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## Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction (Review)

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[Intervention Review]

# Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction

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## ABSTRACT

### Background

Early thrombolysis for individuals experiencing a myocardial infarction is associated with better mortality and morbidity outcomes. While traditionally thrombolysis is given in hospital, pre-hospital thrombolysis is proposed as an effective intervention to save time and reduce mortality and morbidity in individuals with ST-elevation myocardial infarction (STEMI). Despite some evidence that pre-hospital thrombolysis may be delivered safely, there is a paucity of controlled trial data to indicate whether the timing of delivery can be effective in reducing key clinical outcomes.

### Objectives

To assess the morbidity and mortality of pre-hospital versus in-hospital thrombolysis for STEMI.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OVID), EMBASE (OVID), two citation indexes on Web of Science (Thomson Reuters) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for randomised controlled trials and grey literature published up to June 2014. We also searched the reference lists of articles identified, clinical trial registries and unpublished thesis sources. We did not contact pharmaceutical companies for any relevant published or unpublished articles. We applied no language, date or publication restrictions. The Cochrane Heart Group conducted the primary electronic search.

### Selection criteria

We included randomised controlled trials of pre-hospital versus in-hospital thrombolysis in adults with ST-elevation myocardial infarction diagnosed by a healthcare provider.

### Data collection and analysis

Two authors independently screened eligible studies for inclusion and carried out data extraction and 'Risk of bias' assessments, resolving any disagreement by consulting a third author. We contacted authors of potentially suitable studies if we required missing or additional information. We collected efficacy and adverse effect data from the trials.

### Main results

We included three trials involving 538 participants. We found low quality of evidence indicating uncertainty whether pre-hospital thrombolysis reduces all-cause mortality in individuals with STEMI compared to in-hospital thrombolysis (risk ratio 0.73, 95% confidence

interval 0.37 to 1.41). We found high-quality evidence (two trials, 438 participants) that pre-hospital thrombolysis reduced the time to receipt of thrombolytic treatment compared with in-hospital thrombolysis. For adverse events, we found moderate-quality evidence that the occurrence of bleeding events was similar between participants receiving in-hospital or pre-hospital thrombolysis (two trials, 438 participants), and low-quality evidence that the occurrence of ventricular fibrillation (two trials, 178 participants), stroke (one trial, 78 participants) and allergic reactions (one trial, 100 participants) was also similar between participants receiving in-hospital or pre-hospital thrombolysis. We considered the included studies to have an overall unclear/high risk of bias.

### Authors' conclusions

Pre-hospital thrombolysis reduces time to treatment, based on studies conducted in higher income countries. In settings where it can be safely and correctly administered by trained staff, pre-hospital thrombolysis may be an appropriate intervention. Pre-hospital thrombolysis has the potential to reduce the burden of STEMI in lower- and middle-income countries, especially in individuals who have limited access to in-hospital thrombolysis or percutaneous coronary interventions. We found no randomised controlled trials evaluating the efficacy of pre-hospital thrombolysis for STEMI in lower- and middle-income countries. Large high-quality multicentre randomised controlled trials implemented in resource-constrained countries will provide additional evidence for the efficacy and safety of this intervention. Local policy makers should consider their local health infrastructure and population distribution needs. These considerations should be taken into account when developing clinical guidelines for pre-hospital thrombolysis.

## PLAIN LANGUAGE SUMMARY

### Delivering clot-busting therapy before reaching hospital or in hospital to help people who are having heart attacks

Heart disease is the most common cause of death worldwide according to the World Health Organization. A heart attack can either be treated with a drug called a thrombolytic (clot buster) or with surgery. The earlier a thrombolytic is given, the less likely the individual is to die or have disabilities. Usually, thrombolysis is given in a hospital; however, the administration of this therapy before hospital, by paramedics, may be an effective intervention that may save time and reduce death and disability in people with heart attacks.

The aim of this review was to compare the effect of pre-hospital and in-hospital administration of thrombolytic therapy on all-cause death and disability in individuals having a heart attack. We carried out a comprehensive search for all trials that have investigated this outcome. Two authors worked independently to ensure we found all of the trials and obtained the relevant information from them. Overall, we found three trials with 538 participants which could be included in this review. We found low-quality evidence indicating uncertainty whether the numbers of people dying were different when therapy was given before hospital compared to in hospital (3 trials). We found high-quality evidence that giving therapy before hospital reduced the time taken for an individual to receive thrombolytic therapy by more than 30 minutes (two studies) and generally low-quality evidence that side effects, such as allergic reactions and bleeding, were similar whether therapy was given pre-hospital or in hospital. The main limitations of the evidence were the unclear/high risk of bias in the studies and the low numbers of people recruited.

We conclude that clot-busting therapy given before arriving at a hospital reduces the time taken for an individual to receive thrombolytic treatment. The limitations of the evidence we have found should be considered carefully, especially in settings where thrombolysis can be safely and correctly administered by trained staff. We found that there were no trials evaluating pre-hospital thrombolytic therapy in poorer countries, and therefore further research in such settings will provide more information to advise on whether giving this therapy for heart attacks is safe and effective.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction

#### Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction

**Participants or population:** participants with ST-elevation myocardial infarction

**Settings:** USA, France and Germany

**Intervention:** Pre-hospital versus in-hospital thrombolysis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pre-hospital versus in-hospital thrombolysis				
<b>All-cause hospital mortality</b> Follow up: 30 days <sup>1</sup>	<b>73 per 1000</b>	<b>53 per 1000</b> (27 to 103)	<b>RR 0.73</b> (0.37 to 1.41)	538 (3 studies)	⊕⊕⊕⊕ <b>low</b> 2,3	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Follow up ranged from 15 days to 1 month

<sup>2</sup> Downgraded by 1 level for risk of bias due to poor reporting of random sequence generation, allocation concealment (not described and concealment broken) and inadequate outcome reporting in [Castaigne 1989](#)

<sup>3</sup> Downgraded by 1 level for imprecision as CI includes appreciable benefit and appreciable harm.

### Summary of findings 2. Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction

#### Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction

**Participant or population:** participants with ST-elevation myocardial infarction

**Settings:** USA, France and Germany

**Intervention:** Pre-hospital versus in-hospital thrombolysis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pre-hospital versus in-hospital thrombolysis				
<b>Time to thrombolytic treatment [minutes]</b>		The mean time to thrombolytic treatment [minutes] in the intervention groups was <b>37.95 lower</b> (61.12 to 14.77 lower)		438 (2 studies)	⊕⊕⊕⊕ <b>high</b> <sup>1</sup>	
<b>Acute myocardial infarction functional outcomes - ejection fraction [percentage]</b>		The mean acute myocardial infarction functional outcomes - ejection fraction [percentage] in the intervention groups was <b>1.18 lower</b> (3.50 lower to 1.13 higher)		416 (2 studies)	⊕⊕○○ <b>low</b> <sup>2,3</sup>	
<b>Adverse effects - ventricular Fibrillation</b>	<b>25 per 1000</b>	<b>67 per 1000</b> (17 to 268)	<b>RR 2.73</b> (0.68 to 10.86)	178 (2 studies)	⊕⊕○○ <b>low</b> <sup>4</sup>	
<b>Adverse effects - bleeding complications</b>	<b>58 per 1000</b>	<b>51 per 1000</b> (24 to 112)	<b>RR 0.88</b> (0.41 to 1.92)	438 (2 studies)	⊕⊕⊕○ <b>moderate</b> <sup>5</sup>	
<b>Adverse effects - allergic reaction</b>	<b>0 per 1000</b>	<b>0 per 1000</b> (0 to 0)	<b>RR 0</b> (0.19 to 77.03)	100 (1 study)	⊕⊕○○ <b>low</b> <sup>4</sup>	
<b>Adverse effects - Stroke</b>	<b>11 per 1000</b>	<b>23 per 1000</b> (4 to 123)	<b>RR 2.11</b> (0.39 to 11.4)	360 (1 study)	⊕⊕○○ <b>low</b> <sup>4</sup>	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Methodological quality (e.g. no blinding in [Castaigne 1989](#)) not likely to effect this outcome, therefore not downgraded due to risk of bias

<sup>2</sup> Downgraded by 1 level for risk of bias. [Schofer 1990](#) had participants lost to follow up for this outcome (n = 17). Extent of non-differential or differential loss to follow up unknown

- 3 Downgraded for imprecision, CI includes appreciable benefit and appreciable harm
- 4 Downgraded by 2 levels for imprecision. Low event rate and wide CI
- 5 Downgraded by 1 level for imprecision

## BACKGROUND

### Description of the condition

The World Health Organization (WHO) reports that cardiovascular disease is the leading cause of death worldwide, with more than 80% of these deaths occurring in lower- and middle-income countries (LMICs) (Mackay 2004; WHO 2011). Cardiovascular disease is responsible for more than 10% of disability-adjusted life-years lost in LMICs and for more than 18% of disability-adjusted life-years lost in high-income countries (HICs) (Mackay 2004). ST-segment elevation myocardial infarction (STEMI) falls under the umbrella classification of acute coronary syndromes (ACS), which also include non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (Ruff 2011). A STEMI is the development of myocardial necrosis secondary to the interruption of the blood supply to an area of the myocardium identified by the presence of ST segment elevation on electrocardiography or the elevation of cardiac markers, or both. In the United States there has been a striking evolution in the epidemiology of ACS since the 1990s, with a steady decline in the incidence of STEMI and a reciprocal incline in the incidence of NSTEMIs, as reported by Rogers 2008. In LMICs there is an increasing trend in ischaemic heart disease mortality (Mensah 2008) as these countries move through an epidemiological transition of increasing incidence and prevalence of cardiovascular disease (Gersh 2010). Acute myocardial infarction is defined as cardiac muscle death owing to prolonged lack of oxygenation (Thygesen 2007) caused by an abrupt reduction in coronary blood flow to part of the heart (Beers 2006). Symptoms of acute myocardial infarction may be more severe than those associated with angina and usually persist for longer (e.g. more than 15 to 20 minutes). Classic symptoms include chest discomfort or pain but can include other symptoms such as shortness of breath, nausea, sweating, dizziness and vomiting (Goodacre 2002; Goodacre 2003). Health costs relating to people suffering from acute myocardial infarction are diverse, with economic implications to the individual, family, healthcare system and country (IOM 2010).

