*Ontario Health Technology Assessment Series 2004; Vol. 4, No. 10*

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

An Evidence-Based Analysis

August 2004

Ontario

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

## Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Primary angioplasty for the treatment of acute ST-segment elevated myocardial infarction: an evidence-based analysis. *Ontario Health Technology Assessment Series* 2004; 4(10)

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ISSN 1915-7398 (Online)
ISBN 978-1-4249-7282-1 (PDF)

## About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

## About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

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# Abbreviations

| | |
|---|---|
| CI | Confidence interval |
| ECG | Electrocardiogram |
| GP | Glycoprotein |
| ICES | Institute for Clinical Evaluative Sciences |
| MI | Myocardial infarction |
| MU | Million units |
| OR | Odds ratio |
| PCI | Percutaneous coronary intervention |
| ANGIOPLASTY | Percutaneous transluminal coronary angioplasty |
| RCT | Randomized controlled trial |
| STEMI | ST-segment elevated myocardial infarction |
| TIMI | Thrombolysis in myocardial infarction |
| PA | Primary angioplasty |

# Executive Summary

One of the longest running debates in cardiology is about the best reperfusion therapy for patients with evolving acute myocardial infarction (MI). Percutaneous transluminal coronary angioplasty (ANGIOPLASTY) is a surgical treatment to reopen a blocked coronary artery to restore blood flow. It is a type of percutaneous (through-the-skin) coronary intervention (PCI) also known as balloon angioplasty. When performed on patients with acute myocardial infarction, it is called primary angioplasty. Primary angioplasty is an alternative to thrombolysis, clot-dissolving drug therapy, for patients with acute MI associated with ST-segment elevation (STEMI), a change recorded with an electrocardiogram (ECG) during chest pain.

This review of the clinical benefits and policy implications of primary angioplasty was requested by the Ontario Health Technology Advisory Committee and prompted by the recent publication of a randomized controlled trial (RCT) in the *New England Journal of Medicine* (1) that compared referred primary angioplasty with on-site thrombolysis. The Medical Advisory Secretariat reviewed the literature comparing primary angioplasty with thrombolysis and other therapies (pre-hospital thrombolysis and facilitated angioplasty, the latter approach consisting of thrombolysis followed by primary angioplasty irrespective of response to thrombolysis) for acute STEMI.

There have been many RCTs and meta-analyses of these RCTs comparing primary angioplasty with thrombolysis and these were the subject of this analysis. Results showed a statistically significant reduction in mortality, reinfarction, and stroke for patients receiving primary angioplasty. Although the individual trials did not show significant improvements in mortality alone, they did show it for the outcomes of nonfatal reinfarction and stroke, and for an end point combining mortality, reinfarction, and stroke. However, researchers have raised concerns about these studies.

A main concern with the large RCTs is that they lack consistency in methods. Furthermore, there is some question as to their generalizability to practice in Ontario. Across the RCTs, there were differences in the type of thrombolytic drug, the use of stenting versus balloon-only angioplasty, and the use of the newer antiplatelet glycoprotein IIb/IIIa. The largest trial did not offer routine follow-up angioplasty for patients receiving thrombolysis, which is the practice in Ontario, and the meta-analysis included trials with streptokinase, an agent seldom used in hospitals in Ontario. Thus, the true magnitude of mortality benefit can only be surmised from head-to-head comparisons of current standard therapies for primary angioplasty and for thrombolysis.

By taking a more restrictive sample of the available studies, the Medical Advisory Secretariat conducted a review that was more consistent with patterns of practice in Ontario and selected trials that used accelerated alteplase as the thrombolytic agent.

Results from this meta-analysis suggest that the rates for primary angioplasty are significantly better for mortality, reinfarction, and stroke, in the short term (30 days), and for mortality, reinfarction, and the combined end point at 6 months. When primary angioplasty was compared with in-hospital thrombolysis, results showed a significant reduction in adverse event rates associated with primary angioplasty. However, 1 large RCT of pre-hospital thrombolysis (i.e., thrombolysis given by paramedics before arriving at the hospital) compared with primary angioplasty documented that pre-hospital thrombolysis is an equivalent intervention to primary thrombolysis in terms of survival. Furthermore, a meta-analysis of studies that compared pre-hospital thrombolysis with in-hospital thrombolysis showed a reduction in all hospital mortality rates in favour of pre-hospital thrombolysis, supporting the findings of the pre-hospital thrombolysis study. (2)

Clinical trials to date have reported that hospital stay is often reduced for patients who receive primary angioplasty compared with thrombolysis. Using a cost-analysis performed alongside the only study from Ontario, the Medical Advisory Secretariat concluded that there might be savings associated with primary angioplasty. These savings may partly offset the investment the provincial government would have to make to increase access to this technology. These savings should also be shown outside of a clinical trial protocol if the overall efficiencies of primary angioplasty are to be verified.

Based on this health technology policy analysis, the Medical Advisory Secretariat concludes that primary angioplasty has advantages with respect to mortality and combined end points compared with in-hospital thrombolysis (Level 1 evidence). However, pre-hospital thrombolysis improves survival compared with in-hospital thrombolysis (Level 1 evidence) and is equivalent to primary angioplasty (Level 1 evidence).

Results from the literature review raise concerns about the loss of therapeutic advantage due to treatment delays, time lapse from symptom onset to revascularization, time-of-day variations, the hospital volume of procedures, and the ability of hospitals to achieve in practice what RCTs have shown.

Furthermore, questions relevant to applying primary angioplasty widely, involve the diagnosis by paramedics, ambulance diversion protocols, paramedic training, and inter-hospital transfer protocols. These logistical considerations need to be addressed to realise the potential to improve patient outcomes. In its analysis, the Medical Advisory Secretariat concludes that it is unrealistic to reorganise the emergency medical services across Ontario to fully implement a primary angioplasty program.

Finally, it is important to evaluate the potential of this technology in the context of Ontario's health system. This includes urban and rural considerations, the ability to expand access to primary angioplasty and to minimize symptom-to-assessment time through a diverse strategy including public awareness. Therefore, a measured, evaluative approach to adopting this technology is warranted.

Furthermore, the alternative approach to pre-hospital or early thrombolysis, especially within 120 minutes from onset of symptoms, should be considered when developing the approach to improving outcomes for acute MI. This could include efforts to decrease the symptom-to-thrombolysis time through strategies such as a concerted public education program to expedite presentation to emergency rooms after onset of symptoms, a pre-hospital ECG and thrombolysis checklist in ambulances to reduce door-to-needle time on arrival at emergency rooms, and, especially in remote areas, access to pre-hospital thrombolysis.

The Medical Advisory Secretariat therefore recommends that this analysis of primary angioplasty be viewed in the overall context of all interventions for the management of acute MI and, in particular, of improving access to primary angioplasty and maximising the use of early thrombolysis.

Outcomes for patients with acute MI can be improved if efforts are made to optimise the interval from symptom onset to thrombolysis or angioplasty. This will require concerted efforts, including public awareness through education to reduce the symptom-to-emergency room time, and maximising efficiencies in door-to-intervention times for primary angioplasty and for early thrombolysis.

Primary angioplasty and early thrombolysis cannot be considered in isolation from one another. For example, patients who have persistent STEMI 90 minutes after receiving thrombolysis should be considered for angioplasty ("rescue angioplasty"). Furthermore, for patients with acute MI who are in cardiac shock, primary angioplasty is considered the preferred intervention. 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. In remote parts of the province, consideration should be given to introducing pre-hospital thrombolysis as the preferred intervention through upgrading a select number of paramedics to advanced care status.

# Objective

Percutaneous transluminal coronary angioplasty (ANGIOPLASTY) is a surgical treatment to reopen a blocked coronary artery to restore blood flow. It is a type of percutaneous (through-the-skin) coronary intervention (PCI). When performed on patients with acute myocardial infarction (MI), it is called primary angioplasty. Primary angioplasty is an alternative to thrombolysis, clot-dissolving drug therapy, for patients with acute MI associated with ST-segment elevation (STEMI), a change recorded with an electrocardiogram (ECG) during chest pain. This review of the clinical benefits and policy implications of primary angioplasty was requested by the Ontario Health Technology Advisory Committee and prompted by the recent publication of a randomized controlled trial (RCT) in the *New England Journal of Medicine* (1) that compared referred primary angioplasty with on-site thrombolysis in Denmark.

# Background

### Clinical Need: Target Population

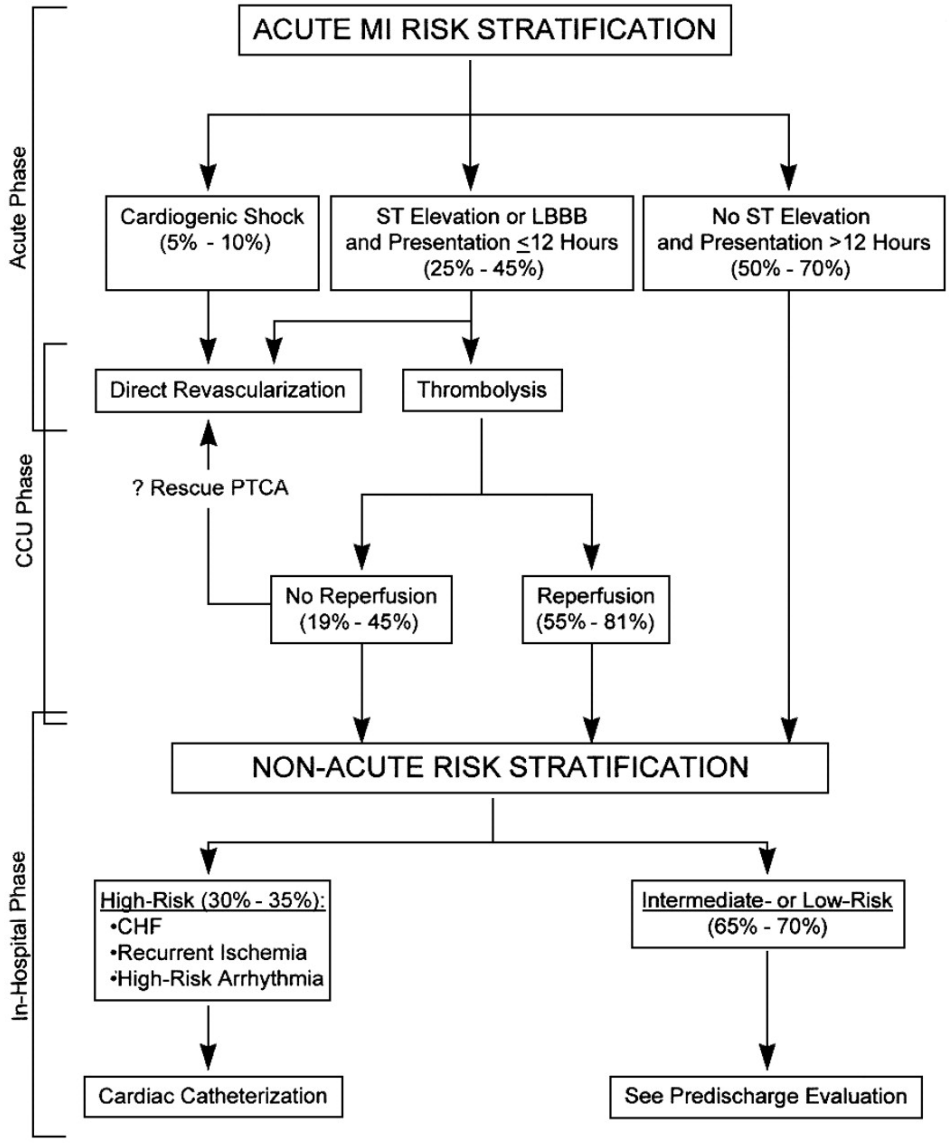
MI is an acute coronary syndrome caused by the blockage of 1 or more coronary arteries, usually by an atherosclerotic plaque, which results in a thrombus (blood clot). Unstable angina, chest pain not caused by a thrombus, is another type of acute coronary syndrome. An ECG differentiates patients with acute coronary syndrome from those with noncoronary chest pain or stable angina. An ECG also determines if an acute MI is associated with ST-segment elevation.

In 1999, there were 25,775 cases of acute MI and 7,628 deaths in Ontario.(3) The estimated number of patients with STEMI annually in Ontario as of 2003 was 11,100. Cardiovascular disease is the leading cause of death among residents of Ontario. Most cardiovascular disease mortality is due to acute MI. (4) The economic burden of cardiovascular disease is severe. It costs the government of Ontario about $5.5 billion annually, about 2% of the provincial gross domestic product. (4)

The risk factors for acute MI are hypertension, diabetes, smoking, obesity, a high fat diet, and a sedentary lifestyle. Ontario's acute MI mortality rates have been declining steadily since 1979. However, as Ontario's population grows and ages, the number of deaths from cardiovascular disease is expected to double by 2018.(4)

The determination that patients with STEMI may benefit from revascularization depends on their timely arrival at a hospital. Patients may take themselves to emergency departments or may be transported by ambulance. About 25% to 45% of patients with acute MI that arrive at emergency departments within 12 hours of experiencing symptoms have ST-segment elevation on ECG and no other contraindications to primary angioplasty or thrombolysis (Figure 1). (5)

**Figure 1: Acute Myocardial Infarction Risk Stratification**




Petersen 1997 (5)

## Existing Treatments Other Than Technology Being Reviewed

Treatment for acute STEMI aims to restore coronary blood flow through the blocked artery promptly. Rapid restoration is associated with better rates of survival, limitation of infarction size, and improved left ventricular function. Primary angioplasty and thrombolytic therapy each are used to treat STEMI.

Treatment of acute MI has improved in the last 10 to 20 years. The adoption of β-blockers, thrombolytic agents, aspirin, statins, and angiotensin-converting enzyme inhibitors are seen as advances. These treatments are being adopted and are benefiting people generally. (6) Population-based studies (7-9) continue to show that acute MI mortality rates are dropping in the short-term (30 days) and in the long-term (1 year).

## Thrombolysis

Among treatments, thrombolysis is the reference standard of care. (10) Thrombolytic therapy is widely available, easily and quickly administered, and highly effective at improving survival in patients with evolving infarctions. Furthermore, it does not require a catheterization laboratory and can be given by a physician, nurse, or technician in the hospital or even before a patient arrives at the hospital. The magnitude of benefit is related to the promptness of the drug's administration.

The benefits of thrombolytic therapy in patients with acute MI have been well established. (11;12) Furthermore, a retrospective analysis (8) associated thrombolysis with 17% of the total 71% reduction in acute MI mortality rates from 1975 to 1995, although using thrombolytic agents increased the risk of cerebral bleeding and stroke. Four thrombolytic agents are marketed in Canada: reteplase, tenecteplase, alteplase, and streptokinase. The risk of cerebral bleeding varies slightly among these agents, but streptokinase may present a lower risk. (13-16)

Streptokinase was the first thrombolytic in widespread use, and several trials of close to 100,000 patients were required before the medical community embraced it. Then, as recombinant alteplase was developed and studied, the question arose as to which agent was better. Another series of trials, the largest recruiting almost 45,000 patients, established that small differences could be measured, and alteplase had better mortality outcomes. (14) Due to these studies, and to the marketing of the companies involved, alteplase has become a dominant choice for patients treated and, more importantly, in total market dollars. The 1.1% difference in absolute risk of mortality translated into 0.14 expected life years gained. This comes at an incremental cost of $2845 (US) per patient ($32,678/life-year gained (US), after discounts). (17)

Alteplase and alteplase derivatives account for 90% of all patient treatments in Canada and is regarded as the standard of care for thrombolysis in Canada. For this review, excluding trials that did not use accelerated alteplase is justifiable for modelling current practice standard in Ontario. Their exclusion also is recognition of the difference between alteplase and streptokinase, and between nonaccelerated alteplase and accelerated alteplase. (14)

The noteworthy difference between thrombolytic therapy and PCI has to do with achieving reperfusion (the restoration of blood flow). Thrombolytic trials have shown that the best clinical outcomes are associated with timely reperfusion. (18) To quantify the reperfusion achieved, the Thrombolysis in Myocardial Infarction (TIMI) trials groups developed an index to measure improvement in blocked arteries. In one study, (18) the accelerated alteplase protocol was the most successful thrombolytic regimen to establish reperfusion. It resulted in the best-grade revascularization, called TIMI 3 flow, in 54% of the patients and TIMI 2 flow in 27% more of the patients within 90 minutes of infusion, for a total reperfusion response of 81%. This alteplase regimen is now the most commonly used. It is a combined bolus (single intravenous injection) and infusion over 90 minutes. As summarized in Figure 1, success rates of thrombolysis in STEMI range from 55% to 81%.

## Pre-hospital Thrombolysis

Ideally, thrombolytic therapy should be started as soon as possible after symptoms appear. In comparing the best practices of thrombolysis and primary angioplasty, researchers have explored the option of pre-hospital thrombolysis – treating patients in the ambulance before or during transport to hospital. In a meta-analysis (19)of trials comparing pre-hospital fibrinolysis (a therapy to dissolve fibrin, a clot-forming insoluble protein) to in-hospital thrombolysis, the pre-hospital strategy was significantly associated with lower total mortality rates: 9.7% versus 11.1% (P=.03), respectively, but none of the trials used the thrombolytic alteplase or the bolus-type recombinants. The safety of pre-hospital or ambulance thrombolysis was also demonstrated in the ASSENT-3 PLUS study. (20) In that study, patients received

the thrombolytic tenecteplase and either enoxaparin (an anticoagulant to prevent blood clots in the legs of patients) or unfractionated heparin (also an anticoagulant). To date, however, only 1 study (21) has compared primary angioplasty with pre-hospital thrombolysis.

Pre-hospital thrombolysis is not the practice standard in Ontario now.

# New Technology Being Reviewed

Primary balloon angioplasty was developed as an alternative to thrombolysis, because it can be used where thrombolysis is contraindicated. In balloon or coronary angioplasty, a balloon catheter is inserted under the skin to reopen blocked coronary arteries and to maintain the patency with the subsequent placement of a coronary stent in a procedure called stenting. Since the advantages of angioplasty plus stenting over angioplasty alone have been established in randomized controlled trials (RCTs) (22-24), primary angioplasty at the time of MI is currently assumed to include the placement of a stent.

Primary angioplasty improves on 2 serious complications of thrombolytic therapy: the risk of reinfarction (having another MI) and the risk of intracranial hemorrhage (bleeding in the brain). During the procedure, the patient with STEMI is admitted to the cardiac catheterization lab without any prior thrombolysis, often bypassing the emergency department. In contrast to thrombolysis, primary angioplasty requires specialized training (interventional cardiology), specialized facilities (catheterization laboratories), and rapid referral systems from emergency departments.

Primary angioplasty results in higher rates of coronary patency and substantially less intracranial hemorrhage than thrombolysis. It results in TIMI 3 flow in 46% to 97% of treated arteries. (25;26). The disadvantages of primary angioplasty are its geographical (i.e., access) constraints, its dependence on highly trained specialists, and its requirement for dedicated facilities.

