥18	ST elevation, bundle branch block	≤24	Yes	Not reported
NCT00148460 (Boehringer Ingelheim, personal communication)	2005	267	Tenecteplase + parenteral anticoagulants (n=130) *vs* alteplase (accelerated) + parenteral anticoagulants (n=137)	18–75	ST elevation	≤6	Yes	60·1%
National Heart Foundation of Australia[57]	1988	144	Parenteral anticoagulants (n=71) *vs* alteplase + parenteral anticoagulants (n=73)	≤75	ST elevation	≤4	Not reported	Not reported
O'Rourke et al[58]	1988	145	Parenteral anticoagulants (n=71) *vs* alteplase + parenteral anticoagulants (n=74)	21–72	ST elevation	<2·5	Yes	Not reported
PAIMS[59]	1989	171	Streptokinase + parenteral anticoagulants (n=85) *vs* alteplase + parenteral anticoagulants (n=86)	20–70	ST elevation	≤3	Not reported	Not reported
RAAMI[60]	1992	281	Alteplase + parenteral anticoagulants (n=138) *vs* alteplase (accelerated) + parenteral anticoagulants (n=143)	Any	ST elevation	<6	Yes	Not reported
RAPID[61]	1995	606	Reteplase + parenteral anticoagulants (n=452) *vs* alteplase + parenteral anticoagulants (n=154)	18–75	ST elevation	≤6	Yes	49·7%
RAPID II[62]	1996	324	Reteplase + parenteral anticoagulants (n=169) *vs* alteplase (accelerated) + parenteral anticoagulants (n=155)	>18	ST elevation, left bundle branch block	≤12	Yes	52·9%
Ronner et al[63]	2000	181	Streptokinase (n=62) *vs* streptokinase + glycoprotein IIb/IIIa inhibitors (n=119)	≥18	ST elevation	≤6	Yes	39·7%
Sarullo et al[64]	2001	120	Alteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=60) *vs* alteplase (accelerated) + parenteral anticoagulants (n=60)	<70	ST elevation	≤6	Yes	Not reported
SPEED[65]	2000	224	Reteplase + parenteral anticoagulants (n=109) *vs* reteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=115)	≥18	ST elevation	≤12	Yes	50·6%
TAMI-3[66]	1989	134	Alteplase (n=70) *vs* alteplase + parenteral anticoagulants (n=64)	<75	ST elevation	≤6	Yes	53·4%
TIMI-1[67]	1987	290	Streptokinase + parenteral anticoagulants (n=147) *vs* alteplase + parenteral anticoagulants (n=143)	≤75	ST elevation	≤7	Yes	Not reported
TIMI-10B[68]	1998	837	Tenecteplase + parenteral anticoagulants (n=526) *vs* alteplase (accelerated) + parenteral anticoagulants (n=311)	<80	ST elevation	≤12	Yes	60·0%
TIMI-14[69]	1999	211	Alteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=139) *vs* alteplase (accelerated) + parenteral anticoagulants (n=72)	18–75	ST elevation	≤12	Yes	70·2%
TIMI-14-reteplase[70]	2000	299	Reteplase + parenteral anticoagulants (n=102) *vs* reteplase + parenteral anticoagulants + glycoprotein IIb/IIIa inhibitors (n=197)	18–75	ST elevation	≤12	Yes	73·3%
White et al[71]	1987	219	Parenteral anticoagulants (n=112) *vs* streptokinase + parenteral anticoagulants (n=107)	<70	ST elevation	<4	Yes	Not reported
White et al[72]	1989	270	Streptokinase + parenteral anticoagulants (n=135) *vs* alteplase + parenteral anticoagulants (n=135)	<70	ST elevation	<3	Yes	Not reported

ECG=electrocardiogram. TIMI=Thrombosis In Myocardial Infarction. ST=ST segment . NS=not specified. *TIMI 3 flow is normal flow that fills the distal coronary bed completely.

Table: **Characteristics of included studies**

Three trials (two published[41,42] and one unpublished [Boehringer Ingelheim, personal communication]) assessed the use of fibrinolytic agents exclusively in Asian patients. The mean age of participants was 58·5 years (SD 3·0). In total, 13·6% of the 128 071 participants had a previous history of myocardial infarction, and 17·2% had a history of previous percutaneous coronary intervention. Fibrinolytic therapy was generally given within 12 h of presentation (mean about 2·9 h [SD 0·6]). Most trials (36 [90%] of 40) clearly specified that aspirin was given as part of treatment. In the 15 studies[43,45,48,50,51,55,61–63,65,66,68–70] (Boehringer Ingelheim, personal communication) that

