Immediate angioplasty after thrombolysis: a systematic review

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Abstract

Background: The role of immediate transfer for percutaneous coronary intervention (PCI) after thrombolysis for ST-segment elevation myocardial infarction remains controversial. We performed a systematic review of the related literature to determine whether thrombolysis followed by transfer for immediate or early PCI is safe, feasible and superior to conservative management.

Methods: A systematic literature search of MEDLINE, EMBASE, the Cochrane Database for Systematic Reviews and Cochrane Central Register of Controlled Trials, and the American Heart Association EndNote 7 Master Library databases, was performed to 2004 for relevant published studies. The level of evidence and the quality of the study design and methods were rated by 2 reviewers according to a standardized classification. A quantitative meta-analysis was performed to assess the effect at 6–12 months on mortality of immediate or early PCI after thrombolysis.

Results: We found 13 articles that were supportive of immediate or early PCI after thrombolysis and 16 that were neutral or provided evidence opposing it. The largest randomized trials and meta-analyses showed no benefit of routine PCI immediately or shortly after thrombolysis. The studies that were supportive were generally more recent and more frequently involved coronary stents. One large trial supported early PCI after thrombolysis for patients with myocardial infarction complicated by cardiogenic shock. Overall, the difference in mortality rates between the invasive strategy and conservative care was nonsignificant. The 3 stent-era trials showed a significantly lower mortality among patients randomly assigned to the invasive strategy (5.8% v. 10.0%, odds ratio 0.55, 95% confidence interval 0.32–0.92). Analysis of variance found a significant difference in treatment effect between stent-era and pre–stent-era trials.

Interpretation: At present, there is inadequate evidence to recommend routine transfer of patients for immediate or early PCI after successful thrombolysis. Results of recent trials using contemporary PCI techniques, including coronary stents, appear more favourable but need to be confirmed in large randomized trials, which are currently in progress. Transfer for immediate PCI is recommended for patients with cardiogenic shock, hemodynamic instability or persistent ischemic symptoms after thrombolysis.

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Although different strategies involving thrombolysis and angioplasty to treat ST-segment elevation myocardial infarction (STEMI) have been evaluated, until now there has been no precise assessment of immediate versus early percutaneous coronary intervention (PCI) after the administration of thrombolytic therapy in the treatment of STEMI. The timing of PCI after thrombolysis can be classified as immediate (as soon as possible after thrombolysis), early (within 24 hours after thrombolysis), rescue (performed only for failed thrombolysis) or deferred (more than 24 hours after thrombolysis).[1] Immediate PCI after thrombolysis is often referred to as facilitated PCI.

The 2004 guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) for treating STEMI recommend PCI immediately after thrombolysis: "Facilitated PCI, *Class IIb* [paragraph] 1. Facilitated PCI might be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low *(Level of Evidence: B)*" (p. 603)[2] and "Percutaneous Coronary Intervention After Fibrinolysis, *Class I* [paragraph] 3. In patients whose anatomy is suitable, PCI should be performed for cardiogenic shock or hemodynamic instability ... (*Level of Evidence: B*)" (p. 604).[2]

The systematic review summarized herein was undertaken, presented and debated as part of the International Liaison Committee on Resuscitation (ILCOR) evidence evaluation process. This process culminated in the 2005 International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations, hosted by the AHA in Dallas, Jan. 23–30, 2005. As part of this process, international consensus documents have been posted on the Internet (available at www.c2005.org) and a summary[3] was published.

The objective of this systematic overview was to determine whether a strategy of thrombolysis, administered in either a prehospital setting or a community hospital emergency department and followed by transfer for immediate or early PCI is safe, feasible and more effective than delayed PCI in the management of STEMI.

Methods

The following electronic databases were searched to 2004: Ovid's MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE; the Cochrane Database for Systematic Reviews and Cochrane Central Register of Controlled Tri-

als; and AHA's EndNote 7 Master Library. Complex search strategies were formulated using medical subject headings and text words to retrieve records that combined terms related to myocardial infarction, fibrinolytic therapy and angioplasty. The data set was refined by searching for articles in which the terms *facilitated, immediate, early, adjunct,* or *combined* occurred within 2–4 words of *angioplasty, percutaneous coronary intervention, PCI, percutaneous transluminal angioplasty* or *PTCA.* In addition, reference lists of articles were hand-searched for other relevant papers. Detailed steps of the electronic database search process are outlined in Appendix 1 (available at www.cmaj.ca/cgi/content/full/173/12/1473/DC1).