### Description of the intervention

STEMIs can be treated effectively using percutaneous coronary interventions (PCIs) or thrombolytic agents, or both (Bonney 2009; Weaver 1993). Thrombolytic agents are enzymes that cause coronary thrombus dissolution through a cascade of effects to degrade fibrin thrombi and fibrinogen (SAMF 2010). These agents can be administered either in the pre-hospital setting or, traditionally, in a hospital setting, and are most effective if given in the first few minutes to hours after onset of a STEMI (Beers 2006; Rawles 2003; Weaver 1993). Various thrombolytic agents are available, all with similar biological effects, efficacy and administration requirements. These include, but are not limited to, the following agents:

- streptokinase, 1.5 million units intravenously (IV) over 30 to 60 minutes;
- alteplase, 15 mg IV 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg IV over 60 minutes;
- reteplase, 10 U + 10 U IV given 30 minutes apart;
- tenecteplase, single IV injection (weight dependent) (Van de Werf 2008).

A thrombolytic agent is administered either by infusion or as a single bolus dose. This distinction is important to note as bolus doses are generally easier to administer, require less resources (e.g. an infusion pump) and expertise. Treatment of STEMI is aimed at early diagnosis and risk stratification, with relief of pain, breathlessness and anxiety coupled with immediate coronary reperfusion either with a pharmacological or mechanical intervention depending on availability and on each individual's context (O'Connor 2010). The standard of care includes anti-ischaemic therapy (oxygen, nitroglycerin, opioids and beta-blockers), antiplatelet therapy (Aspirin, clopidogrel) (Fox 2004; ISIS-2 1988), antithrombin therapies (heparin and low-molecular-weight heparins) (Armstrong 2006) and reperfusion strategies (O'Connor 2010; Van de Werf 2008).

### How the intervention might work

Effective thrombolysis for individuals with STEMI is extremely time sensitive (Sayah 2008). The earlier a thrombolytic agent is initiated the better, with greatest benefit occurring within three hours from symptom onset (Bonney 2009). The goal is to initiate thrombolysis within 30 to 60 minutes after symptom onset (Antman 2008). Despite this goal, achieving this in practice is challenging (Barbagelata 2007). Pre-hospital initiation of thrombolysis has been reported to improve time to thrombolysis and reduce mortality compared with in-hospital thrombolysis (Antman 2008 (narrative); Björklund 2006 (cohort study); Bonney 2009; Brouwer 1996; Rawles 2003 (trials); Curtis 2006 (descriptive); Morrison 2000 (review)).

### Why it is important to do this review

Early thrombolysis has been associated with better mortality and morbidity outcomes (Bonney 2009). Pre-hospital thrombolysis can provide improved time to thrombolysis (Björklund 2006) and a potential reduction in mortality and morbidity compared with in-hospital treatment (Rawles 2003). A previous systematic review by Morrison 2000 found that pre-hospital thrombolysis for acute myocardial infarction significantly decreased all-cause hospital mortality based on a meta-analysis of six randomised controlled trials (RCTs). This review incorporated any new evidence and utilised the GRADE assessment, together with Cochrane Heart Group methodology. It added to current knowledge of pre-hospital thrombolysis by considering system and infrastructure needs for the successful implementation of the models of care and ascertained gaps in current research evidence. The results of this review may guide policy makers and other healthcare stakeholders to invest in the appropriate treatment strategy and health system/service requirements for individuals with STEMI needing thrombolysis, especially in LMICs where other treatment options for STEMI are scarce or not available. This review has important implications for areas where primary angioplasty is unavailable or where pre-hospital transport times are long, such as rural areas - specifically in LMICs.

## OBJECTIVES

To assess the morbidity and mortality of pre-hospital versus in-hospital thrombolysis for STEMI.



## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs excluding cross-over trials.

#### Types of participants

Adults (16 years and older) with STEMI diagnosed by a medical healthcare provider in either the pre-hospital or in-hospital setting. Diagnosis of STEMI will be defined according to the included studies' criteria for STEMI but should include at least two of the following three positive indicators: the individual's history and symptoms, electrocardiogram (ECG) findings and biochemical cardiac markers (cardiac markers are not mandatory for diagnosis, but may be used in certain pre-hospital settings).

#### Types of interventions

Any thrombolytic agent used to treat STEMI in pre-hospital and in-hospital settings.

#### Types of outcome measures

##### Primary outcomes

All-cause hospital mortality at one month (short term) and one year (mid term).

##### Secondary outcomes

1. Time to thrombolytic treatment, measured from symptom onset or first medical contact, or both (or as described by study authors) to the administration of a thrombolytic agent
2. Adverse effects. An adverse event is defined as an event for which a causal relationship between the intervention and the event is a reasonable possibility (e.g. ventricular fibrillation, pulseless ventricular tachycardia, cardiogenic shock, inappropriate use of thrombolytics, hypotension, bradycardia, re-infarction, bleeding, or fatal and non-fatal stroke)
3. Acute myocardial infarction functional outcomes including:
  - ejection fraction, measured using an echocardiogram;
  - classification of heart failure (New York Heart Association functional classification system);
  - time to discharge or days in hospital, measured from admission to discharge in days

### Search methods for identification of studies

#### Electronic searches

In June 2014, we conducted comprehensive electronic searches for RCTs using the following key search terms - thrombolysis, thrombolysis therapy, myocardial infarction, and pre-hospital - and using the Cochrane sensitivity-precision maximising RCT filter (Lefebvre 2011), adapted for use with the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, issue 5 of 12, September 2014, searched 5 June 2014, results: 1491);
- MEDLINE (OVID, 1946 to May Week 4 2014, searched 10 June 2014, results: 1178);
- EMBASE Classic + EMBASE (OVID, 1947 to 5 June 2014, searched 5 June 2014, results: 1196);

- Science Citation Index Expanded (SCI-EXPANDED, 1970 to 5 June 2014) and Conference Proceedings Citation Index- Science (CPCI-S, 1990 to 5 June 2014) on Web of Science (Thomson Reuters) searched 5 June 2014; results: 2489;
- CINAHL Plus with Full Text (EBSCO, 1936 to May 2014, searched 5 June 2014, results: 117).

We added no language or publication restrictions to the search strategies. The search strategies used can be found in [Appendix 1](#).

In developing the search strategy we were assisted by the Cochrane Heart Review Group's Trials Search Co-ordinator who conducted the main search.

#### Searching other resources

We searched grey literature, such as unpublished thesis sources, and the following additional databases: ProQuest Dissertations, Index to theses in Great Britain and Ireland, and DissOnline. We carried out no handsearching and contacted no pharmaceutical companies in order to identify additional studies due to operational time restraints.

We searched the reference lists of included studies and contacted the primary authors of included studies to identify additional relevant studies. We searched the following clinical trial registers: ClinicalTrials.gov ([www.clinicaltrials.gov/](http://www.clinicaltrials.gov/)), International Standard Randomised Controlled Trial Register ([www.controlled-trials.com/isrctn/](http://www.controlled-trials.com/isrctn/)) and the WHO International Clinical Trials Registry Platform ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)).

### Data collection and analysis

#### Selection of studies

We merged the results of the search using reference management software and removed duplicate records. Two review authors (MM and AL) independently examined titles and abstracts to remove obviously irrelevant reports and retrieved the full text of potentially relevant reports. They linked multiple reports of the same study and independently examined full-text reports for compliance with eligibility criteria using a study eligibility form. MM and AL resolved any disagreements regarding study inclusion or exclusion with the assistance of the other author, TK. Neither author was blinded to the names of the study authors, institutions, journal of publication nor results, as this practice has uncertain benefit in protecting against bias (Higgins 2011). We created a PRISMA flow diagram (Moher 2009) to show the process of inclusion and exclusion of RCTs; potentially eligible studies that were excluded are noted in the 'Excluded studies' section.

#### Data extraction and management

Two review authors (MM and AL) independently extracted data from the studies using a data extraction form. We collected the following information:

- study source (name of person extracting data, study ID, report ID, review author, citation and contact details);
- eligibility (confirmation of eligibility for review as per protocol, reason for exclusion);
- methods (study aims, study design, total study duration, unit of allocation, all information required for the 'Risk of bias' tool, ethics approval);

- participants and setting (age, recruitment method, inclusion and exclusion criteria, baseline imbalances, informed consent obtained, number of participants randomised, time of first symptom onset, rural or urban setting, developing or developed country setting, subgroups measured, subgroups reported);
- interventions (group name, number randomised to group, type of medication administered, method of administration, time of medication administration, place of administration, number and explanation for any dropouts, duration of follow up, economic variables);
- outcome measures coupled with results (outcome definition/name, person measuring or reporting, all-cause hospital mortality at 30 days and one year or longer where available, time to thrombolytic treatment, adverse effects, STEMI functional outcomes, comorbidities);
- results (continuous variables of outcome data such as measures of variability, dichotomous data such as total number of events in each arm and numbers of participants), additional notes (key conclusions of study, correspondence with authors needed, clarification of queries, ethics or stated conflicts of interest, duplicate publication, translation required);
- applicability (populations excluded, disadvantaged groups, applicability to developing countries).

We collated data from multiple reports of the same study into one data extraction form. MM collated and entered all data into Review Manager 5 (RevMan 2011). We resolved any disagreements by consensus.

#### Assessment of risk of bias in included studies

Two review authors (MM and AL) independently assessed the risk of bias of included studies using the Cochrane 'Risk of bias' assessment tool (six domains) (Higgins 2011), stating whether the risk of bias was low, high or unclear. The two authors independently pooled the results and discussed any differences with a third author (TK). We addressed the following bias domains: sequence generation, allocation concealment, blinding (blinding of participant and personnel, blinding of outcome assessors), incomplete outcome data, selective outcome reporting and other risks of bias. The review authors followed the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) for assessing bias. We extracted information based on the published data and contacted the authors whenever descriptions were missing or unclear.

#### Measures of treatment effect

##### Dichotomous data

Dichotomous outcomes, such as all-cause hospital mortality, were represented as risk ratios (RR) with 95% confidence intervals (CIs). Adverse effect data were measured as proportions or rates, respectively, depending on the study data.

##### Continuous data

Continuous effect measures included the time from symptom onset to thrombolysis, measured as the mean difference (MD) or standardised MD between individuals receiving thrombolytic therapy in a pre-hospital or an in-hospital setting. Time to discharge, number of days in hospital and ejection fraction were measured as MDs or standardised MDs between groups.

#### Unit of analysis issues

Only RCTs were included. The authors identified no cluster RCTs or multi-arm RCTs. Hence, the unit of analysis was at an individual level.