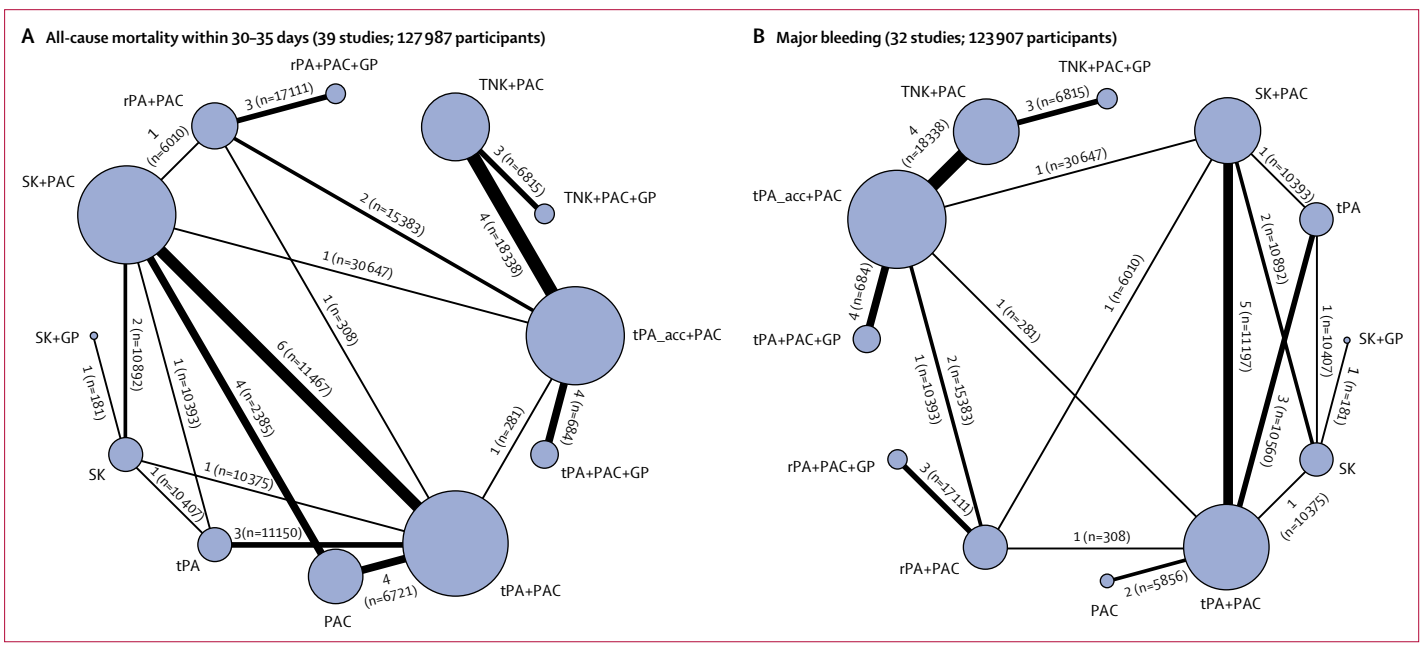

Figure 1: **Network of eligible comparisons for primary efficacy and safety outcomes**
(A) All-cause mortality within 30–35 days. (B) Major bleeding. The size of the node corresponds to the number of individual studies that studied the interventions. The directly compared interventions are linked with a line, the thickness of which corresponds to the number of studies that assessed the comparison. rPA=reteplase. PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. TNK=tenecteplase. SK=streptokinase. tPA=alteplase (non-accelerated infusion). tPA_acc=alteplase (accelerated infusion).

reported angiographic findings, 58·0% of the patients had TIMI 3 flow (complete perfusion) at 60–90 min post-therapy. Other characteristics of the included studies, patients, and treatment protocol are summarised in the appendix (pp 14–53).

Most studies (27 of 40) contained an unclear risk of bias (appendix pp 54–57). None of them had evidence of a definite high risk of bias in terms of random sequence generation, allocation concealment, and incomplete outcome data. Of the 40 included studies, high risk of bias was found in masking of participants and personnel in six studies,[46,53,54,59,62,66] masking of outcome assessment in one,[72] selective outcome reporting areas in two,[58,64] and other bias in six.[40,62,65,66,69,71]

Network diagrams of all the eligible comparisons for the primary and secondary outcomes are presented in figure 1. The 12 treatment regimens included in the network diagram are parenteral anticoagulants, streptokinase, streptokinase plus glycoprotein IIb or IIIa inhibitors, streptokinase plus parenteral anticoagulants, tenecteplase plus parenteral anticoagulants, tenecteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors, reteplase plus parenteral anticoagulants, reteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors, non-accelerated infusion alteplase, non-accelerated infusion alteplase plus parenteral anticoagulants, alteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors, and accelerated infusion alteplase plus parenteral anticoagulants.

Details of all comparators are presented in the appendix (pp 12–13) and network maps are presented in the appendix (p 59). Treatment effects estimated using direct meta-analysis are also presented in the appendix (pp 61–63), without evidence of statistical heterogeneity, except in three pairwise comparisons (accelerated alteplase plus parenteral anticoagulants *vs* reteplase plus parenteral anticoagulants for the outcome of all-cause mortality within 30–35 days; streptokinase plus parenteral anticoagulants *vs* streptokinase for recurrent infarcation; and streptokinase plus parenteral anticoagulants *vs* streptokinase for any type of stroke). Comparisons among all treatment options for all outcomes are presented in the appendix (pp 64–69). 11 regimens were compared against the accelerated infusion alteplase plus parenteral anticoagulants as a standard treatment according to recommendations from guidelines.[2,3]

39 studies involving 127 987 participants[30,32–34,38,40–72] (Boehringer Ingelheim, personal communication) assessed all-cause mortality across 12 different fibrinolytic regimens and 32 studies involving 123 907 participants[30,32–34,38–42,45–51,53,56,58–70] (Boehringer Ingelheim, personal communication) evaluated major bleeding across these 12 regimens (figure 1). Figure 2 shows the full findings of our network meta-analysis for the primary efficacy and safety outcomes. Our analysis showed that conventional regimens (streptokinase plus parenteral anticoagulants and non-accelerated infusion alteplase plus parenteral anticoagulants) were associated with a significantly increased risk of all-cause mortality (RR 1·14 [95% CI 1·05–1·24] for streptokinase

plus parenteral anticoagulants, and 1·26 [1·10–1·45] for non-accelerated infusion alteplase plus parenteral anticoagulants), compared with accelerated infusion alteplase plus parenteral anticoagulants (figure 2A). In other words, accelerated infusion alteplase plus parenteral anticoagulants reduced the risk of mortality by 0·79 (95% CI 0·69–0·91) compared with streptokinase and parenteral anticoagulants, and by 0·88 (0·81–0·95) compared with non-accelerated infusion alteplase plus parenteral anticoagulants. No significant difference in mortality risk was recorded between accelerated infusion of alteplase, tenecteplase, and reteplase with parenteral anticoagulants as background therapy.

However, two conventional regimens (streptokinase plus parenteral anticoagulants and non-accelerated infusion alteplase plus parenteral anticoagulants) were associated with a lower risk of bleeding than accelerated infusion alteplase plus parenteral anticoagulants (risk of bleeding lowered by 0·92 [95% CI 0·70–1·21] with streptokinase plus parenteral anticoagulants and by 0·63 [0·44–0·92] with non-accelerated infusion alteplase plus parenteral anticoagulants; figure 2B). Furthermore, the addition of glycoprotein IIb or IIIa inhibitors significantly increased the risk of major bleeding as evidenced in some regimens (eg, RR 1·47 [95% CI 1·10–1·98] for tenecteplase plus parenteral anticoagulants plus glycoprotein inhibitors; RR 1·88 [1·24–2·86] for reteplase plus parenteral anticoagulants plus glycoprotein inhibitors; figure 2B). Across all fibrin-specific fibrinolytic agents (alteplase, reteplase, and tenecteplase), the relative efficacy was similar, but tenecteplase plus parenteral anticoagulants seemed to have the lowest risk of bleeding (RR 0·79 [95% CI 0·63–1·00] *vs* RR 0·88 [0·69–1·12] for reteplase plus parenteral anticoagulants). Overall results of the network meta-analysis of primary efficacy and safety outcomes are presented in figure 3.

