

## Comparison of Primary Percutaneous Coronary Intervention and Fibrinolytic Therapy in ST-Segment–Elevation Myocardial Infarction

### Bayesian Hierarchical Meta-Analyses of Randomized Controlled Trials and Observational Studies

Thao Huynh, MD, MSC, FRCPC; Stephane Perron, MD, MSC, FRCPC; Jennifer O’Loughlin, PhD; Lawrence Joseph, PhD; Michel Labrecque, MD, PhD; Jack V. Tu, MD, PhD, FRCPC; Pierre Thérioux, MD, FRCPC

**Background**—Published meta-analyses comparing primary percutaneous coronary intervention with fibrinolytic therapy in patients with ST-segment–elevation myocardial infarction include only randomized controlled trials (RCTs). We aim to obviate the limited applicability of RCTs to real-world settings by undertaking meta-analyses of both RCTs and observational studies.

**Methods and Results**—We included all RCTs and observational studies, without language restriction, published up to May 1, 2008. We completed separate bayesian hierarchical random-effect meta-analyses for 23 RCTs (8140 patients) and 32 observational studies (185 900 patients). Primary percutaneous coronary intervention was associated with reductions in short-term ( $\leq 6$ -week) mortality of 34% (odds ratio, 0.66; 95% credible interval, 0.51 to 0.82) in randomized trials, and 23% lower mortality (odds ratio, 0.77; 95% credible interval, 0.62 to 0.95) in observational studies. Primary percutaneous coronary intervention was associated with reductions in stroke of 63% in RCTs and 61% in observational studies. At long-term follow-up ( $\geq 1$  year), primary percutaneous coronary intervention was associated with a 24% reduction in mortality (odds ratio, 0.76; 95% credible interval, 0.58 to 0.95) and a 51% reduction in reinfarction (odds ratio, 0.49; 95% credible interval, 0.32 to 0.66) in RCTs. However, there was no conclusive benefit of primary percutaneous coronary intervention in the long term in the observational studies.

**Conclusions**—Compared with fibrinolytic therapy, primary percutaneous coronary intervention was associated with short-term reductions in mortality, reinfarction, and stroke in ST-segment–elevation myocardial infarction. Primary percutaneous coronary intervention was associated with long-term reductions in mortality and reinfarction in RCTs, but there was no conclusive evidence for a long-term benefit in mortality and reinfarction in observational studies. (*Circulation*. 2009;119:3101-3109.)

**Key Words:** angioplasty ■ coronary disease ■ fibrinolysis ■ myocardial infarction ■ percutaneous coronary intervention ■ thrombolysis

Several randomized controlled trials (RCTs)<sup>1–23</sup> show that primary percutaneous coronary intervention (PCI) is associated with reductions in mortality, reinfarction, and stroke compared with fibrinolytic therapy. However, many aspects of reperfusion therapy might not be optimally assessed in RCTs. First, the benefit of primary PCI may not be replicable under suboptimal conditions such as at low-volume and less expert PCI centers,<sup>24</sup> outside regular working hours, or after lengthy interhospital transfer. Second, use of

rescue or elective PCI was limited ( $< 20\%$ ) in several RCTs,<sup>1,8,11,12,14,16–17,20–22</sup> whereas rescue or elective PCI is generally performed as indicated in the real world. Furthermore, patients with ST-segment–elevation myocardial infarction (STEMI) enrolled in RCTs are generally younger with fewer comorbid conditions than patients in the real world.<sup>25</sup> Therefore, extrapolation of the safety and effectiveness of primary PCI and fibrinolytic therapy observed in RCTs to the real-world STEMI population might not be entirely appropri-

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From the McGill Health University Center (T.H.) and Department of Epidemiology and Biostatistics (L.J.), McGill University, Montreal; Direction of Public Health of Montreal (S.P.), Department of Social and Preventive Medicine (J.O.), and Montreal Heart Institute (P.T.), University of Montreal, Montreal; Department of Family Medicine, Laval University, Quebec (M.L.); and Institute for Clinical Evaluative Sciences, University of Toronto, Toronto (J.V.T.), Canada.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.793745/DC1>. Reprint requests to Dr Thao Huynh, 1650 Ave Cedar, Room E-5200, Montreal, Quebec, H3G-1A4, Canada. E-mail thao.huynhthanh@mail.mcgill.ca © 2009 American Heart Association, Inc.

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ate. Previous meta-analyses included only RCTs. We aim to obviate the limitations of these analyses by examining results from observational studies in addition to those of RCTs. We also include recently published data from several RCTs that were not considered in previous meta-analyses.

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## Methods

### Search Strategy

We retrieved RCTs and observational studies that compared primary PCI and fibrinolytic therapy in STEMI from the following databases: BIOSIS, Cinahl, Embase, PubMed, Web of Science, Cochrane Library, health technology assessment agencies, and Current Contents (up to May 1, 2008) (no language restriction). We used the following keywords: *angioplasty, fibrinolysis, thrombolysis, fibrinolytic therapy, acute myocardial infarction, percutaneous coronary intervention, reperfusion therapy, coronary stent, treatment, and management*. In addition, we manually searched the references of published articles to ensure identification of all published STEMI trials.

### Inclusion Criteria

Only studies that used full-dose commercially approved fibrinolytic therapy such as streptokinase, urokinase, and fibrin-specific agents like tissue plasminogen activators, tenecteplase, and reteplase were retained for analysis. We retained only studies that reported results for both treatment arms (primary PCI and fibrinolytic therapy). Finally, the observational studies retained had to fulfill the quality requirements suggested by Concato et al,<sup>26</sup> including inclusion of concurrent rather than historical controls, clearly defined inclusion criteria, and defined time of entry into the study.

### Exclusion Criteria

We excluded studies that used facilitated PCI, experimental fibrinolytic agents (other than the agents listed above), or intracoronary administration of fibrinolytic therapy, as well as studies that enrolled mainly patients with contraindications to either fibrinolytic therapy or primary PCI. For studies that compared primary PCI, facilitated PCI, and fibrinolytic therapy,<sup>2,16,22</sup> we excluded patients who underwent facilitated PCI from the analysis. We also excluded studies presented at conferences or published only as abstracts or conference proceedings because detailed appraisal of the methodology and potential biases was not possible.

### End Points

All end points were analyzed as distinct events rather than as a composite end point comprising multiple events. The latter approach can be suboptimal because of equal contributions to the composite end point by end points with unequal clinical relevance.<sup>27</sup> Intracranial bleeding was compiled as stroke and therefore excluded from major bleeding. Major bleeding included all hemorrhagic complications that were severe or life-threatening or required transfusion. Short-term end points included all events up to 6 weeks after the index STEMI. Long-term end points included all events that occurred at least 1 year after the STEMI.