#### Dealing with missing data

We asked the authors of one RCT (the European Myocardial Infarction Project (EMIP)) to provide missing data so that the study could potentially be included in the review. Unfortunately they were unable to provide any data and the trial was excluded from the study. We performed no imputing of missing data.

#### Assessment of heterogeneity

We performed a visual inspection of the forest plot for heterogeneity. Heterogeneity was assessed using the Chi<sup>2</sup> test, with a P value < 0.1 considered indicative of significant heterogeneity, and the I<sup>2</sup> statistic. As there was reasonable clinical and methodological similarity between trials, we were able to carry out a meta-analysis. We sought possible reasons for any substantial heterogeneity.

#### Assessment of reporting biases

The use of a funnel plot to explore possible reporting biases was precluded due to the limited number of included studies (< 10).

#### Data synthesis

As the trials were clinically and methodologically similar, we undertook a meta-analysis. We used a fixed-effect meta-analysis if studies were estimating the same treatment effect (no statistical heterogeneity) and a random-effects meta-analysis if studies showed substantial statistical heterogeneity. We used RevMan software to perform the meta-analysis. If we performed a meta-analysis in the presence of high levels of heterogeneity, we sought possible explanations for this heterogeneity.

#### Subgroup analysis and investigation of heterogeneity

We predefined several possible subgroups for meta-analysis:

- practitioner type: paramedic (basic versus advanced) versus physician (emergency versus cardiologist) thrombolytic administration on mortality outcome;
- HIC versus LMIC settings;
- rural versus urban settings;
- remote telemetry with consultant communication versus independent paramedic thrombolytic administration;
- automated versus manual ECG interpretation;
- different types of thrombolytic medication administered compared for mortality and adverse effects;
- anatomical location of STEMI;
- mobile intensive care units compared with primary response;
- adverse effects of pre-hospital thrombolytic agents as administered by paramedics versus physicians.

However, we did not perform any subgroup analyses due to the limited number of included studies. The *Cochrane Handbook for Systematic Reviews of Interventions* recommends a minimum of 10 studies.

## Sensitivity analysis

We performed sensitivity analyses in order to explore the influence of the following factors on effect size:

- fixed-effect model versus a random-effects model meta-analyses;
- exclusion of trials with a high risk of bias.

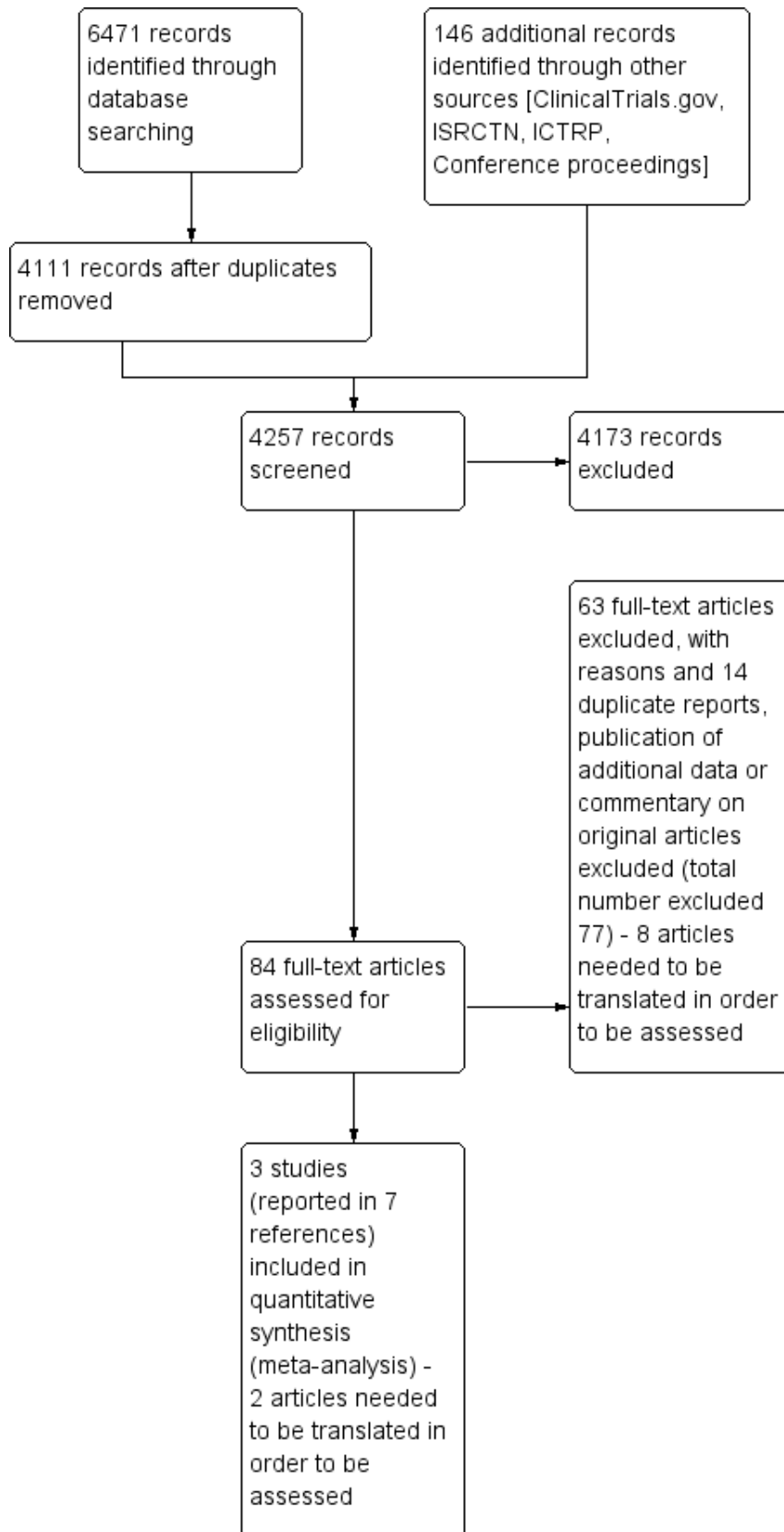
## RESULTS

### Description of studies

#### Results of the search

The electronic database searches identified 6471 titles for potential inclusion. After the removal of duplications, 4111 titles remained of which 4027 titles were found not to be relevant. We retrieved full-text articles for the remaining 84 titles which two authors independently screened for eligibility. We included three studies, reported in six papers, met the eligibility criteria. The trial registry searches revealed 146 potentially eligible studies of which all we excluded ([Figure 1](#)). Ten trials were translated with the help of the Cochrane Heart Group.

**Figure 1. Study flow diagram.**



## Included studies

See: [Characteristics of included studies](#)

We identified three RCTs (538 participants), conducted in France, USA and Germany, which examined the efficacy of pre-hospital versus in-hospital thrombolysis for STEMI. [Castaigne 1989](#) used 30 U anisoylated plasminogen streptokinase activator complex (APSAC) whereas [Schofer 1990](#) used urokinase (2 million U IV) and [Weaver 1993](#) used alteplase 100 mg as the thrombolytic agent in both the intervention and control arms. In [Castaigne 1989](#) and [Schofer 1990](#) physicians in mobile care units administered the pre-hospital thrombolytic agents whereas in [Weaver 1993](#) paramedics administered the thrombolytic. The primary outcomes were similar across all three trials and included mortality, time intervals, angiographic data, ejection fraction and complications.

[Castaigne 1989](#) was a two phase study conducted in the Val de Marne district close to Paris, France. The first phase comprised a simulation pilot study and an education study; the latter evaluated anaesthesiologists' hypothetical decision to correctly thrombolise individuals with chest pain possibly due to ACS in mobile care units. A total of 294 participants were reviewed over 1 year. The second phase of the study was a RCT comparing pre-hospital versus in-hospital thrombolysis conducted over 2 years using 30 U APSAC injected over more than four minutes. The researchers screened 320 individuals with STEMI, and 100 were included in the trial. The intervention in both treatment groups was administered by physicians (including that in mobile care units). The main outcome for phase one of the study was diagnostic accuracy; that for the second phase was the delay between at-home and in-hospital injection for participants having received placebo at home.

[Schofer 1990](#) was an RCT conducted in Germany within the mobile care unit systems of AK Altona, Stadtische Kliniken Kiel

and Darmstadt. The pre-hospital group (40 participants) received urokinase (2 million U IV) at home and placebo at hospital whereas the in-hospital group (38 participants) received placebo at home and urokinase (2 million U IV) at hospital, both followed by 1000 U/hour of heparin at hospital. Urokinase was diluted with 20 mL of injectable water. The mobile care units were staffed with a physician and two emergency medical technicians. The following study endpoints were reported: time intervals, angiographic data and creatine kinase levels, stress test before discharge and complications.

[Weaver 1993](#) was an RCT of pre-hospital versus in-hospital initiated thrombolytic therapy conducted in Seattle metropolitan area and the surrounding King County, in the USA. The trial ran from November 1988 to December 1991, and involved 19 hospitals and all paramedical systems in the Metropolitan area. The pre-hospital-initiated group received Aspirin 325 mg and alteplase 100 mg at home and no placebo at hospital whereas the hospital-initiated group received no placebo at home and Aspirin 325 mg and alteplase 100 mg at hospital. A total of 360 participants were included in the study, 175 and 185 in the pre-hospital and in-hospital treatment arms, respectively. Pre-hospital thrombolysis was performed by paramedics (emergency care professionals) with physician guidance. Study endpoints included diagnostic accuracy of STEMI, time to treatment, pre-hospital and in-hospital complications, ejection fraction and infarct size.

