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Primary Angioplasty and Thrombolysis for the Treatment of Acute ST-Segment Elevated Myocardial Infarction

An Evidence Update

Presented to the Ontario Health Technology Advisory Committee in June 2010

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Medical Advisory Secretariat
Ministry of Health and Long-Term Care

About this Review

This review updates the following evidence-based analysis:

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Table of Contents

Background and Methodology

A literature search was conducted on January 4, 2010 to update the 2004 evidence-based review (1) by the Medical Advisory Secretariat (MAS) on the use of primary angioplasty for the treatment of acute ST-segment elevated myocardial infarction (STEMI) (search details described in Appendix).

The conclusions of the 2004 MAS review (1) were[1]:

1. *Primary angioplasty has advantages with respect to mortality and combined end points compared with in hospital thrombolysis. However, pre-hospital thrombolysis improves survival when compared with in-hospital thrombolysis and is equivalent to primary angioplasty.*
2. *Based on this health technology policy analysis, the provision of emergency medical services in Ontario through upgrading paramedics to provide primary angioplasty within 90 minutes of onset of symptoms is likely to be unrealistic. For the same reason, it is unrealistic to mount a province-wide pre-hospital thrombolysis program.*
3. *Outcomes for patients with acute MI can nevertheless be improved if the capacity for primary angioplasty is enhanced and efforts are made to optimize the interval from symptom onset to thrombolysis or angioplasty. The latter will require concerted efforts, including public education to reduce the symptom-to-emergency room time and maximizing efficiencies in door-to-intervention time for both primary angioplasty and early thrombolysis.*
4. *These technologies cannot be considered in isolation from one another, and in this regard, it is especially important to ensure that patients who have persistent STEMI 90 minutes after receiving thrombolysis proceed directly to angioplasty (rescue angioplasty). Furthermore, for patients with acute MI who are in cardiac shock, primary angioplasty is definitely the preferred intervention.*
5. *The concomitant use of primary angioplasty and thrombolysis (facilitated angioplasty) is considered experimental and has no place in routine management of acute MI at this time.*

Inclusion criteria for the updated 2010 MAS evidence-based review consisted of randomized controlled trials (RCTs) comparing primary percutaneous coronary intervention (PCI) vs. thrombolysis (pre-hospital or in-hospital) as well as 3 new interventions that were not systematically reviewed in the 2004 MAS report:

1. Facilitated PCI vs. primary PCI
2. Rescue PCI vs. repeat thrombolysis
3. Routine early PCI after thrombolysis vs. thrombolysis (and rescue PCI if needed)

[1] 2004 MAS review available at http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas/tech_priangio_110104.html

Results of Evidence-Based Review

The updated literature search identified a total of 10 meta-analyses. Table 1 shows the breakdown of meta-analyses and studies published after the most recent meta-analysis for each comparison.

Table 1: Meta-Analyses Identified in the Literature Search and Studies Published After the Most Recently Published Meta-Analysis.

Comparison	Meta-Analyses Published		Randomized Controlled Trials Published after Most Recent Meta-Analysis	
	Year	Author	Year	Author
Primary PCI vs. thrombolysis (pre-hospital or in-hospital)	2009 2008 2008 2007 2006	Huynh et al. (2) De Luca et al. (3) Huynh et al. (4) Asseburg et al. (5) Boersma et al. (6)	2009	Bonnefoy et al. (7)
Facilitated PCI vs. primary PCI	2007	Sinno et al. (8)	2009 2008	Ellis et al. (9) Ellis et al. (10)
Rescue PCI vs. repeat thrombolysis	2008 2007	Testa et al. (11) Wijeysundera et al. (12)	2009	Carver et al. (13)
Routine early PCI (after thrombolysis) vs. thrombolysis (and rescue PCI if needed)	2008 2006	Wijeysundera et al. (14) Collet et al. (15)	2009 2008	Cantor et al. (16) Di Mario et al. (17)

PCI refers to percutaneous coronary intervention

1. Primary PCI Versus Thrombolysis (Pre-Hospital or In-Hospital)

Five meta-analyses were identified in the literature search. The most recent review by Huynh et al. (2) included both RCTs and observational studies in their analysis. Previous meta-analyses only included RCTs. For consistency with the previous evidence-based analysis by MAS, only RCTs will be reviewed for the purposes of this update.

Meta-Analysis of Randomized Controlled Trials

Huynh et al. meta-analyzed 23 RCTs (N=8,140 patients) using a bayesian hierarchical model. (2) Details of the included studies can be found in Appendix Table 1. Within the meta-analysis by Huynh et al., there were 4 studies that were published after the 2004 evidence-based analysis by MAS. (18-21)

Most RCTs were small with only 6 studies enrolling more than 200 patients in each treatment arm. All studies were underpowered to detect a mortality difference between primary PCI and thrombolysis. (4)

Compared with thrombolysis, primary PCI was associated with significant short-term (≤6 weeks) reductions in mortality and reinfarction and a significant reduction in stroke (Table 2). In addition, primary PCI was associated with significant long-term (≥1 year) reductions in mortality and reinfarction (Table 2).

Table 2: Results of Meta-Analysis by Huynh et al. (2) of Randomized Controlled Trials - Primary Percutaneous Coronary Intervention Versus Thrombolysis

Overall Results (PCI vs. Thrombolysis)			
Outcome	**Number of Studies**	**Number of Patients**	**OR (95% CrI)**
Short Term All Cause Mortality (≤6 weeks)	23	8,140	0.66 (0.51 to 0.82)
Long Term All Cause Mortality (≥1 year)	11	4,320	0.76 (0.58 to 0.95)
Short Term Reinfarction (≤6 weeks)	22	7,937	0.35 (0.24 to 0.51)
Long Term Reinfarction (≥1 year)	9	4,121	0.49 (0.32 to 0.66)
Stroke	21	7,932	0.37 (0.21 to 0.60)
Major Bleeding	15	4,624	1.40 (0.88 to 2.00)

CrI refers to credible interval; PCI, percutaneous coronary intervention; RCT, randomized controlled trial

Absolute risk reductions in short-term mortality, reinfarction, and stroke with primary PCI were 2.2%, 4.5% and 1.2% respectively (Table 3). At long-term followup, primary PCI was associated with an absolute reduction in long term mortality and reinfarction of 3.5% and 3.4% respectively.

Table 3: Absolute Risk Reduction and Number Needed to Treat from the Meta-Analysis by Huynh et al. (2) of Randomized Controlled Trials

Outcome	Events in Thrombolysis Group (%)	Absolute Percent (95% CrI)	Number Needed to Treat with Primary PCI to Prevent 1 Event (95% CI)
Short Term All Cause Mortality	7.1	2.2 (1.3 to3.2)	45 (31 to 77)
Long Term All Cause Mortality	16.7	3.5 (0.7 to 6.4)	29 (16 to 143)
Short Term Reinfarction	6.7	4.5 (3.6 to 5.4)	22 (19 to 28)

Long Term Reinfarction	9.4	3.4 (1.6 to 5.9)	29 (17 to 63)
Stroke	1.9	1.2 (0.8 to 1.5)	83 (67 to 125)

CI refers to confidence interval; CrI, credible interval; PCI, percutaneous coronary intervention

Limitations to the review by Huynh et al. (2) included:

- Time to reperfusion in the RCTs was not analyzed.
- Comparisons of primary PCI with prehospital thrombolysis could not be ascertained with certainty because of the small number of studies that used this reperfusion strategy.
- 12 RCTs reported optimal central randomization to decrease selection bias. (4)
- Since providers of care were not blinded, every study was subject to performance bias (i.e., systematic difference in the type of care apart from the interventions being evaluated). (4) In inter-hospital transfer trials, performance bias may have occurred because of difference in the quality of the adjuvant care, since patients in the thrombolysis arm were generally treated in community hospital and patients in the primary PCI arm were generally treated in tertiary care hospitals. (4)
- Heterogeneity in type of thrombolytic agents used. The authors conducted subanalyses on RCTS that examined fibrin-specific agents (specified ≥50% use of fibrin-specific thrombolytic agents) and this produced results similar to all studies combined for short-term mortality and reinfarction, stroke and major bleeding. There was no significant difference between fibrin-specific agents compared to primary angioplasty in terms of long-term mortality and reinfarction.
- Information on adjuvant in-hospital medical therapy was not reported in 11 RCTs. (4) No study adjusted for differences in ancillary therapy between the treatment groups. (4)
- Systematic administration of thienopyridines (e.g., clopidogrel) in patients who underwent implantation of stents resulted in possible performance bias favouring primary PCI. In many trials, thienopyridines administration differed by more than 25% between the two treatment arms.
- Recourse to rescue interventions differed among the reviewed RCTs. Rescue PCI was provided to 1.9% of thrombolysis patients in DANAMI-2 (22), and to 26% of thrombolysis patients in CAPTIM. (23)
- Of 23 RCTs, 11 trials used a blinded endpoint committee to adjudicate patient outcomes and 1 RCT used a blinded research clinician. (4)
- External validity of these trials may be limited by their relatively short door-to-balloon and prolonged door-needle times.
- It was possible that patients who presented off regular working hours may not have been enrolled in these RCTs. Therefore, the superiority of primary PCI as observed from these RCTs might not be entirely generalizable to primary PCI performed off regular working hours in the "real world". (4) The STAT trial did not randomize patients when the primary PCI facility was unavailable; about 9% of eligible patients were excluded for this reason. (24)
- Most of these trials are older and were conducted in the 1990s, i.e., not contemporary cardiology trials. An expert consultant stated:
    - The outcomes of both primary PCI and thrombolysis in the real-world today are better than what is reported in older RCTs.
    - In general, there were fewer rescue PCIs performed after thrombolytic therapy in older trials compared to more recent RCTs and this may be a factor contributing to better outcomes in contemporary thrombolysis patients.
    - Many of the included trials were conducted in Europe where it is easier to facilitate inter-hospital transfer due to smaller countries with densely populated areas compared to Ontario.
    - The patients in the trials may be different than that seen in routine practice due to the inclusion/exclusion criteria used in the trials.
    - Currently, clopidogrel and statins are routinely given to patients, unlike earlier studies from the 1990s.

The current American Heart Association/American College of Cardiology STEMI guidelines, state that the delay between the patient's first contact with the medical system and the initiation of thrombolysis should be within 30 minutes. (25) For primary PCI, door to balloon time should be within 90 minutes. For patients requiring interhospital transfer, primary PCI should be initiated within 90 minutes of arrival at the initial hospital door.

Impact of Time Delay on Efficacy of Reperfusion Therapy in Studies Included in the Meta-Analysis by Huynh et al.

In a 2008 report on the effectiveness of thrombolysis and primary PCI for STEMI by Huynh and Perron prepared for the Agence d'Évaluation des Technologies et des Mode d'Intervention en Santé (4), Huynh et al. acknowledged that meta-analysis of studies with median door to needle ≤ 30 minutes and door to balloon ≤ 90 minutes would be important for a valid comparison of primary PCI and thrombolysis. However, data concerning door to reperfusion therapy was infrequently and inconsistently reported in the RCTs and the authors were unable to perform such an analysis.

To illustrate this infrequency, data regarding time delay to reperfusion in the RCTs included by Huynh et al. is summarized below based on information supplied from online only supplemental data from Huynh et al. (2) as well as the report for the Agence d'Évaluation des Technologies et des Mode d'Intervention en Santé. (4)

Time to Reperfusion in Randomized Controlled Trials Without Transfer for Primary PCI

Eleven RCTs reported data related to time delay to primary PCI (i.e., starting from randomization, symptom onset, or door to balloon) (Table 4). Randomization to balloon or door to balloon times generally fell within current standards 6 out of 7 RCTs). Trials reporting symptom onset to balloon times did not meet current standards (0 out of 4 RCTs).