There is also a well-documented relationship between procedure volume and patient outcomes, including mortality, with higher volume centres having better outcomes. (27-30) This is not the situation with thrombolysis, because no volume-outcome relationship has been shown. (29)

From these RCTs, researchers have concluded that primary angioplasty is the best reperfusion strategy for most patients with acute STEMI. However, some researchers (31) have argued that these studies have limited bearing on routine practice. These arguments are based on the wide variability in service delivery documented in registry studies and on variations between the ideal setting of clinical trials and the realities of practice. Modern trials of mechanical reperfusion strategies have had to account for logistics, transfer times, and adjunctive drug treatments during transfer. These complex issues pose questions as to the generalizability of these trials into standard practice so that primary angioplasty protocols need to be judged against earliest possible thrombolysis with modern agents.

Furthermore, researchers have noted that any delay in the decision to treat patients with thrombolysis as opposed to transferring them for primary angioplasty also affects outcomes. The terms “time to needle” or “door to needle” describe the time lapse between when a patient presents at a hospital emergency room and when he or she receives thrombolysis parenterally (by needle). This elapsed time measures the performance standard for thrombolysis: a door-to-needle time of 30 minutes or less is optimal. The corresponding variable for primary angioplasty is “time to balloon.” Clinical trials (32;33) have shown better or similar rates of survival with primary angioplasty compared with thrombolysis for patients with STEMI who present early after symptom onset and who can receive angioplasty within 60 minutes of presenting. A recent study (34) reported that delays between symptom onset and treatment were associated with poorer mortality and morbidity in a large cohort of patients receiving angioplasty.

Generally, the use of stents and antiplatelet glycoprotein (GP) IIb/IIIa therapy in primary angioplasty has been supported by evidence from clinical trials (22;35-38) and by registry studies. (39) Adding GP IIb/IIIa to stenting in acute MI has also been supported by RCTs (40;41), to the extent that these are recognized standards of care. These 2 technologies are not always combined, however, because of the anatomy or morphology of the target arteries. To date, the benefits of including stents in acute MI procedures have been limited to the restenosis and revision rates, and have not affected the primary outcomes of mortality, reinfarction, and stroke, compared with balloon angioplasty alone

A Canadian database in British Columbia (42) that collected data from 1994 to 1997 documented improved clinical outcome after widespread use of coronary artery stenting for all angioplasty indications. The study showed that the use of stenting increased to 58.7% by the end of the study period, and it is likely to be significantly higher than this now.

## Combined Thrombolysis and Angioplasty

There are different ways to combine angioplasty and thrombolysis to treat acute MI. Primary angioplasty is a special case of immediate or direct angioplasty to restore blood flow to a blocked artery. Angioplasty can also be performed after thrombolytic therapy, either immediately (as soon as possible), a procedure called facilitated angioplasty, or a bit later in the post-MI period. These post-MI angioplasty procedures are classified as follows:

- Early angioplasty (within several hours or a few days after thrombolysis)
- Delayed angioplasty (within 4 or more days after thrombolysis)
- Rescue angioplasty (for persistent blockage of the infarct-related artery after thrombolysis) (43)

In rescue angioplasty, patients are catheterized only after thrombolysis is considered to have failed based on persistent STEMI. Usually, under these circumstances, patients are not rechallenged with thrombolysis, and patients are "crossed over" to angioplasty. Two trials examining the benefit of a second course of thrombolysis did not yield significant results. (44;45) These trials were performed in centres with emergency PCI services, and the thrombolytic drug was given upon presentation and diagnosis of the patient in the emergency department. Generally, facilitated angioplasty protocols may refer patients receiving thrombolysis for catheterization as soon as the thrombolytic administration is complete.

The term facilitated angioplasty has been used to refer to any version of primary angioplasty combined with thrombolysis, but it is precisely defined as treatment with low-dose thrombolytic drugs, platelet GP IIb/IIIa inhibitors, or both, prior to primary angioplasty. (46) The rationale for this approach is to provide the earliest possible pharmacologic reperfusion before attempting definitive mechanical revascularization of the infarct-related artery. Four RCTs have compared facilitated angioplasty with primary angioplasty. (32;33;47;48) In a separate review, Keeley et al. (49) summarized these trials. They concluded that there has been no demonstrated benefit and noted increased bleeding complications.

O'Neill et al. (47) randomized patients either to primary angioplasty or to streptokinase (1.5 million units [MU]) administered intravenously over 30 minutes with facilitated primary angioplasty. The authors found no difference in mortality rates. Patients receiving facilitated angioplasty required fewer subsequent revascularization procedures (83% versus 92%) since these patients with sufficient reperfusion did not receive angioplasty after they underwent angiography. However, the group receiving facilitated angioplasty needed more emergency coronary artery bypass graft (CABG) surgery, had more vascular complications, and received more blood transfusions. Based on these events, and the difference in hospital costs associated with about 60 patients per arm, the authors did not recommend further study of the combination.

Vermeer et al. (32) justified adding a combined angioplasty and thrombolysis arm to their trial by stating that studies had not included a combined "rescue angioplasty" arm. Patients in the combined arm of this trial received thrombolysis with accelerated alteplase followed by transfer and rescue if indicated. All patients presented to a non-PCI centre and were either given thrombolysis on-site, given thrombolysis and transferred, or only transferred.

Scheller et al. (48) compared thrombolysis and immediate stenting with thrombolysis and delayed stenting. They found immediate stenting was associated with reduced rates of reinfarction and fewer complications. It also eliminated the need for unplanned angiography. The study was designed to accommodate centres that would treat acute MI by thrombolysis first and then refer patients to a PCI centre. The immediate referral came from hospitals within 35 kilometres of the PCI centre. After 6 months, rates of mortality were 4.9% for immediate PCI compared with 11.1% for delayed PCI. Rates of reinfarction were 2.4% for immediate PCI compared with 2.5% for delayed PCI. Rates of stroke were 2.4% for immediate PCI compared with 2.5% for delayed PCI. Because this was a small study, these rates were only significant when a combined end point that included ischemic events was used. Nonetheless, it suggests data supporting the combined approach of thrombolysis and referral to PCI are accumulating.

A special case of facilitated angioplasty is when thrombolysis is combined with transfer for primary angioplasty. Several studies have evaluated this combination. The original PRAGUE study in the Czech republic (33) included a third arm of patients given thrombolytic agents and then transferred. Results showed patients randomized to thrombolysis before transfer for angioplasty bled more.

The guidelines of the American College of Cardiology/American Heart Association (50;51) require that a hospital perform 200 or more PCIs per year, that each physician perform 75 or more PCIs per year, and that door-to-balloon time be less than 120 minutes. The volume-provider relationships have been summarized by Boersma et al. (52)

# Literature Review on Effectiveness

## Objective

This literature search aimed to summarize existing health technology assessments, meta-analyses, and RCTs comparing primary angioplasty with thrombolysis to determine the absolute benefits of each for patient survival, adverse effects, and reinfarction. The secondary purpose, using this summary, was to model current practice in Ontario and to do a cost-benefit analysis, that is, to determine the benefits and costs that may accrue for the policy choices to expand primary angioplasty services in the province. The analysis was undertaken to assist the Ontario Health Technology Advisory Committee in making its recommendation to the Ministry of Health and Long-term Care regarding the use of primary angioplasty in the management of acute MI

RCTs are the evidence standard to determine the superiority of different therapeutic interventions to treat acute MI. Publications based on the provincial MI registry, data collected and maintained by ICES, and guidelines for acute MI comprise the evidence base to determine the model of practice in Ontario.

Ontario, with its large mass, makes optimizing time to treatment for acute MI geographically challenging. This health technology assessment aimed to identify opportunities for real-world selection of patients for optimal treatment with angioplasty, and various types of thrombolysis. The search also sought to address studies that transported patients after randomization, as did Andersen et al. (1)

## Questions Asked

- What is the pooled efficacy of primary angioplasty compared with thrombolysis to treat patients with acute STEMI?
- What is the status quo in Ontario?
- What incremental costs and patient outcome benefits are expected if access to the more effective technology is increased?

## Methods: Literature Review

The methods used in this report were similar to those used in other reports of the Medical Advisory Secretariat. Existing health technology assessments and meta-analyses retrieved from an initial review of the literature were used to determine the starting point for subsequent formal searches for new evidence from RCTs. The literature review was also used to identify studies that characterized current practice patterns and emergent therapies targeted at the same patient population. Overall, the methods comprised a formal search to update the list of RCTs, a meta-analysis of retrieved studies to estimate treatment differences, and a synthesis of practice reports and clinical guidelines to document the normative and consensus standards of care.

The formal literature search was designed to build and supplement the literature search conducted by Keeley et al. (53) In that report, the authors identified all published and unpublished randomized trials done up to 2002 that compared primary angioplasty with thrombolysis for acute STEMI. Their index search was limited to the MEDLINE database, supplemented by reviews of specific cardiology journals and contact with the principal investigators directly. For this analysis, MEDLINE, EMBASE, INAHTA, Cochrane, and NICE were searched.

The search was designed to include all randomized trials comparing primary angioplasty with thrombolysis, all meta-analyses of such studies, and all health technology assessments about primary angioplasty. The search excluded non-systematic reviews, commentaries, and letters.

## Methods: Meta-Analysis

The literature search was designed to identify all trials published since the search by Keeley et al.(53) Published in *Lancet* early in 2003, that meta-analysis included citations up to 2002. This literature search began from there to include all publications published in 2002 and 2003. Because entire calendar years were specified, there were likely overlaps with the period used by Keeley and colleagues.

Departing from the methods of those investigators, this meta-analysis excluded the 23$^{rd}$ study cited by them, the cardiac SHOCK trial (54) that enrolled high-risk patients with acute MI. High-risk patients were excluded from most trials in the entire sample, therefore this review excluded them too. This analysis also used a random-effects model, which assumes that, given a world of conditions, the effects of a study are only a sample, ideally random, of possible effects. It is considered more conservative and is recommended when trial protocols differ moderately, as these trials do.

For example, the 22 trials included in the sample had different cut-off points from time to presentation of between 6 and 12 hours. Some trials had age group restrictions. In some, different thrombolytic agents were used. The trials also differed over time: later trials tended to use newer thrombolytic agents, to include stenting in the primary angioplasty arms, and to include GP IIb/IIIa to varying degrees.

To confirm the adverse event rates reported in meta-analyses to date, the original articles of the selected studies were retrieved, and the event rates were checked. Where discrepancies appeared, the rates in the

original publication were used. If the original paper could not be found, then the event rates used in at least 2 subsequent meta-analyses had to agree for the results to be included.

From there, the authors of this review were able to specify what trials would be included in the Medical Advisory Secretariat's meta-analysis. It's worth noting that understanding the degree to which study populations reflect real patients and their outcomes is vital to determine how, or if, results are generalizable. Therefore, the focus was on identifying trials with factors that best represent normative practice standards in Ontario and provincial clinical guidelines. Parameters to define the status quo for residents of Ontario were taken from the design elements of the RCTs identified. Thus, it was determined that trials had to have included, for the primary angioplasty arm, primary coronary stenting and the option of using GP IIb/IIIa. For the group receiving thrombolysis, patients had to have received the accelerated regimen of alteplase in the hospital and have been offered rescue angioplasty. Heparin and aspirin had to be have been offered to all patients as a matter of protocol, and antiplatelet agents had to be administered for at least 1 month after the MI. These parameters were consistent with the trial characteristics summarized by Keeley et al. (53)

## Results of Literature Review

As noted in the methods, the Keeley et al. (53) meta-analysis was the starting point for the literature search to identify all trials that had been published since that study and that would otherwise have been included in a meta-analysis. An electronic search of the MEDLINE database (1966 to week 3, October 2003 yielded 140 citations. The details of the search strategy, with the keywords, are in Appendix 1. Similar searches of EMBASE and PREMEDLINE yielded 167 and 27 citations, respectively. Combining all results and eliminating duplicate citations yielded 289 citations that were then reviewed manually by reading their abstracts to identify RCTs comparing angioplasty with thrombolysis.

Only evidence from RCTs is summarized (Table 1). Trials with fewer than 100 patients per group, on average, were considered small RCTs. Consistent with the Keeley et al. meta-analysis, trials that included pre-hospital thrombolysis (e.g., the CAPTIM study) (21) were included if the group for comparison was primary angioplasty (or primary stenting).

Upon review, most of the citations were found to be review articles (98) and trials that were not topical (56). There were also many case series (45) and registry studies (49). Conference papers (10) and surveys and letters (10) made up the balance of the dismissed citations. This left 9 RCTs and 7 meta-analyses.

The 7 meta-analyses published from 2002 to 2003 are summarized with the prior meta-analyses in the section below. (31;55-57) Three other meta-analyses (58-60) were excluded because their authors did not conduct independent literature searches for the analyses, but instead used the search results of previous papers.

**Table 1: Quality of Evidence**

| Study Design | Level of Evidence* | No. of Eligible Studies |
|---|---|---|
| Large randomized ctonrolled trial (RCT) | 1 | 6 |
| Systematic reviews of RCTs | | 6 |
| Large RCT unpublished, but reported to an international scientific meeting | 1(g)* | 0 |
| Small RCT | 2 | 12 |
| Small RCT unpublished but reported to an international scientific meeting | 2(g) | 2 |
| Non-RCT with contemporaneous controls | 3a | |
| Non-RCT with historical controls | 3b | |
| Non-RCT presented at international conference | 3(g) | |
| Surveillance (database or register) | 4a | |
| Case series with more than 2 years of follow-up (multisite) | 4b | |
| Case series with fewer than 2 years of follow-up | 4c | |
| Retrospective review, modelling | 4d | |
| Case series presented at international conference | 4(g) | |

*g=grey literature

After completing this review of citations and comparing the remaining studies to those cited by Keeley et al., (53) it was determined that 2 studies (61;62) cited in that review had since been peer-reviewed and formally published. Thus, the additional studies published did not meet the criteria for inclusion in the meta-analysis.

## Summary of Existing Health Technology Assessments

Several health technology assessments were identified: a Cochrane collaborative review, (63) a Norwegian study, (63) and an assessment from the United Kingdom under review. (64)

The Cochrane collaborative review by Cucherat et al. (63) was first done in 1999. It was updated in 2003 to add studies published after the first literature search. The 10 studies included in this meta-analysis were also in the Keeley et al. meta-analysis. The authors excluded 3 studies.(32;54;65) They noted they rejected the Akhras study (65) because its published abstract did not provide clinical end points. They do not appear to have specifically rejected the other 2 studies. The authors included citations of several studies "awaiting assessment" in their update, implying that they will be updating their meta-analysis to include studies published until 2002. From that list, all English-language citations were selected for consideration in this review.

Cucherat et al. excluded 5 studies. Two (66;67) of these used intracoronary thrombolysis, and 1 (68) used intra-aortic balloon counter-propulsion in its primary angioplasty patients. These studies were judged uncombinable with the other studies. Of the 2 other citations, 1 was an abstract of a study subsequently published (69;70), and the other (65) was judged to lack sufficient outcome data.

Based on the studies they did include, Cucherat et al.(63) concluded that, compared with thrombolytic therapy, primary angioplasty was associated with a significant reduction in mortality when all of the end-of-study mortality data were combined (RRR 32%; 95% confidence interval (CI), 5%–50%). Risk reductions were reported for reinfarction (RRR 52%; 95% CI, 30%–67%), recurrent ischemia (RRR 54%; 95% CI, 39%–66%), and stroke (RRR 66%; 95% CI, 28%–84%). The authors also looked at adverse events and found a trend in the reduction of rate of CABG surgery associated with primary angioplasty (RRR 30%; 95% CI, 9%–55%). Interestingly, no significant difference was found for the incidence of major bleeding associated with thrombolysis (relative RR 1.18; 95% CI, 0.73–1.90).

The authors of the Norwegian report (71) concluded that primary angioplasty is better than intravenous thrombolysis in acute STEMI for patients admitted to centres with a PCI laboratory. The authors based their conclusion on a meta-analysis of 17 studies that showed lower rates of mortality, fewer reinfarctions, and fewer strokes. They excluded 2 studies that were (and still are) available only as abstracts (65;72) and 3 studies that have since been published. (73-75)

The Norwegian authors calculated that 1 adverse event was avoided in every 16th patient treated with PCI instead of thrombolysis. They summarized 1-year data on mortality and found that it favoured PCI. They cautioned, however, that patients admitted to a hospital without a PCI laboratory had better outcomes after transfer to a centre for primary PCI only when transfer times were less than 3 hours. They concluded that transferring patients to centres with PCI laboratories during the acute phase involves low risk. They also concluded that time to treatment was a negative factor for both treatments, but was more negative for thrombolysis. They reserved judgement on pre-hospital thrombolysis and facilitated angioplasty.

## Summary of Medical Advisory Secretariat Review: Randomized Controlled Trials

Researchers first demonstrated the clinical efficacy advantages of primary angioplasty compared with thrombolysis in a series of small studies. (66;72) The first randomized studies comparing it to thrombolysis came from highly specialized centres that reported a trend to lower rates of death and reinfarction in primary angioplasty. (25;76) The differences reached significance when combined in a meta-analysis in 1995, (43) and stayed significant in later meta-analyses in 1997 (77;78) and in 2003. (52;53;63) The nature of these differences across different study end points is discussed below. Generally, studies have repeatedly shown primary angioplasty is also the preferred treatment for patients with contraindications to thrombolysis, and is possibly the treatment of choice for those presenting with cardiogenic shock. (54)

The RCTs in this review are characterized by a similar design as follows:

- Strict diagnostic criteria were used to recruit patients.
- Randomization occurred after presentation and before any revascularization treatment.
- Patients were compared for primary end points of death, usually at 30 days; nonfatal reinfarction; and stroke, either ischemic or hemorrhagic.

All of the trials required a diagnosis of Q wave or ST-segment elevation, except one, (70) whose published abstract only indicated it included patients with anterior MI, presumably STEMI. As noted in the introduction, 25% to 45% of presenting acute MI cases may be expected to be ST-segment elevated.

Table 2 summarizes each RCT in this literature search, including the studies cited in the systematic reviews, for 22 trials covered in 28 citations. (1;21;25;26;32;33;65;70;72-74;76;79-93) The trials vary in size and in the types of patients with acute MI included. Some studies specifically excluded high-risk patients; others did not. They all randomly assigned patients either to primary angioplasty or to thrombolysis.

In all reports except 2, subjects were patients with STEMI presenting within 6 to 12 hours of symptom onset. In the first exception (65), the study was published in abstract form only, and the patients were described as having anterior infarctions and presumed by later meta-analysis to be comparable to patients with STEMI. In the other study (54), patients in cardiogenic shock were specifically recruited. In some trials, patients with left bundle branch block were included or at least not specifically excluded; in others, they were excluded. Some trials limited patients by age (aged 75 or 76 years or younger), but later studies did not, and 2 specifically recruited older patients. (See Table 2.)