### Study Quality

We critically appraised the quality of the RCTs and observational studies in conformity with the CONSORT (CONsolidated Standards of Reporting Trials) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines.<sup>28,29</sup> We elected not to use scales to evaluate the quality of each study because this approach is controversial with potentially inappropriate adjustment of the treat-

ment effects and marked variation in treatment effects depending on the scale used.<sup>30</sup>

### Data Extraction

Two reviewers (T.H. and S.P.) independently selected studies for inclusion, extracted data, and evaluated the quality of each study. Disagreements were resolved by consensus between the 2 reviewers. The first author (T.H.) had full access to and takes full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Statistical Analysis

We completed separate meta-analyses for each end point for RCTs and observational studies separately. Because it was unlikely that the effects of primary PCI and fibrinolytic therapy would be similar across studies as a result of differences in study design and patient characteristics, a fixed-effect model was not appropriate. Therefore, we used a bayesian hierarchical random-effects model to take intertrial variation in treatment effects into account.<sup>31</sup>

In our models, the total number of events within each group in each trial was modeled as a binomial random variable. The models allowed for the probability of an event to vary both between treatment arms within each study and between studies. The logarithms of the odds ratios (ORs) were assumed to have a normal distribution. The mean of the normal distribution of the logarithm of the ORs across studies represented the average effect across studies, and the variance represented the variability between studies.

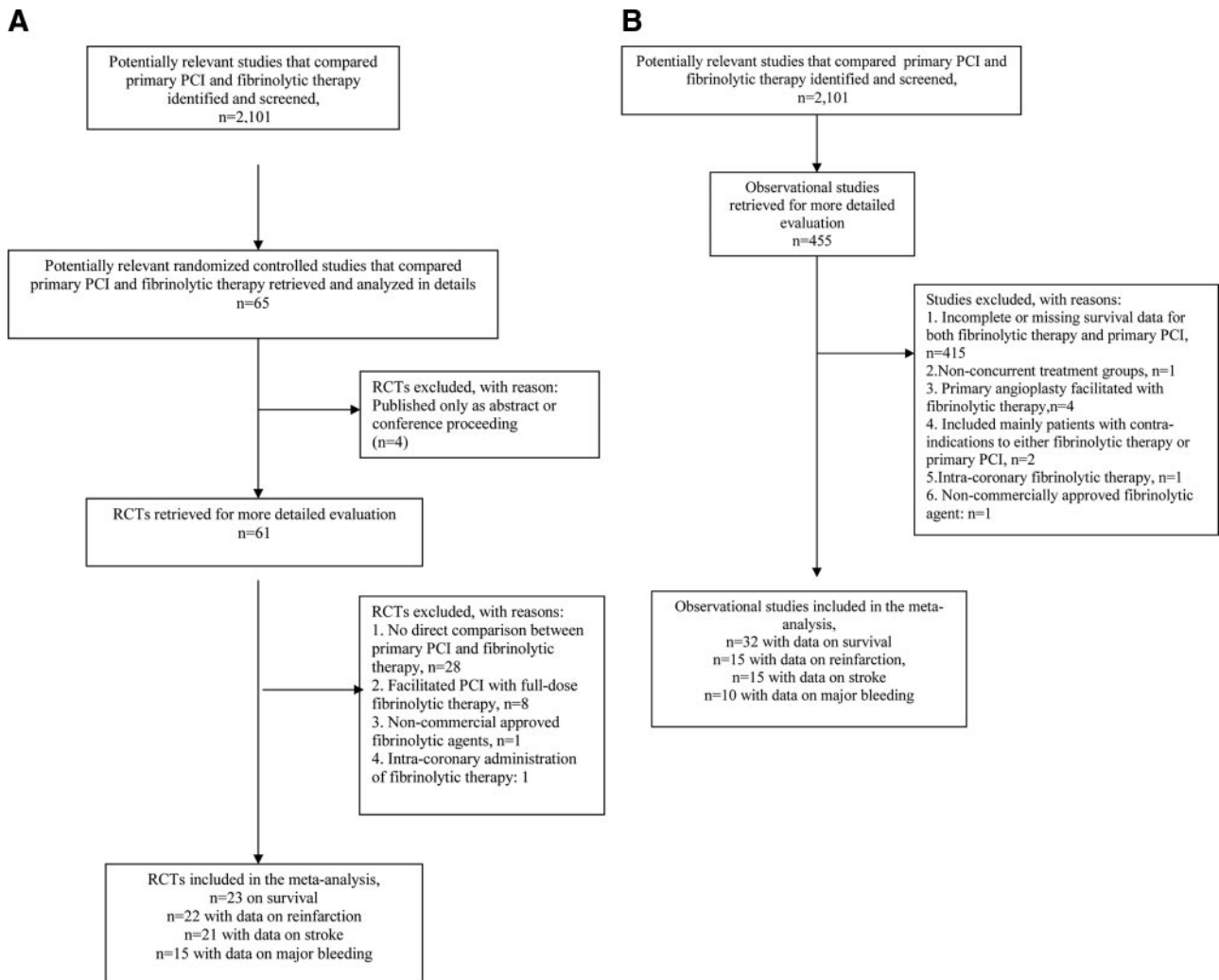
Bayesian analysis allows the integration of new information into existing knowledge. Substantive prior knowledge can be included into bayesian analysis through the choice of a prior distribution. Because we wanted our results (ie, the posterior distributions) to primarily reflect data from previous studies, we selected noninformative prior distributions for all parameters of interest. These included normal densities (mean, 0;  $\tau=0.00001$  [variance of  $10^5$ ]) for the logarithm of the ORs and  $\sigma$  ( $\sigma$ =uniform on the interval [0,2]). Sensitivity analyses varying the prior distributions for a sigma and gamma prior distribution (0.001, 0.001) did not change posterior inferences substantially. Therefore, our estimates of ORs and 95% credible intervals (95% CrIs) were not greatly affected by our a priori choices.

Inferences were calculated with a Gibbs sampler algorithm as implemented through WinBUGS software (version 1.4.2, MRC Biostatistics Unit, Cambridge, UK). To ensure convergence of the Gibbs sampler algorithm, 3 Markov Monte Carlo chains were run, and convergence was assessed after 60 000 iterations. The final summary statistics were based on 120 000 iterations, 100 000 of them for burn-in. The forest plots were completed with R 2.4.1 software ([www.r-project.org/](http://www.r-project.org/)).

We examined for potential publication bias with funnel plots, fail-safe N, and trim and fill ([www.meta-analysis.com](http://www.meta-analysis.com)). Sensitivity analyses were performed with nonbayesian statistical methods, random-effects restricted-maximum-likelihood method (SAS 8.0, SAS Institute Inc, Cary, NC), and random-effects model (DerSimonian-Laird estimator) (NCSS 2007, NCSS, Kaysville, Utah). The results were essentially similar to those obtained by bayesian hierarchical meta-analyses.

## Results

Figure 1 describes the selection of studies for the analysis. Twenty-three RCTs<sup>1–23</sup> and 32 observational studies<sup>24,31–62</sup> were retained. The mean age of patients enrolled ranged from 57 to 80 years in the RCTs and from 57 to 91 years in the observational studies. Two RCTs<sup>2,4</sup> and 7 observational studies<sup>23,35,39,49,61,62</sup> reported prehospital administration of fibrinolytic therapy. Fibrin-specific agents were used primarily in 16 RCTs<sup>1–4,6–12,14,15,19,20,22</sup> and 11 observational studies<sup>24,33,35,37,41,43,44,48,53,57,61</sup> (Tables I and II of the online-only Data Supplement).