Excluded were animal studies, studies published in abstract form only, articles not yet accepted for publication, investigations in which PCI was performed more than 24 hours after thrombolysis, studies in which only intracoronary thrombolysis was used, and trials with fewer than 30 subjects and no control group. Because most articles before 1985 focused on intracoronary thrombolysis, the literature search was initially limited to the year 1985 and onward. Abstracts from reports published from 1979 through 1984 found by means of MEDLINE (9 articles), Ovid MEDLINE In-Process & Other Non-Indexed Citations (9) and EMBASE (3) were later reviewed to confirm this assumption.

The electronic databases were searched by an information specialist (C.P.Z.). After databases were combined and duplicate references were deleted, the search had generated 807 references. Titles and abstracts of each reference were then independently reviewed by 2 physicians (W.J.C. and F.B.); the report was omitted if any of the exclusion criteria listed above were met. If the eligibility of a reference remained in doubt after consideration of the abstract, the published article was examined. The reference lists of review articles were also searched for additional references.

The level of evidence for each article was graded from 1 (the highest level of evidence, such as a large, randomized trial) to 7 (the lowest level, e.g., rational conjecture or common sense; Box 1); and the design and methods, as excellent, good, fair, poor or unsatisfactory, both according to the AHA's ILCOR classification (Box 2).

Box 1: Definitions of levels of evidence, according to the American Heart Association's ILCOR evaluation process

1 Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
2 Randomized clinical trials with smaller or less significant treatment effects
3 *Prospective* controlled, nonrandomized, cohort studies
4 *Historic* nonrandomized, cohort or case-control studies
5 Case series: patients compiled in serial fashion, lacking a control group
6 Animal studies or mechanical model studies
7 Extrapolations from existing data collected for other purposes, theoretical analyses
8 Rational conjecture (common sense); common practices that were accepted before evidence-based guidelines

Note: ILCOR = the International Liaison Committee on Resuscitation.

Box 2: Definitions of ratings of study design and methods, according to the American Heart Association's ILCOR evaluation process

Excellent (*both* of the following) or **good** (*one* of):
- Design — highly appropriate sample or model; randomized; proper choice of controls
- Methods — outstanding accuracy, precision and data collection in its class of study

Fair — one of:
- Design — adequate design, but possibly biased
- Methods — adequate under the circumstances

Poor — one of:
- Design — small or clearly biased population or model
- Methods — weakly defensible in its class; limited data or measures

Unsatisfactory — one of:
- Design — anecdotal, no controls, off target end-points
- Methods — not defensible in its class; insufficient data or measures

Note: ILCOR = the International Liaison Committee on Resuscitation.

A quantitative meta-analysis was performed of only those randomized trials that compared routine PCI performed within 24 hours after thrombolysis with more conservative management. The end points used for the meta-analysis included death and a composite of death and reinfarction by 12 months (or, if that information was unavailable, by 6 months) after the procedure. The statistical analysis was performed and the Forest plots were generated using Comprehensive Meta Analysis software (version 1.0.23, Biostat, Englewood, NJ). The inverse-variance computational model (which uses logs of the odds ratios [ORs]) was used in a fixed-effects model. The type of trial was classified as "pre–stent era" if coronary stents were used in fewer than 50% of PCI cases, or as "stent era" otherwise. Era trial type was used as a moderator variable, and the ANOVA (analysis of variance) option was used to determine whether differences in treatment effect between the 2 era types were significant ($p < 0.05$). The Q statistic was calculated to assess if significant heterogeneity was present between trials.

Results

The electronic database search identified 807 articles, of which only 37 reported on trials that met the inclusion criteria (Fig. 1).[4–40] Eight articles[10–17] reported on studies that were assigned ILCOR design and methods scores of poor quality, and were not included in the 2 summary tables.