## Excluded studies

See: [Characteristics of excluded studies](#)

## Risk of bias in included studies

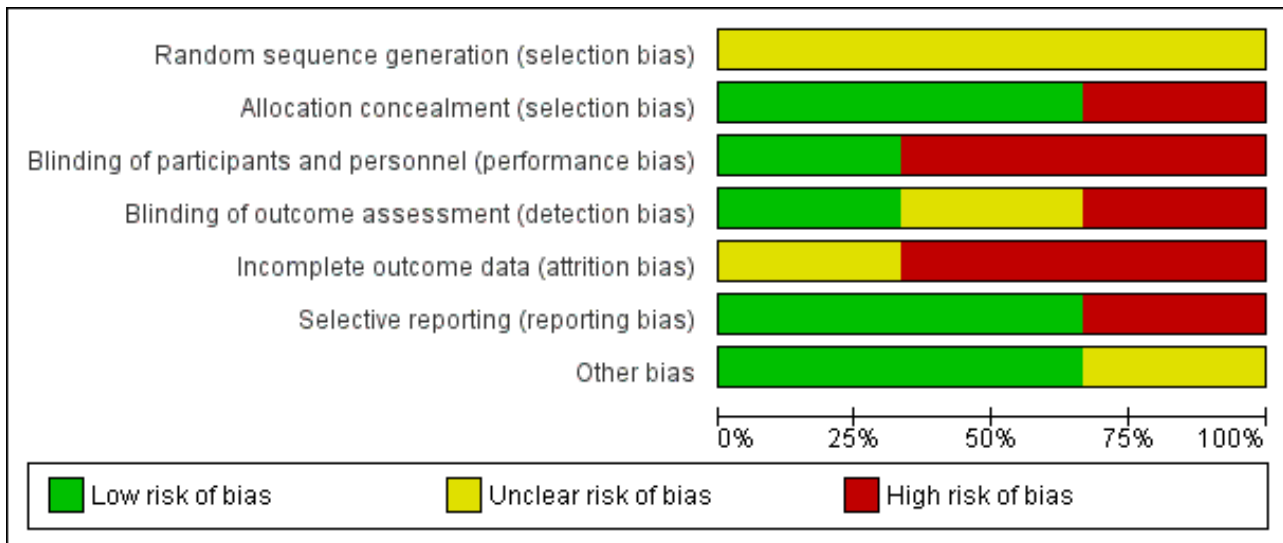
See: 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study ([Figure 2](#)).

**Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Castaigne 1989	?	-	-	-	-	+	?
Schofer 1990	?	+	+	?	-	+	+
Weaver 1993	?	+	-	+	?	-	+

See: 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies (Figure 3).

**Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



**Allocation**

Schofer 1990, Weaver 1993 and Castaigne 1989 provided no description of random sequence generation; as a result we considered the risk of bias to be unclear. We judged the risk of bias for allocation concealment in Castaigne 1989 to be high as the allocation code was broken. We considered Schofer 1990 and Weaver 1993 to have a low risk of bias for allocation concealment.

**Blinding**

We considered the risk of bias for the blinding of participants and personnel, as well as for outcome assessment (detection bias), in Castaigne 1989 to be high. The authors of this study state that the mobile care unit physicians were blinded. However, the blinding is not described and the code could be broken if the physician thought it necessary. Upon arrival at hospital the code was broken as all the other physicians and assessors would have knowledge of the treatment received. In Schofer 1990, we judged the risk of bias due to the blinding of participants and personnel to be low as numbered paired ampoules containing either placebo or thrombolysis were used. For outcome assessment we judged the risk to be unclear as no description was provided. We considered the risk of bias due to blinding of participants and personnel in Weaver 1993 to be high as alteplase was administered in an open manner; we judged the risk of bias for outcome assessment to be low as the groups were unknown to the assessor.

**Incomplete outcome data**

We judged the risk of bias for incomplete outcome data to be high in Castaigne 1989 and Schofer 1990, and unclear in Weaver 1993. Participants in Castaigne 1989 were not assessed according to intention-to-treat analysis and some outcome data were not reported. In Schofer 1990 some data were excluded from analysis and some were missing. Weaver 1993 did not report whether participants were lost to follow up or withdrawn from participation.

**Selective reporting**

We judged Castaigne 1989 and Schofer 1990 to have a low risk of bias for selective reporting. We considered Weaver 1993 to have a high risk as some prespecified complications were not reported in the intervention group.

**Other potential sources of bias**

Schofer 1990 and Weaver 1993 had no indications of other sources of bias and as a result we judged this risk to be low. We judged Castaigne 1989 to have an unclear risk as the report did not include a table of baseline characteristics.

**Effects of interventions**

See: **Summary of findings for the main comparison** Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction; **Summary of findings 2** Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction

**Primary outcome**

Mortality data were available for all three included RCTs. However, none of the studies presented the mortality data over the prespecified time periods (one month and one year); hence, no time period was used and we report the general all-cause mortality rate.

There is low quality evidence indicating uncertainty about whether pre-hospital compared to in-hospital thrombolysis reduces mortality (**Summary of findings for the main comparison**) (RR 0.73, 95% CI 0.37 to 1.41, three RCTs; 538 participants) (**Analysis 1.1**). There was no heterogeneity between studies ( $Chi^2 = 0.29$ ;  $P$  value = 0.86;  $I^2 = 0\%$ ) and we therefore used a fixed-effect model for meta-analysis (**Analysis 1.1**). Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. It should be noted that the meta-analysis included only 538 participants and thus one should interpret these results with caution. We rated the studies as having an overall unclear/high risk of bias (Figure 3).

A sensitivity analysis excluding the trial with a high risk of bias (Castaigne 1989) also found no significant difference between the pre-hospital and in-hospital thrombolysis groups (Analysis 3.1). Excluding Castaigne 1989, however, resulted in a shift of the pooled effect measure towards a stronger protective effect of pre-hospital thrombolysis compared with the non-sensitivity analysis (RR 0.68 compared with 0.73), although the difference between groups remained non-significant.

## Secondary outcomes

### Time to thrombolysis

Schofer 1990 and Weaver 1993 presented data on the time from the onset of symptoms to thrombolysis. There was high-quality evidence (Summary of findings 2) that pre-hospital thrombolysis reduced the mean time to thrombolysis by 38 minutes (MD -37.95 minutes, 95% CI -61.12 to -14.77, two RCTs; 438 participants, Analysis 2.1). We found substantial heterogeneity ( $\text{Chi}^2 = 3.53$ ;  $P$  value = 0.06;  $I^2 = 72\%$ ) and we therefore conducted a random-effects meta-analysis. Heterogeneity was not thought to be sufficiently significant to forgo meta-analysis as a visual inspection revealed overlapping CIs and point estimates in a similar direction. We rated these two studies as having an overall low risk of bias (Figure 2).

### Acute myocardial infarction functional outcomes

All three included RCTs reported mean percentage ejection fraction. However, Castaigne 1989 presented the mean percentage ejection fraction for pre-hospital thrombolysis (56.7%) and in-hospital thrombolysis (53.4%) without providing the standard deviations for the measurements. We therefore conducted a meta-analysis including Schofer 1990 and Weaver 1993 only. We found low-quality evidence (Summary of findings 2) that there may be no difference between the ejection fraction in pre-hospital versus in-hospital thrombolysis (MD -1.18, 95% CI -3.50 to 1.13, two RCTs; 416 participants, Analysis 2.2). As we found no heterogeneity ( $\text{Chi}^2 = 0.16$ ;  $P$  value = 0.69;  $I^2 = 0\%$ ), we therefore used a fixed-effect model for meta-analysis. The low-quality data indicate that further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. We rated these two studies as having an overall low risk of bias (Figure 2).

None of the included RCTs reported data on the acute myocardial infarction functional outcomes, classification of heart failure (New York Heart Association functional classification system) and time to discharge or days in hospital, measured from admission to discharge (proposed secondary outcomes).

### Adverse effects

Four adverse effects were prioritised as clinically important and incorporated in the GRADE assessment: ventricular fibrillation, stroke, allergic reaction and bleeding.

There was low-quality evidence that there may be no difference in the occurrence of ventricular fibrillation (two RCTs), stroke (one RCT) or allergic reactions (one RCT) between groups. There was moderate-quality evidence that was no difference in bleeding complications between groups (two RCTs, Summary of findings 2). We downgraded the evidence due to imprecision as the confidence interval included appreciable harm and appreciable benefit (Analysis 2.3).

## DISCUSSION

### Summary of main results

There is low quality evidence indicating uncertainty about whether pre-hospital compared to in-hospital thrombolysis reduces mortality. Additional data may change this finding (Summary of findings for the main comparison). We rated the included studies as having an overall unclear/high risk of bias (Figure 3).

We found high-quality evidence that the time to thrombolysis in those who were thrombolysed pre-hospital compared with those thrombolysed in hospital was statistically significantly reduced by 38 minutes. We rated the studies included in this analysis as having an overall low risk of bias (Figure 3).

We found low-quality evidence that there may be no difference in acute myocardial infarction functional outcomes (ejection fraction) between pre-hospital and in-hospital thrombolysis. We rated the relevant studies as having an overall low risk of bias (Figure 3).

There was low-quality evidence that there may be no difference in adverse effects between pre-hospital and in-hospital thrombolysis (Summary of findings 2). We rated the relevant studies as having an overall low risk of bias (Figure 3).

### Overall completeness and applicability of evidence

We were able to include only three relatively small trials in this review and this influences the external validity of our findings. We were unable to obtain requested data from a potentially eligible study and therefore have excluded it (EMIP). The excluded study could have contributed to the power of the meta-analysis to detect a difference between groups for the primary outcome. None of the included studies presented data on heart failure classification and days in hospital or time to discharge. The results of this review are applicable to HICs but less so to LMICs, as all the included trials were conducted in developed country settings. We were unable to perform subgroup analyses due to the limited number of included studies.

The findings of this review have strong external validity when generalised to HICs; however, LMICs need to take into consideration their unique health and emergency medical care systems. Local policy makers and clinical directors should consider their local health infrastructure and population distribution needs (rural compared with urban), emergency care systems and availability of the intervention compared with surgical alternatives (e.g. availability of PCI). These considerations should be taken into account when developing clinical guidelines for pre-hospital thrombolysis.

### Quality of the evidence

We used GRADE methodology to explore the quality of the evidence. The primary outcome, mortality, was supported by low-quality evidence only, which was attributable to a high risk of methodological bias and imprecision in the point estimate. Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Secondary outcomes that were reported in the included studies were time to thrombolysis, ejection fraction and adverse effects. There was high-quality evidence that time to thrombolysis is



reduced when treatment is delivered pre-hospital compared with in the hospital. Further research is unlikely to impact our confidence in the estimate. We rated the evidence for the outcome of ejection fraction as low quality, which we downgraded due to the risk of methodological bias and imprecision (the confidence interval includes appreciable benefit and appreciable harm). Only low-quality evidence was available for all the adverse effect outcomes due to high levels of imprecision, with the exception of the evidence for bleeding complications, which we judged to be of moderate quality.

### Potential biases in the review process

We used Cochrane methodology to conduct a comprehensive search to identify all the available trials in order to answer this review question. Data for one potentially eligible study could not be obtained as the authors did not provide the necessary data; hence, we may have omitted additional evidence that could have contributed to the results.

