MONOGRAPH

Comparison of Efficacy, Effectiveness and Safety of Fibrinolysis and Primary Percutaneous Coronary Intervention (PPCI) for ST segment Elevation Myocardial Infarction (STEMI)

Agence d'évaluation des technologies
et des modes d'intervention en santé

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Monograph prepared for AETMIS by

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January 2008

20 ans AVEC VOUS POUR LA SANTÉ

Agence d'évaluation des technologies et des modes d'intervention en santé

Québec

The content of this monograph was written and produced by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) and is available in PDF format on the Agency's Web site.

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How to cite this document:
Thao Huynh and Stéphane Perron. Comparison of Efficacy, Effectiveness and Safety of Fibrinolysis and Primary Percutaneous Coronary Intervention (PPCI) for ST-segment Elevation Myocardial Infarction (STEMI), monograph. (AETMIS 08-02a). Montréal: AETMIS, 2008. xiii-164 p.

Legal deposit
Bibliothèque et Archives nationales du Québec, 2008
Library and Archives Canada, 2008
ISBN 978-2-550-50898-4 (PDF)
ISBN 978978-2-550-50897-7 (Print)

ACKNOWLEDGEMENTS

This monograph was prepared at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) by **Thao Huynh**, MD (cardiology specialist), MSc (epidemiology), and **Stephane Perron**, MD (public health specialist), MSc (public health).

AETMIS also appreciated the following external reviewers and the comittee of results' interpretation for their invaluable comments that greatly contributed to the quality of this monograph.

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Jean Lambert, Professor of biostatistics, Faculty of medicine, Université de Montréal, Consultant Biostatistician, Institut de cardiologie de Montréal.

Dr. Peter Bogaty (specialist in cardiology) also provided inputs into this monograph.

DISCLOSURE OF CONFLICTS OF INTERESTS

Dr. Thao Huynh was the principal investigator of the AMI-QUEBEC study. This study was supported by Hoffmann LaRoche Pharma Canada. Dr. Huynh never received personal honoraria from this company, nor has any financial interest in Hoffmann LaRoche Pharma Canada.

SUMMARY

INTRODUCTION

The *Direction Générale des services de la santé et de la médecine universitaire* (DGSSMU) is currently developing guiding principles for the management of patients with acute ST-segment elevation myocardial infarction (STEMI) in Quebec. To aid its task, the DGSSMU issued a request to AETMIS for an assessment of the safety, efficacy and effectiveness of reperfusion strategies in STEMI. The present report is a systematic review and meta-analysis evaluating published systematic reviews, randomized controlled trials (RCT) and observational studies.

OBJECTIVES AND METHODS

This report compares the safety, efficacy and effectiveness of in-hospital fibrinolysis (FL) and primary percutaneous coronary intervention (PPCI) for the treatment of STEMI. For efficacy and effectiveness, the primary endpoint was all-cause mortality and the secondary endpoint was reinfarction. Safety was assessed by comparing percentages of strokes and major bleeding events between the PPCI and FL.

For all reviewed trials, quality was evaluated by examining internal validity (potential biases and biases adjustment) and external validity. Meta-analyses of all endpoints were performed with a Bayesian random-effects models (WinBugs). Meta-regressions were completed with a linear mixed-effects model using a restricted maximum likelihood method (SAS version 8.2). Risk differences and numbers needed to treat were estimated by using the cumulative incidences of the FL group in the AMI-QUEBEC and ASSENT-2 studies.

SCIENTIFIC LITERATURE REVIEW: RANDOMIZED CONTROLLED TRIALS

The present literature review examined 25 RCTs enrolling 8,080 patients. Most RCTs were small, with only six studies enrolling more than 200 patients in each treatment arm. Thus they were all underpowered to detect a mortality difference between PPCI and FL. Although the risk estimates of most RCTs were in favour of a lower rate of death with PPCI, only four studies reported it as being statistically significant.

There was marked heterogeneity in the method of reperfusion, type of FL agents, use of stents, adjuvant medical care, and criteria for endpoints ascertainment of the reviewed RCTs. Since providers of care were not blinded, every study was subject to performance bias (ie. systematic difference in the type of care apart from the interventions being evaluated[1]). There were also noteworthy imbalances in patient characteristics in 18 RCTs.

The external validities of these RCTs were limited by their relatively long door-to-needle times, short door-to-balloon times and criteria for enrolment of patients. To replicate the effects of PPCI as reported in these RCTs, PPCI should be performed in an expedient manner as in these trials. The magnitude of the superiority of PPCI relative to FL may also have been over-estimated in these RCTs, due to their sub-optimal door-to-needle times and relatively short door-to-balloon times.

1 As defined by the Cochrane Collaboration.

REVIEW OF PUBLISHED META-ANALYSES

Most published sytematic reviews showed lower short-term mortality, reinfarction and stroke rates with PPCI with or without inter-hospital transfer compared to FL. One meta-analysis showed lower long-term mortality and reinfarction rates with PPCI. One meta-analysis showed an excess of 20 major bleeds per 1,000 treated patients with PPCI.

EFFECTIVENESS AND SAFETY OF REPERFUSION THERAPIES AMONG UNSELECTED PATIENTS

There were 31 observational studies reporting short or long-term mortality rates for both PPCI and FL (enrolling more than 132,000 patients). Only three studies reported short-term survival benefits adjusted for patients and STEMI characteristics. These three studies showed adjusted short-term survival benefits with PPCI.

Results of observational studies should be interpreted with caution since they were potentially subject to selection, confounding, performance, detection and attrition biases. Performance and confounding biases were especially frequent in these studies. On the one hand, patients who underwent PPCI were more likely to have higher-risk STEMI. On the other hand, PPCI patients were more likely to receive optimal medical therapy and more complete coronary revascularization than FL patients.

Overall, unselected patients in these studies had clinical characteristics and concomitant medical therapies similar to patients in the AMI-QUEBEC study. However, in contrast to the AMI-QUEBEC patients, the majority of patients enrolled in the European studies underwent PPCI within appropriate timelines. Therefore, in order to apply the results of these studies to Quebec STEMI patients, reperfusion procedures would have to be administered as expediently as possible.

META-ANALYSES AND META-REGRESSIONS PERFORMED FOR THIS REPORT

Rationale

Previously published meta-analyses have been restricted to RCTs and the majority did not have 6-month data and did not identify possible biases nor consider the impacts of these biases. Previous meta-analyses also did not consider important differences in study methodology and patient-related characteristics that may have modified the treatment effect. All except one meta-analysis used either fixed or random-effects non-Bayesian analyses that may not take into account inter- and intra-study variations. Finally, none of previously published meta-analyses considered results from observational studies. Results from observational studies are relevant despite their potential biases since they may provide some insights into the effectiveness and safety of reperfusion therapy in the « real-world » context. In view of the above deficiencies, a new meta-analysis appeared justified.

Results

In agreement with previously published meta-analyses, the present meta-analyses showed lower short-term mortality, reinfarction and strokes rates with PPCI compared to FL. Long-term reinfarction (≥1-year) was also less frequent with PPCI. Although meta-analysis of RCTs was

suggestive of long-term mortality difference, there was no conclusive long-term mortality difference between the two reperfusion strategies in the meta-analysis of observational studies.

STRENGTHS OF THE SYSTEMATIC REVIEW

This review was particularly comprehensive with the inclusion of thirty-one observational studies that had never been systematically evaluated. We extended the search strategy to include non-English language publications, international websites of STEMI registries and health technology assessments. We contacted several individual authors to obtain un-published data. Data extraction and critical analyses were completed by two independent observers for all randomized controlled trials and most observational studies. The Bayesian approach in AETMIS's meta-analyses integrated both inter-and intra-study variations and allowed for uncertainty of all parameters in the model. Each study borrowed strength from the other studies by the overall estimate. This aspect was not considered in previous meta-analyses.

LIMITATIONS OF THE SYSTEMATIC REVIEW

Despite the extensive literature review, it is still possible that pertinent studies may have been missed. Studies that failed to show differences between PPCI and FL may not have been published (publication bias). The lack of significant asymmetry of the funnel plots suggested absence of important publication bias. Despite our intention to review studies published in all languages, it was still conceivable that some studies published in languages other than French or English were not identified.

The lack of individual patient data prevented us from pertinent meta-analyses of subgroups of patients such as the elderly, high-risk STEMI cases, and reperfusion therapy administered within appropriate timelines. The calculation of the absolute risk reductions and numbers needed to treat were based on the cumulative incidences of AMI-QUEBEC and ASSENT-2. The validity of these results was based on the assumption that these incidences were representative of contemporary patients receiving FL in Quebec. Therefore, we may have over-estimated or under-estimated the absolute treatment differences if this assumption was not entirely accurate.

CONCLUSIONS

In summary, when compared to FL, PPCI is associated with short-term reductions of mortality, re-infarction and stroke. PPCI is also associated with a reduction in long-term reinfarction. There is no conclusive long-term mortality difference between the two treatments, particularly for low-risk patients. PPCI is superior to FL for high-risk patients when performed in a timely manner. There is inconclusive data concerning efficacy and effectiveness of PPCI with pre-hospital FL; however the latter strategy has been shown to be superior to in-hospital FL. The efficacy of PPCI compared to pre-hospital FL may be determined by future studies.

The overall evidence suggests that PPCI is superior to in-hospital FL when performed in a timely manner. For patients in cardiogenic shock, high-risk patients and those with contraindications for FL, PPCI would be the preferred treatment. For lower-risk patients, the evidence is inconclusive for a long-term mortality difference between the two treatments. PPCI-related delay should be carefully considered in the choice of reperfusion therapy for every patient

ABBREVIATIONS

ACC: American College of Cardiology

AHA: American Heart Association

AMI: Acute myocardial infarction

BEPC: Blinded endpoint committee

CABG: Coronary artery bypass graft

CI : Confidence interval

CrI : Credible interval

DGSSMU : *Direction générale des services de santé et de la médecine universitaire*

ECG: Electrocardiogram

HR: Hazard ratio

GP: Glycoprotein

MI: Myocardial infarction

NCSS: Number Cruncher Statistical System

NNT: Number needed to treat

NS: Non significant

OR: Odds ratio

PCI: Percutaneous coronary intervention

PPCI: Primary percutaneous coronary intervention

PPCI-related delay: difference between “door-to-balloon time” and “door-to-needle time” within a predefined cohort of patients

RCT: Randomized controlled trial

RD: Risk difference

RR: Risk ratio

SK: Streptokinase

STEMI: ST segment elevation myocardial infarction

TIMI: Thrombolysis in Myocardial Infarction

TNK: Tenecteplase

tPA: Tissue plasminogen activator

ACRONYMS OF RANDOMIZED CONTROLLED CLINICAL (RCTS)

AIR-PAMI: Grines *et al.* (2002)

CAPTIM: Bonnefoy *et al.* (2002)

C-PORT: Aversano *et al.* (2002)

DANAMI-2: Andersen *et al.* (2003)

HIS: Dieker *et al.* (2006)

MAASTRICHT: Vermeer *et al.* (1999)

PAMI-1: Grines *et al.* (1993)

PRAGUE-1: Widimsky *et al.* (2000)

PRAGUE-2: Widimsky *et al.* (2003)

SENIOR-PAMI: Grines (2005)

SHOCK: Hochman *et al.* (1999)

STAT: Le May *et al.* (2001)

STOPAMI-1: Schomig *et al.* (2000)

STOPAMI-2: Kastrati *et al.* (2002)

WEST: Armstrong *et al.* (2006)

Zwolle: de Boer *et al.* (1994) et Zijlstra *et al.* (1997)

ACRONYMS OF OBSERVATIONAL STUDIES

ACOS: Zeymer *et al.* (2006)

ALABAMA Registry of Myocardial infarction: Rogers *et al.* (1994)

AMI-FLORENCE : Buiatti *et al.* (2003)

AMI-QUEBEC : Huynh *et al.* (2006)

CCP : Berger *et al.* (2000)

GRACE : Mehta *et al.* (2004)

MITI: Every *et al.* (1996)

MISTRAL: Myocardial Infarction with Severe prognosis: observation of Treatment with Angiopasty or Lysis): Steffenino *et al.* (2004)

MsAMI: MIYAGI Study group for AMI: Sakurai *et al.* (2003)

MITRA and MIR: Zahn *et al.* (2000)

NRMI-2: Tiefenbrunn *et al.* (1998)

RIKS-HIA: Stenestrand *et al.* (2006)

TRIANA : Bardaji *et al.* (2005)

USIC-1995: Danchin *et al.* (1999)

USIC 2000: Danchin *et al.* (2004)

Vienna STEMI Registry: Kalla *et al.* (2006)

GLOSSARY

Attrition bias: Systematic differences in dropouts (or losses to follow-up) between the two comparison groups

Classification bias: Systematic differences of outcomes assessment between the two comparison groups (e.g. whether blinded or not)

Confounding bias: Distortion of the treatment effect by an extraneous factor associated with both the exposure (the treatment) and the outcome

Confounding by indication*:* Distortion of the effect caused by the presence of an indication or contraindication for the treatment that is also associated with the outcome

Detection bias (Also known as information bias or workup bias): Systematic differences in methods of ascertainment, diagnosis or verification of outcomes between the two comparison groups

Ecological fallacy: Bias that occurs because an association observed between variables on an aggregate level does not necessarily represent the association that exists on an individual level.

Performance bias: Systematic differences in the care provided in the two comparison groups, apart from the intervention being evaluated

Publication bias: Tendency of editors and authors to publish articles containing positive findings in contrast to reports that do not yield significant results. Publication bias can distort the general belief about efficacy of regimens

Selection bias: Systematic differences in the characteristics of the two comparison groups between those who were enrolled and those who were not enrolled into the study

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1 INTRODUCTION

1.1 CONTEXT OF THIS REPORT

Prompted by a recent report by an expert committee from the *Réseau québécois de cardiologie tertiaire* [1], the *Direction Générale des services de la santé et de la médecine universitaire* (DGSSMU) is currently elaborating guiding principles for the management of patients with acute ST-segment elevation myocardial infarction (STEMI) in Québec. To aid its task, the DGSSMU issued a request to AETMIS for an assessment of the safety, efficacy and effectiveness, of reperfusion strategies in STEMI (fibrinolysis [FL] and primary percutaneous coronary intervention [PPCI]). This report was a systematic literature review comparing PPCI with FL. This literature review included previous systematic reviews, randomized controlled trials (RCT), and observational studies.

A follow-up report will focus on the organization of care, applicability of current international and national STEMI guidelines in the Québec context, role of pre-hospital electrocardiograms (ECGs), and quality indicators of STEMI's care. The recommendations for the optimal reperfusion therapy, within Québec's specific medical and socio-demographic context, will be provided at the end of the follow-up report.

1.2 CONTENT OF THIS REPORT

This report is divided into ten sections.

1. Introduction: pathophysiological basis for concepts in STEMI and reperfusion therapy and the Québec's perspectives
2. Methodology
3. Rescue Interventions: safety and efficacy of rescue interventions following PPCI and FL
4. Efficacy and safety of PPCI and FL: in-depth analysis of RCTs
5. Systematic review of previous meta-analyses of RCTs
6. Effectiveness and safety of PPCI and FL: in-depth analysis of observational trials
7. The impact of presentation delays and PPCI-related delays on the relative efficacy of reperfusion therapy
8. Meta-analyses and meta-regressions performed by the report's authors
9. Strengths and limitations of this report
10. Conclusions.

1.3 DEFINITIONS AND CONCEPTS

This section summarize the pathophysiology of STEMI, and the current assessment methods of safety and efficacy of reperfusion therapies.

1.3.1 Acute coronary syndromes

Acute coronary syndromes represent a spectrum of clinical presentation of myocardial ischemia that includes unstable angina and acute myocardial infarction (AMI) (Table 1). According to

statistics from the United States, approximately 30% of all patients with AMI have STEMI [2]. STEMI is one of the three types of acute coronary syndromes [2].

Table 1. Characteristics of the different forms of acute coronary syndrome (ACS)

Form of ACS	Electrocardiographic signs		Cardiac enzymes §	Presence of complete coronary artery occlusion (%) ¶
	Persistent ST-segment elevation	Shift towards a Q-wave AMI		
Unstable angina	None	Rare	None	35–75%
AMI without ST-segment elevation	None	Rare	Yes	35–75%
AMI with ST-segment elevation (STEMI)	Yes	Yes, if no reperfusion therapy is provided	Yes	> 90%

§ Cardiac enzymes (CK, CK-MB) and troponin are markers of myocardial damage measured in the blood.
¶ This probability has been estimated from angiography studies.
Source: Adapted from Antman *et al*., 2004 [2].

1.3.2 Selected concepts of STEMI physiopathology and reperfusion therapy

STEMI is characterized by an elevation of the ST-segment of the electrocardiogram. STEMI results from the rupture or erosion of an atherosclerotic plaque leading to thrombosis and complete occlusion of a coronary artery [3]. This leads to myocardial ischemia, or lack of oxygen in the cardiac muscle perfused by this artery. This ischemia culminates in irreversible necrosis (death) of the myocardial cells if the ischemic time exceeds 15 to 20 minutes [4]. The myocardial necrosis tends to spread rapidly so that after 5 or 6 hours of ischemia, the entire area of the myocardium previously perfused by the occluded artery will be irreversibly necrosed [5].

Reperfusion therapy is defined as an intervention to restore the flow in the occluded artery. The ultimate aim of reperfusion therapy is to minimize the time of coronary artery's occlusion and to limit the extent of irreversibly damaged myocardium [6]. Thus the quality of a reperfusion strategy should be evaluated by its rapidity and its success in re-establishing coronary perfusion. Reperfusion can be accomplished pharmacologically by fibrinolytic therapy or mechanically with PCI.

1.3.3 Fibrinolytic therapy

Fibrinolytic therapy (FL) is the administration of special intravenous medications that dissolve the blood clot occluding a coronary artery. Mortality reduction with FL is well established in STEMI [7]. Several fibrinolytic agents are currently available: (i) non-fibrin specific agents such as streptokinase (SK) and urokinase, (ii) fibrin-specific agents such as tissue plasminogen activator (tPA), reteplase and tenecteplase (TNK) [8].

Of the fibrin-specific agents, tPA is the agent most commonly used in RCTs and observational studies. TPA is generally given in an 'accelerated' mode: a bolus followed by a 90-minute infusion. No mortality difference had been shown between non-accelerated tPA and streptokinase for STEMI patients [9-11]. One large clinical RCT (GUSTO-1) showed a one percent absolute mortality reduction with accelerated tPA compared to SK [12]. The superiority of accelerated tPA over SK remains uncertain and debated in the scientific community and SK is still widely used

outside North America [9, 11, 13]. The efficacy and safety of the three fibrin-specific agents (tPA, Tenecteplase, Retavase) are generally considered equivalent [11].

Patients who receive FL should be anticoagulated and take aspirin indefinitely. Until recently, there was no evidence supporting the routine use of thienopyridines (Ticlopidine and clopidogrel) following FL, except for patients with allergy or intolerance to aspirin. However, recent studies showed that the addition of clopidogrel to aspirin reduced mortality in the COMMIT-2 trial [14] and the ACOS observational study [15]. Clopidogrel was also associated with improved TIMI[2] coronary flow following FL [16].

1.3.4 Primary percutaneous coronary intervention

Percutaneous coronary intervention (PCI) refers to all forms of coronary interventions, with or without insertion of stents (bare metal or drug-eluting). When PCI is performed as the initial treatment of STEMI, it is called *primary PCI* (PPCI). PPCI can only be performed in a specialized catheterization laboratory. PPCI involves gaining arterial access under local anesthesia, guiding a catheter to the site of the occluded artery and then inflating a balloon for restoration of intracoronary flow. There is frequent concomitant intravenous administration of special anti-platelet medication (glycoprotein (GP) IIb/IIIa inhibitor). Although PPCI is technically similar to *elective* PCI, it is generally performed in a more difficult context, with symptomatic patients who may be hemodynamically unstable. Patients who have undergone PCI should receive aspirin indefinitely and clopidogrel for at least one month after implantation of a bare metal stent [2], and at least 12 months after implantation of a drug-eluting stent [17].

1.3.5 Definitions of time intervals

Figure 1. Definitions of time intervals

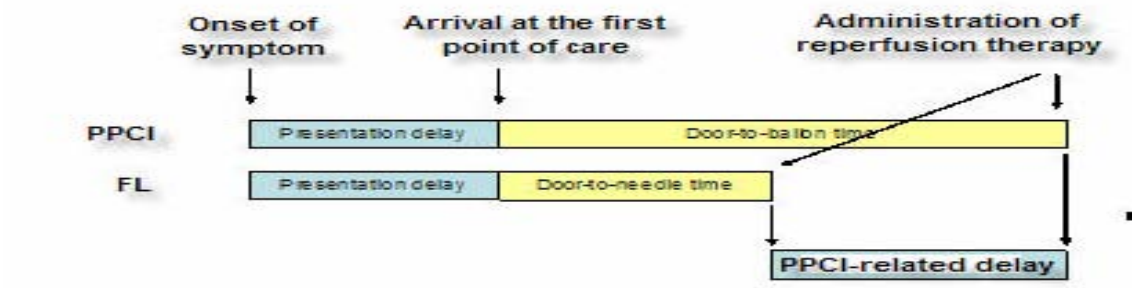


Figure 1 illustrates the different time intervals in the diagnosis of STEMI and the in-hospital initiation of reperfusion therapy.

- Presentation delay has also been called “symptom onset”, “duration of symptoms”, “time from symptom onset”, “time to presentation”, “onset-presentation”, “time from pain to admission”, “prehospital delay” and “time from symptom onset to arrival”. To be consistent, we used the term “presentation delay” to identify this time interval in this report.
- Door-to-needle: time from arrival at the first point of care (hospital for in-hospital FL) to the first injection of FL

2 TIMI coronary flow: method of scoring the flow in the culprit artery responsible at the coronary angiogram. The score is 0 for totally occluded coronary artery, 1 for presence of only a few drops of contrast seen, 2 for slow coronary flow and 3 for normal coroonary flow.

- Door-to-balloon: time from arrival at the first hospital to the first intracoronary balloon inflation.
- PPCI-related delay: the difference between the median door-to-balloon time and the median door-to-needle time within a defined patient cohort.

Appendix A illustrates the different definitions of time delays in the reviewed RCTs.

1.3.6 Measures of reperfusion therapy's success

Successful myocardial reperfusion[3] is manifest clinically, by the relief of ischemic symptoms;electrocardiographically, by at least 50-70% resolution of ST-segment elevation [18, 19]; angiographically, by the re-establishment of normal coronary artery flow (TIMI-3) or by normal myocardial blush [20]. Myocardial reperfusion can also be evaluated by the evaluation of cardiac contractility with echocardiography [21], nuclear medicine (scintigraphic imaging) [22] or nuclear magnetic resonance [23].

The most readily available and non-invasive means to evaluate myocardial perfusion (as opposed to only coronary patency) is the extent of ST-segment resolution following reperfusion therapy. ST-segment resolution has been shown to have strong correlation with short and long-term mortality [19, 24-32]. ST-segment resolution may be a better marker for myocardial perfusion since it is more predictive of mortality than TIMI coronary flow [25]. Partial or complete resolution of ST-segment elevation is associated with better survival with FL [28-31] as well as PPCI [19].

Clinical efficacy measures of reperfusion therapy assessed in previous studies were all-cause mortality, reinfarction, recurrent ischemia, reintervention, and heart failure. Heterogeneous definitions, inconsistent reporting and biases (as detailed further in the section 'quality of RCTs') limited the validity of these endpoints. The most valid and clinically relevant efficacy endpoints in reperfusion therapy are short and long-term all-cause mortality.

1.3.7 Measures of safety of reperfusion therapy

Stroke is a well-recognized complication of both FL and PPCI. Risk of stroke increases with ischemia duration and decreases with prompt administration of reperfusion therapy [33]. Major bleeding may occur following both PPCI and FL [34]. It can be secondary to the direct action of FL or secondary to the adjuvant anticoagulants and antiplatelets [35].

1.4 QUÉBEC'S PERSPECTIVE

1.4.1 Burden of the disease

There are 15,000 annual AMI hospitalizations in Québec (MED-ECHO: dataset of all Québec hospitalizations). The current hospital discharge codifications do not differentiate between STEMI and non-STEMI. Therefore, an accurate number of annual STEMI for Québec or other provinces/countries cannot be obtained. A previous observational study estimated that STEMI constituted up to 30% of all AMI [2]. On this basis, the annual number of STEMI hospitalized in Québec approximates 5,000 cases (incidence of 60-70/100,000).

3 Coronary patency is different from myocardial reperfusion. Indeed, the opening of the artery, whether by FL or by PPCI, does not necessarily lead to successful reperfusion of the myocardium. The determinants of failed myocardial reperfusion despite restoration of coronary patency are not yet fully clarified.

1.4.2 Facilities and administration methods of reperfusion therapy in Québec

There are 123 registered Québec hospitals with at least one AMI hospitalized per year. Of the 104 hospitals that may provide AMI care, there are 15 hospitals (14%) with on-site PCI facilities (RQCT). There are two hospitals with PCI facility in Québec City, nine in Montréal/Laval and one in each of the following health regions: Estrie, Montérégie, Saguenay and Outaouais. Eleven of these hospitals also have on-site cardiac surgery backup. Of the remaining hospitals, 22 are located more than two hours from a PCI-center (www.msss.gouv.qc.ca).

There are a few medical clinics and CLSC in Québec that can provide FL. Contrary to Europe and a few other Canadian provinces (Alberta, Nova Scotia), FL cannot be administered in Québec's pre-hospital settings due to lack of qualified paramedics.

1.4.3 The AMI-QUEBEC Study

The AMI-QUEBEC study was a retrospective charts review of 1,622 patients admitted with a principal diagnosis of STEMI at 17 urban hospitals in 2003 (ten hospitals had on-site PCI facility) [35]. The primary objective of the study was to describe the methods and time delays of reperfusion therapy in Quebec.

Among the 1,189 patients with available door-to-reperfusion therapy times, 535 and 654 patients received FL and PPCI, respectively. Of the 654 patients who underwent PPCI, 199 patients required interhospital transfers. Median times for FL, door-to-PPCI on-site, door-to-PPCI with interhospital transfer were 32, 109 and 142 minutes, respectively. Reperfusion therapy was administered within recommended timelines as recommended by the AHA/ACC guidelines[4] for 49%, 36% and 8% of patients who received FL, on-site PPCI and PPCI with inter-hospital transfer, respectively.

Independent predictors of delayed reperfusion therapy were advanced age, presentation outside daytime working hours, PPCI after interhospital transfer. Patients who presented outside daytime working hours were 50% less likely to receive timely FL and PPCI. PPCI was associated with 40% odds of delayed administration of reperfusion therapy. Patients who required PPCI after interhospital transfer were 80% less likely to undergo PPCI within 90 minutes.

4 Door-to-needle time within 30 minutes and door-to-balloon within 90 minutes (add reference for AHA/ACC guidelines)

2 OBJECTIVES AND METHODS

Primary objective:

To compare the efficacy[5] (using meta-analyses of RCTs) and effectiveness[6] (using meta-analysis of observational studies) of PPCI and FL, in terms of mortality reduction

Secondary objectives:

Efficacy:

- To compare the incidences of reinfarction associated with PPCI and FL

Safety[7]:

- To compare the incidences of strokes associated with PPCI and FL
- To compare the incidences of major bleeds associated with PPCI and FL

2.1 AREAS OF FOCUS IN THIS ASSESSMENT

This report compares the safety, efficacy and effectiveness of in-hospital FL with PPCI with and without inter-hospital transfer. We also reviewed the results of pre-hospital FL because of its potential superiority over in-hospital FL [36].

Facilitated PPCI is not discussed. Facilitated PCI is the administration of a medication or a combination of medications to improve the coronary patency before PPCI [2]. Keeley *et al*. (2006), showed increases in mortality, reinfarction, stroke and major bleeds with facilitated-PCI by glycoprotein IIb/IIIa inhibitors, FL or a combination of these medications [37].

We did not examine the efficacy, effectiveness and safety of PPCI and FL in patients with contra-indications to FL and those with cardiogenic shock. For these patients, urgent coronary intervention has been shown to be beneficial and is recommended by the current STEMI guidelines [2, 38]. Data from the National Registry of Myocardial Infarction (NMRI) 1, 2 and 3 showed that the incidence of STEMI patients eligible for reperfusion therapy with contra-indications to FL was 5.2% [39].

2.2 LITERATURE SEARCH STRATEGY AND STUDY SELECTION

The literature search strategies (i.e., key words) are presented in appendix B.

2.2.1 Randomized RCTs and meta-analysies of randomized RCTs

We searched for all RCTs and meta-analyses of RCTs that compared PPCI and FL for STEMI patients in the following databases: BIOSIS, Cinahl, and Current Contents (1990 to 2006); Embase (January 2003 to October 2006), Pubmed (January 2000 to October 2006), Web of Science (January 1990 to October 2006) and Cochrane Library 2006, issue 4 (no date restrictions;

5 Efficacy is the extent to which a specific intervention produces results under ideal conditions. Ideally, the determination of efficacy is based on the results of randomized controlled trials (Last's Dictionary of Epidemiology, 4rd Edition).
6 Effectiveness is a measure of the extent to which a specific intervention, when deployed in the field in routine circumstances, does what it is intended to do for a specific population (Last's Dictionary of Epidemiology, 4rd Edition).
7 Here the term 'safety' is used in the context of minimizing the risk of adverse events related to the use of a technology.

most recent update October 2006). Instead of performing an exhaustive literature search for all RCTs published between 1990-2006, we compiled all RCTs identified by previous systematic reviews.

Other search strategies included Internet search, review of reference lists of published articles and expert knowledge of recent RCTs. Review was restricted to publications with full details on the research methodology, rather than abstracts, to ensure adequate study quality's evaluation. Only studies with one of the following commercially-approved fibrinolytic agents were reviewed: SK, tissue plasminogen activators, tenecteplase, urokinase, and reteplase. Two independent observers performed the final study selection, and any disagreement was resolved by consensus.

2.2.2 Observational studies

Observational studies were searched in the same manner as above (section 2.2.1.1), except that the start date for the PubMed search was earlier (January 1990). Web sites for registries of STEMI and acute coronary syndromes (see appendix B), health care technology assessment web sites; Cochrane library and reference lists of published studies were also searched. Two independent observers performed the final study selection, and any disagreement was resolved by consensus.

2.3 DEFINITION AND IDENTIFICATION OF BIASES

Bias is a deviation of results or inferences from the truth, or any process leading to such deviation [40]. RCTs and studies with design flaws possibly leading to bias should be compared with those without such flaws to evaluate the potential impacts of these biases on the results. The definitions of the different biases were provided in the glossary.

2.4 DATA ABSTRACTION

Two independent observers (SP and TH) completed the data abstraction: individual RCTs and the meta-analyses of RCTs (SP), observational studies (TH). RCTs' quality was assessed by a component approach (per item) [41], since this method was shown to be more reliable and valid than the scale approach [42]. There is no standardized quality evaluation method validated for observational studies of reperfusion therapy. The STROBE (Standards for the Reporting of Observational Studies in Epidemiology)'s statement focused mainly on the reporting of observational studies rather than their quality assessment[8]. AETMIS's quality evaluation of observational studies was based on the examination of internal validity (potential biases and methods used to adjust for these biases) and external validity of these studies, rather than using a specific score system since these scoring systems had not been validated for observational studies of reperfusion therapy [42].

2.5 CONTACT WITH PRINCIPAL INVESTIGATORS

For all studies, missing information judged pertinent for the integrity of this report (such as study design, conflicting information and missing pertinent outcomes) were obtained by personal communication with the principal investigators (appendix C).

8 Reference: http://www.strobe-statement.org/PDF/STROBE-Checklist-Version3.pdf, accessed 23 January 2007.

2.6 STATISTICAL METHODS

2.6.1 Meta-analyses performed at AETMIS

Short and long-term[9] mortality and re-infarction rates in the RCTs were analysed by Bayesian random-effect meta-analyses. We used the log relative risk scale model as proposed by Warn *et al*. (2002) for the RCTs; log odds ratio scale model was used for observational studies (since we included three case-control studies) [43]. For the inference of each estimate, three Markov Monte-Carlo chains were run and the final summary statistics were obtained after ensuring adequate convergence of the Monte Carlo chains (generally 50,000 iterations for each chain). Meta-analyses were performed with a full Bayesian method (WinBugs). A non-informative prior was used so that the results reflected primarily the results of previous RCTs. The forest plots were completed with R software (version 2.4.1).

Meta-regressions were performed with a linear mixed-effects model using a restricted maximum likelihood method (a random-effects model). We used a SAS version 8.2 (SAS Institute Inc.) Proc MIXED model incorporating random effects using codes proposed by two groups [44, 45].

2.6.2 Other statistical estimates and tests

Risk differences and numbers needed to treat (NNT) were computed by the following formulas:

1) Risk difference = (baseline risk) * (1 – RR) [46]

2) NNT = 1 / (risk differences) [47]

The outcomes of the patients who received FL were highly variable between studies. Thus, the results of meta-analyses of risk differences would be inconsistent and difficult to interpret [46, 48]. On this basis, we opted to derive the risk differences and number needed to treat (NNT) and number needed to harm by using the outcomes of the population of interest as the baseline risks. The baseline risks should be representative of the population of interest [47, 49, 50]. The closest approximation to baseline risks of STEMI patients who received FL in Québec was that of patients who received FL in the AMI-QUEBEC study [35].

Long-term mortality of patients who received FL in the ASSENT-2 trial was used as baseline STEMI risk to estimate the absolute risk difference and NNT (since long-term mortality was not available in the AMI-QUEBEC Study).We chose ASSENT-2 because it was a fairly recent study with a large sample size of patients who received a third-generation fibrin-specific FL (RCT that compared accelerated t-PA and tenecteplase in 16,949 patients [51, 52]).

9 Short term ≤42-day ; Long-term mortality ≥12-month

3 RESCUE PERCUTANEOUS CORONARY INTERVENTIONS

There are inconsistencies between the current definitions of rescue PCI. It is defined as "*PCI for patients who do not achieve reperfusion after FL*" in Braunwald's textbook of heart diseases [53]. ACC/AHA defined rescue PCI as "*PCI performed within 12 hours after failed fibrionolysis for patients with continuing or recurrent myocardial ischemia*" [2]. The clinical diagnosis of "myocardial ischemia" following FL is generally determined by persistence of ischemic symptom or lack of complete ST segment elevation resolution. The European Society of Cardiology (ESC) defined rescue PCI as "*PCI performed on a coronary artery which remains occluded despite FL*" [54]. Thus evidence of persistent myocardial ischemia has to be present for the PCI following FL to be qualified as rescue PCI according to ACC/AHA. Conversely, only the presence of an occluded artery following FL at coronary angiography is required for the PCI to be qualified as rescue PCI by the ESC.

Rescue interventions are integral parts of the initial STEMI management for both FL and PPCI. There are four treatment options for patients who do not have successful response to FL: repeat FL, conservative therapy,[10] rescue PCI or coronary artery bypass surgery (CABG). The uses of these interventions may confound the treatment effect and should be adjusted for in the efficacy comparison between PPCI and FL.

Only two RCTs studied rescue PCI in patients with myocardial ischemia following FL [55, 56]. The five other RCTs enrolled patients with persistently occluded coronary artery without requiring presence of myocardial ischemia [57-61]. In the MERLIN RCT, there was no mortality or reinfarction difference between rescue PCI and conservative therapy with more strokes in patients who underwent rescue PCI [56]. In the REACT study, rescue PCI was compared to either a conservative treatment strategy or with repeat FL [55]. In this trial, there was a trend towards reduced mortality and reinfarction in the rescue PCI group compared to patients in the repeat thrombolysis or conservative therapy groups. Differences in study design and patients characteristics may explain the contradictory results of these two RCTs. Failed FL was determined by less than 50% ST-segment elevation resolution at 60-min (MERLIN) and 90-min (REACT). There were higher percentages of females, anterior STEMI and streptokinase use in the MERLIN study than in the REACT study.

Two meta-analyses reported mortality reduction with rescue PCI compared to conservative therapy [62, 63]. In a third meta-analysis, rescue PCI was associated with reductions in heart failure and reinfarction compared to conservative therapy [64]. A meta-analysis of three RCTs [55, 65, 66] showed no mortality difference between repeat FL and conservative therapy [64]. Therefore based on the available evidence, rescue PCI should be considered as at least equivalent or potentially superior to conservative therapy and repeat FL for patients with unsuccessful FL therapy .

For unsuccessful PPCI, there are two treatment options: CABG and conservative therapy [2]. There are no RCT that compared these two strategies.

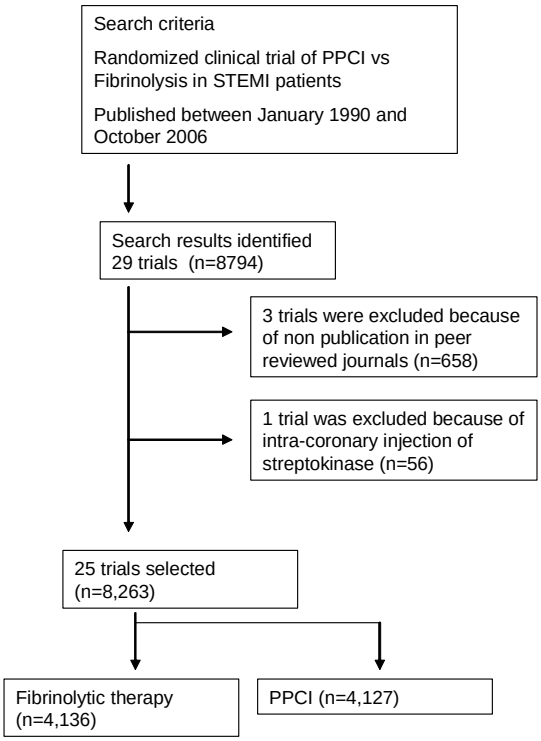
10 Medical treatment with or without intra-aortic balloon counter-pulsation

4 REVIEW OF RANDOMIZED CONTROLLED TRIALS

We identified 29[11] RCTs that compared the efficacy of PPCI and FL [61, 67-92]. The method of study selection is shown in Figure 2. Two small RCTs published only as abstracts were not evaluated [69, 70]. The recently completed SENIOR PAMI trial enrolling 500 patients ≥70 years, was only presented at a conference at the time of writing this report. Hence, this study's quality could not be assessed adequately, and it will be only briefly discussed [68]. One RCT was excluded due to intracoronary SK injection (outdated practice) [67]. This literature review was based on 25 RCTs [61, 71-93].

The majority of these RCTs were are small, with only six[12] that included more than 200 patients in each treatment arm [71, 73, 74, 81, 87]. The results of these RCTs were summarized in appendix D. The inclusion and exclusion criteria for the RCTs were described in appendix E.

Figure 2. Study selection of RCTs



4.1 TYPES OF INTERVENTIONS PROVIDED

The types and methods of FL administration were heterogeneous. SK was used in eight RCTs, [75, 76, 84, 87-90, 93], t-PA in two [78, 79]; accelerated t-PA in 11 RCTs [61, 71, 73, 74, 77, 81-

11 Although 27 references are cited here, we considered the DANAMI-2 study to represent two trials (as noted in section 3.1.5).
12 Consistent with the previous footnote, we counted two trials each time we cite [70] in section 3.2.