**Table 2: Study and Patient Characteristics of 22 Randomized Controlled Trials**

| Study | 1st Year of Publication | Type | Diagnosis | Age restriction, years† | Onset of symptoms, hours (<) |
|---|---|---|---|---|---|
| DeWood et al. (72;79) | 1990 | Abstract | Early Q-wave | <76 | 12 |
| Gibbons et al. (80) | 1993 | Article | STEMI | <80 | 12 |
| Grines et al. (25) | 1993 | Article | STEMI, LBBB excl. | | 12 |
| Ribeiro et al. (83) | 1993 | Article | STEMI | <75 | 6 |
| Zijlstra et al. (76;81;82) | 1993 | Article | STEMI | <76 | 6 |
| Grinfeld et al. (74;84) | 1996 | Article | STEMI | | 12 |
| Ribichini et al.(87;88) | 1996 | Article | STEMI | <80 | <6 |
| Akhras et al. (65) | 1997 | Abstract | STEMI | | 12 |
| GUSTO IIb (26) | 1997 | Article | STEMI | | 12 |
| Zijlstra et al. (85) | 1997 | Article | STEMI | | 6 |
| Garcia et al. (70;89) | 1999 | Article | STEMI, LBBB excl. | | 5 |
| Vermeer et al. (32) | 1999 | Article | STEMI | <80 | 6 |
| Schomig et al. (73) | 2000 | Article | STEMI | | 12 |
| Widimsky et al. (33) | 2000 | Article | STEMI, LBBB incl. | | 6 |
| Le May et al. (90) | 2001 | Article | STEMI | | 12 |
| Aversano et al. (91) | 2002 | Article | STEMI, LBBB incl. | | 12 |
| Bonnefoy et al. (21) | 2002 | Article | STEMI | | 6 |
| de Boer et al. (86;94) | 2002 | Article | STEMI | >76 | 6 |
| Grines et al. (25;92) | 2002 | Article | STEMI, LBBB incl. | >70 | 12 |
| Kastrati et al. (75) | 2002 | Article | STEMI, LBBB incl. | | 12 |
| Andersen et al. (1;61) | 2003 | Article | STEMI, LBBB excl. | | 12 |
| Widimsky et al. (33;93) | 2003 | Article | STEMI | | 12 |

*STEMI represents acute ST-segment elevated myocardial infarction; LBBB, left bundle branch block
†Blank cells indicate no age restriction

For ease of discussion, the resulting group of RCTs in Table 2 can be placed into 2 broad categories: an early group and a later, more definitive, group.

**Early Group of Studies**

This group generally comprises early trials of thrombolysis and angioplasty. These trials were conducted with several different thrombolytic regimens: streptokinase, slow-infusion alteplase, or an investigational version of alteplase called duteplase. Angioplasty was also an earlier form, mostly balloon angioplasty alone (i.e., without stenting or antiplatelet drugs). These studies are also characterized by different inclusions of patients with acute MI, because the definition of STEMI became more consistent in later trials. Most consistently excluded patients ineligible for thrombolysis due to bleeding risks (e.g., previous stroke, previous major surgery). They also were repeatedly published with inconsistent reporting of patient numbers, making meta-analyses difficult. Studies in the early group are summarized in Table 3.

**Table 3: Summary of Early Group of Studies Comparing Primary Angioplasty with Thrombolysis***

| Study | Year | Type | Diagnosis | Thrombolysis Regimen | No. of Patients | | Mortality, % | | Reinfarction, % | | Stroke, % | | Combined, % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | PCI | TBL | PCI | TBL | PCI | TBL | PCI | TBL | PCI | TBL |
| DeWood et al. (72;79) | 1990 | Abstract | "early Q-wave" | Duteplase, 4h | 46 | 44 | 6.5 | 4.5 | | | | | | |
| Gibbons et al. (80) | 1993 | Article | STEMI | Duteplase, 4h | 47 | 56 | 4.3 | 3.6 | 2 | 5 | 0 | 0 | 9 | 14 |
| Grines et al. (25) | 1993 | Article | STEMI | Alteplase, 3h | 195 | 200 | 2.6 | 6.5 | 3 | 7 | 0 | 4 | 5 | 16 |
| Zijlstra et al. (76) | 1993 | Article | STEMI | 15 MU SK, 1h | 152 | 149 | 2.0 | 7.4 | 1 | 8 | 1 | 2 | 4 | 17 |
| Zijlstra et al. (85) | 1997 | Article | STEMI | 15 MU SK, 1h | 47 | 53 | 2.1 | 1.9 | 0 | 13 | 2 | 4 | 4 | 19 |
| Ribeiro et al. (83) | 1993 | Article | STEMI with exclusions | 12 MU SK, 1h | 50 | 50 | 6.0 | 2.0 | 4 | 2 | 0 | 0 | 14 | 6 |
| Grinfeld et al. (84) | 1996 | Article | STEMI | 15 MU SK, 1h | 54 | 58 | 9.3 | 10.3 | 2 | 3 | 2 | 2 | 13 | 16 |
| Akhras et al. (65) | 1997 | Abstract | STEMI | 15 MU SK, 1h | 42 | 45 | 0.0 | 8.9 | | | | | | |

*STEMI represents ST-segment elevated myocardial infarction; PCI, percutaneous coronary intervention (primary angioplasty); TBL, thrombolysis; MU, million units; SK, streptokinase, h, hour

The first, by DeWood et al., was an unpublished study that was presented at 2 meetings, first in1989,(72) and then in 1990. (79) This RCT compared the thrombolytic duteplase with primary angioplasty. (Duteplase is a version of alteplase that was not marketed subsequently, but it is fibrin-specific, as compared with streptokinase, and therefore the results of this study have been grouped with other alteplase trials.) Like slow-infusion alteplase, duteplase is administered over 4 hours. No published article of this study emerged from the literature search, but limited information about the end points of interest can be extracted from the published abstracts as presented at the 2 meetings.

Subsequently, the *New England Journal of Medicine* published 3 studies in 1993 (25;76;80) that compared primary angioplasty with thrombolysis. The first study, by Grines et al.,(25) included patients with STEMI who presented within 12 hours of symptom onset. The thrombolytic regimen was slow-infusion alteplase. In-hospital mortality rates were higher for the thrombolysis group (6.5%) compared with the angioplasty group (2.6%), but this difference was not statistically significant, possibly due to the small sample size. Reinfarction and stroke rates were higher for the thrombolysis group.

The second study, by Gibbons et al., (80) used duteplase. It was performed by the Mayo Clinic group, who published more results in 1994. (95) It looked at TIMI flow rates before and after treatment. It randomized patients presenting with STEMI either to alteplase or to primary angioplasty without stenting.

The third study, by Zijlstra et al., (76) used streptokinase instead of alteplase. The cut-off to presentation was 6 hours instead of 12 hours, although the average time to presentation was similar to that in the other studies. They included patients in shock.

The original *New England Journal of Medicine* article reported on 142 patients. Subsequent reports on this study included 301 patients: 152 randomized to primary angioplasty and 149 randomized to thrombolysis with streptokinase. (81;82) The authors published long-term follow-up data on this trial and on a follow-up study in 1999. (85;96) Across all the studies, there are discrepancies in the numbers of patients included. For the purposes of the meta-analysis by the Medical Advisory Secretariat, the event rates confirmed by Michels and Yusuf (43) and by Weaver et al. (78) were used.

Like the RCT by Zijlstra et al.(76), the results of the follow-up trial by the same authors in 1997 (85) have not been reported consistently in the literature. The original article (85) reported on 95 low-risk patients randomized either to primary angioplasty (n=45) or to streptokinase (n=50). One death was reported in the group receiving primary angioplasty, and there were no deaths in the group receiving streptokinase. In the primary angioplasty group, the cases of non-fatal reinfarction and stroke were 1 and 2, respectively. In the streptokinase group, those numbers were 2 and 8, respectively. When this study was included in the 1997 Weaver meta-analysis, (78) these rates were quoted, but, in the meta-analysis by Keeley et al., (53) the numbers of patients were 47 and 53 subjects in the primary angioplasty and streptokinase groups, respectively. In the primary angioplasty group, there was 1 death, no reinfarctions, and 1 stroke. In the streptokinase groups, there was 1 death, 7 reinfarctions, and 2 strokes. The long-term study articles did not clarify these discrepancies. For the Medical Advisory Secretariat's analysis, the original rates were used.

Ribeiro et al. (83) reported in 1993 on a single-centre study. It excluded patients with "Q-wave infarction in the region of ischemia." Patients had to present to the hospitals within 6 hours of the onset of symptoms, be younger than 75 years, and not have risks of bleeding that would contraindicate thrombolysis. The dose of the thrombolytic streptokinase was slightly lower than conventional doses of the time, at 1.2 MU infused over 1 hour.

Another study, commonly included in relevant reviews, is a published abstract by Grinfeld et al. (84) It was published as a full report in 2003. (74) This was one of the first trials not to restrict age. As a result, the mean age of its patients was 10 years older than its contemporary studies. Of 112 patients, 54 received primary angioplasty, and 58 received thrombolysis (streptokinase). It was a small study powered around the resolution of ST-segment elevation.

It evaluated the Killip class of patients. (Class 1: no sign of heart failure. Class 2: crackles, S3 gallop and elevated jugular venous pressure. Class 3: frank pulmonary edema. Class 4: cardiogenic shock - hypotension (systolic < 90 mm Hg) and evidence of peripheral vasoconstriction [oliguria, cyanosis, sweating]). Although the protocol excluded patients with Killip Class 2 or greater, the authors still described a high proportion of the sample as "not low-risk" patients according to criteria set by the later air PAMI investigators. (92)

This was not a primary stenting trial, although 3 of the patients receiving primary angioplasty also received a stent due to complications. The main end point was STEMI resolution representing reperfusion. Streptokinase dosing was standard, at 1.5 MU over 1 hour. All patients received aspirin, with β-blockers left to the discretion of the treating physician. Heparin was offered only to the primary angioplasty group, and clopidogrel anti-platelet therapy was offered only to those receiving stents. The results reported in the 2 versions are discrepant, and only the earlier version has been included in meta-analyses to date. The final rates reported by the authors are incorporated in our meta-analysis.

Also included in the early group is a study that only appears as a published abstract. (65) The thrombolytic drug was streptokinase, and the angioplasty was performed in a new cardiac unit. The authors reported on 87 patients randomized either to primary angioplasty (n=42) or to streptokinase (n=45). Time to treatment was not reported. There was a high recruitment rate. Only 8 patients were excluded, all due to late presentation of more than 12 hours. The only end point of interest reported was mortality as follows: no deaths in the angioplasty group and 4 deaths in the thrombolysis group.

**Later Group of Studies**

Included in this later, more definitive, group is the GUSTO IIb study, (26) which is a landmark study of thrombolysis. It used the accelerated regimen of alteplase, and concurrent and subsequent studies

comparing thrombolysis with angioplasty did so, too. An exception is a later cluster of European studies that continued to use the standard regimen, streptokinase.

This later group can also be characterized as happening in the era of coronary stenting. Some studies looked at primary stenting specifically. All of the studies were published reports. The reporting of primary events of interest – mortality, reinfarction, and stroke – was also more consistent. Only 1 trial did not report on strokes. Six trials reported 6-month outcomes. The studies comprising the later group are compared in Table 4.

**Table 4: Summary of Later Group Studies Comparing Primary Angioplasty With Thrombolysis***

| Study | Year | Stents | GP IIb/IIIa | Trans | Lytic regimen | No. of Patients | | Mortality, % | | Reinfarction, % | | Stroke, % | | Combined, % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PCI | TBL | PCI | TBL | PCI | TBL | PCI | TBL | PCI | TBL |
| Widimsky et al. (33) | 2000 | Yes | No | Yes | SK std | 101 | 99 | 6.9 | 14.1 | 1 | 10 | 0 | 1 | 8 | 23 |
| Widimsky et al. (93) | 2003 | Yes | Yes | Yes | SK std | 429 | 421 | 6.8 | 10.0 | 1 | 3 | 0 | 2 | 8 | 15 |
| de Boer et al. (86) | 2002 | Yes | No | No | SK std | 46 | 41 | 6.5 | 22.0 | 2 | 15 | 2 | 7 | 9 | 29 |
| Grines et al. (92) | 2002 | Yes | Yes | Yes | SK std or Acc. TPA | 71 | 66 | 8.5 | 12.1 | 1 | 0 | 0 | 5 | 8 | 14 |
| Ribichini et al. (88) | 1998 | Yes | No | No | Acc. TPA | 55 | 55 | 1.8 | 5.5 | 2 | 4 | 0 | 0 | 9 | 4 |
| GUSTO IIb (26) | 1997 | No | No | | Acc. TPA | 565 | 573 | 5.7 | 7.0 | 4 | 6 | 1 | 2 | 10 | 14 |
| Garcia et al. (89) | 1999 | No | No | No | Acc. TPA | 95 | 94 | 3.2 | 12.8 | 4 | 6 | 0 | 3 | 7 | 21 |
| Vermeer et al. (32) | 1999 | Yes | No | Yes | Acc. TPA | 75 | 75 | 6.7 | 6.7 | 1 | 9 | 3 | 3 | 8 | 16 |
| Schomig et al. (73) | 2000 | Yes | Yes | No | Acc. TPA | 71 | 69 | 4.2 | 7.2 | 3 | 6 | | | 7 | 13 |
| Le May et al. (90) | 2001 | Yes | Yes | No | Acc. TPA | 62 | 61 | 4.8 | 3.3 | 5 | 13 | 2 | 3 | 11 | 16 |
| Aversano et al. (91) | 2002 | Yes | Yes | No | Acc. TPA | 225 | 226 | 5.3 | 7.1 | 5 | 9 | 1 | 4 | 11 | 18 |
| Kastrati et al (75) | 2002 | Yes | Yes | No | Acc. TPA | 81 | 81 | 2.5 | 6.2 | 0 | 5 | 1 | 1 | 4 | 12 |
| Andersen et al. (1) | 2003 | Yes | Yes | Yes | Acc. TPA | 790 | 782 | 6.6 | 7.5 | 2 | 6 | 1 | 2 | 8 | 14 |
| Bonnefoy et al. (21) | 2002 | Yes | Yes | Yes | Acc. TPA | 421 | 419 | 4.8 | 3.8 | 2 | 4 | 0 | 1 | 6 | 8 |

* PCI represents percutaneous coronary intervention (primary angioplasty); TBL, thrombolysis; GP IIb/IIIa, glycoprotein IIb/IIIa use permitted or studied; SK std, 1.5 million units (MU) of streptokinase infused over 1 hour; Acc TPA, accelerated alteplase regimen; Trans, included patients randomized to PCI who required transfer to tertiary PCI facility.

For ease of discussion, the later group of studies can be analyzed separately according to type of thrombolytic agent.

**Streptokinase**

Two studies (33;93) compared a system of rapid transfer to tertiary care centres with on-site thrombolysis. Both used streptokinase as the thrombolytic drug.

The first of these studies by Widimsky et al., PRAGUE, (33) also included a group of patients randomized to facilitated angioplasty. Although primary stents were used, GP IIb/IIIa was not. The results of PRAGUE showed inter-hospital transportation of patients with acute MI presenting initially to hospitals without primary angioplasty was safe and feasible.

PRAGUE-2, the follow-up study by Widimsky et al., (93) was larger, where distances from non-PCI hospitals to PCI centres did not exceed 120 kilometres. This second trial used GP IIb/IIIa and streptokinase. The results favoured primary angioplasty when evaluated on the combined end point. Of note, the mortality rates at different PCI centres ranged from 2.8% to 9.1%, with a mean rate of 6.8%. Patients treated within 3 hours of the onset of symptoms did equally well on either therapy (7.4% versus 7.3% mortality rates for thrombolysis and primary angioplasty respectively), but patients receiving thrombolysis did worse when presenting more than 3 hours after the onset of symptoms. (15.3% versus 6.0% mortality for thrombolysis and primary angioplasty, respectively, P<.02).

The third streptokinase trial, by DeBoer et al., (86) was designed to assess a high-risk population aged 76 years or more. Up to this point, the case for older patients had not been confirmed. This trial had only 87 patients, but the authors showed that there was a significant advantage for patients receiving primary angioplasty compared with patients receiving thrombolysis. The composite rate was 9% for primary angioplasty compared with 29% for thrombolysis (P<.01) at 30 days, and 13% and 44% for each group respectively (P<.001) at 1 year. The results reflect thrombolysis with streptokinase, and primary angioplasty with stenting, but only 51% were actually stented. GP IIb/IIIa was not used.

A fourth RCT (92) that used streptokinase allowed hospitals to use either streptokinase or alteplase according to their usual policies. This trial was designed to show that patients could be treated better with transfer PCI than with on-site thrombolysis. Indeed, results showed transferred patients had better outcomes.

This represented a 14% reduction (95% CI, 5.9% to 21.3%) in mortality for accelerated t-PA as compared with the 2 streptokinase-only strategies (P=.001). The rates of hemorrhagic stroke were 0.49%, 0.54%, 0.72%, and 0.94% in the 4 groups, respectively, which represented a significant excess of hemorrhagic strokes for accelerated t-PA (P=.03) and for the combination strategy (P<.001), as compared with streptokinase only. A combined end point of death or disabling stroke was significantly lower in the accelerated-t-PA group than in the streptokinase-only groups (6.9% vs. 7.8%, P=.006).

**Accelerated Alteplase**

The later group of trials that used accelerated alteplase exclusively did so based on the findings of the original GUSTO trial in 1993. (14) The authors of GUSTO found the accelerated regimen was significantly better than streptokinase in absolute mortality (P=.001). Ribichini et al.(87;88) used this regimen in their study. The original publication had 83 patients, and the later version had 110 patients. Each used accelerated alteplase and primary angioplasty with stents. When the original publication was reviewed, discrepancies with later meta-analyses were noted. As noted above in the methods section, the Medical Advisory Secretariat used the event rates of the original publication for its meta-analysis, discussed further in this review.

The GUSTO IIb multicentre study (26) compared primary angioplasty with thrombolysis. The results showed short-term advantages for primary angioplasty. The authors concluded that angioplasty provided a small-to-moderate, short-term clinical advantage over thrombolytic therapy with alteplase, when it can be done promptly at experienced centres. The results were consistent with concurrent and later studies that also used stenting in the primary angioplasty groups.

Garcia et al. reported first in a published abstract in 1997 (70) and then in a full report in 1999. (89) The later report had 220 patients. Garcia et al. reported on this sample, but for meta-analysis purposes, it is notable that 31 (14%) of these patients were also included in the 1997 GUSTO IIb trial. The rates cited by Keeley et al.(53) are discrepant with the 1999 Garcia et al. full report. The small difference in the numbers of patients cannot be explained by the meta-analysts being able to obtain a breakdown of the non-Gusto IIb patients from the authors. The numbers of patients per group are different (95 and 94 versus 109 and 111), as are the number of events, with the meta-analysis numbers being somewhat more generous to the primary angioplasty group. For this review, the rates from the final published original research paper have been included with the note that 31 patients are being counted twice. There is no estimate of how many patients were double-counted in the former trial; therefore, using the smaller patient pool does not minimize the analysis bias.

