REVIEW

Mortality and Prehospital Thrombolysis for Acute Myocardial Infarction

A Meta-analysis

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Context Early administration of thrombolysis for acute myocardial infarction (AMI) may improve survival if safely and appropriately delivered. No systematic reviews that have comprehensively examined this topic exist in the literature.

Objective To perform a meta-analysis of randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI measuring in-hospital mortality.

Data Sources The Cochrane search strategy was used to search MEDLINE, EMBASE, and the Science Citation Index (1982-1999); Dissertation Abstracts (1987-1999); and Current Contents (1994-1999) for the terms *thrombolysis*, *thrombolysis therapy*, *prehospital*, and *acute myocardial infarction*. In addition, text and journal article bibliographies were hand searched, the National Institutes of Health Web site was reviewed, and primary authors and thrombolytic drug manufacturers were contacted for unpublished studies.

Study Selection Randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI measuring all-cause hospital mortality were included. Two authors independently reviewed 175 citations by title, abstract, or complete article. After exclusion of 30 duplicate citations, 145 studies remained, of which 6 studies and 3 follow-up studies met the inclusion criteria.

Data Extraction Independent data abstraction by 2 reviewers blinded to the journal, title, and author was confirmed by consensus. Trial quality was independently assessed by 2 other coauthors, blinded to the author, title, journal, introduction, and discussion.

Data Synthesis The results of the 6 randomized trials (n=6434) were pooled and indicated significantly decreased all-cause hospital mortality among patients treated with prehospital thrombolysis compared with in-hospital thrombolysis (odds ratio, 0.83; 95% confidence interval, 0.70-0.98). Results were similar regardless of trial quality or training and experience of the provider. Estimated (SE) time to thrombolysis was 104 (7) minutes for the prehospital group and 162 (16) minutes for the in-hospital thrombolysis group (P=.007).

Conclusions Our meta-analysis suggests that prehospital thrombolysis for AMI significantly decreases the time to thrombolysis and all-cause hospital mortality.

JAMA. 2000;283:2686-2692 www.jama.com

CARDIOVASCULAR DISEASE REmains the leading cause of death in North America, and acute myocardial infarction (AMI) accounts for a large proportion of these deaths. Although thrombolytic therapy decreases mortality, benefit depends on the time to treatment.[1,2] Clinical research has focused on reducing the time to treatment with the advent of chest pain protocols, rapid triage, and thrombolysis in the emergency department. Despite these efforts, the time to thrombolysis, or "time to needle," remains high.

One way to address this is to administer thrombolysis before the patient arrives in hospital. The National Heart Attack Alert Program concluded in 1997 that prehospital thrombolysis reduces mortality in a subgroup of patients who require long out-of-hospital transport times (>1 hour) to an emergency department.[3] Accordingly, many North American emergency medical services systems have implemented prehospital administration of thrombolytics for patients who sustain AMI out of hospital. This has occurred despite the fact that most advanced emergency medical services systems are situated in urban centers with rapid transit times (<1 hour) and short door-to-needle times.

Previous review articles addressing this issue have not comprehensively searched, selected, critically appraised, or summarized the randomized trials in this field.[3-22] MEDLINE (1992-1999) and EMBASE (1993-1999) searches[23] from 1992-1999 were supplemented with hand searches of bibliographies of texts

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and journal articles to locate systematic reviews and meta-analyses. All review articles were narrative and failed to meet the methodological criteria of a systematic review. Data were pooled in 3 reviews.[6,12,22] One regression analysis reported that prehospital thrombolysis was associated with a significant decrease in mortality ($P=.002$).[22] A reduced time to thrombolysis of 1 hour with prehospital vs in-hospital delivery and a significantly lower short-term mortality (odds ratio [OR], 0.83; $P=.03$) was reported in another review.[6]

The primary objective of this meta-analysis was to critically appraise and summarize all randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI. The primary outcome measure was all-cause hospital mortality; secondary outcome measures were scene times, time to thrombolytic treatment, postinfarct ejection fraction, infarct size, Q-wave infarction, and adverse events, including ventricular fibrillation, cardiogenic shock, hypotension, bradycardia, bleeding, and stroke.