83, 85, 86]; tenecteplase in WEST [72], reteplase in SWEDES [91] and both SK and t-PA were used in AIR-PAMI, [80] reteplase, tenecteplase and accelerated t-PA were administered in HIS [92]. Interventions in the PPCI arms were also heterogeneous. Stents were used rarely or not at all in the older RCTs [61, 75, 77-79, 81, 84, 89, 90]. Stents' use with adjuvant therapy such as GP IIb/IIIa inhibitors and thienopyridines were frequent in more recent RCTs [71-74, 76, 80, 82, 83, 85-88, 91-93].

There were also variations in the administration methods of reperfusion therapy in these studies. PPCI was performed with/without requiring inter-hospital transfers. In CAPTIM, FL was administered in the pre-hospital setting [74]. Randomization was completed in the hospital settings in most studies. For three RCTs, randomization was performed either partially [72, 91] or exclusively [74] in pre-hospital settings. More details related to intervention heterogeneity in the RCTs are provided in the appendix F.

IN BRIEF

- There were heterogeneities in the devices and medicationsco-administered with reperfusion therapy such as variable uses of stents, glycoprotein inhibitors in the reviewed studies.
- There were heterogeneities of the sites of initiation of reperfusion therapy (FL can be initiated at the hospital or in the pre-hospital setting and PPCI can be performed on-site or with inter-hospital transfer).

4.1.1 Heterogeneity in the definitions of endpoints

4.1.1.1 REINFARCTION

There was marked heterogeneity in the endpoint definitions among the RCTs. The endpoints included clinical entities with potentially different prognoses [94-98]. Within the first 18 hours of the index STEMI, reinfarction was diagnosed only with ST-elevation in ≥2 contiguous ECG leads lasting at least 30 minutes in C-PORT and WEST [72, 73]. Beyond 18 hours of the index STEMI, reinfarction was diagnosed by one of the following criteria: new Q waves, new left bundle branch block or re-elevation of biomarkers [72, 73]. In the STAT study, reinfarction was diagnosed with ST re-elevation of any duration, new left bundle branch block or re-elevation of cardiac biomarkers. However, within 18 hours of the index STEMI, re-elevation of cardiac biomarkers was not used as a criterion for reinfarction in the same study [83].

In the other RCTs, in addition to enzymatic criteria and typical chest pain, ECG changes other than ST-elevation were sufficient for a diagnosis of reinfarction [61, 75, 76, 82, 86, 87, 89]. For eight RCTs, ECG changes were not required for the diagnosis of reinfarction [71, 74, 80, 81, 88, 91, 92]. The reinfarction definitions were not provided in three studies [78, 84, 93]. Only DANAMI-2 and WEST defined and ascertained peri-procedural infarcts [72, 99].

4.1.1.2 STROKE

Stroke definitions were also inconsistent in the RCTs. Only DANAMI-2 reported specific diagnostic criteria of stroke [99]. Cerebral CT-Scan or magnetic resonance imaging was required to confirm stroke in several studies [61, 74, 81-83, 86, 89, 91]. Three studies only required clinical confirmation of stroke by a neurologist [61, 73, 89].

Some RCTs reported only disabling stroke [71, 72, 74, 80, 81]. Neurological deficits had to be permanent for C-PORT [73]. Finally, stroke definitions were not provided in eight trials [75-77, 79, 85, 90, 92, 93]. Strokes were not reported in two trials [78, 84].

4.1.1.3 BLEEDING EVENTS

There were also heterogeneities in the definition, documentation or reporting of bleeding events in the RCTs. Some trials included intracranial bleeding in the incidences of major bleedings [74, 75, 81, 82]. Other trials defined major bleeding as bleeding with hemodynamic compromise [72, 74, 81, 82, 86]. Some trials only reported blood transfusions [73, 77, 79, 85, 90, 93]. The need for transfusions were considered as a criterion of major bleedings in some studies [74, 86, 90] and of moderate or minor bleedings in others [72, 81, 82]. The STAT trial defined severe bleeding as a drop in hemoglobin concentration. The definitions of bleeding events were not provided in five studies [61, 76, 88, 91, 92]. Although the DANAMI investigators did define bleeding events, they did not report these outcomes [71, 99]. Finally, some trials did not ascertain bleeding events [78, 80, 87, 89].

The majority of the published RCTs reported a combined endpoint of mortality or non-fatal reinfarction or non-fatal stroke. These events were combined since most trials were underpowered to detect treatment differences. The rationale for combined endpoints was problematic since the combined endpoint may be driven by reinfarction which has a lesser implication than all-cause mortality. Short and long-term all-cause mortality are the most objective, reliable and valid endpoints and should be considered independently.

IN BRIEF

- There were heterogeneities in the definitions and classifications of re-infarctions, strokes and bleeding in the RCTs.
- Short and long-term all-cause mortalities are the most objective, reliable and valid endpoints and should be considered independently.

4.2 PATIENT SUBGROUPS[13]

4.2.1 Elderly

The median patients' ages ranged from 57 to 68 years for all of the RCTs except for that of de Boer *et al.* (2002), in which the median age was 80 years [76]. In de Boer's RCT, patients had to be at least 76 years old to be eligible for enrolment. In this study, FL mortality was the highest of all the reviewed RCTs. PPCI was associated with 30-day mortality reduction [odds ratio (OR)=0.28, 95% confidence intervals (CI) (0.08–0.96)] [76]. In SENIOR-PAMI [68], that enrolled only patients ≥70 years, no mortality difference was seen between the two treatments. The risk estimates for patients of 70 to 80 years, OR=0.60; 95% CI (0.28–1.25), while for patients older than 81 years, OR=1.21; 95% CI (0.49–2.99). The results of the RCT by de Boer (2002) and

13 The odds ratios in this report represented the events reduction associated with PPCI compared to FL, i.e. an odds ratio of less than 1 was in favour of PPCI and an odds ratio of more than 1 was in favour of FL.

SENIOR PAMI were discordant. Hence, there remained uncertainty about the relative efficacy of PPCI and FL in the elderly.

4.2.2 High-risk patients

Two RCTs enrolled only high-risk patients [77, 80]. In the first trial, enrolling only patients with anterior STEMI, PPCI was associated with a reduced in-hospital mortality (OR: 0.23, 95% CI: 0.06-0.85) [77]. In AIR PAMI, patients were required to have at least one of the following inclusion criteria for enrolment: age more than 70 years, anterior STEMI or heart rate more than 100/minute [80]. There was no mortality difference between PPCI and FL in this RCT (OR=0.70; 95% CI:0.25–1.90); however this study was under-powered.].

Analyses of high-risk (and low risk or 'not high-risk') patients subsets were performed in three RCTs. These sub-group analyses were pre-specified in GUSTO IIb and *post hoc* in PAMI and DANAMI-2 [79, 81, 100].[14] Only the DANAMI-2 investigators performed interaction analyses (a method to confirm the association of the difference in treatment effect with the characteristics of the patients) [100].

PPCI was associated with reduced inhospital mortality for high-risk patients in PAMI [2.0% for PPCI and 10.4% for FL, OR=0.18; 95% CI (0.04–0.83)] [79]. There was no 30 day mortality difference between PPCI and FL, among the high-risk patients in the GUSTO-IIb [5.7% for PPCI and 7.0% for FL, OR=0.90; 95% CI (0.55–1.20)] [81].[15] Among the high-risk patients in DANAMI-2, (defined as a TIMI risk score ≥5), 3 year mortality was reduced with PPCI [25.3% with PPCI versus 36.2% for FL, HR=0.66; 95% CI (0.45–0.94)] [100].

The above studies suggested that PPCI was superior to FL for high or "not-low"-risk patients [79, 81, 100].

4.2.3 Low-risk patients

Two RCTs enrolled only lower–risk patients: patients with inferior infarcts [85], and patients with Killip class 1 and without anterior infarction [89]. In one study, PPCI was associated with mortaltity reduction [85], whereas the opposite was observed in the other study [89]. For 'low-risk patients' enrolled in the DANAMI study, there were no short and long-term mortality differences between PPCI and FL [100].

IN BRIEF

- For « not low-risk » or high-risk patients (anterior STEMI, age> 70 or heart rate >100/min or TIMI risk score >4), PPCI was associated with mortality reduction compared to FL. For low risk patients, there were no differences in short and long-term mortality between PPCI and FL.

4.3 QUALITY OF THE RCTS

Two previous meta-analyses evaluated RCTs according to quality components [101, 102]. However, these reviews did not attempt any sensitivity analysis or meta-regression to determine

14 For PAMI and GUSTO IIb, high-risk criteria were age ≥70 years, anterior infarction, and heart rate ≥100/minute. For DANAMI-2, TIMI risk score was used for stratification.
15 Results were extrapolated from a graph presented in the publication.

the impact of RCT's quality on the final results [101, 102]. In this section, we describe the potential biases that may result from suboptimal RCT's design. These consist of selection, performance, classification and attrition biases. A summary of the quality appraisal for each reviewed RCT is shown in appendix G. The definitions of the biases are provided in the glossary.

4.3.1 Selection bias

Selection bias may occur in RCTs with treatment allocation that is not entirely determined by chance. This bias may occur when study personnel can choose the treatment for each individual patient, thus influencing the distribution of patients in the treatment arms. This may occur when the study personnel has the possibility to manipulate the allocation sequence. There are several concealment methods of allocation sequences with some methods that may be more prone to manipulation. For example, an un-blinded allocation schedule is inappropriate since the study personnel may choose to randomize a patient to a particular treatment if they believe that this treatment is superior for that patient. Allocation with sealed envelope is suboptimal since it can also be subject to manipulation [103-105]. The optimal treatment allocation is determined centrally either by telephone or by Internet.

Although some RCTs did not report the concealment method of the randomization sequence, information about the randomization methods were obtained by personal communication with the principal investigators of these four RCTs [72, 77, 86, 92]. For eleven RCTs, randomization was achieved though a telephone service [61, 71, 73, 74, 76, 81, 87-89, 92]. In these RCTs, randomization sequences were sub-optimal with sealed envelopes [72, 75-77, 79, 80, 82-86, 90, 91] and non-central randomization [93]. For one RCT, the information on randomization concealment could not be obtained [78].

4.3.2 Performance bias

An effective method that may attenuate performance bias is to blind both patients and physicians to the treatment received. By the nature of reperfusion therapy, all the RCTs reviewed were un-blinded. The magnitude and direction of this bias is difficult to predict but may be partially adjusted if data on concomitant patient care is available. Optimal medical therapy for STEMI should include aspirin [106], beta-blockers [107], angiotensin-converting-enzyme inhibitors (ACE-inhibitors) [108, 109] or angiotensin receptor blockers for patients with left ventricular systolic dysfunction [110].

Information on adjuvant in-hospital medical therapy was not reported in eleven RCTs. Thus it was not possible to appreciate the potential performance biases in these RCTs [61, 73, 75, 76, 78, 79, 84, 87-90]. GUSTO-IIb was the only trial that reported no difference in adjuvant medical therapy between the two treatment groups [81]. Beta-blockers administration differed by more than 5% between the PPCI and FL groups in four studies [74, 77, 80, 93]; Beta-blockers were preferentially given to the FL group for three studies [74, 77, 80], whereas the patients who underwent PPCI received more beta-blockers than patients who received FL in one study [93]. The use of ACE-inhibitors differed by more than 5% in three RCTs, with higher use in patients in the FL arm in two studies [77, 85] and higher use in patients in the PPCI arm [93].

In more recent RCTs, stents were often used with PPCI, along with adjuvant therapy such as GP IIb/IIIa inhibitors and thienopyridines [71-74, 76, 80, 82, 83, 85-88, 91, 92]. In many trials, thienopyridines administration differed by more than 25% between the two treatment arms [71, 72, 74, 82, 83, 86]. In addition, recourse to rescue interventions differed among the reviewed RCTs. Rescue PCI was provided to only 1.9% of FL patients in DANAMI-2 [71], and to 26% of

FL patients in CAPTIM [74]. Repeat FL was used instead of rescue PCI in the FL arm of DANAMI-2 [71].

Studies with interhospital transfers may be flawed by performance bias because of variation in adjuvant care provided at hospitals with or without PCI facilities. In particular, patients who received on-site in-hospital FL may not have had equal access to tertiary cardiology care. Three European trials may have been more subject to this confounding bias since mortality rates in the FL arms were particularly high in these trials (14% for PRAGUE-1 [88], 10% for PRAGUE-2 [87]and 8.3% in Dobrzycki *et al*. (2006) [93]). The high mortality rate in the patients who received FL may have been due to sub-optimal adjuvant medical care at the primary care hospitals.

4.3.3 Attrition bias

In the reviewed RCTs, losses to follow-up were in general similar for the two treatment groups (appendix G). The incidences of withdrawals were very low and similar for both treatment groups. Therefore, short-term endpoints were unlikely to be affected by this bias in most RCTs. Three studies did not report losses to follow-up [78-80]. Eleven trials reported complete follow-up [61, 73, 76, 82, 83, 85, 86, 89, 90, 92, 111].

In PAMI-1 [80]**,** more "not low-risk" patients were lost to follow-up in the PPCI arm compared to the FL patients (58% versus 48%). Thus, there was a potential attrition bias in favour of PPCI, since there may have been more events in the PPCI arm that were not accounted for [112] .

4.3.4 Classification bias

Classification bias may be particularly important for certain endpoints such as reinfarction and stroke, since the interpretations of symptoms, ECG and the brain CT-scan tend to be subjective. Thus, classification of these events may be biased if the assessor was not blinded to the therapy that the patient received. Classification bias was noted in RCTs without a blinded endpoint committee (BEPC) to adjudicate the events [42].

A DANAMI-2 sub-analysis demonstrated the impact of a BEPC [113]: the sensitivity and specificity of reinfarction as diagnosed by unblinded clinicians were 57% and 95%, respectively compared to the BEPC's validation. Results were less biased with stroke (sensitivity and specificity were 94% and 99.6%, respectively) [113]. Other investigators also demonstrated the importance of a BEPC [114, 115]. In the PURSUIT trial, reinfarction was also underestimated by clinicians [114]. In the PARAGON trial, the clinician's diagnostic sensitivity of reinfarction was 44% compared to a BEPC [115].

Some RCTs did not report whether the outcome adjudication was blinded. Investigators of six RCTs were contacted for information [77, 82, 84-86, 93]. For one RCT, outcome assessment was blinded only for ECG and cardiac enzymes [116],[16] blinded only for ECG assessment in another RCT [90], blinded only for cumulative cardiac enzyme release [76]. Hence, the overall outcome assessment in these three RCTs could not be considered blinded. We could not obtain information for five RCTs, so we consider these RCTs to have unknown status of outcome adjudication [61, 79, 87-89]. Eleven RCTs used a BEPC [71-74, 77, 80-83, 86] and in one RCT the outcomes were adjudicated by a blinded research clinician [92].

16 This study sample is the same as De Boer *et al.*, (1994) [74].

4.3.5 Confounding bias

Confounding bias may occur when there was imbalance in patient's characteristics (covariate associated with both the treatment and outcome) between the two treatment groups [103, 117, 118]. Differences in patients' characteristics were inherent to any trial. Randomisation reduces these imbalances but may not entirely eliminate them. Small studies may have more imbalances in patient's characteristics since randomization may be less effective in distributing comparable patients in the different treatment arms. For example, in the HIS study, which had the smallest sample size, the mean age of FL patients was five years older than the PPCI patients.

Since there were no published recommendations of what constitute important differences in patient's characteristics, it was arbitrarily decided to use an age difference of more than two years as relevant since age correlated with mortality. A difference of cardiogenic shock at initial presentation of ≥ 2% was also used as a criterion for imbalanced patient characteristics since cardiogenic shock was highly correlated with short-term mortality [38]. A difference of ≥ 10% for any other patients' characteristic between the two treatment groups was deemed significant since there were generally less strong associations of these characteristics with mortality (i.e. gender). By using these criteria, six studies did not have any major baseline characteristics difference between the treatment groups.[61, 74, 79, 81, 87, 91], There were imbalances of patients'characteristics that may favour FL in five studies[71, 72, 76, 84, 85], in favour of PPCI in six RCTs PPCI [71, 75, 78, 83, 88, 93].

4.3.6 Survivor bias

This bias occurs when patients who died before the intervention of interest (PPCI or FL) were not accounted for. In all of the reviewed RCTs, patients were randomized at presentation (before PPCI or FL), and results were analysed by intention-to-treat. Since mortality was analyzed according to the assigned treatment, regardless of whether patients received the intervention or not, none of the RCT reviewed was affected by this bias.

IN BRIEF

The results of the RCTs were potentially subject to many biases:

- Selection: Only 12 RCTs reported optimal central randomization to decrease selection bias.
- Performance: Systematic administration of thienopyridines in patients who underwent implantation of intracoronary stents resulted in possible performance bias favoring PPCI in many RCTs.
- In interhospital transfer trials, performance bias may have occured because of differences in the quality of the adjuvant care, since patient in the FL arm were generally treated in community hospital and patients in the PPCI arm were generally treated in tertiary care hospitals.
- Classification bias may have occured in RCTs without blinded endpoint committee.
- There were imbalances in patients' characteristics between the two treatment arms in many RCTs. These imbalances may have biased the estimates of treatment effect.

4.4 EXTERNAL VALIDITY

External validity of RCTs can be defined as the extent to which RCT results can be generalized to other contexts, populations or health care systems. This evaluation of the RCTs' external validity covered three issues: interhospital transfer for PPCI, times to treatment, and uses of fibrin-specific FL. Detailed informations concerning external validity are provided in appendices 5 and 6. Since the external validity of these studies were pertinent to the Québec's context, the results of these studies were compared with those of the AMI-Québec study [35].

According to the current AHA/ACC STEMI guidelines [2], the delay between the patient's first contact with the medical system and the initiation of FL should be within 30 minutes; in the case of PPCI, door-to-balloon time should be within 90 minutes. For patients requiring interhospital transfer, PPCI should be initiated within 90 minutes of arrival at the *initial* hospital door.

4.4.1 RCTs comparing PPCI with transfer to on-site FL

Seven RCTs compared PPCI with inter-hospital transfer and on-site FL [61, 71, 80, 87, 88, 92]. These studies excluded patients with cardiogenic shock [61, 74, 80, 99]. Patients with severe heart failure, life-threatening arrhythmia and mechanical ventilation were also excluded in one study [99]. Patients were also excluded if transportation could not be completed within 30-60 min [61, 87, 88].

Several RCTs implemented organizational measures to ensure prompt PPCI. For example, twenty percent of AIR-PAMI patients underwent inter-hospital transfer by helicopter for longer distances (57±50 miles). To be able to participate in DANAMI-2, eligible hospitals had to document acceptable door-to-balloon times outside of regular working hours. Furthermore, although it was not always specified, it was highly conceivable that there were qualified medical escort during the inter-hospital transfers (i.e. physicians, nurses, or paramedics trained in advanced cardiac life supports) (Table 2).

Six trials had information on the distances covered [61, 71, 80, 87, 88, 93]. The longest distances were observed in DANAMI-2, reaching up to 150 km [71]. The median transportation time was shortest at 20 minutes in Maastricht [61] and longest at 67 minutes in DANAMI-2 [71].

For studies with inter-hospital transfer, the time delays from arrival at the first hospital (door) or randomization-to-balloon in the second hospital varied from 95 to 158 minutes. Except for PRAGUE-1 [88], the door-to-needle times observed in all other trials exceeded current standards. Since FL was initiatiated at the randomization site, without requiring inter-hospital transfer, prolonged door-to-needle times were probably related to the processes of obtaining consent and randomization [119].

Table 2: Transport-related distance, time, adverse events and door-to-reperfusion therapy in RCTs comparing PPCI with inter-hospital transfer and on-site FL.

Study	Number of patients transported	Distance (km) (Range)	Transportation time (mins)[f]	Door-to-balloon	Door-to-needle	Adverse events during transport
MAASTRICHT	75	25-50	20*	85*	45*	2 ventricular arrhythmia, 6 hypotension
PRAGUE-1	101	5-74	35[δ]	95[δ]	22[δ]	2 ventricular fibrillations 2 (worsening of Killip 2 to 4)
PRAGUE-2	429	5-120	48*	97* (randomization-to-balloon) (Door-to-randomization time was not specified)	12* (randomization-to-needle)	2 deaths, 3 ventricular fibrillations
AIR-PAMI	71	51±58	26[f]	155[f]	51	2 hypotensions, 1 confusion
DANAMI-2	559	3-150 (82% less than 76 km)	67[f] (96% less than 2 hours)	90[f] (Randomization-to-balloon) (Door-to-randomization: 22[f])	20[f] (Randomization-to-needle) (Door-to-randomization: 20-25[f] depending on the type of center)	9 ventricular fibrillations 13 intermittent high-grade atrio-ventricular blocks 1 death immediately at arrival at PPCI center (refractory ventricular fibrillation)
Dobrzycki *et al.* (2006)	172	20-150	Not available	158* (Randomization-to-balloon)	44* (Randomization-to-needle)	Mention of no death during transportation No other details available
HIS	25	Not available	Not available	100[f] (Randomization-to-balloon)	20[f] (Randomization-to-needle)	No death during transportation No other details available
Total	1,260					0.2% mortality, 1.5% ventricular fibrillation/arrhythmia, 0.9% hypotension, 1.2% intermittent high-grade atrio-ventricular blocks

[f]: Median, *: Mean, [δ]: Not specified whether this value was mean or median4.5.1.

IN BRIEF

- Organizational structures were implemented to ensure expedient and safe inter-hospital transfer.
- Most of the inter-hospital transfers did not exceed 120 minutes.
- External validity was limited by the relatively long door-to-needle and relatively short door-to-balloon times in these RCTs.

To be able to reproduce the benefit of PPCI with inter-hospital transfer in these RCTs in clinical settings, inter-hospital transfer should be provided in an expedient and safe manner.

4.4.2 Time to reperfusion therapy in RCTs without transfer

Thirteen RCTs without inter-hospital transfer reported door-to-needle and door-to-balloon times [61, 71, 73, 76, 79, 80, 82, 83, 85, 86, 88, 89]. Mean or median times to treatment in the different RCTs were presented in appendix H. Only four of these thirteen RCTs had mean or median door-to-needle times of approximately 30 minutes, all of which were European studies [86, 88, 89]. Half the RCTs had door-to-needle times of 45 minutes or longer [61, 71-73, 80, 83].

Processes were implemented in these studies to minimize the PPCI-related delay in the non-transfer trials. The door-to-balloon times was less than 90 minutes in six trials [76, 79, 82, 85, 86, 89]. The Canadian STAT RCT demonstrated more expedient PPCI during regular working days than on weekends and holidays [83]. For patients treated between 7:00 a.m. and 6:00 p.m. on weekdays, the median interval between *randomization* and balloon dilatation was 62 minutes. For patients treated off regular working hours such as weekend, holidays or between 6:00 PM. and 7:00 AM on weekdays, the median door-to-balloon was 94 minutes.

It was possible that patients who presented off regular working hours may not have been enrolled in these trials. Hence, the superiority of PPCI as observed from these RCT might not be entirely generalizable to PPCI performed off-regular working hours in the "real-world" context. Patient selection limited further the external validity of these RCTs. STAT did not randomize patients when the PPCI facility was unavailable; approximately 9% of eligible patients were excluded for this reason [83].

Overall, the above RCTs' external validity was limited by the relatively long door-to-needle times, short door-to-balloon times and careful patients' selection. Therefore, to replicate the results of PPCI as observed in these RCTs, the delay to PPCI should be within 90 minutes. The magnitude of the relative efficacy of PPCI compared to FL may have been also exaggerated with sub-optimal management of patients who received FL, as shown by sub-optimal door-to-needle times in these RCTs.

4.5 CONCLUSIONS

CONCLUSIONS FROM THE REVIEW OF RCTS

- This review revealed extensive heterogeneity in patient selection, study design, adjuvant treatments and outcomes definitions between RCTs.
- There were potential selection, performance and classification biases in many RCTs.
- External validity of these trials may have been limited by their relatively short door-to-balloon and prolonged door-to-needle times.

5 FINDINGS OF PUBLISHED SYSTEMATIC REVIEWS

Nineteen systematic reviews compared efficacy of PPCI and FL (Table 3) [34, 101, 102, 120-134]. The study periods, numbers of included RCTs and objectives of each analysis vary among the meta-analyses. Some reviews only focused on the overall impact of treatment, whereas others examined the impact of presentation delays, PPCI-related delays[17], interhospital transfer and disease severity. Some reviews were similar in focus and design, with the older meta-analyses included fewer RCTs. Hence, the present analysis focuses on the more recent reviews that include more RCTs.

5.1 RELATIVE EFFICACY OF PPCI COMPARED WITH FL

Almost all meta-analyses demonstrated a short-term benefit[18] for PPCI, either for separate endpoints of mortality, reinfarction or a combined endpoint of death, reinfarction and stroke [34, 101, 102, 123, 125-127, 131, 132]. In the 2003 meta-analysis by Keeley and colleagues, that included the largest number of RCT, a long-term mortality benefit was seen with PPCI [34].

17 "PPCI-related delay" is defined as the mean (or median) difference between "door-to-balloon time" and "door-to-needle time" within a predefined cohort (Kent *et al.*, 2001).
18 This generally includes events occurring during hospitalization, at 30 days and at 6 weeks.

Table 3. Systematic reviews classified by year of publication, data period, number of included RCTs, type and objective of analysis

Systematic review	Data period and number of included RCTs	Type and objective of analysis	Main conclusions
Systematic reviews with individual patient data			
Boersma (2006) [121]	1992-2002; most analysis with 22 RCTs, 23 for some analysis[19]	Meta-analysis studying presentation delay and PPCI-related delay.[20]	PPCI was associated with 30-day mortality reduction relative to FL (OR: 0.63, 95% CI: 0.42-0.84), regardless of presentation delay. PCI was associated with the greatest mortality reduction with PCI-related delay of less than 35 mins
Grines *et al.* (2003) [123]	1990-1999; 11 RCTs	Meta-analysis of comparative efficacy of both treatments, and PCI-related delay (sub-analysis only).	PPCI was associated with a reduction in mortality, reinfarction and stroke compared to FL.
Ziljstra *et al.* (2002) [133]	1993-1999; 10 RCTs	Meta-analysis of presentation delay.	PPCI was associated with mortality reduction relative to FL (OR: 0.62, p:0.01), irrespective of presentation delay
PCAT Collaborators (2003) [123]	1989-1996; 11 RCTs	Meta-analysis comparing PPCI and FL, with adjustment for patients and study-variables	PPCI was associated with 6-month mortality reduction relative to FL (RR: 0.73; 95% CI: 0.55-0.98). The absolute risk reductions increased with increased baseline STEMI risks.
Systematic reviews with RCT data			
Kuukasjärvi *et al.* (2006) [125]	1990-2002; 22 RCTs	Bayesian re-analysis of systematic reviews	There was no mortality benefit with PPCI compared to fibrin-specific FL (RD: 1.2 percentage points, 95% CrI: -2.7 to 0.2). PPCI reduced mortality compared to SK (RD: 4.1 percentage points, 95% CrI: -7.1 to –1.1). Dalby's meta-analysis re-analysis did not show a survival benefit with direct transportation to a PCI center compared to FL (RR: 0.77, 95% CrI: 0.51 to 1.13)
Keeley *et al.*	1990-2002; 23	Meta-analysis	PPCI reduced short and longterm death compared to FL, independent of

19 Most analysis were done without including the CAPTIM trial; however, for sensitivity analysis, CAPTIM was included
20 PCI-related delay is defined as the extra time needed to treat patients with primary angioplasty instead of fibrinolysis.

(2003) [34]	RCTs	comparing short-and long-term results of PPCI and FL	type of FL agent and of inter-hospital transfer (short-term mortality OR: 0.70, 95% CI: 0.58-0.85, excluding the SHOCK trial).
Cucherat *et al.* (2003) [101]	1989-1997; 10 RCTs	Meta-analysis comparing PPCI and FL	PPCI was associated with mortality reduction (RRR: 32%, 95% CI: 5% TO 50%).
Weaver *et al.* (1997) [132]	1990-1997; 10 RCTs	Meta-analysis comparing PPCI and FL	PPCI was associated with in-hospital mortality reduction compared to FL (OR: 0.66, 95% CI: 0.46-0.94)
Michels & Yusuf (1995) [127]	1986-1994; 7 RCTs	Meta-analysis comparing PPCI and FL	PPCI was associated with 6-week mortality reduction compared to FL (OR: 0.56, 95% CI: 0.33-0.94).
Vaitkus (1995) [131]	1986-1994; 5 RCTs	Meta-analysis comparing PPCI and FL	PPCI was associated with in-hospital mortality reduction compared to FL (OR: 0.51, 95% CI: 0.43-0.61).
Health technology assessments with RCT data			
Hartwell *et al.* (2005) [102]	1989-2002; 14 RCTs	Meta-analysis comparing PPCI and FL	PPCI was associated with short-term mortality (0.64, 95% CI: 0.49-0.83).
MAS (2005) [126]	1989-2003; 22 RCTs	Meta-analysis comparing PPCI and FL	PPCI reduced short-term mortality compared to with in-hospital FL (OR: 0.72, 95% CI: 0.59-0.87)
Meta-regressions with RCT data			
Betriu & Masotti (2005) [120]	1990-2002; 21 RCTs	Meta-regression of PPCI-related delay.	PPCI's mortality benefit relative to FL decreased substantially with increasing PPCI-related delay. At a PPCI-related delay of 110 minutes, there was no mortality difference between PPCI and FL.
Tarantini *et al.* (2005) [130]	1990-2002; 22 RCTs[21]	Meta-regression of PPCI-related delay and disease severity.	There was no mortality difference between PPCI and FL in patients with STEMI mortality risk of 4.5% or less. The PCI-related delay time-to-equipoise (when there was no mortality difference between PPCI and FL) increased with increasing STEMI mortality risk.

21 DANAMI-2 was divided in two trials in this systematic review, one that involved patients who underwent randomization at referral hospitals and one that involved patients who were enrolled directly at invasive treatment centers.

Nallamothu *et al.* (2004) [128]	1990-2002; 20 RCTs	Meta-regression of PPCI-related delay stratified by fibrin-specific agents and SK.	Compared to tPA, PPCI's mortality reduction decreased for every additional 10-minute delay. At a PPCI-related delay of 62 minutes, there was no mortality difference between PPCI and tPA. In contrast, the authors did not observe a reduction in PPCI's survival benefit relative to SK with increased PPCI-related delay.
Kent *et al.* (2001) [124]	1990-1997; 10 RCTs	Meta-regression of PPCI-related delay.	For each additional 10 minute PPCI-related delay, PCI-related survival benefit decreased by 1.7%. At a PPCI-related delay of 50 minutes, there was no mortality difference between PPCI and FL.
Tarantini *et al.* (2004) [204]	1993-2003	Meta-regression of PPCI-related delay and presentation delay	There was no mortality difference between PPCI and FL at a PPCI-related delay of 75 minutes. Every additional 10 minutes of PPCI-related delay was associated with 1.1% increase in mortality. Inclusion of only RCT enrolling patients within six hours of symptom, the time-to-equipoise of PPCI-related delay was 57 minutes. There was no time-to-equipoise of PPCI-related delay with analysis restricted to RCTs enrolling patients within 12 hours of symptom. This meta-analysis suggested that for patients with later presentation, PCI is preferred regardless of PCI-related delay.
Systematic reviews of transfer RCTs with RCT data			
Scott *et al.* (2004) [129]	1999-2003; 6 RCTs	Meta-analysis comparing FL to inter-hospital transfer for PPCI	Non-significant 30-day mortality reduction with PPCI. /Excluding pre-hospital FL, PPCI with inter-hospital transfer was associated with mortality reduction (relative risk reduction: 0.24, 95% CI: 0.02-0.41%).
Dalby *et al.* (2003) [122]	1999-2003; 6 RCTs	Meta-analysis comparing FL to inter-hospital transfer for PPCI	PPCI was associated with reduction of the composite endpoint of death/reinfarction/stroke (RR: 0.58, 95%CI: 0.47-0.71).
Zijlstra *et al.* (2003) [134]	1999-2002; 5 RCTs	Meta-analysis that compared PPCI with inter-hospital transfer vs FL at the initial hospital	PPCI was associated with short-term mortality reduction (RR: 0.51, 95% CI: 0.40-0.65).

5.2 RELATIVE EFFICACY OF PPCI COMPARED WITH DIFFERENT CLASSES OF FIBRINOLYTIC AGENTS

The meta-analysis by Keeley *et al.* (2003) demonstrated a short-term mortality reduction with PPCI compared to tPA (OR: 0.79, 95% CI: 0.63 to 0.99 excluding the SHOCK trial). The absolute mortality difference was 5% with SK and 1% with tPA [34]. However these differences in treatment effect may be due to differences in patient selection, study design, concomitant interventions or chance. To confirm that this difference in mortality reduction was truly due to the different FL types, an interaction test should have been performed. In the absence of a formal interaction analysis between the specific type of FL and treatment effect, it is difficult to ascertain whether this treatment difference was truly due to the different types of FL agents used.

The meta-analysis by Boersma (2006), that excluded the CAPTIM[22] RCT, showed a short-term mortality reduction with PPCI compared to tPA [OR= 0.71; 95% CI (0.46 to 0.98), absolute mortality reduction: 1.8 percentage points] [121, 126]. However, a Bayesian meta-analysis by Kuukasjarvi *et al*. (2006), did not show a mortality reduction with PPCI compared to tPA (RD: 1.2 percentage points, 95% CrI:-2.7 to 0.2) [125]. This lack of benefit with PPCI in this meta-analysis may be partially explained by a more conservative Bayesian risk estimate and inclusion of pre-hospital FL (CAPTIM study). The Ontario's Medical Advisory Secretariat (MAS) completed a meta-analysis including CAPTIM and all RCTs using accelerated tPA [126]. There was no difference in short-term mortality between PPCI and accelerated tPA in the MAS meta-analysis [OR=0.82; 95% CI (0.64 to 1.04)].

Overall, excluding pre-hospital FL, PPCI was associated with a 1 to 2 percentage points in short-term mortality reduction compared to tPA. Including CAPTIM study with pre-hospital FL, there was no conclusive mortality difference between PPCI and tPA.

Keeley *et al.* showed an absolute reduction of 3 percentage points in short-term re-infarction with compared to tPA (OR: 0.42, 95% CI: 0.31 to 0.55) [34].

5.3 RELATIVE EFFICACY AND SAFETY OF PPCI WITH INTER-HOSPITAL TRANSFER COMPARED TO ON-SITE FL

Five meta-analyses [34, 122, 125, 129, 134] pooled the results from RCTs with inter-hospital transfers. In five of the six RCTs with inter-hospital transfer, patients who presented to hospitals without PCI facility were randomized to on-site fibrinolytic therapy, or transferred for PPCI. In one RCT, patients were randomized to pre-hospital FL or direct transport to a hospital with PCI facility (CAPTIM) [78].

DANAMI-2 consisted of two distinct substudies: (i) patients who presented to a hospital with PCI facility were randomized to FL or PPCI without inter-hospital transfer and (ii) patients who presented to a hospital with PCI facility were randomized to on-site fibrinolytic therapy or PPCI with inter-hospital transfer. There were 1,129 patients who presented to hospitals without a PCI facility and 443 patients presented to a hospital with a PPCI facility, hence these patients did not require inter-hospital transfer for PPCI.

22 An important characteristic of the CAPTIM study is that randomization was performed earlier. (prehospital and not at the hospital). As a result, fibrinolysis was likely administered in the most expedient manner. Boersma (2006) did not include this study in most of his analyses because he did not have the individual patient's data from this trial.

Only one meta-analysis correctly included only DANAMI-2 patients in the trial that were randomised at the community hospitalsto on-site FL or inter-hospital transfer [134]. PPCI with inter-hospital transfer reduced short-term mortality compared with on-site in-hospital FL in this meta-analysis [RR=0.69 95% CI (0.51–0.92)] [134]. The other meta-analyses included all DANAMI-2 patients (including those who were randomized to hospitals with PCI labs and did not require inter-hospital transfer). Hence, their results were unlikely to reflect accurately the effect inter-hospital transfer on PPCI outcomes.

5.4 THE INTERACTION OF PPCI AND BASELINE MORTALITY RISK

Tarantini *et al*. (2005) postulated that the magnitude of the potential benefit of PPCI depended on the short-term mortality risks of FL patients [130]. This meta-regression showed no survival difference between PPCI and FL with the baseline mortality risk of ≤ 4.8% for tPA or ≤ 4.1% for SK [130]. Although there was an interaction observed between baseline mortality risk and PPCI-related delay in studies of SK, the authors did not explain in more details this finding.

The method used by the authors was potentially confounded because the mortality risk of the FL patients) were also affected by the treatment (FL). This may create a bias to the extent that the association between disease "severity" and treatment effects may be over-estimated [135]. A better approach would have been to use individual patient's data with direct measures of co-morbidities or STEMI severity (such as type of STEMI, Killip class, TIMI score, etc).

5.5 SAFETY OF PPCI COMPARED WITH FL

Adverse effects of interests were strokes and bleeding events. The incidences of strokes were lower with PPCI in all reviewed meta-analyses. The stroke risk reduction associated with PPCI varied from one half to two thirds [34, 101, 102, 123, 126]. The absolute stroke reduction difference was 1 percentage point for PPCI compared to tPA [34]. Hemorrhagic strokes accounted for most of the difference in strokes between PPCI and FL (0% and 1% [34]). There were more major bleeding events with PPCI (7%) than with FL (5%) [34]. There was an excess of 20 major bleeds per 1,000 patients treated with PPCI [34].

5.6 QUALITY OF THE SYSTEMATIC REVIEWS

The different meta-analyses reviewed were of variable quality. Five meta-analyses included RCTs with follow-up limited to the hospitalization stay [101, 102, 127, 131, 132]. This method was susceptible to detection bias since patients who received FL generally had more prolonged hospitalization stays than patients who underwent PPCI.

The meta-analysis by Keeley *et al*. (2003) [34] had several limitations. This meta-analysis included the RCT by Garcia *et al*. (1999) [77], but the figures presented by Keeley and colleagues did not concur with those reported in the original RCT. The AIR-PAMI RCT was classified in the tPA group [80], despite the fact that one third of the FL patients in this RCT were treated with SK.

Furthermore, there was inconsistency in the classification of reinfarction. Except for 3 RCTs that only reported non-fatal reinfarctions, [82,86,87], there was no distinction between fatal and non-fatal reinfarctions in most RCTs. Keeley *et al.* (2003) [34] reported non-fatal reinfarction that included both fatal and non-fatal reinfarctions.

CONCLUSIONS OF THE REVIEW OF SYSTEMATIC REVIEWS
PPCI compared to all FL agents

- PPCI reduced mortality and reinfarction compared to FL.
- PPCI reduced stroke (absolute risk differences of 1%) and increased major bleeding (absolute risk difference of 2%), compared to FL.

PPCI compared to tPA

- Excluding pre-hospital FL, PPCI reduced total mortality compared to tPA (absolute risk difference of 1% to 2%)

- Including pre-hospital FL, there was no no conclusive mortality difference between PPCI and tPA.

PPCI and inter-hospital transfer compared to in-hospital FL

- PPCI with inter-hospital transfer reduced short-term mortality compared with on-site in-hospital fibrinolysis.

6 EFFECTIVENESS AND SAFETY OF REPERFUSION THERAPIES

6.1 RATIONALE FOR OBSERVATIONAL STUDIES OF REPERFUSION THERAPY

Observational studies are often assumed to be of inferior quality when compared with randomized controlled RCTs, since results of observational studies may be flawed by selection, classification and confounding biases [136]. Nevertheless, well-designed observational studies may produce results as relevant as those of well-designed RCTs [136]. High-quality cohort studies should involve concurrent rather than historical controls, clearly defined inclusion criteria, suitable 'zero' time (i.e., study start time) and adequate adjustment for differences in prognostic factors of the comparison groups [137]. Furthermore, the external validity of RCTs (i.e., generalizability of the results to routine clinical settings) may be limited. Indeed, there are features of reperfusion therapy that cannot be properly assessed with RCTs that are discussed below.