A pilot study by Vermeer et al. (32) compared thrombolysis with transfer PCI. Patients were included if they had ST-segment elevation, were younger than 80 years, and the onset of their symptoms was less than 6 hours from randomization. Patients were excluded under conditions of hypertension, risk of bleeding, shock, previous stroke, and if they could not be transported within 1 hour. This last criterion was an opportunity for selection bias, but the authors did not address it. It was a 3-group trial that included a facilitated angioplasty group. The patients receiving facilitated angioplasty were transported only after they were given the bolus alteplase dose. Infusion (over 90 minutes) was initiated immediately after the bolus and was completed during transport or shortly after arrival at the PCI centre. The 6-month mortality rates were 12% in primary angioplasty (9/75) and 8% in thrombolysis (6/75).

From December 1997 to August 1999, Schomig et al. (73) studied patients who presented within 12 hours after the onset of symptoms, had chest pain for at least 20 minutes, and had ST-segment elevation. The researchers excluded patients if they were ineligible for thrombolysis (e.g., due to a recent history of stroke, active bleeding, recent history of trauma, or major surgery). This was a multicentre trial powered on the expected difference in the salvage index, a measure to describe the percentage of the left ventricle that is salvaged, divided by the percentage that is compromised by the initial perfusion defect.

Schomig et al. followed their RCT with a second trial. (75) This RCT compared a primary angioplasty group receiving primary stenting with a thrombolysis group receiving GP IIb/IIIa with accelerated alteplase. The difference was the addition of GP IIb/IIIa to the thrombolytic arm of the trial. Patients had to present within 12 hours. This was a multicentre trial to measure myocardial reperfusion and clinical end points. Results showed that stenting was associated with greater myocardial salvage than alteplase. Mortality, reinfarction, and combined end points were lower for primary stenting, and there was an absolute difference of 24.9% in the number of follow-up revascularization procedures required in the stented group. GP IIb/IIIa did not appear to confer benefits to the thrombolysis group.

Le May et al. (90) published the Canadian STAT trial in 2001. It compared accelerated alteplase with "primary stenting" at the Ottawa Heart Institute. As with the studies by Schomig et al.(73) and by Kastrati et al. (75), it was conducted when stenting primary angioplasty patients was the incremental target for comparative investigation. They at first restricted, then gradually opened up, the protocol to include GP IIb/IIIa. They recruited 123 patients and randomized them when they arrived at the hospital. They measured the rates of mortality, reinfarction, and stroke and looked at number of revascularization procedures at 6 months. The protocol included an early discharge for patients receiving angioplasty at 48 hours. The combined end point favoured primary angioplasty, but the mortality benefit was with thrombolysis.

The Atlantic C-PORT trial by Aversano et al., (91) was designed to analyze if patients with STEMI arriving at non-PCI centres would fare better if given thrombolysis, or if they should be treated with PCI at hospitals where backup cardiac surgery was not present. The authors discussed the logistical changes to consider the randomization and recorded the timed stages of each arm. Patients were included in the trial

following now-standard inclusions and without many of the exclusions from other trials. Although this was a "real-world" trial, the study required that regulatory authorities provide a waiver to allow PCI with backup. The authors did not report the number of patients that refused to participate. The results of the trial measured end points at discharge, 6 weeks, and 1 year. The results significantly favoured primary angioplasty for reinfarction, and for the composite end point, but not for stroke or mortality independently.

The Danish study by Andersen et al. (DANAMI) (1) is the largest trial to date that compared primary angioplasty with thrombolysis. It advanced the research question by including on-site and transfer primary angioplasty patients. The combined end point was death, reinfarction, and *disabling* stroke. Its recruitment strategy differed from that of other trials. Patients were excluded if they were at least 4 mm ST elevated, rather than 1 mm as in all other trials.

This study differed in other ways from previous RCTS, too. First, its 3-group design included PCI centres and non-PCI centres as follows: thrombolysis on-site, PCI on-site, and PCI after transfer. Second, patients receiving thrombolysis in which reperfusion was unsuccessful were given a second course of thrombolysis. This is not a recognized standard of care. (97) When patients receiving thrombolysis did not experience reperfusion, the protocol recommended that they receive a second course of streptokinase up to 12 hours after the first course. As a result, only 15 (1.9%) of 782 patients had rescue angioplasty. These rates are much lower than the rates of rescue angioplasty reported in other trials. Furthermore, this protocol may have increased the risk of reinfarction and death.

Results showed follow-up intervention after the immediate hospitalization was more frequent for patients receiving thrombolysis, but patients receiving angioplasty did not completely avoid these procedures. During the 30 days of follow-up, 148 (18.9%) of the patients receiving thrombolysis had either angioplasty or coronary-bypass surgery, compared with 72 (9.1%) of the patients receiving primary angioplasty.

The researchers stopped the trial after an interim analysis showed significant benefits of primary angioplasty. Overall, 4,278 patients were screened for inclusion, and 1,572 patients were randomized, resulting in a 37% rate of recruitment. Four percent of the patients screened at referral hospitals were excluded, because they were judged unable to tolerate being transported. The low recruitment may also be explained by the unusual 4 mm ST-segment elevation inclusion criterion. The authors noted that at the beginning, only 2 centres did primary angioplasty, but 5 centres were providing it by the end of the study.

Differences among the protocol treatments and current practices should be considered when interpreting the results and generalizing about the benefits of primary angioplasty. Patients in both arms received aspirin and β-blockers, as is the standard of care. However, the thrombolysis arm only represents current practice to the extent that patients received accelerated alteplase and unfractionated heparin. After that, the protocol required that patients for which reperfusion failed, as determined by electrophysiology, had to receive a second course of thrombolysis before being considered for rescue angioplasty. The practice standard now is that patients who fail thrombolysis must be referred for rescue angioplasty immediately.

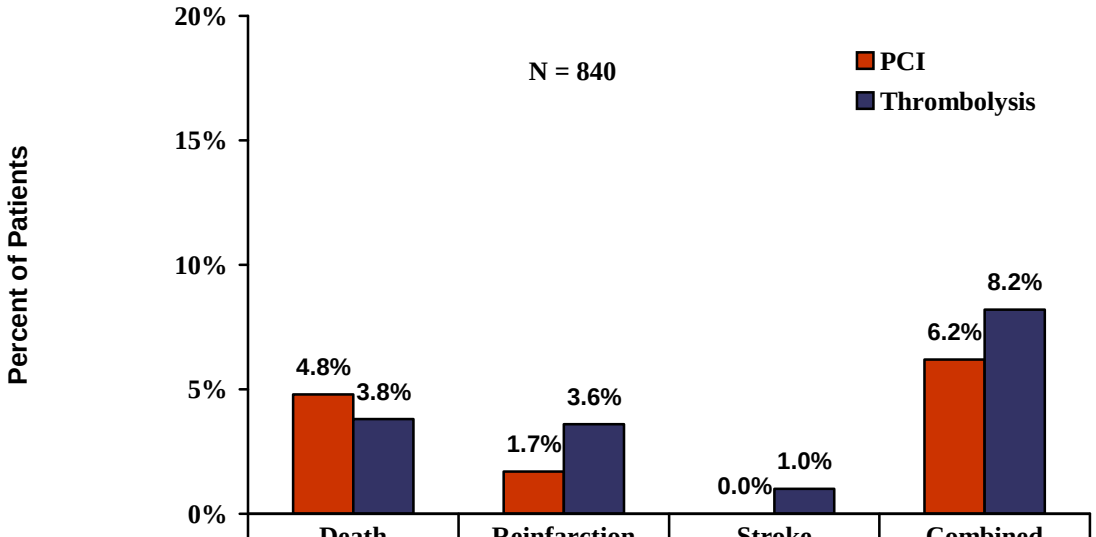
Other criticisms have emerged. For example, Channer, (98) in a letter to the editor of the *New England Journal of Medicine,* noted that the rates of reinfarction and stroke associated with thrombolysis are known to be higher than those of primary angioplasty. He argued that a priori knowledge of this biased the study against thrombolysis, since it was powered on a combined end point of death, reinfarction, and stroke.

**Pre-hospital Thrombolysis Compared With Primary Angioplasty**

Bonnefoy et al.(21) reported on the CAPTIM study, the only RCT to compare pre-hospital thrombolysis with primary angioplasty. Specifically, these investigators recognized that pre-hospital fibrinolysis and primary angioplasty were preferable to in-hospital fibrinolysis and decided to compare them. They enrolled 840 patients with STEMI who presented within 6 hours of the onset of symptoms and who were initially managed by mobile emergency care units. Results showed the median delay between onset of symptoms and treatment was 130 minutes in the pre-hospital fibrinolysis group and 190 minutes in the angioplasty group. The thrombolytic regimen was accelerated alteplase, which, as a combined bolus and infusion, required some logistical support for field administration. The combined end point was death, reinfarction, and disabling stroke. The rate of the combined end point was 8.2% for thrombolysis and 6.2% for primary angioplasty, a difference that was not statistically significant. (See Figure 2.)

Furthermore, 26% of patients receiving thrombolysis were referred for rescue angioplasty immediately after thrombolysis, and another 9% had index hospitalization angioplasties. Only 4% of patients receiving primary angioplasty had subsequent unscheduled revascularizations. The rate of unscheduled catheterizations was high in both groups. Patients in the primary angioplasty group were allowed stents and GP IIb/IIIa inhibitors. Of note, 70% of patients received PCI within 30 days. In the primary angioplasty group, 9 patients with cardiogenic shock were included despite protocol exclusion criteria. Only 26.6% of patients having primary angioplasty received GP IIb/IIIa. Some researchers have suggested that more access to these agents may have improved the results of the primary angioplasty group.(6) Finally, the authors closed the trial early due to slow recruitment.

**Figure 2: Pre-hospital Thrombolysis Compared With Primary Angioplasty**




| | Death | Reinfarction | Stroke | Combined |
|---|---|---|---|---|
| PCI | 4.8% | 1.7% | 0.0% | 6.2% |
| Thrombolysis | 3.8% | 3.6% | 1.0% | 8.2% |

**Pre-hospital Thrombolysis Compared With In-Hospital Thrombolysis**

In a meta-analysis of 6 RCTs comprising 6,434 patients from studies that compared pre-hospital thrombolysis with in-hospital thrombolysis, Morrison et al. (2) found that pre-hospital thrombolysis significantly decreased all-cause mortality in the pre-hospital thrombolysis arms (odds ratio [OR] 0.83; 95% CI, 0.7–0.98). Estimated time to thrombolysis in the pre-hospital thrombolysis group was 104 minutes compared with 162 minutes for the in-hospital thrombolysis group (P=.007). In the meta-

analysis, Morrison et al. (2) reported that pre-hospital thrombolysis reduced the risk of all-cause mortality by 17%. There was no difference in mortality between the groups at 1 and 2 years, though pooled data were reported as being insufficient to show a significant difference for long-term mortality. They also reported that homogeneity was poor in the 1-year follow-up studies and that the number of trials was too small for sensitivity analysis.

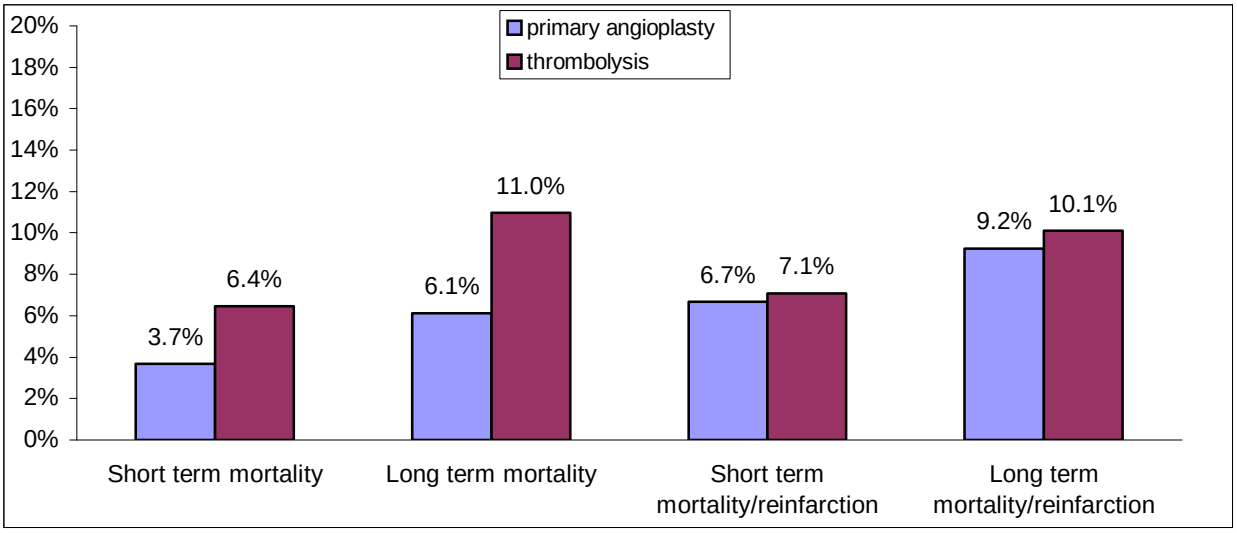
In summary, as is apparent from the discussion of the studies, the clinical results of the RCTs reviewed can be grouped in different ways. Many authors have grouped them by the type of thrombolytic agents used. Others have grouped them by their regimens. Given the context of introducing infrastructure to support more access to primary angioplasty, it seems prudent to organize the list of RCTs according to the specific processes compared, the agreement of the protocols with standard practices, and the generalizability of the results. In this way, the face value of their heterogeneity is apparent while different meta-analyses of these same studies are reviewed in the next section.

As Tables 3 and 4 show, there are many differences in the principal comparisons of each study. These differences are compounded by the different end points and by having a mix of single-centre and multicentre trials.

## Summary of Medical Advisory Secretariat Review: Meta-Analyses

The first meta-analysis to compare angioplasty with thrombolysis was part of a larger analysis by Michels and Yusuf. (43) At the time, most of the studies had an apparent homogeneity to them, and interventions that included stents and glycoproteins had not yet been introduced. Michels and Yusuf identified several types of studies that compared primary angioplasty with thrombolysis according to different timing of therapy. These studies comprised an early study by O'Neill et al. (66) that examined intra-arterial thrombolysis and 6 studies that used intravenous thrombolysis. Two of these (69;72) were published abstracts, and 4 were published articles. (25;76;80;83) The authors of the studies were contacted to provide details to do a meta-analysis. (See Table 5.)

**Table 5: Meta-Analysis of RCTs: Primary Angioplasty Compared With Thrombolysis(43)**



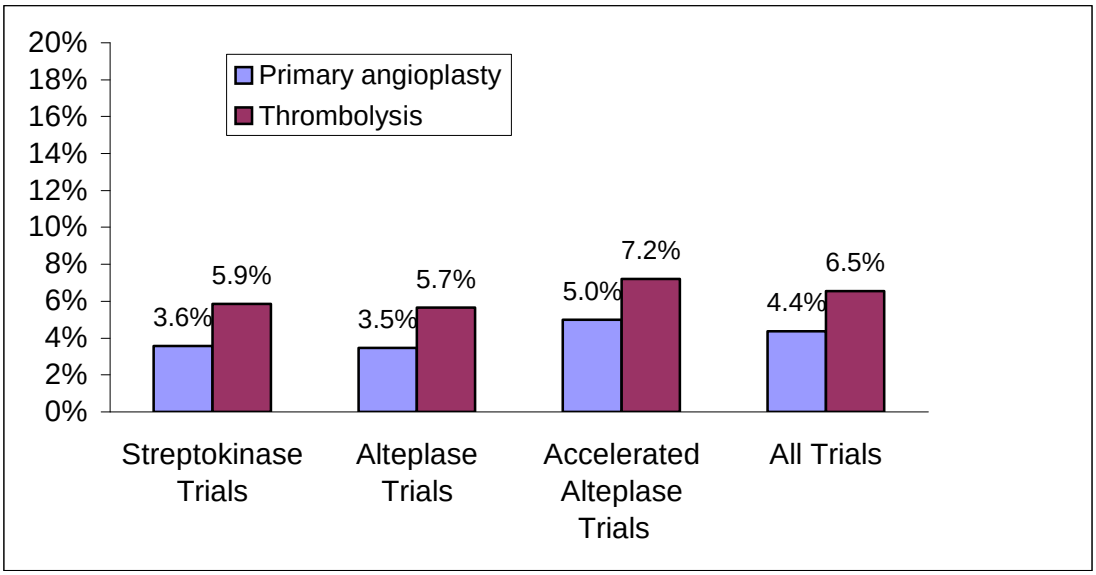

These authors reviewed not just angioplasty compared with thrombolysis, but different options during angioplasty compared with thrombolysis. They concluded that routine elective angioplasty with thrombolysis offered no immediate advantage in short-term mortality over the more conservative thrombolysis-only approach. They qualified this conclusion by noting that longer-term follow-up data were not available and could show benefits for angioplasty. They also concluded that, for rescue

angioplasty, there were few data to show routine angioplasty after thrombolysis is beneficial, and their meta-analysis of these RCTs did not demonstrate a benefit.

When it was published in 1997, the meta-analysis from Weaver et al. (78) included 10 trials with 2606 patients that compared either streptokinase or alteplase with primary angioplasty. Their results showed patients receiving angioplasty had lower rates of mortality (6.5% for thrombolysis versus 4.4% for angioplasty; P=.02), a 47% relative reduction in rates of nonfatal reinfarction (5.3% versus 2.9%; P=.04), and a substantial reduction in rates of hemorrhagic stroke (1.1% versus 0.1%; P<.001) at 30 days (Figure 3). Grouped by thrombolytic agent, the studies included 4 using streptokinase, (85) but the authors excluded the intracoronary streptokinase trial by O'Neill et al. (47) Infusion-only alteplase studies (80) were grouped separately from those that used accelerated alteplase. (26;87)

This meta-analysis built on the work of Michels & Yusuf (43) because it had updated reports of trials cited by them. Elizaga et al. (69) was published in full by Garcia et al. (70) One of the trials with accelerated alteplase was only partially published at the time of the first analysis, and only 83 of 110 patients were included in the meta-analysis, based on the preliminary publication.(87) Kent et al.(55) later used the same sample of studies to build a predictive model for risk-selecting patients.

**Figure 3: Meta-Analysis of Mortality Rates of Primary Angioplasty and Thrombolysis(78)**




A meta-analysis by Grines et al.(57) pooled long-term follow-up data of the effectiveness of primary ANGIOPLASTY and thrombolysis using 6-month follow-up individual patient data from RCTs. The relative reduction in events at 30 days and 6 months was calculated from 11 trials. At 30 days, the mortality rate was 4.3 % (n=1348) for primary angioplasty and 6.9% (n=1377) for thrombolysis (P=.004). At 6 months, the rates were 6.2% for primary angioplasty and 8.2% for thrombolysis (P=.04). When mortality and reinfarction were combined, the rates were, for primary angioplasty and thrombolysis respectively, 7% and 12.9% at 30 days, and 10.2% and 16.1% at 6 months (P=.04).

