Strategy to Reduce Mortality Rates of ST-elevation Acute Myocardial Infarction Using Prehospital Thrombolysis: A Meta-analysis

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Abstract

Importance: Ischemic heart disease is the leading cause of death worldwide. In ST-elevation myocardial infarction (STEMI), delaying reperfusion from the onset of chest pain increases the incidence of mortality and morbidity. Prehospital thrombolysis (PHT) has been evaluated in the setting of STEMI. We performed a systematic analysis of studies of PHT in acute STEMI. **Objective:** The objective of this study was to evaluate the all-cause mortality benefit in STEMI with PHT during short-term and long-term follow-up. **Data Sources:** In December 2020, the Cochrane search strategy was used to analyze randomized control trials, nonrandomized control studies, and registry studies in PubMed, EMBASE, Cochrane Library, Google Scholar, ClinicalKey, and Clinical Trial Registries. The search was repeated, and the included studies were updated in June 2023 to include more recent literature. We restricted the analysis to full-text publications in English. **Study Selection:** Studies using any thrombolytic agent in treating acute myocardial infarction in prehospital and inhospital settings with or without percutaneous Coronary intervention (PCI) were included in the analysis. Selection criteria included patient history and symptoms, electrocardiogram findings, and cardiac markers. **Data Extraction:** We used the Cochrane Handbook for Systematic Reviews of Interventions for assessing bias, the PRISMA flow diagram to show the process of inclusion and exclusion of studies, and RevMan software to perform meta-analysis. **Main Outcomes and Measures:** Outcomes include all-cause hospital mortality rate of PHT versus inhospital thrombolysis (IHT), influence of ischemic median time on all-cause mortality with PHT, and effect of PHT before PCI. The measures must have been observed for a follow-up period of up to 35 days, 1-year, and 5-years. **Results:** Data from 63,814 patients from 32 studies were reviewed. Results indicate a reduction in all-cause mortality in patients assigned to PHT (odds ratio [OR] −0.68, $P < 0.00001$) compared to IHT. There was a significant reduction in mortality when thrombolytics were administered before PCI (OR − 0.78, $P = 0.0001$). The overall survival was better with an ischemic time of <2 h. Mortality was higher with longer ischemic time (3 h and 6 h). Among patients who presented within 2 h of the onset of chest pain, mortality was lower compared to primary PCI (pPCI). **Conclusion:** PHT offers faster reperfusion and reduces all-cause mortality compared to IHT. A strategy of PHT within the first 2-3 h of ischemic pain followed by PCI (if indicated) could offer better survival than pPCI.

Keywords: Inhospital thrombolysis, ischemia, PCI, prehospital thrombolysis, ST-elevation myocardial infarction

Introduction

Ischemic heart disease (IHD) is the leading cause of global death and disability. According to the most recent global disease burden estimates, IHD may account for approximately 9 million deaths worldwide.[1] Acute myocardial infarction (AMI), which accounts for about 10% of all IHD cases, is one of the most common causes of mortality.[2]

India has a huge burden of acute coronary syndrome (ACS), with individuals having a younger age of onset compared to the Western population.[3] In developing countries such as India, patients tend to reach the hospital several hours post the onset of acute chest pain. The infrastructural and socioeconomic

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limitations contribute to the delay in reperfusion therapy when compared to Western counterparts.[4] This increases the risk of morbidity and mortality burden among patients with ACS in the developing world.

In AMI, myocardial salvage is crucial, which is directly linked to early reperfusion. In porcine models of coronary collateral circulation, brief coronary occlusion lasting for 15–30 min does not lead to significant myocardial damage. However, at 90 min, there is about 40%–50% of cell death, and at 120 min, there could be irreversible damage in almost 100% of the wall.[5] Therefore, it is evident that timely intervention is crucial for better clinical outcomes. Early reperfusion has been observed to abort an MI in nearly 10%–25% of patients and facilitate better mortality outcomes in both short- and long-term treatment.[6] Reperfusion after 6 h will likely result in minimal or no myocardial salvage except in situations like stuttering MI. The reperfusion is highly effective when delivered within the ischemic time of <2 h.

Percutaneous coronary intervention (PCI) demands significant execution time to organize and perform after the patient arrives at the hospital. Due to inherent delays in providing primary PCI (pPCI), reperfusion is rarely achieved within an optimal time of 2 h after the onset of symptoms. Door-to-balloon (DTB) times of <90 min and door-to-needle (DTN) times of <30 min are achieved only in a minority of cases.[7]

A detailed review on early thrombolysis (TL) or prehospital thrombolysis (PHT) has not been conducted since 2016, and it is pertinent to update the position of early TL, more so in the context of time delays and increasing PCI procedures. Clinical trials do not always represent real-world experience, although they are among the highest levels of evidence. A treatment's efficacy in the real world is better understood in unselected patient cohorts, i.e. in real-life health-care settings as in registries. Registry data provide valuable information on long-term outcomes backed by a large database.

We, therefore, systematically reviewed the available evidence, including clinical trials and registry data, to evaluate the impact of PHT on mortality benefits. We compared the mortality outcome of PHT with inhospital thrombolysis (IHT) and the effect of PHT before PCI.

Methods

Initiated in December 2020 and subsequently in July 2023 (to provide a recent update on the literature), we conducted a comprehensive electronic search for randomized or nonrandomized control trials and registry studies in PubMed, EMBASE, Cochrane Library, Google Scholar, and ClinicalKey, using the following key search terms: prehospital thrombolysis/fibrinolysis for STEMI, prehospital thrombolysis versus inhospital thrombolysis for STEMI, effect of time delay in thrombolysis for STEMI, prehospital thrombolysis versus primary PCI, prehospital treatment of STEMI, and mobile CCU (coronary care unit). In addition, we searched the following clinical trial registries: ClinicalTrials.gov (www.clinicaltrials.gov/), International Standard Randomized Controlled Trial Register (www.controlled-trials.com/isrctn/), and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We restricted to publications in the English language and the availability of full-text articles. The search strategies used can be found in PROSPERO 2021 CRD42021258680 (Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42021258680). We did not search gray literature or carry out any hand searching. We did not contact any pharmaceutical companies to provide their unpublished studies. A summary is provided in the PRISMA flow diagram [Figure 1]. Data from selected studies were collected and entered into Review Manager 5 (RevMan 2011) for meta-analysis.