METHODS

Data Sources and Study Selection

Using the terms *thrombolysis*, *thrombolysis therapy*, *prehospital*, and *acute myocardial infarction* and the Cochrane search strategy,[24] a comprehensive search was conducted. The search time frames included 1982-1999 for MEDLINE, EMBASE, and Science Citation; 1987-1999 for Dissertation Abstracts; and 1994-1999 for Current Contents. Bibliographies of texts and journal articles were hand searched to locate additional potentially relevant studies. The National Institutes of Health Web site was reviewed for grants pertaining to this subject. Primary authors and manufacturers of thrombolytic agents were contacted for knowledge of unpublished studies of prehospital thrombolysis in AMI. To be included, a study had to be a randomized controlled trial of prehospital vs in-hospital thrombolysis in AMI with an outcome measure of all-cause hospital mortality. Relevance was assessed using a hierarchical approach based on title, abstract, and the full manuscript. When the reviewers disagreed on assignment, the study was included in the next screening level. The reviewers (L.J.M. and P.R.V.) of the full article were blinded to author's name, journal of publication, and results.

Table 1. Excluded Studies Reviewed by Complete Article

Excluded Study, y	Reason for Exclusion
Castaigne et al,[27] 1987	Mortality numbers unclear
Barbash et al,[28] 1990	All mortality at 60 d and 2 y only
Boissel,[29] 1995	Same data set as the European Myocardial Infarction Project trial
Gotsman et al,[30] 1996	Same study as Rozenman et al,[34] published in different journal
McAleer et al,[31] 1992	Open allocation, not a randomized controlled trial, only vascular mortality cited
McNeill et al,[32] 1989	Cardiac mortality cited (not all mortality), trial question unclear, suspect this to be a trial of recombinant tissue-type plasminogen activator
Risenfors et al,[33] 1991	Randomization by convenience, additional concurrent control group, not intent-to-treat analysis
Rozenman et al,[34] 1995	Not a randomized controlled trial, consecutive patients

Quality Assessment and Data Extraction

Two authors (A.C.M. and B.V.S.), who were blinded to the articles' author, title, introduction, discussion, and journal of publication, independently assessed trial quality using the Detsky scale.[25] Data abstraction was independently conducted by 2 authors (P.R.V. and L.J.M.) blinded to the title, author, and journal of publication. The data abstracted for each trial were confirmed by reviewer consensus, then sent to the primary author for verification and additional information if necessary.

Statistical Analysis

Agreement between reviewers was measured by a κ statistic for each screening step. Interrater agreement with 95% confidence intervals (CIs) was measured using the interclass correlation coefficient for random raters. We used the random effects model for meta-analysis, which does not deemphasize the treatment effect of studies with small sample sizes and which implies that the included studies are a random sample of the universe of studies. We calculated the OR, 95% CI, and the number needed to treat. The test of homogeneity was measured using 5 *df* and the Breslow-Day equation.[26] The effect of provider by treatment group on mortality and the interaction between provider and treatment group on outcome were assessed using an analysis of proportions with the weighted least squares method.

RESULTS

Study Selection

Our comprehensive search identified 175 citations, of which 30 were duplicate publications. The resulting 145 citations were sequentially screened independently by 2 authors (P.R.V. and L.J.M.) for inclusion. Initially, 145 citations were screened by title and categorized as "include," "exclude," or "can't tell." Forty-seven citations in the "include" and "can't tell" categories were then screened by abstract. Seventeen citations remained in the include or can't tell categories and were reviewed using the full articles[27-43] (TABLE 1). The weighted κ statistic (SE) was 0.65 (0.09) for titles, 0.87 (0.11) for abstracts, and 0.86 (0.25) for articles. Six randomized, placebo-controlled studies and 3 follow-up studies met the inclusion criteria for the systematic review.[35-43]