The results accorded with the accumulated published evidence (i.e., prior to PRAGUE-2 and DANAMI-2) that primary angioplasty was more effective than thrombolysis. As with other meta-analyses done to then, all studies were included regardless of the type of thrombolytic, the type of regimen, the use of stents, or the use of GP IIb/IIIa. The authors noted that the treatment effect did not vary across clinically important subgroups defined by age, sex, diabetes, prior MI, or level of risk. They concluded that the

greatest absolute benefit was for patients who were at the highest risk and whose responses were sustained for 6 months.

The next meta-analysis, by Zijlstra et al. in 2002, (56) updated the review by Weaver and colleagues, but presented data by time of presentation in an individual patient data meta-analysis. The authors examined data collected from 2635 patients enrolled in 10 RCTs comparing 1302 patients who received primary angioplasty with 1333 patients who received thrombolysis. They were interested in the relationship between presentation delay and outcomes. The end point combined death, non-fatal reinfarction, and stroke. The results were as follows:

- Early presentation (less than 2 hours): 5.8% for angioplasty and 12.5% for thrombolysis
- Intermediate presentation (2 to 4 hours): 8.6% for angioplasty and 14.2% for thrombolysis
- Late presentation (More than 4 hours): 7.7% for angioplasty and 19.4% for thrombolysis

They concluded that adverse cardiac event rates were lower after primary angioplasty compared with thrombolysis, regardless of time to presentation. As time to presentation increased, major adverse cardiac event rates increased only after thrombolysis. They appeared to be relatively stable after angioplasty

The meta-analysis by Keeley et al. (53) has been the index article for much of the discussion in this report. Briefly, it was published in 2003 as a summary of 23 trials, all of which compared the treatments of interest in similar patient populations. The requisite literature search included all unpublished and published trials designed to compare the effectiveness of primary angioplasty with thrombolysis for acute STEMI. They aimed to pool results to ascertain which therapy is most effective. Their literature search produced 23 RCTs comprising 7739 patients.

There are, however, several reasons to consider excluding some of these RCTS from any pooled analysis. Many critics, for example, have noted the heterogeneity of the trials. The authors have responded that a statistical test for this was negative. A negative test for heterogeneity, however, should not be interpreted as a positive test for homogeneity, and a review of the individual trial characteristics reveals that many of the trials have discrepant designs.

For example, included in the 23-study sample was a study, the SHOCK trial, (54) that recruited patients with acute MI and cardiogenic shock. As shown in Figure 1, these patients typically are not considered candidates for thrombolysis and often are referred directly to angioplasty. Furthermore, cardiogenic shock was an exclusion criterion in many of the other studies. To address this disparity, the meta-analysis was divided first into 2 groups of studies according to the type of thrombolysis used, and then overall with and without the SHOCK data.

The authors noted that most patients treated with thrombolytic therapy in the more recent trials received a fibrin-specific drug and that stents and GP IIb/IIIa inhibitors were frequently used, but they nevertheless chose to combine all thrombolytic regimens together and all primary angioplasty regimens together.

Results showed the summary estimate of mortality benefit favoured primary angioplasty (21 lives saved per 1000 patients treated) in the short term, and in the longer term (6 to 18 months). This difference was independent of the fibrin-specificity of the thrombolytic agent used and if reperfusion was delayed due to emergent transfer.

Although the results favoured primary angioplasty, some researchers have criticized this meta-analysis for its aggregation of studies. (99) Fifty percent of the 23 trials included fewer than 100 patients per treatment arm, which increases the risk of selection bias. Eight studies used streptokinase, which is arguably not the thrombolytic therapy of choice for most patients in Canadian hospitals. Another critical analysis (100) of those studies that included only accelerated alteplase found that the difference in mortality became

insignificant (adjusted RR 1.2%, P=.081). The authors noted that primary angioplasty bears an additional absolute risk of major hemorrhage (P=.032).

A meta-analysis by Dalby et al. (31) aimed to determine the best therapeutic strategy for a patient with acute MI presenting to acute care without catheterization facilities. It included 6 clinical trials that compared on-site thrombolysis with transfer for primary angioplasty. The selected trials were the MAASTRICHT study, (32) the PRAGUE study, (33) the air-PAMI study,(92) the CAPTIM trial,(21) the DANAMI-2 trial, (1) and the PRAGUE-2 study. (93) Two used streptokinase (33;93), 3 used alteplase, and 1 used both according to treatment centre protocol.(92)

Additionally, 2 studies used a third arm consisting of facilitated angioplasty. Dalby and colleagues combined the 6 studies, excluded the facilitated angioplasty arms, and summarized the combined end point of death, reinfarction, and stroke. They found the combined end point was reduced in the transferred angioplasty group compared with the on-site thrombolysis group. The mortality rates were slightly lower. All studies had transfer times of fewer than 3 hours. Composite risk reduction was significant, but there was only a trend toward reduced all-causes mortality.

Meta-regression analyzes the relationship between study-level factors and study-level effects. A meta-regression by Kent et al. (55) aimed to devise a risk-assessment model to determine what proportion of patients would benefit from access to primary angioplasty compared with thrombolysis on overall mortality. The authors, recognizing the limited ability for primary angioplasty at most hospitals, sought to be selective about offering primary angioplasty. Rather than provide a single point estimate of the benefits (i.e., 2% absolute mortality benefit for all patients with STEMI), their regression provided a relative risk benefit over a range of "control rates" (rates of mortality after thrombolysis over a distribution represented by the selected clinical trials). Using the studies summarized by Weaver et al., (78) the authors constructed a regression line of absolute risk difference of death after primary angioplasty versus absolute risk of death after thrombolysis.

Assuming a constant relative risk reduction, they concluded that treating only those patients in the highest quartile of risk for mortality could capture 68% of all mortality benefits in their community-based patient sample. Moreover, treating those in the highest half could capture 87% of the benefit. The results of this meta-regression suggest that patients with a risk of death of less than 2% might be unlikely to receive any mortality benefit from primary angioplasty. The authors concluded that primary angioplasty should be considered for patients at high risk of death.

In a meta-regression by Nallamothu & Bates in 2002 (60), the treatment effects were weighted by a combination of trial size and precision and regressed over the median time difference between time to balloon and time to needle in each trial. Results showed that, based on where the regression line crosses zero (the time point where there is no more apparent benefit of primary angioplasty versus thrombolysis), the mortality benefit associated with primary angioplasty in patients with STEMI may be lost if time to balloon is delayed by more than 1 hour. When the combined end point of death, reinfarction, and stroke is considered, the time is closer to 90 minutes.

The weakness of this meta-regression is that 2 large trials – DANAMI-2 (1) and PRAGUE-2 (93) dominated the regression. These trials caused the regression line to slope downward, such that if the trials had not been weighted, the line would have been flat. Nonetheless, the authors recommended that interventional cardiology laboratories trying to achieve the benefits of primary angioplasty as reported in RCTs should aim for short door-to-balloon times.

Boersma et al.(52) synthesized several meta-analyses of acute coronary syndrome. They summarized and compared the most recent meta-analyses, and in some cases updated them to include recent large clinical trials. Overall, they restated the conclusions about primary angioplasty and thrombolysis of Keeley et

al.(53) However, by presenting the results of other trials about STEMI, the authors placed the treatment effects of primary angioplasty in the context of other incremental developments in STEMI therapy: heparins, thrombolytics, GP IIb/IIIa, balloon angioplasty, and stenting. The clinical benefits of reductions in patient death have been incremental. Primary angioplasty represents 23 additional lives out of 1000 saved, but primary stenting compared with balloon angioplasty alone offers no additional mortality gains.

## Medical Advisory Secretariat Meta-Analysis

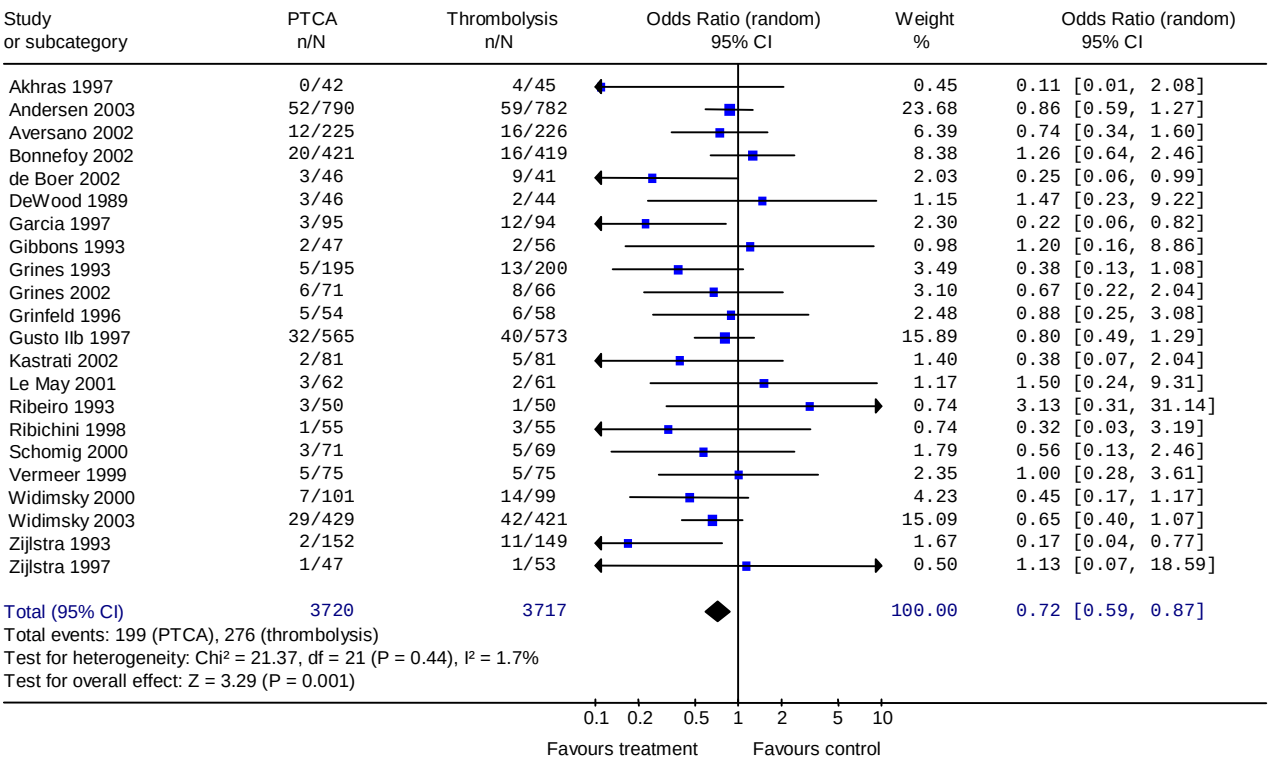
As described in the methods section, the Medical Advisory Secretariat repeated a meta-analysis of all studies comparing thrombolysis with primary angioplasty, using verified data extraction and excluding the SHOCK study. Figures 4 to 7 show the overall effects of primary angioplasty compared with thrombolysis on mortality, reinfarction, stroke (all causes), and a combined end point. Using all 22 studies, and disregarding the different types of primary angioplasty and the different thrombolytic regimens, the lower rate of mortality events for primary angioplasty was significant (Figure 4) at the P=.001 level. This is the level Flather et al.(101) suggests should be used, because the data analysis is retrospective.

Looking at the other rates, reinfarction, shown in Figure 5, was also significantly lower for primary angioplasty (P<.00001). As Figure 6 shows, stroke rates, hemorrhagic or thrombotic, were lower, too (P<.00001). The combined rate of events in the short-term results, seen in Figure 7, also favoured primary angioplasty (P<.00001).

Of note, the number of primary events (those excluding the combined end point) ranged from 27 to 276 on a denominator of about 3700 patients per arm. Thus, the size of this meta-analysis, according to the scale proposed by Flather et al., (101) is too small, and therefore should be limited to summarizing studies and generating hypotheses.

## Figure 4: Mortality Rates for ANGIOPLASTY Compared With Thrombolysis *

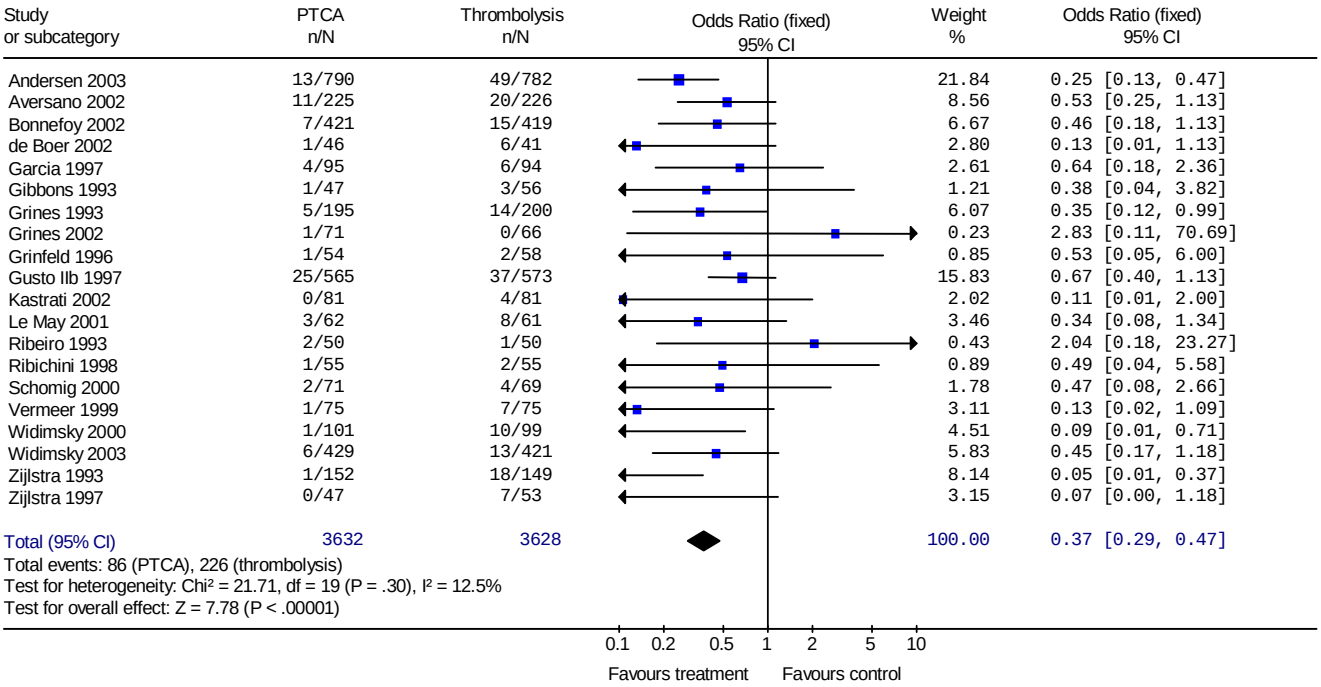
Review: Meta-analysis of Primary Angioplasty versus Thrombolysis Trials
Comparison: 02 22 studies
Outcome: 01 Mortality




* Angioplasty represents primary transluminal coronary angioplasty; CI, confidence interval

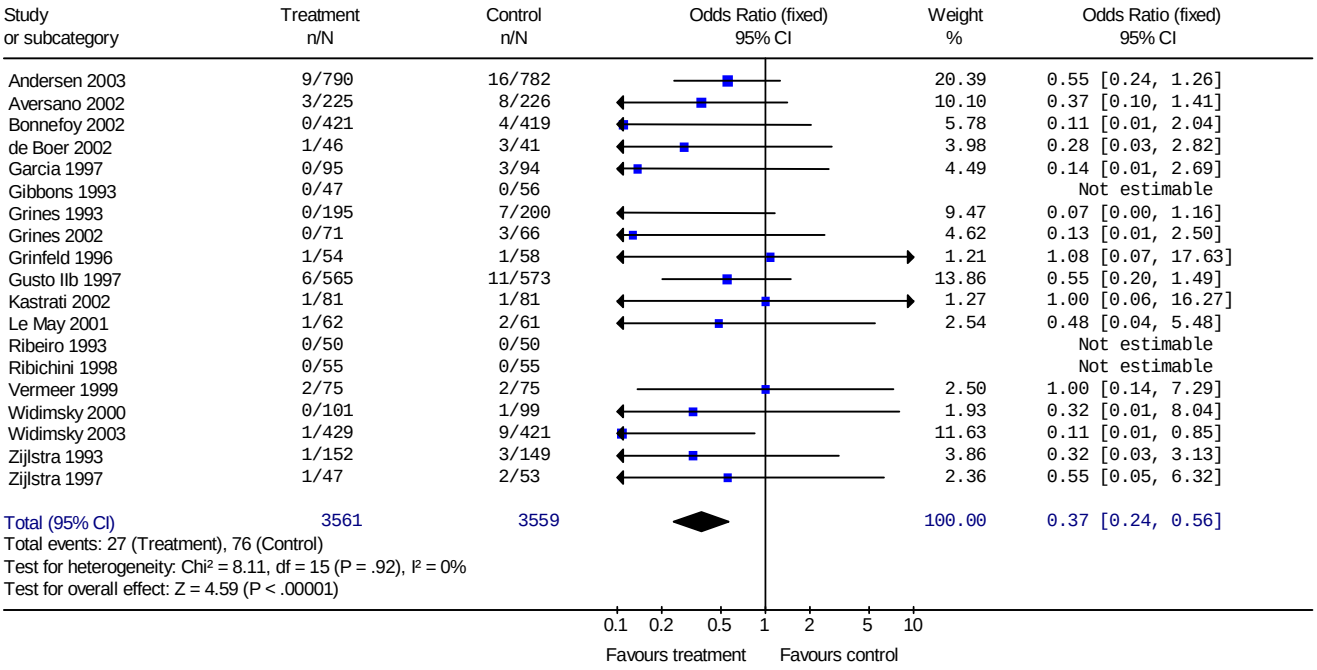
## Figure 5: Reinfarction Rates for Primary Angioplasty Compared with Thrombolysis

Review: Meta-analysis of Primary Angioplasty versus Thrombolysis Trials (22 studies)
Comparison: 02 22 studies
Outcome: 02 Reinfarction