Patients enrolled in RCTs of reperfusion therapies were generally healthier: these studies tended to include younger patients, fewer females and patients with fewer co-morbidities than those not enrolled [138-140]. Five RCTs excluded patients older than 80 years [61, 75, 78, 79, 84]. Patients with high-risk features of STEMI were also frequently excluded: nine RCTs excluded patients who presented in cardiogenic shock [61, 74, 79, 80, 83-85, 89, 90], three RCTs excluded patients with Killip class >2 [80, 89, 90], and one RCT excluded patients with anterior or large STEMI [89]. Thus, the generalizability of RCT's results to unselected STEMI patients in the community (i.e., external validity) may be limited.

The survival benefit of PPCI decreases with prolonged PPCI-related time delay [120, 128, 141, 142]. Most hospitals participating in RCTs implemented protocols to ensure the most expeditious delivery of reperfusion therapy. In situations with projected lengthy times to PPCI (long-distance transfer or unavailability of PPCI facilities), patients were generally not enrolled in the RCTs. Since observational data registries did not select patients on the basis of expected PPCI-related delay, their results are potentially more representative of those obtained with PPCI in routine clinical settings.

Selection of hospitals to participate in RCT was usually restrictive. Although not all RCTs specified a minimum requirement of volume or expertise for PPCI, it was likely that hospitals selection was based on their commitment and dedication to clinical research or expedient PPCI. Thus, the results of PPCI in RCTs may not be entirely representative of the procedure performed at lower-volume and less expert PPCI centres in routine clinical setting.

Restriction of rescue and elective PCIs in patients assigned to FL in many RCTs may have denied these patients the benefit of more successful complete coronary interventions and restoration of coronary blood flow. In the 'real world', rescue and elective coronary interventions following STEMI were generally performed as indicated. Observational studies may be more suitable than RCTs to examine the effects of unrestricted rescue and elective PCI following FL.

Observational studies may also be more appropriate than RCTs to evaluate the adverse effects of reperfusion therapy [143, 144]. Many RCTs routinely excluded patients at increased risk of

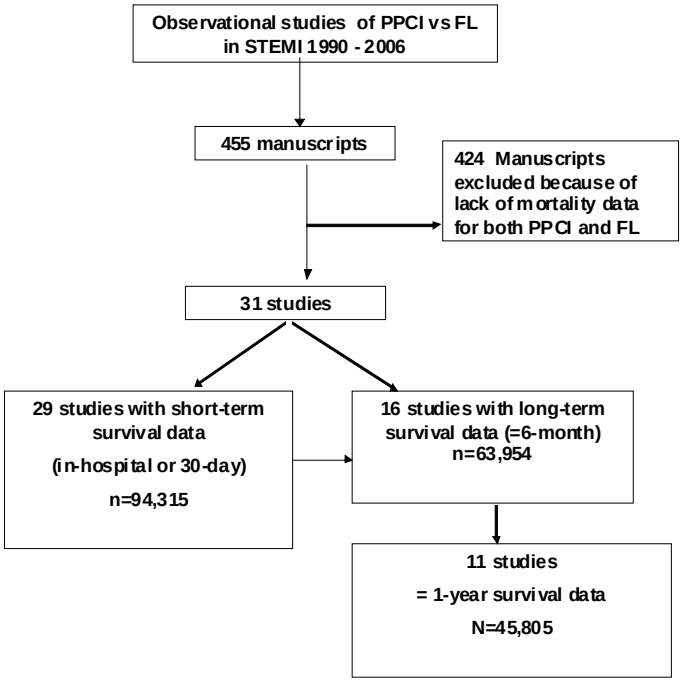
adverse effects from FL (i.e. patients with bleeding diathesis, coagulation disorders, and previous cerebrovascular diseases) and PPCI (i.e. patients with renal insufficiency or poor vascular access). Extrapolating the safety profiles of FL and PPCI from RCTs to the general population of STEMI patients may not be entirely appropriate.

Most of the reviewed RCTs of reperfusion therapy reported only one year or less of follow-up data, with the exception of PRAGUE-2 (5 years) [145], DANAMI-2 (3 years) [100] and PAMI (2 years) [112] and Zwolle (5-years) [146]. One year survival was available in 11 observational studies [147-151] and 3-year survival was reported in two studies [152, 153]. Hence, these observational studies provided better opportunities than most existing RCTs to ascertain whether any potential effectiveness difference between the two reperfusion strategies was sustained over time.

6.2 RESULTS OF THE OBSERVATIONAL STUDIES

We identified 31 observational studies with available short or long-term mortalities for PPCI and FL in STEMI. Study selection process is shown in Figure 3. Seventeen of these were cohort studies with ten being prospective [15, 148-152, 154-169] and eight being retrospective [161, 169-174, 195]. Three were case-controls studies [153, 175, 176].

Figure 3. Selection of observational studies



Short-term data was defined as data available within 30 days of the index STEMI. Long-term data was ≥1-year data. Twelve studies reported both short and long-term studies [148-152, 157, 160, 161, 166, 174, 176, 177]. Three studies only had long-term data [15, 156, 171] and only short-term data were available in 14 studies [154, 155, 159, 162-165, 168-170, 173, 175, 178, 195].

The results of these studies are summarized in appendix I, stratified by short-term and long-term mortality and reinfarction. We also compiled adverse events such as stroke, cardiogenic shock and arrhythmia. These results were further stratified according to the method of administration of FL (predominantly in-hospital[23] or pre-hospital) and whether enrolment was restricted to elderly patients (patients ≥65 years old). When available, results presented were limited to those applicable to "ideal" patients, i.e. those with ST-elevation or LBBB and without cardiogenic shock or contra-indications to a specific reperfusion strategy.

6.2.1 Mortality

6.2.1.1 STUDIES COMPARING PPCI WITH PREDOMINANT IN-HOSPITAL FL

Sixteen studies reported short and long-term survival data. Unadjusted survivals were improved with FL in four studies [149, 156, 157, 173] whereas 12 studies reported improved unadjusted survivals with PPCI [151, 159, 161, 164, 165, 168, 169, 171, 172, 175, 176, 178, 195].

Four studies reported short-term survivals adjusted for characteristics of patients and STEMI. All of these three studies showed improved adjusted short-term survival with PPCI [151, 159, 168, 195]. The absolute mortality reductions with PPCI ranged from 2 [159] to 5 percentage points [151, 168]. Adjusted one-year survival was available only from one study [151]. In this study, Stenestrand *et al.* reported a one-year relative mortality reduction of 32% [(hazard ratio: 0.68, 95% CI (0.60-0.76)] [151].

6.2.1.2 STUDIES COMPARING PPCI WITH PRE-HOSPITAL FL

PPCI was compared with pre-hospital FL in four studies [148, 151, 153, 174]. Two studies reported absolute mortality reductions of 5 percentage points with pre-hospital FL compared to PPCI (1-year and 3-year data) [148, 174]. Short-term survival was similar for both reperfusion strategies in one study [153]. In contrast, Stenestrand *et al.* (2006) reported improved short and long-term survivals with PPCI compared with pre-hospital FL (absolute reduction of 2 percentage points for 1-year mortality) [151].

6.2.1.3 STUDIES WITH EXCLUSIVE ENROLMENT OF ELDERLY PATIENTS

Five studies enrolled exclusively elderly patients (≥ 65 years old) [154, 155, 160, 163, 177]. Subgroup analyses of elderly patients were available from five other studies [162, 166-169]. PPCI was associated with improved short-term survival in five of these ten studies. Only one study reported adjusted short-term survival [163]. In this study, the odds ratio was in favour of mortality reduction with PPCI [OR = 0.62, 95% CI (0.39-0.96)]. Absolute long-term mortality reductions of 2 percentage points with PPCI were noted in two [160, 177] of the these three studies [160, 166, 177].

6.2.2 Reinfarction

Seventeen studies reported reinfarctions [15, 148-152, 160, 161, 163, 164, 166-169, 174, 176, 178]. Only four studies presented definitions of reinfarction [150, 160, 163, 164]. No study differentiated between fatal and non-fatal reinfarction.

23 Specified ≥90% in-hospital FL

PPCI was associated with reduced reinfarction in 8 studies [148, 151, 160, 163, 168, 174, 176, 178]. The absolute reinfarction reduction ranged from 2 [151, 160, 174, 176] to 5 percentage points [163, 178]. Reduced long-term reinfarction with PPCI was noted in four studies [150, 151, 160, 161, 176]. The absolute reduction in long-term reinfarction ranged from 2 [150] to 10 percentage points [160].

6.2.3 Stroke

Data concerning in-hospital stroke were available from 19 studies [15, 148-152, 154, 155, 160, 161, 163, 166-169, 174-177, 195]; 1-year incidence was reported in only one study [15]. Only one study specified that their stroke incidences only included non-fatal stroke [195]. Five studies did differentiate between hemorrhagic and non-hemorragic stroke [154, 161, 167, 176, 178]. The incidence of in-hospital stroke ranged from 0% [149] to 5% [147] for FL and from 0% [148] to 5% [147, 160] for PPCI.

Reduced in-hospital stroke with PPCI was noted in 13 of the 19 reviewed studies [148, 151, 152, 154, 161, 163, 166, 167, 169, 174-176, 195]. The absolute stroke reduction with PPCI ranged from 0.5 to 4 percentage points [154, 175]. Similar stroke incidences for PPCI and FL were noted in five studies [15, 149, 150, 168, 177]. Two studies reported 1 percentage point absolute stroke increase with PPCI [155, 160]. The increased stroke incidence with PPCI was due to ischemic strokes in one study [160] and was unexplained in the other [155].

Bueno *et al.* (2005) reported the highest strokes incidences for both PPCI and FL (5.5% and 4.3%, respectively) [155]. Although this study enrolled only patients older than 75 years, age did not appear to explain entirely the increased stroke incidences, particularly with PPCI. Among STEMI patients with similar age (≥75 years old) in two other studies, the stroke incidences were 1% and 5% with PPCI and FL, respectively [154, 169].

6.2.4 Major hemorrhage

Data concerning major hemorrhages was available for only 3,855 patients (8 studies) [149, 153, 158, 160, 161, 163, 169, 178]. We excluded two studies because the authors did not distinguish between major and minor hemorrhage [147]. Only one study provided a definition of major hemorrage [161]. Only five studies specified exclusion of intracranial bleeds in the total compilation of major hemorrhages [153, 160, 163, 169, 178].

PPCI was associated with increased major hemorrhages or transfusions in two studies [169, 178]. FL was associated with increased major hemorrhages or transfusions in four studies [149, 158, 160, 163]. Two studies reported similar incidences of major bleeds or transfusions with PPCI and FL [153, 161]. The incidences of major hemorrhages or transfusion ranged from 3% to 7% for both PPCI and FL.

Magid *et al.* reported higher rates of in-hospital major bleeds with FL except in low-volume PCI hospitals where there were more major bleeds with PPCI [195]. This increase in major bleeds at low-volume PCI hospitals were likely due to less expert PCI personnel. Remarkably high incidences of major hemorrhages and transfusion with FL were noted in two studies (17% and 16%, respectively) [149, 160]. The explanations for these high bleeding complications in these studies were not provided. One study enrolled patients older than 70 years, and one study was completed in the early 1990s where there may have been higher doses of anticoagulants.

Overall, there were more major bleeds with FL. The incidences of hemorrhagic complications varied remarkably among the studies. This may be due to inconsistencies in the definition, detection and ascertainment of hemorrhagic complications or differences in adjuvant anticoagulation anti-platelet agents use and less expert PCI skills.

6.2.5 Other adverse cardiovascular events

Data concerning in-hospital cardiogenic shock was available in 11 studies [148, 149, 154, 155, 157, 163, 164, 170, 174-176]. Only one study excluded patients with cardiogenic shock at initial presentation [155]. There were more in-hospital cardiogenic shocks with PPCI [148, 149, 154, 155, 157, 163, 164, 170, 175]. The true incidences of cardiogenic shock following reperfusion therapy could not be reliably estimated because none of the authors excluded patients with cardiogenic shock at initial presentation. Physicians may have preferred PPCI to reperfuse these "sicker" patients who presented with cardiogenic shock and arrhythmia. This confounding bias by indication is discussed in more detail, in section 6.3.

The incidences of ventricular arrhythmias such as ventricular fibrillation, ventricular tachycardia were reported in six studies [148, 153, 154, 157, 160, 175]. Three studies reported arrhythmia of unspecified types [164, 170, 176]. The incidences of ventricular tachycardia/ventricular fibrillation were similar between FL and PPCI for most studies. One study reported 3.2% of ventricular arrhythmia with PPCI and 0% for FL. Arrythmia of un-specified types were more frequent with FL in 2 studies [170, 176]. Overall, there was no increase in ventricular arrhythmia associated with one particular reperfusion strategy.

6.2.6 Conclusions about the results from the reviewed observational studies

6.2.6.1 EFFECTIVENESS:

Compared to in-hospital FL, PPCI improved adjusted short and long-term survivals in three studies. Short and long-term mortality reductions with PPCI were noted in most cohorts of elderly patients. Compared to pre-hospital FL, the relative effectiveness of PPCI was inconsistent in the reviewed studies.

6.2.6.2 SAFETY:

PPCI reduced in-hospital strokes in most studies. There were less major hemorrhages noted with PPCI in most studies.

IN BRIEF

- Unadjusted survival was improved with PPCI in most studies.
- Survival adjusted for characteristics of patients and STEMI were reported in only three studies. All of these three studies showed improved adjusted short and long-term survival with PPCI.
- Improved short and long-term survival with PPCI was noted in most studies with exclusive enrolment of elderly patients.
- PPCI was associated with reduced in-hospital stroke in most studies.
- There were less major hemorrhages with PPCI in the majority of the reviewed studies.

6.3 QUALITY OF THE OBSERVATIONAL STUDIES

Results of observational studies should be interpreted with caution since they were particularly subject to many biases related to selection, confounding, performance, detection and attrition. The potential impacts of these biases on the results of the reviewed 31 observational studies are discussed in this chapter. More details on the internal validity of these studies are presented in appendix J.

6.3.1 Selection bias

6.3.1.1 INTENTION TO TREAT

In observational studies, selection bias would occur if only patients with successful PPCI were included, while all patients who received FL were included regardless of their response to FL. To adjust for this bias, investigators should include all patients in both treatment groups, regardless of their responses to the initial reperfusion therapy.

This bias should be minimal in studies that included patients who did not undergo PPCI (unsuitable coronary anatomy) and patients with unsuccessful PPCI [152, 153, 160, 174]. The observational studies that included only patients with successful PPCI contained selection bias against FL [147, 148, 150, 157, 159, 163, 167, 179, 180, 195]. No information concerning this inclusion process was provided for the other reviewed studies.

To estimate the magnitude of selection bias, we examined the percentages of patients who did not undergo PPCI and of those with unsuccessful PPCI in the studies that included all patients regardless of PPCI outcome. These percentages varied from 2% [160] to 11% [152] of patients in the PPCI groups. This raises a significant concern for the internal validity of studies that included only patients with successful PPCI, if as many as 10% of patients in the PPCI group were not tallied in their analyses. This is especially pertinent because failure to establish coronary patency was associated with increased risk of major cardiovascular events [181]. Hence, the incidences of major adverse cardiovascular events assigned to PPCI may have been underestimated in these studies.

6.3.1.2 TRANSFERRED-IN PATIENTS

Selection bias also occured when a study included transferred-in patients from other hospitals. Transferred-in patients often had more high-risk STEMI, or had had unsuccessful FL. Inclusion of all hospitals within the geographical territory of interest should obviate this selection bias, since all patients with STEMI would be included regardless of whether they were transferred-in or not.

Only six studies explicitly excluded transferred-in patients [35, 147, 149, 152, 195]. Two studies included all patients with STEMI or all hospitals within the studied geographical territory references. The remaining studies did not explicitly exclude transferred-in patients and did not enrol all hospitals within their territories. The potential inclusion of transferred-in patients may have created a selection bias of sicker patients in these studies. The magnitude and direction of this bias could not be estimated with accuracy because the proportions of transferred-in patients varied according to clinical practice and geographical location.

6.3.1.3 "IMMORTAL-TIME" OR "SURVIVOR BIAS"

All studies only included patients who survived until the coronary angiogram. Patients who died before receiving the assigned reperfusion therapy would not be compiled in any observational study. This bias would favour PPCI more than FL since the wait time for PPCI was generally longer than for FL.

6.3.2 Confounding bias

Confounding bias may occur in the presence of important differences in patient characteristics associated with both the choice of reperfusion therapy and the outcomes of that therapy. In general, PPCI patients in the reviewed observational studies had more anterior myocardial infarction and prior myocardial infarction, PCI, CABG and stroke [152, 157] and longer symptom duration [147, 150, 159, 164, 180]. There were more patients in shock in the PPCI group in several studies [35, 148, 150, 159, 160, 163, 167, 174], while only three studies reported more cardiogenic shocks in the FL group [149, 151, 153].

Four studies reported more elderly patients and females (age difference of 2 years, and 5% to 10% increase in females) in the FL arm [148, 150, 151, 154]. It was noteworthy that patients who received pre-hospital FL were generally the youngest, were more likely to be males and had no prior history of cardio-vascular diseases compared to patients who received PPCI and in-hospital FL. Patients who received pre-hospital FL also had shorter symptom duration than patients who received in-hospital FL and PPCI [148, 174].

The confounders described above were of a particular type "*Confounder by indication"*. This type of confounder occured when the characteristic may be an indication or a contra-indication for the treatment and was also associated with the outcome. For example, PPCI was the recommended treatment for patients in cardiogenic shock [147, 163] (*shock=indication)*. Patients in cardiogenic shock had very high in-hospital mortality [53] (*shock associated with outcome)*. Hence, mortality associated with PPCI may have been over-estimated in studies with more patients in shock who underwent PPCI than with FL, because of this confounder by indication.

6.3.3 Performance bias

This bias was defined by the Cochrane collaboration as systematic differences in the care provided in the two comparison groups, apart from the intervention being evaluated. This may include differences in the expertise of the physicians and hospitals, medical and intervention provided to the patients. Physicians'expertise and high-volume hospitals, optimal coronary revasularization and medical therapy were associated with improved survival [53].

Patients who underwent PPCI were more likely to receive optimal medical therapy and complete coronary revascularization than patients who received FL [157, 160, 163, 169]. PPCI patients were more likely to be treated by cardiologists and hospitalized at higher-volume facilities in two studies [147, 163]. This performance bias would favour PPCI in these studies. There was no detail on concomitant care in the other studies. Hence, the magnitude of this bias could not be estimated since this information was missing in most studies (25 of the 31 reviewed studies).

6.3.4 Detection bias

Detection bias was inherent to studies that report short-term adverse events as in-hospital rates [149, 150, 155, 159, 162-164, 167-170, 175, 176] rather than at fixed time periods (i.e. 7 or 30-day). This practice may slightly increase the number of events in the FL group since

hospitalization stays were generally longer by one day in these patients compared with those of PPCI patients [75-79, 83, 85, 87, 93]. It was nevertheless unlikely that this bias had a significant impact on these studies' results, since adverse events generally occured early during hospitalization. These issues should not affect long-term results since the events were censored at fixed time points such as 6-month, 1-year and 3-year [147, 148, 156, 157, 160, 174].

6.3.5 Classification bias

None of the reviewed observational studies reported blinded classification and adjudication of events. Thus, their results may have been potentially flawed by this bias. It was not possible to estimate the magnitude and direction of these biases since they would depend on the prior belief of the adjudicators of the individual studies.

6.3.6 Attrition bias

The percentages of transferred-out patients may be important in studies that did not explicitly exclude transferred-out patients and did not capture data at the second hospitals. This bias may have occured for both PPCI and FL. After PPCI, patients may have been transferred back to the referral hospitals. Patients who received FL may also have been transferred to other hospitals for additional tertiary cardiology care. If the second hospitals did not participate in the registry, in-hospital adverse events that occured at these subsequent hospitals would not have been compiled for these patients.

In long-term studies, this bias tended to favour the treatment arm with the largest number of patients lost to follow-up, since these patients may have been counted as alive at the end of the observation period. However, this bias may be still present in studies with equal loss to follow-up in both treatment arms, if inequal proportions of high-risk patients who receive PPCI and FL were lost to follow-up. There would be differential under-estimation of the total count of major adverse events between the two treatments arms. Thus, any degree of loss to follow-up could have created attrition bias.

There is no general agreement about an acceptable percentage of patients lost to follow-up. The Food and Drug Administration's guidelines recommended that "patients follow-up to be as close to 100% as possible and that the follow-up percentages to be similar across comparison groups and across study sites" [182]. Finally, studies that determined survival status by linkage with administrative databases may have less attrition bias since events censoring were potentially more complete with these datasets.

Only five studies reported ≤6% patients lost to follow-up [15, 149, 150, 155, 174]. Survival status was corroborated with administrative datasets in five studies [150-152, 156, 177]. There was no detail provided on loss to follow-up in the remaining studies. Two studies reported differential losses of follow-up with more loss to follow-up for FL (i.e., 11%–17% for the FL group and 2%–8% for PPCI) [35, 167]. In these two studies, this may have biased results in favour of FL since patients who experienced adverse events after being lost to follow-up would be counted as subjects without events. In the remaining observational studies that did not provide attrition data, it was highly possible that there was under-estimation of adverse events for both treatments.

6.3.7 Specific observations about the large observational studies

We scrutinized the large observational studies (more than 10,000 patients) [151, 177, 183, 195] since the validity of meta-analyses was highly dependent on the internal validity of these

observational studies. There were more cardiogenic shocks and anterior STEMI [167] and longer presentation delays for patients who underwent PPCI compared to FL [151, 183]. In contrast, in the Stenestrand *et al.* (2006) study, patients who received FL had more high-risk features than patients who underwent PPCI (mean age of 69 vs 64 years, 34% vs 27% females, 20% vs 17% previous heart failure, 12% vs 9% Killip 3 and 4 classes) [151].

6.3.8 Conclusions about the quality of the reviewed observational studies

Performance and confounder biases were common in the majority of the reviewed studies. The distribution of high-risk features was heterogenous. There were more patients with high-risk STEMI in the PPCI group except for the largest observational study (Stenestrand *et al.* (2006) [151]) where there were more high-risk patients in the FL group. On the other hand, PPCI patients received more optimal medical therapy and coronary interventions than patients who received FL. They were more likely to have been treated by expert personnel and at high-volume AMI hospitals than patients who received FL. It was not possible to estimate with accuracy the magnitude of the above confounding and performance biases.

All studies were potentially flawed by the absence of blinded classification and adjudication of events. Detection bias's impact was probably small for in-hospital events, since hospitalization stay was marginally prolonged with FL (1-2 days) [35, 149, 150, 152].

The biases with potentially the most prominent impacts on the results were those related to selection and attrition. The percentages of patients not accounted for, may reach 11% for selection bias and 17% for attrition bias, respectively [152, 167]. Four studies did not have the selection bias related to inclusion of only patients with successful PPCI, since they included all patients assigned to PPCI regardless of the treatment response ("*intention-to-treat" analysis)* [152, 160, 174]. Six studies did not have significant attrition bias, with almost complete follow-up (>94%) [148-150, 160, 163, 174]. The results of these studies may be the most valid, being less affected by these two important biases. However, almost all of these studies were underpowered to detect a mortality difference between the two treatments. Meta-analysis of these better-quality observational studies may provide more valid estimates of the relative treatment effect than each individual study.

IN BRIEF

- Observational studies are limited by many potential biases that include selection, confounder, detection, ascertainment and attrition.
- Patients who underwent PPCI had more high-risk STEMI with more anterior STEMI, cardiogenic shock and longer symptom duration.
- Patients who underwent PPCI received more optimal medical therapy and coronary intervention. They were more likely to be treated by cardiologists and at higher-volume hospitals.
- The results of observational studies should be interpreted with care, in light of many potential biases.

6.4 EXTERNAL VALIDITY

More detailed informations related to the external validity of the reviewed studies are provided in appendix K.

6.4.1 Applicability of the results of the reviewed observational studies to Québec

Patients enrolled in the reviewed observational studies were fairly representative of patients with STEMI in the routine clinical setting in Québec. Mean age varied from 56 [153, 175] to 64 years in the studies without specific age restrictions. There was variable enrolment of females, ranging from 15% [153, 175] in studies without age restrictions and up to 40% in studies enrolling only elderly patients [155, 163]. The percentages of patients in cardiogenic shock ranged from 2% to less than 10% in the majority of studies [152, 155, 157, 159, 161, 163, 177]. One study reported a remarkably high incidence of cardiogenic shock at 30% [158]. The percentages of anterior myocardial infarction ranged from 35% [175] to 50% [150, 152-155]. Symptom duration ranged from two [177] to three hours [148, 153, 159, 178].

Seven studies reported the incidences of rescue PCI [152, 156, 157, 160, 162, 165, 174]. Rescue PCI ranged from less than 15% [156, 160, 167] to more than 40% [152, 162, 165]. This diverse rates of rescue PCI's suggested potential heterogeneity in ascertainment of rescue PPCI in these observational studies.

Thirty to seventy percent of patients in the FL arm underwent elective PCI during the index hospitalization [149, 152, 160-163, 174, 177]. Most patients enrolled in the more recent studies received coronary stents (90–100%) [35, 156, 160, 162]. Glycoprotein IIb/IIIa inhibitors were administered to the majority of patients who received stents (>80%). There was suboptimal use of medical therapy in many observational studies, including the one completed in Québec, with beta-blockers and statins prescribed in less than 75% of patients at hospital discharge [35, 148, 160, 180].

The majority of these studies were completed in Europe (Romania, France, Switzerland, Italy, Sweden, Denmark, Poland, Spain and Germany) [15, 148, 150, 154-157, 162, 164, 168, 170, 171, 176]. Five studies were completed in the United States [149, 152, 175, 177, 195], two in Japan [165, 178], three in Israel [158, 160, 166], one in Québec [35], one in Singapore [161]. One study was international with 55% of patients enrolled from Europe [163]. The total number of European patients is 54,325 (14,620 PPCI and 39,705 FL) thus constituted more than 55% of the 94,449 patients of the reviewed studies.

Most studies were multi-centric [15, 148-152, 154, 156-158, 160, 162, 163, 165-170, 172, 176, 195]. The hospitals that participated in these studies were generally high-volume PPCI centers, affiliated with medical schools and located in urban areas [150, 155, 161, 164-167, 171, 176]. Two studies took place within an organized pre-hospital and inter-hospital network of STEMI care [148, 162].

Times-to-reperfusion therapy was optimal in the European studies, with median door-to-balloon times less than 90 minutes [150, 153, 156, 159, 162, 176, 180]. Door-to-balloon times exceeded 90 minutes in all of the North American studies that provided data on time door-to-reperfusion therapy [149, 167, 169].

TNK was administered in only three studies: in 12% of patients in Kalla *et al.* [162], to 74% of patients in the Québec study [35], and an unspecified majority of patients in the TRIANA registry

[154] TPA was used for more than 50% of patients in 10 studies [149, 151, 152, 154, 155, 160, 162, 163, 167, 174]. Accelerated administration of tPA was specified in four studies [160, 162, 167, 179, 180]. Details concerning the types of fibrinolytic agents were not provided in the remaining studies. Of 55,313 patients with available details provided for the FL agent used, tPA and its derivatives were used in 68% of these patients (n =37,554).

6.4.2 Conclusions of the section on external validity

Overall, patients in these observational studies had similar clinical characteristics (with respect to age, percentage of females and cardiogenic shock) as STEMI patients in the AMI-QUEBEC study [35]. Concomitant medical therapies were also comparable to those used in the AMI-QUEBEC study. However, the majority of patients underwent PPCI within appropriate delays in the European studies. Thus, in order to apply the results of these studies to STEMI patients in Québec, reperfusion therapy should be administered as expediently as possible in Québec.

IN BRIEF

- Patients with STEMI enrolled in the reviewed observational studies had similar clinical characteristics to Québec patients.
- Fibrin-specific agents were the most commonly used FL agents.
- The majority of these patients from these cohorts received reperfusion therapy in European context where door-to-reperfusion therapy was generally optimal.
- Time delay to reperfusion therapy was generally prolonged in North American observational studies.
- To be able to generalize the results of these observational studies to Québec, reperfusion therapy should be administered as promptly as possible in Québec.

6.5 SPECIAL ISSUES CONCERNING REPERFUSION THERAPY IN ROUTINE CLINICAL SETTINGS

6.5.1 Outside regular working hours

▪ As PCI teams are generally present at the hospitals during daytime working hours (8.00-17.00 on weekdays) only, PPCI outside these hours would require mobilization of these teams back to the hospitals. Reduced interhospital transportation facilities may further aggravate the delays for patients who require interhospital transfer. The concern of time delays for PPCI outside regular working hours is particularly relevant since the majority of STEMI patients present during these hours (57% of the 102,086 patients enrolled in NRMI 3-4) [184]. Can reperfusion therapy be provided in an expedient manner to most patients who present outside daytime working hours?

▪

▪ Data derived from RCT may provide only incomplete information in this topic. No RCT provided details concerning patient's enrolment outside daytime working hours. It was highly

possible that many STEMI patients who presented outside daytime working hours would not be enrolled. As a consequence, generalizability of the results of RCT to the routine clinical setting outside daytime working hours is problematic.

- Two observational studies reported similar PPCI success and in-hospital mortalities for patients who presented during daytime and nighttime [185, 186]. However, both of these studies were underpowered due to their small sample sizes (288 and 491, respectively). Angeja *et al*.[187] and Magid *et al*.[184] reported prolongation of door-to balloon times by at least 20 minutes in 41,948 patients who presented outside working daytime hours relative to 31,706 patients who presented during regular working hours (NRMI 1-4). Magid *et al*. [184] also showed increased in-hospital mortality among the patients who presented outside working daytime hours (RR : 1.07, 95% CI : 1.01-1.11). After adjustment for door-to-balloon time, the risk associated with presentation outside working daytime hours was partially attenuated, suggesting that PPCI-related delay may have contributed to this increased mortality (adjusted RR: 1.02, 95% CI: 0.95-1.16).

- Despite similar door-to-balloon times, the Zwolle Myocardial Infaction Study showed increased 30-day mortality in 703 patients admitted outside 8.00-18.00 compared to 909 patients who presented during these hours (4.2% versus 1.9%) [188]. The increased mortality was likely secondary to the lower procedural success (post-procedure TIMI 3 flow and residual stenosis ≤50%) in the first patients group relative to the other patients (6.9% versus 3.9%). This study raised concerns about the quality of PPCI outside regular working daytime hours, when fatigue and sleep deprivation may have had an impact on the PPCI personnel's performance.

6.5.2 Interhospital transfer

- The extrapolation of safety data from RCTs to « real-world » clinical settings should be made with caution. Careful patient selection, qualified medical escort and short interhospital distance limit the external validity of these results. Observational studies may provide safety data concerning interhospital transfer for PPCI that are more relevant to unselected patients in routine clinical settings than RCT.

Nevertheless, only few observational studies specified inclusion of patients transferred for PPCI. Of eight studies enrolling 8,853 patients who underwent interhospital transfers for PPCI, only three reported safety data during transfers for 333 patients (3.8% of the 8,654 patients) [189-191]. The interhospital distances ranged from 5-68 km by ground ambulance [189, 190]. Five patients had life-threatening ventricular arrythmia (4 ventricular fibrillations and 1 ventricular tachycardia). Two patients required inotropic support for hypotension and one patient required intubation during transfer. Excluding 12 patients in cardiogenic shock before transfer, major adverse events occured in 2.3% of patients enrolled in these studies. It is also of note that all three studies were completed in Europe with qualified medical escort (physician or highly trained paramedics), short inter-hospital distances and temperate climates. The safety of interhospital transfers for PPCI among unselected patients, with interhospital distances exceeding 70 km and without qualified medical escort has not been demonstrated. Therefore, it remains unclear whether the safety data from the above three studies can be applied to Québec's context.

- Door-to-balloon times for PPCI with interhospital transfer were reported in only three observational studies [169, 192, 193]. Door-to-balloon times were markedly prolonged in these studies with medians of 180, 142, and 103 minutes, respectively. Door-to-balloon within 90 minutes was achieved in only 4% and 8% of the NRMI and AMI-Quebec cohorts, respectively.

Every 30-minute interhospital delay is associated with a 50% increase in adjusted mortality risk. (95% CI: 1.07-2.12) [194].

6.5.3 Volume of the PCI facility and personnel

- Observational studies may be more suitable than RCT to study the impact of hospital structure and processes of STEMI care since hospital selection is generally less restrictive in the former type of studies. As with any therapeutic intervention, the volume of the hospital and personnel may have direct impacts on PPCI quality and outcomes. Magid *et al.* reported improved in-hospital survival with PPCI relative to FL only at hospitals with more than 16 PPCI/year [195]. Vakili *et al.* showed that patients who underwent PPCI by high-volume physicians (more than 11 PPCI/year) at high-volume hospitals (more than 57 PPCI/year) had reduced in-hospital mortality compared to patients treated by low-volume physicans at low-volume hospitals (adjusted RR: 0.51, 95% CI: 0.26-0.99). Based on these results, ACC/AHA recommended that PPCI should be performed by physicians who perform more than 75 elective PCI and 11 PPCI per year at hospitals with more than 400 elective PCI and 36 PPCI per year [196].

- There is no data concerning volume of PPCI in Québec. A total of 16,282 PCI were performed in 2006 (1). This would yield a mean volume of 1,085 PCI/year per PCI facility (n: 15) and 226 PCI/year for each interventional cardiologist in Québec (n: 72) (1). Hence, these indirect evidences suggest that most Québec PCI facilities and personnel do have sufficient volumes to ensure optimal quality of PPCI.

IN BRIEF

- The majority of STEMI patients present outside daytime working hours. A few observational studies reported increased procedures failures and mortality among patients who underwent PPCI outside daytime working hours. Prolonged door-to-balloon and personel's fatigue may impair the quality of PPCI and contribute to the increased mortality among these patients.

- There were very limited data concerning the frequency and safety of inter-hospital transfer for PCI in the "real-world" clinical settings. There was 2.3% incidence of major adverse cardiac events in 356 patients who underwent interhospital transfer for STEMI with qualified medical escort. The safety of interhospital transfer for PPCI among unselected patients, with interhospital distances exceeding 70 km and without qualified medical escort had not been demonstrated.

- Door-to-balloon time was generally prolonged among patients who underwent PPCI with interhospital transfer. Every 30-minute interhospital delay was associated with a 50% increase in mortality risk.

- Patients who underwent PPCI by high-volume personel at high-volume hospitals had better in-hospital survival compared to patients who underwent PPCI by low-volume personel at low-volume hospitals. Patients who underwent PPCI by high-volume personel at high-volume hospitals also had improved survival compared to patients who received FL at these hospitals.

7 IMPACT OF PRESENTATION DELAY AND PPCI-RELATED DELAY ON EFFICACY OF REPERFUSION THERAPY

7.1 PRESENTATION DELAY

In the PRAGUE-2 study, 30-day mortality was 6% with PPCI compared to 15% for FL among patients who presented later than three hours [87]. In the CAPTIM study, in-hospital mortality was lower with prehospital FL compared to PPCI for patients who presented within two hours of symptoms (2% vs 6%) [74]. In this study, patients who presented later than two hours from symptom onset, mortality was higher with prehospital FL compared to PPCI (6% vs 4%). In a meta-analysis of ten RCTs, Zijlstra *et al.* demonstrated little differences in six-month mortality with increased presentation delays for PPCI (5% for presentation delay of less than two hours and 7% for presentation delay exceeding four hours) [133]. In contrast, long-term mortality markedly increased with prolonged presentation delays for FL (5% for presentation delay of less than two hours and 15% with presentation delays exceeding four hours). However all of these studies were flawed by subgroup analyses testing with significant results that may have occured by chance and the association of presentation delays with treatment efficacy may also be confounded by patients' characteristics such as age, gender, diabetes, etc.

Boersma *et al.* completed the most rigorous evaluation of the association of presentation delay on the relative efficacy of reperfusion therapy by performing meta-analysis of individual patients data with adjustment for patients' characteristics [121]. He showed that PPCI was associated with a lower 30-day mortality than FL, regardless of presentation delay [121]. The absolute mortality reduction with PPCI was 1 percentage point for presentation delays of less than one hour to 4 percentage points when delay exceeded six hours.

Three observational studies examined the relationship of presentation delay and the effectiveness of reperfusion therapy in unselected patients. Among patients who received FL in the Vienna STEMI Registry, the in-hospital mortality increased from 5% for presentation delays of less than two hours to 29% for presentation delays of 6-12 hours [162]. In the same cohort, mortality was 8% for presentation delays of less than two hours to 13% for presentation delays of 6-12 hours. De Labriolle *et al.* and Ferrier *et al.* showed that prolonged presentation delays (exceeding 150 minutes and 180 minutes, respectively) were associated with independent increase in mortality risk with FL [171, 197].

7.2 PPCI-RELATED DELAY

Six systematic reviews analyzed the impact of PPCI-related delay on mortality (Table 3) [120, 121, 123, 124, 128, 130]. Nallamothu *et al.* showed that the time-to-equipoise for PPCI-related delay was 62 minutes for tPA [128] (The "time to equipoise" is the PPCI-related delay that results in similar mortality between PPCI and FL). The "time-to-equipoise" between PPCI and SK was estimated to be 170 minutes in this study. However this "time-to-equipoise" for SK was an extrapolation from the meta-regression curve. Thus the validity of this extrapolation remains to be proven. In an aggregate of studies using SK and tPA, Betriu *et al.* reported that time-to-equipoise of PPCI-related delay was 110 minutes [120]. This PPCI-related delay is intermediate between

that observed with tPA (62 minutes) and estimated with SK (170 minutes) in the meta-regression by Nallamothu *et al.* (2004) [128].

However, the PPCI-related delays used in the above meta-regressions are the means of the delays as measured in each RCT. These values do not necessarily correspond to the delays experienced by individual patients and hospitals. This may result in an ecological fallacy. This bias occurs with inaccurate inferences on individual characteristics are based on correlations of group-level characteristics [198].

Using individual patients and hospital data, Boersma *et al.* showed the lowest 30-day mortality at 2.8% with PPCI-related delay of less than 35 minutes that increased to 6.6% when delays exceeded 80 minutes [121]. The greatest mortality difference between the two treatments was observed for PPCI-related delays of less than 35 minutes (2.8% for PPCI vs 8.2% for FL). However, there was no data for PPCI-related delays exceeding 120 minutes in RCTs, resulting in a limited range of PPCI-related delays in the RCTs.

Tarantini *et al*. (2004) studied the impact of presentation delays on PPCI-related delays. With exclusive inclusion of RCT enrolling patients within six hours of symptom onset, the mean time-to-equipoise of PPCI-related delay was 57 minutes [204]. In patients presenting within 12 hours of symptom onset, the authors did not find any PPCI-related delay when FL may be equivalent to PPCI. This meta-analysis suggested that for patients with later presentation, PPCI might be preferred regardless of PCI-related delay. However, the validity of this study was potentially limited by its absence of interaction analysis and adjustment for patients and study-characteristics.