Twelve RCTs reported data related to time to needle (from randomization, symptom onset, or door to needle) (Table 4). Door to needle times did not fall within current standards (1 out of 4 RCTs) but randomization to needle times met current standards (4 out of 4 RCTs). Trials reporting symptom onset to needle failed to meet current standards (0 out of 4 RCTs). In another report of this systematic review, Huynh and Perron (4) cautioned that the RCTs external validity was limited by the relatively long door to needle times, short door to balloon times and careful patient selection.

Table 4: Number of Randomized Controlled Trials Without Transfer for Primary PCI Reporting Time Delay to Balloon or Needle Reperfusion in Huynh et al. (2)

Time Delay to Balloon Reperfusion		
Randomization to Balloon *(reported in 4 RCTs)*	**Symptom Onset to Balloon** *(reported in 4 RCTs)*	**Door to Balloon** *(reported in 3 RCTs)*
All 4 RCTs reported mean/median *time* ≤90 minutes	No RCTs reported mean/median time ≤120 minutes	2 RCTs reported mean/median time ≤90 minutes
Time Delay to Needle Reperfusion		
Randomization to Needle *(reported in 4 RCTs)*	**Symptom Onset to Needle** *(reported in 4 RCTs)*	**Door to Needle** *(reported in 4 RCTs)*
All 4 RCTs reported mean/median *time* ≤30 minutes	No RCTs reported mean/median time ≤120 minutes	1 RCT reported mean/median time ≤30 minutes

RCT refers to randomized controlled trial

Time to Reperfusion in Randomized Controlled Trials Requiring Transfer for Primary PCI

Eight RCTs reported data related to time delay to primary PCI (i.e., starting from randomization, symptom onset, or door to balloon) (Table 5). Time delays from arrival at the first hospital (door) or randomization to balloon in the second hospital varied from 90 to 155 minutes, generally exceeding current standards.

Eight RCTs reported data related to time to needle (from randomization, symptom onset, or door to needle) (Table 5). Time delays for door to needle times generally exceeded current standards. Since thrombolysis was initiated at the randomization site, without requiring interhospital transfer, Huynh and Perron (4) suggested that prolonged door to needle times were probably related to processes of obtaining consent and randomization.

Table 5: Number of Randomized Controlled Trials Requiring Transfer for Primary PCI Reporting Time Delay to Balloon or Needle Reperfusion in Huynh et al. (2)

Time Delay to Balloon Reperfusion		
Randomization to Balloon *(reported in 2 RCTs)*	**Symptom Onset to Balloon** *(reported in 1 RCT)*	**Door to Balloon** *(reported in 5 RCTs)*
All 2 RCTs reported mean/median time ≤90 minutes	No RCT reported mean/median time ≤120 minutes	1 RCT reported mean/median time ≤90 minutes
Time Delay to Needle Reperfusion		
Randomization to Needle *(reported in 2 RCTs)*	**Symptom Onset to Needle** *(reported in 1 RCT)*	**Door to Needle** *(reported in 5 RCTs)*
All 2 RCTs reported mean/median time ≤30 minutes	1 RCT reported mean/median time ≤120 minutes	2 RCTs reported mean/median time ≤30 minutes

RCT refers to randomized controlled trial

Comment on Literature Examining Impact of Time to Reperfusion and Efficacy of Reperfusion Therapy

Huynh et al. reviewed systematic reviews reporting on the impact of presentation delay (the time between onset of symptoms and arrival at point of care) and primary PCI related delay (the difference between door to balloon and door to needle time) on the efficacy of reperfusion therapy. (4) Their conclusions were:

- Mortality increases with increased PCI related delays.
- The relationship between the 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 primary PCI and thrombolysis" (the primary PCI related delay that results in similar mortality between primary PCI and thrombolysis) may not be valid for all patients.
- For each patient, the primary PCI related delay varies according to the *type of STEMI* and *presentation delay.*

Quebec Study to Investigate Timeliness of Reperfusion and Outcomes

Lambert et al. (26) undertook a systematic province-wide evaluation of STEMI care in Quebec. The objectives were to obtain a contemporary portrait of reperfusion treatments and their delays across Quebec and to determine whether STEMI reperfusion treatment outside of the guideline-recommended delays is associated with poorer outcomes than treatment within recommended delays.

The main outcome measures were death at 30 days and at 1 year and the combined endpoint of death or hospital readmission for acute MI or congestive heart failure at 1 year.

Of 1,832 patients treated with reperfusion, 392 (21.4%) received thrombolysis and 1440 (78.6% received primary PCI. Thrombolysis was >30 minutes in 54% and primary PCI was >90 minutes in 68% of patients.

At 30 days, patients treated with primary PCI outside of recommended times had higher mortality (OR 1.87; 95%CI, 1.02 to 3.41) as did patients treated outside of recommended times with thrombolysis (OR 2.75; 95%CI, 1.07 to 7.08). The increase in mortality of untimely treatment was sustained at 1 year for both untimely primary PCI (OR 1.71; 95%CI, 1.06 to 2.76) and untimely thrombolysis (OR 2.41; 95% CI, 1.04 to 6.00). Overall, the composite end point of death or readmission for heart failure or acute MI at 1 year occurred significantly more frequently when treatment was untimely among both patients who received thrombolysis and those who underwent primary PCI.

When the 2 reperfusion techniques were combined, patients treated outside of recommended delays had an adjusted higher risk of death at 30 days (6.6% vs. 3.3%; OR 2.14; 95% CI , 1.21 to 3.93) and a statistically nonsignificant increase in risk of death at 1 year (9.3% vs. 5.2%; OR 1.61; 95% CI, 1.00 to 2.66) compared with patients who received timely treatment. Patients treated outside of recommended delays also had an adjusted higher risk for the combined outcome of death or hospital readmission for heart failure or acute MI at 1 year (15.0% vs. 9.2%; OR 1.57; 95% CI, 1.08-2.30).

Lambert et al. (26) concluded:

1. Primary PCI is the predominant reperfusion strategy in Quebec, with most primary PCI patients transferred from non-PCI hospitals.
2. Time to reperfusion exceeded recommended delays in a substantial proportion of patients treated with thrombolysis and primary PCI, particularly in patients transferred for primary PCI.
3. The risk of adverse events was similar in patients treated with primary PCI and thrombolysis but higher in those treated outside of the maximum recommended delays, regardless of the reperfusion strategy.
4. Timeliness of treatment with either reperfusion mode was a strong predictor of overall regional mortality but no association was observed with choice of reperfusion treatment within health care regions.

Meta-Analysis of Studies Reporting Median Door-to-Needle Time Less Than 30 Minutes and Door-to-Balloon Time Less Than 90 Minutes

A meta-analysis of studies with median door to needle time ≤ 30 minutes and door to balloon time ≤ 90 minutes was conducted in order to make a valid comparison of primary PCI and thrombolysis. Four studies that were included in the meta-analysis by Huynh et al. (2) were included in the MAS meta-analysis. (22;24;27;28) All 4 studies compared accelerated alteplase in-hospital with primary angioplasty. Ideally, *all* patients should be treated within the recommended time frame, not a median time of ≤ 30 minutes for door to needle or ≤ 90 minutes for door to balloon.

For mortality and stroke, there was no significant difference between primary angioplasty and thrombolysis (Figure 1). However, there was a significant difference between the two interventions for reinfarction and the combined endpoint of mortality, reinfarction and stroke (Figure1).

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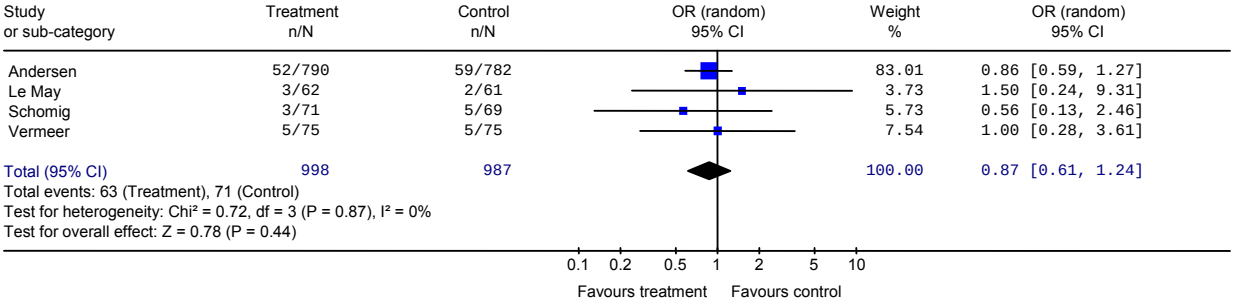
Outcome: 01 Mortality



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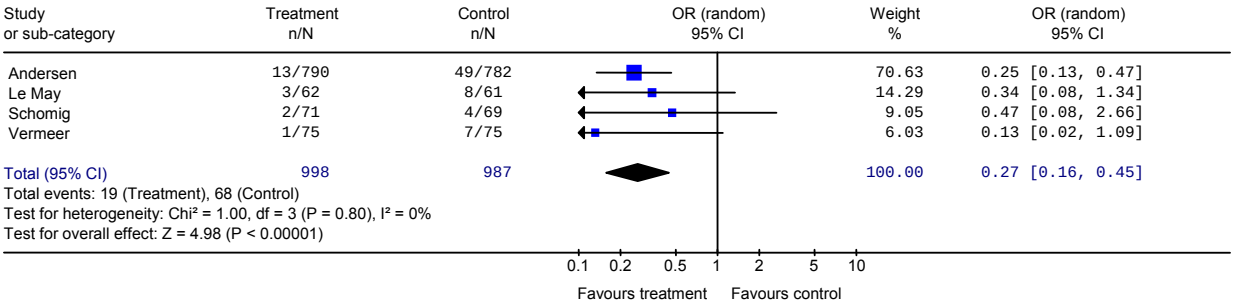
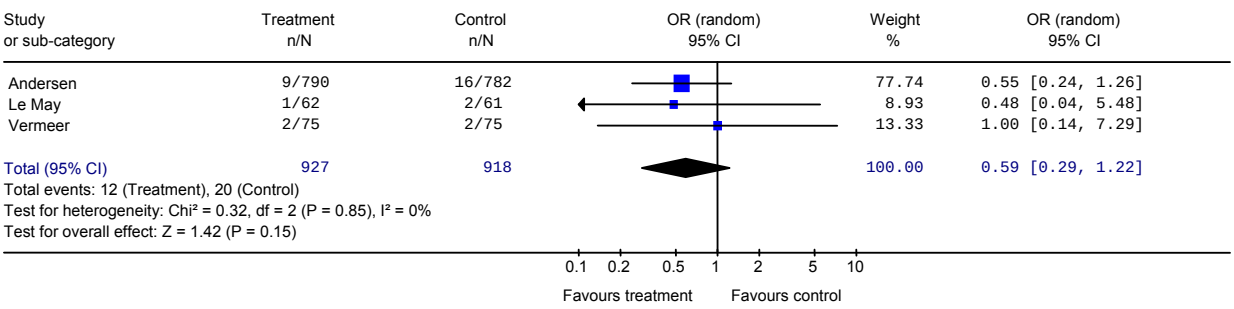
Outcome: 02 Reinfarction