Dichotomous outcomes, such as all-cause hospital mortality, were represented as odds ratios (ORs) with 95% confidence intervals (CIs). The unit of analysis was at an individual level. We identified some studies with a different mean time to intervention. Our study focused on a cutoff time of 2 h as the time to intervene for comparison. We also recorded issues with the study follow-up period ranging from 15–35 days to 5 years. We have done a subgroup analysis to negate any possible misinterpretations.

The forest plot for heterogeneity using the Chi-square test at a 1% level of significance and I^2 statistic indicated a reasonable clinical and methodological similarity between trials. Hence, we were able to carry out a meta-analysis. Reporting biases were assessed using funnel plots [Supplementary Figures 1-7].

All studies observed adults (≥16 years) diagnosed with AMI in either a prehospital or inhospital setting. The diagnosis was defined according to the included studies' criteria for STEMI and included at least two of the following three positive indicators: (1) the individual's history and symptoms, (2) electrocardiogram findings, and (3) biochemical cardiac markers (not mandatory for diagnosis). Studies using any thrombolytic agent in treating AMI in prehospital and inhospital settings with or without PCI were included in the analysis.

Outcome measures

1. All-cause hospital mortality – PHT versus IHT
2. Influence of ischemic median time on all-cause mortality with PHT for a follow-up period of up to 35 days, 1 year, and 5 years
3. Effect of intervention with thrombolytics within 2 h versus 3 h and 6 h time lag on mortality rate for a follow-up period of up to 5 years
4. Effect of PHT before PCI on 30-day mortality
5. Relationship of actual ischemic time before TL/TL + PCI on the mortality outcomes for a follow-up duration of up to 35 days, 1 year, and 5 years.

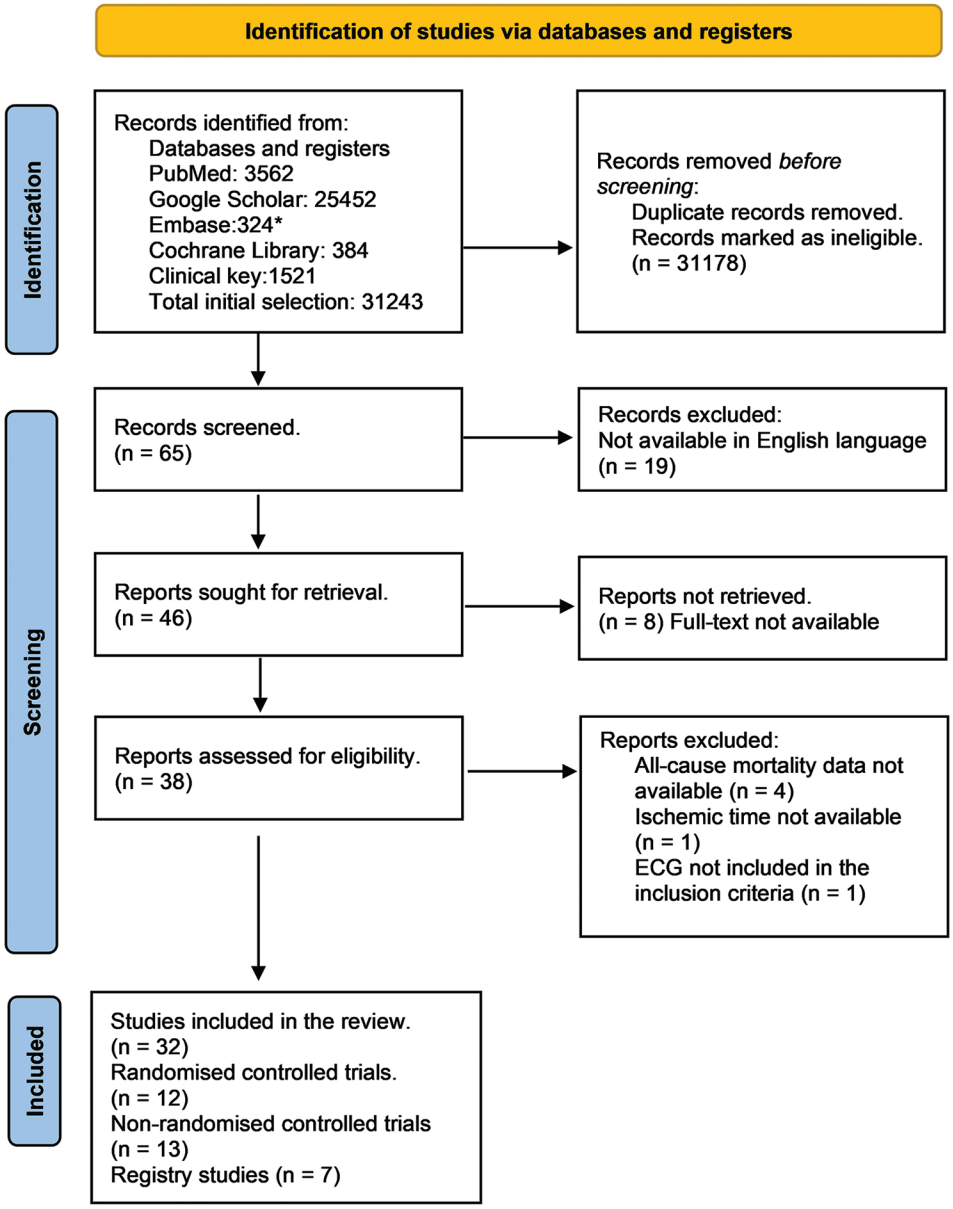

Figure 1: PRISMA flow diagram of systematic review methodology. *Search results from EMBASE were similar to search results from other databases. Hence, the search in EMBASE has been conducted only until December 2020

Results

Study characteristics and risk of bias tabulation

Data from 32 studies with 63,814 patients were included in this meta-analysis [Table 1]. The risk-of-bias (RoB) estimation was carried out using Cochrane "RoB" assessment tools (ROBINS tool, RoB2.0) (Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258680) and displayed in Supplementary Figure 1. RoB analysis for registries was not performed. The publication of Stenestrand *et al*. (RIKS-HIA) had a higher risk of bias in the author's view and is explained in detail in the upcoming section on mortality rate and ischemic time.[34]

There are two comparator groups: patients receiving either PHT or IHT treatment. The data analyzed included the mortality rate (follow-up period of up to 35 days) as the number of events in the total patient population in each comparator group. There were 20 included studies in this analysis based on the availability of complete information [Figure 2a]. Since the heterogeneity of the data between the studies was not significant in a random-effects model, the fixed-effects model is presented here. The reduction in mortality in the PHT group was significant ($P < 0.00001$) compared to the IHT group (OR = 0.68; 95% CI [0.62–0.74]). For verifying sensitivity, the analysis was repeated in studies that were only RCTs [Figure 2b]. The inferences were reproducible with a significant reduction ($P = 0.008$) in mortality among the PHT compared to the IHT group (OR = 0.8; 95% CI [0.68–0.94]).