The only data concerning PPCI-related delays in unselected patients in clinical settings is provided by Pinto *et al.* (2006) [199]. In contrast to Boersma *et al*. (2006), PPCI-related delays exceeded 120 minutes for many patients in a "real-world" context. [121, 199]. These investigators reported mean time-to-equipoise for PPCI-related delay of 114 minutes for the overall cohort of 192,509 STEMI patients. More detailed analysis adjusting for patient's characteristics and presentation delays showed that the PPCI-related delay time-to-equipoise was highly dependent on STEMI type, patient's age, and presentation delay. Time-to-equipoise for PPCI-related delay increased when presentation delay exceeded three hours, in patients older than 65 years and in non-anterior STEMI. Pinto *et al.* showed that the time-to-equipoise for PPCI-related delay may be as short as 40 minutes for patients <65 years with anterior STEMI to 3 hours in patients ≥65 years with a presentation delay greater than 2 hours and a non-anterior myocardial infarction [199].

In summary, mortality increases with prolonged PPCI-related delays. The relationship between the relative efficacy of the reperfusion therapies and PPCI-related delay is complex and cannot be entirely clarified by this review. A single « time-to-equipoise for PPCI-related delay» may not be valid for all patients. For each patient, the PPCI-related delay varies according to the type of STEMI and presentation delay.

CONCLUSIONS ON THE IMPACTS OF PRESENTATION DELAY AND PPCI-RELATED DELAY ON THE EFFICACY OF REPERFUSION THERAPY

- Mortality increases with increased PCI-related delays.
- The relative relationship between the relative efficacy of the reperfusion therapies and PCI-related delay is complex and cannot be entirely clarified by this review.
- A single « time-to-equipoise for PPCI and fibrinolysis» may not be valid for all patients.
- For each patient, the PPCI-related delay varies according to the type of STEMI and presentation delay.

8 META-ANALYSES AND META-REGRESSIONS

Detailed analysis and discussion of previous published systematic reviews are provided in chapter 5. In this chapter 8, our meta-analyses and meta-regressions are presented and discussed.

8.1 META-ANALYSES AND META-REGRESSIONS OF THE RANDOMIZED CONTROLLED TRIALS

8.1.1 Meta-analyses of efficacy and safety outcomes

Rationale for the present meta-analysis of RCT

The present meta-analyses of RCT differ from pre-existing publications in several ways. These meta-analyses are the most up-to-date since they incorporate four new RCTs [72, 91-93]. Previous meta-analyses were restricted to RCTs and the majority did not have 6-month data and did not identify biases nor discuss the impacts of these biases. Previous meta-analyses also did not consider important differences in study and patient-related characteristics that may modify the treatment effect. All except one meta-analysis used either fixed or random-effects non-Bayesian analyses that may not take into account the inter-and intra-study variations. In view of the above deficiencies of the previous meta-analyses, we undertook our own meta-analyses.

Sensitivity analysis and meta-regression are completed to evaluate the impact of trial quality, concomitant therapy and inter-hospital transfer on the treatment effect. Details of the RCTs included in each meta-analysis are presented in appendices C to G and L.

The results of the meta-analyses are presented in Tables 4 and 5. The efficacy outcomes are shown in Table 4 and the safety outcomes are presented in Table 5. The results in Table 4 are divided into three parts: short-term (≤6 weeks), long-term (≥ 6 months), and with/without inter-hospital transfers.

PPCI is associated with short-term mortality and reinfarction reductions. In the meta-analysis of all RCTs, PPCI reduces relative short-term mortality by 33% (95% CrI: 0.54-0.82). PPCI is associated with 25% relative mortality reduction in the meta-analysis of studies using tPA and its derivatives (95% credible intervals: 0.57-0.995). For meta-analysis limited to studies with SK, the relative mortality reduction is more remarkable at 45% with PPCI (95% CrI: 0.34-0.83). PPCI is associated with mortality reduction in the meta-analyses of RCTs using glycoprotein IIb/IIIa inhibitors (more recent studies) and RCTs with in-hospital randomization. Absolute mortality reductions with PPCI range from 1 to 2 percentage points.

As shown in Table 6, meta-regression demonstrated that the presence of a BEPC modifies the magnitude of the reinfarction reduction with PPCI. Hence, the estimates from trials with a BEPC are more likely to be representative of the true treatment difference (absolute risk difference of -2.3 percentage points [CrI 95% (-2.8 to -1.6)].

PPCI is associated with long-term re-infarction reduction. Meta-analysis of long-term mortality (1 year or more) is inconclusive for a long-term mortality difference between PPCI and FL.

Short-term mortality and reinfarction are reduced with PPCI. These reductions are more pronounced with exclusion of the CAPTIM study. As shown in Table 6, there is an interaction between short-term reinfarction and whether the transfer trials had a BEPC. Although this interaction was not significant, the estimate is similar to the one obtained for short-term reinfarction of all trials.

The safety outcomes considered are stroke and major bleeding excluding hemorrhagic stroke (Table 5). FL is associated with one absolute percentage point excess strokes. This excess risk is constant across the different sensitivity analyses. There is no conclusive increased bleeding risk with PPCI.

Table 4a. Bayesian meta-analyses of the short and long-term mortality outcomes for RCTs

Trials included	Number of trials	Number of patients	Odds ratios[24] (95% CrI)	Risk differences [percentage point (95% CrI)]	Numbers needed to treat (95% CrI)
Short-term mortality					
ALL STUDIES[25]	25	8,263	0.67 (0.54-0.82)	-2.0 (-2.8 to -1.1)	51 (36 to 93)
Mortality, trials with accelerated tPA or 3rd generation fibrin-specific agents)[26]	14	5359	0.76 (0.57-0.995)	-1.4 (-2.6 to -0.03)	69 (39 to 3333)
Mortality, trials with streptokinase	8	2086	0.53 (0.34-0.83)	-2.8 (-4.0 to -1.0)	35 (25 to 98)
Mortality, trials with optimal randomisation and minimal imbalances of baseline patients characteristics	4	2978	0.83 (0.55-1.33)	NA	NA
Mortality trials without prehospital randomization	22	6835	0.64 (0.51-0.79)	-2.2 (-2.9 to -1.3)	46 (34 to 79)
Mortality trials with prehospital randomization	3	1245	0.85 (0.16-2.64)	NA	NA
Mortality, trials with more than 5% use of glycoprotein IIb/IIIa inhibitors	11	4793	0.72 (0.53-0.95)	-1.7 (-2.8 to -0.3)	60 (35 to 333)
Mortality, trials with inter-hospital transfer[27]	8	3695	0.70 (0.50-0.96)	-1.8 (-3.0 to -0.2)	56 (33 to 417)
Mortality, trials with inter-hospital transfer[28]	7	2855	0.63 (0.44-0.87)	-2.2 (-3.4 to -0.8)	45 (30 to 128)
Long-term mortality					
Six-month mortality	9	2691	0.71 (0.46-1.06)	NA	NA
Mortality at ≥1 year	10	3,447	0.77 (0.55-1.03)	NA	NA
Mortality at ≥1 year,(only trials with accelerated tPA	4	1835	0.84 (0.38-1.57)	NA	NA

24 A risk ratio less than 1 favours PPCI whereas a risk ratio greater than 1 favours FL.
25 Assuming a mortality risk of 6% for FL.
CrI: Credible intervals, NA: Non applicable values; analyses are not done in instances with no differences of effectiveness between the two reperfusion strategies
26 WEST, SWEDES and HIS used tenecteplase and reteplase in the fibrinolytic arm; since these agents are presumed to be as effective as accelerated tPA, trials with these agents are included in the accelerated tPA group of studies.
27 Assuming a mortality risk of 6% for FL
28 Excluding CAPTIM which included only patinents with prehospital transfer

Table 4b. Bayesian meta-analyses of the short and long-term reinfarction for RCTs

Trials included	Number of trials	Number of patients	Odds ratios[29] (95% CrI)	Risk differences [percentage point (95% CrI)]	Numbers needed to treat (95% CrI)
Short-term reinfarction					
ALL STUDIES[30]	21	6672	0.32 (0.19-0.44)	-2.7 (-3.2 to -2.3)	38 (31 to 44)
Reinfarction, trials with a BEPC	10	4729	0.43 (0.29-0.61)	-2.3 (-2.8 to -1.6)	44 (35 to 64)
Reinfarction, trials with an absence of BEPC/unknown status of BEPC	12	2199	0.17 (0.09-0.32)	-3.3 (-3.6 to -2.7)	30 (27 to 37)
Reinfarction, trials with transfer	7	2847	0.26 (0.13-0.47)	-3.0 (-3.5 to -2.1)	34 (29 to 47)
Reinfarction trials with transfer and BEPC	4	2154	0.37 (0.11-1.87)	NA	NA
Long-term reinfarction					
6-month reinfarction	5	1832	0.48 (0.12-1.06)	NA	NA
Reinfarction at ≥1-year	7	3220	0.58 (0.42-0.78)	NA	NA

BEPC: Blinded Endpoint Committee

29 A risk ratio less than 1 favours PPCI whereas a risk ratio greater than 1 favours FL.

30 Assuming a mortality risk of 6% for FL.

CrI: Credible intervals, NA: Non applicable values; analyses are not done in instances with no difference in treatment effect.

Table 5. Bayesian meta-analyses of RCTs comparing the safety of PPCI and FL

Studies included	Number of studies	Number of patients	Odds ratios[31] (95% CrI)	Risk differences[32,33] [percentage point (95% CrI)]	Number needed to treat (95% CrI)
Strokes					
ALL STUDIES	22	6928	0.41 (0.26-0.66)	-1.2 (-1.5 to -0.7)	85 (68 to 147)
Trials with accelerated tPA	12	5057	0.48 (0.27-0.83)	-1.0 (-1.5 to -0.3)	96 (68 to 294)
Trials with SK	7	1236	0.45 (0.14-1.27)	NA	NA
Trials with BEPC	10	4729	0.44 (0.22-0.77)	-1.1 (-1.6 to -0.5)	89 (64 to 217)
Major bleeds (excluding intracranial haemorrhage)					
ALL STUDIES	16	4465	1.22 (0.69-1.76)	NA	NA
Trials with accelerated tPA	10	3129	1.35 (0.73-2.30)	NA	NA
Trials with GIIb/IIIa	6	1731	1.45 (0.44-4.43)	NA	NA
Trials with SK	5	939	0.64 (0.10-2.15)	NA	NA
Trials with a BEPC	6	2566	1.56 (0.61-5.71)	NA	NA

31 An odds ratio less than 1 favours PPCI and an odds ratio greater than 1 favours FL.
32 Assuming a stroke risk of 2% for FL
33 Assuming a major bleeding risk of 5% for FL

Table 6. Short-term results for the multivariate meta-regressions

Reinfarction and the presence of a BEPC	**Relative risk ratios[34] (95% CI)**
Short-term reinfarction (22 RCTs)	
Presence of a BEPC	Reference
Absence of a BEPC or unknown BEPC status	0.44 (0.23-0.83)
Reinfarction transfer RCTs (7 RCTs)	
Presence of a BEPC	Reference
Absence of a BEPC or unknown BEPC status	0.38 (0.12 -1.26)

8.1.2 Interpretation

The results of section 8.1.1 show short and long term reductions in mortality, reinfarction and strokes with PPCI, when compared with FL. PPCI is associated with 1 to 3 percentage points short and long-term mortality reductions. These risk differences are similar for RCTs with inter-hospital transfers. There is no effect modification by randomisation process (by envelope or through a central telephone service) on total mortality (data not shown).

PPCI is associated with short and long-term reinfarction reductions. There is effect modification of PPCI by the presence of a BEPC (table 6). Therefore, reinfarction reductions obtained in the absence of a BEPC should be considered as potentially unreliable. Hence, the absolute risk reduction of 1.6 to 2.8 percentage points for PPCI, as derived from RCTs with BEPC, are more likely to be valid than the results of RCTs without BEPC.

For safety outcomes, when compared with FL, PPCI is associated with an absolute stroke reduction from 0.7 to 1.5 percentage points. The risk estimates are inconclusive for bleeding events. The wide credible intervals for the estimates of the bleeding events may be due to heterogeneity of the definitions of major bleeds, type of FL and concomitant anti-platelets and anti-coagulants.

All of the above results should be interpreted with caution. Most of these RCTs had long door-to-needle times and relatively short door-to-balloon times. Increased ischemic time may have decreased FL's efficacy [200]. Hospitals that participate in these RCTs generally had protocols to ensure expedient PPCI. Thus, these results may over-estimate the true difference between the two treatments, because of the potential bias against FL due to the relatively long door-to-needle times.

Since prehospital randomisation might decrease the total ischemic times for both treatment arms, one may expect that the PPCI-survival benefit may also decrease with prehospital randomization. This was indeed observed in the meta-analysis including only RCTs with pre-hospital randomization (table 4). However, the lack of benefit of PPCI in this sensitivity analysis may also due to the lack of power secondary to smaller sample size of studies.

34 An odds ratio smaller than one favours the primary PCI arm whereas odds ratio greater than one favours fibrinolysis.

Most RCTs enrolled patients of all categories of STEMI mortality risk. Therefore, the results of these meta-analyses should apply to all patients regardless of their mortality risk. However subgroups analyses of high-risk patients in a few RCTs suggest that high-risk patients might benefit more from PPCI than low risk patients. A meta-analysis of individual patient data stratified according to STEMI mortality risk may clarify further this question.

In the RCTs with inter-hospital transfer, there is a large absolute short-term mortality difference between the two treatments [RD = -3.4 percentage points 95% CrI (-2.2 to -0.7)]. However, this large risk difference may not be solely attributable to treatment effects. Indeed, this risk difference may have been confounded by the differences in the quality of adjuvant medical care, since patients in the FL arm were generally treated at community hospital and patients in the PPCI arm were treated at tertiary centers. This hypothesis is supported by the high mortality rates in the FL arm treated in Eastern Europe [87, 88, 93]. In most of these trials, inter-hospital transfer was rapid while door-to-needle times were suboptimal. This may limit the external validity of the results obtained from RCTs with interhospital transfer.

IN BRIEF

- The absolute short-term mortality risk reduction associated with PPCI in RCTs ranges from 1 to 3 percentage points.
    - This may be an over-estimate of the true mortality difference between the two treatments, because of the potential bias against FL due to the relatively long door-to-needle times in the reviewed RCTs.
- For interhospital transfer RCTs, the short-term mortality reductions with PPCI ranges from 1 to 3 percentage points.
    - This may be an over-estimate of the true mortality difference between the two treatments, due to the relatively long door-to-needle and short door-to-balloon times in the RCTs. This result might also be confounded by potential differential quality of the adjuvant medical care provided to the two treatment groups.
- The absolute risk reduction in short-term reinfarction associated with PPCI ranges from 1.6 to 2.8 percentage points.
- The absolute risk reduction in short term stroke associated with PPCI ranges from 0.7% and 1.5 percentage points.
- There is no conclusive major bleeding difference between PPCI and FL.
- There is no conclusive long-term mortality difference between PPCI and FL.

8.2 META-ANALYSES OF THE OBSERVATIONAL STUDIES

Results of the meta-analyses of effectiveness and safety of PPCI and FL in observational studies are presented in Tables 7 and 8. We combined all short-term (in-hospital or 30-day) and long-term mortality, re-infarction, stroke, and major bleed. Most studies reported one-year data except for two with 6-month results [156, 171] and two studies with 3-year results [152, 174].

We completed multiple sensitivity analyses with restriction to studies with predominant use of tPA (≥50%), pre-hospital FL, recent studies (enrolling patients after 1996), and exclusion of transferred-in or transferred-out patients. Sensitivity analyses restricted to studies with predominant use of tPA and pre-hospital FL were justified by a potential superior efficacy of tPA over SK and pre-hospital FL over in-hospital FL. We examined the potential impacts of selection and attrition biases by exclusion of studies with transferred-in and transferred-out patients. Finally, contemporary studies (those enrolling patients during the last decade, i.e. after 1996) might have superior external validity than the earlier studies. These recent studies with greater use of glycoprotein inhibitors, thienopyridines, and stents provided results more applicable to patients with STEMI in 2007.

Subgroup analyses such as elderly, high-risk patients and those with a presentation delay ≤6 hours were completed to examine the treatment effects in these patients. Although subgroup analyses of females, and patients in cardiogenic shock are of interest, there was insufficient data for separate analyses for these patients. Sensitivity analysis of studies with optimal treatment delays would also be ideal to determine the effectiveness of reperfusion strategy performed within ideal conditions. However, there were only three studies that specify median times door-to-reperfusion therapy within recommended delays (door-to-needle ≤30 min and door-to-balloon ≤90 min). Meta-analysis of only these three studies would provide unreliable risk estimate, in view of the small sample sizes of patients and trials.

Data was the most complete for short-term mortality. We did not have sufficient data of long-term mortality for the elderly and high-risk patients to complete the analyses for these subgroups. For reinfarction, we only had sufficient data for studies with minimal attrition bias and recent studies to perform the necessary sensitivity analyses.

Data concerning strokes were reported in 20 observational studies. Sensitivity analyses were performed for recent studies, studies excluding transferred-in and transferred-out patients. We also completed subgroup analyses for studies with predominant use of tPA, patients ≥65 years and patients with high-risk features. Data concerning major bleeds were available in 9 studies. The same sensitivity analyses, as specified above, were completed for subgroups of interests.

PPCI is associated with a short-term relative mortality reduction of 20% and absolute risk difference of 1 percentage point in most of the sensitivity analyses. This relative risk reduction is the most remarkable at 25% in the meta-analysis of the more recent studies (OR: 0.74, 95% CrI: 0.60-0.92). Results from meta-analyses of studies with pre-hospital FL and exclusion of transferred-out patients have wide credible intervals suggesting some uncertainties about their risk estimates. Sensitivity analyses of studies with exclusion of transferred-in patients and predominant use of tPA also have credible intervals that include a potential 17% relative benefit with tPA. Thus, the short-term mortality reduction with PPCI is most certain, when performed in contemporary settings, or when compared to SK or in-hospital FL.

All of the risk estimates of long-term mortality and reinfarction have relatively wide credible intervals that included unity. The risk ratios in this section are conflicting with odds ratios in favour of PPCI in recent studies and studies with exclusion of transferred-in patients, while these risk estimates are in favour of FL when restricted to studies with predominant use of tPA and pre-hospital FL. This suggests uncertainty of a long-term mortality and reinfarction difference between the two reperfusion strategies.

PPCI is associated with relative short-term reinfarction reduction of about 40%. PPCI is associated with a 50% relative stroke reduction. There is remarkable heterogeneity of the risk estimates for major bleeds. However, most of the risk estimates indicate increased bleeding risk with FL. The marked variation in these risk estimates likely reflects the inconsistent detection and ascertainment of major bleeds in these trials.

8.2.1 Conclusion of the meta-analyses of the observational studies

The aggregate data from the reviewed observational trials suggest a 20% relative short-term mortality reduction with PPCI. Other short-term benefits with PPCI include reinfarctions and strokes relative reductions of 40% and 50%, respectively. The absolute short-term reductions in mortality, reinfarction and stroke are 1, 2 and 1 percentage points, respectively. There was no conclusive evidence for a long-term mortality and reinfarction difference between PPCI and FL from the aggreagate results of the observational studies.

IN BRIEF

- PPCI reduces short-term mortality by 20% (absolute difference 1 percentage point) compared to FL. The mortality benefit is the most remarkable when compared to SK, in-hospital FL and in contemporary studies (completed since 1996).
- PPCI reduces short-and long-term reinfarction by 40% compared to FL. For short-term reinfarction the absolute difference was 2 percentage points.
- PPCI reduces short-term stroke by 50% compared to FL (absolute difference 1 percentage point).
- There is no conclusive long-term mortality difference between PPCI and FL.

Table 7a. Bayesian meta-analyses comparing comparing mortality between PPCI and FL in observational studies

Studies included	Number of studies	Number of patients	Odds ratios[35] (95% CrI)	Risk differences [percentage point (95% CrI)]	Numbers needed to treat (95% CrI)
Short-term mortality					
ALL STUDIES[36]	31	132,020	0.79 (0.67-0.95)	-1.2 (-1.9 TO –0.3)	83 (54 TO 333)
Predominant use of tPA and its derivatives (≥50%)	10	52,949	0.82 (0.60-1.17)	NA	NA
Pre-hospital FL	3	11,094	0.91 (0.25-4.98)	NA	NA
Patients ≥65 years old	10	20,837	0.78 (0.65-0.96)	-1.3 (-2.1 to -0.2)	76 (48 to 417)
Presentation delay <6 hours	9	41,976	0.79 (0.61-1.07)	NA	---
Recent studies (enrolling patients after 1996)	22	114,577	0.73 (0.62-0.89)	-1.6 (-2.4 to –0.5)	64 (42 to 208)
High-risk patients	10	26,866	0.84 (0.63-1.09)	NA	NA
Specified exclusion of transferred-in patients	11	124,725	0.83 (0.62-1.13)	NA	NA
Studies without transferred-out patients	7	97,061	0.84 (0.52-1.46)	NA	NA
Long-term mortality (≥1 year)					
ALL STUDIES	11	47,382	0.88 (0.60-1.21)	NA	NA
Predominant use of tPA and its derivatives (≥50%)	6	24,545	1.00 (0.74-1.62)	NA	NA
Studies with pre-hospital FL	3	11,094	1.19 (0.53-5.78)	NA	NA
Presentation delay < 6 hours	6	3,965	0.95 (0.53-1.81)	NA	NA
Recent studies (enrolling patients after 1996)	9	35,389	0.80 (0.62-1.06)	NA	NA
Specified exclusion of transferred-in patients	8	40,667	0.76 (0.49-1.22)	NA	NA
Studies with minimal attrition bias (≤6% loss to follow-up specified or use of administrative databases)	8	40,651	1.11 (0.65-2.01)	NA	NA
Recent studies with minimal attrition bias	5	29,802	0.91 (0.36-2.56)	NA	NA

35 A risk ratio less than 1 favours PPCI whereas a risk ratio greater than 1 favours FL.
36 Assuming a mortality risk of 6% for FL.
CrI: Credible intervals, NA: Non applicable values; analyses are not done in instances with no difference in treatment effect

Table 7b. Bayesian meta-analyses comparing reinfarction between PPCI and FL in observational studies

Short-term reinfarction

Studies included	Number of studies	Number of patients	Risk ratios[37] (95% CrI)	Risk differences[38] [percentage point (95% CrI)]	Number needed to treat (95% CrI)
All studies	14	45,294	0.56 (0.41-0.79)	-1.8 (-2.4 to -0.8)	57 (42 to 119)
Studies with minimal attrition bias (no transferred-out patients)	7	27,414	0.78 (0.65–0.94)	-0.9 (-1.4 to -0.2)	114 (71 to 417)
Recent studies (enrolling patients after 1996)	10	41,513	0.51 (0.36-0.77)	-2.0 (-2.6 to -0.9)	51 (39 to 109)

Long-term reinfarction (≥1 year)

All studies	5	32,413	0.57 (0.40-0.92)	NA	NA
Studies with minimal attrition bias (≤6% loss to follow-up specified)	3	26,725	0.56 (0.25-2.31)	NA	NA
Recent studies (enrolling patients after 1996)	5	31,296	0.79 (0.22-2.41)	NA	NA

37 A risk ratio less than 1 favours PPCI whereas a risk ratio greater than 1 favours FL.
38 Assuming a reinfarction risk of 4% for FL.
NA: Non applicable values; analyses are not done in instances with no differences of effectiveness between the two reperfusion strategies

Table 8. Bayesian meta-analyses of observational studies comparing the safety of PPCI and FL

Studies included	Number of studies	Number of patients	Odds ratios[39] (95% CrI)	Risk differences[40,41] [percentage point (95% CrI)]	Number needed to treat (95% CrI)
Strokes					
ALL STUDIES	18	102,441	0.56 (0.41-0.79)	-0.9 (-1.2 to -0.4)	114 (85 TO 238)
Predominant use of tPA and its derivatives	9	50,028	0.57 (0.27-1.16)	NA	NA
Patients ≥65 years old	6	17,967	0.64 (0.35-1.01)	NA	NA
Recent studies (enrolling patients after 1996)	11	108,914	0.53 (0.36-0.82)	-0.9 (-1.3 to -0.1)	111(76 to 714)
Specified exclusion of transferred-in patients	6	48,166	0.48 (0.27-0.69)	-1.0 (-1.5 to -0.6)	96 (68 to 161)
High-risk patients [42]	6	20,381	0.70 (0.43-1.14)	NA	NA
Studies with minimal attrition bias (no transferred-out patients)	7	75,657	0.67 (0.36-1.06)	NA	NA
Major bleeds					
ALL STUDIES	9	61,412	0.76 (0.28-1.71)	0.61 (0.14-1.97)	NA
Exclusion of transferred-in patients	6	80,143	1.07 (0.40-2.16)	0.40 (0.04-2.58)	NA
Minimal attrition bias (no transferred-out patients)	5	63,209	0.48 (0.05-2.71)	0.67 (0.10 -2.86)	NA

39 An odds ratio less than 1 favours PPCI and an odds ratio greater than 1 favours FL.
40 Assuming a stroke risk of 2% for FL
41 Assuming a major bleeding risk of 5% for FL
42 High-risk patients: One of the following characteristic: age ≥70 years *or* anterior myocardial infarction *or* PAMI high-risk features

8.3 SUMMARY OF META-ANALYSES OF RCT AND OBSERVATIONAL STUDIES

The following forest plots represent the syntheses of the present meta-analyses of RCTs and observational studies. Figure 4 shows the short-term (in-hospital or 30-day) mortality risk estimates. PPCI is associated with 30% relative mortality reduction in RCTs and 20% relative mortality reduction in observational studies. The homogeneity of the risk estimates in the RCTs suggests a consistent benefit of PPCI in these studies. The heterogeneity of the treatment estimates in the observational studies reflects the different levels of patient's risks, the quality and timeliness of reperfusion therapy and the use of adjuvant therapies in these studies. The differences in the magnitude of the treatment effect may also reflect a combination of factors more favourable to PPCI in RCTs (patients selection, more prolonged door-to-needle and shorter door-to-balloon in these studies) and potential confounding biases with sicker patients in the PPCI group in the observational studies.

According to our sensitivity analysis, the short-term mortality benefit of PPCI remains present even with analysis restricted to studies with fibrin-specific agents (RCT: OR: 0.72, 95% CrI: 0.56-0.94), accelerated tPA and 3rd generation fibrin-specific agents (see Tables 4A and 7-A). In the observational studies, Stenestrand *et al.* (2006) have markedly divergent results from the other studies [151]. In particular, patients who received FL were older and had more high-risk characteristics. In a sensitivity analysis excluding Stenestrand *et al.* (2006), we still noted a conclusive short-term mortality reduction with PPCI (OR: 0.85, 95% CrI:0.74-0.99) .

Figure 5 shows the short-term reinfarction risk estimates. The risk estimates are consistent with short-term reinfarction reduction with PPCI for both RCT and observational studies. This benefit is the most remarkable with a 70% relative reinfarction reduction in the RCTs. Meta-analysis of RCTs without a BEPC shows a relative short-term reinfaction risk reduction of 57% while meta-analysis of RCTs without BEPC shows a smaller reinfarction reduction. This difference in treatment effect may be due to a classification bias of RCTs without BEPC. In the observational studies, PPCI is associated with relative short-term reinfarction reduction of 40%.

Figure 6 shows the long-term mortality estimates. The risk estimates for the RCTs suggest a 20% long-term relative mortality reduction with PPCI. There was marked heterogeneity of the mortality estimates in the observational studies. The 95% credible intervals include unity for both types of studies; this suggests no conclusive long-term mortality difference between the two treatments. Figure 7 shows the long-term reinfarction estimates. PPCI is associated with a 40% long-term relative reinfarction reduction in the RCTs and in the observational studies.

Estimated numbers of short-term deaths, reinfarctions, strokes prevented by PPCI of 100 patients are shown in Figures 8 (inferred from RCT) and 9 (inferred from observational studies). In the ideal clinical conditions similar to the RCT settings (timely PPCI and patients without significant co-morbidities), for every 100 patients treated with PPCI, there are two deaths, three reinfarctions and one stroke prevented (Figure 8). In the "real-life" context, when PPCI may be delayed and with patients with co-morbidities, for every 100 patients treated with PPCI, the benefits may be lower with one death, one reinfarction and one stroke prevented (Figure 9).

It is of note that these endpoints were counted as distinct events, i.e. each death, reinfarction and stroke is counted as one event. However, patients may have more than one event, i.e. fatal reinfarction or fatal stroke (up to 40% of strokes in STEMI [201]). Thus these projected numbers of events prevented by PPCI in 100 patients may over-estimate the true benefit of PPCI.

CONCLUSION OF META-ANALYSES AND META-REGRESSIONS

- PPCI is associated with a 30% short-term mortality reduction relative to FL
- PPCI is associated with a 40% short-term reinfarction reduction relative to FL
- There is no conclusive long-term mortality difference between PPCI and FL
- PPCI is associated with a 40% long-term reinfarction reduction relative to FL in RCTs, whereas there is no conclusive long-term reinfarction reduction in the observational studies.

Short-term: In-hospital up to 42-day
Long-term: At one year or more from the index STEMI