Of the 29 articles remaining, the findings of 13 studies were supportive of immediate or early PCI after thrombolysis (Table 1); those of 7 were neutral; and the results from 9 provided evidence opposing immediate or early PCI with increased mortality or requirements for transfusion or coronary

artery bypass grafting in the treatment group (Table 2; more detailed versions of these 2 tables can be accessed through the Internet, by going to www.cmaj.ca/cgi/content/full/173/12/1473/DC2).

Studies showing benefit by qualitative assessment

Evidence from 6 relatively small trials (level 1 evidence for 2 studies, level 2 for 4 studies) showed a benefit for immediate or early PCI after thrombolysis.[18–23] Of these trials, 3 used coronary stents for the majority of patients undergoing PCI.[18,20,21]

A strategy of thrombolysis combined with transfer for immediate or early PCI was supported by 3 good-quality but relatively small randomized trials (levels of evidence 1[19,20] and 2[18]) and 3 small randomized trials[21–23] of fair quality (level 2). Other supportive randomized trials had been presented at scientific meetings but not yet published (CAPITAL AMI,[41,42] GRACIA-2). Timing of PCI after thrombolysis, inclusion of patients requiring transfer for PCI, use of coronary stents and control-group interventions differed considerably among these trials. The efficacy of this strategy is also supported by 2 post-hoc nonrandomized comparisons (levels 3[24] and 7[25]); its feasibility, by 2 level-7 trials[14,26] in which fibrinolysis or placebo was administered before immediate cardiac catheterization and PCI as necessary.

Studies showing neutral effect or no benefit by qualitative assessment

Evidence from 5 randomized trials (level 1 evidence for 3 studies, and levels 2 and 7 for one study apiece) and 3 level-1 meta-analyses showed no benefit of immediate or early PCI after thrombolysis. Most of these trials did not involve transfer for PCI and did not use contemporary pharmacotherapy and contemporary angioplasty techniques.

A strategy of thrombolysis combined with transfer for immediate or early PCI was not supported by 3 level-1 randomized trials,[27–29] one level-2[30] and one level-7 trial,[31] and several nonrandomized studies or secondary analyses of trials. Several level-1 meta-analyses[32–34] also showed no benefit of immediate or early PCI. However, all but one of these trials were carried out before the era of coronary stenting, and none utilized modern pharmacological therapies or contemporary PCI techniques. The most recent study[30] was fairly small (100 patients per treatment group) and showed a benefit of immediate PCI with prolonged follow-up.[18]

Quantitative meta-analysis findings

The results of the quantitative meta-analysis are shown in Fig. 2 and Fig. 3. The 37 articles identified in the search strategy included 18 randomized controlled trials. Of these, 5 trials compared immediate or early PCI after thrombolysis with primary PCI; 4 trials evaluated PCI for failed thrombolysis or cardiogenic shock; and one trial had no long-term outcomes reported. The 8 remaining trials (5 pre–stent-era and 3 stent-era trials) were included in the quantitative meta-analysis. Outcomes were reported at 12 months for all but one trial, SIAM-3,[21] which only reported outcomes up to 6 months.

Overall, there were no statistically significant differences in mortality (OR 0.89, 95% confidence interval [CI] 0.67–1.19; Fig. 2) or in a composite of death and reinfarction (OR 0.81, 95% CI 0.65–1.01; Fig. 3) within 12 months (6 mo, for SIAM-3[21]) between the "invasive" strategy (immediate or early