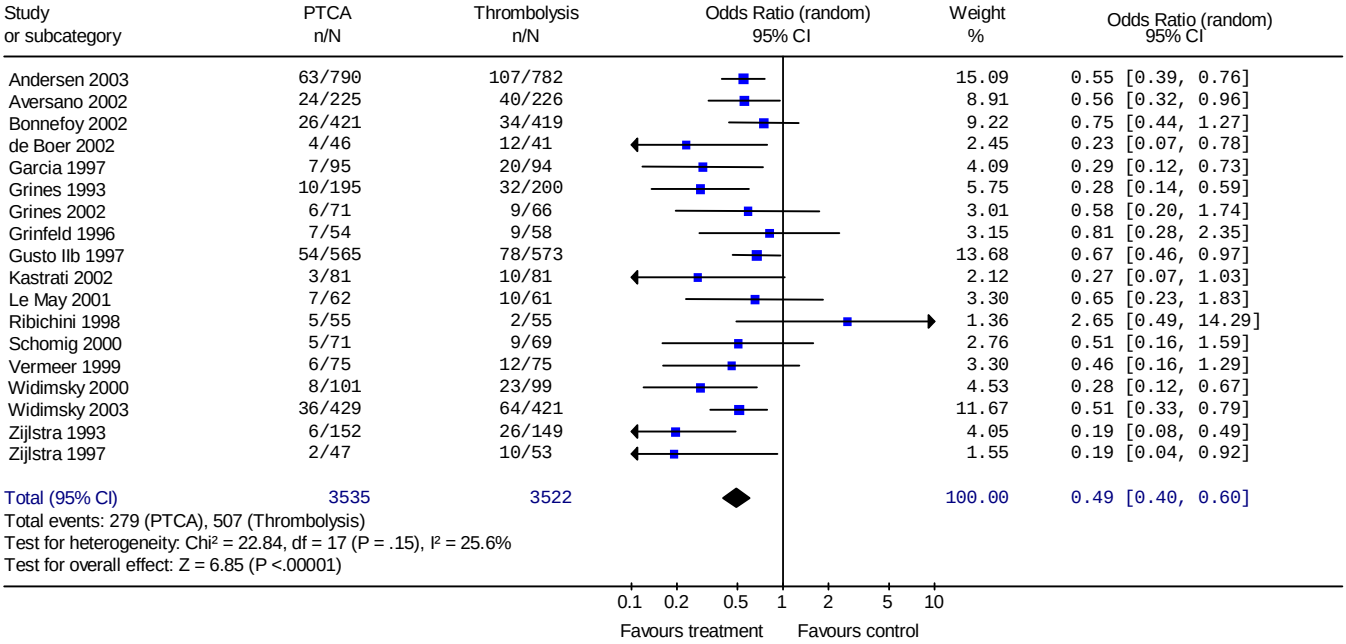

## Figure 6: Stroke Rates for Primary Angioplasty Compared With Thrombolysis

Review: Meta-analysis of Primary Angioplasty versus Thrombolysis Trials (22 studies)
Comparison: 02 22 studies
Outcome: 03 Total Stroke



## Figure 7: Combined Death, Reinfarction, and Stroke Rates for Primary Angioplasty Compared With Thrombolysis

Review: Meta-analysis of Primary Angioplasty versus Thrombolysis Trials (22 studies)
Comparison: 02 22 studies
Outcome: 04 Combined Mortality Reinfarction Stroke




When reviewing the RCTs, the Medical Advisory Secretariat recommends that readers pay attention to the differences among the types of thrombolytic therapy. Furthermore, the extent to which stenting is used in Ontario should be considered when selecting the trials to summarize the treatment differences. Accordingly, on the basis of treatment differences alone, studies that used streptokinase can be excluded, because a large RCT (14) concluded that accelerated alteplase was superior to streptokinase. The 8 streptokinase trials were conducted from 1993 to 2003, (33;65;76;83-86;93) and only 3 studies (33;62;86) used coronary stents in the angioplasty arm. Only the most recent (62) was conducted with stenting and GP IIb/IIIa. Stenting and GP IIb/IIIa were more common in the alteplase trials. Stenting has not been shown to improve survival or reinfarction, but it has been shown to improve longer-term outcomes of restenosis and revision. (52) Therefore, trials that included balloon angioplasty, stenting, or both were included. The resulting pool of trials is shown in Table 6.

**Table 6: Summary of Comparisons in All Studies**

| Study comparison | Number of Studies | References |
|---|---|---|
| Primary balloon angioplasty vs, streptokinase | 5 | (65;76;83-85) |
| Primary stenting vs. streptokinase | 2 | (33;86) |
| Primary stenting and GP Iib/IIIa vs. streptokinase | 1 | (93) |
| **Total streptokiinase trials** | **8** | |
| Primary balloon angioplasty vs. duteplase | 2 | (72;79;80) |
| Primary angioplasty vs. alteplase standard | 1 | (25) |
| Primary balloon angioplasty vs. accelerated altepase | 2 | (26;70;89) |
| Primary stenting vs. accelerated alteplase | 2 | (32;87;88) |
| Primary stenting and GP Iib/IIIa vs. accelerated alteplase | 5 | (1;73;75;90;91) |
| Primary stenting and GP Iib/IIIa vs. pre-hospital alteplase | 1 | (21) |
| **Total alteplase trials** | **14** | |
| Transfer for PCI vs. accelerated alteplase or streptokinase † | 1 | (92) |

*Excluding cardiogenic SHOCK trial
†PCI represents percutaneous coronary intervention

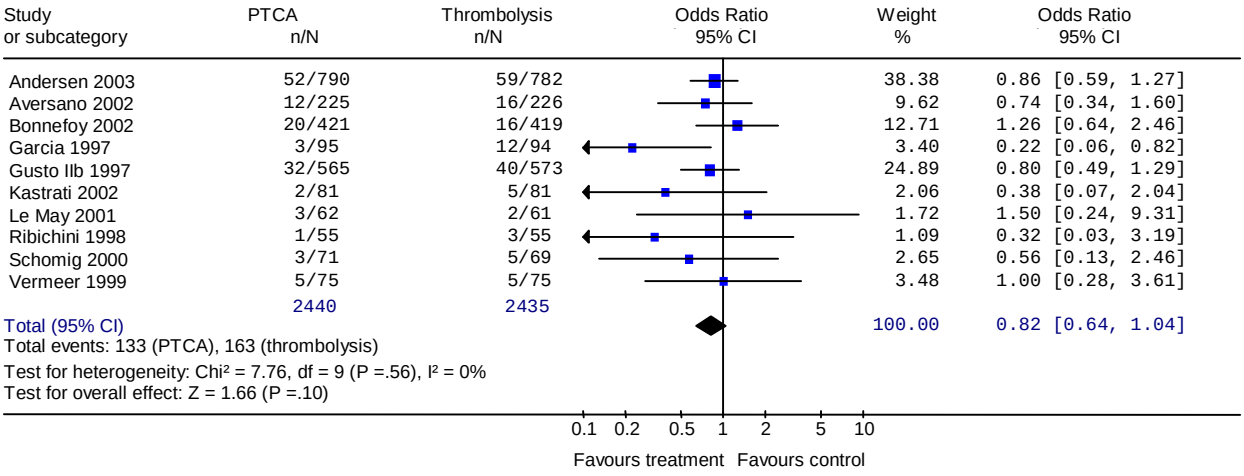
This meta-analysis looked at a subset of 9 studies from Table 6. The CAPTIM study (21) of pre-hospital thrombolysis was excluded, because it is not the standard in Ontario, and the Grines study (25) was excluded, because patients receiving streptokinase could not be separated from those receiving alteplase. Trials that compared accelerated alteplase in-hospital with primary angioplasty were selected. The study designs were as follows:

- Primary balloon angioplasty compared with accelerated alteplase
- Primary stenting compared with accelerated alteplase
- Primary stenting and GP IIb/IIIa compared with accelerated alteplase

The results are presented in Figures 8 to 11. Figure 8 shows the differences in mortality rate, which overall were significant at the P=.04 level. Figure 9 shows the differences in reinfarction rates, and Figure 10 shows the significant difference in stroke events between primary angioplasty and accelerated alteplase. The combined end point results were predictably significant (Figure 11). Again, the reader is cautioned that the absolute numbers of events is low, and therefore these types of meta-analyses are considered most suitable for hypothesis generating. Furthermore, the results may be interpreted more accurately at a P=.001 level of significance.

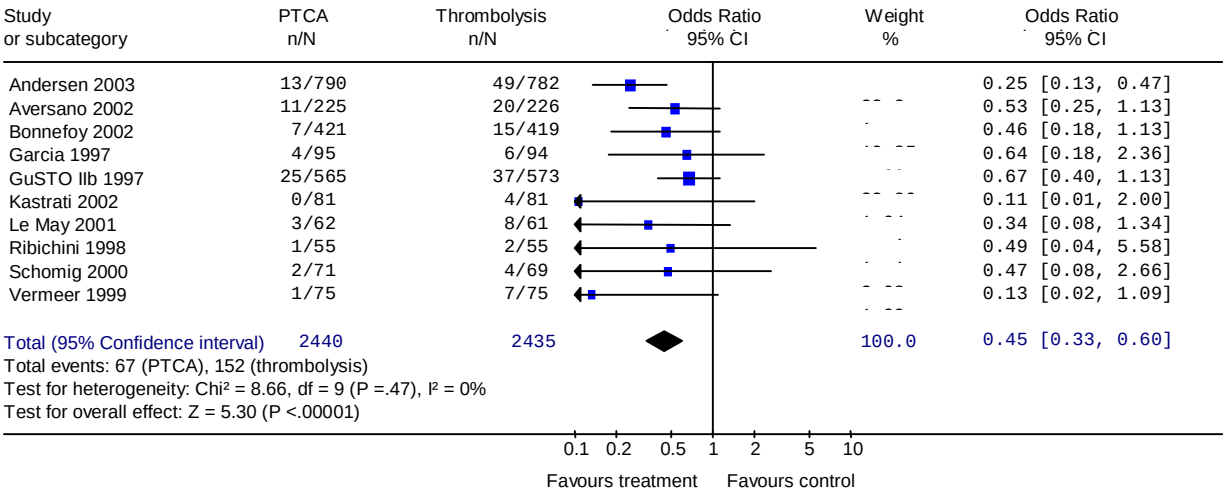
## Figure 8: Mortality Rates for Selected Primary Angioplasty Versus Thrombolysis Trials

Review: Meta-analysis of Primary Angioplasty versus Thrombolysis Trials
Comparison: 03 Studies versus Accelerated Alteplase
Outcome: 01 Mortality

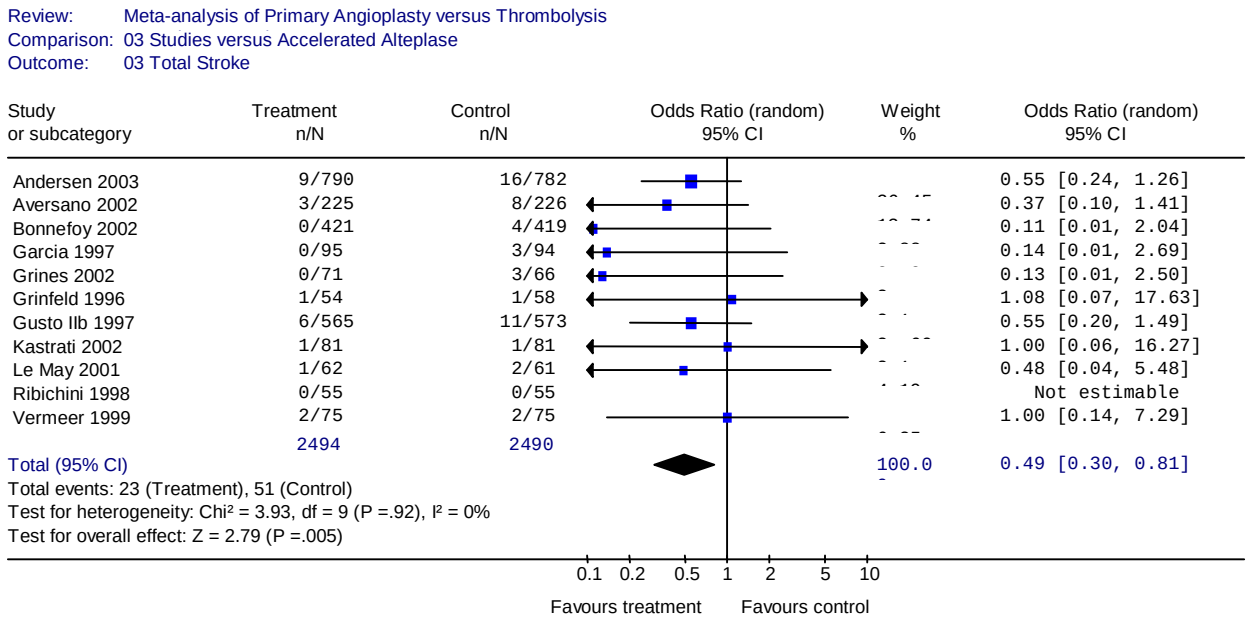



## Figure 9: Reinfarction Rates for Selected Primary Angioplasty Versus Thrombolysis Trials

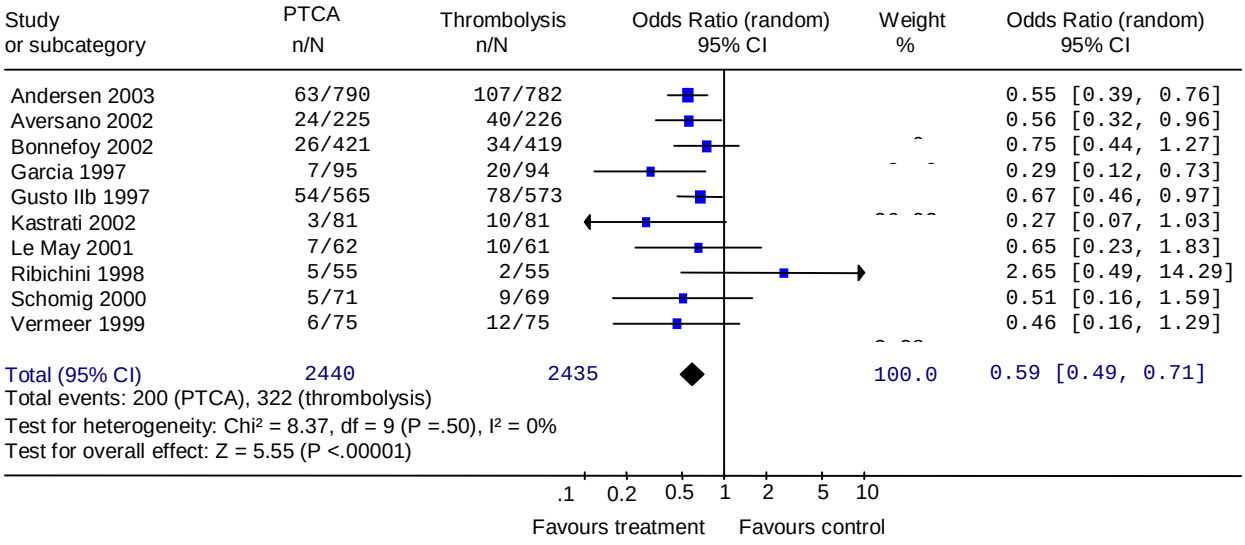
Review: Meta-analysis of Primary Angioplasty versus Thrombolysis
Comparison: 03 Studies versus Accelerated Alteplase
Outcome: 02 Reinfarction



## Figure 10: Total Stroke Rates for Selected Primary Angioplasty Versus Thrombolysis Trials




## Figure 11: Combined Death, Reinfarction and Stroke Rates for Selected Primary Angioplasty Versus Thrombolysis Trials*



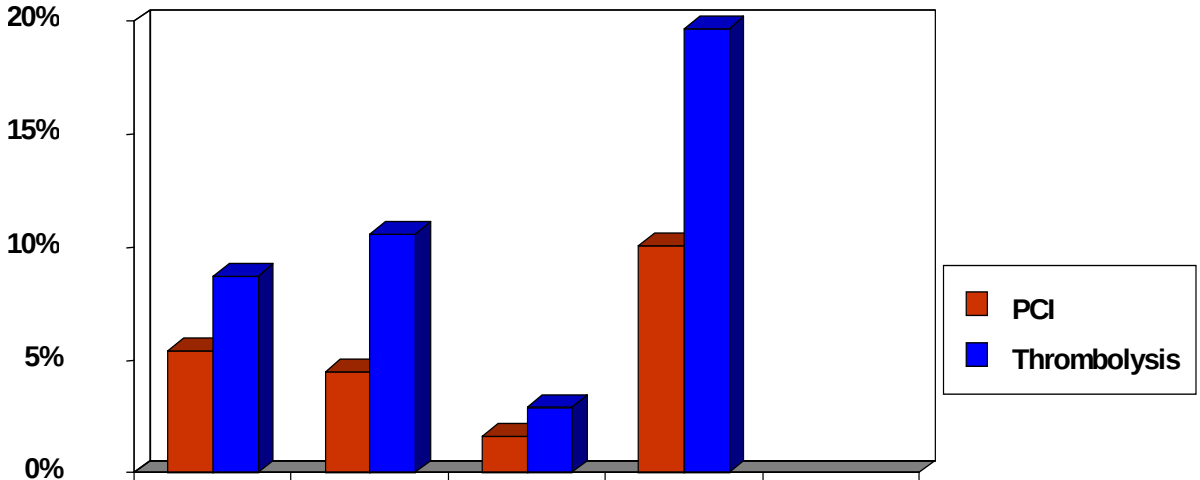

The result of selecting a subset of the trials in Table 6 is that the mortality rate difference stays significant when only accelerated alteplase is used as a comparison treatment, and the ORfor reinfarction, stroke, and the combined end point, while still significant, are lower (Table 7). The mortality rates for accelerated thrombolysis appear to be lower than when combined with the results of the streptokinase trials. The difference appears to be 1.24% in absolute terms when compared with primary angioplasty.

**Table 7: Comparison of Meta-Analyses: All Trials and Selected Trials**

| Meta-analysis of 22 Studies (any PCI* versus any thrombolysis) | No. of Studies | No. of Patients | Random Effects Model Odds Ratio (95% CI)† | Rate for Primary Angioplasty, % | Rate for Thrombolysis, % |
|---|---|---|---|---|---|
| 01 Mortality | 22 | 7437 | 0.72 (0.59–0.87) | 5.35 | 7.43 |
| 02 Reinfarction | 20 | 7260 | 0.37 (0.29–0.47) | 2.37 | 6.23 |
| 03 Total stroke | 16 | 7120 | 0.37 (0.24–0.56) | 0.76 | 2.14 |
| 04 Combined (mortality, reinfarction , and stroke) | 18 | 7057 | 0.51 (0.44–0.59) | 7.89 | 14.40 |
| **Meta-analysis of 10 Studies (PCI versus accelerated alteplase)** | | | | | |
| 01 Mortality | 9 | 4035 | 0.77 (0.59–0.99) | 5.60 | 7.29 |
| 02 Reinfarction | 9 | 4035 | 0.44 (0.31–0.62) | 2.97 | 6.80 |
| 03 Total stroke | 7 | 3895 | 0.52 (0.31–0.88) | 1.13 | 2.21 |
| 04 Combined (mortality, reinfarction ,and stroke) | 9 | 4035 | 0.57 (0.46–0.69) | 8.62 | 14.29 |

Figure 12 shows the results of combining the long-term follow-up data for 6 studies (73) that reported these end points at least 6 months after follow-up. Notably, the differences at 6 months were significant for mortality, reinfarction, and the combined end point, but not for stroke.