Quality Assessment

The quality scores ranged from 0.43-0.93 on a scale where 1.0 is the maximum. The European Myocardial Infarction Project (EMIP),[36] Grampian Region Early Anistreplase Trial (GREAT),[37] and the Myocardial Infarction Triage and Intervention (MITI) Trial[38] achieved the highest quality scores of at least 0.78. The majority of studies failed to report concealment of allocation and blinded

assessment of outcomes. All of the trials showed no statistically significant difference between prehospital and in-hospital mortality: 1 trial reported a post hoc power calculation and 95% CIs.[36] The interclass correlation coefficient for random raters was 0.73 (TABLE 2).

Data Synthesis

We invited the primary authors to review the final data set; 2 responded with minor changes in the trial characteristics (TABLE 3) and inclusion and exclusion criteria (TABLE 4) that did not affect the comparability of the studies.

Population

Inclusion criteria were similar except in the GREAT study, which used the judgment of the general practitioner without interpretation of the electrocardiogram (ECG).[37] The EMIP trial[36] stratified patients by ECG changes into 2 groups: patients with and without ST-segment elevation. The latter stratum included ECG changes such as a QRS greater than 0.12, depressed ST-segments, or tall T-waves and a history of coronary artery disease, without electrocardiographic evidence of AMI. The EMIP trial[36] excluded patients at the discretion of the investigator at the time of randomization. The MITI Trial[38] allowed the base hospital physician to decide whether to randomize each patient. Therefore, the discretionary application of the exclusion criteria may have introduced a selection bias into trial populations and may limit the generalizability of these studies.

Roth et al[39] included a nonrandomized concurrent prehospital group merged with the randomized prehospital group for the analysis. The data are reported in such a way that it is not possible to separate randomized from nonrandomized patient data. The study by Castaigne and colleagues[35] allowed patients to be crossed over after randomization. These crossover patients were not included in the analysis, despite its being reported as an intention-to-treat analysis.

Thrombolytic Administration

Drug exposure varied between studies. The thrombolytic agents included urokinase,[40] anistreplase,[35-37] and recombinant tissue-type plasminogen activator.[38,39] The clinical difference between agents is small, and combining studies appears biologically plausible.[15,20,41-46] The provider in the mobile intensive care unit was an intensivist.[35,36,39,40] In the GREAT study, a general practitioner administered thrombolysis.[37] The MITI trial employed paramedics.[38] Although training and field experience may vary considerably between these 3 provider groups, this information was not reported, and the investigators attempted to minimize these differences. For example, in 1 study, the base hospital

Table 2. Interrater Agreement on Quality Assessments*

Study	Score (No. of Points, Maximum = 15)		Mean (SE) Score
	Rater 1	Rater 2	
Castaigne et al,[35] 1989	0.53 (8)	0.43 (6.5)	0.48 (0.05)
EMIP group,[36] 1993	0.83 (12.5)	0.87 (13)	0.85 (0.02)
GREAT group,[37] 1992	0.93 (14)	0.63 (9.5)	0.78 (0.15)
MITI trial,[38] 1993	0.90 (13.5)	0.93 (14)	0.915 (0.02)
Roth et al,[39] 1990	0.70 (10.5)	0.60 (9)	0.65 (0.05)
Schofer et al,[40] 1990	0.63 (9.5)	0.63 (9.5)	0.63 (0.00)
Overall mean score	0.74 (0.06)	0.67 (0.07)	$P = .45$
Interclass correlation coefficient for random raters			0.73

*EMIP indicates European Myocardial Infarction Project; GREAT, Grampian Region Early Anistreplase Trial; and MITI, Myocardial Infarction Triage and Intervention.