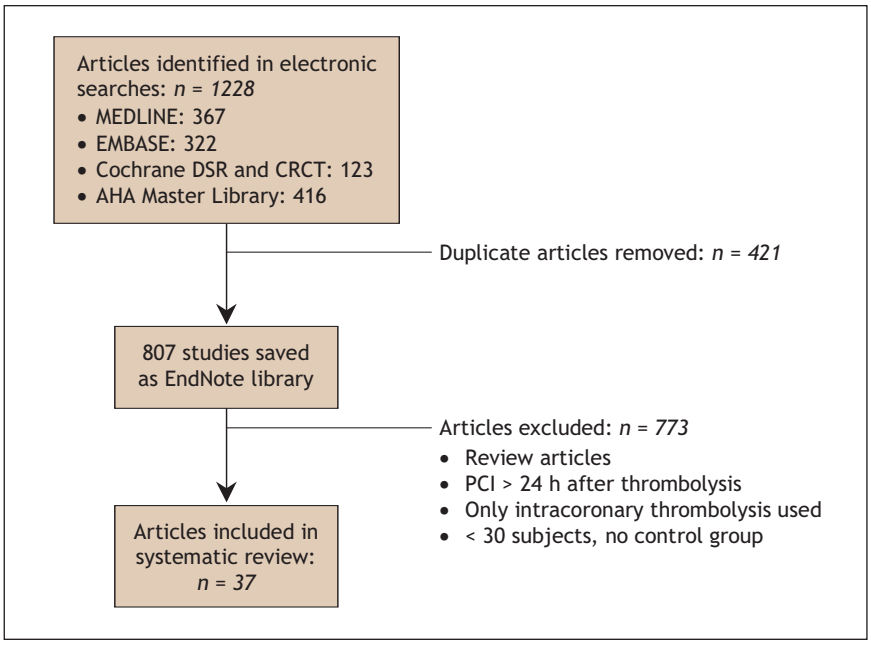

Fig. 1: Literature-search flow chart. DSR = Database for Systematic Reviews, CRCT = Cochrane Central Register of Controlled Trials, AHA = American Heart Association, PCI = percutaneous coronary intervention.

PCI after thrombolysis) and the "conservative," noninvasive strategy. Similarly, among the 5 pre–stent-era trials there were no significant differences in mortality or in combined death and reinfarction within 12 months. However, in the 3 stent-era trials, there were significantly lower rates of death (OR 0.55, 95% CI 0.32–0.92; Fig. 2) and death or reinfarction (OR 0.59, 95% CI 0.39–0.89; Fig. 3) within 12 months for patients randomly assigned to the invasive strategy.

There was no evidence of significant heterogeneity among the 8 trials overall (Q = 9.99, $p = 0.19$ for death; Q = 9.61, $p = 0.21$ for combined death and reinfarction, each within 12 mo), among the 5 pre–stent-era trials (Q = 4.86, $p = 0.30$ for death; Q = 3.65, $p = 0.45$ for death/reinfarction) or among the 3 stent-era trials (Q = 0.29, $p = 0.86$ for death; Q = 0.21, $p = 0.90$ for death/reinfarction, each within 12 mo). The ANOVA results indicated a significant difference in treatment effects between the stent-era and pre–stent-era trial groups ($p = 0.03$ for death, $p = 0.01$ for death/reinfarction within 6–12 mo). Funnel plots for death and for a composite of death and reinfarction (which are available online as Appendixes 2 and 3, respectively, at www.cmaj.ca/cgi/content/full/173/12/1473/DC1) within 6–12 months did not reveal any obvious asymmetry, which suggests that publication bias did not influence the findings of the meta-analysis.

Studies of PCI treatment for cardiogenic shock or failed thrombolysis

In the SHOCK randomized trial (level 1),[35,43] early revascularization in patients with myocardial infarction complicated by

Table 1: Studies that found an advantage for early percutaneous coronary intervention after thrombolysis versus delayed intervention