The cluster rank plot (figure 4) shows that tenecteplase plus parenteral anticoagulants is the regimen associated not only with the lowest risks of all-cause mortality within 30–35 days but also major bleeding. SUCRAs are provided in the appendix (pp 70–75).

A global inconsistency test was performed and suggested no evidence of inconsistency of treatment effects for all-cause mortality within 30–35 days and major bleeding (appendix p 60).

The estimated RRs comparing all fibrinolytic regimens for secondary outcomes are presented in figure 5. Although the outcome definitions varied across studies for recurrent infarction (37 studies, 127 239 participants[30,32–34,38,39,41–54,56–68,70–72] [Boehringer Ingelheim, personal communication]) and stroke (21 studies, 121 911 participants[30,32–34,38,40,44,46–49,53,56,57,60–63,65,68] [Boehringer Ingelheim, personal communication]), our analysis showed that most agents carry similar risks except for reteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors which had a significantly reduced risk for recurrent infarction (RR 0·63 [95% CI 0·49–0·80]), as did tenecteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors for recurrent infarction (0·68 [0·47–0·97]). Streptokinase plus parenteral anticoagulants was associated with the lowest risk of haemorrhagic stroke (33 studies, 126 744 participants[30,32–34,38,40–49,51–53,56–58,60–63,65,66,68–72] [Boehringer Ingelheim, personal communication]) with RR 0·69 (95% CI 0·53–0·91). Analyses of death from cardiovascular causes and combined cardiovascular outcomes were attempted but there were inadequate data to perform these prespecified analyses.

The net clinical benefit analysis comparing benefit in reducing mortality and risks of major bleeding of various fibrinolytic therapy regimens showed that the net clinical benefit value ranged from –4·422% to 1·496% for the different regimens (appendix p 78). The non-accelerated alteplase plus parenteral anticoagulants plus

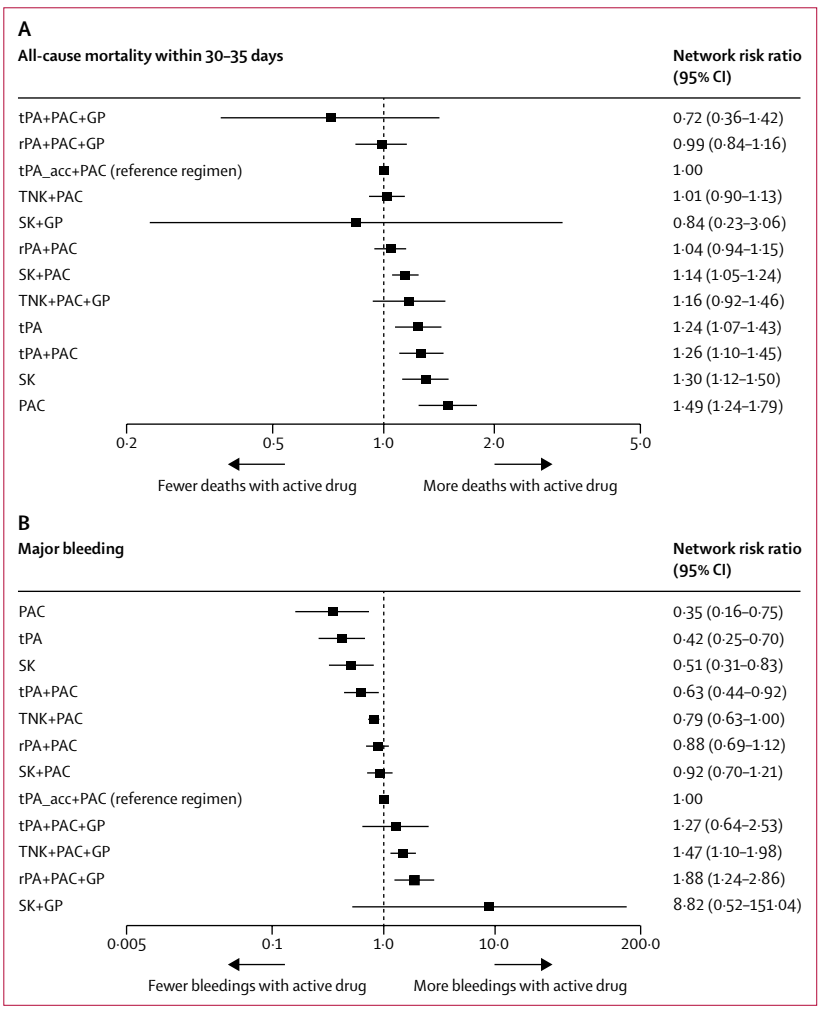

Figure 2: **Network meta-analysis of reperfusion therapy with fibrinolytic drugs compared with accelerated infusion alteplase plus parenteral anticoagulants for primary efficacy and safety outcomes**
(A) All-cause mortality within 30–35 days. (B) Major bleeding. Summary estimates represent risk ratio (95% CI) of all-cause mortality within 30–35 days and major bleeding. Interventions are ranked by Surface Under the Cumulative RAnking curve values. tPA=alteplase (non-accelerated infusion). PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. tPA_acc=alteplase (accelerated infusion). rPA=reteplase. TNK=tenecteplase. SK=streptokinase.