Outcome: 03 Stroke



Outcome: 04 Combined Mortality Reinfarction Stroke

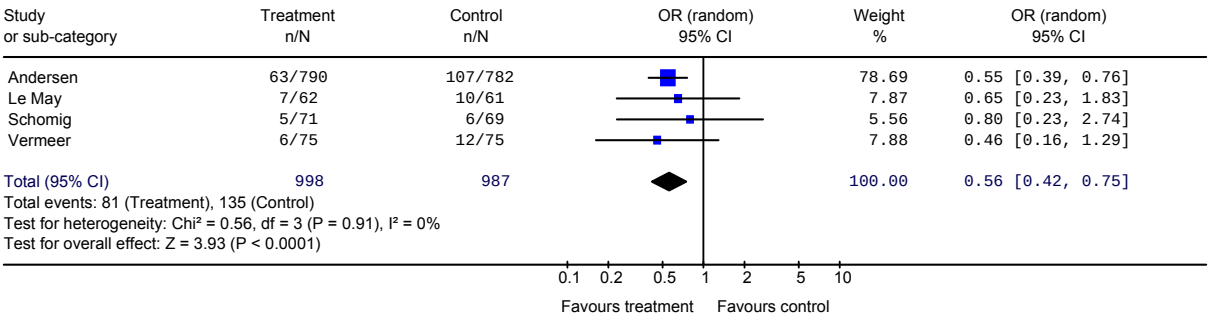


Figure 1: Meta-Analysis by the Medical Advisory Secretariat Comparing the Efficacy of Primary PCI and Thrombolysis in Studies Reporting Median Door-to-Needle Time Less Than 30 Minutes and Door-to-Balloon Time Less Than 90 Minutes in Patients with Acute STEMI

Studies Published After Most Recent Meta-Analysis for Primary PCI Versus Pre-Hospital Thrombolysis

Bonnefoy et al. (7) published a 5 year followup to the 2002 study that compared primary angioplasty to pre-hospital thrombolysis (N=840 patients). The 2002 study was powered to detect a 5% absolute difference between the study groups (N=1200). (23) However, due to lack of funding, the study was terminated with a final sample size of N=840. The primary endpoint of the study was a composite of death, nonfatal reinfarction and nonfatal disabling stroke within 30 days. The rate of the primary endpoint was 8.2% in the prehospital thrombolysis group and 6.2% in the PCI group (risk difference 1.96, 95% CI -1.53 to 5.46). There was no significant difference between prehospital thrombolysis and primary angioplasty for any of the individual components of the primary endpoint.

Limitations to the 2002 study by Bonnefoy et al. (23) included:

- Reduced statistical power. Only 70% of the originally planned N=1,200 patients were accrued for the trial. A sample size of 840 patients means about a power of 60% to detect a 5% difference.
- Significantly more urgent angioplasty for recurrent ischemia in pre-hospital thrombolysis group
    - 6.7% vs. 2.1%, *P*=0.001
- Significantly more beta blocker usage in pre-hospital thrombolysis group
    - 93% vs. 86%, *P*=0.003
- Approximately 70.4% of patients in the pre-hospital thrombolysis group underwent any angioplasty up to day 30.
- Significant difference in time to treatment, *P*<0.001
    - Pre-hospital thrombolysis median 130 min (1st and 3rd quartile: 95-180)
    - Primary angioplasty median 190 min (1st and 3rd quartile: 149-255)
- In the primary PCI group, 9 patients with cardiogenic shock were included despite protocol exclusion criteria.
- 23% of primary PCI patients received GpIIbIIIa antagonists (not reported for pre-hospital thrombolysis).
- Significantly more patients in the primary angioplasty group received clopidogrel or ticlopidine compared to the pre-hospital thrombolysis group (76% vs. 60% respectively, *P*=0.0001).

Unlike the primary endpoint of the original study (a composite of death, nonfatal reinfarction and nonfatal disabling stroke within 30 days), the primary endpoint of the 5 year followup was all-cause mortality. (7) Data regarding other components of the main composite endpoint in 2002 (i.e., reinfarction and stroke) were not reported by the authors.

The sample size for the followup study was N=795 (66% of the originally planned 1,200 patients). Neither a sample size nor power calculation was reported or discussed by the authors for the all-cause mortality endpoint. Furthermore, it is unclear if the 5 year followup endpoint was decided a priori.

Using intent to treat analysis, the overall mortality was 9.7% (n=40) in the pre-hospital thrombolysis group and 12.6% (n=52) in the primary angioplasty group, hazard ratio 0.75 (95% CI, 0.50 to 1.14), *P*=0.18. (7)

In a subanalysis, Bonnefoy et al. (7) reported the effect of time to randomization on the outcome of treatment (Table 6). The overall interaction between treatment assignment and delay from symptoms was not statistically significant (*P*=0.10).

Table 6: Effect of Time to Randomization on Outcome of Treatment Comparison in the 5-Year Followup Study by Bonnefoy et al. (7)

Mortality	Patients Included ≤2 Hours of Symptom Onset		Patients Included >2 Hours of Symptom Onset	
	Pre-Hospital Fibrinolysis	Primary PCI	Pre-Hospital Fibrinolysis	Primary PCI
% (n)	5.8% (n=13)	11.1% (n=25)	14.5% (n=27)	14.4% (n=26)
HR (95% CI)	0.50 (0.25 to 0.97), *P*=0.04		1.02 (0.59 to 1.75), *P*=0.92	
Interaction of treatment strategy with time to randomization HR (95% CI)	1.02 (0.59 to 1.75), *P*=0.10			

HR refers to hazard ratio; CI, confidence interval

Limitations to the 5-year followup study by Bonnefoy et al. (7) included:

- All of the limitations previously discussed for the 2002 study by Bonnefoy et al. (23)
- Type 2 error for the overall mortality results. A common criticism of angioplasty versus thrombolysis trials is that all have been underpowered to show improved survival (N=4400 patients are needed to show a 2% mortality difference with 80% power and a *P* value less than 0.05). (6;29)
- No information regarding other components of the main composite endpoint from the initial 2002 trial (e.g., reinfarction and stroke) nor medication usage.
- The sample size is limited for the subgroup analyses. The authors stated *"P values should be interpreted with extreme caution and should be viewed as hypothesis generating given that these analyses were not prespecified and the multiplicity of analyses was not planned."*
- *P* value significance was not adjusted for multiplicity of analyses.

2. Facilitated PCI Versus Primary PCI

According to Collet et al., facilitated PCI involves the administration of thrombolytic therapy to improve flow in the infarct related artery before and/or during ***transfer for PCI***. (15)

Meta-Analysis of Randomized Controlled Trials

Sinno et al. performed a meta-analysis of RCTs comparing the efficacy and safety of adjunctive use of reduced-dose thrombolytics and glycoprotein GpIIbIIIa inhibitors to the sole use of GpIIbIIIa inhibitors before PCI in patients with acute STEMI. (8) Since full dose thrombolytic facilitated PCI has been shown to result in worse outcomes than primary PCI alone (15;30) and combined full dose thrombolysis with full dose GpIIbIIIa inhibitor facilitated PCI is associated with increased bleeding (31;32), reduced-dose thrombolytics for facilitated angioplasty was assessed by Sinno et al. (8)

The primary outcome and inclusion criteria for the meta-analysis are shown in Table 9. The literature search strategy spanned January 1966 to December 2005.

Table 9: Primary Outcome and Inclusion Criteria for the Meta-Analysis by Sinno et al. (8)

Primary Outcome	Inclusion Criteria
At 30 days followup: ➢ All cause mortality ➢ Reinfarction rate ➢ Major bleeding events	➢ RCTs ➢ Patients randomized within 12 hours of symptom onset to either GpIIbIIIa inhibitors or combination therapy (thrombolytic + GpIIbIIIa inhibitor) followed by preplanned angiography and angioplasty if indicated

Four trials (N=725) were included in the meta-analysis. Overall, there was no significant difference in the 30-day all cause mortality or reinfarction rate, however major bleeding events were significantly increased in the combination therapy group (Table 10).

Table 10: Results of the Meta-Analysis by Sinno et al. (8) Combination Therapy Versus GpIIbIIIa

30-Day All Cause Mortality (RR, 95% CI)	30-Day Reinfarction (RR, 95% CI)	Major Bleeding Events (RR, 95% CI)
1.47 (0.52 to 4.14), *P*=0.46	0.96 0.23 to 1.02), *P*=0.96	2.15 (1.17 to 3.94), *P*=0.01

Limitations to the meta-analysis include:

- Clinical heterogeneity
  - There were some differences between the studies regarding the type and dose of thrombolytic and/or GpIIbIIIa inhibitors used.
- Small overall sample size.
  - Sinno et al. (8) stated that the meta-analysis did not have sufficient statistical power for clinical outcomes such as mortality. In most cases, the individual trials were underpowered.

Studies Published After the Most Recent Meta-Analysis for Facilitated PCI Versus Primary PCI

Ellis et al. (10) conducted a RCT entitled Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE). Patients with STEMI were randomly assigned to:

- Combination facilitated PCI (early administration of GpIIbIIIa inhibitor plus half dose reteplase); or
- GpIIbIIIa inhibitor facilitated PCI (early administration of GpIIbIIIa only); or
- Primary PCI (GpIIbIIIa administered immediately before PCI)

The primary outcome and inclusion criteria are shown in Table 11.

Table 11: Primary Outcome and Inclusion Criteria for FINESSE (10)

Primary Outcome	Inclusion Criteria
Composite of: ➢ Death from all causes ➢ Ventricular fibrillation occurring >48 hours after randomization ➢ Cardiogenic shock ➢ Congestive heart failure during first 90 days after randomization	➢ Patients with STEMI who presented ≤ 6 hours after the onset of symptoms ➢ Eligible for fibrinolytic therapy or primary PCI ➢ Estimated time to diagnostic catheterization was 1 to 4 hours after randomization.

A total of 2,542 patients were randomly assigned to one of the 3 treatment groups. The planned enrollment of 3,000 patients was not met due to complexities and cost overruns arising from the recruitment of patients in community hospitals and their subsequent transfer to hub centres that had PCI capability, changing patterns of patient referral, limitations on the initial dosing of heparin and the concern at sites in the United States that the time needed for assignment of patients to study groups would adversely affect the new "quality indicator" of door to balloon time. (10) For these reasons, the trial sponsors mandated closure of the study, to which the steering committee agreed. (10)

The median door to balloon time for all patients was 2.2 hours (interquartile range, 1.8 to 2.8).

The 90 day primary composite endpoint occurred in 9.8% of the patients in the combination facilitated PCI group, 10.5% of patients in the GpIIbIIIa facilitated PCI group and 10.7% of patients in the primary PCI group. The hazard ratio and 95% confidence interval were only reported for combination facilitated PCI vs. primary PCI, 0.91 (0.67–1.23). P values were reported as follows:

$P = 0.55$ for comparison of primary PCI with combination-facilitated PCI
$P = 0.86$ for comparison of primary PCI with GpIIbIIIa facilitated PCI
$P = 0.68$ for comparison of GpIIbIIIa facilitated PCI with combination facilitated PCI

There was no significant difference between the study arms for the individual components of the primary endpoint.

Safety data are shown in Table 12. Overall, there was a graded increase in the rates of bleeding, intracranial hemorrhage and transfusions in the PCI facilitated groups.