Table 3. Trial Characteristics*

Study, y	Provider	Thrombolytic Agent	Quality Score	Time From Symptom Onset to Thrombolysis			All-Cause Hospital Mortality		
				Mean (SE) Minutes		Interval Difference or *P* Value	Prehospital, No./Total	In-Hospital, No./Total	OR (95% CI)
				Prehospital	In-Hospital				
MITI trial,[38] 1993	Paramedics	rt-PA	0.91	92 (58); 77 [Median]	120 (49); 110 [Median]	$P<.001$; 33 min (18)	10/175	15/175	0.69 (0.30-1.57)
EMIP group,[36] 1993	MICU	Anistreplase	0.85	130 [Median]	190 [Median]	55 min [Median]	251/2750	284/2719	0.86 (0.72-1.03)
GREAT study,[37] 1992	GPs	Anistreplase	0.78	101 [25-360] Median [range]	240 [80-540] Median [range]	130 [40-370] min, Median [range]	11/163	17/148	0.56 (0.25-1.23)
Roth et al,[39] 1990	MICU	rt-PA	0.65	94 (36)	137 (45)	$P<.001$	4/72	3/44	0.80 (0.17-3.77)
Schofer et al,[40] 1990	MICU	Urokinase	0.63	85 (51)	137 (50)	$P<.001$	1/40	2/38	0.46 (0.04-5.31)
Castaigne et al,[35] 1989	MICU	Anistreplase	0.48	131 [Median]	180 [Median]	60 min	3/57	3/43	0.74 (0.14-3.86)

*Odds ratio (OR) is the ratio of the odds of mortality in the treatment group (prehospital) to the odds of mortality in the control group (in-hospital). CI indicates confidence interval; MITI, Myocardial Infarction Triage and Intervention; rt-PA, recombinant tissue-type plasminogen activator; EMIP, European Myocardial Infarction Project; MICU, mobile intensive care unit; GREAT, Grampian Region Early Anistreplase Trial; and GP, general practitioner.

physician delegated treatment to the paramedics and interpreted the ECG.[38] Specific inclusion criteria were used to minimize inappropriate thrombolysis in the GREAT study, and enrollment did not depend on ECG interpretation by the general practitioner.[37]

Outcomes

The 6 studies (n=6434)[35-40] provided sufficient data to pool the results for time to thrombolytic treatment and all-cause hospital mortality. The point estimates of each study consistently favored prehospital thrombolysis, although the CIs crossed unity (1.0), and none showed statistically significant differences. Data were insufficient to pool for an evaluation of long-term mortality benefit at 30 days[36] and 60 days[28,39] (n=193). The GREAT and MITI trials measured 1-year mortality. The GREAT study results, favoring prehospital administration of thrombolytics, were significant at 1 year, with an OR of 0.42 (95% CI, 0.21-0.83; $P=.007$).[41] The MITI trial showed no significant difference in 1-year mortality (OR, 1.14; 95% CI, 0.51-2.53; $P=.73$).[43] The trial by Barbash et al[28] and the MITI[43] trial both measured outcome at 2 years. These studies had point estimates that favored in-hospital administration of thrombolytics, but the CIs included no treatment effect and, as such, were negative trials. The GREAT study was the only one to report 5-year mortality data. Survival curves for these data showed a significantly higher mean survival for the prehospital group (difference, 208 days; 95% CI, 42-374; $P<.03$).[42] Secondary outcomes of ejection fraction, infarct size, scene time, and Q-wave myocardial infarction frequency and complications were defined inconsistently and variably reported in each study.

Test of Homogeneity and Overall Results

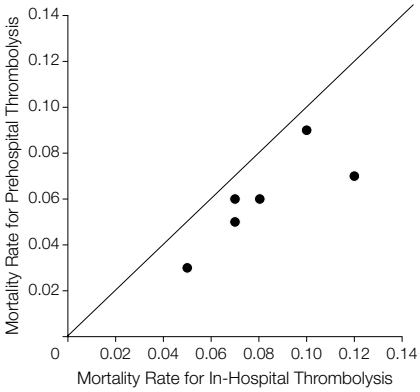
The test of homogeneity yielded a P value of .90 for the 6 studies that measured short-term hospital mortality. Since the power of the test is low, data were plotted on a graph for visual display of consistent outcome rates (FIGURE 1). The OR for each study is listed in FIGURE 2. On biological, clinical, and statistical grounds, we pooled the interventions in these trials, resulting in a pooled OR of 0.83 (95% CI, 0.70-0.98; $P=.03$), favoring prehospital thrombolysis (Figure 2). Prehospital thrombolysis reduced the relative