All-cause mortality within 30–35 days

Major bleeding

tPA+PAC +GP	0·68 (0·30–1·52)	1·61 (0·78–3·31)	0·14 (0·01–2·69)	1·45 (0·70–3·01)	1·38 (0·66–2·90)	0·86 (0·41–1·83)	**3·02 (1·28–7·15)**	2·02 (0·92–4·41)	**2·50 (1·08–5·82)**	**3·64 (1·30–10·20)**	1·27 (0·64–2·53)
0·72 (0·36–1·46)	rPA+PAC +GP	**2·37 (1·45–3·89)**	0·21 (0·01–3·71)	**2·15 (1·53–3·02)**	**2·04 (1·36–3·06)**	1·28 (0·76–2·14)	4·47 (2·48–8·07)	**2·98 (1·84–4·82)**	3·69 (2·09–6·53)	5·38 (2·35–12·29)	**1·88 (1·24–2·86)**
0·71 (0·35–1·42)	0·98 (0·81–1·19)	TNK+PAC	0·09 (0·01–1·56)	0·90 (0·64–1·29)	0·86 (0·58–1·27)	**0·54 (0·39–0·73)**	**1·88 (1·02–3·46)**	1·25 (0·78–2·00)	1·56 (0·88–2·76)	**2·26 (1·00–5·11)**	**0·79 (0·63–1·00)**
0·85 (0·20–3·64)	1·17 (0·32–4·27)	1·20 (0·33–4·35)	SK+GP	10·06 (0·59–171·49)	9·56 (0·57–161·57)	5·99 (0·34–104·16)	**20·95 (1·22–359·78)**	13·96 (0·82–236·59)	**17·32 (1·05–284·33)**	**25·20 (1·37–462·41)**	8·82 (0·52–151·04)
0·69 (0·34–1·38)	0·95 (0·84–1·08)	0·97 (0·84–1·13)	0·81 (0·22–2·95)	rPA+PAC	0·95 (0·76–1·18)	**0·60 (0·41–0·87)**	**2·08 (1·28–3·38)**	1·39 (0·99–1·95)	**1·72 (1·09–2·72)**	**2·50 (1·18–5·32)**	0·88 (0·69–1·12)
0·63 (0·31–1·25)	0·87 (0·74–1·02)	0·89 (0·77–1·02)	0·74 (0·21–2·68)	0·91 (0·82–1·02)	SK+PAC	**0·63 (0·42–0·94)**	**2·19 (1·42–3·38)**	**1·46 (1·10–1·93)**	**1·81 (1·21–2·72)**	**2·64 (1·27–5·47)**	0·92 (0·70–1·21)
0·62 (0·30–1·27)	0·85 (0·65–1·13)	0·87 (0·71–1·06)	0·73 (0·20–2·69)	0·90 (0·70–1·15)	0·98 (0·77–1·26)	TNK+PAC +GP	**3·50 (1·93–6·34)**	**2·33 (1·45–3·75)**	**2·89 (1·63–5·12)**	**4·21 (1·85–9·59)**	1·47 (1·10–1·98)
0·58 (0·29–1·17)	**0·80 (0·65–0·98)**	**0·82 (0·68–0·98)**	0·68 (0·19–2·47)	**0·84 (0·71–0·99)**	0·92 (0·81–1·04)	0·94 (0·71–1·23)	tPA	0·67 (0·43–1·02)	0·83 (0·50–1·37)	1·20 (0·54–2·68)	**0·42 (0·25–0·70)**
0·57 (0·28–1·14)	**0·78 (0·64–0·95)**	**0·80 (0·67–0·96)**	0·67 (0·18–2·41)	**0·82 (0·70–0·96)**	0·90 (0·80–1·01)	0·92 (0·70–1·20)	0·98 (0·87–1·10)	tPA+PAC	1·24 (0·81–1·90)	1·81 (0·92–3·54)	**0·63 (0·44–0·92)**
0·55 (0·27–1·11)	**0·76 (0·62–0·93)**	**0·78 (0·65–0·94)**	0·65 (0·18–2·34)	**0·80 (0·68–0·94)**	**0·88 (0·78–0·99)**	0·89 (0·68–1·17)	0·95 (0·84–1·08)	0·98 (0·87–1·10)	SK	1·46 (0·66–3·23)	**0·51 (0·31–0·83)**
0·48 (0·24–0·98)	**0·66 (0·53–0·84)**	**0·68 (0·55–0·84)**	0·57 (0·16–2·06)	**0·70 (0·57–0·85)**	**0·77 (0·65–0·90)**	0·78 (0·58–1·04)	**0·83 (0·70–0·99)**	**0·85 (0·74–0·98)**	0·87 (0·73–1·04)	PAC	**0·35 (0·16–0·75)**
0·72 (0·36–1·42)	0·99 (0·84–1·16)	1·01 (0·90–1·13)	0·84 (0·23–3·06)	1·04 (0·94–1·15)	**1·14 (1·05–1·24)**	1·16 (0·92–1·46)	**1·24 (1·07–1·43)**	**1·26 (1·10–1·45)**	**1·30 (1·12–1·50)**	**1·49 (1·24–1·79)**	tPA_acc +PAC

Treatment | Primary efficacy outcome (all-cause mortality within 30–35 days; RR [95% CI]) | Primary safety outcome (major bleeding; RR [95% CI])

Figure 3: **Network meta-analysis of primary efficacy (all-cause mortality within 30–35 days) and safety (major bleeding) outcomes**
Interventions are ordered by ranking for all-cause mortality within 30–35 days. Results are the RRs (95% CIs) from the network meta-analysis between the column-defining intervention and row-defining intervention. Comparisons should be read from left to right. Numbers in bold represent statistically significant results. tPA=alteplase (non-accelerated infusion). PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. rPA=reteplase. TNK=tenecteplase. SK=streptokinase. tPA_acc=alteplase (accelerated infusion). RR=risk ratio.