**Figure 12: Medical Advisory Secretariat Meta-analysis of 6-Month Outcomes**




| | Deaths n = 1215 p=.024 | Non-fatal Reinfarction n = 1075 p<.001 | Stroke n = 886 p=.175 | Combined n = 1026 p<.001 | 6 months/1 yr |
|---|---|---|---|---|---|
| PCI | 5.40% | 4.50% | 1.60% | 10.10% | |
| Lysis | 8.70% | 10.60% | 2.90% | 19.70% | |

To summarize the meta-analysis by the Medical Advisory Secretariat, the results show significant differences in 30-day event rates for mortality, reinfarction, and stroke for patients receiving primary angioplasty. This suggests that primary angioplasty is more effective than in-hospital thrombolysis. The results do not hold true for pre-hospital thrombolysis, because the only trial comparing the 2 technologies found no difference in outcomes.

# Economic Analysis

The economic analysis aimed to review and summarize the literature on primary angioplasty in the context of Ontario. Additionally, it was designed to compare the costs of primary angioplasty with those of thrombolysis and to aggregate the difference in costs compared with the expected difference in patient outcomes. Importantly, the benefits of the more effective technology must be compared with the expense of setting up and operating that technology and then adapting Ontario's health care system to reach as many residents as possible. This section reviews costs analyses for each technology and comparative economic analyses. It also presents a decision model that compares the expense of shifting to the more effective strategy with the costs and outcomes of maintaining the current services.

## Results of Literature Review on Economics

Four studies have directly compared the cost-effectiveness of primary angioplasty with thrombolysis. (80;82;102;103) De Boer et al. (82) and Gibbons et al. (80) considered only hospitalization costs associated with the initial admission. De Boer et al. showed 1-year costs were almost equal for the 2 treatment strategies in a trial conducted in the Netherlands (equivalent of $17,366 (US) for primary angioplasty versus $16,681 (US) for thrombolysis using streptokinase, P=.22). Data in the PAMI trial described earlier (25) was used by Stone et al. (102) to perform a cost comparison of the 2 treatment modalities in the United States that also found no statistically significant difference ($27,653 (US) for primary angioplasty vs. $30,227 for thrombolysis using t-PA, P=.21). However, Le May et al. (103) showed that actual costs over 6 months in a Canadian/Ontario setting were significantly lower for patients receiving primary angioplasty than for patients receiving thrombolysis, largely due to fewer hospitalization days. Of note, the primary angioplasty group in this protocol (STAT) had to be discharged at 48 hours, but the thrombolysis group did not.

Other cost implications can be drawn from the literature on these 2 therapies. For example, Mark et al. (17) found that accelerated alteplase is cost-effective compared with streptokinase. Suryapranata (104) did a cost-effectiveness analysis and reported that the added cost of stenting was cost-effective compared with balloon angioplasty alone.

### Differences in Length of Stay in Randomized Controlled Trials

RCTs have consistently reported a relative reduction in the number of hospital days associated with primary angioplasty. Gibbons et al. (80) did an intention-to-treat analysis of costs and found the angioplasty group had about $4,500 (US) less in initial hospital costs. This difference was not statistically significant. The savings were because patients receiving angioplasty stayed in the hospital a mean 3 days fewer. Similarly, considerably lower 6-month follow-up costs were associated with fewer readmissions in the angioplasty group, a cost difference of about $6,800.

They found no significant differences in costs according to treatment received and excluding patients who did not receive the assigned treatment. They noted that the higher costs and number of hospital days in the intention-to-treat analysis related to costs for 5 patients who were initially randomly assigned to thrombolysis but who then received immediate angioplasty due to medical contraindications to thrombolysis. This group had the highest hospital charges and the most hospital days. Nine other authors reported the same trend in shorter length of stay, thus representing 10 of the 22 studies reviewed (Table 8).

**Table 8: Length-of-Stay Differences for 10 of the 22 Studies Reported**

| | PCI, mean (SD) | Thrombolysis, mean (SD) | P* |
|---|---|---|---|
| Gibbons et al. (80) | 7.7 (2.9) | 10.6 (8.1) | .01 |
| Grines et al. (25) | 7.5 (3.3) | 8.4 (4.6) | .03 |
| Zijlstra et al. 1993 (76) | 12 | 13.5 | n/r |
| Ribichini et al. 1998(88) | 9.2 (2.5) | 12.4 (3.7) | .0001 |
| GUSTO IIb 1997 (26;89) | 8 | 10 | n/r |
| Garcia et al. 1999 | 15 | 15 | ns |
| Le May et al. 2001 (90) | 4 | 7 | .001 |
| Aversano et al. (91) | 4.5 | 6 | .02 |
| DeBoer et al. 2002 (86) | 5 | 5 | ns |
| Widimsky et al. 2003(93) | 11 (4) | 13 (5) | .05 |

*n/r represents not reported; ns, not significant

## Budget Impact Analysis

To date, no study has considered the entire set of costs to increase access to primary angioplasty for patients with STEMI that are receiving thrombolysis.

Le May et al., (103) the authors of the Canadian STAT study that compared primary angioplasty and stenting with thrombolysis, followed-up their clinical study by analyzing the hospitalization costs associated with the 2 therapies. They documented hospitalization costs for the initial hospitalization and during the 6-month follow-up period. They collected data on direct costs and resource utilization prospectively during the trial for each patient. Included were physician fees (Ontario Health Insurance Plan) and hospitalization costs. The authors found there were fewer hospital days associated with the initial event and the following 6 months for the primary angioplasty group. Furthermore, initial hospitalization costs were lower for these patients (Table 9).

**Table 9: Canadian Cost Analysis of Initial Hospitalization and at 6 Months: Primary Angioplasty vs. Thrombolysis***

| Costs | ANGIOPLASTY† (primary angioplasty plus stenting) | Thrombolysis (alteplase) | P |
|---|---|---|---|
| Initial Hospitalization, mean days (SD) | 6.7 (11.3) | 8.7 (6.7) | <.001 |
| Total hospitalization at 6 months, mean days (SD) | 8.3 (13) | 12.1 (14.0) | .001 |
| Initial Hospitalization, mean $Cdn (SD) | $6,354 (6,382) | $7,893 (4,429) | .001 |
| Total hospitalization at 6 months, mean $Cdn (SD) | $7,100 ($7,111) | $9,559 ($6,933) | .001 |

*Le May et al., (103)
†ANGIOPLASTY represents primary transluminal coronary angioplasty

In considering the potential budget impact in Ontario, the Medical Advisory Secretariat asked the following question: What is the incremental cost-effectiveness of substituting primary angioplasty for thrombolysis in the province? To measure the economics of expanding access to primary angioplasty in Ontario, it was necessary to model acute MI treatment based on current practices, to populate this model with estimates of the patterns of care provided in Ontario, and to select evidence from the literature search to describe the baseline and alternative scenarios for emergency coronary care.

Of note, Alter et al.(105) analyzed the acute MI referral pattern in Ontario as follows:

- At the time of the analysis, 182 (92.5%) of the 201 hospitals in Ontario did not offer on-site angiography services; only 9 of the 15 that did provided revascularization for patients with acute MI.

- Most revascularization happened during follow-up, but a few patients had surgical revascularization on the same day as the index event, which is suggestive of primary angioplasty.
- In that cohort, 4.6% of patients admitted to hospitals with acute MI with the required invasive services received primary revascularization, and less than 0.2% of patients admitted to nonangiography hospitals underwent revascularization on the first day.
- It is explanatory that the median distance to the nearest tertiary centre that offered invasive revascularization was more than 50 kilometres. Only 16% of all hospitals were fewer than 10 kilometres away.

**Estimated Savings of Primary Angioplasty**

Based on the Canadian STAT trial cost analysis, hospitals with PCI centres can expect savings from lower follow-up costs and fewer hospitals days. Thus, primary angioplasty appears to be an efficient use of existing PCI facilities as an alternative to thrombolysis. For these hospitals, using the balance of residents of Ontario as a population, it can be estimated that the hospital sector could save $3 million to $30 million (Cdn) (Table 10).

**Table 10: Ontario Hospitals Budget Impact Analysis Using Existing PCI* Centres**

Estimated 27,800 hospitalizations for acute myocardial infarctions in Ontario
Estimated 11,100 STEMI patients
Assume between 10% to 50% uptake
Cost savings of primary angioplasty ranges from $2,820 to $5,259 per capita

| | 10% Uptake | 50% Uptake |
|---|---|---|
| Low Estimate†, (Cdn) | 3,116,975 | 15,584,874 |
| High Estimate‡ (Cdn) | 5,812,517 | 29,062,584 |

*PCI represents percutaneous coronary intervention; STEMI, ST-segement elevated myocaridal infarction
†Excluding patients with STEMI who have coronary artery bypass graft surgery, major bleeding, and/or stroke
‡All patients with STEMI

**Estimated Costs of Primary Angioplasty**

The estimated costs of primary angioplasty are based on the assumptions that 80% of the population can access the 11 PCI centres in Ontario within 90 minutes, 40% to 50% of patients with acute MI arrive at emergency rooms without an ambulance ("drop-ins"), and 40% of patients with acute MI are candidates for primary angioplasty (i.e., have ST-segment elevation). Based on a proposal the Ministry of Health and Long-Term received from one PCI centre, the estimated costs of moving to a 24/7 operation, assuming no increased caseload, are as follows:

- Additional operating costs: $2 million per centre
- One-time capital costs: $3 million per centre

Therefore, the estimate to move 11 PCI units to 24/7 operations, assuming no increased caseload (and similar costing for all PCI centres, which is unlikely) is $22 million in additional operating costs.

Again, based on the proposal from one PCI centre, the estimated costs of assuming 50% referral caseload for primary angioplasty with ambulance redirect are as follows:

- Further additional operating costs: $3 million (total additional $5 million per centre)
- Incremental capital costs (CCU beds): $3 million (total additional $6 million per centre)

Therefore, the estimate to move 11 PCI units to 24/7 operations, assuming a 50% referral caseload, is as follows (again, assuming similar costing for all PCI centres, which is unlikely):

- Incremental operating costs: $22 million
- Incremental capital costs: $33 million

The total estimated operating costs of converting all 11 PCI units to 24/7 and assuming 50% referral caseload is as follows:

- Assuming cost offsets from shorter hospital stays can be realized (Le May 2001) and that these average out at $20 million:
    - $41 million (including $6 million for stents*)
- Assuming cost offsets cannot be realized:
    - $61 million (including $6 million for stents*)

The total estimated one-time capital costs of converting all 11 PCI Units to 24/7 operations and assuming 50% referral caseload is $66 million.

These estimates assume that operating costs will be phased in over 16 years. See paramedic issues, below.

**Incremental Costs of Stents for Primary Angioplasty**

* The estimated costs of primary angioplasty outlined above include the costs due to incremental use of stents. Based on 2001 figures, there were about 11,000 patients who experienced acute MI with STEMI, and the total number of stents used for patients with acute MI was 20% of 25,775 patients, then about 5,000 stents were used for patients with acute MI that year. If the total number of stents needed in the province is 11,000, then 6,000 stents will be required for 100% uptake in the proposed PCI centres. Assuming each stent costs $2,000 (averaging bare metal and drug-eluting stents), then the cost of this increased stent requirement is about $12 million ($6 million for 50% uptake).

**Potential Costs of Emergency Medical Services**

There are considerable human resource costs associated with introducing pre-hospital thrombolysis or primary angioplasty to accommodate a 60-minute/100-kilometre rule. These costs are mainly due to training and maintaining personnel to support inter-hospital transfer, upgrading the system to support inter-regional transport and back-fill coverage, and changing the system to have ambulances available for cardiac transfer cases. The following analysis is based on discussions with Emergency Medical Services and the paramedic-training program in Ontario. The following annual cost estimates assume that 3,200 paramedics will be upgraded to advanced care paramedic over 16 years at maximum of 200 per year.

First-Year and One-time Expenditures:

- Cost due to salary/wage adjustments: $69 million (phased in over 16 years)
- Cost due to training**: ($7.4 million/year) $118 million (’03 $ over 16 years)
- Cost due to vehicle upgrades: $37 million (’03 $ over 16 years)

**Total one-time/first year costs: $224 million (’03 $)**

**Training costs includes:

| | |
|---|---|
| PCP backfill | (44%) |
| Tuition and course materials 12 weeks @ 8hrs per day | (32%) |
| Travel and accommodation for 83% of paramedics | (24%) |

These estimates of impacts to the ambulance and emergency medical services do not include the transportation costs to relocate patients to hospitals closer to where they live after they have been stabilized. Furthermore, there are other important logistics to address, such as ambulances crossing municipal boundaries to transport patients to the nearest PCI unit.

**Annual Base Budget Impact**

| | |
|---|---|
| Salary/wage adjustments | $69 million per year |
| CE/CME (ACP > PCP) | $13 million per year |
| Increased Vehicle Direct operating exp. | $1.2 million per year |
| Thrombolytics resupply | $15.4 million per year |
| **Total increase to annual base budget** | **$99 million per year** |

Potential cost efficiencies from upgrade - ($20–$30 million per year)

- Ability to provide pre-hospital care will reduce number of retransit runs from local hospitals to regional centres for asthma, trauma, etc.
- Fewer patient-transfer runs from local hospitals to regional centres for treatment requiring sending hospital medical (RN/RT) staff escort. (Also, might have impact on asthma, trauma patients as well.)
- Potential impact on hospital staffing patterns.
- Improved emergency department through put.
- Improved hospital and emergency department bed utilization.
- Potential reduction in patient emergency inter-facility transfers

Overall, the estimated annual costs of 3 different options reforming coronary interventions for STEMI are as follows (M represents millions of dollars):

| | Primary angioplasty (80% uptake with EMS upgrade) | †Early thrombolysis with no increase in primary angioplasty | Primary angioplasty (50% uptake plus early thrombolysis without EMS upgrade) |
|---|---|---|---|
| PA year 1 | $ 10–22M | N/A | $10–22M |
| ‡PA year 16 | $ 41–61M | N/A | $41–61M |
| #EMS year 1 | $ 14 M | $14M | N/A |
| *EMS year 16 | $ 99M | $99M | N/A |
| Total year 1 | $ 24–36M | $0 -14M | $10–22M |
| ‡Total year 16 | $140–160M | $0 -99M | $41–61M |
| One-time capital | $33–66M | | $33–66M |

*Annual base increases according to ACP availability
† With or without ($0)] EMS; EMS upgrade assumes pre-hospital thrombolysis
‡Lower cost factors in possible cost offset of $20M ($15-29M for 50% by Le May, 2003)
#Between years 1 and 16, $224 million in one-time/first year costs will be expended

# Existing Guidelines for Use of Technology

The European Cardiac Society (ECS) and American Heart Association/American College of Cardiology Guidelines (AHA/AMC) each recommend primary angioplasty for patients with STEMI, but link their recommendations to time. ECS specifies that primary angioplasty should be offered if it can be performed within 90 minutes of first medical contact. The ACC/AHA are revising their guidelines, but the updated 1999 version recommends primary angioplasty in a timely fashion presentation. They also require that hospitals do 200 or more PCIs per year, that physicians perform 75 or more PCIs per year, and that door-to-balloon time be less than 120 minutes. (50;51)

The literature indicates that primary angioplasty is being adopted as the standard of care in Europe apart from the ECS recommendations. First, the PRAGUE-2 (93) and DANAMI-2 (1) trials were conducted in the Czech Republic and Denmark, respectively. The Netherlands also has a fully deployed primary angioplasty referral program. In Germany, Zahn et al. (106) reported that 18.5% of hospitals were offering angioplasty, and that primary angioplasty was being performed on about 45% of patients with acute MI presenting to these hospitals.

In France, the site of the CAPTIM study, (21) personnel in medical care ambulances provide pre-hospital thrombolysis. In that study, of patients with STEMI, 9% had pre-hospital thrombolysis, 28% had thrombolysis at the hospital, and 27% had angioplasty within 48 hours of admission, including 9% who had rescue angioplasty. Fifty-seven percent of patients with STEMI received reperfusion therapy. In Sweden, two-thirds of hospitals provide pre-hospital thrombolysis (107).

Elsewhere, the United Kingdom's national cardiology association has submitted a blueprint documenting the human resources requirements for expanding its primary angioplasty capabilities. (108) Scotland has adopted pre-hospital thrombolysis in a region where transport to in-hospital thrombolysis is likely to be prolonged.(109)

# Summary of Findings

RCTs show that, overall, primary angioplasty leads to better patient outcomes than thrombolysis. These benefits apply particularly to patients with acute STEMI who present at specialized PCI centres providing angioplasty. (25;73;90) When the results of all such trials are combined, trends in patient mortality and in the combined rate of mortality, reinfarction, and stroke end points support primary angioplasty.

Readers should interpret the significance of these trends cautiously, however, due to the assumptions of meta-analysis. This is because findings come from 22 RCTs that are a mixed bag of interventions and processes that can only generally be categorized as either primary angioplasty or thrombolysis. Thus, these trials differ sufficiently from each other to limit the generalizability of these results. The Medical Advisory Secretariat recommends that a selective sampling of the results from the most representative trials be used to formulate policy options.

Furthermore, most of the trials were at high-volume centres. Variance between clinical trial efficacy and real-world effectiveness, however, can be enough to erase or reverse observed trial differences between primary angioplasty and thrombolysis. Thus, performance indicators may be required to ensure that optimal clinical effectiveness in the real world is achieved.

In this review, the Medical Advisory Secretariat did a targeted meta-analysis of 9 RCTs, taken from 22 studies published in 1 meta-analysis, (53) that can be viewed as the most representative of practice

patterns in Ontario, with close regard to the use of accelerated alteplase. This analysis compared accelerated alteplase with primary angioplasty with or without stenting, because results from clinical trials have not shown that stenting improves rates of mortality, reinfarction, and stroke compared with balloon angioplasty alone. Generally, the results of this meta-analysis suggest that primary angioplasty represents an absolute risk reduction versus in-hospital thrombolysis as follows: mortality, 1.7%; reinfarction, -3.8%; stroke, -1.1%; combined end point, -5.7%.

Of note, the meta-analysis excluded RCTs examining pre-hospital thrombolysis. A review of the single study that compared primary angioplasty with pre-hospital thrombolysis (21) suggests that primary angioplasty is not superior to earlier administration of thrombolytic therapy. This finding, combined with the results of a meta-analysis showing pre-hospital thrombolysis is better than in-hospital thrombolysis, leads to the conclusion that pre-hospital, or early thrombolysis may be a feasible alternative technology to primary angioplasty.(2)

Costs analyses so far have been limited to in-study analyses for existing PCI centres. If a full analysis of cost-effectiveness is needed to fund angioplasty, then opportunity costs will need to be assessed.

## Access and Feasibility Issues

Even though the general conclusion of this review is that angioplasty is the superior reperfusion strategy to in-hospital thrombolysis for most patients with acute STEMI, it has been argued that RCTs have limited bearing on routine practice. (31) These arguments are based on the wide variability in service delivery documented in registry studies and on variations between the ideal settings of clinical trials and the realities of practice. Furthermore, modern trials of mechanical reperfusion strategies have had to account for logistics, transfer times, and adjunctive drug treatment during transfer. Such protocols need to be judged against earliest possible thrombolysis with modern agents.