Table 12: Safety Endpoints Through Discharge or Day 7 in FINESSE (10)

Endpoint	Primary PCI (n=795)	GpIIbIIIa Facilitated PCI (n=805)	Fibrinolysis and GpIIbIIIa Facilitated PCI (n=814)
Nonintracranial TIMI bleeding major or minor – no. (%)	55 (6.9)	81 (10.1)*	118 (14.5)*
Major	21 (2.6)	33 (4.1)	39 (4.8)*
Minor	34 (4.3)	48 (6.0)	79 (9.7)*
Stroke – no. (%)	8 (1.0)	4 (0.5)	9 (1.1)
Intracranial hemorrhage	1 (0.1)	0	5 (0.6)
Ischemic	7 (0.9)	4 (0.5)	4 (0.5)
Transfusions – no. (%)	24 (3.0)	31 (3.9)	52 (6.4)*
Packed red cells or whole blood	19 (2.4)	28 (3.5)	46 (5.7)*
Platelets	13 (1.6)	7 (0.9)	11 (1.4)

* $P<0.05$ for the comparison with primary PCI

Limitations to FINESSE include:

- The trial was terminated prematurely. The authors stated that early termination was unlikely to have changed the outcome of the study since the observed results of 2,542 patients showed that there was less than a 2% chance that the primary treatment group difference would be significant if the trial continued, assuming a relative benefit of 27% for the remainder of the 3,000 patients. (10) The study was originally powered on the basis of an assumed event rate of 15% in the primary PCI group.

In a later publication, Ellis et al. reported 1 year survival data (a prespecified secondary endpoint) from the FINESSE trial. (9) One year mortalities for the combined facilitated PCI, GpIIbIIIa inhibitor facilitated PCI, and primary PCI groups were 6.3%, 7.4% and 7.0% respectively (*P*=not significant). Of note, a limitation to this substudy is that it was not powered to assess mortality between the study groups.

Updated MAS Meta-Analysis Including FINESSE Trial

An updated meta-analysis of RCTs comparing the efficacy and safety of adjunctive use of combined reduced-dose thrombolytics and GpIIbIIIa inhibitors to the sole use of GpIIbIIIa inhibitors before PCI in patients with acute STEMI was performed by MAS. Trials included in the updated meta-analysis were those already included in the review by Sinno et al. (8) in addition to the FINESSE study. (10)

Similar to the meta-analysis by Sinno et al., there was no significant difference in mortality or reinfarction between combined thrombolytics and GpIIbIIIa inhibitors and the sole use of GpIIbIIIa inhibitors before PCI (Figure 3). There was significantly more bleeding in the combined thrombolytics and GpIIbIIIa compared to the GpIIbIIIa inhibitor group (Figure 3).

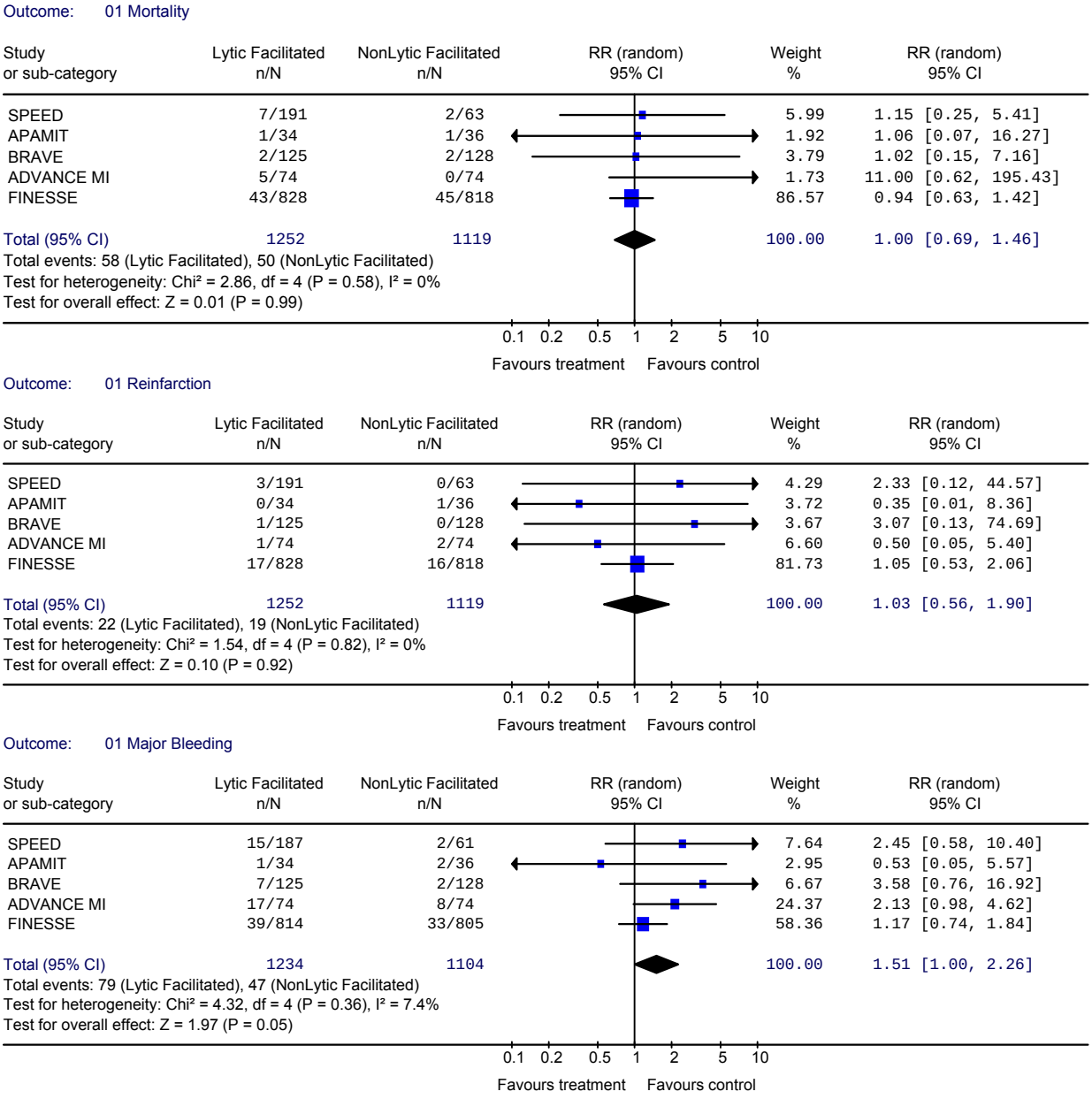


Figure 3: Meta-Analysis by the Medical Advisory Secretariat Comparing the Efficacy and Safety of Combined Thrombolytics and GpIIbIIIa Inhibitors to the Sole use of GpIIbIIIa Inhibitors Before PCI in Patients with Acute STEMI

3. Rescue PCI Versus Repeat Thrombolysis

According to Collet et al., rescue PCI is attempted when there is failure of thrombolysis, usually documented by ongoing chest pain and/or persistent STEMI at 60 to 90 minutes after initiation of thrombolysis. (15)

Meta-Analysis of Randomized Controlled Trials

Testa et al. performed an adjusted indirect meta-analysis to compare rescue PCI in patients with failed thrombolysis to repeat thrombolysis (RT). (11) The primary outcome and inclusion criteria are shown in Table 13. The literature search strategy spanned January 1966 to September 2007.

Table 13: Primary Outcome and Inclusion Criteria for the Meta-Analysis by Testa et al. (11)

Primary Outcome	Inclusion Criteria
Major adverse events (composite of overall mortality and reinfarction)	➢ RCTs comparing rescue PCI versus conservative therapy (CT) and/or repeat thrombolysis (RT) versus CT in the setting of STEMI patients with failed thrombolysis ➢ CT defined as no further immediate reperfusion therapy

Eight trials (N=1,318) were included in the meta-analysis. Six trials compared rescue PCI to CT and 3 trials compared RT to CT (1 trial compared rescue PCI versus RT versus CT). Followup durations in the trials ranged from hospital discharge to 6 months. The characteristics of the rescue PCI and RT trials are shown in Table 14.

Table 14: Characteristics of Rescue PCI and Repeat Thrombolysis Trials Included in the Meta-Analysis by Testa et al. (11)

Study	Design	N	Followup	Symptom Onset to Lytic (min)	Symptom Onset to Rescue PCI (min)	Symptom Onset to RT (min)
REACT (33)	Rescue PCI vs. CT vs. RT	427	6 months	140 (95-220)*	414 (350-505)*	332[†]
MERLIN (34)	Rescue PCI vs. CT	307	1 month	180 ± 120[‡]	327 ± 121[‡]	NA
RESCUE II (35)	Rescue PCI vs. CT	29	1 month	210 ± 156[‡]	294 ± 252[‡]	NA
RESCUE (36)	Rescue PCI vs. CT	151	1 month	Not reported	270 ± 110[‡]	NA
TAMI (37)	Rescue PCI vs. CT	108	In hospital	176 ± 62[‡]	268 ± 71[‡]	NA
Belenkie et al. (38)	Rescue PCI vs. CT	28	In hospital	<180	257 ± 57[‡]	NA
Sarullo et al. (39)	RT vs. CT	90	In hospital	112 ± 55[‡]	NA	NA
Mounsey et al. (40)	RT vs. CT	37	1.5 months	216 (36-648)[§]	NA	360 (126-648)[§]

*Median and interquartile range
[†] Median
[‡] Mean and standard deviation
[§] Median and range
CT refers to conventional therapy; MERLIN, Middlesbrough Early Revascularization to Limit Infarction trial; NA, to not applicable; REACT, Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis Trial; RESCUE, Randomized Comparison of Rescue Angioplasty with Conservative Management of Patients with Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction trial; RT, repeat thrombolysis; TAMI, Thrombolysis and Angioplasty in Myocardial Infarction Study

The results of the adjusted indirect comparison, although modest, favoured rescue PCI over repeat thrombolysis. Most of the outcomes showed no significant difference between rescue PCI and repeat

thrombolysis (Table 15). Rescue PCI was associated with a significant reduction in the risk of reinfarction and an increase in the risk of minor bleeds.

Table 15: Results of the Meta-Analysis Using the Adjusted Indirect Comparison by Testa et al. (11) – Rescue PCI Versus Repeat Thrombolysis*

Major Adverse Events (overall mortality and reinfarction)	Overall Mortality	Reinfarction	Congestive Heart Failure	Stroke	Major Bleed	Minor Bleed
0.93 (0.26-3.35) *P*=0.4	1.01 (0.52-1.95) *P*=0.15	0.32 (0.14-0.74) *P*=0.008	0.74 (0.28-1.96) *P*=0.6	5.03 (0.64-39.1) *P*=0.58	0.5 (0.1-2.5) *P*=0.1	2.48 (1.08-5.7) *P*=0.04

* Results expressed as odds ratio and 95% confidence intervals.

Limitations to the meta-analysis include:

- An indirect comparison was made between rescue PCI and repeat thrombolysis due to the absence of studies reporting a direct comparison of these interventions.
- Of note, the results and conclusions from the study by Testa et al. (11) are similar to those reported in a meta-analysis by Wijeysundera et al. (12) , however, the latter meta-analysis did not use an adjusted indirect comparison for rescue PCI versus repeat thrombolysis. Rather, summary statistics were reported for rescue PCI vs. conservative treatment and repeat thrombolysis versus conservative treatment. (12)

Studies Published After the Most Recent Meta-Analysis for Rescue PCI Versus Thrombolysis

In 2009, the authors of the REACT trial published 1-year outcomes for rescue PCI vs. RT vs. CT. (13) The original study's primary endpoint was a composite of death, reinfarction, stroke, or severe heart failure within six months. (33) The REACT trial ended early due to slow recruitment with 41 less patients than initially planned. (33) The results of the original study are shown in Table 16.