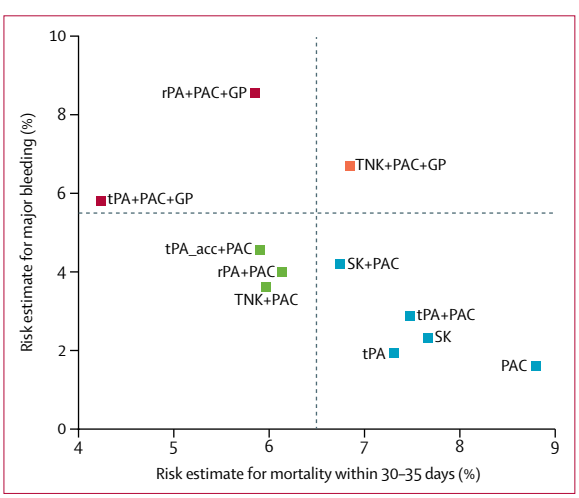

Figure 4: **Cluster rank plot of risk estimates for mortality within 30–35 days and major bleeding**
The risk estimate plot of treatment with streptokinase plus glycoprotein IIb/IIIa inhibitors is omitted because it is out of the range of the plot. The dashed lines represent the different quadrants of the risk estimates. rPA=reteplase. PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. TNK=tenecteplase. tPA=alteplase (non-accelerated infusion). tPA_acc=alteplase (accelerated infusion). SK=streptokinase.

glycoprotein IIb or IIIa inhibitors regimen provided the highest net survival gain of 1·496% followed by tenecteplase plus parenteral anticoagulants (0·082%) and reteplase plus parenteral anticoagulants (–0·141%), based on a weighting factor of 0·15. The sensitivity of the effect of this weighting factor (varying from 0·15 to 0·6) on the net clinical benefit value is also presented (appendix p 79). The net clinical benefit of most treatment regimens rose with increasing weighting factor, except for regimens containing glycoprotein IIb or IIIa inhibitors (appendix p 79).

In our subgroup analyses, the RRs of regimens for major bleeding tended to be larger in Asian populations than in the main network meta-analysis (appendix p 95). Similarly, the RRs of most regimens for all-cause mortality were slightly increased in those aged older than 65 years and in the Asian population (appendix p 94). We were unable to do our other prespecified subgroup analyses because of insufficient data.

Results of our sensitivity analyses are reported in appendix pp 96–101. The findings were generally robust and no significant changes in treatment hierarchy were detected for all primary outcomes. Comparison-adjusted funnel plots showed no evidence of asymmetry (appendix pp 102–106).

The quality of direct evidence for all outcomes was generally rated as low to moderate in most comparisons (appendix pp 80–93). When GRADE was applied to our network meta-analysis evidence, a better rating of quality of evidence for mortality outcome than that for direct evidence was found in most comparisons. More details of the quality of evidence are presented in the appendix (pp 80–93).

Discussion

This study offers a single framework for a comparison of efficacy and safety outcomes among various fibrinolytic regimens used for patients with STEMI. The results suggest that fibrin-specific agents in combination with parenteral anticoagulants were one of the most effective regimens and had an acceptable level of bleeding risk. Our analysis added new data from a study performed in three Asian countries on tenecteplase (Boehringer Ingelheim, personal communication) over the previous pairwise analysis,[11] strengthening the current understanding that tenecteplase offers a more favourable safety profile with similar survival benefits compared with other fibrin-specific agents. Streptokinase, a less expensive option compared to fibrin-specific agents, offers a similar risk of major bleeding with slight increase of less than 1% in mortality within 30–35 days, compared with tenecteplase. Additional information such as cost-effectiveness and consideration of antigenicity[73] need to be taken into account when formulating national or institutional policy decisions.

The addition of glycoprotein IIb or IIIa inhibitors might be undesirable given the significant increase in bleeding risk despite the potential added benefit of mortality reduction. Although our net clinical benefit analysis and cluster rank plot show that non-accelerated alteplase plus parenteral anticoagulants plus glycoprotein inhibitors might seem to perform well compared with the reference regimen and other regimens with glycoprotein inhibitors, we caution readers to consider interpreting this finding carefully. The data for this combination regimen were based entirely on phase 2 trials with only 433 patients from four studies.[48,51,64,69] Moreover, the quality of these four studies was graded as very low to low quality (appendix pp 80–93) with a wide confidence interval of pooled risk estimates as presented in appendix p 78. By contrast, the quality of data for tenecteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors and reteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors is high because of the large number of patients and high quality of studies included. However, our sensitivity analysis of net clinical benefit (appendix p 78) shows that the benefit of all glycoprotein inhibitor-based regimens is reduced when the severity of bleeding is increased (eg, intracranial haemorrhage), as indicated by the downward shifting of the degree and direction of the positive net benefit offered by these regimens. Notably, the percentage of rescue percutaneous