**Figure 1.** Quality of Reporting of Meta-analyses flow diagram of RCTs (A) and observational studies (B).

Primary PCI was associated with an  $\approx 34\%$  short-term reduction in mortality (OR, 0.66; 95% CrI, 0.51 to 0.82) in RCTs (Figure 2) and an  $\approx 23\%$  lower mortality in observational studies (OR, 0.77; 95% CrI, 0.62 to 0.95; Figure 3). There was no conclusive difference in mortality in the meta-analysis of observational studies that used prehospital fibrinolytic therapy.<sup>23,35,39,49,61,62</sup> An estimate of the difference in mortality between primary PCI and prehospital fibrinolytic therapy could not be done with certainty because only 2 RCTs used prehospital fibrinolysis.<sup>2,4</sup>

In RCTs, primary PCI was associated with a 24% reduction in long-term mortality (OR, 0.76; 95% CrI, 0.58 to 0.95; Figure 4). However, in observational studies, there was no conclusive difference between the 2 reperfusion strategies in long-term mortality (OR, 0.88; 95% CrI, 0.68 to 1.18; Figure 5). Reductions in short-term reinfarction of 65% and 53% were observed in RCTs and observational studies, respectively (Table 1). An  $\approx 51\%$  reduction associated with primary PCI in long-term reinfarction was noted in RCTs, whereas there was no conclusive difference in reinfarction between treatments in the observational studies (Table 1). Primary PCI was associated with a 60% reduction in stroke in both RCTs and observational studies

(Table 1). Although inconclusive because of the limited number of studies available, the risk estimates were consistent with a possible increase in major bleeding associated with primary PCI (Table 1).

Absolute risk reductions in short-term mortality with primary PCI were  $\approx 2.2\%$  (95% CrI, 1.3 to 3.2) in RCTs and 1.1% (95% CrI, 0.4 to 1.5) in observational studies (Table 2). Absolute risk reductions in short-term reinfarction were  $\approx 4.5\%$  in RCTs and 2.9% in observational studies. Absolute reductions in stroke were  $\approx 1.2\%$  in RCTs and 0.6% in observational studies. At long-term follow-up, primary PCI was associated with absolute reductions in long-term mortality of 3.5% (95% CrI, 0.7 to 6.4) and in reinfarction of 3.4% (95% CrI, 1.6 to 5.9) in RCTs, without conclusive evidence for reductions in long-term mortality and reinfarction in observational studies.

The number needed to treat to prevent 1 short-term death with primary PCI was 45 in RCTs and 91 in observational studies (Table 2). The number needed to treat to prevent 1 long-term death was 29 in RCTs. More specifically, for 100 patients treated with primary PCI, in conditions similar to those in the RCTs, there would be 2 deaths and 5 reinfarctions prevented in the short term and



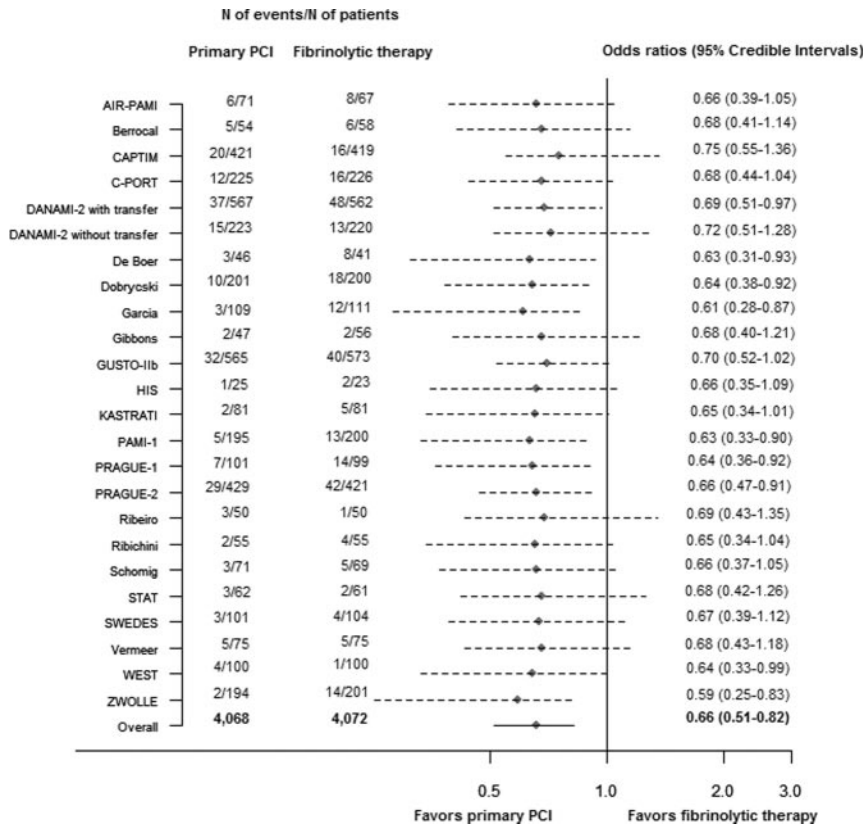


Figure 2. Bayesian forest plot of all-cause short-term mortality rates in RCTs.

3 deaths and 5 reinfarctions prevented in the long term. For 100 patients treated with primary PCI, in conditions similar to those in observational studies, 1 death and 3 reinfarctions would be prevented in the short term, with no

conclusive long-term benefit. For stroke reduction, ≈1 event would be prevented in 100 patients treated with primary PCI in conditions similar to those in the RCTs, whereas only 1 stroke would be prevented in ≈200

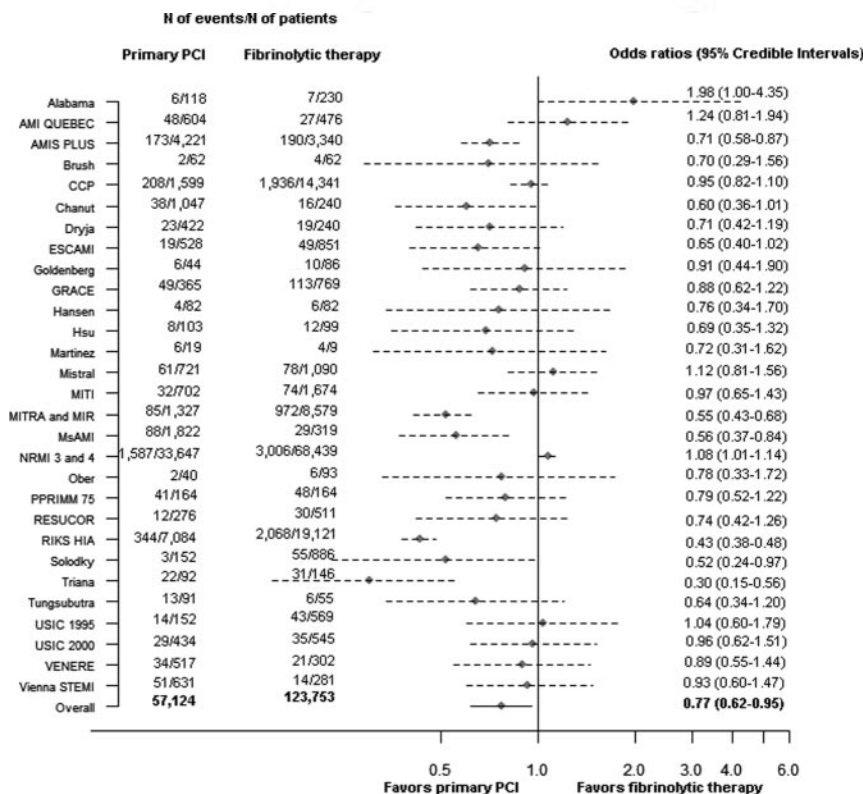


Figure 3. Bayesian forest plot of all-cause short-term mortality rates in observational studies.