Table 4. Inclusion and Exclusion Criteria for Patient Population*

Study, y	Inclusion	Exclusion
Castaigne et al,[35] 1989	Age <75 y Chest pain onset <6 h and lasting 30 min to 3 h not responding to nitrates ST-segment elevation of ≥0.2 mV in 2 or more standard leads or 3 precordial leads	History of severe hypertension, classic contraindications to thrombolysis (not defined)
EMIP group,[36] 1988-1992	Chest pain duration from 30 min to <6 h from symptom onset or chest pain <30 min and not responding to nitrates Patients stratified by ECG changes into ST-segment elevation group (at least 2.0 mm in at least 2 precordial leads, at least 1 mm in 2 limb leads, or both) or no ST-segment elevation group (QRS >0.12 s or isolated ST-segment level depression or tall T-waves with coronary artery disease)	Use of oral anticoagulants (antiplatelet allowed), hemorrhagic diasthesis, pyloric ulcer disease, stroke, surgery or major trauma <6 mo previously, external cardiac massage, SBP >200 mm Hg and/or DBP >120 mm Hg, pregnancy, coronary angioplasty less than 2 wk prior, no consent, withdrawal at the discretion of the investigator
GREAT study,[37] 1988-1991	General practitioner's clinical suspicion of AMI Symptoms of AMI present between 20 min and 4 h Transportation to ICU within 6 h from onset of symptoms Verbal consent given	Thrombolysis <6 mo prior, surgery or major trauma <10 d prior, active gastrointestinal bleeding <6 mo prior, CVA or neurosurgery procedure <2 mo prior, intracranial aneurysm or neoplasm, history of thrombocytopenia, bleeding diasthesis or use of anticoagulants, pregnancy, heavy vaginal bleeding, diabetic proliferative retinopathy, BP >200/120 mm Hg, recent CPR, previous trial participant
Roth et al,[39] 1988-1989	Age <73 y, severe chest pain typical for AMI >30 min and <4 h ST-segment elevation ≥0.1 mm in 2 or more contiguous leads	DBP >120 mm Hg, LBBB, history of heart failure/cardiac surgery, terminal illness, risk of bleeding (ie, CVA <6 mo prior/recent trauma/bleeding diasthesis/use of anticoagulants)
Schofer et al,[40] 1986-1988	Age ≤70 y Chest pain for <30 min or chest pain on arrival of ambulance < 4 h from symptom onset ST-segment elevation >2 mm in at least 2 leads (inferior) ST-segment elevation >3 mm in at least 2 precordial leads	Prior AMI, contraindications to thrombolysis (not defined)
MITI trial,[38] 1989-1991	Age <75 y Suspected AMI with <6 h of chest pain SBP <180 mm Hg, DBP <120 mm Hg ECG interpretation by physician Physician decision to include, based on interpretation of ECG	Bleeding risks (history of CVA, recent bleeding and/or surgery, known renal/liver disease)

*ECG indicates electrocardiogram; SBP, systolic blood pressure; DBP, diastolic blood pressure; AMI, acute myocardial infarction; ICU, intensive care unit; CVA, cerebrovascular accident; CPR, cardiopulmonary resuscitation; and LBBB, left bundle-branch block. Trial names are expanded in the footnote to Table 3.