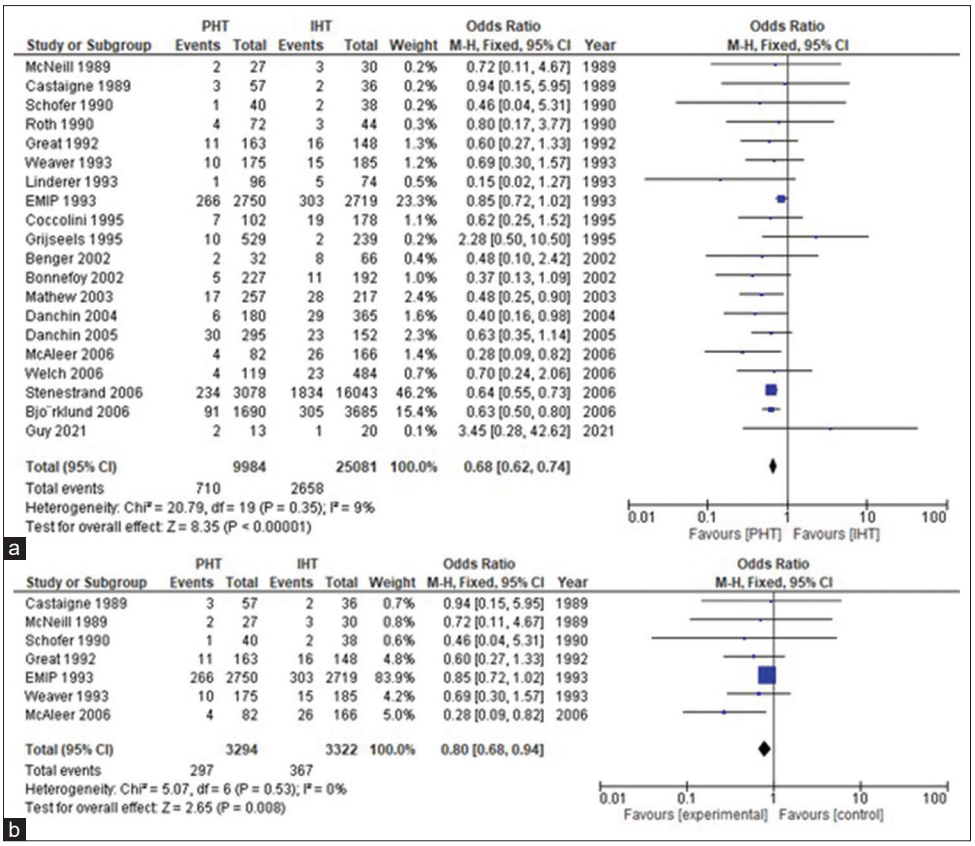

Figure 2: Effect of prehospital thrombolysis versus inhospital thrombolysis on all-cause mortality rate. Forest plot representation – Comparing the effect for a follow-up period of up to 35 days from studies including (a) randomized control trials, nonrandomized trials, and registry data, and (b) only randomized control trials. The size of the squares is proportional to the weight of the study. Horizontal lines represent a 95% confidence interval (CI) of the study. The diamond indicates the pooled estimate with 95% CI. *N* is the number of individuals, OR: Odds ratio, CI: Confidence interval

To quantitatively compare the short- and long-term mortality effect of median ischemic time of <2 h, the analysis was performed for a follow-up period of up to 35 days [Figure 3a], up to 1 year [Figure 3b], and up to 5 years [Figure 3c]. The 35-day mortality rate data from 10 studies indicated that ischemic time of <2 h had a significant impact ($P < 0.00001$) on survival with an OR of 0.64 (95% CI [0.53–0.78]). Similarly, results from studies with a follow-up duration of 1 year ($n = 5$ studies) [Figure 3b] and 5 years ($n = 3$ studies) [Figure 3c] indicated a significant reduction ($P < 0.00001$) in all-cause mortality, when the thrombolytic intervention was given within 2 h.

Mortality rate and ischemic time

The influence of ischemic time on mortality rate was analyzed. Based on the CAPTIM trial and various other studies,[12,40,41] we did a 2-h cutoff analysis and compared it with other time periods. From available literature, the mortality rate following an ischemic time of 2 h, 3 h, and 6 h and a follow-up duration of 30 days, up to 1 year, and up to 5 years were analyzed. Figure 4 shows the survival plot as a function of ischemic time for a follow-up period of up to 5 years. The results indicate a better survival rate when the ischemic time was <2 h, and the mortality progressively rises with increasing ischemic time (3 h and 6 h plots) [Figure 4].

We extended the analysis to study the effect of prehospital thrombolytics administered before PCI on mortality. We studied the two comparator groups: prehospital thrombolytics given before the PCI procedure (PHT + PCI) and pPCI. Eight studies contained complete information for the analysis. Statistical tests indicated a significantly high heterogeneity ($I^2 = 80\%$, $P < 0.00001$). Therefore, we employed a random-effects model comparing the mortality outcome. Although there was an indication for a reduction in mortality when for PHT + PCI, the effect is not statistically significant ($P = 0.11$) [Figure 5a]. One large-scale publication by Stenestrand *et al*., in 2006,[34] skews the effect response. This registry analysis had concerns of severe bias in including more patients with a lower risk of cardiac events in the primary PCI group at a particular instance of the study period.[42] Therefore, we have analyzed by excluding Stenestrand *et al*.'s 2006 study [Figure 5b]. Following this, the effect of administration of TL before PCI had statistically significant benefits in reducing mortality (OR = 0.56, 95% CI [0.36–0.89]; $P = 0.01$) than the pPCI alone [Figure 5b].