Table 16: Results of the 2005 REACT trial by Gershlick et al. (33)

Primary end-point events	Repeat Thrombolysis (N = 142)	Conservative Therapy (N = 141)	Rescue PCI (N = 144)	P Value
Death from any cause - no. (% of patients)	18 (12.7)	18 (12.8)	9 (6.2)	0.12
Death from cardiac causes - no. (% of patients)	15 (10.6)	14 (9.9)	8 (5.6)	0.26
Recurrent acute myocardial infarction - no. (% of patients)	15 (10.6)	12 (8.5)	3 (2.1)	<0.01
Cerebrovascular event - no. (% of patients)	1 (0.7)	1 (0.7)	3 (2.1)	0.63
Severe heart failure - no. (% of patients)	10 (7.0)	11 (7.8)	7 (4.9)	0.58
Composite primary end point - no. (% of patients)	44 (31.0)	42 (29.8)	22 (15.3)	<0.01

The primary composite endpoint was not reported in the 1-year outcome study, nor were data reported for each of the endpoints that formed the composite endpoint for the 3 arms of the trial. (13) The authors stated they collected information on all the components of the primary end point between 6 months and 1 year and reported the overall event free survival. (13) The rate of event-free survival at 1 year in patients randomized to rescue PCI was 81.5%, compared with 64.1% in the RT and 67.5% in CT (overall

P=0.004). Adjusting for age and infarct site, the hazard ratios (HR) at 1 year were 0.44 (95% CI: 0.28 to 0.71; *P*=0.0008) for rescue PCI versus RT and 0.51 (95% CI: 0.32 to 0.83; *P*=0.007) for rescue-PCI versus CT. (13) There was no difference between RT and CT (HR: 0.87; 95% CI: 0.58 to 1.30; *P*=0.48). (13)

The original REACT publication in 2005 similarly reported the rate of event-free survival among patients treated with rescue PCI was 84.6%, as compared with 70.1% among those receiving CT and 68.7% among patients undergoing RT (overall *P* = 0.004). (33)

4. Routine Early PCI After Thrombolysis Versus Thrombolysis (and Rescue PCI if Needed)

Routine early PCI involves full dose thrombolysis followed by PCI (2-24 hours after thrombolysis). It is also referred to as a "pharmacoinvasive" approach.

Meta-Analysis of Randomized Controlled Trials

Wijeysundera et al. performed a meta-analysis to compare routine early PCI after **full dose** thrombolysis to ischemia guided management after thrombolysis in patients with STEMI. (14)

The rationale for this analysis was based on previous RCTs of balloon angioplasty that evaluated an early invasive strategy in STEMI patients and showed an increased risk of adverse effects and a lack of benefit associated with routine PCI after thrombolysis compared to thrombolysis alone (and rescue PCI if needed). (15) However, given advances in catheter-based therapies, i.e., stents and adjunctive pharmacotherapy, Wijeysundera et al. (14) stated it is questionable if the results of the older balloon angioplasty trials are applicable to contemporary practice. Furthermore, Wijeysundera et al. stated there is significant enthusiasm to perform early cardiac catheterization after STEMI and data from the United States indicate that almost 80% of STEMI patients who were treated with thrombolysis undergo cardiac catheterization during their initial hospitalization. (14)

The primary outcome and inclusion criteria of the meta-analysis by Wijeysundera et al. are shown in Table 17. The literature search strategy spanned January 1950 to February 2007.

Table 17: Primary Outcome and Inclusion Criteria for the Meta-Analysis of Routine Early PCI Versus Thrombolysis by Wijeysundera et al. (14)

Primary Outcome	Inclusion Criteria
All cause mortality and reinfarction Stroke and in-hospital major bleeding	➢ RCTs that enrolled patients with STEMI treated with full-dose intravenous thrombolysis and compared a routine early invasive strategy versus ischemia guided management (thrombolysis). ➢ RCTs subdivided into contemporary trials (defined as >50% stent use during PCI) or balloon angioplasty trials.

Nine trials (5 contemporary PCI trials with stents [N=1,235 patients] and 4 balloon angioplasty trials [N=4,612 patients]) were included in the meta-analysis. Followup durations in the trials ranged from 30 days to 1 year. The characteristics of the trials are shown in Table 18.

Table 18: Characteristics of Trials Included in the Meta-Analysis of Routine Early PCI Versus Thrombolysis by Wijeysundera et al. (14)

Trial/Year	Number of Patients	Followup Duration	Stent Use (%)	Time from Thrombolysis to PCI in Early Invasive Arm (median)	Patients in Thrombolysis Arm With Inhospital Angiogram [and Rescue PCI] (%)
Contemporary Trials					
WEST / 2006 (18)	204	30 days	97	295 minutes	58 [14]
CAPITAL AMI / 2005 (41)	170	6 months	89	90 minutes	67 [9]
GRACIA-1 / 2004 (42)	499	12 months	80	17.6 hours	21 [NA]

SIAM III / 2002 (43)	163	6 months	100	210 minutes	24 [11]
PRAGUE / 2000 (44)	199	12 months	79	68 minutes	14 [7]
Balloon Angioplasty Trials					
SWIFT / 1991 (45)	397	12 months	0	Within 48 hours	13 [NA]
Rogers et al. / 1990 (46)	586	12 months	0	32 hours	18 [NA]
TIMI-II / 1989 (47)	3262	42 days	0	32.5 hours	33 [NA]
Simoons et al. / 1998 (48)	367	3 months	0	42 minutes	6 [NA]

CAPITAL AMI refers to Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis alone in Acute Myocardial Infarction study; GRACIA-1, Grupo de Analisis de al Cardiopatia Isquemica Aguda trial; NA, not available; PRAGUE, Primary Angioplasty in patients transferred from general community hospitals to specialized percutaneous transluminal coronary angioplasty units with or without emergency thrombolysis trial; SIAM III, Southwest German Interventional Study in Acute Myocardial Infarction study; SWIFT, Should We Intervene Following Thrombolysis Trial; TIMI, Thrombolysis in Myocardial Infarction trial; WEST, Which Early ST-elevation myocardial infarction therapy trial.

For the contemporary trials, routine early PCI was associated with significant reduction in mortality and reinfarction compared with ischemia guided management (Table 19). There were no significant differences in the risk of stroke or major bleeding.

For balloon angioplasty trials, there was no significant difference in mortality, reinfarction or stroke between routine early PCI and ischemia guided management (Table 19). Routine early PCI was associated with a significant increase in major bleeding compared to ischemia guided management.

Table 19: Results of Meta-Analysis of Routine Early PCI Versus Thrombolysis by Wijeysundera et al. (14)

	Death *OR (95% CI)*	**Reinfarction** *OR (95% CI)*	**Stroke** *OR (95% CI)*	**Major Bleeding** *OR (95% CI)*
Contemporary trials	0.55 (0.34-0.90)	0.53 (0.33-0.86)	1.31 (0.42-4.10)	1.41 (0.74-2.69)
Balloon angioplasty trials	1.14 (0.81-1.61)	1.02 (0.80-1.31)	1.06 (0.57-2.03)	1.35 (1.13-1.61)

CI refers to confidence interval; OR, odds ratio

Wijeysundera et al. emphasized that these results are distinct from facilitated PCI. In trials of facilitated PCI, patients randomized to facilitated and primary PCI had similar door-to-balloon times and all patients underwent protocol mandated cardiac catheterization. Studies in the meta-analysis by Wijeysundera et al. had an average delay of 8.4 hours between thrombolysis administration and cardiac catheterization with a range from 68 minutes to 16.7 hours.

Limitations to the meta-analysis include:

- The optimal timing of coronary angiography after thrombolysis is unclear.
- Many trials had low rates of rescue PCI likely reflecting evidence to support the benefit of rescue PCI has only recently emerged. As such, the results may be overestimating the true benefit of an invasive strategy if all patients who failed thrombolysis received rescue PCI.
- The designs of the trials were varied for number of treatment arms and the delay from thrombolysis to coronary angiography.
- For all of the above reasons, Wijeysundera et al. (14) state that the results of the meta-analysis should be considered hypothesis generating rather than conclusive.

Studies Published After the Most Recent Meta-Analysis for Routine Early PCI after Thrombolysis Versus Thrombolysis (and Rescue PCI if Needed)

In the CARESS in AMI trial, Di Mario et al. (17) randomized 600 patients with STEMI treated by **half-dose** thrombolysis and GpIIbIIIa antagonists at a noninterventional hospital to:

- Immediate transfer for PCI, or
- Standard medical therapy with transfer for rescue PCI.

The primary outcome and inclusion criteria are shown in Table 20.

Table 20: Primary Outcome and Inclusion Criteria in the CARESS in AMI Trial (17)

Primary Outcome	Inclusion Criteria
Composite of: ➢ All cause mortality ➢ Reinfarction ➢ Refractory myocardial ischemia Within 30 days of randomization	Patients ≤75 years with STEMI admitted to a centre without PCI facilities within 12 hour from onset of symptoms with one or more high risk features: ➢ Extensive ST-segment elevation ➢ New onset left bundle branch block ➢ Previous MI ➢ Killip class >2 ➢ Left ventricular ejection fraction ≤35%

Times from symptom onset to first admission, randomization, and thrombolysis were similar between the study groups (Table 21).

Table 21: Times from Symptom Onset to First Admission, Randomization and Thrombolysis in CARESS in AMI (17)

Times	Immediate PCI (N=298) *Median (Interquartile Range)*	Standard Care/Rescue PCI (N=300) *Median (Interquartile Range)*
Symptom onset to first admission (minutes)	120 (72-205)	120 (74-191)
Symptom onset to randomization (minutes)	153 (99-245)	151 (100-226)
Symptom onset to thrombolysis (minutes)	165 (115-254)	161 (120-245)

In the immediate PCI group, 255 patients received PCI and rescue PCI was performed in 91 patients in the standard care/rescue PCI group. The primary outcome occurred in significantly fewer patients in the immediate PCI group compared to the standard care/rescue PCI group (hazard ratio 0.40; 95% CI 0.21 to 0.76) (Table 22). There were no significant differences between the groups in the incidence of major bleeding. However, there was significantly more minor bleeding in the immediate PCI group compared to the standard care/rescue PCI group (P=0.002).

Table 22: Thirty-day Event Results from the CARESS in AMI Trial (17)

Outcome	Immediate PCI (N=297)	Standard Care/ Rescue PCI (N=300)	*P* Value
Primary Endpoint	13 (4.4%)	32 (10.7%)	0.005
Death	9 (3.0%)	14 (4.7%)	0.40
Reinfarction	4 (1.3%)	6 (2.0%)	0.75
Refractory ischemia	1 (0.3%)	12 (4.0%)	0.003

Bleeding Events			
Major	10 (3.4%)	7 (2.3%)	0.47
Minor	32 (10.8%)	12 (4.0%)	0.002

Significantly more patients in the *immediate PCI group* received aspirin (P=0.0006) and clopidogrel (P<0.0001) than in the standard care/rescue group.