Figure 4-A : Short-term mortality in RCTs

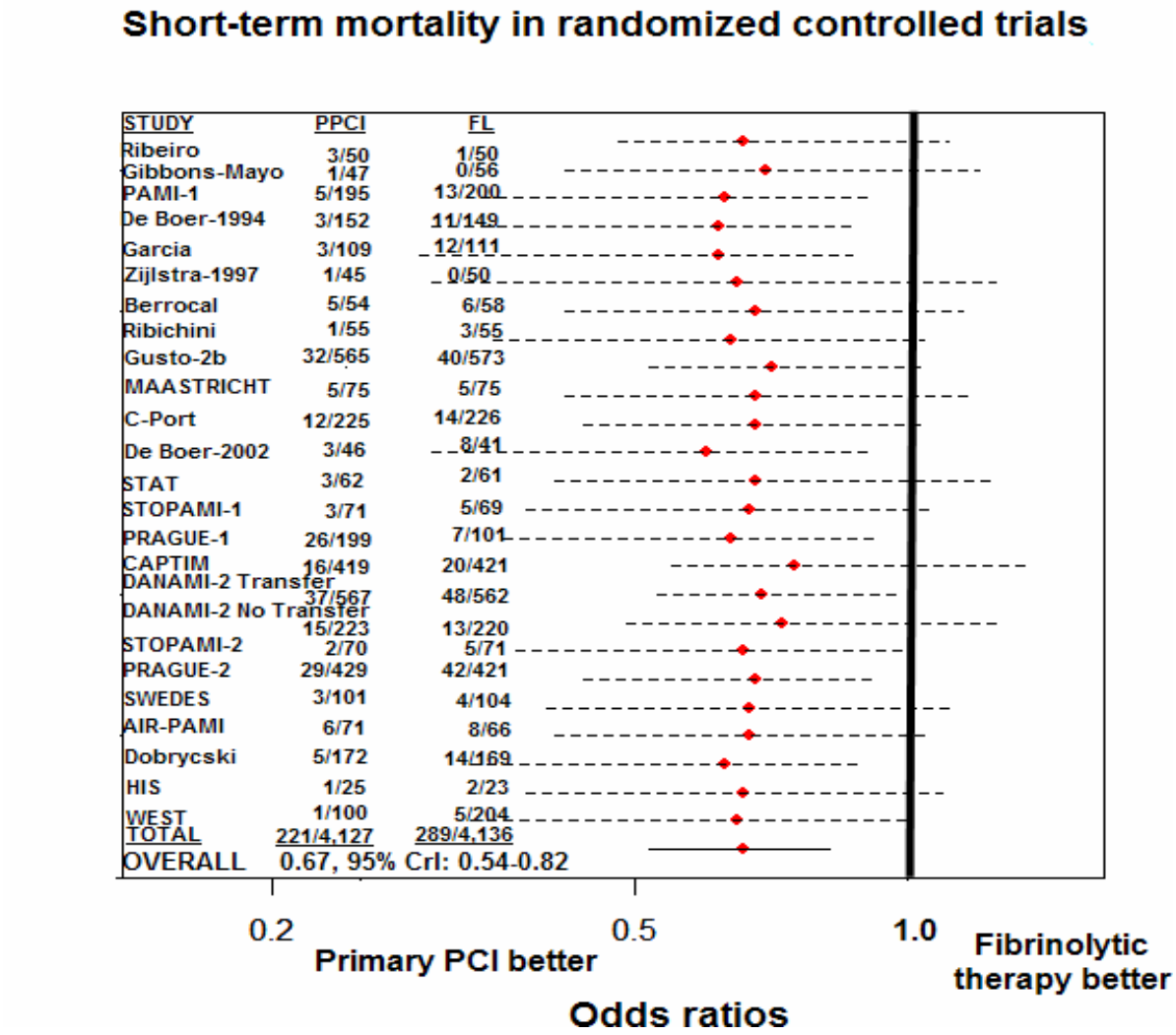


Figure 4-B. Short-term mortality in observational studies

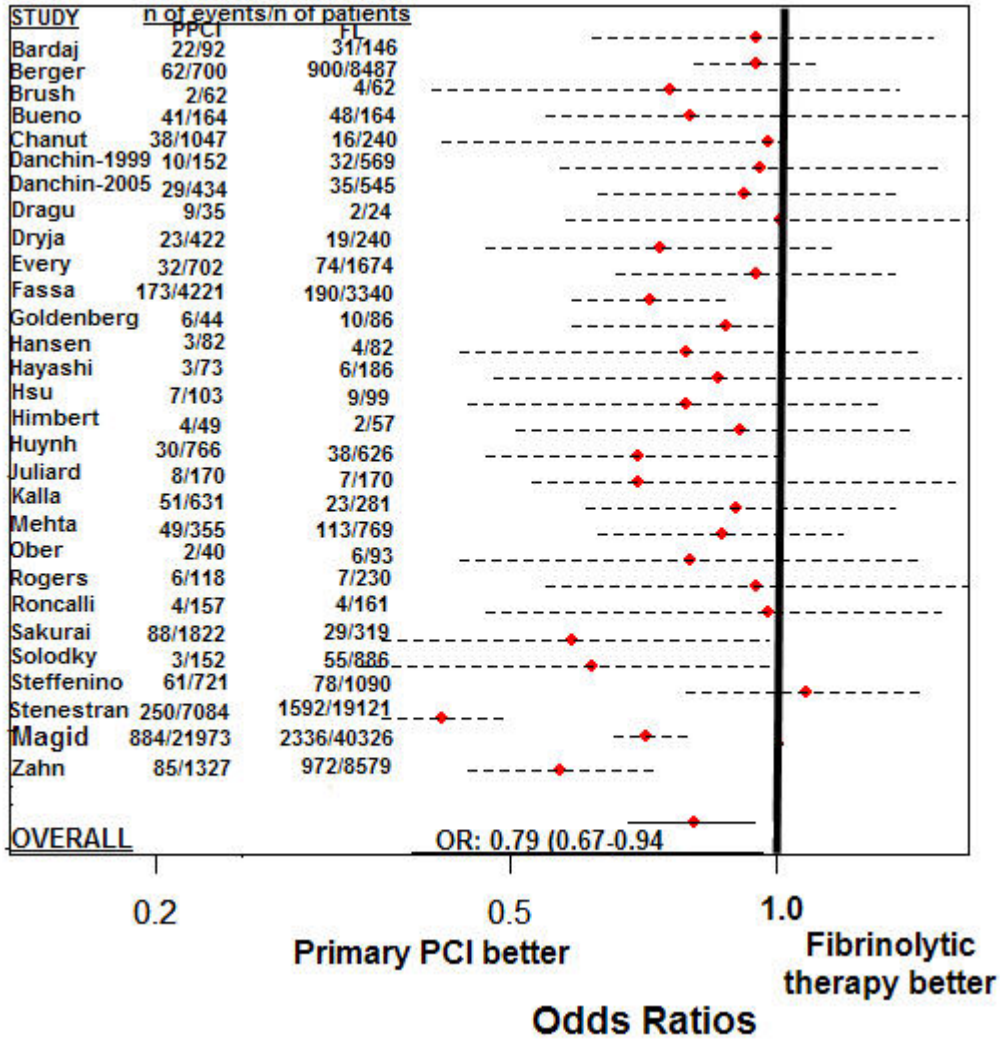


Figure 5-A : Short-term reinfarction in randomized controlled studies

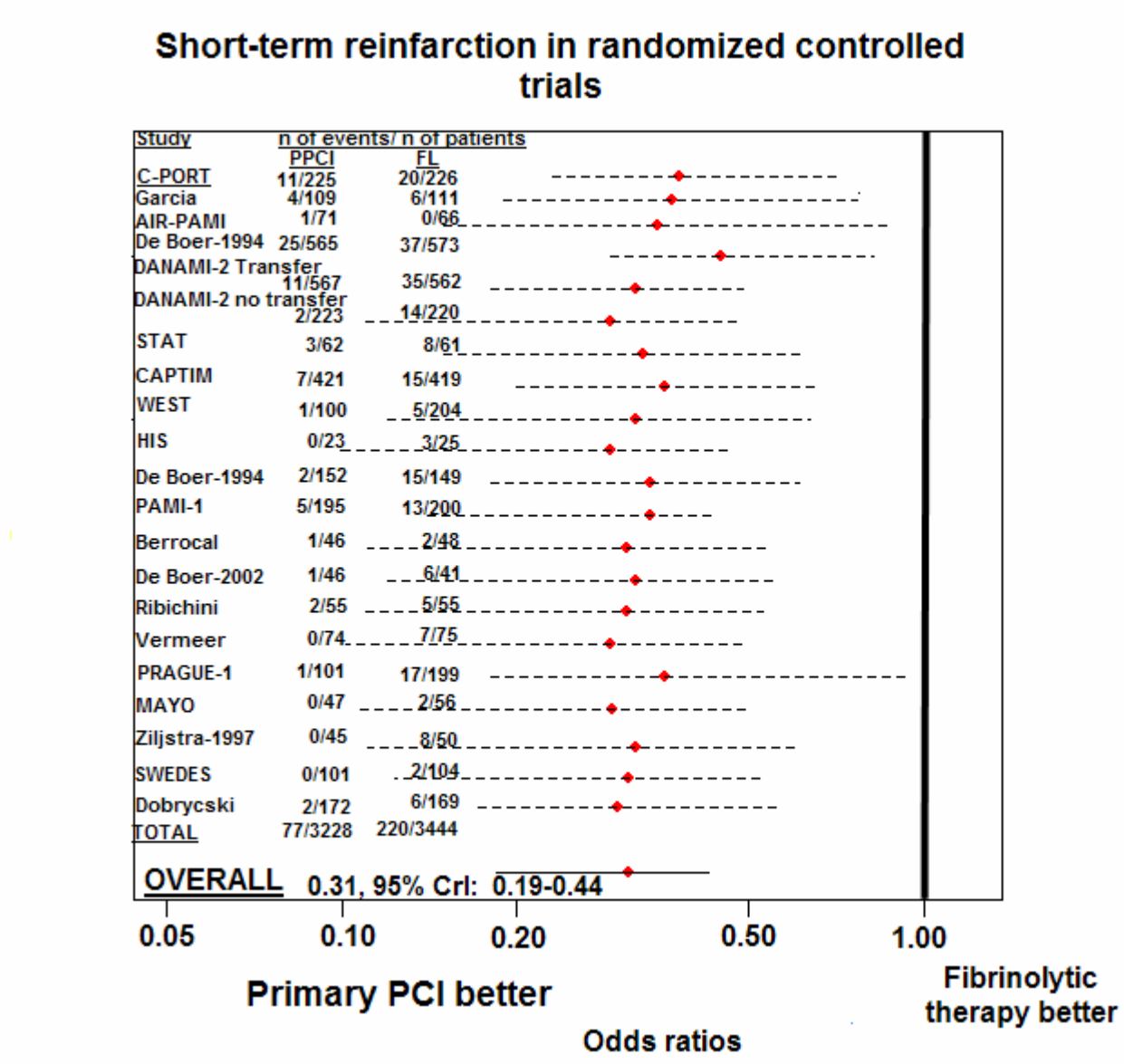


Figure 5-B : Short-term reinfarction in observational studies

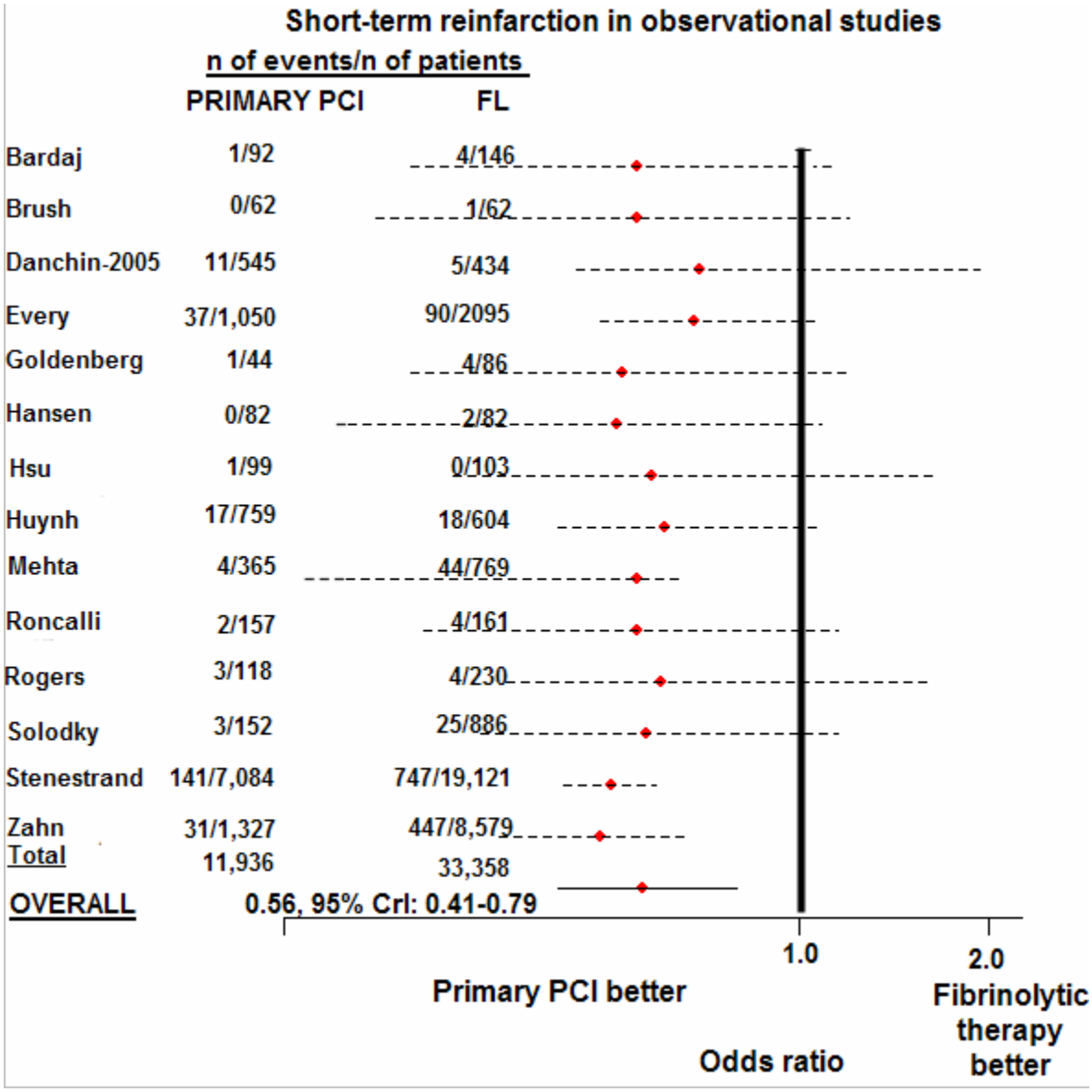


Figure 6-A. Long-term mortality in randomized controlled studies

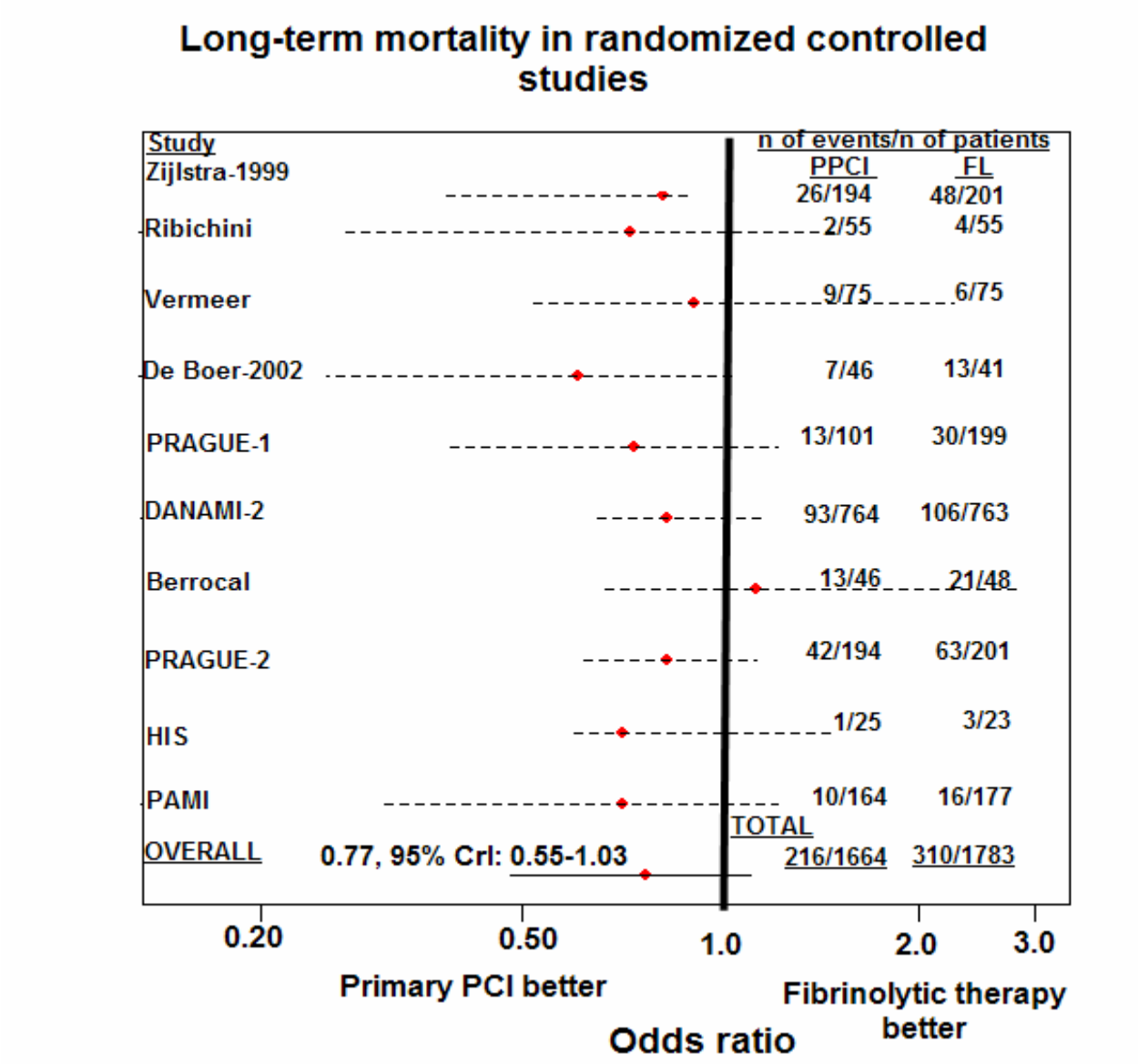


Figure 6-B. Long-term mortality of observational studies

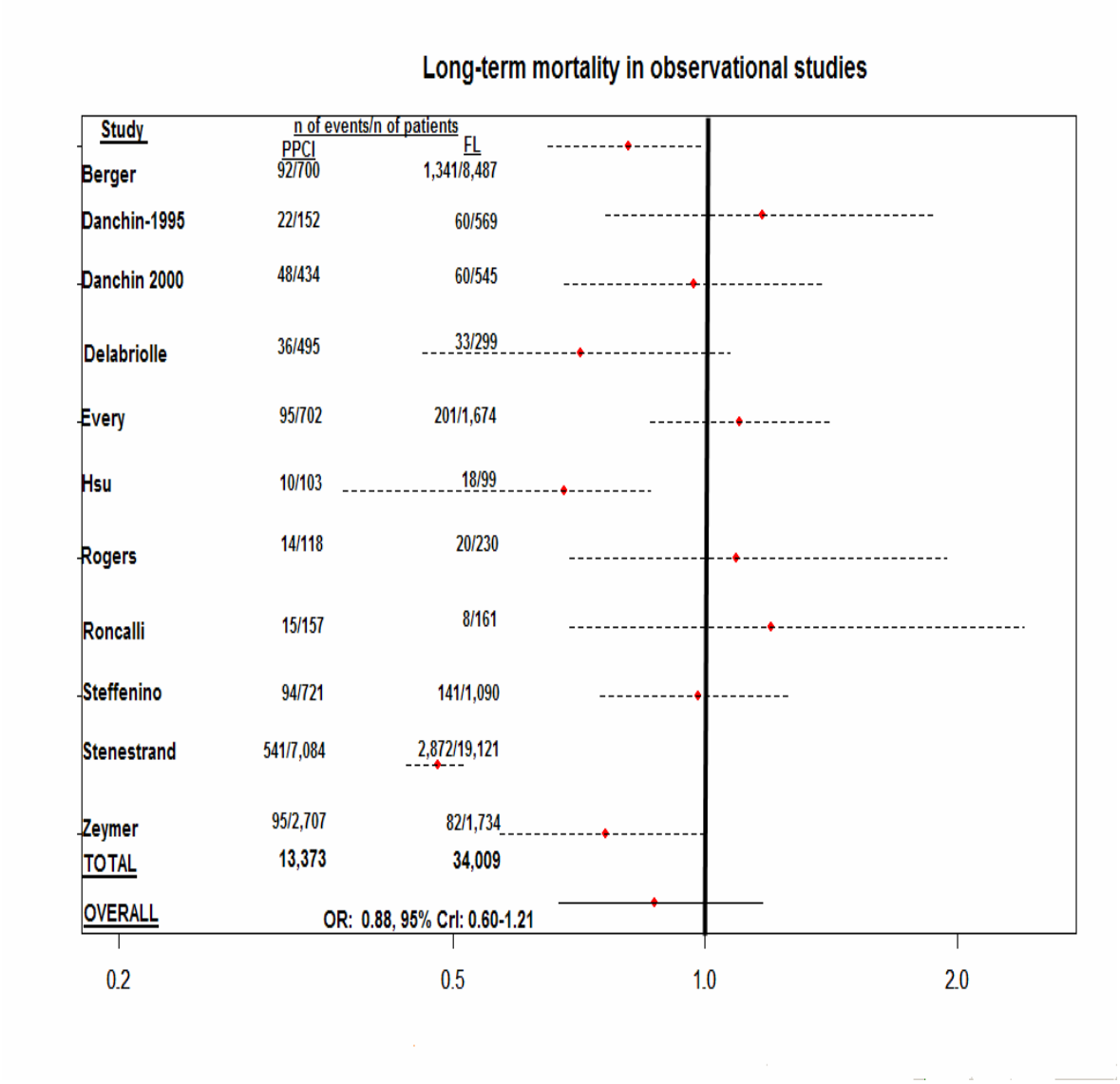


Figure 7-A. Long-term reinfarction in randomized controlled studies

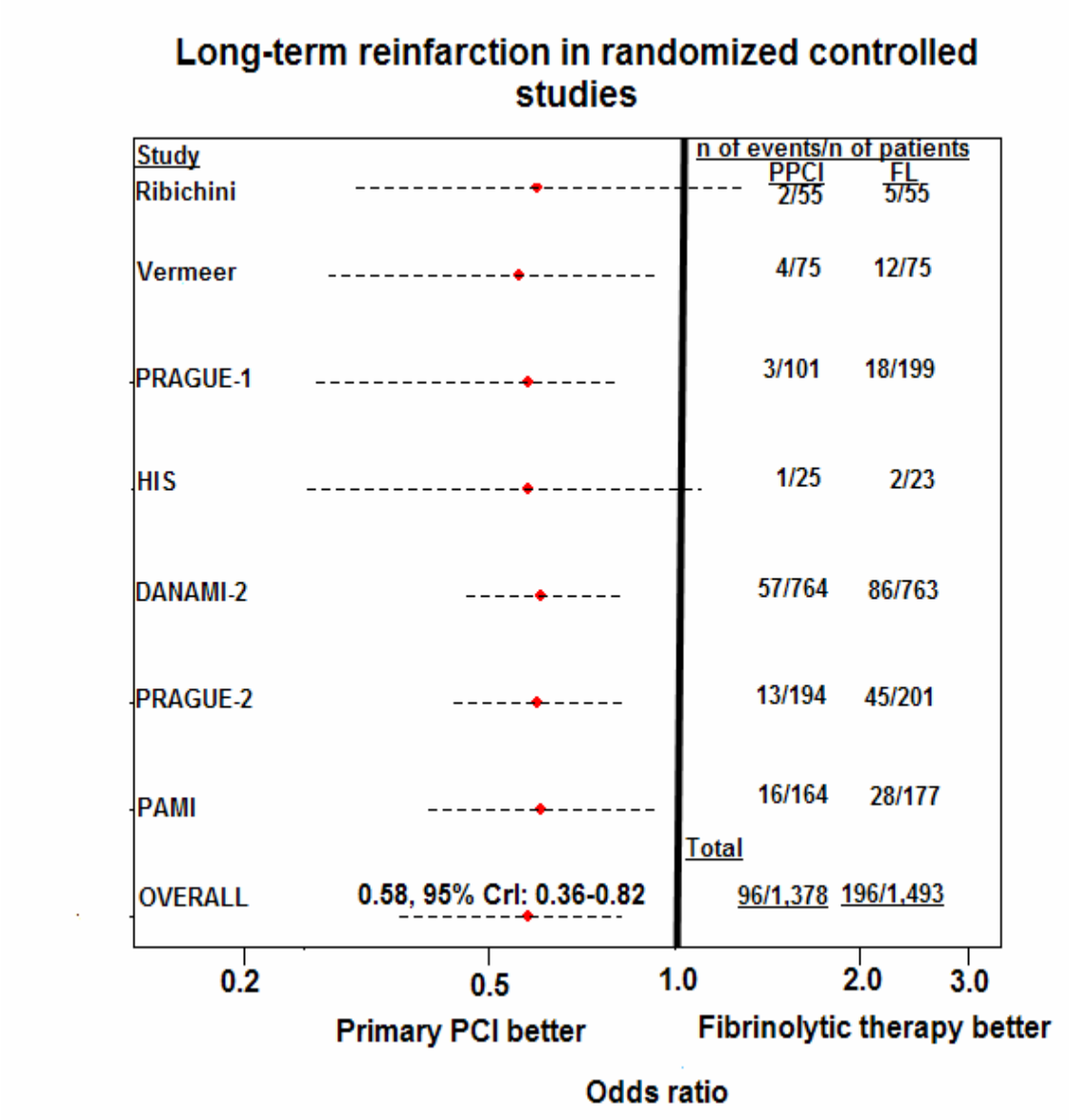


Figure 7-B. Long-term reinfarction in observational studies

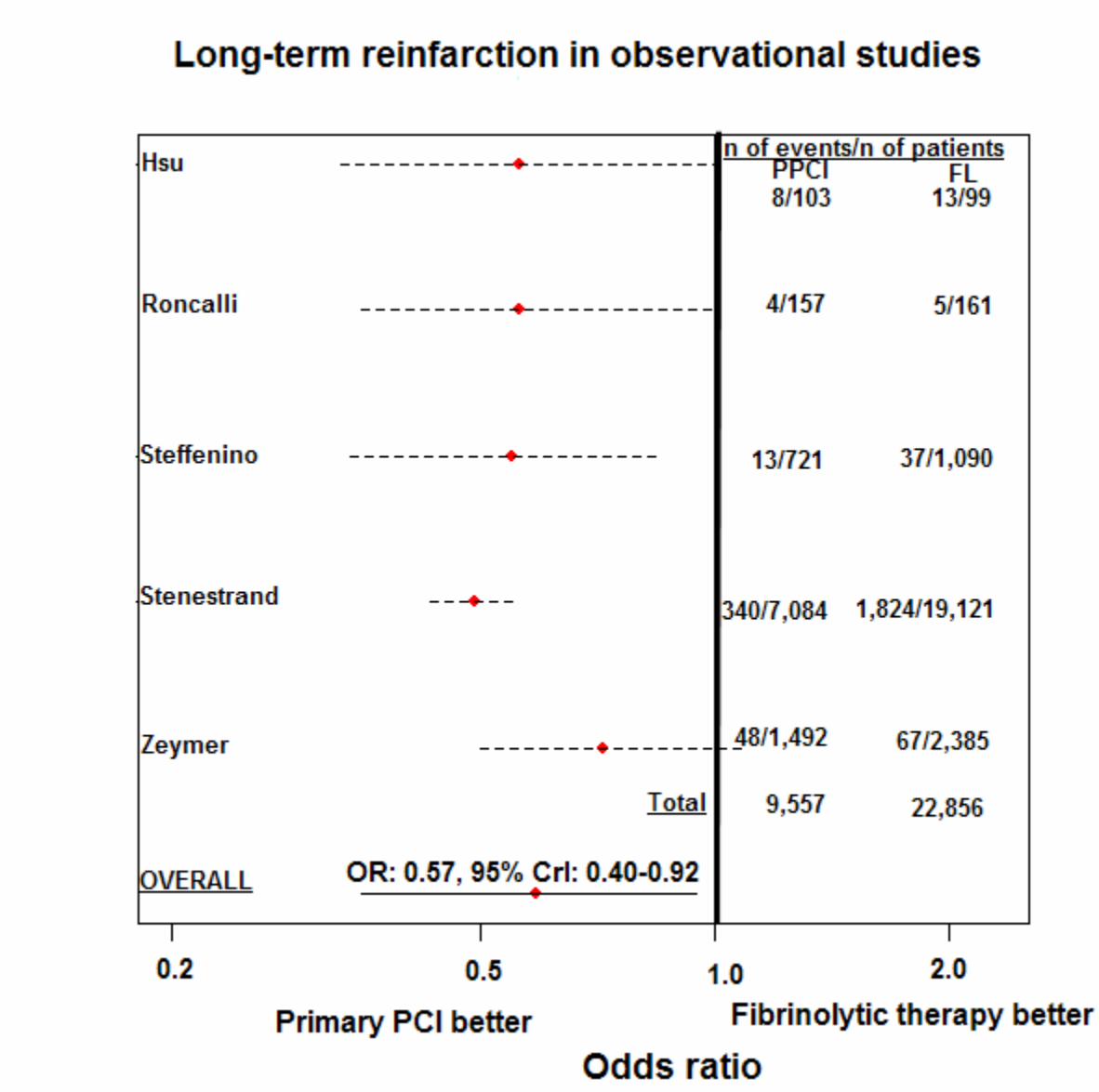


Figure 8. Estimated number of events prevented by PPCI of 100 patients (inferred from RCT's data).

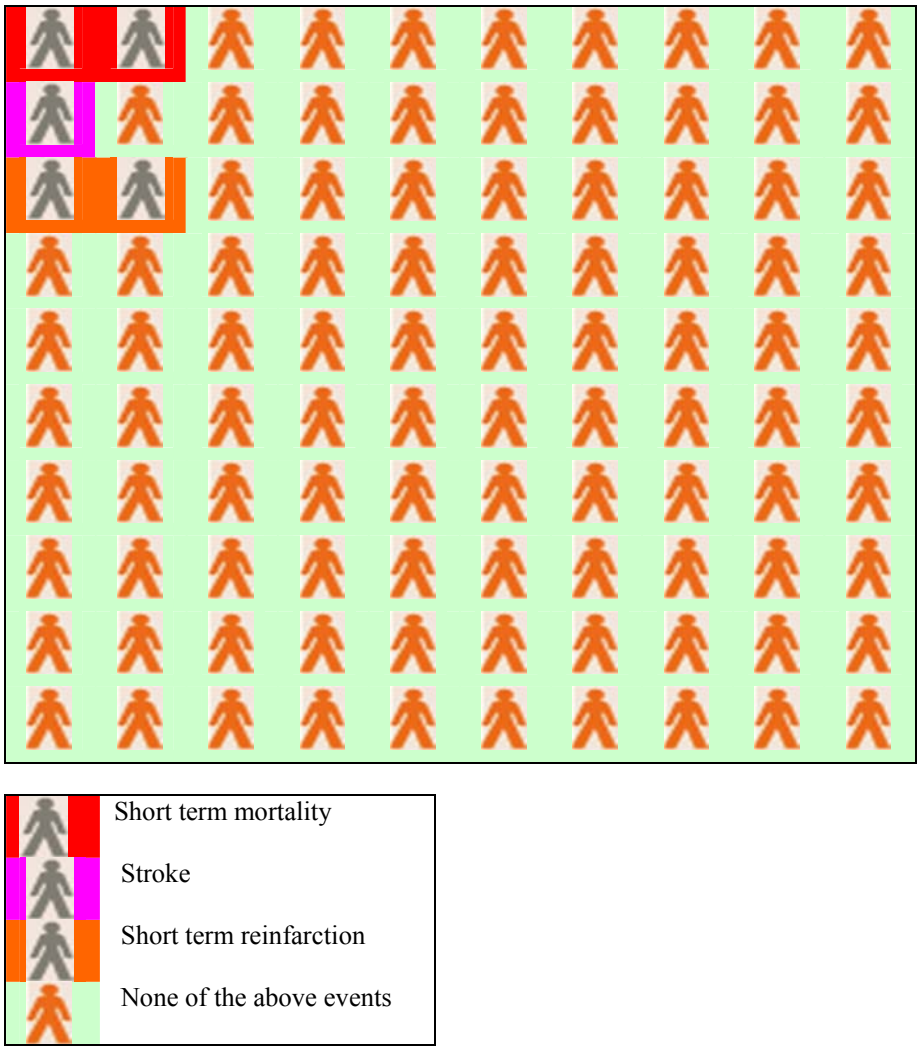
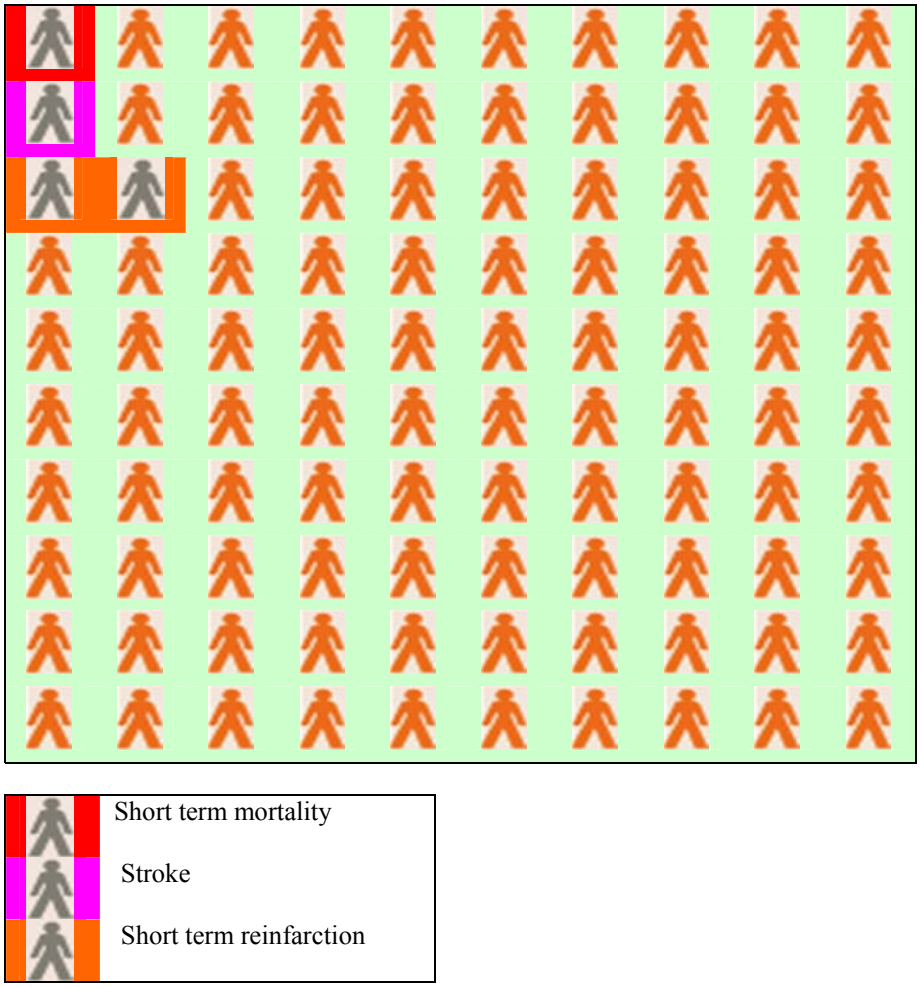


Figure 9. Estimated numbers of events prevented by PPCI of 100 patients (inferred from observational studies)



9 STRENGTHS AND LIMITATIONS OF THE PRESENT SYSTEMATIC REVIEW

9.1 STRENGTHS

This review was particularly comprehensive with inclusion of observational studies that had never been systematically evaluated. The search strategy was extended to include non-English publications, international websites of STEMI registries and health technology assessment. We contacted numerous individual authors to obtain un-published data concerning study design and pertinent results (appendix C). Two independent observers performed data abstraction and critical analyses of the majority of the studies.

Application of Bayesian meta-analysis allowed for uncertainty of all parameters in the model. This aspect was not considered in previous frequentist meta-analyses. Finally, all of AETMIS's meta-analyses were computed by three different methods (linear mixed-effects model using a restricted maximum likelihood method with SAS, der Simonian and Laird with Number Cruncher Statistical System (NCSS), and full Bayes with WinBug). The reliability of the estimates was supported by similar results from the three methods.

9.2 LIMITATIONS

9.2.1 Literature search

The literature review was extensive and thorough with searches of Pubmed, Embase, Cochrane, BIOSIS, Cinahl, Current Contents, Web of Science, Internet sites of STEMI registries, health technology assessment. We included all studies published in all languages. Most studies were published in English (three studies wer published in French [159, 171, 173]. We identified two German manuscripts that were duplicates of other English reports [15, 168]. However it was still conceivable that we may have missed some pertinent publications in other languages than English or French that were not cited in the above literature databases.

Potential publication bias should be also noted. Authors and editors were more likely to report and publish studies that showed efficacy or effectiveness differences between the comparison groups more than studies that did not show difference in treatment effect. Reports with positive findings were also more likely to be cited more frequently; thus they were more likely to be identified in this search. The lack of asymmetry in the funnel plots (appendix M) is reassuring that it was less likely that we have missed important negative trials.

We excluded studies for which we could not obtain full information on design and limitations such as abstracts or conference proceedings (SENIOR-PAMI, de Wood, NRMI-5, MACSTRAKS) because their results could not be interpreted in light of their potential biases and limitations. However large observational studies such as NRMI-5 or MACSTRAKS could have provided important insights had they been published.

9.3 BIASES OF INDIVIDUAL STUDIES

There were heterogeneities in administration methods of reperfusion therapy, the type of FL agents used, patient's characteristics, ancillary treatments, definitions/ascertainment of outcomes and durations of follow-up in both the reviewed RCTs and observational studies. Noteworthy imbalances in patients' characteristics were seen in both RCTs and observational studies. Proper randomization should have theoretically precluded selection bias in RCTs so that patient characteristics were comparable between the two treatment groups. Selection bias and confounding bias may have still existed by chance in RCTs. RCTs with suboptimal randomization processes and studies with small sample sizes were particularly susceptible to this bias. Adjustment for imbalances in patients and STEMI characteristics were inconsistently done in the RCTs and observational trials.

Performance bias was noted in several studies (RCTs comparing PPCI with inter-hospital transfer to FL at the initial hospital and many observational studies). More adjuvant medical therapy was provided to patients who underwent PPCI than for patients who received FL. It was of note that no study adjusted for differences in ancillary therapy between the treatment groups.

Attrition bias may also confound the treatment effect. Most RCTs reported minimal loss to follow-up. This bias may be particularly relevant for observational studies as only five studies reported ≤6% patients lost to follow-up.

9.4 LIMITATIONS OF PUBLISHED META-ANALYSES

There were some limitations of previous meta-analyses with lack of adjustment for study quality [121] and miss-classification of endpoints and FL agents used in many meta-analyses [34]. These limitations were discussed in more details in chapter 5. Furthermore, fixed-effect models were used in 2 studies [34, 122]. The authors justified their method by the absence of heterogeneity detected by statistical testing. However, heterogeneity between studies may still be present despite non-significant heterogeneity test [49] and the treatment effect may have been over-estimated by the inappropriate use of fixed-effect model [202].

9.5 LIMITATIONS OF THE PRESENT META-ANALYSES

As mentioned above, the reviewed RCTs and observational trials were heterogenous in many aspects. Although the random-effects Bayesian model used in this analysis did control partially for this heterogeneity, amalgamation of very dissimilar studies, endpoints, patients groups may not be entirely appropriate. For example, estimate of bleeding risk may be flawed by inconsistent definition of hemorrhagic complications. To illustrate further this point, estimate of efficacy/effectiveness could be imprecise because of combination of studies enrolling patients of different mortality risks.

The lack of individual patient's data precluded us from undertaking other relevant meta-analyses. Meta-analyses of patient's subgroups such as elderly, high-risk STEMI could provide invaluable information of efficacy and safety of reperfusion therapy for these patients. These meta-analyses were possible with only observational studies. There were insufficient published data concerning these patients from the RCTs to enable this type of analysis.

Meta-analysis of studies with median door-to-needle ≤30 min and door-to-balloon ≤90 min would be pertinent for a fair comparison of both PPCI and FL when the two reperfusion therapies were

performed within optimal time delays. Information concerning door-to-reperfusion therapy was infrequently reported in RCTs and observational studies. Therefore, we could not perform this pertinent analysis.

Our estimates of the absolute treatment differences and numbers needed to treat were based on the risks of patients who received FL (short and long-term results of AMI-Quebec and ASSENT-2 studies, respectively). Thus, the validity of the results was based on the assumption that these incidences were representative of contemporary patients receiving FL in Québec. Therefore, the absolute treatment difference may have been over-estimated or under-estimated if this assumption was not entirely accurate.

10 CONCLUSIONS

We completed a comprehensive review of 25 RCTs, 19 meta-analyses and 33 observational studies that evaluated efficacy, effectiveness and safety of PPCI and FL. Our in-depth review of the RCTs was enhanced by inclusion of short-term data from three recent trials (WEST, HIS and Dobrzycki *et al.*) and recent long-term data from three RCTs (PRAGUE-2, DANAMI-2 and Zwolle). The review of our observational studies is the first meta-analysis of this source of data ever performed for reperfusion therapy in STEMI.

The impact of specific flaws that may have limited the internal validity of many studies such as blinded endpoint committee adjudication, imbalances between patients baseline characteristics, selection and performance biases were identified and evaluated. Finally, AETMIS performed meta-analyses and meta-regressions taking into account the quality, study designs and types of FL used in the previous studies.

10.1 SHORT-TERM EVENTS (IN-HOSPITAL UP TO 42 DAY)

PPCI is associated with mortality reduction in meta-analyses of all RCTs and observational studies. The absolute mortality differences are 2 percentage points in RCTs and 1 percentage point in observational studies. PPCI is associated with absolute reinfarction and stroke reductions that are 3 and 1 percentage points, respectively. The numbers of patients need to treat with PPCI are estimated to be 50-100 to save one death; 30-50 for one reinfarction and 100 for one stroke. The evidence is inconclusive for a bleeding risk difference between PPCI and FL.

10.2 LONG-TERM EVENTS (AT ONE YEAR OR MORE FROM THE INDEX STEMI)

PPCI is associated with 40% long-term relative reinfarction reduction in RCTs. Although the risks ratios are in favour of PPCI, the credible intervals of AETMIS's meta-analyses of RCTs and observational studies suggest uncertainty of a long-term mortality difference between the two treatments.

There is no data on long-term stroke incidence. Since stroke complicating reperfusion therapy usually occur during the index hospitalization, long-term data on strokes are neither available nor pertinent for this report.

10.3 PPCI OUTSIDE REGULAR WORKING HOURS

There is insufficient data concerning safety and efficacy of PPCI outside regular working hours (8:00-17:00 during week days). PPCI performed outside regular hours, in the "real-world" context is associated with prolonged door-to-balloon time delays. One study reported high mortality and procedure failures outside regular working hours even when PPCI was performed within appropriate delays [188].

10.4 INTER-HOSPITAL TRANSFER FOR PPCI

The safety of inter-hospital transfer for PPCI in the "real-world" has never been systematically studied. Of 333 patients who underwent inter-hospital transfer with qualified medical escort (physician or paramedics trained in advanced cardiac care); there was a 2.3% incidence of major adverse events (life-threatening ventricular arrhythmias, severe hypotension and intubation). Furthermore, all of these inter-hospital transfers were completed within 70 km and in temperate European climates. Thus the safety of inter-hospital transfer of STEMI patients for PPCI beyond 70 km, without qualified medical escort, remains to be established in Québec.

10.5 THE IMPORTANCE OF VOLUME-OUTCOME

Patients who underwent PPCI by high-volume personel at high-volume hospitals had better in-hospital survival compared to patients who underwent PPCI by low-volume personel at low-volume hospitals.

10.6 THE IMPORTANCE OF PRESENTATION DELAYS

Systematic reviews of RCTs and observational registries show increased mortality with prolonged presentation delays for both FL and PPCI. PPCI is superior to in-hospital FL for presentation delays between 0 and 12 hours.

10.7 THE IMPORTANCE OF PPCI-RELATED DELAY

Prolonged PPCI-related delays reduce the survival benefits of PPCI. Characteristics such as a patient's baseline mortality risk, presentation delay, available resources, risk of FL should be considered in the decision of what is an appropriate PPCI-related delay for an individual patient. A single time-to-equipoise for PPCI-related delay (when PPCI is equivalent to FL) may not be valid for all patients for all settings.

10.8 THE IMPORTANCE OF STEMI MORTALITY RISK

Meta-regression and subgroup analysis of RCT data (Gusto-IIB, AIR-PAMI, DANAMI-2 and Henriques) suggest that higher-risk patients might derive more benefits from PPCI. High-risk patients are defined as patients with one of the following risk factors (age ≥70 years, anterior STEMI or heart rate >100/min) or TIMI risk score ≥5[43].

10.9 SUMMARY

In summary, when compared to FL, PPCI is associated with short-term reductions of mortality, re-infarction and stroke. PPCI is also associated with a reduction in long-term reinfarction. There is no conclusive long-term mortality difference between the two treatments, particularly for low-risk patients. PPCI is superior to FL for high-risk patients when performed in a timely manner. There is inconclusive data concerning efficacy and effectiveness of PPCI with pre-hospital FL; however the

43 Score composed of age, previous history of diabetes mellitus or hypertension or angina, systolic blood pressure <100 mmHg, heart rate >100/min, Killip II-IV, weight ≤67kg, anterior STEMI or LBBB, time to treatment >4 hours.

latter strategy has been shown to be superior to in-hospital FL. The efficacy of PPCI compared to pre-hospital FL may be determined by future studies.

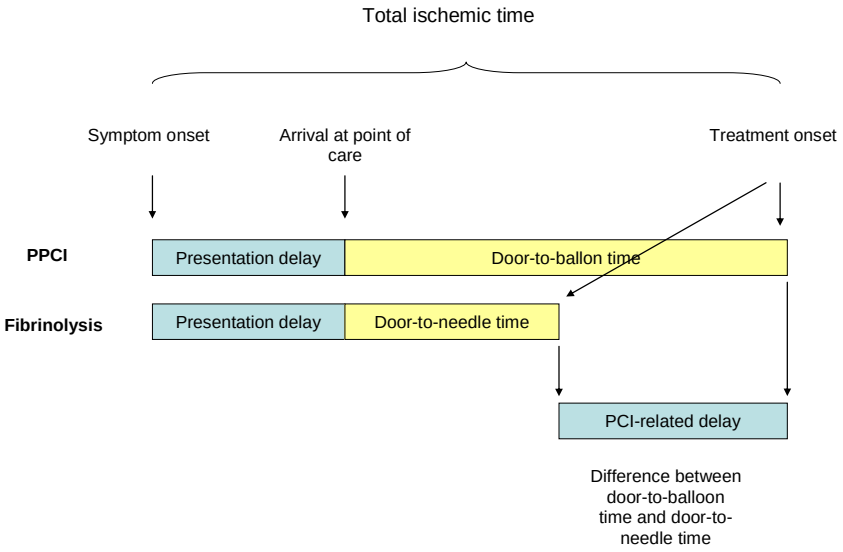
The overall evidence suggests that PPCI is superior to in-hospital FL when performed in a timely manner. For patients in cardiogenic shock, high-risk patients and those with contraindications for FL, PPCI would be the preferred treatment. For lower-risk patients, the evidence is inconclusive for a long-term mortality difference between the two treatments. PPCI-related delay should be carefully considered in the choice of reperfusion therapy for every patient.

APPENDIX A. DEFINITIONS OF TIME DELAYS

The different categories of time intervals are presented in Figure 1. “Presentation delay” begins with the onset of the first symptoms and ends at the time of the first medical contact. “Presentation delay” is often called “symptom duration” by many authors. “Door-to-needle time” begins when the patient arrives at the hospital and ends with the injection of the fibrinolytic agent. “Door-to-balloon time” begins when the patient arrives at the (first) hospital and ends with the first balloon inflation in the coronary artery. The “total ischemic time” is the time elapsed from symptom onset to injection for fibrinolysis, or to balloon for PPCI. “PPCI-related delay” is defined as the mean (or median) difference between “door-to-balloon time” in PPCI and “door-to-needle time” in FL within a predefined cohort[44] [124].