### Agreements and disagreements with other studies or reviews

[Morrison 2000](#) is a systematic review and meta-analysis of pre-hospital versus in-hospital thrombolysis for acute myocardial infarction that assesses mortality. The study authors report a statistically significant difference in all-cause hospital mortality in favour of pre-hospital thrombolysis. [Morrison 2000](#) included RCTs that assessed the efficacy of thrombolysis for both STEMI and NSTEMI. The current review specifically sought to investigate thrombolysis for STEMI as this type of therapy is not recommended for NSTEMI ([O'Connor 2010](#)). [Morrison 2000](#) found a mean time difference of 60 minutes between pre-hospital and in-hospital thrombolysis for acute myocardial infarction. Our results are consistent with those of this previously published review.

## AUTHORS' CONCLUSIONS

### Implications for practice

Pre-hospital thrombolysis reduces time to thrombolytic treatment, based on the results of three studies conducted in HICs. In settings where it can be safely and correctly administered by trained staff, pre-hospital thrombolysis may therefore be an appropriate intervention. We were unable to determine whether pre-hospital thrombolysis is superior to in-hospital thrombolysis with regard to mortality, ejection fraction or adverse effects. Pre-hospital

thrombolysis for STEMI has the potential to reduce the burden of disease in LMICs, especially in individuals who have limited access to in-hospital thrombolysis or PCI (e.g. those living in rural areas). Local policy makers and clinical directors should consider their local health infrastructure and population distribution needs (rural compared with urban), emergency care system and the availability of thrombolytic therapy compared to surgical alternatives (e.g. the availability of PCI). These considerations should be taken into account when developing clinical guidelines for pre-hospital thrombolysis. In [Weaver 1993](#), pre-hospital thrombolysis was performed by paramedics (emergency care professionals) with physician guidance, highlighting the advantage of a paramedic lead with physician teamwork as an alternative to a physician-led thrombolysis team, especially when considering physician availability in LMICs.

### Implications for research

The implications of these findings for research into STEMI are less clear. Further research required may include studies that take STEMI into consideration as opposed to AMI in general. We found no RCTs that evaluated the efficacy of pre-hospital thrombolysis for STEMI in LMICs. Large high-quality multicentre RCTs implemented in LMICs have the potential to develop those countries' health infrastructure and service delivery capacity. A pragmatic approach to conducting these RCTs would be most advantageous in order to determine the efficacy and efficiency of pre-hospital thrombolysis, especially taking into consideration the health challenges of LMICs. Pragmatic RCTs (including feasibility studies) would contribute to the required infrastructure, health system co-ordination, training models and policy development necessary for the implementation and facilitation of pre-hospital thrombolysis in LMICs.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

**Castaigne 1989**

Methods	Two-phase study conducted in the Val de Marne district near Paris, France  Phase 1: Simulation and education over 1 year  Phase 2: Randomised trial conducted over 2 years
Participants	Criteria for inclusion in trial:  1) Age < 75 years  2) Typical ischaemic chest pain for > 30 minutes and < 3 hours that did not respond to nitrates  3) ST-segment elevation of 0.2 mV or more in at least 2 standard leads (posterior infarction) or 3 precordial leads (anterior infarction)  4) No hypertension  5) No classic contraindication to thrombolytic therapy
Interventions	Pre-hospital group: participants received nitrates and 30 U anisoylated plasminogen streptokinase activator complex (APSAC) injected over > 4 minutes or placebo

**Castaigne 1989** (Continued)

In-hospital group: on arrival in the coronary care unit, the code was broken and, if the individual had received placebo at home he/she received APSAC 30 U over > 4 minutes. The coronary care unit physician decided whether thrombolytic treatment was appropriate

Outcomes	Study endpoints:  1) Diagnostic accuracy, delay between phone call to emergency medical service and arrival in coronary care unit for individuals included in or excluded from the trial 2) Delay between at-home and in-hospital injection for individuals having received placebo at home  3) Events intervening during the pre-hospital phase
Notes	Secondary reference (Dubois-Rande 1989) translated by Aurelie Jeandron

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
Allocation concealment (selection bias)	High risk	No description of allocation concealment. Allocation codes were broken.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Mobile care unit physician was blinded to the treatment; however, no description of blinding provided. Furthermore, it is stated that the code could be broken if the physician thought it necessary or if a cardiologist was present when the ambulance reached the individual's home.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Code broken upon arrival at hospital and therefore the assessor will have had knowledge of treatment received.
Incomplete outcome data (attrition bias) All outcomes	High risk	Individuals did not appear to be assessed according to intention to treat. Incomplete data.
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.
Other bias	Unclear risk	Did not report a baseline characteristics table – insufficient information to exclude other possible biases.

**Schofer 1990**

Methods	Double-blind randomised controlled trial in Germany
Participants	Criteria for inclusion in trial:  1) Severe chest pain typical of myocardial ischaemia lasting > 30 minutes  2) Arrival of the ambulance doctor within 4 hours after the onset of symptoms  3) $\geq 2$ mm of ST-elevation in $\geq 2$ ECG leads for inferior AMI and $\geq 3$ mm of ST-elevation in $\geq 2$ precordial leads for anterior AMI  4) Age $\leq 70$ years



**Schofer 1990** (Continued)

- 5) No prior AMI
- 6) No contraindications against thrombolysis

Interventions	Pre-hospital group: urokinase (2 million U intravenously) at home or placebo at hospital In-hospital group: placebo at home or urokinase (2 million U intravenously) at hospital Followed by 1000 U/hour of heparin at hospital
Outcomes	Study end points: 1) Time intervals 2) Angiographic data and creatine kinase 3) Stress test before discharge 4) Complications
Notes	Secondary reference (Mathey 1990) translated by Joerg Weber

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation. Authors only state participants were randomly assigned to ampoule pairs.
Allocation concealment (selection bias)	Low risk	Randomly assigned to the next in the series of ampoule pairs.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medac (Hamburg, Federal Republic of Germany) prepared numbered pairs of ampoules containing either urokinase in ampoule A and placebo in ampoule B, or vice versa.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 individual was diagnosed with pulmonary embolism and the data excluded. Some missing data for ejection fraction (see figure 3).
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.
Other bias	Low risk	No indication of other bias.

**Weaver 1993**

Methods	Randomised controlled clinical trial conducted in the city of Seattle and the surrounding King County from November 1988 to December 1991
Participants	Criteria for inclusion in trial: 1) Individuals with suspected acute myocardial infarction, pain for 6 hours or less

**Weaver 1993** (Continued)

- 2) aged  $\leq 75$  years, with no risk of bleeding (no history of stroke, recent bleeding or uncontrolled systolic (less than 180 mmHg) or diastolic (less than 120 mmHg hypertension) .
- 3) 12-lead ECG was obtained and a physician reviewed the findings over the telephone and made the final decision to randomise

Interventions	<p>Pre-hospital-initiated group: Aspirin 325 mg and alteplase 100 mg at home and no placebo at hospital</p> <p>Hospital-initiated group: no placebo at home and Aspirin 325 mg and alteplase 100 mg at hospital</p> <p>All participants received basic medical care including oxygen, rhythm monitoring devices and intravenous access. Additionally, morphine sulphate was used for pain, lidocaine and atropine for arrhythmias, and vasopressors and diuretics for treatment of hypotension and pulmonary oedema (prescribed by the remote physician)</p> <p>Sodium heparin administered to both groups on hospital arrival (5000 U bolus, followed by continuous intravenous infusion for at least 48 hours)</p>
Outcomes	<p>Study endpoints:</p> <ol style="list-style-type: none"> <li>1) Accuracy of diagnosis</li> <li>2) Time to treatment</li> <li>3) Complications</li> <li>4) Ejection fraction</li> <li>5) Infarct size</li> </ol>

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
Allocation concealment (selection bias)	Low risk	Sealed treatment kits were identical in terms of weight, balance and sound.
Blinding of participants and personnel (performance bias) All outcomes	High risk	For participants allocated to hospital-initiated treatment, no placebo was given in the field but an active treatment kit was available in the emergency department. Alteplase was infused in an open-label manner.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For assessment of infarct size and ventricular function measures after hospital discharge the core laboratory personnel were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It does not appear as if any participants withdrew or were lost to follow up; this is not reported in the text.
Selective reporting (reporting bias)	High risk	Some complications are not reported in intervention groups.
Other bias	Low risk	No indication of other bias.

ECG, electrocardiogram  
 AMI, acute myocardial infarction

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
<a href="#">Armstrong 2010</a>	Comparator percutaneous coronary intervention
<a href="#">Aufderheide 1992</a>	Not randomised controlled trial. No thrombolytic therapy was administered in the field during this study (feasibility study)
<a href="#">Bata 2009</a>	Participants randomly assigned to receive primary percutaneous coronary intervention or fibrinolysis
<a href="#">BEPS</a>	Pilot study for GREAT trial - no randomised trial, no hospital thrombolysis intervention
<a href="#">Brugemann 1992</a>	Data reported unclear - no mortality data (missing outcome data)
<a href="#">Cannon 2000</a>	Not randomised controlled trial - used historical controls
<a href="#">Castaigne 1987</a>	Outcome unclear - does not report number of participants in intervention or control groups
<a href="#">Castaigne 1990</a>	Unclear mortality data, unclear time measurement and unclear ECG confirmation
<a href="#">Castle 2007</a>	Not randomised controlled trial - retrospective descriptive analysis
<a href="#">Coccolini 1998</a>	Not pure randomised controlled trial - consecutive participant allocation
<a href="#">Cuccia 1988</a>	Thrombolysis (IV streptokinase) vs standard therapy. Translated by Deirdre Beecher
<a href="#">Danchin 2004</a>	French Nationwide Registry study
<a href="#">Doherty 2004</a>	Not randomised controlled trial
<a href="#">Dussoix 2003</a>	Compared pre-hospital thrombolysis to usual hospital care (in-hospital thrombolysis and mechanical intervention)
<a href="#">EMIP</a>	Participants included those with non-ST segment elevated myocardial infarction. Authors contacted for stratified (STEMI) data. Unable to provide missing data
<a href="#">Fokina 2008</a>	Not randomised controlled trial. Translated by Marina Karanikolos
<a href="#">Goldstein 2005</a>	Not randomised controlled trial
<a href="#">Grajek 2007</a>	Not randomised controlled trial - discusses mitral regurgitation. Translated by Ela Gohil
<a href="#">GREAT</a>	Participation eligibility was not based on ECG findings (STEMI) but rather on strong clinical suspicion of acute myocardial infarction by physician
<a href="#">Grijseels 1995</a>	Not randomised controlled trial - retrospective control arm
<a href="#">Herve 1988</a>	Randomised controlled trial with no description of participant selection, no inclusion criteria, no indication of age group or of how participants were diagnosed. Translated by Lynn Grignard
<a href="#">Hervé 1988a</a>	Randomised controlled trial comparing home thrombolysis to placebo. Translated by Lynn Grignard.