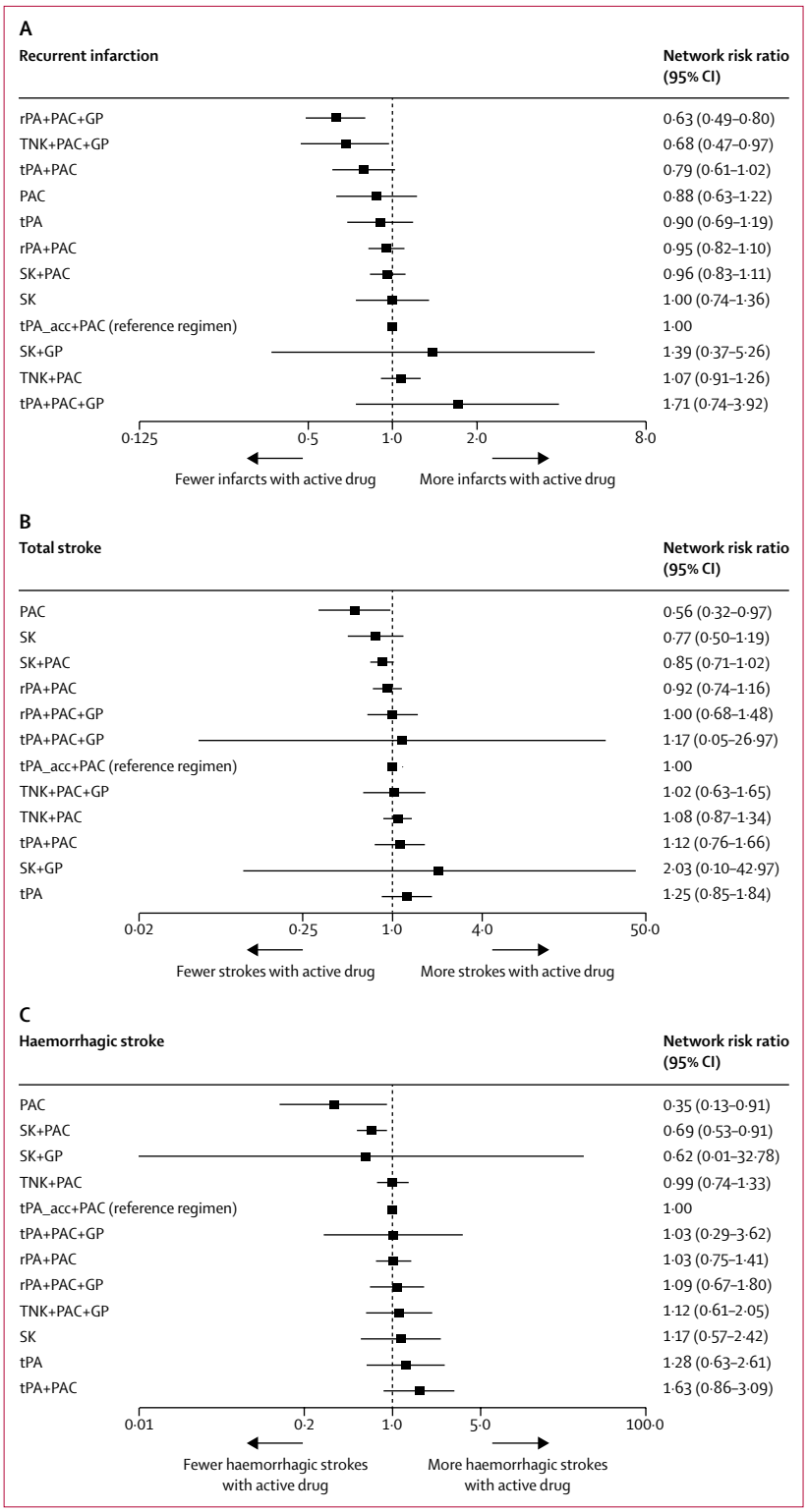

Figure 5: **Network meta-analysis of reperfusion therapy with fibrinolytic drugs compared with accelerated infusion alteplase plus parenteral anticoagulants for secondary efficacy and safety outcomes**
(A) Recurrent infarction. (B) Total stroke. (C) Haemorrhagic stroke. Summary estimates represent risk ratio (95% CI) of recurrent infarction, all-type stroke, and haemorrhagic stroke. Interventions are ranked by Surface Under the Cumulative RAnking curves values. rPA=reteplase. PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. TNK=tenecteplase. tPA=alteplase (non-accelerated infusion). SK=streptokinase. tPA_acc=alteplase (accelerated infusion).

coronary intervention in studies investigating the non-accelerated alteplase plus parenteral anticoagulants plus glycoprotein IIb or IIIa inhibitors regimen was as high as 30–60%. Our recommendation regarding the addition of glycoprotein inhibitors to standard fibrinolytic regimens is largely consistent with those posited by previous analysis of a similar nature.[74]

Our network meta-analysis strengthens the evidence and improves the precision of our findings compared with a direct evidence analysis (pairwise meta-analysis). Only one randomised controlled trial directly compared non-accelerated and accelerated infusion regimens of alteplase given concomitantly with parenteral anticoagulants,[6] and reported no significant differences in all-cause mortality or major bleeding. The claim of superiority of accelerated over non-accelerated infusion regimen of alteplase was believed to be developed from an indirect relation of evidence mainly reported in the GUSTO-I trial.[30] Before the GUSTO-I trial, non-accelerated infusion of alteplase was shown to be similar to streptokinase in terms of efficacy.[40,41,46,53,59,67,72] However, the GUSTO-I trial showed that accelerated infusion of alteplase was superior to streptokinase. Consequently, the indirect association that accelerated infusion of alteplase might be superior to non-accelerated infusion was drawn. By pooling direct and indirect evidence in our network meta-analysis, we found that an accelerated infusion of alteplase significantly reduced mortality while slightly increasing the risk of major bleeding compared with a non-accelerated infusion. When analysed using net clinical benefit, the accelerated regimen was found to offer significant advantages over the non-accelerated infusion regimen, lending support to use of the accelerated infusion regimen in clinical practice guidelines and national formularies.

This study has some limitations. First, heterogeneity of the definition of major bleeding is an important concern because standardised bleeding definitions were adopted for use in clinical trials later in the course of this research line. To overcome this issue, we have matched the definition of bleeding events reported in each trial with the definition established by the BARC[16] as much as possible. We included studies with reported bleeding definition into the quantitative analysis for the primary safety outcome if the definition was similar to BARC bleeding type 3a, 3b, or 3c. We also have done sensitivity analyses to assess the robustness of our conclusions based on these differences. The approach of defining major bleeding as BARC type 3a, 3b, or 3c was chosen because of clear evidence of its validity against other well-recognised bleeding definitions.[75,76] Second, timely and successful thrombolysis is likely to carry long-term mortality and morbidity benefits independent of the shorter-term benefit, yet our analyses were unable to provide evidence beyond the short-term period. Third, because of the absence of details about the methods used for diagnosis of stroke, the effect of fibrinolytics on stroke outcomes should be interpreted with caution. As is the case with other meta-analyses, it is very likely that some details or data about relevant factors were not fully obtained and thus could not be adjusted for in our analyses. Moreover, differences in standard treatment and changes in practice over time could potentially affect the outcomes of the studies we included in our analysis. This factor needs to be taken into account in the interpretation of our results. Finally, a pharmacoinvasive strategy (in which fibrinolytic therapy is given either in the pre-hospital setting or in a hospital where percutaneous coronary intervention cannot be done, followed by early coronary angiography and percutaneous coronary intervention when appropriate[2]) for patients with STEMI has gained much attention recently.[77] Ultimately, we should be cautious that findings derived from this study might not be directly inferable to this treatment strategy without extrapolating beyond the original data. Notably, most of the trials used fibrinolytic agents at a reduced dose and agents with a lower bleeding risk profile, such as tenecteplase.