Based on this evidence of mortality benefits with early TL, a subgroup analysis was performed. Figure 6a shows that early intervention within 70 min of onset of symptoms provides significant mortality benefits in 1-year and 5-year follow-ups. This clearly demonstrates that salvaging the cardiac tissues from

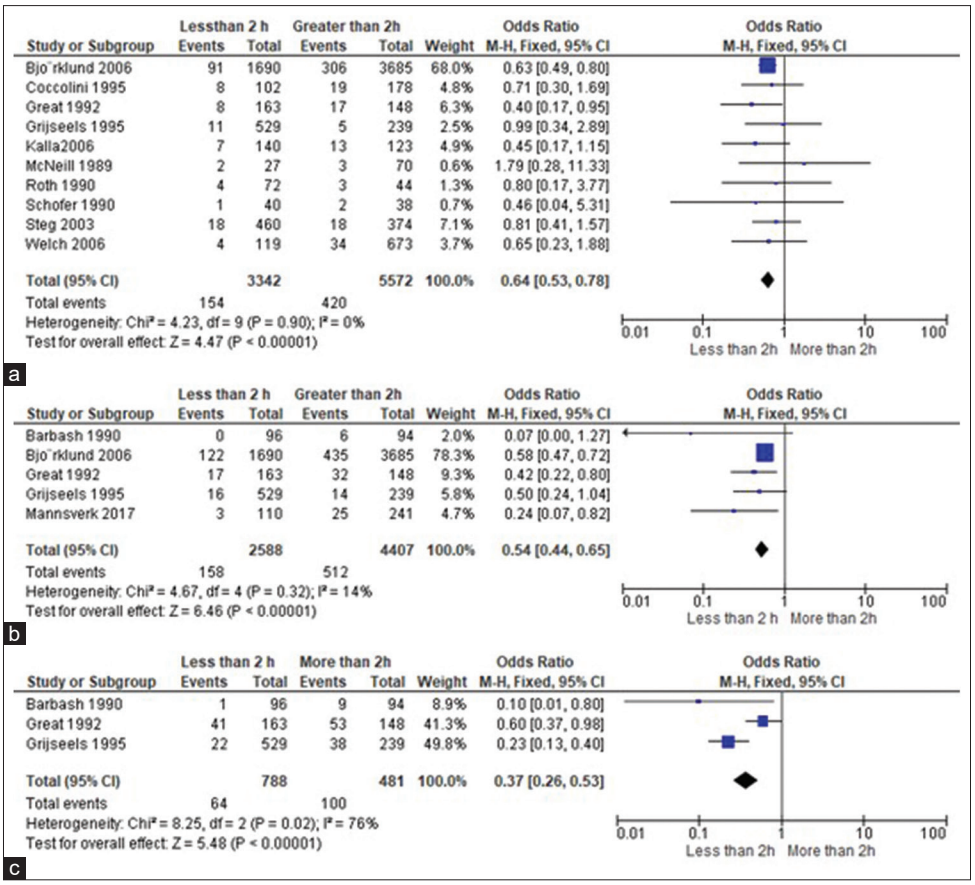

Figure 3: Influence of ischemic median time on all-cause mortality: (a) Follow-up period of 35 days, (b) Follow-up period of 1 year, (c) Follow-up period of 5 years. Forest plot representation of the influence of ischemic median time on all-cause mortality rate for a follow-up period of (a) 35 days, (b) 1 year, and (c) 5 years. The size of the squares is proportional to the weight of the study. Horizontal lines represent a 95% confidence interval (CI) of the study. The diamond indicates the pooled estimate with 95% CI. *N* is the number of individuals, OR: Odds ratio, CI: Confidence interval

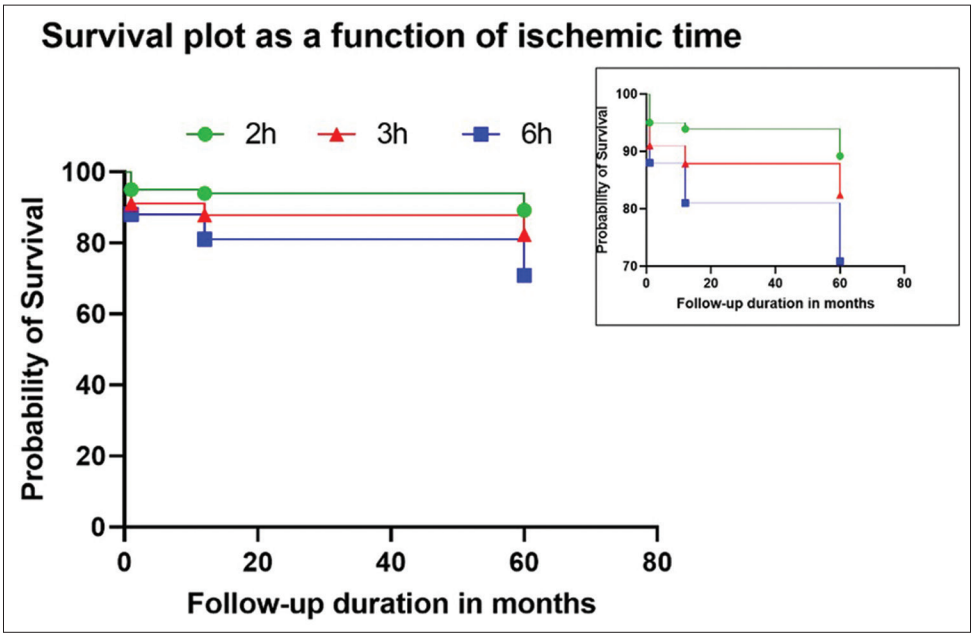

Figure 4: Effect of time of intervention on mortality rate. The Kaplan–Meier survival analysis plot based on the effect of time of intervention in patients with acute events on mortality rate for a follow-up period of up to 5 years. The inset provides a zoomed-in view of the plot