Figure 1. Mortality Rates in Control and Treatment Groups for Each Prehospital Thrombolytic Trial



Diagonal line represents equal rates. Above diagonal, favors in-hospital thrombolysis; below diagonal, favors prehospital thrombolysis. Rate is measured as total number of deaths per total number of patients treated in either group.

risk of all-cause hospital mortality by 17%. The absolute risk reduction of 2% translates into 1 life saved for every 62 patients with overt AMIs who accessed the regional prehospital system and were treated with thrombolytics in the prehospital rather than in-hospital setting.

The test of homogeneity for studies with 1-year[37,38] and 2-year outcomes[28,38] yielded *P* values of .04 and .86, respectively. The pooled OR for 1-year mortality (0.68; 95% CI, 0.26-1.80; *P*=.44) and 2-year mortality (1.18; 95% CI, 0.62-2.22; *P*=.62) showed no significant difference between in-hospital vs prehospital thrombolysis. No additional analysis of this long-term mortality data was done, as homogeneity was poor in the 1-year follow-up studies and the overall number of trials was too small for sensitivity analysis.

Sensitivity Analyses

We had 2 a priori hypotheses: (1) the influence of prehospital thrombolysis may be lower when only trials with higher quality scores are reported, and (2) the influence of thrombolysis may be greater when administered by physicians in a mobile intensive care unit. Excluding the trials with lower quality scores[35,39,40] yielded a pooled OR of 0.84 (95% CI, 0.70-0.99) (Figure 2), which was similar to the overall analysis of all trials. The influence of provider qualifications on the overall results was evaluated by considering only the 4 mobile intensive care unit studies that used an intensive care physician to administer the thrombolytic agent[35,36,39,40] (Figure 2). When the analysis excluded the paramedic trial[38] and the study that involved thrombolytic therapy administered by general practitioners,[37] the overall OR was 0.80 (95% CI, 0.72-1.02). Therefore, results were similar regardless of trial quality score or provider training.

The effect of provider by treatment group was not significant (*P*=.16). The interaction analysis demonstrated no differential effect of provider on mortality (*P*=.58). The studies had qualitatively and quantitatively similar point estimates, indicating that they shared the same direction and magnitude of effect favoring prehospital thrombolysis.

Time to Thrombolysis

The time difference (SE) to thrombolysis between the prehospital group (104 [7] minutes) and the in-hospital group (162 [16] minutes) was approximately 60 minutes (*P*=.007). This interval difference supports the finding that prehospital thrombolysis significantly improved time to needle for thrombolysis. Recruitment in the GREAT study occurred in towns and villages at distances that compromised transfer time to Aberdeen, Scotland[37]; therefore, we repeated the analysis without the GREAT study. The approximate overall time interval difference for the treatment group (104.67) and the control group (149.33) was approximately 45 minutes (*P*=.01).

COMMENT

We found that prehospital thrombolysis for AMI significantly decreased all-cause hospital mortality based on a meta-analysis of 6 randomized controlled trials. Pooled data were insufficient to show a statistically significant difference in longer-term mortality at 1 or 2 years. The GREAT study follow-up results show that the benefit of prehospital thrombolysis is maintained at 5 years for cases of AMI treated out-of-hospital that required long transit times to definitive care.[42] The overall treatment effect of this meta-analysis was primarily determined by 3 of the 6 selected studies. These 3 studies had high homogeneity and quality scores and a collective sample size of 6140 patients. We combined the results of all 6 trials using 3 different providers but found a similar treatment effect when only 1 type of these providers was considered. The overall estimate of the benefit of prehospital thrombolysis may therefore be generalizable to many providers (paramedics, general practitioners, or medical intensivists) in diverse health care delivery systems involved in the safe administration of thrombolytics for AMI. The difference in complication rates and need for adjuvant pharmacological or surgical therapy were not comparable across trials because of the lack of clear definitions and outcome measures. The time-to-treatment interval from time of symptom onset to thrombolysis was also significantly improved by prehospital administration of thrombolytic agents.