First author, year, no. of participants	Intervention	Comparison group	ILCOR LoE	Main result
Califf[19] 1991 *n* = 575	Immediate cath ± rescue PCI for failed thrombolysis	Cath at 5–10 d after thrombolysis	1	Fewer adverse outcomes (33% v. 45%; $p = 0.004$) and a trend toward higher patency with immediate cath
Hochman[35] 1999 *n* = 302	Emergency PCI/CABG for cardiogenic shock	Conservative non-interventional strategy	1	Survival improved at 6 mo with emergency revascularization (OR 0.80, 95% CI 0.54–0.98)
Fernandez-Aviles[20] 2004 *n* = 500	PCI (stent) within 24 h of thrombolysis (25% required transfer)	Conservative non-interventional strategy	1	Less revascularization (OR 0.30, 95% CI 0.15–0.62) and a trend toward lower rates of death/MI at 1 yr (OR 0.59, 95% CI 0.33–1.05)
Bednar[18] 2003 *n* = 300	Group B: thrombolysis during transfer for cath, PCI (stent)	Group A: thrombolysis without transfer Group C: transfer for primary PCI	2	No difference in overall mortality; lower cardiac mortality for early presenters (within 2 h): group A 18%, B 3%, C 8% ($p < 0.05$)
Topol[22] 1987 *n* = 28	PCI 120 min after tPA	Angiography at 120 min, no PCI	2	Less recurrent ischemia and reinfarction (7% v. 53%; $p = 0.01$); greater improvement within infarct zone in regional left-ventricular function
Scheller[21] 2003 *n* = 197	PCI (stent) 6 h after reteplase	PCI (stent) 2 wk after reteplase	2	Fewer ischemic events (5% v. 28%; $p = 0.001$) and higher LVEF at 2 wk and at 6 mo
Ellis[37] 1994 *n* = 151	Rescue PCI after failed thrombolysis	Conservative non-interventional strategy	2	Trend toward lower rates of death/severe CHF (6% v. 17%; $p = 0.05$) and improvement in exercise LVEF with rescue PCI
Vermeer[23] 1999 *n* = 224	tPA followed by transfer for immediate cath, rescue PCI if needed	tPA alone, or transfer for primary PCI	2	No complications during transport; no significant differences in outcomes
Herrmann[24] 2000 *n* = 323	PCI (stent) 90 min after reteplase and/or abciximab	Conservative non-interventional strategy	3	Less reinfarction (1.2% v. 4.9%; $p = 0.03$) and need for urgent revascularization (1.6% v. 9.3%; $p = 0.001$)
Kurihara[14] 2004 *n* = 39	Monteplase + PCI (stent)	Primary PCI (stent)	7	Higher rate of patency pre-PCI with monteplase; no difference in LVEF
Ross[26] 1999 *n* = 606	50 mg tPA prior to immediate cath/PCI	Placebo prior to immediate cath/PCI	7	tPA associated with improved IRA patency pre-PCI; no difference in left-ventricular function
Schweiger[25] 2001 *n* = 1938	Immediate PCI (stent) 90 min after thrombolysis	Conservative non-interventional strategy	7	Lower rate of death/MI in multivariate model (OR 0.46, 95% CI 0.24–0.87)
Berger[36] 1997 *n* = 2200	Early angiography, PCI/CABG for cardiogenic shock	No early angiography for cardiogenic shock	7	Independently associated with lower 30-day mortality (OR 0.43, 95% CI 0.34–0.54)

Note: A more detailed version of this table is available on the Web (at www.cmaj.ca/cgi/content/full/173/12/1473/DC1).
ILCOR = International Liaison Committee on Resuscitation, LoE = level of evidence, cath = cardiac catheterization, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery, OR = odds ratio, CI = confidence interval, tPA = tissue plasminogen activator, LVEF = left-ventricular ejection fraction, CHF = congestive heart failure.

cardiogenic shock (within 36 hours after infarction and within 12 hours after onset of shock) was shown to improve mortality at 6 months and 1 year compared with initial medical stabilization. About half of the patients in that trial had received thrombolysis. Among those randomly assigned to early revascularization, PCI accounted for 64% of initial revascularization procedures; bypass surgery, for 36%. Median time from myocardial infarction to randomization was 11 hours; from randomization to PCI, 0.9 hours. These findings were further supported by retrospective analysis in the GUSTO-1 trial[36] (level 7), which found that early angiography (within 24 hours of onset of cardiogenic shock) and revascularization was associated with lower mortality at 30 days.