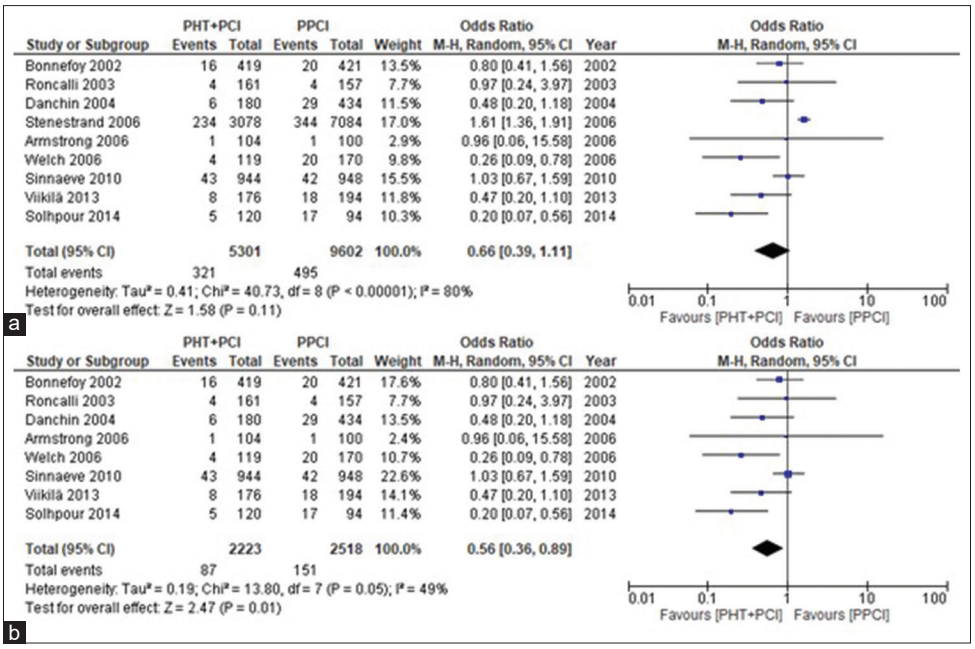

Figure 5: Effect of prehospital thrombolytic treatment before percutaneous coronary intervention on 30-day mortality. (a) Including Stenestrand's 2006 study, (b) Excluding Stenestrand's 2006 study. Forest plot representation of the effect of prehospital thrombolysis before PCI on all-cause mortality rate: (a) Including Stenestrand's 2006 study, (b) excluding Stenestrand's 2006 study. The size of the squares is proportional to the weight of the study. Horizontal lines represent a 95% confidence interval (CI) of the study. The diamond indicates the pooled estimate with 95% CI. *N* is the number of individuals, OR: Odds ratio, CI: Confidence interval

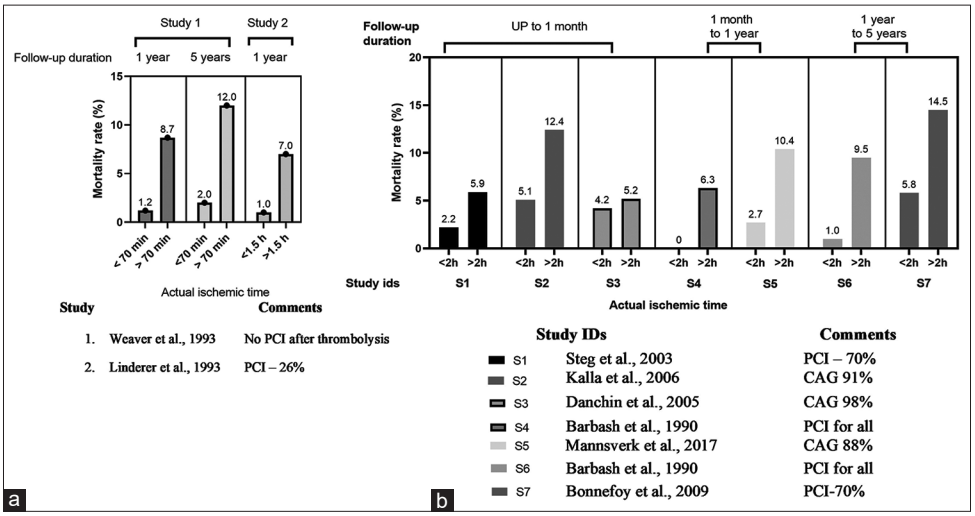

Figure 6: Relationship of actual ischemic time before thrombolysis (TL)/TL + PCI on the mortality outcomes for a follow-up duration of up to 35 days, 1 year, and 5 years. The included studies in the bar graphs consider (a) actual ischemic time of less than or >70 min or 1.5 h; (b) actual ischemic time of < or > 2 h. The inset provides a tabulated list with additional information on the included study population of the corresponding study

injury through early intervention can provide significant mortality benefits. Many studies indicate favorable mortality outcomes when intervention is offered at least within 2 h [Figure 6b]. TL alone or TL + PCI or PCI alone administered later than 2 h had lower benefits in comparison to interventions given <2 h. Hence, it becomes evident that time is critical for reducing myocardial damage and short/medium/long-term mortality benefits.

Moreover, when patients present within 2 h, the PHT strongly reduces mortality compared to pPCI. In the CAPTIM study, there was a greater absolute reduction in mortality by 3.4% at 30 days (2.2% in PHT vs. 5.7% pPCI) and 5.3% at 5 years (PHT 5.8% vs. pPCI 11%). French registry USIC 2000 data also support the CAPTIM findings.[12,33] In this registry, PHT was associated with a 0.49 relative risk of death at 1 year compared to pPCI, showing an absolute reduction of 5% (PHT + PCI 5% and pPCI 11%). When the time from symptom onset to admission after TL is <3.5 h, the inhospital mortality is nil, and at 1 year, mortality is 1%. In contrast, in the case of later admissions, the registry shows the inhospital