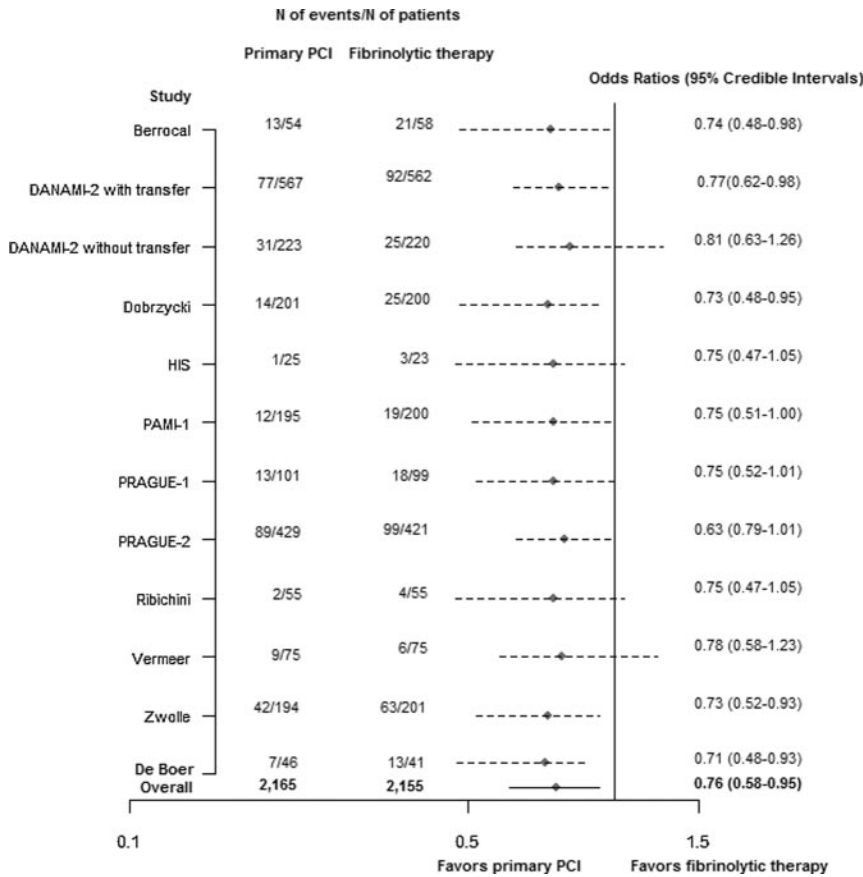


Figure 4. Bayesian forest plot of all-cause long-term mortality rates in RCTs.

patients treated with primary PCI in conditions similar to those in the observational studies.

### Discussion

Our meta-analyses improve on previous systematic reviews by including short-term results from 3 recent RCTs<sup>2,19–21</sup> and including observational studies.<sup>28,32–62</sup> Our study incorporates events at  $\geq 1$  year and includes long-term results from 5 RCTs that were not considered in earlier reviews (data at 1 year from Dobrycki et al<sup>21</sup> and the PRAGUE [Primary Angiography in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis]-1 trial,<sup>63</sup> at 2 years from the PAMI [Primary Angioplasty in Myocardial Infarction]-1 trial,<sup>64</sup> at 3 years from the DANAMI [DANish trial in Acute Myocardial Infarction]-s-2,<sup>65</sup> at 5 years from the PRAGUE-2 study,<sup>66</sup> and at 8 years from the Zwolle Study<sup>67</sup>). Given the marked heterogeneity in study designs and patient populations across studies, our random-effects hierarchical bayesian meta-analyses are more appropriate models<sup>37</sup> than the fixed-effects models.

Several biases may affect the internal validity of RCTs, including lack of central randomization and a blinded adjudication committee, both of which may affect the integrity of randomization and objective ascertainment of end points. Only 10 RCTs specified use of central randomization.<sup>1,3–5,10,16,17,20,22,23</sup> Outcome adjudication by a blinded committee was mentioned in only 10 RCTs.<sup>1,2,4–6,9–12,15</sup>

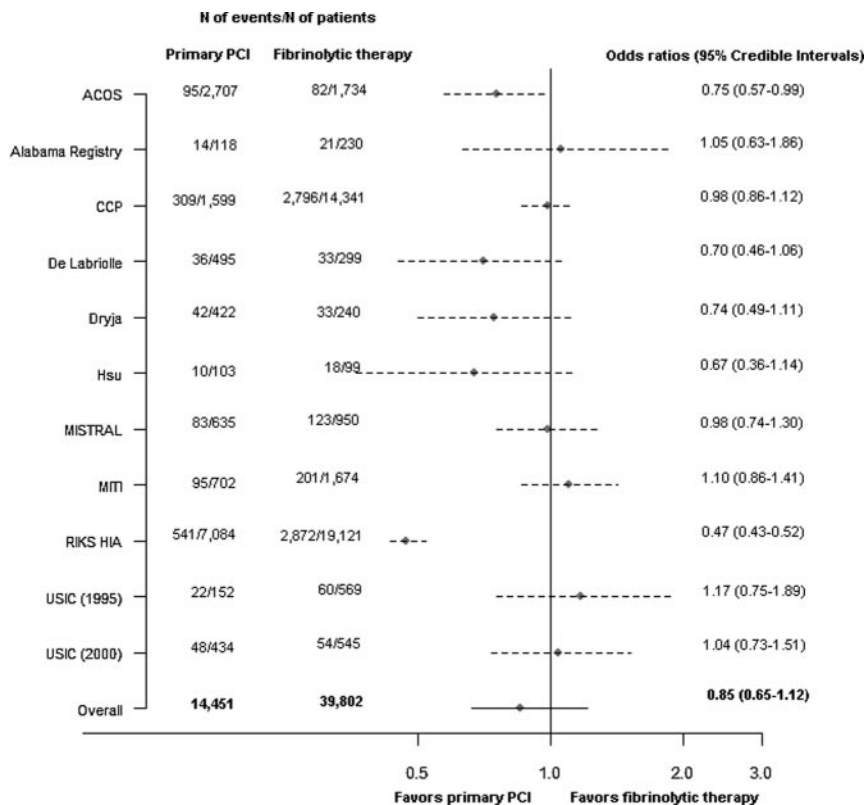
Observational studies are susceptible to many biases, including selection and confounding biases. Observational studies that

exclude patients who did not undergo a planned primary PCI may be subject to selection bias. Only 3 observational studies included all patients assigned to primary PCI regardless of whether they underwent successful PCI.<sup>24,38,39</sup>

Confounding bias may occur in observational studies when patient characteristics affect the treatment received and the outcomes. Patients who received fibrinolytic therapy were older than patients who received primary PCI in 3 observational studies.<sup>34,35,40</sup> There were more patients with anterior STEMI, heart failure, or cardiogenic shock in the primary PCI group in 6 studies<sup>34,39–41,45,48</sup> and in patients who received fibrinolytic therapy in 2 studies.<sup>33,35</sup> Primary PCI patients received more optimal medical therapy and coronary intervention and were more likely to be treated at high-volume hospitals than patients who received fibrinolytic therapy.<sup>35,41,44,48</sup>

The internal validity of both RCTs and observational studies may be affected by differential loss to follow-up in the treatment groups. Except for 1 study<sup>64</sup> that reported high attrition (16%), long-term follow-up was almost complete in most RCTs. Five observational studies reported at least 95% long-term follow-up.<sup>33,34,39,45,62</sup> Our risk estimates remained virtually unchanged when restricted to studies with optimal follow-up.