Limitations to the CARESS in AMI trial include:

- The study used a half-dose of thrombolytic agent rather than a full dose. The authors stated that *"the thrombolytic regimen used in the present study is not recommended by current STEMI guidelines".* (17)
- The combined endpoint was largely affected by refractory ischemia, a difficult endpoint to assess in an open label trial. (49)
- Patients in the standard care/rescue group were on unfractionated heparin for a very brief duration (24 hours, or half the duration recommended by United States guidelines), coupled with significantly lower use of aspirin and clopidogrel than the immediate PCI group. (49)
- The optimal timing for PCI for immediate PCI is unclear. (49)
- Elderly patients were excluded from CARESS in AMI since the drug regimen caused an excess of intracranial hemorrhage in patients older than 75 years in the GUSTO V trial. (50) This deprived CARESS in AMI of the population in whom early complications are the most frequent. (49)
- The hub and spoke PCI organization in CARESS in AMI may not be generalizable to other jurisdictions. There was excellent cooperation between primary care hospitals and PCI centres that achieved short times for rescue intervention in the standard care/rescue group (211 minutes compared with 135 minutes in the immediate PCI group).

In the TRANSFER-AMI trial, Cantor et al. (16) randomly assigned 1,059 high risk patients who had STEMI and were receiving **full dose** thrombolysis at centers not capable of PCI to:

- Immediate transfer for PCI within 6 hours of thrombolysis, or
- Standard treatment with transfer for rescue PCI

The primary outcome and inclusion criteria are shown in Table 23.

Table 23: Primary Outcome and Inclusion Criteria for TRANSFER-AMI (16)

Primary Outcome	Inclusion Criteria
Combined incidence of the following at 30 days: ➢ Death ➢ Reinfarction ➢ Recurrent ischemia ➢ New or worsening heart failure ➢ Cardiogenic shock	Patients with STEMI who presented within 12 hours after the onset of symptoms to participating centres that did not have the capability of performing PCI and who were treated with thrombolysis and had at least one of: ➢ Systolic blood pressure <100 mmHg ➢ Heart rate >100 bpm ➢ Killip class II or III ➢ ST segment depression ≥2 mm in anterior leads ➢ ST segment elevation ≥1mm in right sided lead V4 All patients received tenecteplase, aspirin and unfractionated heparin or enoxaparin in the emergency department. Concomitant clopidogrel was strongly recommended at the time of thrombolysis.

A sample size of 1,200 patients was calculated, however due to slow enrollment and lack of additional funding, the steering committee ended the trial with 1,059 patients enrolled.

The time delays to thrombolysis were comparable between the groups (Table 24).

Table 24: Time Delay to Reperfusion in the TRANSFER-AMI Trial (16)

Time	Standard Treatment *Median (interquartile range)*	Routine Early PCI *Median (interquartile range)*	*P* Value
Symptom onset to administration of tenecteplase (minutes)	115 (75-191) N=522	113 (74-182) N=535	0.72
Hospital presentation to administration of tenecteplase (minutes)	25 (16-41) N=522	27 (17-44) N=536	0.07
Randomization to first balloon inflation (hours)	21.9 (3.9-73.8) N=348	3.2 (2.5-4.2) N=455	<0.001
Administration of tenecteplase to first balloon inflation (hours)	22.7 (4.5-74.3) N=348	3.9 (3.1-4.9) N=454	<0.001

At 30 days, the primary end point occurred in 11% of patients assigned to routine early PCI and in 17.2% of patients assigned to standard treatment, *P*=0.004 (Table 25). There was a significant difference between the study groups for only 1 of the 5 individual components that comprised the combined endpoint, namely recurrent ischemia (*P*=0.003). There was no significant difference in bleeding rates between the study groups, *P*=0.06.

Table 25: Clinical Endpoints in the TRANSFER-AMI Trial (16)

Endpoint	Standard Treatment (N=522)	Routine Early PCI (N=536)	Relative Risk with Routine Early PCI (95% CI)	*P* Value
Efficacy Endpoints at 30 Days - number (%)				
Primary endpoint	90 (17.2)	59 (11.0)	0.64 (0.47-0.87)	0.004
Death	18 (3.4)	24 (4.5)	1.30 (0.71-2.36)	0.39
Reinfarction	30 (5.7)	18 (3.4)	0.57 (0.33-1.04)	0.06
Recurrent ischemia	11 (2.1)	1 (0.2)	0.09 (0.01-0.68)	0.003
New or worsening congestive heart failure	29 (5.6)	16 (3.0)	0.54 (0.30-0.98)	0.04
Cardiogenic shock	16 (3.1)	24 (4.5)	1.46 (0.79-2.72)	0.23
Efficacy Endpoints at 6 Months – number/total (%)				
Death	23/511 (4.5)	30/528 (5.7)	1.27 (0.77-2.23)	0.39
Reinfarction	33/511 (6.5)	21/528 (4.0)	0.60 (0.34-1.05)	0.07

TRANSFER-AMI was conducted mainly in Ontario centres, and as such, the findings are relevant to Ontario.

Limitations to the TRANSFER-AMI trial included:

- Significantly lower use of clopidogrel in the standard therapy group at the time of thrombolysis and

at discharge (P<0.001).

- The trial was not powered to detect differences in any of the individual components of the primary endpoint. (16)
- The only individual endpoint of the combined primary endpoint that showed a significant difference between the study groups was recurrent ischemia. It may be argued that a reduction in the rate of recurrent ischemia alone does not necessarily justify the strategy of routine early PCI after successful thrombolysis since presumably a patient can be transferred for elective or urgent PCI if ischemia recurs. (16)

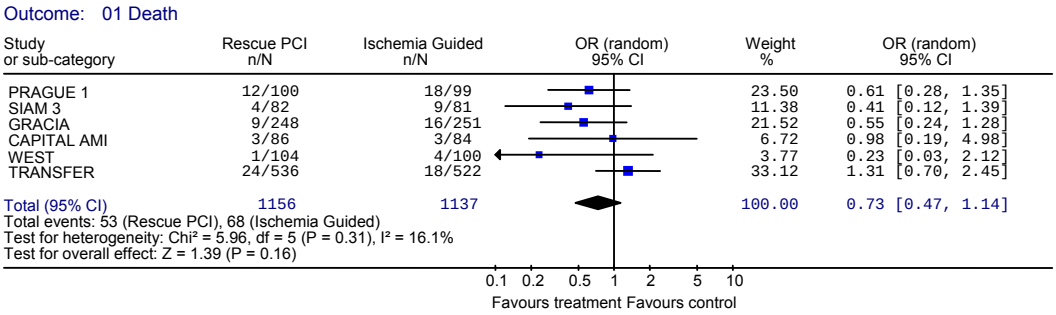
Updated MAS Meta-Analysis Including the TRANSFER-AMI Trial

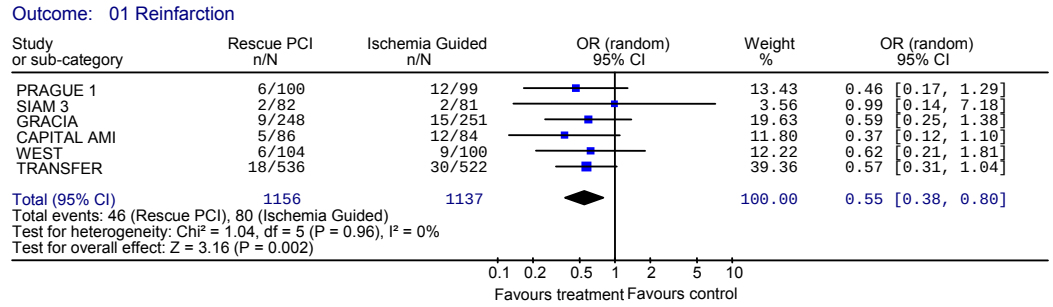
An updated meta-analysis of RCTs comparing the efficacy and safety of routine early PCI versus thrombolysis in patients with acute STEMI was performed by MAS. Trials included in the updated meta-analysis were the contemporary studies already included in the review by Wijeysundera et al. (14) in addition to the TRANSFER-AMI trial. (16) The CARESS in AMI trial was not included in the MAS meta-analysis because a half-dose thrombolytic agent was administered to patients rather than a full dose. (17)

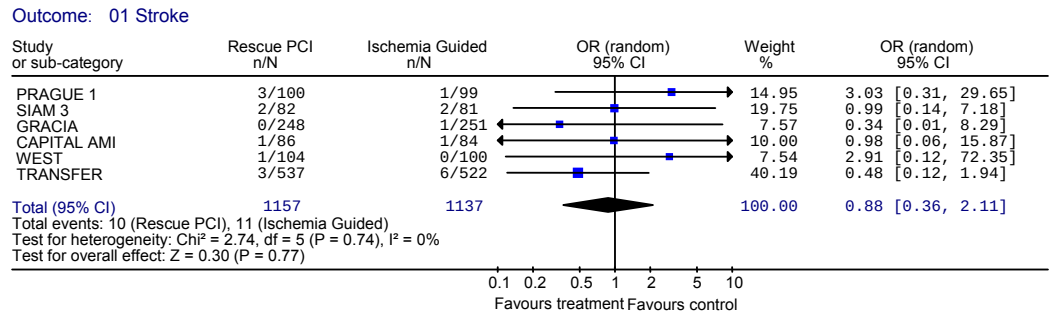
Similar to the meta-analysis by Wijeysundera et al., routine early PCI was associated with a significant reduction in reinfarction compared to thrombolysis (Figure 4). In addition, there was no significant difference in stroke or major bleeding events between routine early PCI compared to thrombolysis (Figure 4).

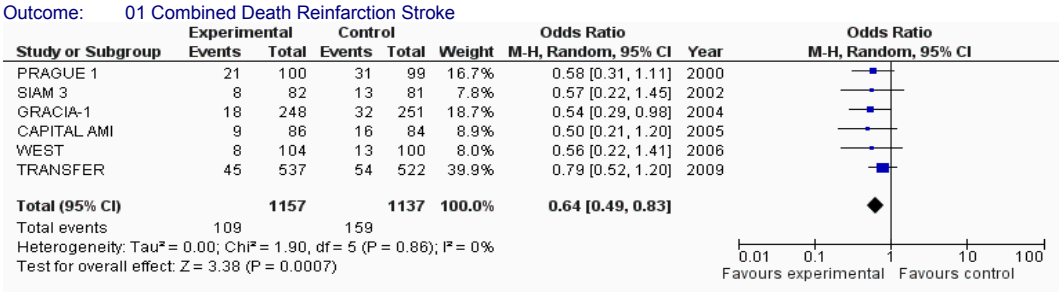
In contrast to the study by Wijeysundera et al., there was no significant difference in mortality between the study arms (Figure 4).

Routine early PCI was associated with a significant reduction in the combined endpoint of mortality, reinfarction and stroke compared to thrombolysis (Figure 4).









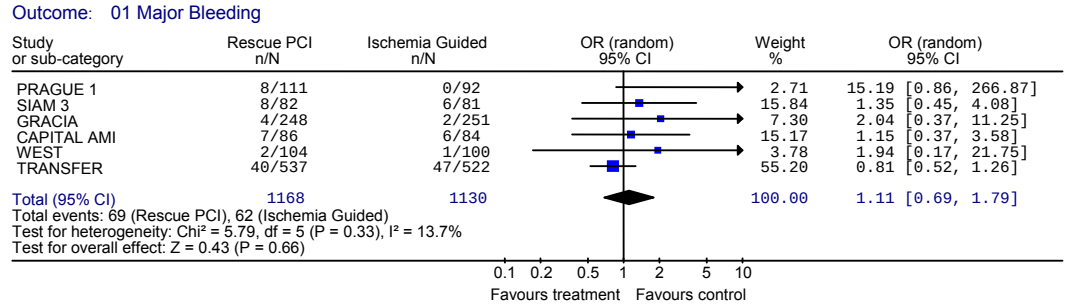


Figure 4: Meta-Analysis by the Medical Advisory Secretariat Comparing the Efficacy and Safety of Routine Early PCI Versus Thrombolysis in Patients with Acute STEMI

Overall Summary of Results

A summary of results for the evidence-based review by MAS is shown in Table 26.