Table 1: List characteristics of included studies

References	Population size (*n*)	Comparator groups	Treatment duration	Assessment duration of primary outcome
Randomized control trials				
Armstrong, 2006[8]	304	Group 1=TL + usual care; Group 2=TL + PCI; Group 3=PPCI	Group 1=91 min Group 2=119 min	30-day composite outcome
Barbash *et al*., 1990[9]	190	PHT + PCI and IHT and PCI	<2 h and >2 h	At 60 days and at 24 months
Bøhmer *et al*., 2010[10]	276 patients with acute STEMI	Early invasive group versus conservative group		At 30 days and at 1 year
CAPTIM trial 2002 and 2009[11]	840	PHT + PCI versus PPCI	<2 h versus ≥2 h	At 30 days and at 5 years
CAPTIM[12]	834	PHT + PCI versus PPCI	<2 h versus ≥2 h	30-day mortality
Castaigne *et al*., 1989[13]	100	PHT, IHT	PHT=131 min, IHT=180 min	Inhospital mortality
EMIP, 1993[14]	5469	PHT, IHT	PHT 130 min, IHT 190 min	Overall mortality at 30-days
GREAT, 1992[15]	311	PHT versus IHT	PHT=101 min, IHT=240 min	At hospital discharge, at years 1, 5, and 10
McAleer and Varma, 2006[16]	248	PHT versus IHT	PHT=136 min, IHT=196 min	At 30 days and at years 1 and 5
McNeill *et al*., 1989[17]	57	PHT versus IHT	PHT=119 min, IHT=187 min	Inhospital mortality
Schofer *et al*., 1990[18]	78	PHT versus IHT	PHT=85 min, IHT=137 min	Inhospital
Sinnaeve *et al*., 2014[19]	1892	PHT + PCI versus PPCI	PHT + PCI=100 min PPCI=178 min	30 days, 1 year
MITI[20]	360	PHT versus IHT	PHT=77 min, IHT=110 min	Inhospital, 2 years
Nonrandomized trials				
Benger, 2002[21]	98	PHT, IHT	PHT=133 min, IHT=178 min	Inhospital
Coccolini *et al*., 1998[22]	280	Rural hospital transfer to CCU	Rural 90 min, CCU 165 min	35 days
Gilon *et al*., 2000[23]	358	Effect of very early thrombolysis	<1.5 h, between 1.5 h and 4 h	Major CV events during 3 months, 1, 2, 3, and 4 years
Grijseels *et al*., 1995[24]	768	PHT versus IHT	< 2 h and >2 h	Hospital 1 year and 5 years
Khan *et al*., 2020[1]	484	PHT versus PPCI		1, 2, 3, 4, and 5 and 6.2 years
Linderer *et al*., 1993[25]	170	Early thrombolysis – cutoff time of 1.5 h	≤1.5 h and >1.5 h	21 days
Mathew *et al*., 2003[26]	750	PHT versus IHT	PHT=2.3 h, IHT=4 h	Inhospital
Roncalli *et al*., 2003[27]	318	Primary angioplasty and PHT	PHT=145±81 min, PTCA=237±90 min	Inhospital and 3 years
Roth *et al*., 1990[28]	116	MICU versus CCU	MICU 94±35 min, CCU 137±44 min	Inhospital
Solhpour *et al*., 2014[29]	214	TT + PCI versus PPCI	TT + PCI 151 min PPCI 165 min	30 days
Viikilä *et al*., 2013[30]	448	PPCI versus PHT		30 days and 1 year
Welsh *et al*., 2006[31]	1095	PHT versus IHT	PHT=1 h 43 min, IHT=2 h 38 min	Inhospital
Guy *et al*., 2021[32]	33	PHT versus IHT	PHT=25 min, IHT=84 min	
Registry studies				
Danchin *et al*., 2004[33]	1922	PHT, IHT, PPCI, and no reperfusion	Median time from symptom onset to admission in the PHT group was 3.5 h and greater in the IHT group	Inhospital 1 year
Stenestrand *et al*., 2006[34]	26,205	PHT, IHT, and PPCI	≤2 h and >2h	Inhospital, at 7 days, 30 days, and 1 year
Björklund *et al*., 2006[35]	5375	PHT versus IHT	PHT=113 min, IHT=165 min	1 year
Mannsverk *et al*., 2019[36]	385	PHT versus IHT	<2 h and >h	1 year
Danchin *et al*., 2014[37]	1492	PHT versus IHT		5 years
Kalla *et al*., 2006[38]	1053	PHT, IHT, and PPCI	0–2, 2–6, and 2–12 h	Inhospital mortality
Jortveit *et al*., 2022[39]	9787	Effect of very early thrombolysis	≤ 2 h, 2–3 h, and >3 h	6 years

PHT: Prehospital thrombolysis, IHT: Inhospital thrombolysis, PTCA: Percutaneous transluminal coronary angioplasty, TT: Thrombolytic therapy, PCI: Percutaneous coronary intervention, PPCI: Primary PCI, MICU: Mobile intensive care unit, CCU: Coronary care unit, CV: Cardiovascular, STEMI: ST-elevation myocardial infarction, TL: Thrombolysis

mortality at 6% and the 1-year mortality rate at 10%. Vienna study[38] shows that when the treatment was given within 2 h of symptoms onset, the inhospital mortality rates favored TL over pPCI (pPCI 7.8%, TL 5.1%).

In addition, when we analyzed the data from CAPTIM, CAPTIM, and WEST (combined analysis), and the Vienna study, we can observe that within 2 h of ischemic pain, PHT followed by PCI provides better mortality benefits than pPCI alone at 30 days, 1-year, and 5-year follow-up. This observation necessitates a closer look at STEMI management when patients present within 2 h of ischemic pain.[43,44]

Discussion

IHD is among the leading causes of death and disability in developing countries, and measures to offer the quickest possible reperfusion therapy after the onset of acute chest pain could evade life-threatening irreversible myocardial damage. The importance of early intervention has been well recognized, studied, and proven in several large-scale studies and registries. When all ages are considered, 40% of the deaths from AMI occur within 1 h of the onset of symptoms.[45] Among men of middle and younger ages, 63% of the deaths occur within 1 h of the onset of symptoms. With few exceptions like stuttering MI, reperfusion attempted after 6 h of the onset of symptoms is of minimal to no benefit in preventing myocardial damage.[46]

The definitive treatment in acute STEMI is reperfusion therapy. Among the two reperfusion therapies, namely, TL and primary angioplasty, primary angioplasty is considered a better method of reperfusion, but its greater value is compromised when it cannot be delivered within the recommended time limit.[47] Practical difficulties in completing the primary angioplasty within the recommended time limit of 180 min from symptom onset most often exist because much depends on the time taken by the patients seeking medical help and the transportation facility.[48]

Studies show that prehospital delay is longer among people of old age (>55 years), women, with lower socioeconomic status, and those with a previous history of angina and diabetes mellitus.[49] Patients in developing countries tend to get extremely delayed reperfusion therapy compared to patients in Western geographies. This increases the risk of mortality and morbidity in patients with STEMI in the developing world.[4] Lack of education and awareness, misreading of the symptoms, attempts with home remedies, economic reasons, lack of ambulance services, major traffic congestions of the city roads in the case of the urban population, long distances to be covered for hospitalization amidst rural population, and late referrals by the attending health-care professional are all some of the common causes for the delay in reaching out to a cardiac care center. Most basic requirements for quick balloon deployment are untenable even in metropolitan cities of developing countries.[50]

McNamara *et al*. showed that DTB times of <90 min and DTN times of <30 min are achieved only in a minority of cases.[7] In the National Registry of Myocardial Infarction (NRMI) databases 3 and 4, the guideline-recommended DTB time of 1.5 h was achieved in only 4.2% of patients.[51]

When primary angioplasty is delayed, its advantage over TL is lost. The ESC guidelines permit a PCI-related time delay over fibrinolysis (DB-DN time) of up to 120 min. Pinto *et al*., based on NRMI studies, have pointed out that it is not uniform for all STEMI patients.[52] In an anterior wall, MI patient <65 years old who presents within 2 h of symptom onset, the mortality advantage is lost if the DB-DN time is >40 min.