The applicability of results from RCTs to the real-world setting is generally limited. Several RCTs excluded elderly patients,<sup>7,13,14,21,22</sup> patients with renal disease,<sup>3,4,10,12</sup> those in cardiogenic shock,<sup>1,4,7,9,14,19,22</sup> patients with Killip class  $\geq 2$ ,<sup>18,20,23</sup> and patients with left bundle-branch block,<sup>1,6,8,18,21</sup> so their results may not be applicable to these high-risk patient groups.



**Figure 5.** Bayesian forest plot of all-cause long-term mortality in observational studies.

The long-term attenuation of the early reductions in mortality and reinfarction associated with primary PCI may be due to optimal long-term medical therapy that may have delayed the long-term progression of coronary artery disease equally in both treatment arms. The reduced magnitudes of risk reductions associated with primary PCI in observational studies compared with those in RCTs might reflect real-world practice. Greater use of in-hospital PCI ( $\geq 30\%$ ) after fibrinolytic therapy in observational studies<sup>24,35,41,43,44,55,62</sup> may partially explain the smaller reductions in short-term mortality and reinfarction associated with primary PCI. In the real world, primary PCI also may be less successful when per-

formed in less-than-optimal conditions. In observational studies, the lack of conclusive long-term benefits with primary PCI may be explained by optimal medical therapy and/or the judicious use of coronary interventions in patients who received fibrinolytic therapy.

### Study Limitations

These meta-analyses have several limitations that warrant mention. First, the comparison of primary PCI with prehospital fibrinolysis could not be ascertained with certainty because of the small number of studies that used this reperfusion strategy. The efficacy and safety of prehospital fibrinolysis compared with primary PCI may be better evaluated in future large studies. Second, the greater use of thienopyridines in primary PCI than in the fibrinolytic therapy arm might have partially confounded the results. The mortality difference between primary PCI and fibrinolytic therapy may be attenuated with more systematic administration of thienopyridines after fibrinolytic therapy. On the other hand, recent technological advances in primary PCI may further increase the mortality and reinfarction benefits associated with primary PCI. Third, the validity of our meta-analysis of long-term mortality in observational studies was potentially limited by the lack of long-term data from the large observational NRMI-3/4 studies.<sup>56</sup> Nonetheless, it would be unlikely that long-term data from NRMI-3/4 would modify our results because there was no short-term mortality difference between the 2 treatment arms in this study. Fourth, our estimate of long-term mortality may have been influenced by the large observational RIKS-HIA study.<sup>35</sup> However, sensitivity analyses excluding the RIKS-HIA study showed essen-

**Table 1. Meta-Analyses of Major Adverse Outcomes**

Outcome	Studies, n	Patients, n	OR (95% CrI)
<b>RCTs</b>			
Short-term mortality	23	8140	0.66 (0.51–0.82)
Long-term mortality	11	4320	0.76 (0.58–0.95)
Short-term reinfarction	22	7937	0.35 (0.24–0.51)
Long-term reinfarction	9	4121	0.49 (0.32–0.66)
Stroke	21	7932	0.37 (0.21–0.60)
Major bleeding	15	4624	1.40 (0.88–2.00)
<b>Observational studies</b>			
Short-term mortality	29	180 877	0.77 (0.62–0.95)
Long-term mortality	12	54 571	0.88 (0.60–1.18)
Short-term reinfarction	15	45 087	0.47 (0.32–0.67)
Long-term reinfarction	4	32 181	0.58 (0.29–1.21)
Stroke	15	35 158	0.39 (0.29–0.61)
Major bleeding	10	19 459	1.30 (0.37–4.42)

**Table 2. Absolute Risk Reductions and Numbers Needed to Treat**

Outcomes	Events in the Fibrinolytic Therapy Group, %		Absolute Percent (95% CrI)		Number Needed to Treat With Primary PCI to Prevent 1 Event	
	RCT	Observational Studies	RCT	Observational Studies	RCT	Observational Studies
	Short-term mortality	7.1	7.3	2.2 (1.3–3.2)	1.1 (0.4–1.5)	45 (31–77)
Short-term reinfarction	6.7	9.4	4.5 (3.6–5.4)	2.9 (1.3–4.8)	22 (19–28)	35 (21–77)
Long-term mortality	16.7	11.7	3.5 (0.7–6.4)	1.1 (3.0 reduction–2.4 increase)	29 (16–143)	NA
Long-term reinfarction	9.4	5.8	3.4 (1.6–5.9)	2.4 (4.0 reduction–5.7 increase)	29 (17–63)	NA
Stroke	1.9	0.8	1.2 (0.8–1.5)	0.6 (0.5–0.7)	83 (67–125)	166 (143–200)

NA indicates not applicable because there was no conclusive benefit with primary PCI.

tially similar results with no conclusive difference in long-term mortality between the 2 treatment arms. Finally, reports with positive findings are more likely to be reported, published, and cited.<sup>68</sup> However, the lack of asymmetry in the funnel plots suggests that we did not miss important negative studies.

**Conclusions**

Compared with fibrinolytic therapy in STEMI, primary PCI was associated with short-term reductions in mortality, reinfarction, and stroke in both RCTs and observational studies and with long-term reductions in reinfarction and mortality in RCTs. There was no conclusive difference in long-term mortality and reinfarction between primary PCI and fibrinolytic therapy in the observational studies reviewed. The potential benefit of prehospital fibrinolysis compared with primary PCI cannot be reliably ascertained from the present review.

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**Disclosures**

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## CLINICAL PERSPECTIVE

The American Heart Association Mission Lifeline recently recommended major reorganizations in the structures and processes involved in reperfusion therapy for acute myocardial infarction with ST-segment elevation. In view of the major investments required for these reorganizations, systematic reviews of randomized controlled trials (RCTs) and observational studies to compare primary percutaneous coronary intervention and fibrinolytic therapy in diverse patient populations and clinical contexts are particularly timely. Meta-analyses of both RCTs and observational studies are consistent in showing short-term reductions in mortality and reinfarction with primary percutaneous coronary intervention, attesting to the superiority of this reperfusion strategy. The smaller reductions in short-term mortality and reinfarction with primary percutaneous coronary intervention reported in observational studies compared with RCTs may relate to confounding and selection bias, as well as less optimal application of primary percutaneous coronary intervention in the real world. The inconclusive evidence in observational studies for differences between the 2 reperfusion strategies in long-term mortality and reinfarction may be due to optimal long-term medical therapy and coronary intervention in the patients who received fibrinolytic therapy that may have attenuated the early benefits associated with primary percutaneous coronary intervention. The potential benefits of prehospital fibrinolysis could not be ascertained in this systematic review and may be better evaluated in large RCTs and observational studies.