Study	Reason for exclusion
<a href="#">Kasper 1999</a>	Not randomised controlled trial. Translated by Nicole Martin
<a href="#">Kelly 2003</a>	Not randomised controlled trial
<a href="#">Kelly 2010</a>	Compared pre-hospital thrombolysis with half-dose pre-hospital thrombolysis and PCI
<a href="#">Khan 2009</a>	Not randomised controlled trial - prospective cohort, no interventions
<a href="#">Koefoed-Nielse 2002</a>	Quasi-experimental study (before and after trial)
<a href="#">Kudenchuk 1998</a>	ECG study – outcomes focused on ECG abnormalities secondary to thrombolysis
<a href="#">Lamfers 1999</a>	Not randomised controlled trial - retrospective review
<a href="#">Lamfers 2003</a>	Not randomised controlled trial. Study of two different thrombolysis medications administered in the pre-hospital setting
<a href="#">Lamfers 2004</a>	Not randomised controlled trial
<a href="#">Linderer 1993</a>	Not randomised controlled trial
<a href="#">Liu 2003</a>	Randomised controlled trial comparing pre-hospital thrombolysis versus immediate angiography
<a href="#">Mathew 2003</a>	Review of hospital data
<a href="#">McAleer 1992</a>	Open allocation - not randomised controlled trial
<a href="#">McAleer 2006</a>	Open allocation - not randomised controlled trial
<a href="#">McKendall 1991</a>	Not randomised controlled trial
<a href="#">McNiell 1989</a>	Some of the participants included in the trial were randomised for inclusion at the emergency department. Study does not present all-cause mortality data, only cardiac-cause mortality data
<a href="#">McNiell 1991</a>	Between 3 to 24 hours after administration of anistreplase, participants were randomised to receive either intervention or conventional therapy
<a href="#">Millin 2008</a>	Literature review
<a href="#">Morrison 2000</a>	Systematic review including randomised controlled trials of pre-hospital vs in-hospital thrombolysis in AMI with an outcome measure of all-cause hospital mortality. Selection criteria for participants were not similar to those of the current systematic review
<a href="#">Morrow 2002</a>	Feasibility trial comparing pre-hospital thrombolysis to sequential in-hospital controls from 6 to 12 months before
<a href="#">Rawles 1999</a>	Randomised controlled trial reporting 5-year mortality
<a href="#">Risenfors 1991</a>	Randomisation unclear - ECG criteria not used to include participants but recorded only after administration and treatment
<a href="#">Roque 1995</a>	Not randomised controlled trial. Translated by Joerg Weber
<a href="#">Rosell-Ortiz 2008</a>	Prospective database cohort

Study	Reason for exclusion
<a href="#">Rosenberg 2002</a>	Open-label pilot study administering a first bolus of reteplase before emergency department arrival and the second bolus after emergency department arrival
<a href="#">Roth 1990</a>	Not randomised controlled trial - used alternative monthly allocation
<a href="#">Rozenman 1994</a>	Not randomised controlled trial - alternative allocation
<a href="#">Rozenman 1995</a>	Not randomised controlled trial
<a href="#">Ruda 2009</a>	Participants with spontaneous reperfusion were randomised to be treated with emergency coronary angiography and, in case of stenosis >50%, balloon angioplasty or conservative treatment. Translated by Marina Karanikolos
<a href="#">Smalling 2007</a>	Randomised controlled trial comparing pre-hospital thrombolysis with PCI
<a href="#">Smith 2011</a>	Prospective data collection for all individuals admitted to Chesterfield Royal Hospital who received thrombolysis for a presumed myocardial infarction over a 12-month period
<a href="#">Stewart 1993</a>	Not randomised controlled trial
<a href="#">Svensson 2003</a>	Feasibility study, no randomisation
<a href="#">Tatu-Chitoiu 2002</a>	Pre-hospital accelerated streptokinase combined with enoxaparin and in-hospital accelerated streptokinase combined with enoxaparin compared to in-hospital standard streptokinase with heparin
<a href="#">Topol 1986</a>	Not randomised controlled trial
<a href="#">Trent 1995</a>	Secondary analysis of GREAT data
<a href="#">Walletin 2003</a>	Pateints with STEMI in the pre-hospital setting were randomised to receive tenecteplase and either (1) intravenous bolus of 30 mg enoxaparin followed by 1 mg/kg subcutaneously twice daily for a maximum of 7 days or (2) weight-adjusted unfractionated heparin for 48 hours
<a href="#">Weaver 1994</a>	Not randomised controlled trial
<a href="#">White 1990</a>	Participants were randomised to receive intravenous streptokinase plus rt-PA placebo over 3 hours or streptokinase placebo infused over 30 minutes plus rt-PA infusion over 3 hours
<a href="#">Woollard 2005</a>	Randomised to telemetry and conventional treatment - no active thrombolysis
<a href="#">Zeymer 2009</a>	Report on the data of the German Prehospital Myocardial Infarction Registry

AMI, acute myocardial infarction

ECG, electrocardiogram

IV, intravenously

PCI, percutaneous coronary intervention

rt-PA, recombinant tissue plasminogen activator

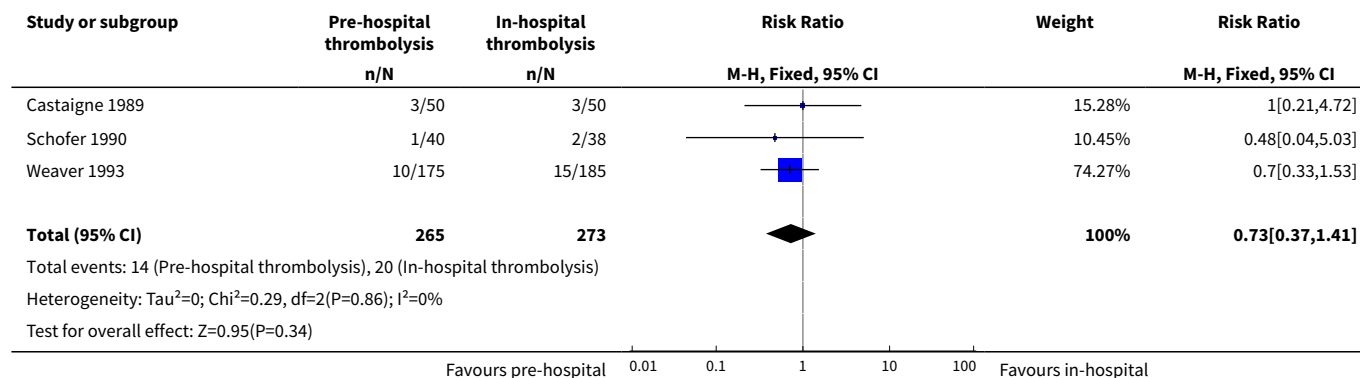
STEMI, ST-elevation myocardial infarction

## DATA AND ANALYSES

**Comparison 1. Pre-hospital versus in-hospital thrombolysis mortality**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause hospital mortality	3	538	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.37, 1.41]

**Analysis 1.1. Comparison 1 Pre-hospital versus in-hospital thrombolysis mortality, Outcome 1 All cause hospital mortality.**