Thrombolysis has a substantial role even in the era of primary percutaneous coronary intervention in settings where access to mechanical reperfusion is limited.[78] The key to success for STEMI care is to provide timely reperfusion therapy.[79] Despite increasing resources in support of having adequate hospitals capable of providing percutaneous coronary intervention,[6,80] a strong need remains for the development of integrated health-care systems to create a therapeutic interface between thrombolysis[81] and primary percutaneous coronary intervention, especially in low-income and middle-income countries. National efforts are needed to allow emergency medical systems to provide aggressive thrombolytic treatment for acute STEMI,[82] based on local infrastructure and population distribution needs. Our systematic review and network meta-analysis provides a comprehensive summary of evidence of fibrinolytic regimens, which could be crucial for the formulation of national policies on thrombolysis care.

In summary, our analysis suggests that fibrin-specific agents in combination with parenteral anticoagulants offer the highest level of efficacy in terms of short-term mortality reduction in patients with STEMI. Tenecteplase ranks the lowest in terms of bleeding risk and has a similar mortality benefit across all other fibrinolytics. Our findings are useful for guideline development, and for clinical and national policy setting for treatment of STEMI, especially in settings where access to primary percutaneous coronary intervention is limited.[83]

Contributors

NC, PJ, and SN designed and organised research for this study. NC supervised the study. PJ, JK, NC, SN, and CYF acquired, analysed, and interpreted the data. PJ, AT, and NC did the statistical analysis. CYF, NC, PJ, SN, and AT wrote the report. AP and CMR critically revised the report for important intellectual content and approved the final version of the Article. All authors critically revised the Article for important intellectual content and approved the final version of the Article.

Declaration of interests
We declare no competing interests.

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References

1 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386:** 743–800.

2 O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61:** e78–140.

3 Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.

4 Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; **348:** 771–75.

5 Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated *vs* hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA* 1993; **270:** 1211–16.

6 ACCESS Investigators. Management of acute coronary syndromes in developing countries: acute coronary events–a multinational survey of current management strategies. *Am Heart J* 2011; **162:** 852–59.e22.

7 Rashid MK, Guron N, Bernick J, et al. Safety and efficacy of a pharmacoinvasive strategy in ST-segment elevation myocardial infarction: a patient population study comparing a pharmacoinvasive strategy with a primary percutaneous coronary intervention strategy within a regional system. *JACC Cardiovasc Interv* 2016; **9:** 2014–20.

8 Sim DS, Jeong MH, Ahn Y, et al. Pharmacoinvasive strategy versus primary percutaneous coronary intervention in patients with ST-segment-elevation myocardial infarction: a propensity score-matched analysis. *Circ Cardiovasc Interv* 2016; **9:** pii: e003508.

9 Siontis KC, Barsness GW, Lennon RJ, et al. Pharmacoinvasive and primary percutaneous coronary intervention strategies in st-elevation myocardial infarction (from the Mayo Clinic STEMI Network). *Am J Cardiol* 2016; **117:** 1904–10.

10 Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: a systematic review. *QJM* 2003; **96:** 103–13.

11 Guillermin A, Jun Yan D, Perrier A, Marti C. Safety and efficacy of tenecteplase versus alteplase in acute coronary syndrome: a systematic review and meta-analysis of randomized trials. *Arch Med Sci* 2016; **12:** 1181–87.

12 University of York Centre for Reviews and Dissemination. Jinatongthai P, Kongwatcharapong J, Phrommintikul A, Nathisuwan S, Chaiyakunapruk N. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patient with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis. July 5, 2016. PROSPERO 2016:CRD42016042131. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042131 (accessed Nov 1, 2016).

13 Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162:** 777–84.

14 Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.

15 ACTIVASE (alteplase) prescribing information. Feb 13, 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103172s5203lbl.pdf (accessed Nov 23, 2016).

16 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123:** 2736–47.

17 GRADEpro GDT. https://gradepro.org/ (accessed Jan 9, 2017).

18 Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64:** 401–06.

19 Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2015; **350:** h3326.

20 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.

21 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

22 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; **23:** 3105–24.

23 Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331:** 897–900.

24 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; **29:** 932–44.

25 Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64:** 163–71.

26 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013; **8:** e76654.

27 Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. *JAMA* 2014; **312:** 623–30.

28 Macdonald F. 80% of data in Chinese clinical trials have been fabricated. Oct 1, 2016. http://www.sciencealert.com/80-of-the-data-in-chinese-clinical-trial-is-fabricated (accessed Oct 24, 2016).

29 Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014; **311:** 2414–21.

30 Topol E, Califf R, Van de Werf F, et al. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329:** 673–82.

31 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; **335:** 775–82.

32 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997; **337:** 1118–23.

33 Van de Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.

34 Van De Werf FJ. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358:** 605–13.

35 White H, White HD, Simes RJ, et al. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001; **358:** 1855–63.

36 Mehta RH, Stebbins AS, Lopes RD, et al. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. *Am J Cardiol* 2012; **109:** 320–26.

37 Multiple treatments meta-analysis. Using STATA for network meta-analysis. http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis (accessed Oct 20, 2016).

38 Simoons M, Krzeminska-Pakula M, Alonso A, et al. Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. *Eur Heart J* 2002; **23:** 1282–90.

39 Bleich SD, Nichols TC, Schumacher RR, Cooke DH, Tate DA, Teichman SL. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990; **66:** 1412–17.

40 Taylor GJ, Moses HW, Koester D, et al. A difference between front-loaded streptokinase and standard-dose recombinant tissue-type plasminogen activator in preserving left ventricular function after acute myocardial infarction (the Central Illinois Thrombolytic Therapy Study). *Am J Cardiol* 1993; **72:** 1010–14.

41 Cherng WJ, Chiang CW, Kuo CT, Lee CP, Lee YS. A comparison between intravenous streptokinase and tissue plasminogen activator with early intravenous heparin in acute myocardial infarction. *Am Heart J* 1992; **123:** 841–46.

42 Binbrek AS, Rao NS, Neimane D, Hatou E, Abdulali S, Sobel BE. Comparison of rapidity of coronary recanalization in men with tenecteplase versus alteplase in acute myocardial infarction. *Am J Cardiol* 2004; **93:** 1465–68.