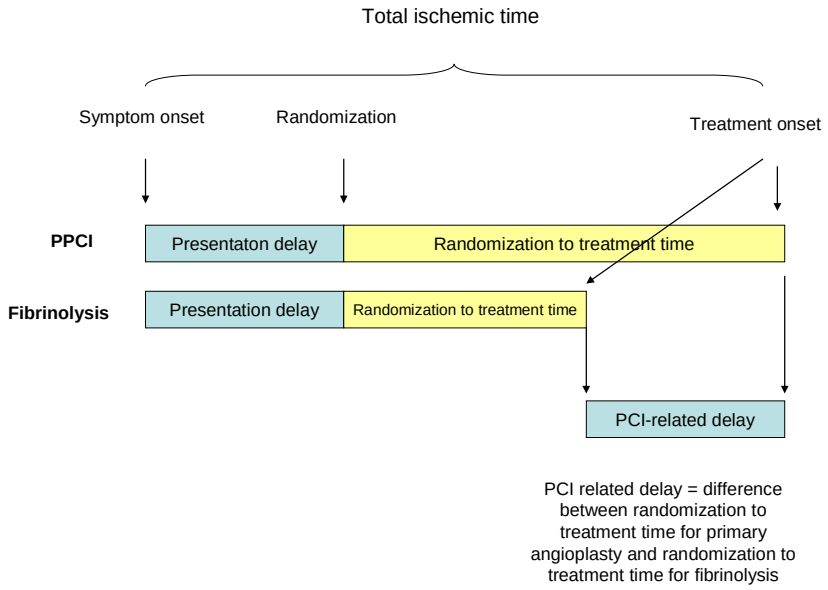
As illustrated in Figure 2, Boersma (2006) uses different definitions for presentation delay and PPCI-related delay, the former being defined as the time from symptom onset to randomization, and the latter as the median time from randomization to PPCI minus median time from randomization to fibrinolysis per hospital [121]. The main difference between Boersma’s definitions of “presentation delay” and “PPCI-related delay” and the definitions most commonly used in current guidelines, previous meta-analyses and RCT is the substitution of “time of first medical contact” for “time of randomization”.

Figure A-1. Presentation of the different time intervals



44 A cohort of patient can, for example, consist of all randomised in a trial or admitted to a given hospital

Figure A-2. Presentation of the time intervals as defined in the meta-analysis by Boersma *et al.* (2006)



Evidence stemming from studies not comparing directly fibrinolysis and PPCI demonstrates the impact of total ischemic times is important for both reperfusion strategies. The benefit of fibrinolytic therapy is the greatest in the first hour following symptom onset with mortality reduction of about 50% when compared to placebo [4, 7, 200]. The benefit of fibrinolytic therapy decreased with increasing time delay to reperfusion [200]. Better survival with shorter door-to-balloon times [147, 206] and with shorter total ischemic time is also observed for PPCI [207].

APPENDIX B. COMPARATIVE EFFICACY AND EFFECTIVENESS OF FIBRINOLYSIS AND PPCI: LITERATURE SEARCH METHODS

Cochrane Library

(Angioplasty OR angioplasties OR endoluminal repair* OR ((PTCA OR PCI) AND coronary) OR ((Transluminal OR balloon) AND (artery OR arteries OR arterial OR coronary) AND dilatation*))

AND

(Fibrinolysis in Keywords OR thrombolytic therapy in Keywords OR
anistreplase OR "plastimogen activators" OR "Urinary Plasminogen Activator" OR "Tissue Plasminogen Activator" OR "plastimogen activator" OR Streptokinase OR Anistreplase OR Urokinase OR Retavase OR Abbokinase OR Kabikinase OR “BM 06.022” OR streptase OR tenecteplase OR SUN9216 OR “SUN-9216” OR lanoteplase OR "SUN 9216" OR "YM 866" OR "monteplase" OR "duteplase" OR Renokinase OR “U-PA” OR Alteplase OR Activase OR Actilyse OR TTPA OR TPA OR “rt-PA” OR “rtPA” OR “rt PA” OR Avelizin OR Awelysin OR Celiase OR Distreptase OR Kabivitrum OR Streptodecase OR Anistreplase OR Eminase OR Iminase OR “BRL-26921” OR “BRL26921” OR “BRL 26921” OR Varidase OR Rapilysin OR Reteplase OR tPA OR “t-PA” OR Metalyse)

Web of Science (1990-2006)

((registry OR registries OR (clinical same trial*) OR (TI=clinical AND TI= trial*) OR outcome* OR effectiveness OR efficacy OR efficiency OR cohort)

AND

Angioplasty OR angioplasties OR (endoluminal same repair*) OR ((PTCA OR PCI) AND coronary) OR ((Transluminal OR balloon) AND (artery OR arteries OR arterial OR coronary) AND dilatation*)

AND

(TI= (Fibrinolysis OR (thrombolytic same therapy)) OR (TS= (Fibrinolysis OR (thrombolytic same therapy)) OR
(TS=(anistreplase OR (plastimogen same activators) OR (Urinary same Plasminogen same Activator) OR (Tissue same Plasminogen same Activator) OR (plastimogen same activator) OR Streptokinase OR Anistreplase OR Urokinase OR Retavase OR Abbokinase OR Kabikinase OR BM$06$022 OR streptase OR tenecteplase OR SUN9216 OR SUN$9216 OR lanoteplase OR SUN$9216 OR YM$866 OR monteplase OR duteplase OR Renokinase OR U$PA OR Alteplase OR Activase OR Actilyse OR TTPA OR TPA OR rt$PA OR rtPA OR rt$PA OR Avelizin OR Awelysin OR Celiase OR Distreptase OR Kabivitrum OR Streptodecase OR Anistreplase OR

Eminase OR Iminase OR BRL$26921 OR BRL26921 OR Varidase OR Rapilysin OR Reteplase OR tPA OR t$PA OR Metalyse))

Biol Abs -BIOSIS (1990-2006); Cinahl, Current Contents (2000- 2006), Medline (2000-2006)

(Angioplasty or angioplasties or (endoluminal adj1 repair$) or ((PTCA or PCI) and coronary) or ((Transluminal or balloon) and (artery or arteries or arterial or coronary) and dilatation$)).mp.

AND

(registry or registries or (clinical adj1 trial$) or outcome$ or effectiveness or efficacy or efficiency or cohort).mp. OR (clinical and trial$).ti.

AND

(Fibrinolysis or thrombolytic therapy).mp. OR exp Fibrinolysis OR exp Fibrinolytic Therapy OR (anistreplase or (plastimogen adj1 activator$) or (Urinary adj1 Plasminogen adj1 Activator$) or (Tissue adj1 Plasminogen adj1 Activator$) or Streptokinase or Anistreplase or Urokinase or Retavase or Abbokinase or Kabikinase or (BM adj1 "06" adj1 "022") or streptase or tenecteplase or SUN9216 or (SUN adj1 "9216") or lanoteplase or (SUN adj1 "9216") or (YM adj1 "866") or monteplase or duteplase or Renokinase or (U adj1 PA) or Alteplase or Activase or Actilyse or TTPA or TPA or (rt adj1 PA) or rtPA or Avelizin or Awelysin or Celiase or Distreptase or Kabivitrum or Streptodecase or Anistreplase or Eminase or Iminase or (BRL adj1 "26921") or BRL26921 or Varidase or Rapilysin or Reteplase or tPA or (t adj1 PA) or Metalyse).mp.

Limit to human

PubMed years covered 2000-2006

Fibrinolysis [mh] OR thrombolytic therapy [mh] OR anistreplase [mh] OR plastimogen activators [mh] OR Urinary Plasminogen Activator [mh] OR Tissue Plasminogen Activator [mh] OR Streptokinase [mh] OR Anistreplase [mh] OR “Streptodornase and Streptokinase” [mh] OR 133652-38-7 [rn] OR "tenecteplase"[Substance Name] OR Urokinase OR Retavase OR Abbokinase OR Kabikinase OR “BM 06.022” [Substance Name] OR streptase OR tenecteplase OR SUN9216 OR “SUN-9216” OR lanoteplase OR "salivary plasminogen activator alpha 1, Desmodus rotundus"[Substance Name] OR "SUN 9216"[Substance Name] OR "YM 866"[Substance Name] OR "monteplase"[Substance Name] OR "duteplase"[Substance Name] OR (“Plasminogen Activator” OR Renokinase OR “U-PA” OR Alteplase OR Activase OR Actilyse OR TTPA OR TPA OR “rt-PA” OR “rtPA” OR “rt PA” OR Avelizin OR Awelysin OR Celiase OR Distreptase OR Kabivitrum OR Streptokinase OR Streptodecase OR Anistreplase OR Eminase OR Iminase OR “BRL-26921” OR “BRL26921” OR “BRL 26921” OR Varidase OR Rapilysin OR Reteplase OR tPA OR “t-PA” OR Metalyse)

AND

Angioplasty [mh] OR Angioplasty, Balloon, Laser-Assisted [mh] OR Angioplasty, Transluminal, Percutaneous Coronary [mh] OR Angioplasty, Balloon [mh] OR Angioplasty, Laser [mh] OR

Angioplasty OR angioplasties OR endoluminal repair* OR ((PTCA OR PCI) AND coronary) OR ((Transluminal OR balloon) AND (artery OR arteries OR arterial OR coronary) AND dilatation*)

AND

(Registries [mh] OR clinical trial [pt] OR “clinical trials” [mh] OR "cohort studies” [mh] OR "outcome and process assessment health care"[mh] OR «outcome assessment health care"[mh] OR Treatment Outcome [mh] OR Treatment Failure [mh] OR "controlled clinical trial"[pt] OR Controlled Clinical Trials [mh]) NOT "randomized controlled trial"[pt]) OR ((registry OR registries OR “clinical trial” OR “clinical trials” OR (clinical [tiab] AND trial*[tiab]) OR outcome* OR effectiveness OR efficacy OR efficiency OR cohort) NOT "randomized controlled trial"[pt])

4. Additional searching for observational studies: **PubMed** January 1990-November 2006

“thrombolytic therapy” [tw] OR “thrombolytic therapy” [mh] OR “fibrinolytic therapy” [tw] OR “fibrinolysis” [tw] OR fibrinolysis” [mh] OR "angioplasty"[mh] OR “reperfusion therapy” [tw] OR “myocardial reperfusion "[mh] OR “percutaneous coronary angioplasty” [tw] OR “percutaneous coronary intervention” [tw]

AND

(“myocardial infarction” [tw] OR "myocardial infarction" [mh])

AND

“observational studies” [tw] OR “registries” [mh] OR registries [tw] OR registry [tw] OR “cohort studies” [mh] OR cohort [tiab] OR “case-control-studies” [mh] OR “case-control-studies” [tw]

Embase (via Ovid) 2004-2006
(Angioplasty or angioplasties or (endoluminal adj1 repair$) or ((PTCA or PCI) and coronary) or ((Transluminal or balloon) and (artery or arteries or arterial or coronary) and dilatation$)).mp

AND

(Fibrinolysis or thrombolytic therapy).mp. or exp Fibrinolysis/ or exp Fibrinolytic Therapy/ or (anistreplase or (plastimogen adj1 activator$) or (Urinary adj1 Plasminogen adj1 Activator$) or (Tissue adj1 Plasminogen adj1 Activator$) or Streptokinase or Anistreplase or Urokinase or Retavase or Abbokinase or Kabikinase or (BM adj1 "06" adj1 "022") or streptase or tenecteplase or SUN9216 or (SUN adj1 "9216") or lanoteplase or (SUN adj1 "9216") or (YM adj1 "866") or monteplase or duteplase or Renokinase or (U adj1 PA) or Alteplase or Activase or Actilyse or TTPA or TPA or (rt adj1 PA) or rtPA or Avelizin or Awelysin or Celiase or Distreptase or Kabivitrum or Streptodecase or Anistreplase or Eminase or Iminase or (BRL adj1 "26921") or BRL26921 or Varidase or Rapilysin or Reteplase or tPA or (t adj1 PA) or Metalyse).mp OR Fibrinolytic Agent/

AND

Human

AND

(registry or registries or (clinical adj1 trial$) or outcome$ or effectiveness or efficacy or efficiency or cohort).mp. or (clinical and trial$).ti.

APPENDIX C. INVESTIGATORS CONTACTED AND INFORMATION OBTAINED FOR RCTS

Some reviewed RCTs did not report whether the outcome adjudication was blinded. Investigators of seven RCTs were contacted for information [77, 82, 84-86, 90, 93]. We could not obtain information from the principal investigators of 5 RCTs, so we consider these RCTs to have unknown status of outcome adjudication [61, 79, 87-89].

Some RCTs did not report the concealment method of the randomization sequence, information about the randomization methods were obtained by personal communication with the principle investigators of four RCTs [72, 77, 86, 92]. We could not obtain information from one RCT [78].

The table presents the investigators contacted and information obtained regarding BEPC and concealment methods

Table C-1. Investigators contacted, trials and information obtained

Investigator contacted	Trial	BEPC	Concealment method
E Garcia	[77]	Yes	Sealed envelope
A Kastrati	[86]	Yes	Sealed envelope
A Kastrati	[82]	Yes	Not applicable
EE Ribeiro	[84]	No	Not applicable
G Steffenino	[85]	No	Not applicable
S Dobrzycki	[93]	No	Not applicable
LR Grinfeld	[90]	No	Not applicable
M Adam	[72]	NA	Sealed envelope
HJ Dieker	[92]	NA	Telephone service

APPENDIX D. OUTCOMES IN THE RCTS

Table D-1. Comparative cumulative mortality for PPCI and fibrinolysis

Study	Period of enrolment	Outcomes and timelines	Cumulative incidence PPCI	Cumulative incidence fibrinolysis	Risk ratios[45] (IC 95%)	P values
Ribeiro *et al.*, 1993 [84]	1989	In-hospital mortality	N=50 6%	N=50 2%	3.00 (0.32-27.85)	NS
Gibbons *et al.*, 1993 [78]	1989-1991	In-hospital mortality	N=47 4.3%	N=56 3.6%	1.19 (0.17-8.14)	NS
Grines *et al.*, 1993 [79]	1990-1992	In-hospital mortality	N=195 2.6%	N=200 6.5%	0.39 (0.14-1.08)	NS
de Boer *et al.*, 1994 [75]	1990-1993	In-hospital mortality	N=152 2.0%	N=149 7.4%	0.27 (0.08-0.94)	0.026
Garcia *et al.*, 1999 [77]	1991-1996	In-hospital mortality	N=109 2.8%	N=111 10.8%	0.25 (0.07-0.88)	0.018
Berrocal *et al.*, 2003 [90]	1993-1995	In-hospital mortality	N=54 9.3%	N=58 10.3%	0.90 (0.29-2.76)	NS
Ribichini *et al.*, 1998 [85]	1993-1996	In-hospital mortality	N=55 1.8%	N=55 5.5%	0.33 (0.36-3.11)	NS
Zijlstra *et al.*, 1997 [89]	1993-1995	Short term mortality	N=45 2.2%	N=50 0%	3.33 (0.14-79.63)	NS
GUSTO IIB, 1997 [81]	1994-1996	30 days mortality	N=565 5.7%	N=573 7.0%	0.81 (0.52-1.27)	NS

45 Mantel-Haenszel risk ratios

Vermeer *et al.*, 1999 [61]	1995-1997	42 days mortality	N=75 6.7%	N=75 6.7%	1.00 (0.30-3.31)	NS
Aversano *et al.*, 2002 [73]	1996-1998	42 days mortality	N=225 5.2%	N=226 6.2%	0.75 (0.36-1.56)	NS
De Boer *et al.*, 2002 [76]	1996-1999	30 days mortality	N=46 6.5%	N=41 22.0%	0.28 (0.08-0.96)	0.029
Widimsky *et al.*, 2000 [88]	1997-1999	30 days mortality	N=101 6.9%	N=99 14.1%	0.49 (0.21-1.16)	NS
Le May *et al.*, 2001 [83]	1997-1999	42 days mortality	N=62 4.8%	N=61 3.3%	1.48 (0.26-8.53)	NS
Schomig *et al.*, 2000 [86]	1997-1999	30 days mortality	N=71 4.2%	N=69 7.2%	0.58 (0.14-2.35)	NS
Bonnefoy *et al.*, 2002 [74]	1997-2000	30 days mortality	N=421 4.8%	N=419 3.8%	1.24 (0.65-2.37)	NS
Andersen *et al.*, 2003 with transfer [71]	1997-2001	30 days mortality	N=567 6.5%	N=562 8.5%	0.76 (0.51-1.15)	NS
Andersen *et al.*, 2003 on-site PPCI [71]	1997-2001	30 days mortality	N=223 6.7%	N=220 5.9%	1.14 (0.55-2.34)	NS
Kastrati *et al.*, 2002 [82]	1999-2001	30 days mortality	N=81 2.5%	N=81 6.2%	0.40 (0.08-2.00)	NS
Widimsky *et al.*, 2003 [87]	1999-2002	30 days mortality	N=429 6.8%	N=421 10.0%	0.68(0.43-1.07)	NS
Grines *et al.*, 2002 [80]	Published in 2002	30 days mortality	N=71 8.4%	N=66 12.1%	0.70 (0.25-1.90)	NS

Svensson *et al.,* 2006 [91]	2001-2003	30 days mortality	N=101 3.0 %	N=104 3.8%	0.77 (0.18-3.36)	NS
Dobrzycki *et al.,* 2006 [93]	2002-2003	30 days mortality	N=172 3.5%	N=169 8.9%	0.39 (0.16-0.99)	0.044
Dieker *et al.,* 2006 [92]	2003-2004	30 days mortality	N=25 4.0%	N=23 8.7%	0.46 (0.04-4.74)	NS
Armstrong *et al.*, 2006 [72]	Published in 2006	30 days mortality	N=100 1.0%	N=100 4.0%	0.25 (0.03-2.20)	NS
Gibbons *et al.*, 1993 [78]	1989-1991	6 months mortality	N=56 3.6%	N=47 6.3%	0.56 (0.10-3.21)	NS
Grines *et al.*, 1993 [79]	1990-1992	6 months mortality	N=195 3.7%	N=200 7.9%	0.43 (0.17-1.07)	NS
Garcia *et al.*, 1999 [77]	1991-1996	6 months mortality	N=109 4.6%	N=111 11.7%	0.39 (0.14-1.06)	NS
Zijlstra *et al.*, 1997 [89]	1993-1995	6 months mortality	N=45 2.2%	N=50 0%	3.33 (0.14-79.63)	NS
GUSTO IIB, 1997 [81]	1994-1996	6 months mortality	N=499 6.6%	N=503 7.0%	0.95 (0.57-1.58)	NS
Aversano *et al.,* 2002 [73]	1996-1998	6 months mortality	N=225 6.2%	N=226 7.1%	0.88 (0.44-1.76)	NS
Schomig *et al.*, 2000 [86]	1997-1999	6 months mortality	N=71 4.2%	N=69 13.0%	0.32 (0.09-1.15)	NS
Le May *et al.*, 2001 [83]	1997-1999	6 months mortality	N=62 4.8%	N=61 3.3%	1.48 (0.26-8.53)	NS
Kastrati *et al.*,	1999-2001	6 months	N=81	N=81	0.57 (0.17-1.88)	NS

2002 [82]		mortality	4.9%	8.6%		
Ribichini *et al.*, 1998 [85]	1993-1996	1 year mortality	N=55 3.6%	N=55 7.3%	0.50 (0.10-2.62)	NS
Vermeer *et al.*, 1999 [61]	1995-1997	1 year mortality	N=75 12.0%	N=75 8.0%	1.50 (0.56-4.01)	NS
De Boer *et al.*, 2002 [76]	1996-1999	1 year mortality	N=46 10.9%	N=41 29.3%	0.37 (0.14-0.96)	0.032
Widimsky *et al.*, 2000 [88]	1997-1999	1 year mortality	N=101 12.9%	N=99 18.2%	0.71 (0.37-1.37)	NS
Dieker *et al.*, 2006 [92]	2003-2004	1 year mortality	N=25 4.0%	N=23 13.0%	0.31 (0.03-2.74)	NS
PAMI-1, 1999 [112]	1990-1992	2 year mortality	N=164 6.2%	N=177 9.5%	0.61 (0.27-1.38)	NS
Berrocal *et al.*, 2003 [90]	1993-1995	3 years mortality	N=54 24.1%	N=58 36.2%	0.66 (0.37-1.19)	NS
DANAMI-2, 2005 [100]	1997-2001	3 years mortality	N=764 12.2%	N=763 13.9%	0.88 (0.68-1.14)	NS
Zijlstra *et al.*, 1999 [146]	1990-1995	5 +/- 2 years mortality	N=194 13.4%	N=201 23.9%	0.56 (0.36-0.87)	0.010
Widimsky *et al.*, 2007 [208]	1999-2002	5 years mortality	N=428 20.7%	N=416 23.5%	0.88 (0.69-1.14)	NS

Table D-2. Comparative cumulative total reinfarction incidence for PPCI and fibrinolysis

Study[46]	Period of enrolment	Outcomes and timelines	Cumulative incidence PPCI	Cumulative incidence fibrinolysis	Risk ratios[47] (IC 95%)	P value[48]
Ribeiro *et al.*, 1993 [84]	1989	In-hospital Reinfarction[49]	N=50 4%	N=50 2%	2.00 (0.19-21.37)	NS
Gibbons *et al.*, 1993 [78]	1989-1991	In-hospital Reinfarction [50]	N=47 2.2%	N=56 5.7%	0.40 (0.04-3.69)	NS
Grines *et al.*, 1993 [79]	1990-1992	In-hospital Reinfarction	N=195 2.6%	N=200 5.5%	0.47 (0.17-1.32)	NS
de Boer *et al.*, 1994 [75]	1990-1993	In-hospital Reinfarction	N=152 1.3%	N=149 8.1%	0.16 (0.04-0.72)	0.006
Garcia *et al.*, 1999 [77]	1991-1996	In-hospital Reinfarction	N=109 3.7%	N=111 5.5%	0.68 (0.20-2.34)	NS
Berrocal *et al.*, 2003 [90]	1993-1995	In-hospital Reinfarction	N=54 1.9%	N=58 3.4%	0.54 (0.05-5.75)	NS
Ribichini *et al.*, 1998 [85]	1993-1996	In-hospital Reinfarction	N=55 1.8%	N=55 3.6%	0.50 (0.05-5.36)	NS
De Boer *et al.*, 2002 [76]	1996-1999	30 days Reinfarction	N=46 2.2%	N=41 2.4%	0.89 (0.06-13.8)	NS
Zijlstra *et al.*, 1997[51] [89]	1993-1995	Short term Reinfarction	N=45 0%	N=50 16%	0.07 (0.00-1.10)	0.009

46 Total stroke data could not be obtained for three studies because only non fatal stroke was reported: Kastrati *et al.*, (2002); Schomig *et al*., (2000); Widimsky *et al*., (2003).
47 Mantel-Haenszel risk ratios
48 Fisher's exact test
49 Data from Keeley *et al*., (2003)
50 Data derived from the meta-analysis of Keeley *et al*., (2003).

Study[46]	Period of enrolment	Outcomes and timelines	Cumulative incidence PPCI	Cumulative incidence fibrinolysis	Risk ratios[47] (IC 95%)	P value[48]
GUSTO IIB, 1997 [81]	1994-1996	30 days Reinfarction	N=565 4.4%	N=573 6.5%	0.69 (0.42-1.12)	NS
Vermeer *et al.*, 1999 [61]	1995-1997	42 days Reinfarction	N=75 1.3%	N=75 9.3%	0.14 (0.02-1.13)	0.030
Aversano *et al.*, 2002 [26]	1996-1998	42 days Reinfarction	N=225 4.9%	N=226 8.8%	0.55 (0.27-1.13)	NS
Widimsky *et al.*, 2000 [88]	1997-1999	30 days Reinfarction	N=101 1.0%	N=99 9.1%	0.11 (0.01-0.84)	0.009
Le May *et al.*, 2001 [83]	1997-1999	42 days Reinfarction	N=62 4.8%	N=61 13.1%	0.37 (0.10-1.33)	NS
Bonnefoy *et al.*, 2002 [74]	1997-2000	30 days Reinfarction	N=421 1.4%	N=419 3.3%	0.44 (0.17-1.13)	NS
Andersen *et al.*, 2003 [71][52]	1997-2001	30 days Reinfarction	N=567 1.9%	N=562 6.2 %	0.31 (0.16-0.61)	0.0003
Andersen *et al.*, 2003 [71] on-site PPCI	1997-2001	30 days Reinfarction	N=223 0.9%	N=220 6.4 %	0.14 (0.03-0.61)	0.002
Grines *et al.*, 2002 [80]	Published in 2002	30 days Reinfarction	N=71 0%	N=66 0%	NA	NS
Svensson *et al.*, 2006 [91]	2001-2003	30 days Reinfarction	N=101 0 %	N=104 1.9 %	0.21 (0.01-4.24)	NS

51 Short term data were not available from the original study, but were presented in Keeley *et al*. (2003). However, the number of short term events presented in Keeley *et al*. (2003) is higher than that presented in the original study at six months. Hence, six months data from the original study were used.
52 Peri-procedural infarcts were not included

Study[46]	Period of enrolment	Outcomes and timelines	Cumulative incidence PPCI	Cumulative incidence fibrinolysis	Risk ratios[47] (IC 95%)	P value[48]
Dobrzycki *et al.*, 2006 [93]	2002-2003	30 days Reinfarction	N=172 1.2%	N=169 5.9%	0.20 (0.04-0.88)	0.019
Dieker *et al.*, 2006 [92]	2003-2004	30 days Reinfarction	N=25 0.0%	N=23 4.3%	0.31 (0.01-7.20)	NS
Armstrong *et al.*, 2006 [72]	Published in 2006	30 days Reinfarction	N=100 3%	N=100 9%	0.33 (0.09-1.20)	NS
Garcia *et al.*, 1999 [77]	1991-1996	6 months Reinfarction	N=109 5.5%	N=111 7.2%	0.76 (0.27-2.13)	NS
Zijlstra *et al.*, 1997 [89]	1993-1995	6 months Reinfarction	N=45 0%	N=50 16%	0.07 (0.00-1.10)	0.009
GUSTO IIB, 1997 [81]	1994-1996	6 months Reinfarction	N=475 7.4%	N=468 7.5%	0.98 (0.64-1.52)	NS
Aversano *et al.*, 2002 [73]	1996-1998	6 months Reinfarction	N=225 5.3%	N=226 10.6%	0.50 (0.26-0.98)	0.039
Le May *et al.*, 2001 [83]	1997-1999	6 months Reinfarction	N=62 6.5%	N=61 16.4%	0.39 (0.13-1.19)	NS
Ribichini *et al.*, 1998 [85]	1993-1996	1 year Reinfarction	N=55 3.6%	N=55 3.6%	1.00 (0.15-6.85)	NS
Vermeer *et al.*, 1999 [61]	1995-1997	1 year Reinfarction	N=75 5.3%	N=75 12.0%	0.44 (0.14-1.38)	NS
Widimsky *et al.*, 2000 [88]	1997-1999	1 year Reinfarction	N=101 3.0%	N=99 12.1%	0.24 (0.07-0.84)	0.014
Dieker *et al.*, 2006	2003-2004	1 year	N=25	N=23	0.46 (0.04-4.74)	NS

Study[46]	Period of enrolment	Outcomes and timelines	Cumulative incidence PPCI	Cumulative incidence fibrinolysis	Risk ratios[47] (IC 95%)	P value[48]
[92]		Reinfarction	4.0%	8.7%		
PAMI-1, 1999 [112]	1990-1992	2 year Reinfarction	N=164 10.8%	N=177 16.0%	0.69 (0.40-1.21)	NS
DANAMI-2, 2005 [100]	1997-2001	3 years Reinfarction	N=764 7.5%	N=763 11.3%	0.66 (0.48-0.91)	0.011
Widimski *et al.*, 2007 [208]	1999-2002	5 years Reinfarction	N=428 13.3%	N=416 20.0%	0.67 (0.49-0.91)	0.012

Table D-3. Comparative cumulative total stroke incidence for PPCI and fibrinolysis

Study[53]	Period of enrolment	Outcomes and timelines	Cumulative incidence PPCI	Cumulative incidence fibrinolysis	Risk ratios[54] (IC 95%)	P value[55]
Ribeiro *et al.*, 1993 [84]	1989	In-hospital stroke[56]	N=50 0%	N=50 0%	NA	NA
Gibbons *et al.*, 1993 [78]	1989-1991	In-hospital stroke	N=56 0%	N=47 0%	NA	NA
Grines *et al.*, 1993 [79]	1990-1992	In-hospital stroke	N=195 0%	N=200 3.5%	0.07 (0.004-1.19)	0.014
de Boer *et al.*, 1994 [75]	1990-1993	In-hospital stroke	N=152 1.0%	N=149 2.0%	0.49 (0.04-5.35)	NS
Garcia *et al.*, 1999 [77]	1991-1996	In-hospital stroke	N=109 0%	N=111 2.7%	0.15 (0.01-2.78)	NS
Berrocal *et al.*, 2003 [90]	1993-1995	In-hospital stroke	N=54 1.9%	N=58 1.7%	1.06 (0.07-16.45)	NS
Ribichini *et al.*, 1998 [85]	1993-1996	In-hospital stroke	N=55 0%	N=55 0%	NA	NS
De Boer *et al.*, 2002 [76]	1996-1999	In-hospital stroke	N=46 2.2%	N=41 4.9%	0.45 (0.04-4.74)	NS
Zijlstra *et al.*, 1997 [89][57]	1993-1995	Short term stroke	N=45 2.2%	N=50 4.0%	0.56 (0.05-5.92)	NS

53 Total stroke data could not be obtained for three studies because only non fatal stroke was reported: Kastrati *et al.*, (2002); Schomig *et al*., (2000); Widimsky *et al*., (2003).
54 Mantel-Haenszel risk ratios
55 Fisher's exact test
56 Data from Keeley *et al*., 2003
57 From Keeley *et al*., 2003.

GUSTO IIB, 1997 [81]	1994-1996	30 days stroke	N=565 0.2%	N=573 0.9%	0.20 (0.02-1.73)	NS
Vermeer *et al.*, 1999 [61]	1995-1997	42 days stroke	N=75 2.7%	N=75 2.7%	1.00 (0.14-6.91)	NS
Aversano *et al.*, 2002 [73]	1996-1998	42 days stroke	N=225 1.3%	N=226 3.5%	0.38 (0.10-1.40)	NS
Widimsky *et al.*, 2000 [88]	1997-1999	30 days stroke	N=101 0%	N=99 1.01%	0.33 (0.01-7.93)	NS
Le May *et al.*, 2001 [83]	1997-1999	42 days stroke	N=62 1.6%	N=61 3.3%	0.49 (0.05-5.29)	NS
Bonnefoy *et al.*, 2002 [74]	1997-2000	30 days stroke	N=421 0%	N=419 1.0%	0.11 (0.01-2.05)	NS
Andersen *et al.*, 2003 with transfer [71]	1997-2001	30 days stroke	N=567 1.6%	N=562 2.0%	0.81 (0.34-1.94)	NS
Andersen *et al.*, 2003 on-site PPCI [71]	1997-2001	30 days stroke	N=223 0%	N=220 2.3%	0.09 (0.01-1.61)	0.030
Grines *et al.*, 2002 [80]	Published in 2002	30 days stroke	N=71 0%	N=66 4.5%	0.13 (0.01-2.53)	NS
Svensson *et al.*, 2006 [91]	2001-2003	30 days stroke	N=101 0 %	N=104 2.9 %	0.15 (0.01-2.81)	NS
Dobrzycki *et al.*, 2006 [93]	2002-2003	30 days stroke	N=172 0.6%	N=169 1.2%	0.49 (0.05-5.37)	NS
Dieker *et al.*, 2006 [92]	2003-2004	1 year Reinfarction	N=25 0%	N=23 0%	NA	NA

Armstrong *et al.*, 2006 [72]	Published in 2006	30 days stroke	N=100 1%	N=100 0%	3.00 (0.12-72.77)	NS
Zijlstra *et al.*, 1997 [89]	1993-1995	6 months stroke	N=45 2.2%	N=50 4.0%	0.56 (0.05-5.92)	NS
Aversano *et al.*, 2002 [73]	1996-1998	6 months stroke	N=225 2.2%	N=226 4.0%	0.56 (0.19-1.64)	NS
Le May *et al.*, 2001 [83]	1997-1999	6 months stroke	N=62 1.6%	N=61 4.9%	0.33 (0.04-3.07)	NS
Vermeer *et al.*, 1999 [61]	1995-1997	1 year stroke	N=75 2.7%	N=75 2.7%	1.00 (0.14-6.9)	NS

APPENDIX E. INCLUSIONS AND EXCLUSIONS CRITERIA FOR EACH RCT

Trial	Age (inclusion)	Symptoms to door (inclusion)	Co-morbidity (exclusion)	Severity criteria (exclusion)	Contraindication to fibrinolysis (exclusion)	Contraindication to PPCI (exclusion)
de Boer *et al.*, 1994 [75]	75 years or less	Less than 6 hours; between 6 and 24 hours if persistence of ischemia		Inclusion of cardiogenic shock (Zijlstra *et al.*, 1993)	Previous stroke, other intracranial disease, recent surgery or trauma, refractory hypertension, active bleeding, prolonged cardio-pulmonary resuscitation (Zijlstra *et al.*, 1993)	
Gibbons *et al.*, 1993 [78]	79 years or less	12 hours or less		Cardiogenic shock	Contraindications to fibrinolysis	
Grines *et al.*, 1993 [79]	No age restriction	12 hours or less	Dementia	Complete LBBB, cardiogenic shock	Above average risk of bleeding	
Ribeiro *et al.*, 1993 [84]	74 years or less	6 hours or less		Previous CABG, Q wave infarct with the same distribution as current infarct	Stroke, major surgery or trauma within the last six months; history of abnormal bleeding	
Zijlstra *et al.*, 1997 [89]		Less than 6 hours; between 6 and 24 hours if persistence of ischemia	Life expectancy of less than six months, condition resulting in significant impairment in quality of life.	Killip 2 or more, EKG evidence of anterior infarct or extensive myocardial infarct	Contraindications to fibrinolysis	
Berrocal *et al.*, 2003 [90]		12 hours or less		Killip 2 or more, LBBB	Contraindications to fibrinolysis	
Garcia *et al.*, 1999 [77]	18 years or more	5 hours or less		LBBB	Contraindications to fibrinolysis	
GUSTO		12 hours or less		Renal failure (creatinine >	Use of warfarine, active	

Trial	Age (inclusion)	Symptoms to door (inclusion)	Co-morbidity (exclusion)	Severity criteria (exclusion)	Contraindication to fibrinolysis (exclusion)	Contraindication to PPCI (exclusion)
IIB, 1997 [81]				177 µmol per litre)	bleeding, history of stroke, systolic blood pressure above 200 mm Hg or diastolic blood pressure above 110 mm HG	
Vermeer *et al.*, 1999 [61]	79 years or less	Less than 6 hours before randomisation		Cardiogenic shock	Contraindications to fibrinolysis, severe hypertension not responding to treatment, elevated bleeding risks, stroke in the previous 12 months	
Widimsky *et al.*, 2000 [88]		Less than 6 hours			Contraindications to fibrinolysis	Absence of femoral pulse
Aversano *et al.*, 2002 [73]	18 years or more	Less than 12 hours		Creatinine level greater than 132.6 µmol/L for men or 123.8 µmol/L for women	Contraindications to fibrinolysis	Metformin
Bonnefoy *et al.*, 2002 [74]		Less than 6 hours	History of CABG	Severe renal failure, cardiogenic shock	Known bleeding diathesis or any other contraindications to fibrinolysis, treatment with an anticoagulant	Aorto-femoral bypass or any condition affecting femoral artery access.
De Boer *et al.*, 2002 [76]	76 years or more	Less than 6 hours; between 6 and 24 hours if persistence of ischemia			Contraindications to fibrinolysis such as stroke history, intracranial disease, recent trauma or surgery, refractory hypertension (systolic blood pressure of 180 mm Hg or more, diastolic blood pressure 110 mm Hg or more, prolonged bleeding or prolonged cardiopulmonary resuscitation	

Trial	Age (inclusion)	Symptoms to door (inclusion)	Co-morbidity (exclusion)	Severity criteria (exclusion)	Contraindication to fibrinolysis (exclusion)	Contraindication to PPCI (exclusion)
Grines *et al.*, 2002 [80]	70 years or more	12 hours or less	Life expectancy of less than one year	**Inclusion factors**[58] : Heart rate of 100 beats or more per minute, systolic blood pressure of less than 100 mm Hg in the absence of volume depletion, Killip II or III, LBBB or anterior myocardial infarct	Contraindications to fibrinolysis such as (history of stroke or transient cerebral event in the last six months, major surgery or active gastrointestinal bleeding within the previous two months, organ biopsy within two weeks, cardiopulmonary resuscitation lasting more than 10 min or resulting in rib fracture, systolic BP more than 200 mm Hg or diastolic BP more than 110 mm Hg),	
Ribichini *et al.*, 1998 [85]	79 years or less	6 hours or less		Cardiogenic shock, systolic blood pressure of less than 80 mm Hg	Contraindications to fibrinolysis	Anticipation that the femoral artery will not be accessible.
Widimsky *et al.*, 2003 [87]		Less than 12 hours			Contraindications to fibrinolysis such as stoke in the previous 12 months, any history of hemorrhagic stroke, intracranial tumour, active internal bleeding, aortic dissection	Absence of femoral pulse
Andersen *et al.*, 2003 [71]		Less than 12 hours	History of CABG or any non ischemic cardiac disease	Cardiogenic shock, creatinine of more than 250 µmol per litre, LBBB, myocardial infarct and fibrinolysis in the last 30 days, sustained systolic blood pressure below 65 mm Hg, possibly fatal	Contraindications to fibrinolysis	Metformin; absence of femoral pulse

58 Inclusion factors, not exclusion factors

Trial	Age (inclusion)	Symptoms to door (inclusion)	Co-morbidity (exclusion)	Severity criteria (exclusion)	Contraindication to fibrinolysis (exclusion)	Contraindication to PPCI (exclusion)
				arrhythmias and mechanical ventilation		
Armstrong *et al.*, 2006 [72]			History of CABG	EKG criteria for large infarcts	Contraindications to fibrinolysis	Use of glycoprotein IIb/IIIa within the last 7 days
Kastrati *et al.*, 2002 [82]		12 hours or less			Stroke in the last three months, bleeding diathesis or active bleeding, trauma or major surgery in the last month, suspected aortic dissection, non compressible vascular puncture, warfarin-related therapies, systolic blood pressure of more than 180 mm Hg not responding to therapy	
Le May *et al.*, 2001 [83]		12 hours or less	PTCA within the preceding six months, previous stenting of the presumed infarct-related artery, previous CABG, intolerance to aspirin, other medical condition likely to result in death within 12 months, pregnancy or inability to provide informed consent, participation in another study within the past four weeks	cardiogenic shock, hematocrit < 30%, creatinine more than 300 μmol/L	Active bleeding, history of stroke, major surgery or trauma within three months, systolic blood pressure of 200 mm Hg or more or diastolic blood pressure of 120 mm Hg or more, cardiopulmonary resuscitation lasting more than 10 min, international normalized ratio more than 2, platelet count of less than 100,000/mm3	Inadequate vascular access
Schomig *et al.*, 2000 [86]		12 hours or less			Stroke in the last three months, bleeding diathesis or active bleeding, trauma or major surgery in the last month, suspected aortic dissection,	

Trial	Age (inclusion)	Symptoms to door (inclusion)	Co-morbidity (exclusion)	Severity criteria (exclusion)	Contraindication to fibrinolysis (exclusion)	Contraindication to PPCI (exclusion)
					non compressible vascular puncture, warfarin-related therapies, systolic blood pressure of more than 180 mm Hg not responding to therapy	
Svensson *et al.*, 2006 [91]	18 years or more	6 hours or less	Body weight more than120 kg, and known renal insufficiency	Blood pressure more than 180/110 mm Hg at any time, cardiogenic shock, cerebral deterioration and peripheral coldness, cardiopulmonary resuscitation lasting more than 10 minutes within 2 weeks before inclusion, ongoing treatment with anticoagulants such as low-molecular-weight heparin or warfarin	Known bleeding disorders, or any contraindication to fibrinolysis, allergy to study drugs	Allergy to study drugs
Dobrzycki *et al.*, 2006 [93]	18 to 80 years	From 30 minutes to 12 hours	Severe neoplastic disease or any organ dysfunction drug addiction, alcohol addiction or pregnancy, recent surgical revascularisation	Left bundle branch block, shock	Contraindication to fibrinolysis	
Dieker *et al.*, 2006 [92]	21 years or more	4 ½ hours or less	Previous CABG; severe concomitant disease with a life expectancy of less than 12 months	Killip class II or more; coma	Known contraindication to thrombolytic therapy;	Pulseless femoral arteries; known allergy or hypersensitivity to aspirin, clopidogrel, enoxaparin or abciximab

APPENDIX F. INTERVENTIONS IN THE TWO ARMS OF THE RCTS

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
Ribeiro *et al.*, 1993 [84]	Streptokinase		Not mentioned	Yes	Not mentioned	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned
	PPCI		4% CABG	Yes	Not mentioned	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned
Gibbons *et al.*, 1993 [78]	Duteplase		Not mentioned	Yes	Not mentioned	Not mentioned	Yes	Yes	Not mentioned	Not mentioned
	PPCI		Not mentioned	Yes	Not mentioned	Not mentioned	Yes	Yes	Not mentioned	Not mentioned
Grines *et al.*, 1993 [79]	t-PA (Activase)		15% rescue PCI	Yes	Not mentioned	Not mentioned	At discretion of the investigator	Yes	Not mentioned	Not mentioned
	PPCI		5% CABG after angiography without attempting PPCI	Yes	Not mentioned	Not mentioned	At discretion of the investigator	Yes	Not mentioned	Not mentioned
De Boer *et al.*, 1994 [75]	Streptokinase		11% rescue PCI	Yes	No[59]	No	Yes (% unknown) (Zijlstra *and al*, 1993)	Yes	Not mentioned	Not mentioned
	PPCI		2% CABG	Yes	No	No	Yes (% unknown)	Yes	Not mentioned	Not mentioned

59 See [209] Henriques JP, Zijlstra F, van 't Hof AW, de Boer MJ, Dambrink JH, Gosselink AT, *et al.* Primary percutaneous coronary intervention versus thrombolytic treatment: long term follow up according to infarct location. Heart. 2006 Jan;92(1):75-9.