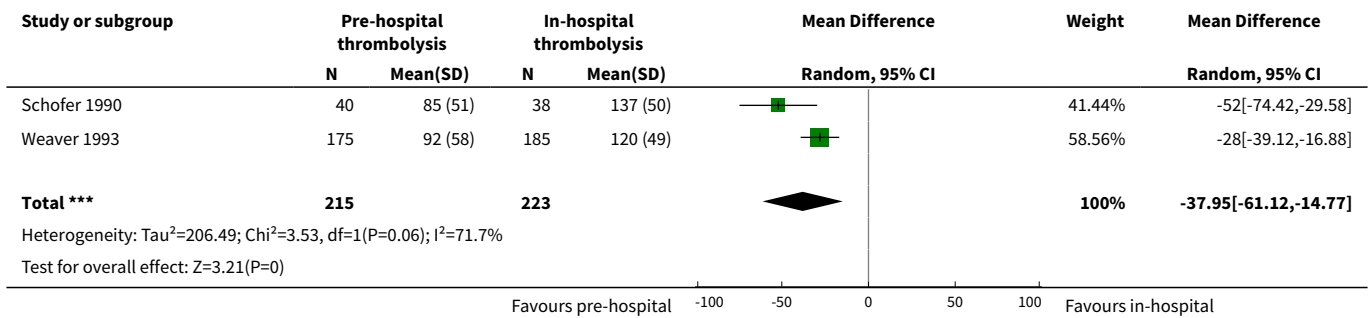


**Comparison 2. Pre-hospital versus in-hospital thrombolysis morbidity**

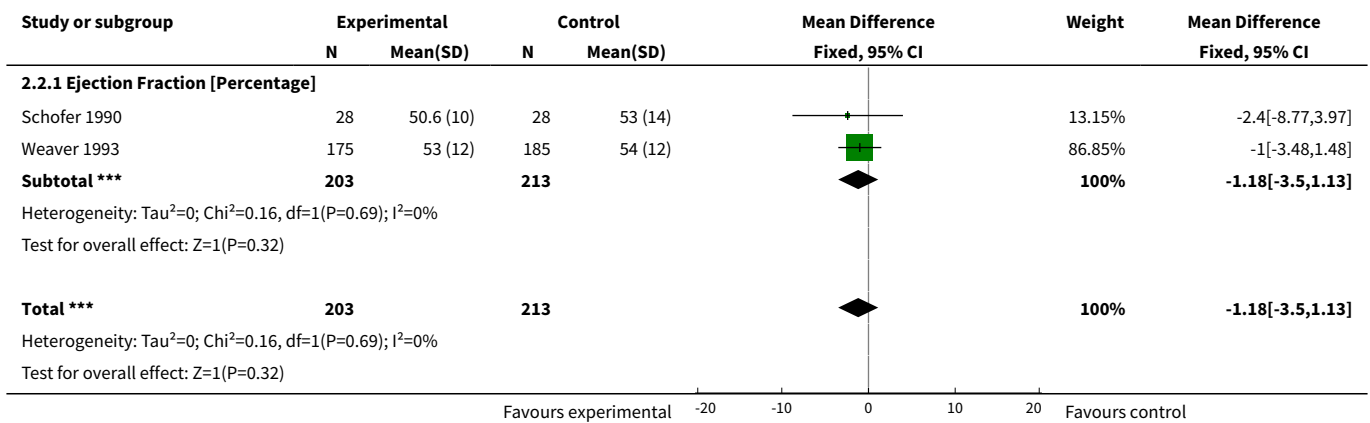
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to thrombolytic treatment	2	438	Mean Difference (IV, Random, 95% CI)	-37.95 [-61.12, -14.77]
2 Acute myocardial infarction functional outcomes	2	416	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-3.50, 1.13]
2.1 Ejection Fraction [Percentage]	2	416	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-3.50, 1.13]
3 Adverse effects	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Ventricular Fibrillation	2	178	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.68, 10.86]
3.2 Hypotension	2	178	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.47, 3.49]
3.3 Bleeding complications	2	438	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.41, 1.92]
3.4 Allergic Reaction	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [0.19, 77.03]
3.5 Intubation	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.06, 14.65]
3.6 Cardiac Massage	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.55]
3.7 Ventricular tachycardia	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.48, 3.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8 Wrong Diagnosis	1	78	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.97]
3.9 Pulmonary Congestion	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.40, 2.28]
3.10 Post-infact Angina	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.14, 6.41]
3.11 Bradycardia	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.22]
3.12 Reinfaction	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.22, 2.62]
3.13 Percutaneous transluminal coronary angioplasty	1	78	Risk Ratio (M-H, Fixed, 95% CI)	3.8 [0.44, 32.49]
3.14 Coronary Artery Bypass Graft	1	78	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.97]
3.15 Stroke	1	360	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [0.39, 11.40]

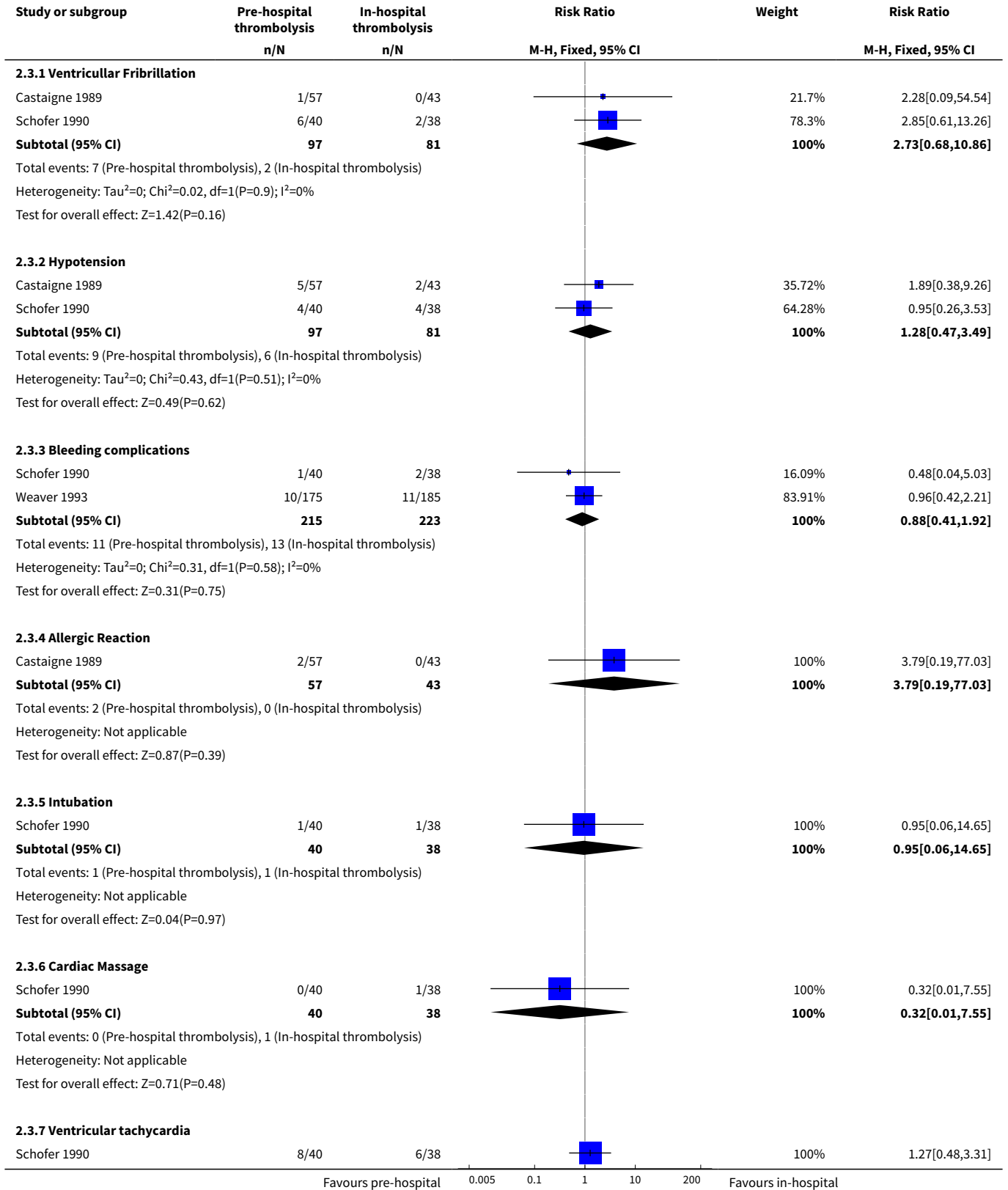
**Analysis 2.1. Comparison 2 Pre-hospital versus in-hospital thrombolysis morbidity, Outcome 1 Time to thrombolytic treatment.**



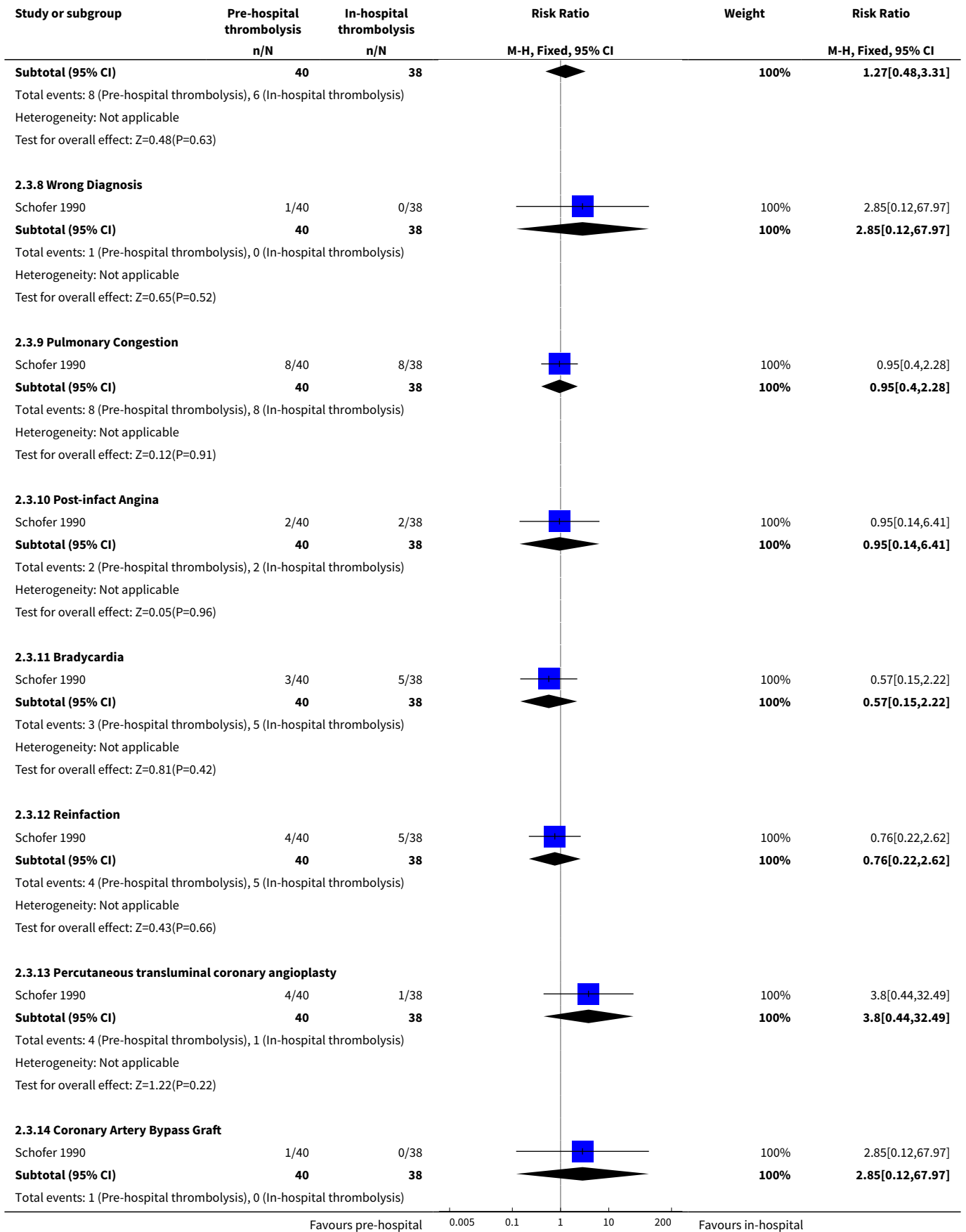
**Analysis 2.2. Comparison 2 Pre-hospital versus in-hospital thrombolysis morbidity, Outcome 2 Acute myocardial infarction functional outcomes.**