Table 26: Summary of Results for MAS Evidence Based Review

Comparison	Effect
Primary PCI vs. Thrombolysis (Pre-Hospital or In-Hospital)	***Meta-Analysis of 4 RCTs that report time to reperfusion within guideline standards*** **Short term mortality** OR 0.87 (95% CI, 0.61 to 1.24) **Short-term reinfarction** OR 0.27 (95% CI, 0.16 to 0.45) **Short-term Stroke** OR 0.59 (95% CI, 0.29 to 1.22) **Combined Endpoint** OR 0.56 (95% CI, 0.42 to 0.75)
Primary PCI vs. Thrombolysis (Pre-Hospital)	**At 30 days, primary endpoint (composite of death, nonfatal reinfarction and nonfatal disabling stroke):** 8.2% prehospital thrombolysis 6.2% PCI Risk difference 1.96, 95% CI -1.53 to 5.46 **At 5 years, overall mortality:** 9.7% pre-hospital thrombolysis 12.6% primary angioplasty HR 0.75, 95% CI 0.50 to 1.14, *P*=0.18. **Treatment <2 hours after symptom onset** Pre-hospital thrombolysis 5.8% (13 patients) vs. angioplasty 11.1% (25 patients); RR 0.50; 95% CI 0.25–0.97; *P*=0.04 **Treatment >2 hours after symptom onset** No significant difference 14.5% (27 patients) vs. 14.4% (26 patients); HR 1.02; 95% CI 0.59–1.75; *P*=0.92 **Interaction between treatment and delay from symptoms** Not significant (*P*=0.10)
Facilitated PCI vs. Primary PCI	***MAS Meta-Analysis: Followup 30 days in 4 studies, 90 days in 1 study*** **Mortality** RR 1.00 (95% CI, 0.69 to 1.46) **Reinfarction** RR 1.03 (95% CI, 0.56 to 1.90) **Major Bleed** RR 1.51 (95% CI, 1.00 to 2.26)
Rescue PCI vs. Repeat Thrombolysis	***Meta-Analysis: Followup from hospital discharge to 6 months*** **Major adverse events (overall mortality and reinfarction** OR 0.93 (95% CI, 0.26-3.35), *P*=0.4 **Overall mortality** OR 1.01 (95% CI, 0.52-1.95), *P*=0.15 **Reinfarction** OR 0.32 (95% CI, 0.14-0.74), *P*=0.008 **Congestive Heart Failure** OR 0.74 (95% CI, 0.28-1.96), *P*=0.6 **Stroke** OR 5.03 (95% CI, 0.64-39.1), *P*=0.58 **Major Bleed** OR 0.5 (95% CI, 0.1-2.5), *P*=0.1 **Minor Bleed** OR 2.48 (95% CI, 1.08-5.7), *P*=0.04
Routine Early PCI after Thrombolysis Versus Thrombolysis (and Rescue PCI if Needed)	***MAS Meta-Analysis: Followup from 1 month to 12 months*** **Death** OR 0.73 (95% CI, 0.47 to 1.14) **Reinfarction** OR 0.55 (95% CI, 0.38 to 0.80) **Stroke**

	OR 0.88 (95% CI, 0.36 to 2.11) **Major Bleeding** OR 1.11 (95% CI, 0.69 to 1.79) **Combined Endpoint** OR 0.64 (95% CI, 0.49 to 0.83)

CI refers to confidence interval; HR, hazard ratio; OR, odds ratio; PCI, percutaneous coronary intervention; RR, risk ratio,

GRADE Quality of the Evidence

The quality of evidence for the use of primary angioplasty for the treatment of acute STEMI was examined according to the GRADE Working Group criteria for interventions (Table 27). (51)

Table 27: Quality Assessment of Primary Angioplasty Studies

Design	Study Quality	Consistency	Directness	Limitations	Effect	Overall GRADE Quality
Primary PCI vs. Thrombolysis (Pre-Hospital or In-Hospital)						
Meta-analysis of RCTs (Primary PCI vs. pre and in-hospital)	High → Moderate (see limitations)	No serious uncertainty	Some uncertainty (possible selection bias for patients during regular working hours at PCI facility – uncertain generalizability to "real world")	➢ Greater use of clopidogrel in primary PCI than in thrombolysis arm. ➢ Possible performance bias due to difference in quality of adjuvant care: community hospital (thrombolysis) vs. tertiary care hospital (primary PCI). ➢ Providers of care not blinded. ➢ Meta-analysis performed for studies that kept within recommended timeframe for reperfusion.	***Meta-Analysis of 4 RCTs that report median time to reperfusion within guideline standards*** Short term mortality OR 0.87 (95% CI, 0.61 to 1.24) **Short-term reinfarction** **OR 0.27 (95% CI, 0.16 to 0.45)** Short-term Stroke OR 0.59 (95% CI, 0.29 to 1.22) **Combined Endpoint** **OR 0.56 (95% CI, 0.42 to 0.75)**	Moderate
RCT (Pre-hospital vs. primary PCI)	High → Moderate (see limitations)	Uncertainty (One RCT) Moderate → Low	No serious uncertainty	➢ Greater use of clopidogrel in primary PCI than in thrombolysis arm. ➢ Study underpowered for primary outcome and 5 year followup outcome. ➢ ~70.4% of patients in the prehospital thrombolysis group underwent any angioplasty up to day 30. ➢ Significantly more beta blocker usage in pre-hospital thrombolysis group (*P*=0.003) ➢ Significant difference in time to treatment, *P*<0.001	At 30 days, primary endpoint (composite of death, nonfatal reinfarction and nonfatal disabling stroke): 8.2% prehospital thrombolysis 6.2% PCI Risk difference 1.96, 95% CI -1.53 to 5.46 At 5 years, overall mortality: 9.7% pre-hospital thrombolysis 12.6% primary angioplasty Hazard ratio 0.75, 95% CI 0.50 to 1.14, *P*=0.18. Treatment <2 hours after symptom onset Mortality lower in pre-hospital thrombolysis 5.8% (13 patients) vs. 11.1% (25 patients); RR 0.50; 95% CI 0.25–0.97; *P*=0.04 Treatment >2 hours after symptom onset No significant difference 14.5% (27 patients) vs. 14.4% (26 patients); HR 1.02; 95% CI 0.59–1.75; *P*=0.92 Interaction between treatment and delay from symptoms Not significant (*P*=0.10).	Low

Design	Study Quality	Consistency	Directness	Limitations	Effect	Overall GRADE Quality
Facilitated PCI vs. Primary PCI						
Meta-analysis of RCTs	High → Moderate (see limitations)	No serious uncertainty	No serious uncertainty	➢ Some differences in type and dose of thrombolytic and/or GpIIbIIIa used.	***MAS Meta-Analysis: Followup 30 days in 4 studies, 90 days in 1 study*** Mortality RR 1.00 (95% CI, 0.69 to 1.46) Reinfarction RR 1.03 (95% CI, 0.56 to 1.90) **Major Bleeding** **RR 1.51 (95% CI, 1.00 to 2.26)**	Moderate
Rescue PCI vs. Repeat Thrombolysis						
Meta-Analysis of RCTs	High → Moderate (see limitations)	No serious uncertainty	No serious uncertainty	➢ Indirect comparison was made between rescue PCI and repeat thrombolysis due to the absence of studies reporting a direct comparison of these interventions.	***Meta-Analysis: Followup from hospital discharge to 6 months*** Major adverse events (overall mortality and reinfarction OR 0.93 (95% CI, 0.26-3.35), *P*=0.4 Overall mortality OR 1.01 (95% CI, 0.52-1.95), *P*=0.15 **Reinfarction** **OR 0.32 (95% CI, 0.14-0.74), *P*=0.008** Congestive Heart Failure OR 0.74 (95% CI, 0.28-1.96), *P*=0.6 Stroke OR 5.03 (95% CI, 0.64-39.1), *P*=0.58 Major Bleed OR 0.5 (95% CI, 0.1-2.5), *P*=0.1 **Minor Bleed** **OR 2.48 (95% CI, 1.08-5.7), *P*=0.04**	Moderate
Routine Early PCI After Thrombolysis vs. Thrombolysis (and Rescue PCI if Needed)						
Meta-Analysis of RCTs	High → Moderate (see limitations)	No serious uncertainty	No serious uncertainty	➢ Optimal timing of early PCI after thrombolysis unclear. ➢ Design of trials varied in delay from thrombolysis to coronary angiography. ➢ Significantly lower use of clopidogrel in the standard therapy group at the time of thrombolysis and at discharge (TRANSFER-AMI).	***MAS Meta-Analysis: Followup from 1 month to 12 months*** Death OR 0.73 (95% CI, 0.47 to 1.14) **Reinfarction** **OR 0.55 (95% CI, 0.38 to 0.80)** Stroke OR 0.88 (95% CI, 0.36 to 2.11) Major Bleeding OR 1.11 (95% CI, 0.69 to 1.79)	Moderate

Design	Study Quality	Consistency	Directness	Limitations	Effect	Overall GRADE Quality
					Combined Endpoint **OR 0.64 (95% CI, 0.49 to 0.83)**	

CI refers to confidence interval; HR, hazard ratio; OR, odds ratio; PCI, percutaneous coronary intervention; RR, risk ratio,

Conclusion

A summary of conclusions for each section of the MAS rapid review is shown in Table 28

Table 28: Summary of conclusions for each section of the MAS rapid review

Comparison	Conclusion	Overall GRADE Quality
Primary PCI vs. In-Hospital Thrombolysis	Based on a meta-analysis of 4 RCTs that report median door to needle and door to balloon times that meet current guidelines: Primary PCI has advantages over thrombolysis for short-term reinfarction and a combined endpoint (mortality/reinfarction/stroke).	Moderate
Primary PCI vs. Pre-Hospital Thrombolysis	Based on 1 RCT: Primary PCI has no significant advantage over pre-hospital thrombolysis for a short-term composite endpoint (mortality/reinfarction/stroke) or 5 year mortality.	Low
Facilitated PCI vs. Primary PCI	Based on meta-analysis of 5 RCTs: Facilitated PCI has no benefit over primary PCI for short-term mortality or reinfarction. Facilitated PCI is associated with an Increase in major bleeding.	Moderate
Rescue PCI vs. Repeat Thrombolysis	Based on meta-analysis of 8 RCTs: Rescue PCI has advantages over repeat thrombolysis for short-term reinfarction. Rescue PCI is associated with an increase in minor bleeding.	Moderate
Routine Early PCI after Thrombolysis vs. Thrombolysis (and Rescue PCI if Needed)	Based on meta-analysis of 6 RCTs: Routine early PCI has advantages over thrombolysis for short-term reinfarction and a combined endpoint (mortality/reinfarction/stroke).	Moderate

Primary Angioplasty in Ontario

Percutaneous coronary interventions are funded through Ontario Provincial Programs. The average cost for a PCI is approximately $5,000 CDN per procedure.