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
Garcia *et al.*, 1999 [77]	Accelerated t-PA		Not mentioned	98%	Not mentioned	No	53%	Yes	51%	Not mentioned
	PPCI	13%	1% CABG	98%	Not mentioned	No	48% Not specified	Yes	45% Not specified	Not mentioned
Berrocal *et al.*, 2003 [90]	Streptokinase		17% rescue PCI	Yes (100 to 250 mg)	No	Not mentioned	At discretion of the physician	Not mentioned	Not mentioned	Not mentioned
	PPCI	6.4%	Not mentioned	Yes (100 to 250 mg)	If stents 500 mg BID for 1 month	Not mentioned	At discretion of the physician	Yes	Not mentioned	Not mentioned
Ribichini *et al.*, 1998 [85]	Accelerated t-PA		4% rescue PCI	In ED = 100%, 72% per hospitalization	24%	Not mentioned	67% per hospitalization	Yes	40% per hospitalization	13% per hospitalization
	PPCI	58%	0% CABG	In ED = 100%, 11% per hospitalization	90% (in the protocol = ticlopidin 500 mg die for 1 month)	Not mentioned	64% per hospitalization	Yes	33% per hospitalization	15% per hospitalization

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
Zijlstra *et al.*, 1997 [89]	Streptokinase	Not mentioned	Not mentioned	Yes	No[60]	No	Yes, except if contraindicated (% unknown)	Yes	Patients with cardiac insufficiency and with ejection fraction lower than 40% (% unknown)	Not mentioned
	PPCI	Not mentioned	2% CABG after angiography without attempting PPCI		No	No	Yes, except if contraindicated (% unknown)	Yes		Not mentioned
GUSTO IIB, 1997 [81]	Accelerated t-PA		Not mentioned	98.1%	Not mentioned	Not mentioned	IV = 30.1% Oral = 72.7%	Yes	45.1%	Not mentioned
	PPCI	5%	3.7% had same day CABG	98.0%	Not mentioned	Not mentioned	IV = 26.9 Oral = 69.9	Yes	40.3%	Not mentioned
Vermeer *et al.*, 1999 [61]	Accelerated t-PA		No rescue PCI was allowed in this arm	Yes	Not mentioned	No	Not mentioned	Yes	Not mentioned	Not mentioned
	Transfer PPCI	21%	Not mentioned	Yes	Not mentioned	No	Not mentioned	Yes	Not mentioned	Not mentioned
Aversano *et al.*,	Accelerated t-PA		Not mentioned	Yes	Not mentioned	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned

60 See Henriques *et al.*, 2006 [209].

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
2002 [73]	PPCI	63%	No CABG	Yes	Not mentioned	76%	Not mentioned	Not mentioned	Not mentioned	Not mentioned
de Boer *et al.*, 2002 [76]	Streptokinase		Not mentioned	Yes	Not mentioned	No	Not mentioned	Yes	Not mentioned	Not mentioned
	PPCI	51%	Not mentioned	Yes	For patients with stents, ticlopidin for two weeks	No	Not mentioned	Yes	Not mentioned	Not mentioned
Widimsky *et al.*, 2000 [88]	Streptokinase		7% rescue PCI (in Bednar *et al.*, 2003))	Yes (900 mg IV)	Ticlopidin 500 mg for one month	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned
	Transfer PPCI	79%	Not mentioned	Yes (900 mg IV)	Ticlopidin 500 mg for one month	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned
Le May *et al.*, 2001 [83]	Accelerated t-PA		11.5% rescue PCI	Yes	Ticlopidin or clopidogrel 42.3% at hospital discharge	Not mentioned	86.4% at hospital discharge; 78% at 6 months	Yes	42.4% at hospital discharge ; 45.8% at 6 months	57.6% at hospital discharge ; 63.8% at 6 months
	PPCI	81%	6.5% CABG after angiography without attempting PPCI. No rescue CABG	Yes	Ticlopidin or clopidogrel 78% at hospital discharge	Not mentioned	84.7% at hospital discharge; 79.7% at 6 months	Yes	45.8% at hospital discharge; 37.3% at 6 months	33.9% at hospital discharge; 61% at 6 months

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
Schomig *et al.*, 2000 [86]	Accelerated t-PA		Not mentioned	Yes	Not mentioned	Not mentioned	At baseline = 87.0%	Yes	At baseline = 87.0%	At baseline = 84.1%
	PPCI	99%	Not mentioned	Yes	Ticlopidin 250 mg BID for four weeks	99%	At baseline = 85.9%	Yes	At baseline = 88.7%	At baseline = 83.1%
Bonnefoy *et al.*, 2002 [74]	Accelerated t-PA		Rescue PCI = 26%	95.8%	59.8%	Not mentioned	93%	Yes	53.8%	Statins = 57%
		72%	0% CABG	97.3%	75.6%	23%	86.3%	Yes	49.2%	Statins = 54.7%
Andersen *et al.*, 2003 [71]	Accelerated t-PA		5% repeat fibrinolysis; 3% rescue PCI	96% for both groups following randomization	Not mentioned	Not mentioned	87%; no statistical difference between arms	Yes	36%; no statistical difference between arms	51%; no statistical difference between arms
	PPCI	81%	0.1% CABG		If stents, ticlopidin (500 mg) or clopidogrel (75 mg) for 1 month	39%		Yes		
Kastrati *et al.*, 2002 [82]	Accelerated t-PA		6% rescue PCI	Yes	?	100%	97%	Yes	93%	90%
	PPCI	95%	0% CABG	Yes	Clopidogrel 75mg for 4 weeks	100%		Yes		
Widimsky *et al.*,	Streptokinase		6.4% rescue PCI			No	Not mentioned	Yes	Not mentioned	Not mentioned

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
2003 [87]	PPCI after transfer	63%	Not mentioned	Aspirin 500 mg IV	Clopidogrel 75 mg for one month	Yes (% unknown)	Not mentioned	Yes	Not mentioned	Not mentioned
Grines *et al.*, 2002 [80]	Streptokinase 32% and t-PA 68%		Not mentioned	95%	Not mentioned	Not mentioned	68%	Yes	65%	Not mentioned
	PPCI	34%	Not mentioned	96%	Not mentioned	Not mentioned	51%	Yes	68%	Not mentioned
Svensson *et al.*, 2006 [91]	Reteplase		23%	100%	Not mentioned	No	Not mentioned	Yes	Not mentioned	Not mentioned
	PPCI	Use encouraged (% unknown)	1%	100%	If stent (% unknown)	All per protocol	Not mentioned	Yes	Not mentioned	Not mentioned
Dobrzycki *et al.*, 2006 [93]	Streptokinase		3.6% rescue PCI	100%	Not mentioned	No	82%	92%	75%	79%
	PPCI after transfer	78.9 %	Not mentioned	100%	Not mentioned	100%	93%	95%	90%	83%
Dieker *et al.*, 2006 [92]	43% reteplase, 35% tenecteplase and 22% accelerated tPA		48% rescue PCI	100%	Not mentioned	No	Not mentioned	Yes	Not mentioned	Not mentioned
	PPCI	Yes	Not mentioned	100%	Yes if stent	100%	Not mentioned	Yes	Not mentioned	Not mentioned

Study	Arm	Stents	Rescue interventions	Aspirin	Thienopyridines	Glycoprotein IIb/IIIa inhibitors	B-Blockers	Heparin	ACE inhibitors	Lipid treatment
Armstrong *et al.*, 2006 [72]	Tenecteplase		14% rescue PCI	99%	0%	0%	Not mentioned	Yes	Not mentioned	Not mentioned
	PPCI	97%		98%	97%	97% of 91 patients	Not mentioned	Yes	Not mentioned	Not mentioned

APPENDIX G. METHODOLOGICAL QUALITY OF THE RANDOMIZED CONTROLLED TRIALS

Study	Selection bias		Performance bias	Attrition bias	Classification bias	
	Randomization		Similar use of ancillary interventions[2]	Similar withdrawals in both groups[61]	Blinded outcome assessment	Similar follow-up for ascertainment of events
	Method of concealment of allocation schedule	Similar dropouts in both groups [62]				
Ribeiro *et al.*, 1993 [84]	Suboptimal (sealed envelope)	Adequate: 2% of approached patients refused to participate.	No description	Adequate	No blinded outcome assessment (personal communication)	Inadequate : in-hospital period
Gibbons *et al.*, 1993 [78]	Unknown	No description	No description	No description	No description	Inadequate : in-hospital period
Grines *et al.*, 1993 [79]	Suboptimal (sealed envelope)	No description	No description	No description	No description	Inadequate : in-hospital period
de Boer *et al.*, 1994 [75]	Suboptimal (sealed envelope)	No description	No description	Adequate	Blinded assessment of ECG and cardiac enzymes. (Zijlstra *et al.*, 1993)	Inadequate : in-hospital period
Garcia *et al.*, 1999	Suboptimal (sealed envelope)	Inadequate: 23% of patients were	Inadequate	Adequate	Presence of a BEPC (personal	Adequate

61 Considered adequate if information provided, inadequate if not
62 Considered adequate if information provided, inadequate if not or if there was more than a 10% loss

Study	Selection bias		Performance bias	Attrition bias	Classification bias	
	Randomization		Similar use of ancillary interventions[2]	Similar withdrawals in both groups[61]	Blinded outcome assessment	Similar follow-up for ascertainment of events
	Method of concealment of allocation schedule	Similar dropouts in both groups [62]				
[77]		not randomised because of exclusion criteria, patient refusal or physician's preference.			communication)	
Berrocal *et al.*, 2003 [90]	Suboptimal (sealed envelope)	No description	No description	Adequate	Blinded assessment of ECG	Inadequate : in-hospital period
Ribichini *et al.*, 1998 [85]	Suboptimal (sealed envelope)	Adequate	Inadequate	Adequate	No blinded outcome assessment (personal communication)	Inadequate : in-hospital period
Zijlstra *et al.*, 1997 [89]	Optimal (telephone service)	Inadequate: 15% refused to participate because of patient or physician's preference	Inadequate	Adequate	No description	Adequate
GUSTO IIB, 1997 [81]	Optimal (telephone service)	No description	Adequate	Adequate	Presence of a BEPC	Adequate
Vermeer *et al.*, 1999 [61]	Optimal (telephone service)	No description	No description	Adequate	No description	Adequate
Aversano *et al.*, 2002 [73]	Optimal (telephone service)	Inadequate: 5% of patients randomized in the	No description	Adequate	Presence of a BEPC	Adequate

Study	Selection bias		Performance bias	Attrition bias	Classification bias	
	Randomization		Similar use of ancillary interventions[2]	Similar withdrawals in both groups[61]	Blinded outcome assessment	Similar follow-up for ascertainment of events
	Method of concealment of allocation schedule	Similar dropouts in both groups [62]				
		fibrinolysis arm had contraindications to fibrinolysis treatment but were still included in the analysis. According to the protocol, they should have been removed.				
De Boer *et al.*, 2002 [76]	Optimal (telephone service)	Adequate	No description	Adequate	Blinded assessment of cumulative cardiac enzyme release	Adequate
Widimsky *et al.*, 2000 [88]	Optimal (telephone service)	Inadequate: 125 eligible patients refused to participate in the study. There were 300 patients that agreed.	No description	Adequate	No description	Adequate
Le May *et al.*, 2001 [83]	Suboptimal (sealed envelope)	Inadequate: 218 patients met inclusion criteria; 123 were randomized.	Inadequate	Adequate	Presence of a BEPC	Adequate

Study	Selection bias		Performance bias	Attrition bias	Classification bias	
	Randomization		Similar use of ancillary interventions[2]	Similar withdrawals in both groups[61]	Blinded outcome assessment	Similar follow-up for ascertainment of events
	Method of concealment of allocation schedule	Similar dropouts in both groups [62]				
Schomig *et al.*, 2000 [86]	Suboptimal (sealed envelope)	No description	Inadequate	Adequate	Presence of a BEPC (personal communication)	Adequate
Bonnefoy *et al.*, 2002 [74]	Optimal (telephone service)	Adequate	Inadequate	Adequate	Presence of a BEPC	Adequate
Andersen *et al.*, 2003 [71] *considered as 2 trials*	Optimal (telephone service)	Inadequate: 505 patients refused randomization; 334 did not participate for unknown reasons. 1572 patients were included in the study.	Inadequate.	Adequate	Presence of a BEPC	Adequate
Kastrati *et al.*, 2002 [82]	Suboptimal (sealed envelope)	Adequate: 39 patients declined to participate. 162 patients were randomized.	Inadequate	Adequate	Presence of a BEPC (personal communication)	Adequate
Widimsky *et al.*, 2003 [87]	Optimal (telephone service)	No description	No description	Adequate	No description	Adequate
Grines *et al.*, 2002 [80]	Suboptimal (allocation was concealed through telephone service in the USA, but elsewhere, concealment was through envelope)	No description	Inadequate	No description	Presence of a BEPC	Adequate

Study	Selection bias		Performance bias	Attrition bias	Classification bias	
	Randomization		Similar use of ancillary interventions[2]	Similar withdrawals in both groups[61]	Blinded outcome assessment	Similar follow-up for ascertainment of events
	Method of concealment of allocation schedule	Similar dropouts in both groups [62]				
Svensson *et al.*, 2006 [91]	Suboptimal (sealed envelope)	No description	Inadequate	Adequate	Blinded assessment of EKGs up to six hours after randomization. Blinded assessment of coronary angiograms	Adequate
Dobrzycki *et al.*, 2006 [93]	Suboptimal (Randomisation was not done in a site remote from the RCT)	Adequate (no dropouts)	Inadequate	Adequate	No blinded outcome assessment (personal communication)	Adequate
Dieker *et al.*, 2006 [92]	Optimal (interactive voice response system)	No description	Inadequate	No description	Single blinded research physician	Adequate
Armstrong *et al.*, 2006 [72]	Suboptimal (sealed envelope) (personal communication)	No description	Inadequate	Adequate	Presence of a BEPC	Adequate

APPENDIX H. TREATMENT DELAYS, STUDY SITES AND NUMBER OF CENTERS FOR THE RCTS

Study / Host countries	Number of centres	Door-needle delay (median time unless noted)	Door-balloon delay (median time)	PPCI-related delays
Ribeiro *et al.*, 1993 / Brazil [84]	1	Not mentioned	Not mentioned	59 minutes (238 – 179)[63]
Gibbons *et al.*, 1993 / United States [78]	1	Not mentioned	Not mentioned	45 minutes (277 – 232)[64]
Grines *et al.,* 1993 / Europe and United States [79]	$\geq$ 3	32 minutes[65]	60 minutes	12 minutes (229 – 241)[66]
de Boer *et al.*, 1994 / the Netherlands[67][75]	Not mentioned	Not mentioned	Not mentioned	19 minutes (195 – 176)[68]
Garcia *et al.*, 1999 / Spain [77]	1	Not mentioned	Not mentioned	47 minutes (197– 150)
Berrocal *et al.*, 2003 / Argentina [90]	1	Not mentioned	Not mentioned	74 minutes (299 – 225)
Ribichini *et al.*, 1998 / Italy [85]	1	36 minutes[69]	67 minutes	29 minutes (219 – 190)
Zijlstra *et al.*, 1997 / the Netherlands [89]	1	29 minutes[70]	68 minutes	Not mentioned
GUSTO IIB[71], 1997 [81]	$\geq$ 3	72 minutes[72]	114 minutes	48 minutes (228 – 180)
Vermeer *et al.*, 1999 / the Netherlands [61]	$\geq$ 3	45 minutes[73]	140 minutes	95 minutes (230 – 135)
Aversano *et al.,* 2002 / United States [73]	$\geq$ 3	46 minutes	101 minutes	55 minutes
de Boer *et al.*, 2002 / the Netherlands [76]	1	31 minutes	59 minutes	23 minutes (266 – 243)
Widimsky *et al.*, 2000 / Czech Republic [88]	$\geq$ 3	22 minutes[74]	95 minutes	83 minutes (215 – 132)

63 In the text: *time to treatment*, without further specification on this time interval.
64 Mean
65 Mean
66 Difference between door-angiography and door- needle (and not door-balloon minus door-needle)
67 All studies from the Netherlands come from the same team of researchers: De Boer *et al.*, (1994), Zijlstra *et al.*, (1993), Zijlstra *et al.*, (1997)
68 Mean
69 Mean
70 Mean
71 Countries that participated in GUSTO IIB were: United States, Canada (2 patients), Spain, Belgium, Italy, Germany, Sweden, Switzerland, and Australia
72 Mean
73 Mean
74 Impossible to determine if the numbers correspond to mean or median values.

Study / Host countries	Number of centres	Door-needle delay (median time unless noted)	Door-balloon delay (median time)	PPCI-related delays
Le May *et al.*, 2001 / Canada [83]	1	52 minutes	138 minutes	90 minutes (230 – 140)
Schomig *et al.*, 2000 / Germany [86]	2?	30 minutes	65 minutes	35 minutes (215 – 180)
Bonnefoy *et al.*, 2002 / France [74]	$\geq$ 3	Not mentioned	Not mentioned	60 minutes (190– 130)
Andersen *et al.*, 2003 With transfer / Denmark [71]	$\geq$ 3	45 minutes	112 minutes	55 minutes
Andersen *et al.*, 2003 On-site PPCI / Denmark [71]	$\geq$ 3	50 minutes	91 minutes	28 minutes
Kastrati *et al.*, 2002 / Germany [82]	2	35 minutes	75 minutes	60 minutes (225 – 165)
Widimsky *et al.*, 2003 / Czech Republic [87]	$\geq$ 3	Not mentioned	Not mentioned	92 minutes (277 – 185)[75]
Grines *et al.*, 2002 / United States [80]	$\geq$ 3	51 minutes	155 minutes	Cannot determine
Svensson *et al.*, 2006 / Sweden [91]	7	Not mentioned	Not mentioned	88 minutes (202– 114)
Dobrzycki *et al.*, 2006 / Poland [93]	14	44 minutes[76]	158[77]	118 minutes (301 -183)
Dieker *et al.*, 2006 / the Netherlands [92]	12	Not mentioned	Not mentioned	60 minutes (230 -170)
Armstrong *et al.*, 2006 / Canada (prehospital randomization) [72]	4	46 minutes	104 minutes	49 minutes
Armstrong *et al.*, 2006 / Canada (hospital randomization) [72]	4	61 minutes	143 minutes	88 minutes
Armstrong *et al.*, 2006 / Canada (total) [72]	4	51 minutes	127 minutes	63 minutes

75 Impossible to determine if the numbers correspond to mean or median values.
76 Median randomisation to treatment
77 Median randomisation to treatment

APPENDIX I-1. SHORT AND LONG-TERM MORTALITY IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH PREDOMINANTLY FL (BY ENROLMENT PERIOD)

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Every *et al.*, [152] Myocardial Infarction Triage and Intervention Project (MITI Project) 1988-1994	In-hospital	n = 1,050 (whole cohort) 5.5 n = 702 ideal* 4.4 n = 599 high-risk 8.7	n = 2,095 (whole cohort) 5.6 n = 1,674 ideal* 4.6 n = 1,144 high-risk 8.1	0.96 (0.72-1.37)	NA
	3-year	For the whole cohort: NA n = 702 ideal* 13.6 n = 599 high risk** 24.8	For the whole cohort: NA n = 1,674 ideal* 12.0 n = 1,144 high-risk** 17.8	0.95 (0.8-1.2)	For the whole cohort 1.23 (0.61-2.49) Ideal patients* 1.00 (0.74-1.40) High-risk: 1.10(0.82-1.53)

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Rogers *et al.*, [149] Alabama Registry of Myocardial Ischemia 1990-1992	In-hospital	n = 118 5.1	n = 230 3.0	1.72 (0.59-5.04)	NA
	1-year	n = 118 12.0	n = 230 9.0	1.23 (0.61-2.49)	1.9 (0.7-4.8)
Brush *et al.*, [175] 1990-1994	In-hospital	n = 62 3.2	n = 62 6.5		
Hayashi *et al.*, [178] Japan 1990-2001	30-day	n = 74 4.1	n = 186 3.2		NA
De Labriolle *et al.*, [171] 1992-2004	1-year	n = 495 7.3	n = 299 11.0		1.57 (0.97-2.59)
Sakurai *et al.*, [165] Miyagi Study Group for AMI Japan 1992-2000	30-day	n = 1,822 4.8	n = 319 9.1		NA
Tiefenbrunn *et al.*, [167] Second National Registry of Myocardial Infarction (NRMI-2) 1994-1995	In-hospital	Subgroup ST elevation n =3,087 5.2	Subgroup ST elevation or LBBB n =21,641 5.4	0.96 (0.83-1.12)	NA

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
		n = 170	n = 321		
INCLUDED IN THE MAGID ET AL.'S STUDY	Subgroup of patients with cardiogenic shock	32.4	52.3	0.44 (0.30-0.65)	NA
Magid *et al.*, [195]	In-hospital	N = 21,973 4.0	N = 40,326 5.8	NA	NA
NATIONAL REGISTRY OF MYOCARDIAL INFARCTION USA 1994-1998 Zahn *et al.*, [183] Maximal Individual Therapy in acute myocardial infarction (MITRA) and the Myocardial Infarction Registry (MIR) 1994-1998	In-hospital	n = 1,327 6.4	n = 8,579 11.3		0.58 (0.44-0.77)
Danchin *et al.*, [157] Nationwide French survey USIC-1995 1995	30-day	n = 152 9.2	n = 569 7.6	1.27 (0.68-2.36)	NA
	1-year	14.5	10.5		

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Hansen *et al.*, [176] Denmark 1995	In-hospital	n = 82 3.6	n = 82 4.9		NA
	6-month	4.9	7.3		NA
Himbert *et al.*, [173] Patients' enrolment period unknown Published in 1997	In-hospital	n = 49 8.2	n = 57 3.5		
Hsu *et al.*, [161] 1997-1999	30-day	n = 103 7.8	n = 99 12.1		NA
	1-year	9.7	18.2		NA

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Fassa *et al.*, [159] Acute myocardial infarction in Switzerland (AMIS Plus) Project 1997-2005	In-hospital	n = 4,221 4.1	n = 3,340 5.7		0.68 (0.48-0.97)
Steffenino *et al.*, [150] Myocardial Infarction with Severe prognosis: observation of Treatment with Angioplasty or Lysis (MISTRAL) 1998-1999	In-hospital 1-year	n = 721 8.5 13.0	n = 1,090 7.2 12.9	1.20 (0.85-1.70) 1.01 (0.l76-1.34)	NA NA
Solodky *et al.*, [166] (5-months survey of 1996, 2-months surveys of 1998 and 2000)	30-day	n = 152 2	n = 886 6.3		0.84 (0.16-3.29)
Ober *et al.*, [164] 2000-2002	In-hospital	n = 40 5.0	n = 93 6.5	0.87 (0.19-3.95)	NA
Danchin *et al.*, [148] Nationwide French survey Unités des soins intensives coronariens (USIC-2000) 2000	In-hospital 1-year	n = 434 6.7 11	n = 365 8.0 11	0.83 (0.48-1.41) 1.01 (0.76-1.34)	NA NA

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Buiatti *et al.*, [156] AMI-Florence 2000-2001	6-month	n = 461 10.2	n = 45 8.9	1.06 (0.38-2.93)	NA
Zeymer *et al.*, [15] ACOS Registry 2000-2002	1-year	n = 2,707 3.5	n = 1,734 4.7		
Dryja *et al.*, [172] Poland 2003	30-day	N = 422 5.5	N = 240 7.9		NA
Huynh *et al.*, [169] AMI-QUEBEC 2003	In-hospital	n = 766 3.9	n = 626 6.1		NA
	(Excluded patients in shock and with contra-indications to FL)	N = 613 3.5	N = 545 5.0		
Kalla *et al.*, [162] Vienna STEMI Registry††† 2003-2004	In-hospital	n = 631 8.1	n = 281 8.2	0.98 (0.59-1.62)	NA

First author and study, Patient enrolment period	Mortality time frame	PPCI Total number of patients in the group % of patients with event	FL Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
	Subgroups:				
	Women	12.3	15.8	0.74 (0.35-1.58)	NA
	Cardiogenic shock	47.3	48.6	1.00 (0.46-2.20)	NA NA
Stenestrand *et al.*, [151] Swedish National Prospective Registry 1999-2004		n =7,084	n =16,043		
	7-day	3.5	8.8	0.38 (0.33-0.44)	0.61 (0.51-0.73)
	1-year	7.6	15.9	0.45 (0.41-0.50)	0.68 (0.60-0.76)

NA: not available, *Ideal patients in the Every study: patients without contraindications to fibrinolytic therapy, systolic blood pressure <180 mmHg, no shock, no prior bypass surgery, stroke or bleeding. **: PAMI high-risk features: one of the following age>70 years, anterior STEMI, heart rate>100/min

APPENDIX I-2. SHORT AND LONG-TERM MORTALITY IN THE ELDERLY PATIENTS IN OBSERVATIONAL STUDIES

First author and study, Patient s' enrolment period	Minimum age of enrolled patients	Mortality time frame	PPCI Total number of patients in the group % of patients with event	Fibrinolysis Total number of patients in the group % of patients with event	Odds ratios or risk ratios for PPCI versus FL (95% CI)	
					Unadjusted	Adjusted
Berger *et al.*, [177] Cooperative Cardiovascular Project (CCP) United States 1994-1996	≥ 65 years	30-day	n = 700 8.9	n = 8,487 10.6		
		1-year	13.1	15.8		
Zahn *et al.*, [183] MIR and MITRA studies Germany 1994-1998	≥ 65 years	In-hospital	n = 561 10.6	n = 4,081 17.2		NA
Subgroup analysis	≥ 75 years	In-hospital	n = 202 14.3	n = 1,428 24.7		NA
Tiefenbrunn *et al.*, [167] National Registry of Myocardial Infarction (NRMI-2) United States 1995	≥ 75 years	In-hospital	n = 632 14.4	n = 3,370 16.5		NA
Goldenberg *et al.*, [160] Israel 1998-1999	≥ 70years	In-hospital	n = 44 14.0	n = 86 12.0	1.23 (0.43-3.52)	NA

		6-month	18.2	19.8	0.92 (0.37-2.30)	NA
Bueno et al., [155] PPRIMM75 Registry Spain 1988-2000	≥75 years	In-hospital	n = 164 25.0	n = 164 29.3		
Solodky *et al.*, [166] Israel 5-month surveys 1996, 2-month surveys 1998 and 2000)	≥75 years	30-day	n = 22 13.6	n = 139 18.7		1.43 (0.19-10.0)
Subgroup analysis Mehta *et al.*, [163] Global Registry of Acute Coronary Events (GRACE) Multi-national 1999-2002	≥ 70 years	In-hospital	n = 365 13.5	n = 769 14.8	0.90 (0.63-1.30)	0.62 (0.39-0.96)
Bardaji *et al.*, [154] TRIANA-2 Registry Spain 2002	≥75 years	In-hospital	n = 92 23.9	n = 146 21.2	1.17 (0.63-2.17)	NA
Huynh *et al.*, [169] AMI-QUEBEC Canada 2003	≥65 years	In-hospital	n = 295 5.8	n = 214 13.6		
Subgroup analysis	≥75 years	In-hospital	n = 133 10.5	n = 104 18.2		
Kalla *et al.*, [162] Vienna STEMI Registry Austriche 2003-2004	>75 years	In-hospital	n = 109 22.1	n = 54 18.2	1.19 (0.53-2.67)	NA

PPCI: Primary PCI, FL: Fibrinolytic therapy, NA: not available

APPENDIX I-3. MORTALITY IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH PRE-HOSPITAL FIBRINOLYSIS

First author and study, Patient enrolment period	Mortality	PPCI n in group %	Fibrinolysis n in group %	Odds ratios for PCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Roncalli *et al.*, [174] 1995-1999	In-hospital	n = 157 2.5	n = 161 2.5	1.03 (0.27-3.86)	NA
	3-year	9.7	4.9	1.96 (0.83-4.67)	NA
Juliard *et al.*, [153] Patients' enrolment period unknown Published in 1999	In-hospital	N = 170 4.7	N = 170 4.1		NA
Danchin *et al.*, [148] Nationwide French survey Unités des soins intensives coronariens (USIC-2000) 2000	In-hospital	n = 434 6.7	n = 180 3.3	1.95 (0.82-4.65)	NA
	1-year	11	6	1.85 (0.94-3.61)	NA

APPENDIX I-4. REINFARCTION IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH IN-HOSPITAL FIBRINOLYSIS

First author and study, Patient s' enrolment period	Reinfarction time frame	PPCI n in group %	Fibrinolysis n in group %	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
Every *et al.*, [152] Myocardial Infarction Triage and Intervention Project (MITI Project) 1988-1994	In-hospital	n = 1,050 3.5	n = 2,095 4.3	0.82 (0.56-1.21)	NA
Rogers *et al.*, [149] Alabama Registry of Myocardial Ischemia 1990-1992	In-hospital	n = 118 2.5	n = 230 1.7	1.53 (0.37-6.28)	NA
Tiefenbrunn *et al.*, [167] Second National Registry of Myocardial Infarction (NRMI-2) 1994-1995	In-hospital	n =4,052 2.5	n =24,705 2.9	0.96 (0.83-1.12)	NA
Hayashi *et al.*, [178] Japan 1990-2001	30-day	n = 74 0	n = 186 5.3		NA
Hansen *et al.*, [176] Denmark	In-hospital	n = 82 0	n = 82 2.4		NA

1995	6-month	1.2	7.3		NA
Zahn *et al.*, [180] Maximal Individual Therapy in acute myocardial infarction (MITRA) and the Myocardial Infarction Registry (MIR) 1994-1998	In-hospital	n = 1,385 2.3	n = 8,733 5.2	0.43 (0.28-0.67)	NA
Steffenino *et al.*, [150] Myocardial Infarction with Severe prognosis: observation of treatment with Angioplasty or Lysis (MISTRAL) 1998-1999	In-hospital	n = 721 1.7	n = 1,090 1.5	1.14 (0.55-2.41)	NA
	1-year	1.8	3.4	0.54 (0.45-0.94)	NA
Hsu *et al.*, [161] 1997-1999	30-day	n = 103 2.9	n = 99 2.0		NA
	1-year	n = 103 7.8	n = 99 13.1		NA
Danchin *et al.*, [148] Nationwide French survey Unités des soins intensives coronariens (USIC-2000) 2000	In-hospital	n = 434 1.1	n = 365 1.6	0.58 (0.17-1.93)	NA
Zeymer *et al.*, [15] ACOS Registry 2000-2002	1-year	N = 2,707 2.5	N = 1,734 2.8		
Solodky *et al.*, [166] (5-month survey 1996, 2-months surveys 1998, 2000)	In-hospital	n = 152 2.0	n = 886 2.8		NA

		n = 759	n = 604		
Huynh *et al.*, [169] Registry of Acute Myocardial Infarction in Quebec (AMI-QUEBEC) 2003	In-hospital	2.3	3.0	1.14 (0.72-1.37)	NA
Stenestrand *et al.*, [151]		n = 7,084	n = 16,043		
RIKS-HIA 1999-2004	7-day	2.0	4.0	0.49 (0.41-0.59)	0.79 (0.70-0.88)
	1-year	4.8	9.6	0.47 (0.42-0.53)	0.61 (0.53-0.71)

NA: not available

APPENDIX I-5. REINFARCTION IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH FIBRINOLYSIS AND ENROLLING ONLY ELDERLY PATIENTS

Name of first author and study Period of patients' enrolment	Age of enrolled patients	e-infarction	PPCI n in group %	Fibrinolysis n in group %	Odds ratios for PPCI versus fibrinolysis (95% CI)	
					Unadjusted	Adjusted
Goldenberg *et al.*,‡‡ [160] 1998-1999	≥70 years	In-hospital	n = 44 2.2	n = 86 4.6	0.63 (0.08-0.40)	NA
		6-month	2.3	12.8	0.65 (0.45-0.94)	NA
Mehta *et al.*, [163] Global Registry of Acute Coronary Events (GRACE) ‡‡ 1999-2002	≥70 years	In-hospital	n = 365 1.1	n = 769 5.7	0.19 (0.08-0.40)	0.15 (0.05-0.44)

APPENDIX I-6. REINFARCTION IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH PRE-HOSPITAL FIBRINOLYSIS

Name of first author and study Period of patients' enrolment	Re-infarction time frame	PPCI n in group %	Fibrinolysis n in group %	Odds ratios for PPCI versus fibrinolysis (95% CI)	
				Unadjusted	Adjusted
		n = 157	n = 161		
Roncalli *et al.*, [174] 1995-1999	In-hospital	1.3	2.5	0.57 (0.12-2.74)	NA
	3-year	2.5	3.1	0.83 (0.24-2.96)	NA
Danchin *et al.*, [148] Nationwide French survey Unités des soins intensives coronariens (USIC-2000) 2000		n = 434	n =180		
	In-hospital	1.1	2.8	0.33(0.09-1.18)	NA
Stenestrand *et al.*, [151]		n = 7,084	n = 3,078		
RIKS-HIA 1999-2004	7-day	2.0	3.4	0.57 (0.45-0.74)	NA
	1-year	4.8	9.0	0.51 (0.43-0.60)	NA

APPENDIX I-7. IN-HOSPITAL STROKE IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH IN-HOSPITAL FIBRINOLYSIS

First author and study, Patients' enrolment period	PPCI Total number of patients in the group % of patients with event	Fibrinolysis Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI)	
			Unadjusted	Adjusted
Every *et al*., [152] Myocardial Infarction Triage and Intervention Project (MITI Project) USA 1988-1994	n = 1,050 0.7	n = 2,095 1.5	0.50 (0.23-1.12)	NA
Rogers *et al*., [149] Alabama Registry of Myocardial Ischemia USA 1990-1992	n = 118 0.8	n = 230 0		NA
Brush *et al.*, [175] USA 1990-1994	N = 62 0	N = 62 4.8		NA
Magid *et al.*, [195] *NATIONAL REGISTRY OF MYOCARDIAL INFARCTION* USA 1994-1998	N = 21,973 0.4	N = 40,326 9.7	NA	NA
Zahn *et al.*, [183] MIR and MITRA Germany 1994-1996	n = 1,327 1.5	n = 8,579 1.5		1.03 (0.64-1.65)

Roncalli *et al.*, [174] France 1995-1999	n = 157 0.6	n = 161 1.8		
Hansen *et al.*, [176] Denmark	n = 82 0.7	n = 82 2.0		NA
Hsu *et al.*, [161] 1997-1999	n = 103 1.9	n = 99 3.0		NA
Steffenino *et al.*, [150] Myocardial Infarction with Severe prognosis: observation of Treatment with Angioplasty or Lysis (MISTRAL) 1998-1999	n = 721 0.5	n = 1,090 0.5	1.00 (0.35-4.32)	NA
Mehta *et al.*, [163] GRACE 1999-2002	n = 365 1.1	n = 769 2.7		NA
Solodky *et al.*, [166] (5-months survey 1996, 2-month surveys 1998, 2000)	n = 152 0.8	n = 886 2.1%		NA
Stenestrand *et al.*, [151] RIKS-HIA 1999-2004	n = 7,084 1.4	n = 19,121 4.3		NA
Danchin *et al.*, [148] Nationwide French survey Unités des soins intensives coronariens (USIC-2000) 2000	n = 434 0.2	n = 365 1.4	0.23 (0.04-1.39)	NA
Zeymer *et al.*, [15] ACOS Registry 2000-2002*	n = 2,707 0.8	n = 1,734 0.5		NA
Huynh *et al.*, [169] Registry of Acute Myocardial Infarction in Quebec (AMI-QUEBEC) 2003	n = 759 0.7	n = 604 2.3	0.28 (0.14-0.89)	NA

NA: not available
*: In-hospital strokes not available, data presented are for 1-year cumulative incidences

APPENDIX I-8. IN-HOSPITAL STROKE IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH FIBRINOLYSIS AND ENROLLING ONLY ELDERLY PATIENTS

First author and study, Patients' enrolment period	Age of enrolled patients	PPCI Total number of patients in the group % of patients with event	Fibrinolysis Total number of patients in the group % of patients with event	Odds ratios for PPCI versus fibrinolysis (95% CI) Unadjusted	 Adjusted
Berger *et al.*, [177] Cooperative Cardiovascular Project (CCP) ‡ 1994-1996	≥ 65	n = 2,038 2.1	n = 18,645 3.0	0.70 (0.52-0.97)	NA
Goldenberg *et al.*, [160] 1998-1999	≥70	n = 44 2.2	n = 86 1.1	2.00 (0.20-19.46)	NA
Mehta *et al.*, [163] Global Registry of Acute Coronary Events (GRACE) 1999-2002	≥70	n = 365 1.1	n = 769 2.8	0.39 (0.15-0.94)	0.43 (0.13-1.34)
Bueno *et al.*, [155] 1988-2000	≥75	n = 164 5.5	n = 164 4.3		
Bardaji *et al.*, [154] Triana Registry 2002	≥ 75	n = 92 1.2	n = 146 5.5	0.45 (0.11-1.89)	NA
Huynh *et al.*, [169] AMI-QUEBEC 2003 Substudy	≥ 75	n = 109 0.9	n = 88 4.6		

APPENDIX I-9. IN-HOSPITAL STROKE IN THE OBSERVATIONAL STUDIES COMPARING PPCI WITH PRE-HOSPITAL FIBRINOLYSIS

First author and study, Patients' enrolment period	PPCI n in group %	Fibrinolysis n in group %	Odds ratios for PPCI versus fibrinolysis (95% CI)	
			Unadjusted	Adjusted
Roncalli *et al.*, [174] 1995-1999	n = 157 0.6	n = 161** 1.9	0.43 (0.06-2.98)	NA
Danchin *et al.*, [148] Nationwide French survey Unités des soins intensives coronariens (USIC-2000) 2000	n = 434 0.2	n = 180 1.1	0.25 (0.03-1.88)	NA

NA: not available

APPENDIX I-10. HEMORRHAGIC COMPLICATIONS IN OBSERVATIONAL STUDIES COMPARING PRIMARY PCI WITH IN-HOSPITAL FIBRINOLYTIC THERAPY

Name of first author and study/Country/ Patients' enrolment period	Hemorrhagic complication or transfusion as described by the authors	Primary PCI %	Fibrinolytic therapy %	Odds ratios for primary PCI versus fibrinolytic therapy (95%CI)	
				Unadjusted	Adjusted
Rogers *et al.*, [149] Alabama Registry of Myocardial Ischemia USA 1990-1992	Transfusion	n = 118 5.9	n = 230 16	0.38 (0.17-0.87)	NA
Magid *et al.*, [195] *NATIONAL REGISTRY OF MYOCARDIAL INFARCTION* USA 1994-1998	Non-intra-cranial bleeding with hemodynamic compromise	N = 21,973 3.7	N = 40,326 3.9	NA	NA
Hayashi *et al.*, [178] Japan 1990-2001	Transfusion	n = 73 6.9	n = 186 4.3	NA	NA
Hsu *et al.*, [161] Singapore 1997-1999	Moderate or severe*	n = 103 4.9	n = 99 4.0	NA	NA
Juliard *et al.*, [153] Patients' enrolment period unknown France Published in 1999	Required transfusion without coronary bypass surgery	n = 170 4.7 n = 759	n = 170 4.1 n = 604	NA	NA
Huynh *et al.*, [169] Registry of Acute Myocardial Infarction in Quebec (The AMI-QUEBEC Study) Canada 2003	Transfusion	5.8	2.9	1.96 (1.13-3.41)	NA NA

Studies enrolling only elderly patients

		n = 44	n = 86		
Goldenberg *et al.*, [160]	Haemorrhage	0.0	17.4	0.05 (0.00-0.89)	NA
Israel					
1998-1999					
Patients ≥70 years					
Mehta *et al.*, [163]					
Global Registry of Acute Coronary Events (GRACE)	Major bleeding	n = 365	n = 769	1.44 (0.88-2.37)	NA
Multi-national		8.6	5.9		
1999-2002					
Patients ≥ 70 years					

*: Moderate: required blood transfusion without hemodynamic compromise. Severe: intracranial bleed or with hemodynamic compromise.