It is often challenging to perform PCI immediately on the patient's arrival at the hospital since it demands extensive inhospital organization and infrastructural facility. Most often than a matter of exception, there is a delay in the primary PCI, and thus, the reperfusion is rarely achieved within an optimal time of 2 h after the onset of symptoms. In this context, PHT has a time gain of approximately 60 min over IHT in urban areas (approximately 30 min of transport and another 30 min in the DTN time in the hospital)[13] and 75 min in a rural study.[22] PHT saved 131 min compared to pPCI in a real-world registry study (NORWAY study).[10]

In this systematic review, we have evaluated the available evidence from clinical trial data and real-world registry data to evaluate the impact of early PHT on mortality benefits.

The main findings of our review are:

1. PHT significantly reduces mortality compared to IHT (OR-0.68, $P < 0.00001$). This sharply contrasts the commonly known 2% absolute reduction in mortality with pPCI over IHT. We infer that PHT given in time offers far greater benefits than interventions given later than 2 h, irrespective of the type of intervention
2. Early thrombolytics followed by PCI provided better mortality benefits (OR-0.78, $P = 0.0001$) [Figure 3b]. PHT delivered within the first 2–3 h of the onset of symptoms of AMI followed by PCI shows better survival rates than pPCI
3. Our analysis shows a far superior survival rate when the median ischemic time is <2 h (OR 0.64 at 30 days, 0.54 at 1 year, and 0.37 at 5 years: P =0.00001). The mortality increases with longer ischemic time [3 h and 6 h plots of Figure 4].

Mobile CCU reduces the short-term community (prehospital and inhospital) mortality in STEMI by an absolute 9.7%. It results from (a) prevention or correction of ventricular fibrillation outside the hospital before transport; (b) stabilization of patients before transfer which eliminates death during transport and in casualty departments; and (c) diminution of hospital mortality by a reduction in the incidence of shock and pump failure in patients receiving prehospital care.[53] Our meta-analysis shows a reduction in all-cause short-term mortality associated with the PHT (7.1%) compared to IHT (10.6%), an absolute reduction of 3.4%.

Our study findings indicated an increasing mortality trend with an increase in median ischemic time [3 h vs. 6 h plots

of Figure 4]. Similar results were reported by Eric Boersma, who conducted a meta-analysis of 22 trials with 50246 patients and found that the 35-day mortality reduction in patients treated <2 h versus later was 44% versus 20%.[40]

Recently, microvascular obstruction (MVO) has been shown to predict major adverse cardiovascular events than infarct size itself. MVO, in turn, is more closely related to ischemic time than types of reperfusion therapy. Thus, the ischemic time critically influences prognosis rather than the type of reperfusion.[54]

Conclusion

This meta-analysis reveals a significant reduction in mortality with PHT compared to IHT. The definitive treatment in patients with STEMI is reperfusion at the earliest. Compared to inhospital reperfusion, it hastens reperfusion by more than an hour in rural and urban areas. This reduction in ischemic time translates as improved survival and yields an absolute reduction in short-term mortality of 3.4%.

TL is universally available, economical, and can be given anywhere, even at odd hours. Patients with STEMI ineligible for TL can be stabilized at home and transferred to the PCI center directly, reducing time to balloon and improving results.

With the movement of thrombolytic therapy from the catheterization laboratory to the critical care unit and then to the emergency department, the delay in TL of acute MI has been dramatically reduced. It is time to move TL to a home or mobile cardiac care ambulance for maximal benefit.

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Conflicts of interest

There are no conflicts of interest.

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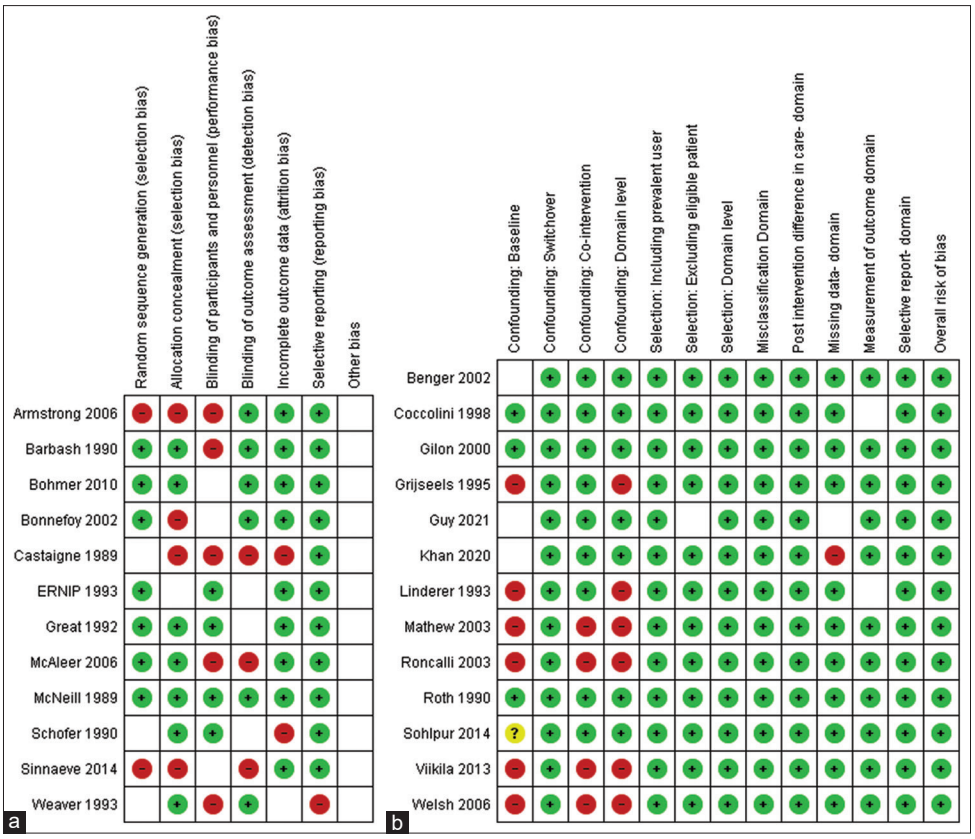
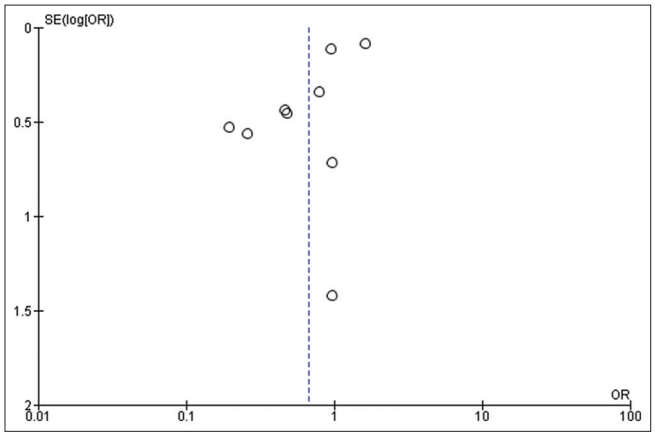
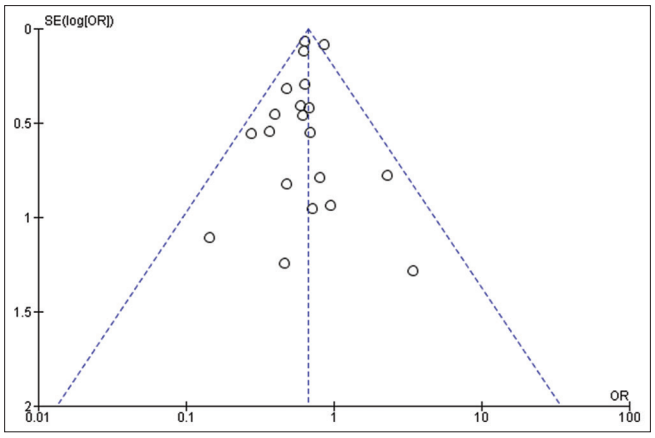