The published evidence to support rescue PCI for patients who do not reperfuse after thrombolysis is more limited. One small randomized trial[37] (level 2) showed an improvement in exercise left-ventricular ejection fraction and a reduction in combined death and congestive heart failure with

Table 2: Studies that did not show an advantage for early coronary intervention after thrombolysis versus delayed intervention

First author, year, no. of participants	Intervention	Comparison group	ILCOR LoE	Main result
TIMI Research[28] 1988, *n* = 389	Immediate PCI after tPA	Cath/PCI at 18–48 h after tPA	1	Increased transfusion and CABG (16% v. 8%; $p = 0.01$); no difference in LVEF
Rogers[6] 1990 *n* = 586	Immediate PCI after tPA	PCI at 18–48 h after tPA, or ischemia-guided PCI	1	No improvement in mortality, increased transfusion or CABG; no difference in LVEF
Simoons[27] 1988 *n* = 367	Immediate PCI after tPA	Conservative non-interventional strategy	1	Trend toward higher mortality at 14 d (7% v. 3%; $p = 0.08$); no difference in infarct size or LVEF
Michels[33] 1995 *n* = 2243	Immediate PCI after thrombolysis	Delayed or no PCI after thrombolysis	1	No difference in death/reinfarction at 6 wk and 1 yr (OR 1.38, 95% CI 0.81–2.34)
Topol[29] 1987 *n* = 197	Transfer for cath 90 min after tPA, immediate PCI	Transfer for cath 90 min after tPA, elective PCI at 7–10 d	1	No difference in death, reocclusion; no difference in regional left-ventricular wall motion
Jovell[32] 1993 *n* = 5882	Early PCI after thrombolysis	Conservative non-interventional strategy	1	No difference in mortality, reinfarction
Topol[34] 1988 *n* = 1142	Immediate PCI after thrombolysis	See Topol[87], Simmoons[88] and TIMI Research[88]	1	No improvement in mortality or LVEF; increased rates of transfusion and CABG
Arnold[7] 1991 *n* = 291	Immediate PCI after tPA	Conservative non-interventional strategy	2	No difference in regional left-ventricular wall motion
Arnold[8] 1992 *n* = 367	Immediate PCI after tPA	Conservative non-interventional strategy	2	Trend toward increased mortality at 1 yr (9% v. 5%; $p = 0.16$)
De Bono[4] 1988 *n* = 367	Immediate PCI after tPA	Conservative non-interventional strategy	2	Trend toward increased mortality at 3 mo; no difference in LVEF, infarct size or coronary patency
Widimsky[30] 2000 *n* = 300	Group B: thrombolysis during transfer for cath, PCI (stent)	Group A: thrombolysis without transfer Group C: transfer for primary PCI	2	Rates of death, reinfarction and stroke similar to those of group A, higher than those of group C
Erbel[5] 1989 *n* = 206	PCI after intravenous and subcutaneous streptokinase	Conservative non-interventional strategy	3	No difference in mortality at 3 yr; no improvement in left-ventricular function
Ellis[9] 1994 *n* = 108	Immediate PCI after thrombolysis with TIMI-2 flow	Conservative non-interventional strategy	7	No difference in death or CHF; slightly higher LVEF improvement with early PCI
O'Neill[31] 1992 *n* = 122	Streptokinase followed by immediate PCI	Primary PCI	7	Higher rate of transfusion and emergency CABG (10% v. 1.6%; $p = 0.03$); no difference in LVEF or patency
Sutton[38] 2004 *n* = 307	Rescue PCI after failed thrombolysis	Conservative non-interventional strategy	2	Higher rate of transfusion (11% v. 1%; $p < 0.001$) and stroke (5% v. 1%; $p = 0.03$); at 30 d, no difference in mortality or regional wall motion
Kastrati[40] 2004 *n* = 253	Half-dose reteplase + abciximab followed by transfer for immediate PCI	Abciximab followed by transfer for immediate PCI	7	No difference in death, reinfarction or stroke; trend toward increased bleeding with reteplase (6% v. 2%; $p = 0.16$); no difference in SPECT infarct size at 5–10 d

Note: A more detailed version of this table is available on the Web (at www.cmaj.ca/cgi/content/full/173/12/1473/DC1).
ILCOR = International Liaison Committee on Resuscitation, LoE = level of evidence, PCI = percutaneous coronary intervention, tPA = tissue plasminogen activator, CABG = coronary artery bypass graft surgery, LVEF = left-ventricular ejection fraction, LV = left-ventricular, CHF = congestive heart failure, SPECT = single-photon emission computed tomography.

rescue PCI. A more recent level-2 trial[38] showed a reduced requirement for subsequent revascularization with rescue PCI but an increased need for transfusion and no difference in 30-day mortality.