There are 3 stand alone PCI centres in Ontario:

- Hotel Dieu Grace (Windsor)
- Rouge Valley (Toronto)
- Thunder Bay Regional Health Sciences

Other PCI centres in the province are:

- London Health Sciences Centre
- St. Mary's (Kitchener)
- Hamilton Health Sciences
- Trillium Health Centre (Mississauga)
- St. Michael's Hospital (Toronto)
- Sunnybrook Health Sciences Centre (Toronto)
- Southlake Regional Health Centre (Newmarket)
- Kingston General Hospital
- Ottawa Heart Institute
- Sudbury Regional Hospital
- University Health Network (Toronto)

The number of angioplasty procedures, and associated costs (in Canadian dollars), that were performed in Ontario between fiscal years 2005 and 2009 are shown in Table 29 (data from Provincial Programs). Of note, there is no way of obtaining data specifically for primary angioplasty since Provincial Programs pays for PCIs but does not differentiate as to the type of PCI. Any costs that exceed the cost per case are absorbed by the hospital budget. Physicians bill for the procedure through the Ontario Schedule of Benefits.

Table 29: Costs for Percutaneous Coronary Interventions in Ontario For Fiscal Years 2005 to 2009

Fiscal Year	Angioplasty Volumes	Cost Per Procedure	Angioplasty Cost	Stent Volumes*	Cost per Procedure	Stent Cost	Total Cost
2005/06	19,151	$4,915	$94,127,165	4,788	$2,338	$11,193,760	$105,320,925
2006/07	19,908	$4,915	$97,847,820	4,977	$2,338	$11,636,226	$109,484,046
2007/08	18,576	$4,915	$91,301,040	4,644	$2,338	$10,857,672	$102,158,712
2008/09	19,993	$4,915	$98,265,595	4,998	$2,338	$11,685,909	$109,951,504

*Province funds drug eluting stents at 25% of angioplasty volumes

The fee code for angioplasty from the Ontario Schedule of Benefits (52) is shown below:

Transluminal coronary angioplasty

Z434 - one or more sites on a single major vessel	$471.60
G262 - each additional major vessel	add $212.45
G298 - coronary angioplasty stent, per stent	$78.95

An expert consultant stated the current cost of a dose of tenecteplase (a thrombolytic agent) is approximately $2700 CDN.

According to an Ontario expert consultant:

- A number of Ontario regions have paramedics trained to perform electrocardiograms (ECGs) and

bypass the local hospital. A study from Ottawa showed that guideline door to balloon times were more often achieved when trained paramedics independently triaged and transported patients directly to a designated primary PCI centre than when patients were referred from emergency departments. (53)

- Approximately 50% of STEMI patients in Ontario self-present to local hospitals rather than calling emergency medical services.
- The EFFECT study showed approximately 50% of STEMI patients in Ontario in 2004 received primary PCI or thrombolysis in a timely manner (≤ 90 minutes or ≤ 30 minutes respectively). (54)
- The Cardiac Care Network provincial primary PCI registry showed that in 2006/2007, 2007/2008 and 2008/2009, median door to balloon times in Ontario were 107, 107 and 101 minutes. (55)
- The exact penetration rate and timeliness of primary PCI versus thrombolysis in Ontario is unknown.
- Many patients in Ontario are currently transferred to angioplasty centres the next day or two after experiencing a STEMI. The transfer is undertaken during daylight working hours which is logistically easier compared to immediate transfer during non-working hours.
- Time to reperfusion rather than treatment strategy may be more important in terms of patient outcomes. (26)

Primary Angioplasty in Quebec

At the request of the Quebec Ministry of Health and Social Services, the Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) examined the applicability of existing evidence and clinical guidelines for Quebec, by considering the current context of care and related issues with respect to organization and resources. (56)

The 2008 report concluded:

"According to these guidelines and available evidence, it cannot be affirmed that one of these methods of reperfusion is superior to the other for all patients in all clinical situations, at all times of the day. In this context, the best treatment for a particular patient will be that which is clinically appropriate and administered in a timely fashion, that is, within recommended delays. Such management is dependant on optimal organization and delivery of care and services."

AETMIS recommended:

1. Fibrinolysis and PPCI be recognized as complementary modes of intervention where the choice of treatment depends on a variety of clinical and practical considerations;

2. Treatment delays be minimized for both therapies, at each point of care from emergency medical services (with regards to any initial care or interhospital transfer) to the initial receiving hospital and to PCI hospitals that may receive patients for PPCI;

3. Recourse to PPCI not be the preferred option when the expected door-to-balloon time exceeds the delay recommended in clinical practice guidelines, and that the initial decision to proceed to fibrinolysis or PPCI (when such a choice is possible) be based on an evaluation of the individual patient's risk profile and the anticipated delays to both treatments;

4. Performance monitoring of prehospital ECG initiatives be implemented at the local, regional, and provincial level;

5. Implementation of pilot projects for the administration of prehospital fibrinolysis be considered,

particularly in remote regions, as a strategy to markedly reduce delays to reperfusion treatment in STEMI;

6. Interested and concerned organizations establish protocols of understanding and encourage discussion between the diverse participants in STEMI care and collaboration between hospitals and ambulance services;

7. Training in emergency medicine and cardiology include theoretical and practical education on both modes of reperfusion for STEMI;

8. Performance (especially timeliness of reperfusion treatment) be monitored at the provincial level across the continuum of care — in the prehospital phase, in the emergency room, in the catheterization laboratory, and particularly in the case of interhospital transfer — and that regular, timely feedback be provided to all caregivers involved;

9. Incentives be introduced to facilitate and reinforce appropriate use of fibrinolysis and PPCI by health professionals and institutions.

A 2010 study by Lambert et al. of STEMI care for 6 months during 2006 to 2007 in 80 hospitals that treated >95% of patients with acute MI in Quebec suggested that time to reperfusion rather than treatment strategy may be more important in terms of patient outcomes. (26)

Appendix

Final Search - Primary Angioplasty

Search date: January 4, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to December Week 4 2009>
Search Strategy:
---
1 exp Myocardial Infarction/ (51602)
2 (myocardial infarct* or heart infarct* or heart attack or mi).ti,ab. (63162)
3 1 or 2 (79104)
4 exp Angioplasty/ (29559)
5 (angioplast* or percutaneous coronary intervention* or PCI or stent*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (63084)
6 exp Stents/ (31942)
7 or/4-6 (63330)
8 exp Thrombolytic Therapy/ (10331)
9 exp Fibrinolysis/ (4293)
10 exp Fibrinolytic Agents/ (55309)
11 (thromboly* or fibrinoly* or alteplase or streptokinase).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (33313)
12 or/8-11 (70413)
13 3 and 7 and 12 (4525)
14 limit 13 to (english language and humans and yr="2008 -Current") (301)
15 limit 14 to (controlled clinical trial or meta analysis or randomized controlled trial) (77)
16 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (39775)
17 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (797)
18 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (77709)
19 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (423450)
20 exp Double-Blind Method/ (58545)
21 exp Control Groups/ (897)
22 exp Placebos/ (10305)
23 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (105518)
24 or/15-23 (545767)
25 14 and 24 (122)

Database: EMBASE <1980 to 2009 Week 52>
Search Strategy:
---
1 exp heart infarction/ (126979)
2 (myocardial infarct* or heart infarct* or heart attack or mi).ti,ab. (99036)
3 exp heart infarction/ (126979)
4 (myocardial infarct* or heart infarct* or heart attack or mi).ti,ab. (99036)
5 3 or 4 (151231)
6 exp angioplasty/ (37293)
7 (angioplasty or percutaneous coronary intervention* or PCI or stent*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (89728)
8 exp coronary stent/ (11946)
9 or/6-8 (89737)
10 exp fibrinolysis/ (32087)
11 exp fibrinolytic agent/ (60465)
12 (thromboly* or fibrinoly* or alteplase or streptokinase).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (56743)
13 or/10-12 (81399)
14 5 and 9 and 13 (6779)
15 limit 14 to (human and english language and yr="2008 -Current") (861)
16 Randomized Controlled Trial/ (177715)
17 exp Randomization/ (27231)
18 exp RANDOM SAMPLE/ (1695)
19 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (318031)
20 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (755)
21 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (73004)
22 Double Blind Procedure/ (75236)
23 exp Triple Blind Procedure/ (14)
24 exp Control Group/ (5229)
25 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (229541)
26 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (461939)
27 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (300594)
28 or/16-27 (851635
29 15 and 28 (309)

Characteristics of Randomized Controlled Trials Included in Meta-Analysis by Huynh et al. (2)

Appendix Table 1: Characteristics of Randomized Controlled Trials Included in Meta-Analysis by Huynh et al. (2)

Name of Study or First Author	Study Period	N	Transfer for Primary PCI Required	Pre-Hospital Fibrinolysis	Type of Fibrinolysis	Glycoprotein Inhibitor	Stent	Time Delay to Reperfusion Therapy (Median min)	
								Door to Balloon	Door to Needle
Air PAMI	NA Published in 2002	138	Yes	No	68% tPA 32% SK	NA	NA	155	Mean 174 ± 80
Berrocal	1993-1995	112	No	No	SK	NA	NA	82*	15*
CAPTIM	1997-2000	840	No	100%	Accelerated tPA	NA	Yes	190†	130
C-PORT	1996-1999	451	No	No	Accelerated tPA	Yes	Yes	102	46
DANAMI-2 With transfer	1997-2001	1,129	Yes	No	Accelerated tPA	Yes	Yes	90*	20*
DANAMI-2 without transfer	1997-2001	443	Yes	No	Accelerated tPA	-	-	63*	20*
De Boer	1996-1999	87	No	No	SK	No	Yes	NA	NA
Dobrzycki	2002-2003	401	Yes	No	SK	Yes	Yes	145	35
Garcia	1991-1996	220	No	No	Accelerated tPA	NA	Yes	NA	197†
Gibbons	1989-1991	108	No	No	Nonaccelerated tPA	NA	NA	277 ±144†	232 ±174†
GUSTO IIB	1994-1996	1,138	No	No	Accelerated tPA	NA	NA	3.8 hours†	3.0 hours†
GUSTO HIS	NA Published in 2006	48	Yes	NA	Fibrin specific	Yes	NA	NA	NA
Kastrati	1999-2001	141	No	No	Accelerated tPA	Yes	Yes	NA	NA
PAMI-1	1990-1992	395	No	No	Nonaccelerated tPA	NA	NA	Mean 60 ±41*	Mean 32 ± 22*
PRAGUE-1	1997-1999	200	Yes	No	SK	NA	Yes	95	22
PRAGUE-2	1999-2002	850	Yes	No	SK	NA	Yes	Mean 97 ± 28*	Mean 12 ± 10*

Name of Study or First Author	Study Period	N	Transfer for Primary PCI Required	Pre-Hospital Fibrinolysis	Type of Fibrinolysis	Glycoprotein Inhibitor	Stent	Time Delay to Reperfusion Therapy (Median min)	
								Door to Balloon	Door to Needle
Ribeiro	1989	100	No	No	SK	NA	NA	Mean 238 ± 112†	Mean 179 ± 98†
Ribichini	1993-1996	110	No	No	Accelerated tPA	NA	Yes	Mean 53	Mean 36
Schomig	1997-1999	140	No	No	Accelerated tPA	100%	100%	65	30
SWEDES	2001-2003	205	Yes	No	Reteplase	100%	NA	202†	114†
STAT	1997-1999	123	No	No	Accelerated tPA	19%	98%	77*	15*
Vermeer	1999	150	Yes	No	Accelerated tPA	NA	Yes	Mean 85 ± 25	Mean 10 SD not available
WEST	NA Published in 2006	200	Yes	42%	Tenecteplase	Yes	NA	127	51
Zwolle	1990-1995	395	No	No	SK	NA	NA	NA	NA

NA refers to not available; SK, streptokinase; tPA, tissue plasminogen activators
* From randomization
† From symptom onset

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