**Appendix**

**Table 1. Summary of randomized controlled studies that compared primary percutaneous coronary intervention and fibrinolytic therapy**

Name of study or first author	Study period	N of patients	Age Median Q1,Q3		Transfer for primary PCI required	Pre-hospital FL	Type of FL	GP inhibitor	Stent %	Time delay to reperfusion therapy Median, min	
			Primary PCI	FL						D-B Q1,Q3	D-N Q1,Q3
			Mean	Mean						mean	mean
Air-PAMI <sup>9</sup>	NA Published in 2002	138	Mean 62 ±12	Mean 64 ±12	Yes	No	68% tPA 32% SK	NA	NA	155 118,194	174 ±80
Berrocal <sup>18</sup>	1993-5	112	68 57,74	69 59,77	No	No	SK	NA	NA	82** 55,100	15** 10,26
CAPTIM <sup>4</sup>	1997-2000	840	58 50,68	58 49,69	No	100%	Accelerated tPA	NA	Yes	190* 149,255	130 95,180
C-PORT <sup>3</sup>	1996-9	451	Mean 63 ±13	Mean 64 ±12	No	No	Accelerated tPA	Yes	Yes	102	46
DANAMI-2 with transfer <sup>1</sup>	1997-2001	1,129	62 53,82	64 54,74	Yes	No	Accelerated tPA	Yes	Yes	90** 74,108	20** 15,30
DANAMI-2 without transfer <sup>1</sup>	1997-2001	443	64 56,74	62 54,73	Yes	No	Accelerated tPA			63** 49,77	20** 13,30
De Boer <sup>5</sup>	1996-9	87	80 77,84	80 77-84	No	No	SK	No	Yes	NA	NA
Dobrzycki <sup>21</sup>	2002-3	401	Mean 63 ±12	Mean 64 ±11	Yes	No	SK	Yes	Yes	145 120,178	35 25,50
Garcia <sup>6</sup>	1991-6	220	63 53,71	60 53,74	No	No	Accelerated tPA	NA	Yes	NA	197* 150,250
Gibbons <sup>7</sup>	1989-91	108	Mean 60 ±11	Mean 62 ±13	No	No	Non- accelerated tPA	NA	NA	277±144*	232±174*
GUSTO- IIB <sup>10</sup>	1994-6	1,138	64 53,71	62 52,71	No	No	Accelerated Tpa	NA	NA	3.8 hours* 3.0,5.3	3.0 hours* 2.0,4.3
HIS <sup>20</sup>	NA Published in 2006	48	Mean 61 ±13	Mean 66 ±16	Yes	NA	Fibrin-specific	Yes	NA	NA	NA

**Table 1(cont) Summary of randomized controlled studies that compared primary percutaneous coronary intervention and fibrinolytic therapy**

Name of study or first author	Study period	n of patients	Age (mean)		Transfer for primary PCI required	Pre-hospital FL	Type of FL	GP inhibitor	Stent %	Time delay to reperfusion therapy Median, min	
			Primary PCI	FL						D-B	D-N
Kastrati <sup>11</sup>	1999-2001	141	61 51,73	61 54,69	No	No	Accelerated tPA	Yes	Yes	NA	NA
PAMI-1 <sup>8</sup>	1990-2	395	Mean 60 ±11	Mean 60 ±11	No	No	Non-accelerated tPA	NA	NA	Mean 60±41**	Mean: 32±22**
PRAGUE-1 <sup>16</sup>	1997-9	200 <sup>ε</sup>	Mean 61 ±12	Mean 61 ±10	Yes	No	SK	NA	Yes	95	22
PRAGUE-2 <sup>17</sup>	1999-2002	850	65	64	Yes	No	SK	NA	Yes	Mean 97±28**	Mean 12±10**
Ribeiro <sup>13</sup>	1989	100	57±10	55±10	No	No	SK	NA	NA	Mean 238±112*	Mean 179±98*
Ribichini <sup>14</sup>	1993-6	110	63	60	No	No	Accelerated tPA	NA	Yes	Mean 53	Mean 36
Schomig <sup>15</sup>	1997-9	140	58 52,70	61 52,80	No	No	Accelerated tPA	100%	100%	65 53,85	30 23,40
SWEDES <sup>19</sup>	2001-3	205	65±11	64±12	Yes	No	Retepase	100%	NA	202* 83,197	114* 154,276
STAT <sup>12</sup>	1997-9	123	61±12	60±11	No	No	Accelerated tPA	19%	98%	77** 58,97	15** 10,21
Vermeer <sup>22</sup>	1999	150 <sup>ε</sup>	58±11	59±11	Yes	No	Accelerated tPA	NA	Yes	Mean 85±25*	Mean 10, standard deviation NA
WEST <sup>2</sup>	Study period NA, Published in 2006	200 <sup>ε</sup>	60 49,71	58 51,69	Yes	42%	Tenecteplase	Yes	NA	127 93,159	51 37,75
Zwolle <sup>23</sup>	1990-5	395	59±11	60±10	No	No	SK	NA	NA	NA	NA
Total	23 studies 1989-2006										



GP: Glycoprotein inhibition

<sup>£</sup>: For patients who received primary PCI, <sup>\*</sup>: From symptom onset, <sup>\*\*</sup>: From randomization, <sup>€</sup>: We excluded patients who underwent routine coronary angiogram following fibrinolytic therapy

NA: Not Available

FL: Fibrinolytic therapy, SK: Streptokinase, tPA: Tissue plasminogen activators

PCI: percutaneous coronary intervention, D-B: Door-to-Balloon's inflation, D-N: Door-to-Needle (first injection of fibrinolytic therapy), Q1,Q3: first and third quartiles

Acronyms of studies:

AIR-PAMI: Air Primary Angioplasty in Acute Myocardial Infarction

CAPTIM: Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction

C-PORT: Atlantic Cardiovascular Patient Outcomes Research Team

DANAMI-2: Danish Trial in Acute Myocardial Infarction-2

GUSTO-IIb: Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes-IIb

HIS: Holland Infarction Study

PAMI-1: Primary Angioplasty in Acute Myocardial Infarction

PRAGUE 1 and 2: Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis 1 and 2

STAT: Stenting vs Thrombolysis in Acute Myocardial Infarction Trial

SWEDES: Swedish Early Decision Reperfusion trial

WEST: Which Early ST-elevation myocardial infarction Therapy

**Table 2. Summary of the observational studies that compared primary PCI and fibrinolytic therapy**

Name of study or first author	Study period	n of patients	Age (mean)		Transfer for primary PCI required	Pre-hospital FL	Type of FL	GP inhibitor $\xi$	Stent $\xi$	Time delay to reperfusion therapy Median, min Q1,Q3	
			Primary PCI	FL						D-B	D-N
ACOS <sup>32</sup>	2000-2	4,441	NA	NA	NA	NA	NA	NA	NA	NA	
Alabama Registry of Myocardial Ischemia <sup>33</sup>	1990-2	348	58 SD NA	58 SD NA	No	No	76% non-accelerated tPA	NA	NA	Mean: 252* SD NA	Mean: 180* SD NA
AMI-Quebec <sup>48</sup>	2003	1,189	61±13	60±13	30%	No	80% Fibrin-specific agents	Yes	Yes	Without transfer: 109 (79,115) With transfer: 142 (115,194)	32
AMIS Plus <sup>34</sup>	1997-2005	7,561	61 SD NA	63 SD NA	NA	NA	NA	NA	NA	65 Q1,Q3 NA	30 Q1,Q3 NA
Brush <sup>52</sup>	1990-4	124 SD NA	56 SD NA	56	No	No	NA	NA	NA	NA	NA
CCP <sup>54</sup>	1994-6	15,940 Patients ≥65 years	Mean 74±6	Mean 73±6	No	No	NA	NA	NA	NA	NA
Chanut <sup>49</sup>	2000	1,287	69 (data was not provided separately for the two treatment arms)		NA	Yes	NA	NA	NA	NA	NA
De Labriolle <sup>50</sup>	1992-2004	794	Mean 63±14	Mean 60±12	No	6.6%	NA	Yes	NA	Mean 65±35	Mean 30±44
Dryja <sup>51</sup>	2003	662	58	64	Yes	NA	99%SK	NA	NA	48±40	86±42
ESCAMI <sup>61</sup>	1998-2000	1,379	58±11	60±10	NA	NA	51% fibrin-specific	36%	81%	86±42	Mean 48
Goldenberg <sup>41</sup>	1998-9	130 Patients ≥70 years	77±5	76±5	No	No	100% accelerated tPA	Yes	Yes	NA	NA

**Table 2(cont). Summary of observational studies that compared primary PCI and fibrinolytic therapy**

Name of study or first author	Study period	n of patients	Age (mean)		Transfer for primary PCI required	Pre-hospital FL	Type of FL	GP inhibitor <sup>£</sup>	Stent <sup>£</sup>	Time delay to reperfusion therapy, Median, min	
			Primary PCI	FL						D-B	D-N
GRACE <sup>44</sup>	1999-2002	1,134 Patients	76 Q1,Q3	76 Q1,Q3	NA	NA	54% tPA 43% SK 3% other	Yes	90%	105 Q1,Q3	40 Q1,Q3
Hansen <sup>53</sup>	1995	≥70 years 164	62±10	62±10	Yes	NA	65% accelerated tPA	2%	57%	217* (range 0-160)	216* (range 0-170)
Hsu <sup>42</sup>	1997-9	202 diabetics	Mean 60±9	Mean 61±10	No	No	20% tPA	63%	94%	Mean 104	Mean 68
Martinez-Selles <sup>59</sup>	1998-2004	28 patients ≥89 years	90	91	No	No	NA	NA	NA	NA	NA
MISTRAL <sup>34</sup>	1998-1999	1,811 <sup>α</sup>	63	64	3%	No	NA	31%	Yes	Mean 73	Mean 42
MITI <sup>24</sup>	1988-94	3,145 <sup>∞</sup>	60±12	60±12	Yes	8%	65% tPA	NA	NA	Mean 1.7±1.2	Mean 1.0±1.0
MITRA and MIR <sup>55</sup>	1994-8	9,906	62 <sup>β</sup> 54,70	64 <sup>β</sup> 55,72	18%	NA	28% tPA, 50% SK, 17%, other	NA	NA	NA	NA
MsAMI <sup>46</sup>	1992-2000	2,141	66	62	Yes	NA	5%NA	NA	NA	NA	NA
NRMI-3/4 <sup>56</sup>	1999-2002	68,439	62(13)	62(13)	No	NA	NA	NA	NA	94 <sup>§</sup> 116 <sup>§§</sup>	33 <sup>§</sup> 34 <sup>§§</sup>
Ober <sup>45</sup>	2000-2	133	57±14	58±12	No	NA	NA	NA	Yes	Mean 4.1±1.8*	Mean 3.6±1.9*
PPRIMM75 <sup>37</sup>	1998-2000	328 patients ≥75 years	78 76,83	79 76,84	NA	NA	68% tPA	NA	NA	NA	NA
RESUCOR <sup>57</sup>	2002-3	787	65	61	NA	Yes	100% Tenecteplase	82%	NA	102	30



**Table 2(cont). Summary of observational studies that compared primary PCI and fibrinolytic therapy**

Name of study or first author	Study period	n of patients	Age (mean)		Transfer for primary PCI required	Pre-hospital FL	Type of FL	GP inhibitor <sup>£</sup>	Stent <sup>£</sup>	Time delay to reperfusion therapy Median, min	
			Primary PCI	FL						D-B	D-N
RIKS-HIA <sup>35</sup>	1999-2004	26,205	64±12	In-hospital 68±12 Pre-hospital 66±11	NA	16	37% SK	NA	NA	3.3 hours*	In-hospital 2.5** hrs Pre-hospital 2.0 hrs
Roncalli <sup>62</sup>	1995-1999	318	59±11	59±11	No	Yes	100% tPA	Yes	NA	Mean 237±90	Mean 44, sd NA
Solodky <sup>47</sup>	3 surveys: 1996,1998, 2000	1,038	59	61	NA	NA	63% SK 31% tPA 6% other	NA	NA	Mean 3.6 hours*	Mean 3.3hours*
TRIANA 1-2 <sup>36</sup>	2002 for TRIANA 2 NA for TRIANA 1	238 patients ≥75 years old	79±4	80±4	NA	NA	NA	Yes	NA	90 60,143	49 30,88
Tungsubutra <sup>58</sup>	2002-4	146	64	60	NA	NA	7% tPA	14%	NA	120	135
USIC 1995 <sup>38</sup>	1995	721	67±14	67±14	NA	NA	NA	NA	Yes	NA	NA
USIC 2000 <sup>39</sup>	2000	979	62 50,72	64 <sup>αα</sup> (50,73) 59 <sup>ααα</sup> (49,70)	NA	33%	NA	46%	NA	NA	NA
VENERE <sup>60</sup>	NA, published 2005	819	NA	NA	26%	NA	NA	NA	NA	NA	NA
Vienna STEMI <sup>43</sup>	2003-4	912	62±14	61±13	No	Yes	70%	100%	Yes	Mean 81±51	Mean 17±13
TOTAL: 32 studies	1988-2005										

£: For patients who received primary PCI, \*: From symptom onset, \*\*: From randomization, §: During regular hours, §§: Off-hours, SD: Standard deviation

<sup>α</sup>: One of the following high-risk criteria: age >70 years, diabetes and age >70 years, Killip class >1, systolic blood pressure <100 and heart rate >100/min, ST elevation in <4 leads, previous q wave MI, contra-indication to fibrinolytic therapy (7% of patients who underwent primary PCI)