43 de Bono DP, Simoons ML, Tijssen J, et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992; **67:** 122–28.

44 Van de Werf F, Arnold AE. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. *BMJ* 1988; **297:** 13742–79.

45 Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation* 2002; **105:** 1642–49.

46 Feruglio GA, Lotto A, Rovelli F, et al. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990; **336:** 652–71.

47 Topol EJ. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001; **357:** 19052–14.

48 Ohman EM, Kleiman NS, Gacioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators. *Circulation* 1997; **95:** 8462–54.

49 Wilcox RG. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995; **346:** 3292–36.

50 Giugliano RP, Roe MT, Harrington RA, et al. Combination reperfusion therapy with eptifibatide and reduced-dose tenecteplase for ST-elevation myocardial infarction: results of the integrilin and tenecteplase in acute myocardial infarction (INTEGRITI) phase II angiographic trial. *J Am Coll Cardiol* 2003; **41:** 12512–60.

51 Brener SJ, Zeymer U, Adgey AAJ, et al. Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) trial. *J Am Coll Cardiol* 2002; **39:** 377–86.

52 Schroder R, Neuhaus KL, Leizorovicz A. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.). Mortality, morbidity, and infarct size at 21 days. *N Engl J Med* 1986; **314:** 1465–71.

53 Van de Werf F, Wilcox RG, Barbash GI, et al. In-hospital mortality and clinical course of 20 891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990; **336:** 71–75.

54 Janousek S, Lupinek Z, Toman J, et al. First results of a randomized investigation of thrombolytic treatment of acute myocardial infarction–evaluation of the early period. *Vnitrni Lekarstvi* 1988; **34:** 1145–54 (in Czech).

55 Kennedy JW, Martin GV, Davis KB, et al. The western Washington intravenous streptokinase in acute myocardial infarction randomized trial. *Circulation* 1988; **77:** 345–52.

56 Hampton J, Wilcox R, Armstrong P, et al. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993; **342:** 759–66.

57 National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. *Lancet* 1988; **1:** 203–08.

58 O'Rourke M, Baron D, Keogh A, et al. Limitation of myocardial infarction by early infusion of recombinant tissue-type plasminogen activator. *Circulation* 1988; **77:** 1311–15.

59 Magnani B. Plasminogen Activator Italian Multicenter Study (PAIMS): comparison of intravenous recombinant single-chain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol* 1989; **13:** 19–26.

60 Carney RJ, Murphy GA, Brandt TR, et al. Randomized angiographic trial of recombinant tissue-type plasminogen activator (alteplase) in myocardial infarction. *J Am Coll Cardiol* 1992; **20:** 17–23.

61 Smalling RW, Bode C, Kalbfleisch J, et al. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation* 1995; **91:** 2725–32.

62 Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II Investigators. *Circulation* 1996; **94:** 891–98.

63 Ronner E, Van Kesteren HAM, Zijnen P, et al. Safety and efficacy of eptifibatide *vs* placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction: a phase II dose escalation, randomized, double-blind study. *Eur Heart J* 2000; **21:** 1530–36.

64 Sarullo FM, Di Pasquale P, D'Alfonso G, Amerigo L, Cannizzaro S, Castello A. Safety and efficacy of thrombolysis with alteplase (50 mg) plus tirofiban versus alteplase (100 mg) alone in acute myocardial infarction: preliminary findings. *Ital Heart J* 2001; **2:** 605–11.

65 Ohman EM. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. *Circulation* 2000; **101:** 2788–94.

66 Topol EJ, George BS, Kereiakes DJ, et al. A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989; **79:** 281–86.

67 Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987; **76:** 142–54.

68 Cannon CP, Gibson CM, McCabe CH, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation* 1998; **98:** 2805–14.

69 Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation* 1999; **99:** 2720–32.

70 Antman EM, Gibson CM, De Lemos JA, et al. Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14. *Eur Heart J* 2000; **21:** 1944–53.

71 White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987; **317:** 850–55.

72 White HD, Rivers JT, Maslowski AH, et al. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. *N Engl J Med* 1989; **320:** 817–21.

73 Squire IB, Lawley W, Fletcher S, et al. Humoral and cellular immune responses up to 7·5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J* 1999; **20:** 1245–52.

74 Sinno MC, Khanal S, Al-Mallah MH, Arida M, Weaver WD. The efficacy and safety of combination glycoprotein IIbIIIa inhibitors and reduced-dose thrombolytic therapy-facilitated percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized clinical trials. *Am Heart J* 2007; **153:** 579–86.

75 Vranckx P, Leonardi S, Tebaldi M, et al. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. *Eur Heart J* 2014; **35:** 2524–29.

76 Kikkert WJ, van Geloven N, van der Laan MH, et al. The prognostic value of bleeding academic research consortium (BARC)-defined bleeding complications in ST-segment elevation myocardial infarction: a comparison with the TIMI (Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and ISTH (International Society on Thrombosis and Haemostasis) bleeding classifications. *J Am Coll Cardiol* 2014; **63:** 1866–75.

77 Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **368:** 1379–87.

78 Gershlick AH, Banning AP, Myat A, Verheugt FW, Gersh BJ. Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention? *Lancet* 2013; **382:** 624–32.

79 Lambert L, Brown K, Segal E, Brophy J, Rodes-Cabau J, Bogaty P. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *JAMA* 2010; **303:** 2148–55.

80 Global Atlas on Cardiovascular Disease Prevention and Control. World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. 2011. http://www.world-heart-federation.org/fileadmin/user_upload/images/CVD_Health/Global_CVD_Atlas.pdf (accessed Dec 7, 2016).

81 McCaul M, Lourens A, Kredo T. Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction. *Cochrane Database Syst Rev* 2014; **9:** CD010191.

82 James SK, Spertus JA. Evidence-based treatments for STEMI: are we doing enough? *Lancet* 2013; **382:** 576–79.

83 Shimony A, Grandi SM, Pilote L, et al. Utilization of evidence-based therapy for acute coronary syndrome in high-income and low/middle-income countries. *Am J Cardiol* 2014; **113:** 793–97.