APPENDIX I-11. IN-HOSPITAL CARDIOGENIC SHOCK IN OBSERVATIONAL STUDIES COMPARING PRIMARY PCI WITH IN-HOSPITAL FIBRINOLYTIC THERAPY

Name of first author and study/Country/ Patients' enrolment period	**Primary PCI %**	**Fibrinolytic therapy %**	**Odds ratios for primary PCI versus fibrinolytic therapy (95%CI)**	
			Unadjusted	**Adjusted**
Rogers *et al.*, [149] USA 1990-1992	N = 118 9.3	N = 230 7.0		
Brush *et al.*, [175] USA 1990-1994	n = 62 4.8	n = 62 0		
Danchin *et al.*, [157] USIC-1995 France 1995	n = 152 7.8	n = 569 5.4		
Hansen *et al.*, [176] Denmark 1995	n = 82 6.1	n = 82 7.3		
Roncalli *et al.*, [174] France 1995-1999	n = 157 3.8	n = 161 2.5		
Danchin *et al.*, [148] USIC-2000 France 2000	n = 434 7.8	n = 545 4.6		
Chanut *et al.*, [170] France 2000	n = 1047 6.1	n = 240 4.2		

Ober *et al.*, [164] Patients' enrolment period unknown Published in 2004	n = 40 15.0	n = 93 8.6
Bueno *et al.*, [155] PPRIMM75 (patients ≥75 years old) Spain 1988-2000	n = 164 11.0	n = 164 7.3
Mehta *et al.*, [163] GRACE (patients ≥70 years) Multinational 1999-2002	n = 365 11.2	n = 769 11.4
Bardaji *et al.*, [154] TRIANA Registry (patients ≥75 years old) Spain 2002	n = 92 16.5	n = 146 15.1

APPENDIX I-12. IN-HOSPITAL LIFE-THREATENING VENTRICULAR ARRHYTHMIA IN OBSERVATIONAL STUDIES COMPARING PRIMARY PCI WITH IN-HOSPITAL FIBRINOLYTIC THERAPY

Name of first author and study/Country/ Patients' enrolment period	Primary PCI %	Fibrinolytic therapy %	Odds ratios for primary PCI versus fibrinolytic therapy (95%CI)	
			Unadjusted	Adjusted
Brush *et al.*, [175] USA 1990-1994	n = 62 3.2	n = 62 0		
Danchin *et al.*, [157] USIC-1995 France 1995	n = 152 10.5	n = 569 10.5		
Juliard *et al.*, [153] France Patients' enrolment period was not specified Published in 1999	n = 170 2.9	n = 170 3.5		
Danchin *et al.*, [148] USIC-2000 France 2000	n = 434 5.1	n = 545 4.4		
Studies with exclusive enrolment of elderly patients				
Goldenberg *et al.*, [160] (patients ≥70 years old) Israel 1998-1999	n = 44 4.5	n = 86 5.8		

Bardaji *et al.*, [154] TRIANA Registry (patients ≥75 years old) Spain 2002	n = 92 15.2	n = 146 13.0
Arrhythmia of un-specified type		
Hansen *et al.*, [176] Denmark 1995	n = 82 11.0	n = 82 25.6
Chanut *et al.*, [170] France 2000	n = 1,047 7.1	n = 240 12.5
Ober *et al.*, [164] Patients' enrolment period was not specified Romania Published in 2004	n = 40 20.0	n = 93 18.3

APPENDIX J. INTERNAL VALIDITY AND POWER OF THE OBSERVATIONAL STUDIES

(Listed in alphabetical order by first author name)

First author, study, recruitment period	Selection bias	Confounding bias	Performance bias	Detection bias	Classification (adjudication) bias	Attrition bias
Bardaji *et al.*, TRIANA Registry [154]	No clear specification about inclusion of only patients with successful PPCI and no specification about inclusion of transferred-in patients.	More patients with prior coronary artery disease, fewer females and more patients with dementia among those who underwent PPCI.	More thienopyridines and glycoprotein IIb/IIIa inhibitors among patients who underwent PPCI than patients who received fibrinolysis (89 vs 24%, 48 vs 8%, respectively)	Potential bias for detection of in-hospital events. None for 1-year censoring.	No details provided for classification and adjudication.	No data provided on loss to follow-up or transferred-out patients.
Berger *et al.*, CCP, 1994-1996 [177]	1. Potential bias with inclusion of only patients with successful PPCI. 2. No bias with transferred-in patients (they were excluded).	Longer symptom duration (68 mins vs 54 mins), less heart failure on initial presentation (12 vs 10%) in the PPCI versus the fibrinolysis group	1. Possibility of more evidence-based therapy in the PPCI group than in the fibrinolysis group; PPCI patients were admitted to larger-volume hospitals (316 vs 186 annual AMI) and were treated more often by cardiologists (59 vs 36%) than patients who received fibrinolysis. 2. Potential bias for more complete coronary revascularization with more in-hospital CABG in the PPCI group than the fibrinolysis group (6 vs 4%)	None: events were censored at 30 days and 1 year.	No details provided for classification and adjudication.	No data provided (survival status was determined by Medicare Database).
Buiatti *et al.*, AMI-Florence, 2000-2001 [156]	1. Included only patients with successful PPCI.	No data provided on characteristics of patients who received	No details provided on evidence-based medications and concomitant	None: events were censored at 6 months.	No details provided for classification and adjudication.	No data on completeness of follow-up. Six-month survival was

	2. Potential bias of transferred-in patients.	fibrinolysis. Selected group which represented <10% of patients in the PPCI group.	revascularization.			determined by administrative dataset.
Danchin *et al.*, Nationwide French survey, 1995 [157]	1. Possible (only 84% of hospitals that participated in the initial survey agreed to participate in the 1-year follow-up). No details provided on the rates of participation in the 2 treatment groups. 2. Included only patients with available 1-year survival status (98% of eligible patients). No data provided on potential differences in eligibility for the 2 treatment groups. 3. Included only patients who underwent PPCI within 24 hrs of admission.	1. PPCI group had more prior MI (16 vs 13%) than patients in the fibrinolysis group. No details were provided on the high-risk features of the MIs.	More use of ACEI (52 vs 48%), lipid-lowering medications (23 vs 16%) and non-ASA antiplatelet therapy (33 vs 6%), and less use of anti-arrhythmic (14 vs 21%) for patients who underwent PPCI than for patients who received fibrinolysis.	None: ascertainment of events was done at 5 days and 30 days.	No details provided.	Complete follow-up.
Danchin *et al.*, Nationwide French survey: Unités des soins intensives coronariens (USIC), 2000 [148]	No details were provided for: 1. Eligible hospitals that did not participate. 2. Inclusion / exclusion of transferred-in and	PPCI group had more diabetes mellitus (21 vs 12%, prior MI (17 vs 10%), renal failure (3 vs 1%) and shock (46 vs 34%) than	1. Similar % of evidence-based medical therapy at discharge. 2. No data provided on coronary revascularization after the index event.	None: events were censored at 5 days, 30 days and 1 year for all treatment groups.	No details provided.	No details provided on loss to follow-up.

	transferred-out patients.	patients in the fibrinolysis group. No details provided on the high-risk features of the MIs.				
Every *et al.*, *MYOCARDIAL INFARCTION TRIAGE AND INTERVENTION PROJECT* (MITI Project), 1988-1994 [152]	None: included all patients who underwent coronary angiography (even those who did not undergo PPCI after diagnostic coronary angiography)	Longer time-to-treatment in the PPCI group than in the fibrinolysis group (1.7 hr vs 1.0 hr). No details were provided concerning symptom duration.	No details provided on concomitant medications and in-hospital revascularizations.	Shorter hospitalization duration by 1.1 day for patients who underwent PPCI.	No details provided.	No details provided on loss to follow-up.
Fassa *et al.*, Acute myocardial infarction in Switzerland (AMIS Plus) Project, 1997-2003 [203] *a sub-group of [159]*	None	Potential bias for sicker patients in the PPCI group than in the fibrinolysis group (cardiogenic shock: 4 vs 2%, symptom duration 3.6 hr vs 2.6 hr).	No details provided on concomitant medical therapy.	No details provided on duration of hospital stay.	No details provided.	No details provided on whether there were patients transferred to non-participating hospitals (thus incomplete in-hospital data)
Fassa *et al.*, AMIS Plus, 1997-2005 [159] *includes 2 more years of patient enrolment than [203]*	No mention of symptom duration and whether transferred-in or transferred out patients were included.	Longer symptom duration and younger patients in the PPCI group than in the fibrinolysis group (3.4 hr vs 2.5 hr) and (mean 61 years vs 63 years)	No details provided on concomitant medical therapy.	No details provided on length of stay.	No details provided.	No details provided on whether in-hospital survival status was available for all patients.
Goldenberg *et al.*, 1998-1999 [160]	1. Included patients who did not have successful PPCI. 2. No mention on transferred-in patients.	More patients with Killip 3 (25 vs 12%) and shock (7 vs 3%) in the PPCI group than in the fibrinolysis group.	1. More ACEI prescribed at discharge for the PPCI group (75 vs 63%). 2. Less in-hospital CABG in the PPCI group (5 vs 2%).	Adequate: censoring at 6 months.	Details were provided for classification, but not for adjudication.	No details provided on loss to follow-up.
Huynh *et al.*, AMI-	Bias of inclusion of	More patients in cardiogenic	More evidence-based medical	Hospital stay was 1 day	Potential bias secondary to	11 and 8% patients in the

QUEBEC study, 2003 [169]	transferred-in patients for PPCI.	shock in the PPCI group than in the fibrinolysis group (7 vs 3%) and longer symptoms duration (median: 95 vs 90 minutes).	therapy* used in the PCI group than the fibrinolysis group (42 vs 56%).	shorter for the PPCI group (potential bias for detection of more in-hospital events).	non-blinded classification and adjudication.	PPCI and fibrinolysis groups, respectively, were transferred out to non-participating hospitals. Thus, data concerning in-hospital events were incomplete for these patients.
Juliard *et al.*, 1999 [153]	No details were provided on case selection.	Fewer patients in cardiogenic shock in the PPCI group than in the fibrinolytic group (0.5 vs 2%).	No details provided on use of evidence-based therapy and coronary revascularization during the index hospitalization.	No details provided on duration of hospital stay.	No details provided on event classification and adjudication.	No details provided on follow-up.
Kalla *et al.*, Vienna STEMI Registry, 2003-2004 [162]	No specification whether patients who could not undergo PPPCI (due to unsuitable anatomy) were included.	None detected. Patients in the two treatment groups had similar clinical characteristics and high-risk features of MI and shock.	No details provided on use of evidence-based in-hospital medications.	No details provided on duration of hospitalization.	No details provided on event classification and adjudication.	No details provided on completeness of follow-up.
Magid *et al.*, [195] NATIONAL REGISTRY OF MYOCARDIAL INFARCTION USA 1994-1998	Included only patients who underwent PPCI. Excluded transferred-in patients	More patients with prior PCI in the PPCI group (12% vs 10%) than the FL group	Less beta-blockers in the PPCI (50% vs 55%) and more ACEI than the FL group (15% vs 13%)	No details provided on duration of hospitalization	No details provided on event classification and adjudication	Excluded patients without complete data on in-hospital stay (transferred-out patients)
Mehta *et al.*, GRACE, 1999-2002 [163]	1. Included only patients with successful PPCI. 2. No bias with transferred-in patients (they were excluded).	More patients in cardiogenic shock (4.2 vs 2.5%) and with anterior myocardial infarction (56 vs 46%) in the PPCI group than in the fibrinolysis group.	Patients in the PPCI group were more likely to be admitted to teaching hospitals (71 vs 59%) than those in the fibrinolysis group.	Shorter hospitalization stay (by 1 day) in the PPCI group.	Details were provided for classification but not for adjudication. Treatment arm for patients who received ½ dose fibrinolysis + immediate PPCI not specified.	No details provided on transferred-out patients.
Ober *et al.*,	1. No details	1. Longer	No details	Shorter	Details were	Complete in-

2000-2002 [164]	provided on inclusion of patients who did not have successful PPCI. 2. No details on transferred-in patients.	symptom duration in PPCI group than in the fibrinolysis group (4.1 vs 3.6 hrs.) 2. No details provided on the high-risk features of the STEMIs.	provided on concomitant medical therapy.	duration of hospitalization by 2 days in the PPCI group.	provided only on classification. No mention of whether adjudication was blinded.	hospital data was provided for the 2 treatment groups.
Peterson *et al.*, NRMI-2 *(patients with prior CABG in [167])*, 1994-1995 [179]	Excluded patients whose coronary anatomy was not amenable to PPCI.	More left bundle branch block (6 vs 4%) in the PPCI group than the fibrinolysis group.	Less optimal medical therapy in the PPCI group than in the fibrinolysis group (ASA: 84 vs 91%).	No details provided on the duration of hospitalization.	No details provided.	No details provided on % of transferred-out patients.
Rogers *et al.*, Alabama Registry of Myocardial Ischemia, 1990-1992 [149]	Transferred-in patients allowed for the fibrinolysis group. No details provided on whether patients transferred for primary PPCI were included.	Less cardiogenic shock (1 vs 3%), and pulmonary oedema (0 vs 1%) in the PPCI group than in the fibrinolysis group.	1. Less in-hospital CABG in the PPCI group (9 vs 15%). 2. No details were provided on concomitant medications.	Shorter hospitalization stays by 1.3 day for the PPCI group.	No details provided.	98% complete follow-up; however, no details provided on the potential for differences in loss to follow-up.
Roncalli *et al.*, 1995-1999 [174]	1. No mention of transferred-in patients. 2. Included patients who did not have successful PPCI in the PPCI group.	Older patients (mean 59 vs 56 yrs), longer symptom duration (206 vs 145 mins, more women (19.5 vs 9%) and more cardiogenic shock (4 vs 1%) in the PPCI group than in the fibrinolysis group.	No details provided on evidence-based therapy and coronary revascularization during the index hospitalization.	Adequate, with 3- year censoring.	No details provided on event classification and adjudication.	2% loss to follow-up. No details provided on the potential for differences in loss to follow-up.
Steffenino *et al.*, Myocardial Infarction with Severe prognosis:	1. Unclear whether transferred-in patients were included.	Less elderly patients (>70 years) (28 vs 32%), more patients with Killip3-4 (9	Less beta-blockers prescribed at discharge for the PPCI group than the fibrinolytic group (38 vs	Shorter hospitalization duration by 2 days in the PPCI group.	Adequate details provided on event classification, but no mention	95% complete follow-up. No details provided on the potential for differences

observation of Treatment with Angioplasty or Lysis (MISTRAL), 1998 [150]	2. Included patients with contra-indications for fibrinolysis (10%, of which 2.5% underwent primary PPCI). 3. Excluded patients who did not undergo primary PPCI after diagnostic coronary angiography. 4. Differential participation rates at the 2 types of hospitals (19 vs 27% for hospitals with predominant use of fibrinolysis therapy and primary PPCI, respectively).	vs 3%), systolic blood pressure <100 mmHg (10 vs 7%), and anterior myocardial infarction (53 vs 46%) in the PPCI group than in the fibrinolysis group.	57%).		of whether adjudication was blinded.	in loss to follow-up.
Stenestrand *et al.*, Swedish National Prospective Registry, 1999-2004 [151]	Included only patients who had PPCI.	Fewer females, fewer elderly persons, less heart failure and fewer with Killip IV among those in the PPCI group than in the fibrinolysis group.	More use of ASA, lipid lowering therapy and thienopyridines among patients with PPCI.	None: event censoring was done at 7 days, 30 days and 1 year.	No details on whether ascertainment was blinded.	No details provided on attrition of follow-up. Follow-up was performed with administrative databases.

Tiefenbrunn *et al.*, NRMI-2, 1994-1995 [167]	Excluded patients whose coronary anatomy was not amenable to PPCI.	More anterior myocardial infarction (39 vs 36%), less patients with features of not low-risk STEMI** (51 vs 55%), and more cardiogenic shock (4 vs 1%) in the PPCI group than in the fibrinolysis group.	Details of in-hospital revascularization and concomitant medications were incomplete since transferred-out patients were allowed (17% and 2% of patients who received fibrinolytic therapy and primary PPCI, respectively).	Potential bias for less events for the fibrinolytic therapy group since 17% were transferred out (shorter observation period at the participating hospital).	No details provided.	Only in-hospital events were captured (17 and 2% of the fibrinolysis and primary PPCI groups did not have complete hospitalization data, respectively).
Zahn *et al.*, MITRA and MIR, 1994-1998 [180]	1. No mention of total number of patients screened and recruited for each treatment group. 2. Potential bias, with inclusion of only patients with successful PPCI.	Patients in the PPCI group had longer symptom duration than patients in the fibrinolysis group (154 vs 121 minutes).	No details provided on evidence-based medical therapy beyond 48 hours of hospitalization.	No details provided on duration of hospital stay	No details provided.	No details provided on whether patients were transferred to non-participating hospitals (thus, incomplete follow-up).

CABG: Coronary artery bypass surgery
PPCI: Primary percutaneous coronary intervention
ASA: Aspirin
ACEI: Angiotensin converting enzymes inhibitors
*: Were prescribed all four of these types of medications at hospital discharge: aspirin, beta-blockers, ACEI/ARB and lipid-lowering medications

** Not low-risk STEMI: One or more of the following: age ≥70 years, previous myocardial infarction, first blood pressure <100 mm Hg and pulse rate >100/min, Killip ≥2, or anterior myocardial infarction.

APPENDIX K. EXTERNAL VALIDITY OF THE OBSERVATIONAL STUDIES

(Listed in alphabetical order by first author name)

First author, study, recruitment period	**Inclusion criteria/ characteristics of enrolled patients**	**Patients excluded**	**Concomitant interventions/ medications**	**Numbers of hospitals/ countries**	**Door-to-balloon (mins)** (median unless otherwise specified)	**Door-to-needle (mins)** (median unless otherwise specified)	**Fibrinolytic agent used**
Berger *et al.*, CCP, 1994-1996 [177]	≥ 65 years, ≤12 hrs of symptoms, first AMI, Mean age: 77 43% females 3% cardiogenic shock	≥ 1 absolute contra-indication for fibrinolytic therapy††† and transferred-in patients	No details provided on concomitant medications, use of stents, GP IIb/IIIa inhibitors, thienopyridines In-hospital interventions: PPCI group: 10% CABG Fibrinolytic group: 37% PCI 6% CABG	All Medicare beneficiaries in the United States	131[δ]	62[δ]	Use of both SK and TPA. No details were provided on % of use for each agent, or method of administration of TPA.
Bardaji *et al.*, TRIANA Registry [154]	≥ 75 years, no specification of symptom duration, Mean age: 79, 40% females	None specified	ASA: 98% in-hospital use for groups, 89% thienopyridines and 48% GP IIb/IIIa inhibitors among PPCI patients. No details provided on neither lipid-lowering medications nor in-hospital interventions.	26/50 Spanish hospitals that performed at least 50 angioplasties per year	90	49	Tenecteplase was the most frequently administered fibrinolytic agent (% not specified).
Buiatti *et al.*, AMI-Florence 2000-2001 [156]	<24 hrs of symptoms, 7% shock in the PPCI group (no details provided for % shock in	None specified	In-hospital interventions: PPCI group: 96% stents Fibrinolytic group 13% rescue PCI	Population-based prospective study involving all hospitals in Florence (1 and 5 with and without	45	NA	NA

	the fibrinolytic group)		No details were provided for GPIIb/IIIa inhibitors nor thienopyridines	PPCI facilities, respectively) Centralized emergency service with physician-assisted ambulance transportation			
Danchin *et al.*, Nationwide French survey-1995 [157]	1. ≤ 6 hrs of symptoms. 2. Included patients in shock (% not specified) Mean age: 61 18% females	Patients without 1-year follow-up	<u>In-hospital interventions:</u> PPCI group: 33% stents and ticlodipine Fibrinolytic group: 9% rescue PCI (<24 hrs) 6% ticlodipine No mention of GPIIb/IIIa inhibitor use.	337/501 intensive care units in France. Comparison of characteristics of units that participated vs those that did not was not provided.	NA	NA	NA
Danchin *et al.*, Nationwide French survey Unités des soins intensives coronariens (USIC-2000) [148]	≤ 48 hours of symptoms, elevated troponins, included patients in shock. Mean age: 61 22% females 3% shock	As per their inclusions, this would exclude aborted STEMI (may be more prevalent in pre-hospital fibrinolytic group).	Low % of evidence-based therapy prescribed at discharge: 50% ACEI/ARB 67% statins	Voluntary participation of 83% of French hospitals. Comparison of characteristics of hospitals that participated vs those that did not was not provided.	NA	NA	NA
Every *et al.*, Myocardial Infarction Triage and Intervention Project (MITI Project), 1988-1994 [152]	Reperfusion therapy ≤ 6 hrs Mean age: 59 24% females 11% systolic blood pressure <100 mm HG	Missing ECG data.	<u>In-hospital interventions:</u> PPCI group: 93% PPCI 3% emergent CABG 4% no reperfusion therapy Fibrinolytic group: 74% angiography 33% rescue PCI 26% same day PPCI No details provided on	19 Seattle hospitals: 58% and 32% with on-site PPCI and CABG, respectively.	NA	NA	8% pre-hospital fibrinolytic therapy. TPA (65%), SK (32%) Urokinase (3%)

			stents, GPIIb/IIIa inhibitors nor thienopyridines.				
Fassa *et al.*, Acute myocardial infarction in Switzerland (AMIS Plus) Project, 1997-2003 [203]	Mean age: 62 No mention of duration of symptoms. Patients present relatively early, median symptom duration (3 hrs) 2% shock.	Unclear cases of STEMI, unclear or missing details on reperfusion therapy.	No details were provided on concomitant medical therapy and coronary revascularization	54/106 hospitals in Switzerland. Comparison of characteristics of hospitals that participated vs those that did not participate was not provided.	NA	NA	NA
Fassa *et al.*, AMIS Plus 1997-2005 [159] *(sub-group of [203])*	Mean age: 62 21% females 3% shock	No exclusion criteria provided	No details provided	68 hospitals in Switzerland	65††	30††	Details not provided
Goldenberg *et al.*, 1998-1999 [160]	≥ 70 years and with ≤12 hrs of symptoms Mean age: 76 59% females 5% cardiogenic shock	None mentioned. Patients were consecutively enrolled.	<u>In-hospital interventions:</u> PPCI group: 91% stents and ticlodipine 53% abciximab Fibrinolytic group: 5% rescue PCI 43% elective PPCI 36% stents 5% elective CABG 2% emergent CABG <u>In-hospital medications for both treatment groups</u>: 100% Aspirin, less optimal use of ACEI and beta-blockers (67%)	Two university hospitals with on-site PPCI and CABG facilities in Israel.	NA	NA	Accelerated TPA for all patients in the fibrinolytic group.
Huynh *et al.*, AMI-	<12 hrs of symptoms, included	Patients with re-infarctus in the same year	High % of evidence-based therapy prescribed at discharge:	17 hospitals (10 with PPCI and 7 without PPCI	110 for on-site PPCI and	32	72% Tenecteplase, 8% TPA,

QUEBEC, 2003 [22]	transferred-in, transferred-out patients. Mean age: 61, 25% females, 6% shock		91% stents 82% GP IIB/IIIA inhibitors 75% beta-blockers 64% ACEI/ARB 73% statins	facilities in Quebec) of 104 hospitals with at least 1 AMI hospitalized/year	142 for PPCI with inter-hospital transfer		11% Reteplase 8% SK
Juliard *et al.*, 1999*** [153]	No details were provided on symptom duration. Mean age: 57 14% females 1.5% hock	Conventional contra-indications of fibrinolytic therapy	1. Pre-hospital administration of fibrinolytic therapy with routine 90-min angiography and rescue PCI as indicated. 2. No details provided for the use of stents, GP IIbIIIa inhibitors, thienopyridines, ACEI nor statins.	Single tertiary care center in Paris	NA	Symptom-needle: 151[δ] Needle-door[†]: 58[δ]	74% TPA
Kalla *et al.*, Viennese STEMI Registry, 2003-2004 [162]	< 12 hrs of symptoms Mean age: 61 28% females 12% shock	No specified exclusion criteria	<u>In-hospital interventions:</u> PPCI group: 100% stents (90% bare-metal) 97% GPIIb/IIIa inhibitors Fibrinolytic group: 50% immediate PCI (25% rescue, 25%facilitated) 41% elective coronary angiography 9% no coronary angiography (very old patients without residual angina or small MI) 85% stents in those who underwent acute or elective PCI (90% bare metal) 4% in-hospital CABG	5 hospitals with on-site PPCI facilities: 1 with permanent 24-hr on-call service and rotating service between the other 4 hospitals. One central triage system for STEMI with physicians in ambulance.	81[fff] (mean)	17[fff] (mean)	12% received pre-hospital TNK (34 patients) In-hospital fibrinolytic therapy included TNK, TPA and reteplase (% not specified)
Magid *et al.*, [195]	<12 hours of symptom and ST elevation or	Contra-indications of FL and	No details available	Low-volume (≤16 PPCI/year): 112 hospitals	Means 145	Means 48	NA

NATIONAL REGISTRY OF MYOCARDIAL INFARCTION USA 1994-1998	LBBB	cardiogenic shock		Intermediate volume (16-49 PPCI/year): 223 hospitals High-volume (≥49 PPCI/year): 111 hospitals	131 120	49 51	
Mehta *et al.*, GRACE, 1999-2002 [163]	>70 years, No mention of symptom duration. Median age: 76 26% ≥80 years 40% females 1% shock	Transferred-in patients and conventional contra-indications of fibrinolytic therapy	<u>In-hospital interventions:</u> PPCI group: 90% stents 68% thienopyridines 65% GPIIb/IIIa inhibitors Fibrinolytic group: 30% coronary angiography 9% rescue PCI 9% elective PPCI	95 hospitals with 66% on-site cath lab, 50% on-site CABG, 57% patients enrolled in Europe, less than 24% of patients enrolled in USA, New Zealand, Australia and Canada (% of Canadian patients not specified).	NA	NA	45%TPA, 43% SK, 11% others 1% half-dose followed by PPCI
Ober *et al.*, 2000-2002 [164]	No mention of symptom duration or % cardiogenic shock Mean age: 58 25% females	None specified	No details provided	One center (Heart Institute Cluj-Napoca) in Romania	NA	NA	NA
Peterson *et al.*, NRMI-2 *(patients with prior CABG in [167])*, 1994-1995 [179]	Patients with previous CABG, ≤ 12 hours of symptoms and ≥48 hours in-hospital follow-up. Mean age: 65 18% ≥75 years 20% females	Transferred-in patients, patients in cardiogenic shock and patients with contra-indications for fibrinolytic therapy	No details on GPIIb/IIIa inhibitors, stents or thienopyridine use.	1,550 hospitals. Compared to American hospitals that did not participate, NRMI-hospitals were larger, more likely to be affiliated with medical schools, with on-site interventional cardiac care facilities.	NA	NA	100% TPA (no details on pre-hospital administration nor whether administration of TPA was accelerated)

Rogers *et al.*, Alabama Registry of Myocardial Ischemia, 1990-1992 [149]	<12 hrs of symptoms. Mean age: 58 29% females 2% cardiogenic shock	Patients in coma and those who did not give consent for follow-up.	<u>In-hospital interventions</u>: PPCI group: 2% emergency CABG Fibrinolytic group: 90% angiography 49% PCI 15% CABG	1 university hospital and 11 large community hospitals (235-704 beds) in Alabama	104	64	TPA used in 74% of fibrinolytic patients.
Roncalli *et al.*, 1995-1999 [174]	≤ 6 hrs of symptoms 3 % cardiogenic shock Young patients (mean age for PPCI group: 59; for fibrinolysis group: 56) 14% females	>80 years	<u>In-hospital interventions:</u> PPCI group: 69% stents 29% abciximab no mention of in-hospital CABG Fibrinolytic therapy group: 26% rescue PPCI 58% elective angioplasty, 83% in-hospital coronary angiography 4% CABG	Single-center study in France	112[δ] Symtom-cath lab: 348[δ]	Needle-door[†]: 46[δ] Symptom-needle: 191[δ]	Pre-hospital accelerated TPA and in-hospital coronary angiography for the fibrinolytic therapy group.
Steffenino *et al.*, Myocardial Infarction with Severe prognosis: observation of Treatment with Angioplasty or Lysis (MISTRAL) 1998 [150]	≤12 hrs of symptoms and high-risk features[ff]. Mean age: 64 30% >70 years 25% females 5% Killip 3 or 4	Patients who did not give consent.	<u>In-hospital interventions:</u> PPCI group: 85% GP IIb/IIIa inhibitors, 12% stents Fibrinolytic therapy group: 4% elective PPCI, No mention of % rescue PCI Sub-optimal evidence-based therapy prescribed at discharge: 49% beta-blockers, 24% statins; no mention of use of thienopyridines.	47 hospitals in Italy, 17and 30 with/without PPCI facilities, respectively. No comparison of characteristics of hospitals that participated and those that did not was provided.	50	30	78% TPA, 17% SK 5% other fibrinolytic drugs
Stenestrand *et al.*, RIKS-HIA Registry	ST elevation or LBBB	No specified exclusion criteria	No mention of in-hospital concomitant interventions. Sub-optimal lipid lowering therapy among patients	75/78 Swedish hospitals	NA	NA	Not specified

1999-2004 [151]			who received in-hospital fibrinolytic therapy (56%), (66% and 71% among patients who received pre-hospital fibrinolytic therapy and PPCI, respectively). ASA, beta-blocker use: 85%-90% for all three groups of patients.				
Tiefenbrunn *et al.*, NRMI-2, 1994-1995 [167]	≤12 hrs of symptom s Mean age: 61 15% >70 years 30% females	Patients with unavailable 48-hr survival status and patients in cardiogenic shock at initial presentation.	Sub-optimal use of anti-platelets in the PPCI group (86% of ASA, no details on thienopyridines, GPIIbIIIa inhibitors or stents). In-hospital interventions: PPCI group: 3% emergent, 7% elective CABG 16% second PPCI 21% IABP Fibrinolytic therapy group: 4% rescue PCI, 19% elective PPCI, 7% elective CABG, 3% IABP	1,550 hospitals. Compared to American hospitals that did not participate, NRMI-hospitals were larger, more likely to be affiliated with medical schools, with on-site interventional cardiac care facilities.	111	42	100% TPA, 92% accelerated administration
Zahn *et al.*, MITRA and MIR, 1994-1998 [180]	≤12 hrs of symptoms 28% females 4% shock Median ages: 62 and 64 years for the PPCI and fibrinolytic groups, respectively.	Contra-indications for fibrinolytic therapy[f]	No details on GPIIb/IIIa inhibitors, stents or thienopyridines. Optimal use of ASA (>95%); relatively low % use of beta-blockers (65%)	217 hospitals (mainly community) in Germany. No comparison of hospitals that participated and those who did not was provided.	Median values were provided for each year 1994-1998. Of the year with the majority	30	No details provided on % of SK and TPA. Accelerated TPA was used.

											of patients who underwent primary PPCI (47%): median was 70 minutes

CABG: Coronary artery bypass surgery; PPCI: Primary percutaneous coronary intervention; ASA: Aspirin; ACEI: Angiotensin converting enzymes inhibitors; NA: Not available; TPA: Tissue plasminogen activator; SK: Streptokinase

**: Were prescribed all four of these types of medications at hospital discharge: aspirin, beta-blockers, ACEI/ARB and lipid-lowering medications.

***: The period of patient enrolment was not specified; the manuscript was published in 1999.

†: Pre-hospital fibrinolytic therapy was used, thus fibrinolytic administration precedes arrival to hospital (needle-door).

††: The authors did not specify whether these values were median or mean values.

†††: Active bleeding, bleeding disorder, stroke < 1 year or terminal illness

f: Stroke ≤ 3 months, surgery or trauma ≤ 14 days or active bleeding

fff: First medical contact (ambulance physician) or arrival to hospital

APPENDIX L. TRIALS USED FOR THE META-ANALYSES OF THE RCTS

Endpoints	Number of trials	Trials
Short-term mortality		
Mortality	24	[61, 71-93]
Mortality, trials with accelerated tPA [78]	13	[61, 71-74, 77, 81-83, 85, 86, 91, 92]
Mortality, trials with streptokinase	8	[75, 76, 84, 87-90, 93]
Mortality, trials with optimal randomisation and minimal imbalances of baseline patients characteristics	4	[61, 74, 81, 87]
Mortality trials without prehospital randomization	21	[61, 71, 73, 75-90, 92, 93]
Mortality trials with prehospital randomization	3	[72, 74, 91]
Mortality, trials with glycoprotein IIb/IIIa inhibitors (more than 5%)	10	[71-74, 82, 86, 87, 91-93]
Mortality, trials with transfer[79]	8	[61, 71, 74, 80, 87, 88, 92, 93]
Mortality, trials with inter-hospital transfer[80]	7	[61, 71, 80, 87, 88, 92, 93]
Short-term reinfarction		
Reinfarction	21	[61, 71-81, 83-85, 88-93]
Reinfarction, trials with a BEPC	9	[71-74, 77, 80, 81, 83, 92]
Reinfarction, trials with an absence of BEPC/unknown status of BEPC	13	[61, 75, 76, 78, 79, 84, 85, 87-91, 93]
Reinfarction, trials with transfer	7	[61, 71, 74, 80, 88, 92, 93]
Reinfarction trials with transfer and BEPC	4	[71, 74, 80, 92]
Long term mortality		
Mortality, 6 months[81]	9	[73, 77-79, 81-83, 86, 89]
Mortality, 1 year or more[82]	7	[61, 76, 85, 100, 111, 146, 208]
Mortality 1 year or more, trials with accelerated tPA	4	[61, 85, 92, 100]
Long term reinfarction		
Reinfarction 6 months	5	[73, 77, 81, 83, 116]

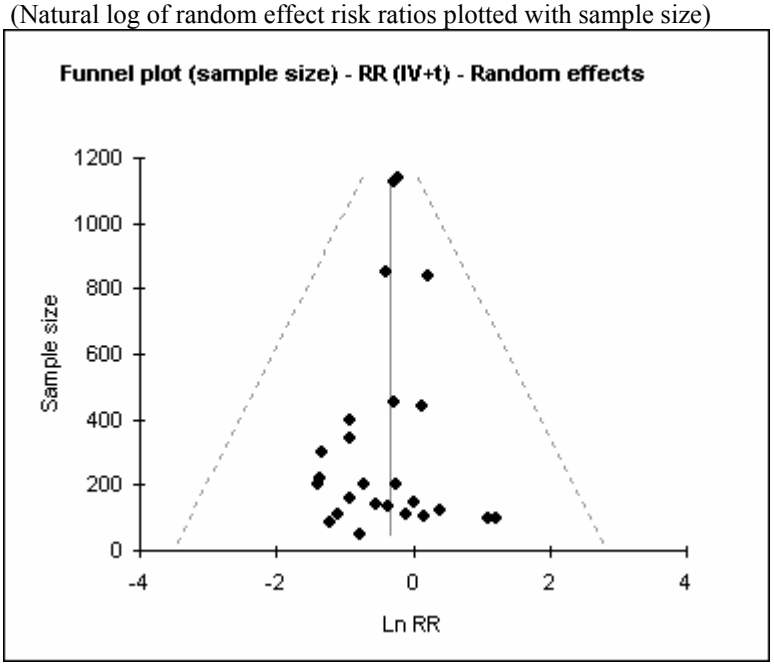
78 WEST, SWEDES and HIS used tenecteplase and reteplase in the fibrinolytic arm; since these agents are known to be as effective as accelerated tPA, these trials are included in the accelerated tPA group of studies.
79 Assuming a mortality risk of 6% of patients in the FL group
80 Excluding CAPTIM which included only patinents with prehospital transfer
81 Ziljstra 1997 was used
82 Ziljstra 1999 was used

Endpoints	Number of trials	Trials
Reinfarction 1 year or more	6	[61, 85, 92, 100, 111, 208]

Endpoints	Number of trials	Trials
Stroke		
All trials	21	[61, 71-81, 83-85, 88-93]
Trials with accelerated tPA	11	[61, 71-74, 77, 81, 83, 85, 91, 92]
Trials with SK	7	[75, 76, 84, 88-90, 93]
Trials with BEPC	9	[71-74, 77, 80, 81, 83, 92]
Major bleeding events (excluding intracranial haemorrhage)		
All trials	16	[61, 72, 74-77, 79, 81-86, 90, 92, 93]
Trials with accelerated tPA	10	[61, 72, 74, 77, 81-83, 85, 86, 92]
Trials with glycoprotein IIb/IIIa inhibitors (more than 5%)	6	[72, 74, 82, 86, 92, 93]
Trials with SK	5	[75, 76, 84, 90, 93]
Trials with a BEPC	6	[72, 74, 77, 81, 83, 92]

APPENDIX M. FUNNEL PLOT OF ALL RCTS

(Natural log of random effect risk ratios plotted with sample size)



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