<sup>αα</sup>: In-hospital fibrinolytic therapy, <sup>ααα</sup>: Pre-hospital fibrinolytic therapy

∞: 2,376 ideal patients included in our meta-analyses (ideal patients: confirmed ST-segment elevation, no contra-indications to FL and no shock)

NA: Not Available

FL: Fibrinolytic therapy SK: Streptokinase, tPA: Tissue plasminogen activators

PCI: Percutaneous coronary intervention, D-B: Door-to-Balloon's inflation, D-N: Door-to-Needle (first injection of fibrinolytic therapy)

Acronyms of studies:

ACOS: Acute Coronary Syndromes

AMI-QUEBEC: Acute Myocardial Infarction in Quebec

AMIS-Plus: Acute Myocardial Infarction in Switzerland

CCP: Cooperative Cardiovascular Project

ESCAMI: Evaluation of the Safety and Cardioprotective effects of eniporide in Acute Myocardial Infarction

GRACE: Global Registry of Acute Coronary Events

MISTRAL: Myocardial Infarction with Severe prognosis: observation of treatment with Angioplasty or Lysis Study

MITI: Myocardial Infarction Triage and Intervention Project Study

MITRA: Maximal Individual Therapy in Acute Myocardial Infarction. MIR; Myocardial Infarction Registry

MsAMI: Miyagi Study Group for Acute Myocardial Infarction

NRMI: National Registry of Myocardial Infarction

PPRIMM-75: Pronostico del Primer Infarto de Miocardio en Mayores de 75 Anos

RESUCOR: Reseau des Urgences Coronaires

RIKS-HIA: Register of Information and Knowledge about Swedish Heart Intensive Care Admissions

TRIANA: TRatamiento del Infarto Agudo de miocardio eN Ancianos Registry

VENERE: VENEto acute myocardial infarction REgistry

USIC: Unites des Soins Intensives Coronariens

**Table 3a. Meta-analyses of short-term mortality**

Randomized controlled studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>1-23</sup>	23	8,140	0.66 (0.51-0.82)
Fibrin-specific agents* <sup>1-4,6-12,14-15, 19-20,22</sup>	16	5,921	0.73 (0.53-0.95)
Inter-hospital transfer (excluding CAPTIM) <sup>1-2,9,16-17,20-22</sup>	8	3,272	0.64 (0.43-0.90)
Studies with optimal central randomization <sup>1,3-5,10,16-17,20,22-23</sup>	10	5,731	0.66 (0.42-0.91)
Studies with blinded endpoint adjudication <sup>1-2,4-6,9-12,15</sup>	10	4,825	0.74 (0.50-1.05)
Observational studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>24,33-49, 51-62</sup>	29	180,665	0.77 (0.62-0.95)
Fibrin-specific agents* <sup>24,33,35,37,41,43-44,48,53,57,61</sup>	11	34,913	0.88 (0.62-1.28)

**Table 3b. Meta-analyses of long-term mortality**

Randomized controlled studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>1,5,14,16-18,21-23,64</sup>	10	4,320	0.76 (0.58-0.95)
Fibrin-specific agents* <sup>1,14,22,64</sup>	4	2,275	0.86 (0.55-1.25)
Inter-hospital transfer <sup>20-22,65-67</sup>	6	2,730	0.79 (0.59-1.06)
Observational studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>24,32-33,35,38-39,42,50-51,54,61-62</sup>	12	47,382	0.88 (0.60-1.21)
Fibrin-specific agents* <sup>24,35,62</sup>	3	21,944	1.00 (0.34-3.01)

Odds ratio <1 is in favour of 1 for primary PCI, odds ratio >1 is in favour of fibrinolytic therapy.

\*: Specified use in ≥50% of patients



**Table 4a. Meta-analyses of short-term reinfarction**

Randomized controlled studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>1-10,12-23</sup>	22	7,937	0.35 (0.24-0.51)
Fibrin-specific agents* <sup>1-4,6-10,12,14-15, 19-20,22</sup>	15	5,979	0.32 (0.17-0.56)
Inter-hospital transfer <sup>1-2,9,16-17,20-22</sup>	8	3,272	0.37 (0.12-0.98)
Studies with optimal central randomization <sup>1,3-5,10,16-17,20,22-23</sup>	10	5,731	0.32 (0.19-0.48)
Studies with blinded endpoint adjudication <sup>1-2,4-6,9-12,15</sup>	10	4,825	0.33 (0.29-0.57)
Observational studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>24,33-35,39,41-42,45,47-48,52-53,55,59,61</sup>	15	45,087	0.47 (0.32-0.67)
Fibrin-specific agents* <sup>24,33,35,41,44,48,61</sup>	7	30,549	0.45 (0.20-0.84)

**Table 4b. Meta-analyses of long-term reinfarction**

Randomized controlled studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>14,20-22,64-68</sup>	9	4,121	0.49 (0.32-0.66)
Fibrin-specific agents* <sup>14,20,22,64-65</sup>	5	2,676	0.63 (0.35-1.00)
Inter-hospital transfer <sup>14,20-22,63,66</sup>	6	2,092	0.53 (0.21-0.99)
Observational studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>33,34-35,42</sup>	4	32,181	0.58 (0.29-1.21)

Odds ratio <1 is in favour of 1 for primary PCI, odds ratio >1 is in favour of fibrinolytic therapy.

\*: Specified ≥50% use of fibrin-specific fibrinolytic agents

**Table 5. Meta-analyses of strokes**

Randomized controlled studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>1-6,8-10,12-23</sup>	21	7,932	0.37 (0.21-0.60)
Fibrin-specific agents* <sup>1-4,6, 8-10, 12,14-15, 19-20,22</sup>	14	5,887	0.36 (0.17-0.65)

Observational studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>33-34,37,39,41-42,44,48-49,51-55,58</sup>	15	35,158	0.39 (0.29-0.61)
Fibrin-specific agents* <sup>33,37,41,44,48,53</sup>	6	5,546	0.32 (0.15-0.85)
Studies that enrolled elderly patients (≥65 years old) <sup>36-37, 41,44,54</sup>	5	17,770	0.32 (0.08-1.33)

Odds ratio <1 is in favour of 1 for primary PCI, odds ratio >1 is in favour of fibrinolytic therapy.

\*: Specified ≥50% use of fibrin-specific fibrinolytic agents

Table 6. Meta-analyses of major bleeding

Randomized controlled studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>1-6,8,10-15,20,22</sup>	15	4,624	1.40 (0.88-2.00)
Fibrin-specific agents <sup>*1-4,6, 8, 10,12,14-15, 20,22</sup>	12	4,011	1.50 (0.90-2.31)
Observational studies			
Types of studies	N of studies	N of patients	Odds ratios (95% Credible Intervals)
All studies <sup>33,36,41-42,44,49,54,58-59,61</sup>	10	19,459	1.30 (0.37-4.42)
Studies that enrolled elderly patients (≥65 years old) <sup>36-37,41-42,54</sup>	5	17,470	1.95 (0.09-0.44)

Odds ratio <1 is in favour of 1 for primary PCI, odds ratio >1 is in favour of fibrinolytic therapy.

\*: Specified ≥50% use of fibrin-specific fibrinolytic agents