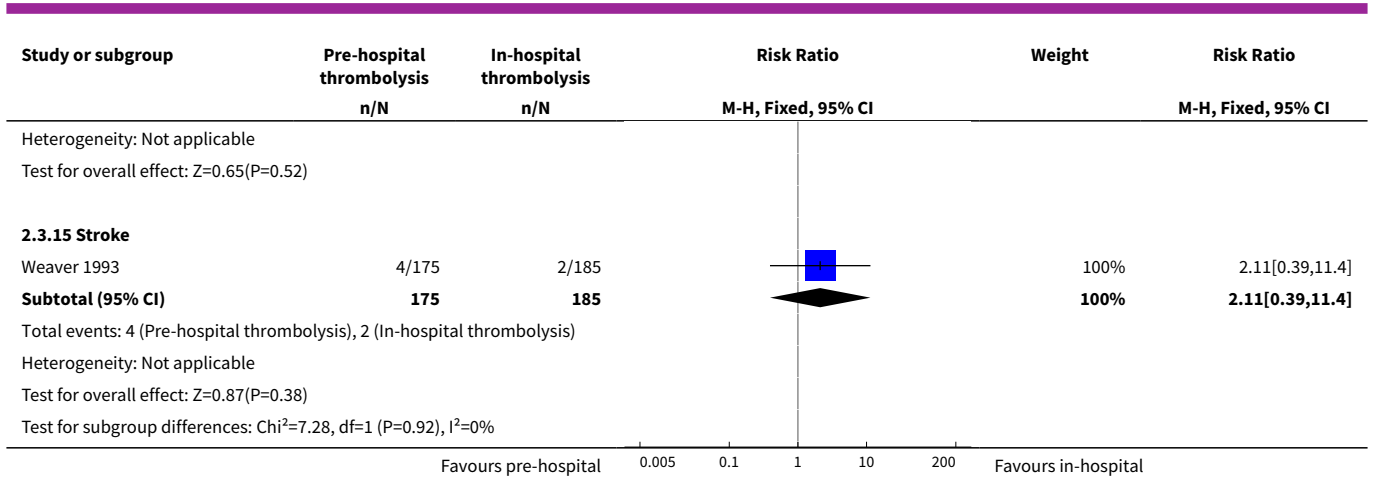


**Analysis 2.3. Comparison 2 Pre-hospital versus in-hospital thrombolysis morbidity, Outcome 3 Adverse effects.**





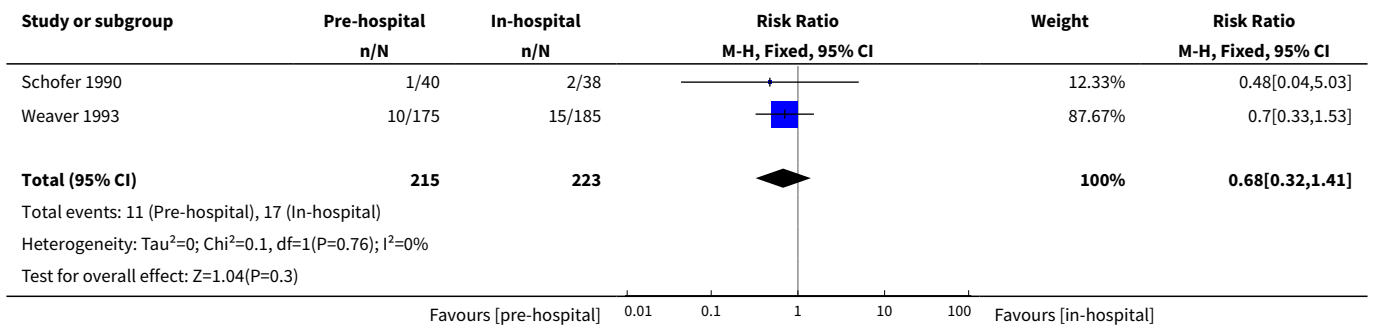




**Comparison 3. Pre-hospital versus in-hospital thrombolysis: Mortality sensitivity analysis**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause hospital mortality	2	438	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.32, 1.41]

**Analysis 3.1. Comparison 3 Pre-hospital versus in-hospital thrombolysis: Mortality sensitivity analysis, Outcome 1 All cause hospital mortality.**



**APPENDICES**

**Appendix 1. Appendix**

**CENTRAL**

#1 MeSH descriptor: [Myocardial Infarction] explode all trees

#2 "myocardial infarct\*"

#3 "heart infarct\*"

#4 ami

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Fibrinolytic Agents] this term only

#7 MeSH descriptor: [Thrombolytic Therapy] this term only

#8 thromboly\*

#9 alteplase

#10 reteplase

#11 streptokinase

#12 tenecteplase

#13 urokinase

#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #5 and #14

#16 MeSH descriptor: [Hospitals] explode all trees

#17 hospital\*

#18 prehospital\*

#19 pre-hospital\*

#20 #16 or #17 or #18 or #19

#21 #15 and #20

1. exp Myocardial Infarction/

2. myocardial infarct\$.tw.

3. heart infarct\$.tw.

4. ami.tw.

5. 1 or 2 or 3 or 4

6. Fibrinolytic Agents/

7. Thrombolytic Therapy/

8. thromboly\$.tw.

9. alteplase.tw.

10. reteplase.tw.

11. streptokinase.tw.

12. tenecteplase.tw.

13. urokinase.tw.

14. or/6-13

15. 5 and 14

16. exp Hospitals/

17. hospital\$.tw.

18. prehospital\$.tw.

19. pre-hospital\$.tw.
20. 16 or 17 or 18 or 19
21. 15 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. clinical trials as topic.sh.
27. randomly.ab.
28. trial.ti.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. exp animals/ not humans.sh.
31. 29 not 30
32. 21 and 31

**MEDLINE OVID**

1. exp Myocardial Infarction/
2. myocardial infarct\$.tw.
3. heart infarct\$.tw.
4. ami.tw.
5. 1 or 2 or 3 or 4
6. Fibrinolytic Agents/
7. Thrombolytic Therapy/
8. thromboly\$.tw.
9. alteplase.tw.
10. reteplase.tw.
11. streptokinase.tw.
12. tenecteplase.tw.
13. urokinase.tw.
14. or/6-13
15. 5 and 14
16. exp Hospitals/
17. hospital\$.tw.
18. prehospital\$.tw.
19. pre-hospital\$.tw.
20. 16 or 17 or 18 or 19

21. 15 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. clinical trials as topic.sh.
27. randomly.ab.
28. trial.ti.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. exp animals/ not humans.sh.
31. 29 not 30
32. 21 and 31

**EMBASE OVID**

1. exp heart infarction/
2. myocardial infarct\$.tw.
3. heart infarct\$.tw.
4. ami.tw.
5. or/1-4
6. fibrinolytic agent/
7. fibrinolytic therapy/
8. thromboly\$.tw.
9. alteplase.tw.
10. reteplase.tw.
11. streptokinase.tw.
12. tenecteplase.tw.
13. urokinase.tw.
14. or/6-13
15. 5 and 14
16. exp hospital/
17. hospital\$.tw.
18. prehospita\$.tw.
19. pre-hospita\$.tw.
20. or/16-19
21. 15 and 20
22. random\$.tw.

23. factorial\$.tw.
24. crossover\$.tw.
25. cross over\$.tw.
26. cross-over\$.tw.
27. placebo\$.tw.
28. (doubl\$ adj blind\$).tw.
29. (singl\$ adj blind\$).tw.
30. assign\$.tw.
31. allocat\$.tw.
32. volunteer\$.tw.
33. crossover procedure/
34. double blind procedure/
35. randomized controlled trial/
36. single blind procedure/
37. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. (animal/ or nonhuman/) not human/
39. 37 not 38
40. 21 and 39
41. limit 40 to embase

**Web of Science**

- #19 #18 AND #17
- #18 TS=(random\* or blind\* or allocat\* or assign\* or trial\* or placebo\* or crossover\* or cross-over\*)
- #17 #16 AND #12 AND #4
- #16 #15 OR #14 OR #13
- #15 TS=pre-hospital\*
- #14 TS=prehospital\*
- #13 TS=hospital\*
- #12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
- #11 TS=urokinase
- #10 TS=tenecteplase
- #9 TS=streptokinase
- #8 TS=reteplase
- #7 TS=alteplase
- #6 TS=thrombolyt\*
- #5 TS=fibrinolyt\*

#4 #3 OR #2 OR #1

#3 TS=ami

#2 TS=(heart SAME infarct\*)

#1 TS=(myocardial SAME infarct\*)

#### **CINAHL**

S21 S20 Limiters - Exclude MEDLINE records

S20 S17 and S18 and S19

S19 S13 or S14 or S15 or S16

S18 S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12

S17 S1 or S2 or S3 or S4

S16 AB pre-hospital\* or TI pre-hospital\*

S15 AB prehospital\* or TI prehospital\*

S14 AB hospital\* or TI hospital\*

S13 (MH "Hospitals+")

S12 AB urokinase or TI urokinase

S11 AB tenecteplase or TI tenecteplase

S10 AB streptokinase or TI streptokinase

S9 AB reteplase or TI reteplase

S8 AB alteplase OR TI alteplase

S7 AB thromboly\* or TI thromboly\*

S6 (MH "Thrombolytic Therapy")

S5 (MH "Fibrinolytic Agents")

S4 AB ami or TI ami

S3 AB "heart infarct\*" or TI "heart infarct\*"

S2 AB "myocard\* infarct\*" or TI "myocard\* infarct\*"

S1 (MH "Myocardial Infarction+")

#### **CONTRIBUTIONS OF AUTHORS**

Conceiving, designing and coordinating the review (MM). Data collection (MM and AL). Designing search strategies and undertaking searches (Cochrane Heart Group). Screening search results and organising, screening and appraisal of papers (MM and AL). Obtaining translations of papers and screening unpublished studies (MM, AL and Cochrane Heart Group). Data management and entering data into RevMan (MM). Analysis, interpretation of data and methodological, clinical and policy perspective (MM, AL and TK). TK provided overall general advice and guidance on the review.

#### **DECLARATIONS OF INTEREST**

None known.

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## SOURCES OF SUPPORT

### Internal sources

- South African Cochrane Centre, South Africa.  
Expertise, internal peer-review and project working space
- Stellenbosch University, South Africa.  
Access to electronic databases and library services

### External sources

- Cochrane Heart Group, UK.  
Search strategy and primary electronic search, obtaining full text articles and translation of foreign language articles. Peer-review and author support

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title was changed from "Pre-hospital versus in-hospital thrombolysis for acute myocardial infarction" to "Pre-hospital versus in-hospital thrombolysis for ST-elevation myocardial infarction". We were unable to find data on mortality at the times prespecified in the protocol and have therefore analysed mortality in general. No handsearching was done and pharmaceutical companies were not contacted due to operational time restraints.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Emergency Medical Services; \*Thrombolytic Therapy [adverse effects] [mortality]; Fibrinolytic Agents [\*administration & dosage] [adverse effects]; Hemorrhage [chemically induced]; Myocardial Infarction [\*drug therapy] [mortality]; Randomized Controlled Trials as Topic; Time-to-Treatment

### MeSH check words

Humans