Interpretation

We conducted a systematic review of clinical trials examining the use of routine immediate transfer of patients with STEMI from community hospitals to cardiac catheterization centres for immediate or early PCI after thrombolysis. Our findings indicate that at present, there is inadequate evidence to recommend routine transfer of patients for immediate or early PCI after successful prehospital or inhospital thrombolysis and initial stabilization in community hospital emergency departments.

The potential benefits of routine immediate or early PCI after thrombolysis include prevention of reinfarction and recurrent ischemia, and reduction of infarct size in patients who fail to reperfuse after thrombolysis. Risks include bleeding, vascular complications, and cardiac arrhythmias or arrest during ambulance transportation. The cost-effectiveness of this strategy, including consideration of the need for additional cardiac catheterization laboratories, staffing, ambulances and paramedics, has not been studied.

Published findings are conflicting, and the related literature is difficult to interpret. Because the pharmacological management of STEMI and PCI techniques and adjunct pharmacotherapy have changed considerably (e.g., coronary stents, thienopyridines and glycoprotein [GP] IIb/IIIa inhibitors), it may be inappropriate to compare the large randomized trials conducted in the 1980s with more recent studies. Whereas the older trials showed no benefit of immediate or early PCI after thrombolysis and trends toward increased rates of adverse events, this may have resulted from higher rates of reocclusion and reinfarction after initially successful PCI.[4] Advances in percutaneous coronary intervention and adjuvant pharmacotherapy since that time have led to lower rates of reocclusion and reinfarction.

More recent observational studies and small randomized trials have been more supportive of immediate or early PCI after thrombolysis.[21] Many recent studies have been presented in abstract form but were not yet published at the time this analysis was conducted (e.g., GRACIA-2, CAPITAL AMI[41]) and were therefore not included in this worksheet, as per the ILCOR guidelines. Our meta-analysis showed significantly lower rates of death and of death or reinfarction at 6 months[21] to 1 year with immediate or early PCI after thrombolysis compared with conservative care in the 3 published randomized trials involving coronary stents. Furthermore, differences in treatment effects between trials carried out in the pre–stent and stent eras were significant. Nevertheless, given the small number of trials, limited numbers of patients and differences in study design, these results should be viewed as hypothesis-generating and require confirmation in large randomized trials using contemporary PCI techniques and pharmacotherapy. Such trials[39,44,45] are in progress.

Another limitation of published studies is that most of the trials evaluating immediate or early PCI after thrombolysis have been carried out in centres with on-site angioplasty facil-

Study type	Citation	Total *n*	Effect (OR)	95% CI Lower	95% CI Upper	*p*
Pre-stent era	Erbel	206	0.780	0.390	1.560	0.481
	ESCG	367	1.782	0.793	4.004	0.157
	TAMI 1	197	3.097	0.609	15.735	0.153
	TAMI 5	575	1.223	0.660	2.267	0.522
	TIMI II A	392	0.791	0.397	1.576	0.504
Total (5 studies)		1737	1.099	0.784	1.543	0.583
Stent era	GRACIA-1	499	0.553	0.240	1.276	0.160
	PRAGUE-1	199	0.614	0.278	1.353	0.223
	SIAM-3	163	0.410	0.121	1.390	0.142
Total (3 studies)		**861**	**0.548**	**0.326**	**0.921**	**0.023**
Combined (8 studies)		**2598**	**0.893**	**0.673**	**1.186**	**0.436**

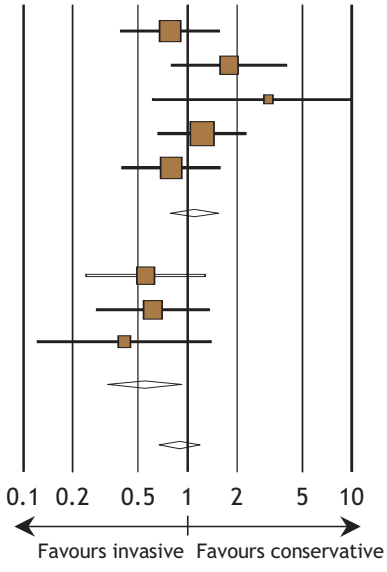

Fig. 2: Forest plot of odds ratios for death within 12 months (6 months, in the SIAM-3 trial). This plot shows a fixed-model analysis; similar numbers from a random-model analysis are included in an online version of Fig. 2 (available at www.cmaj.ca/cgi/content/full/173/12/1473/DC3).