Individually, each of the trials included in this meta-analysis favored prehospital thrombolysis yet failed to show a statistically significant difference in mortality; however, we conducted a comprehensive search to identify unpublished trials. Selected authors in the field and all pharmaceutical companies involved in the manufacturing of thrombolytic agents were asked for information regarding unpublished trials. Granting agencies and thesis registries were searched for relevant information, and abstracts for scientific meetings were included in the original data set. Thus, although there may be negative unpublished trials evaluating prehospital thrombolysis, the influence of publication bias on our results seems unlikely.

Woo and White[12] published a nonsystematic review with a pooled analysis that showed an 18.4% (95% CI, 2%-29.8%; *P*=.03) reduction in short-term mortality (using results from 5 studies. The study by Barbash et al[28] was

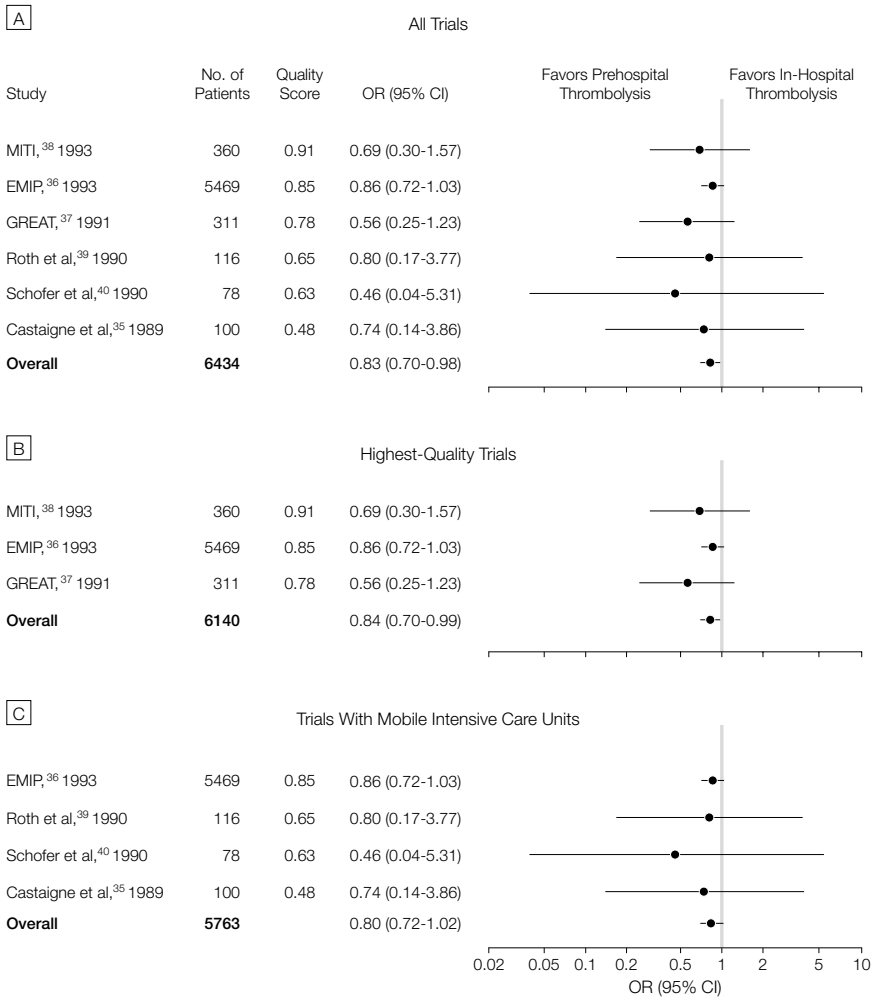
excluded from our meta-analysis because the mortality end point of 60 days was not equivalent to the in-hospital mortality end point used in the other 6 studies. Le Feuvre et al[6] found a pooled OR of 0.83 (no 95% CI reported; $P=.03$) from 5 studies, which is similar to the OR reported in our meta-analysis. The study by Roth et al,[39] which we included, was excluded from the analyses by Woo and White[12] and Le Feuvre et al.[6]