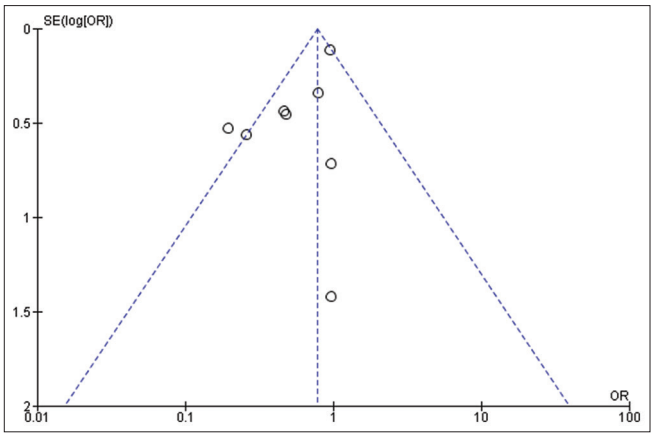
Supplementary Figure 1: Risk-of-bias summary of included (a) randomized control trials and (b) nonrandomized trials



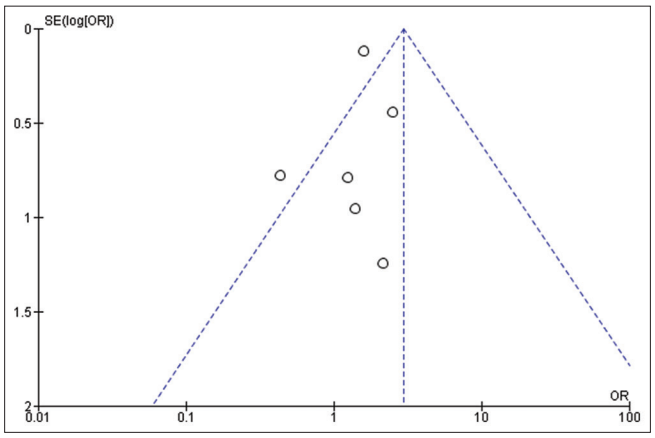
Supplementary Figure 2: Funnel plot of comparison: Prehospital thrombolysis versus inhospital thrombolysis follow-up of up to 30 days, outcome: All-cause mortality



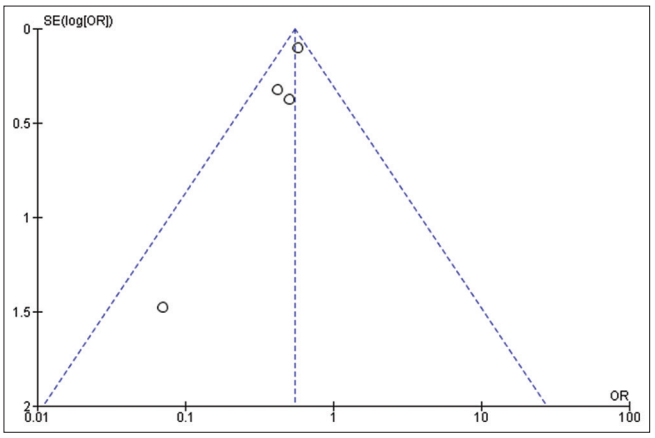
Supplementary Figure 3: Funnel plot of comparison: 3 Thrombolytics + PCI versus PPCI, outcome: 3.1 thrombolysis + PCI versus PPCI (inclusive of Stenestrand *et al*.'s study). TL: Thrombolysis, PPCI: Primary PCI



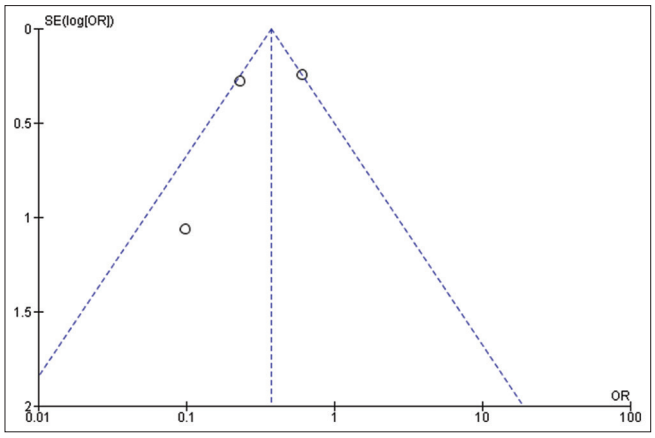
Supplementary Figure 4: Funnel plot of comparison: 3 Thrombolytics + PCI versus PPCI, outcome: 3.2 thrombolysis + PCI versus PPCI (without Stenestrand *et al*.'s study). PPCI: Primary PCI, TL: Thrombolysis



Supplementary Figure 5: Funnel plot of comparison: 2 elapsed time, outcome: 2.1 ischemic time versus 30-day mortality rate



Supplementary Figure 6: Funnel plot of comparison: 2 elapsed time, outcome: 2.2 ischemic time versus 1-year survival



Supplementary Figure 7: Funnel plot of comparison: 4 ischemic time of 2 h versus 5-year mortality, outcome: 4.1 ischemic time and 5-year survival rate