### Patient Outcomes: Medical and Clinical

As explained earlier in this review, time to needle describes the time between patient presentation to a hospital emergency room and the parenteral administration of a thrombolytic. A door-to-needle time of 30 minutes or less is considered the optimal performance standard. The corresponding performance standard for primary angioplasty is time to balloon. Recent studies by the Institute for Clinical Evaluative Sciences (ICES) indicate that 41% of eligible patients do not receive thrombolytic therapy, and, for many hospitals, the time-to-needle could be improved if emergency room physicians could start therapy instead of waiting for cardiology consultation or transfer to the critical care unit.

As the literature review has shown, clinical trials have shown better or similar survival rates for primary angioplasty compared with thrombolysis for patients with STEMI who present early after symptom onset and who receive angioplasty within 60 minutes. Recently, the same relationship was found in a large cohort of patients with angioplasty: delays in time between symptom onset and treatment were associated with poorer mortality and morbidity. (34)

Thus, for early-presenting patients (fewer than 6 hours from symptom onset), until arriving within reach of medical attention, the preference for primary angioplasty over thrombolysis depends on ready access to primary angioplasty. It also depends on relative contraindications. For patients presenting later, studies have reported an advantage of primary angioplasty over thrombolysis when the time-to-treatment window exceeds 3 hours from the onset of symptoms. In these studies, patients presenting from 3 to 12 hours after the onset of symptoms had a higher risk of mortality and did better with angioplasty than with thrombolysis. (110;111)

Authors of studies favouring primary angioplasty have concluded that because primary angioplasty is superior to in-hospital thrombolysis, it should be offered to patients presenting with acute STEMI. However, timing has been a factor. Starting with the PRAGUE study (2000), (33) authors have recommended that transport for angioplasty be offered in deference to thrombolysis if the procedure can be done within 90 minutes. In their follow-up study, (93) they have repeated their time-dependency guideline.

Indeed, the prognostic role of time to therapy in patients with STEMI treated by thrombolysis is also well established. (12;56;112) Less well established is whether door-to-balloon time, or symptom-to-balloon time better predicts mortality. For example, Brodie et al.(113) and Berger et al. (114) observed better outcomes among patients undergoing primary angioplasty when the cut-off was 2 hours from symptom onset.

In the same context, Cannon et al. (51) found door-to-balloon time, and not symptom-onset-to-balloon time, was associated with mortality. Consistent with these data, Zijlstra et al., (56) in a recent pooled analysis of several RCTS comparing primary angioplasty with thrombolysis, found a relationship between time of onset of symptoms and mortality – but only for thrombolysis, not for primary angioplasty. Retrospective analyses by De Luca et al. (115) found that symptom-onset-to-balloon time predicted 1-year mortality, while door-to-balloon time did not. Using multivariate analysis, a symptom-onset-to-balloon time of more than 4 hours independently predicted death at 1 year. The decision to provide thrombolysis or to stent a patient with STEMI therefore, must consider not just anticipated door-to-balloon times, but, perhaps more importantly, symptom-onset-to-balloon time.

**Volume-Outcome Relationships**

Also relevant when discussing clinical policy implications, is the documented relationship between procedure volume and patient outcomes, including mortality. That is, higher volume centres are associated with better outcomes. (27-29;116) This is not the situation with thrombolytic agents, as no volume-outcome relationship has been found.(29) Boersma et al. (52) have summarized these relationships.

The real-world analysis is also informed by the volume-outcome data from the United States. (28) The ACC/AHA guidelines require that hospitals perform 200 or more PCIs annually, that physicians perform 75 or more PCIs annually, and that door-to-balloon time be shorter than 120 minutes. (50;51)

**Diffusion**

The effectiveness of primary referred primary angioplasty depends on the efficiency of patient transport from the point of STEMI diagnosis to a qualified treatment centre. In the PRAGUE-2 study, (93) 95% of Czech Republic residents had access to primary angioplasty at a distance of fewer than 100 kilometres from their homes. In the DANAMI study, (117) the hospitals participating in the trial served 62% of Denmark's population. Transport was limited to 3 hours. In Ontario, the extent to which residents can be served by a primary angioplasty program is limited by where catheterization centres are located.

The distribution of cardiac catheterization and surgical services in Ontario is shown in Table 11.

**Table 11: Ontario Cardiac Catheterization Centres**

| Region | Hospital | Services Provided |
|---|---|---|
| **Advanced Cardiac Centres With Advanced Arrhythmia Programs** | | |
| T | St. Michael's Hospital | Cardiac surgery<br>Cardiac catheterization<br>Coronary angioplasty (stents & glycoprotein IIb/IIIa inhibitors)<br>Electrophysiology study<br>Ablation therapy<br>Implantable cardioverter/defibrillation insertion<br>Pacemaker insertion |
| T | University Health Centre | |
| T | Sunnybrook & Women's College Health Sciences Centre | |
| CE | Southlake Regional Health Centre | |
| CS | Hamilton Health Sciences Centre | |
| SW | London Health Sciences Centre | |
| E | Kingston General Hospital | |
| E | Ottawa Heart Institute | |
| **Advanced Cardiac Centres** | | |
| N | Sudbury Regional Hospital | Cardiac surgery, cardiac catheterization and coronary angioplasty (stents & glycoprotein IIb/IIIa inhibitors)<br>Pacemaker onsertion |
| SW | Trillium Health Centre | |
| SW | St. Mary's General Hospital | |
| **Stand-Alone Cardiac Catheterization Centres** | | |
| T | Toronto General Hospital | Cardiac catheterization<br>Pacemak3er insertion |
| CE | Peterborough Regional Centre | |
| SW | Hotel Dieu Grace Hospital, Windsor | |
| N | Thunderbay Regional Hospital | |
| N | Sault Area Hospitals | |
| **Programs in Transition** | | |
| T | Rouge Valley Health System | Cardiac catheterization<br>Pilot stand -alone angioplasty program<br>Pacemaker insertion |

**Primary Angioplasty Offsets of Cardiac Care After Acute Myocardial Infarction**

After the acute phase of MI, patients with noninvasive evidence of persistent or recurrent ischemia are believed to benefit from angiography and revascularization.(117) For patients without symptoms, angiography after MI has not been shown to be beneficial. (77)

Furthermore, there are few data showing that routine angioplasty after thrombolysis is beneficial, and a meta-analysis of trials comparing angioplasty with no angioplasty after thrombolysis has failed to demonstrate a benefit.(43) Nonetheless, even though the benefit is questionable, coronary angiography is done frequently in 30% to 81% of patients. Routine angiography after thrombolysis has not been not supported by evidence to date, and has not been shown to improve left ventricular function or survival. (118)

To address the potential impact of primary angioplasty on cardiac care patterns, it is important to assess what post-acute MI care may be altered or displaced by primary angioplasty. Currently, many patients with acute MI receive angiography post-MI. Some of these patients undergo angioplasty or CABG surgery. Presumably, if these patients had primary angioplasty, the need for these procedures would decrease. In this regard, the provincial practice of referring patients for coronary angiography after acute MI has been shown to depend on on-site procedural capacity, geographical proximity to tertiary centres, and socioeconomic status. (119)

Khaykin et al. (120) documented an increasing rate of angiography after acute MI in Ontario from 23.2% in 1992 to 35.5% in 1999. The variations in referral rates noted in this study suggest that wider monitoring and explicit referral criteria may be required to ensure an appropriate needs-based use of provincial cardiac services. Ontario Hospital Insurance Program data obtained and analyzed by ICES

since then has summarized the growing incidence of follow-up catheterization and surgical revascularization among patients with acute MI in Ontario (Table 12). Data confirm a growing trend for post-MI care (i.e., angiography, angioplasty, and CABG).

**Table 12: Ontario Rates of Surgical Revascularization for Acute MI Admissions***

| Year | Catheterization (angiography), % | Percutaneous Coronary Intervention (angioplasty), % | Coronary Artery Bypass Graft Surgery, % |
|---|---|---|---|
| 1997 | 33.0 | 10.4 | 10.6 |
| 1998 | 36.1 | 12.8 | 11.2 |
| 1999 | 39.3 | 14.8 | 11.4 |
| 2000 | 43.2 | 18.1 | 11.5 |
| 2001 | 45.0 | 20.0 | 11.2 |

*Data obtained and analyzed by the Institute for Clinical Evaluative Sciences;
MI represents myocardial infarction

**Impact on Human Resources**

The health human resource requirements for expanding angioplasty are considerable. Cardiologists must be trained, and nurses and technicians are needed to staff facilities. Formal cardiology training programs teach residents basic diagnostic catheterization, but angioplasty is more complex and requires an additional structured training program.

According to the Cardiac Care Network, (121) cardiology residency programs offer limited exposure to angioplasty, and formal angioplasty training must be sought in post-residency fellowship programs. Practising cardiologists with diagnostic catheterization qualifications need more training to perform angioplasty, and they may require supervised practice after training.

Introducing a full primary angioplasty or pre-hospital thrombolysis service would also affect the training and supply of paramedics. There are 5,811 paramedics in Ontario. Most are at the primary care level. Only 21% are at the acute care level. Primary angioplasty or pre-hospital thrombolysis requires paramedics to be at the acute care level to read 12 lead ECG, deliver appropriate drugs, and monitor patients. Experts advise that 3,200 primary care paramedics would need to be upgraded to acute care level to implement a full primary angioplasty or pre-hospital thrombolysis program.

Optimistically, the province can train a maximum of 200 acute care paramedics annually. This means that the full complement of acute care paramedics can only be achieved over 16 years.

**Impact on the Hospital System**

The protocol being considered would require the primary hospital to readmit the patient with acute MI from the PCI centre as soon as the procedure is complete and the patient is stable. How the funding for such cases would flow between the referring centre and the treating centre is undetermined. The savings from not using thrombolysis would be accrued by the primary receiving hospitals, not the PCI centre.

**Access Implications**

The potential for geographic disparity between residents of the province who can access primary PCI and those who cannot is real. An analysis of patients at ICES with acute MI by postal code suggests that nearly 20% of residents of Ontario cannot access a PCI centre within a 100-kilometre zone.

The discrepancy among hospitals in their use of thrombolysis is also problematic. A report from ICES estimates that 40% of patients with acute MI in Ontario do not receive thrombolysis. Also, the mortality rate for acute MI is 12%, and it is not known if achieving the clinical trial ideal of 5% is more likely to

occur by providing better access to PCI, or, instead, by providing better access to thrombolysis. If this is true, supporting further PCI could be construed as investing in a new therapy when the current standards are not being adequately supported.

Throughout this analysis, it has been pointed out that pre-hospital, or early, thrombolysis, may offer similar outcomes to primary angioplasty. The Medical Advisory Secretariat conducted 2 focus groups with emergency room physicians, nurses, and administrators and was informed that while door-to-needle time in Ontario was close to the 30-minute standard, the real issue was improving symptom-onset-to-needle time and that this could equally apply to door-to-angioplasty times. Some recommendations made by the focus groups included the following:

- Conduct a sustained public awareness educational effort to encourage patients with chest pain to present themselves to an emergency room as soon as possible. This is especially important since 40% of patients with chest pain arrive at emergency rooms using their own transportation.
- Improve pre-hospital assessments to further reduce the door-to-needle time, including transmitting an in-ambulance ECG to the receiving hospital and obtaining a thrombolysis checklist before the patient arrives at the emergency room.
- Try to ensure that advanced care paramedics are deployed in remote areas of the province so that pre-hospital thrombolysis can be administered to patients with STEMI.

# Conclusions

Primary angioplasty has advantages with respect to mortality and combined end points compared with in-hospital thrombolysis (Level 1 evidence). However, pre-hospital thrombolysis improves survival when compared with in-hospital thrombolysis (Level 1 evidence) and is equivalent to primary angioplasty (Level 1 to 2 evidence).

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.

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.

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. 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.

# Appendices

## Appendix 1: Literature Search Strategies

Medline 1966 to October 2003 week 3
1. random$.mp.
2. clin$ trial$.mp.
3. (control$ and (trial$ or stud$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. placebo$.mp.
6. (meta-anal$ or metaanaly$ or meta analy$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (systematic$ and (review$ or overview$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8. compar$.mp.
9. (controlled clinical trial or randomized controlled trial or clinical).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Clinical Trials/
12. exp Drug Therapy/
13. exp Treatment Outcome/
14. Comparative Study/
15. exp feasibility studies/ or exp pilot projects/
16. exp Clinical Protocols/
17. exp Research Design/
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp ANGIOPLASTY/
20. exp Plasminogen Activators/ or exp Fibrinolytic Agents/ or exp Alteplase/ or exp Thrombolytic Therapy/
21. exp Myocardial Infarction/
22. 19 and 20 and 21
23. 18 and 22
24. limit 23 to yr=2002-2003
25. Case Report/
26. 24 not 25
27. limit 26 to (comment or editorial or letter or review or review, academic or review, multicase or review, tutorial or review literature or review of reported cases)
28. 26 not 27

EMBASE <1980 to 2003 Week 43>
1. random$.mp.
2. clin$ trial$.mp.
3. (control$ and (trial$ or stud$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. placebo$.mp.
6. (meta-anal$ or metaanaly$ or meta analy$).mp. [mp=title, abstract, subject headings, drug trade name,

original title, device manufacturer, drug manufacturer name]
7. (systematic$ and (review$ or overview$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8. compar$.mp.
9. (controlled clinical trial or randomized controlled trial or clinical).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
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11. Clinical Trials/
12. exp Drug Therapy/
13. exp Treatment Outcome/
14. Comparative Study/
15. exp feasibility studies/ or exp pilot projects/
16. exp Clinical Protocols/
17. exp Research Design/
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp ANGIOPLASTY/
20. exp Plasminogen Activators/ or exp Fibrinolytic Agents/ or exp Alteplase/ or exp Thrombolytic Therapy/
21. exp Myocardial Infarction/
22. 19 and 20 and 21
23. 18 and 22
24. limit 23 to yr=2002-2003
25. Case Report/
26. 24 not 25
27. (comment or editorial or letter or review or note).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
28. 26 not 27

MEDLINE® In-Process & Other Non-Indexed Citations
1. random$.mp.
2. clin$ trial$.mp.
3. (control$ and (trial$ or stud$)).mp. [mp=title, abstract]
4. ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$)).mp. [mp=title, abstract]
5. placebo$.mp.
6. (meta-anal$ or metaanaly$ or meta analy$).mp. [mp=title, abstract]
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8. (systematic$ and (review$ or overview$)).mp. [mp=title, abstract]
9. compar$.mp.
10. (controlled clinical trial or randomized controlled trial or clinical).mp. [mp=title, abstract]
11. 1 or 2 or 3 or 4 or 5 or 6 or 8 or 9 or 10
12. drug therapy.mp. [mp=title, abstract]
13. treatment outcome.mp. [mp=title, abstract]
14. comparative study.mp. [mp=title, abstract]
15. (research design or clinical protocol or feasibility stud$).mp.
16. (fibrinolytic or thrombolytic or plasminogen).mp.
17. (myocardial infarction or mi or coronary infarction).mp.
18. (angioplasty or ANGIOPLASTY or angioplasty).mp.
19. 11 or 12 or 13 or 14 or 15
20. 16 and 17 and 18
21. 19 and 20

# Glossary

| | |
|---|---|
| **Acute coronary syndrome** | A sudden and severe condition of the heart that includes unstable angina, acute myocardial infarction, and sudden cardiac death |
| **Alteplase** | A tissue plasminogen activator made by recombinant DNA technology; used in fibrinolytic therapy for acute myocardial infarction and as a thrombolytic to treat acute ischemic stroke |
| **Angioplasty** | An angiographic procedure for elimination of areas of narrowing in blood vessels |
| **Anticoagulant** | Medication that reduces or impairs the ability of the blood to form clots (also called blood thinners) |
| **Atherosclerotic plaque** | Deposits of fatty substances, cholesterol, cellular waste products, etc., that can build up in the inner lining of an artery |
| **Balloon angioplasty** | Angioplasty using a balloon-tip catheter that is inflated inside an artery, stretching the intima and leaving a ragged interior surface after deflation, which triggers a healing response and breaking up of plaque |
| **Confidence interval** | A range of numerical expressions within which one can be confident the population value the study is intended to estimate lies |
| **Coronary artery bypass graft (CABG)** | A type of surgery that transplants a section of a vessel from another part of the body (usually the leg or breast) to make a detour around a blockage in a coronary artery (also called open heart surgery) |
| **Electrocardiogram** | A recording of the electrical activity of the heart |
| **Facilitated angioplasty** | When percutaneous transluminal coronary angioplasty is performed after thrombolytic therapy immediately (as soon as possible) |
| **Fibrinolysis** | Therapy with clot dissolving drugs, also referred to as thrombolytic therapy |
| **Glycoprotein IIb/IIIa** | Antiplatelet glycoprotein drugs to prevent blood clotting |
| **Meta-analysis** | A systematic overview of studies that pools results of 2 or more studies to obtain an overall answer to a question of interest or hypothesis |
| **Mortality rate** | Rate of death |
| **Myocardial infarction** | Necrosis of a portion of cardiac muscle caused by obstruction in a coronary artery |
| **Odds ratio** | The ratio of the odds of disease for the experimental group relative to the odds of disease in the control group |
| **Percutaneous coronary** | A type of heart procedure that includes a balloon angioplasty |

| | |
|---|---|
| **intervention** | (percutaneous transluminal coronary angioplasty) and stents. The balloon is used to open a blocked artery. The stent is used to help keep the artery open after the balloon is removed. |
| **Percutaneous transluminal coronary angioplasty (ANGIOPLASTY)** | A type of balloon angioplasty in which the catheter is inserted through the skin; it is used to enlarge the lumen of a sclerotic coronary artery, an alternative to bypass cardiac surgery for selected patients with ischemic heart disease |
| **Primary angioplasty** | Angioplasty performed on acute MI patients without prior thrombolysis (also called direct angioplasty) |
| **Primary percutaneous transluminal coronary angioplasty (ANGIOPLASTY)** | Increasingly used to open blocked arteries in patients with acute myocardial infarction (also called direct ANGIOPLASTY) |
| **Random-effects model** | Assumes that, given a world of conditions, the effects of a study are only a sample, ideally random, of possible effects |
| **Reperfusion** | Restoration of blood flow to an area that was ischemic (without a sufficient supply of blood, in cardiology usually due to a myocardial infarction or blocked artery) |
| **Reteplase** | A mutant of alteplase having a longer half-life than the parent compound, used as a thrombolytic agent to treatment myocardial infarction |
| **Revascularization** | A procedure undertaken to restore blood flow to areas of the heart muscle not reached due to weakened or blocked arteries |
| **Stent** | A metal or plastic tube that is inserted into a coronary artery to prevent constriction and closure |
| **Streptokinase** | A thrombolytic agent to restore blood flow |
| **Tenecteplase** | A thrombolytic agent used to treat myocardial infarction that is administered over 5 seconds in a single dose |
| **Thrombolysis** | Therapy with clot-dissolving drugs |
| **Thrombus** | A blood clot inside the blood vessel |

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