The American Heart Association and the American College of Cardiology task force practice guidelines for thrombolysis in AMI recommend a door-to-needle time of 30 minutes.[47] The overall interval difference of 45 minutes in this meta-analysis was clinically significant and theoretically may spare myocardial damage and improve outcomes. The reduction in time with prehospital thrombolysis was seen in all 6 studies (range, 33-130 minutes). Boersma et al[22] performed a weighted regression of 8 randomized trials to examine average delay from symptom onset to initiation of thrombolytic therapy and reported a 1-hour–longer delay in treatment in the in-hospital group when compared with prehospital initiation of thrombolysis, which resulted in an associated benefit of 21 lives saved per 1000 treated ($P=.002$). The MITI trial[38] showed that a statistically significant reduction in the combined outcome of hospital mortality, ejection fraction, and infarct size was seen in the patients treated within 70 minutes of onset of symptoms ($P<.009$). At 2 years, no significant reduction in mortality was seen for any time interval subgroup (ie, >70 or <70 minutes; $P=.46$).[43] Follow-up information at 1, 2, and 5 years and subgroup analysis from the GREAT study[42,43] has demonstrated a significant reduction in mortality in the patients with more than a 120-minute reduction in the time from symptom onset to thrombolysis, regardless of point of administration or who administered the thrombolytic. Both trials[42,43] and the pooled analysis by Boersma et al[22] suggest that early thrombolysis may be beneficial and that patients with prolonged out-of-hospital times may benefit most from point-of-care thrombolysis.

Urban emergency medical services systems with rapid response times may have a greater impact on mortality and infarct size by means of accurate identification of AMI patients and rapid transit to centers that can provide definitive care, including thrombolysis and adjuvant pharmacological, technical, or surgical therapies. Canto et al[48] suggested that all patients who received prehospital 12-lead electrocardiography without thrombolysis were more likely to receive in-hospital thrombolytic therapy, undergo primary angioplasty, coronary arteriography/angioplasty, and bypass surgery ($P<.001$). The crude and adjusted mortality difference was significant for the group that received a prehospital ECG (OR for in-hospital mortality was 0.83, 95% CI, 0.71-0.96; $P=.01$).[48]

In this meta-analysis, we pooled the results of different thrombolytic agents, because whether delivered prehospital or in-hospital, the agent used varies among institutions and emergency medical services systems. Today the choice of agent remains less important than making the correct diagnosis and rapid and safe administration of the thrombolytic agent.[15,20,46] The decision to use a thrombolytic agent is dependent on patient-specific factors such as risk-

Figure 2. Results of Randomized Trials of Prehospital Thrombolysis on Hospital Mortality



Panel A, z score=−2.14; $P=.03$. Panel B, z score=−2.06; $P=.04$. Panel C, z score=−1.73; $P=.08$. OR indicates odds ratio; CI, confidence interval; EMIP, The European Myocardial Infarction Project; and GREAT, Grampian Region Early Anistreplase Trial.

benefit and cost-benefit ratios. The most suitable prehospital thrombolytics may prove to be the fourth-generation agents given as a single bolus, which have not yet been tested in randomized trials in the prehospital setting.

We have identified a clinically important and statistically significant decrease in all-cause hospital mortality when patients with AMI receive prehospital vs in-hospital thrombolysis. Notwithstanding the encouraging results about the benefit of prehospital thrombolysis for AMI, implementing such clinical policies may be subject to the constraints of different health care systems. There is sufficient evidence to suggest that prehospital thrombolysis reduces the delay to treatment in settings with long transit times. In urban settings with relatively short transit times, prehospital thrombolysis should be evaluated in comparison to 12-lead ECG interpretation with advance notification and rapid transportation to definitive care.

Previous Presentations: Society of Academic Emergency Medicine annual meeting, Chicago, Ill, May 18, 1998, and the Royal College of Physicians and Surgeons annual meeting, Toronto, Ontario, September 26, 1998.

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