ities, where patients did not require transfer to another institution for PCI. Nevertheless, several large series have documented the safety and feasibility of transferring patients to PCI centres after thrombolysis.[16,23,30] Ongoing randomized trials are comparing the secondary transfer of patients for immediate or early PCI after thrombolysis with initial stabilization in community emergency departments or in prehospital settings.[44,45]

All of the studies included in this systematic overview used in-hospital administration of thrombolysis. The use of prehospital thrombolysis with initial stabilization in a community hospital followed by transfer for routine immediate or early PCI has not been studied. The comparison of prehospital thrombolysis to primary PCI is covered in a separate review by the ILCOR Acute Coronary Syndrome/Acute Myocardial Infarction Task Force.

To further complicate the interpretation of the existing literature, there is significant heterogeneity in the control groups among the studies included in our systematic review. Diagnostic coronary angiography for control-group patients was performed immediately in one trial,[29] delayed (> 24 h after thrombolysis) in several[19,28] and performed only for recurrent ischemia in others.[20,27] In some studies, patients in the control group routinely underwent delayed PCI,[21,28] whereas in others, patients in the control groups were treated medically unless they had spontaneous or inducible ischemia.[20,27] For studies in which all control-group patients underwent primary PCI,[14,26,31,40] no inference could be made on the efficacy of immediate or early angioplasty after thrombolysis compared with delayed angioplasty, and only the safety and feasibility of this approach was evaluated. The symmetry seen in the funnel plots and the large number of published studies with neutral or opposing results suggest that publication bias was unlikely to have had a major impact on the findings of this systematic overview.

The evidence for early revascularization in patients with cardiogenic shock is clearer. The SHOCK trial[35,43] demonstrated a significant mortality benefit with early coronary revascularization within 12 hours of shock onset. Among the patients who were randomly assigned to early revascularization, 64% underwent PCI and 36% underwent bypass surgery. Over 50% of the patients enrolled in this trial had received thrombolytic therapy. These findings were supported by a nonrandomized analysis from the first GUSTO trial.[36] The 2004 ACC–AHA STEMI guidelines[2] list emergent rescue angioplasty for patients with cardiogenic shock as a class 1 recommendation for patients younger than 75 years, and a class IIa recommendation for selected patients 75 years or older. A benefit of rescue PCI for patients who fail to reperfuse after thrombolysis was observed in one small randomized trial[37] (level 2), which showed improvement in exercise left-ventricular ejection fraction and lower rates of death and congestive heart failure. In the MERLIN trial,[38] rescue PCI reduced the need for subsequent revascularization but was associated with increased transfusions and had no effect on 30-day survival rates or left-ventricular function. More compelling evidence for a benefit from rescue PCI was documented in a recent trial (the REACT trial[46]) that resulted in a lower incidence of death, reinfarction, stroke and heart failure at 6 months compared with conservative management. Although

Study type	Citation	Total *n*	Effect (OR)	95% CI Lower	95% CI Upper	*p*
Pre-stent era	Erbel	206	0.710	0.399	10.262	0.242
	ESCG	367	0.929	0.534	10.617	0.795
	TAMI 1	197	30.097	0.609	150.735	0.153
	TAMI 5	575	0.971	0.583	10.616	0.909
	TIMI II A	392	0.974	0.564	10.681	0.924
Total (5 studies)		**1737**	**0.927**	**0.709**	**10.213**	**0.580**
Stent era	GRACIA-1	499	0.563	0.301	10.054	0.070
	PRAGUE-1	199	0.505	0.259	0.983	0.043
	SIAM-3	163	0.884	0.353	20.212	0.792
Total (3 studies)		**861**	**0.591**	**0.393**	**0.890**	**0.012**
Combined (8 studies)		**2598**	**0.809**	**0.647**	**1.013**	**0.065**

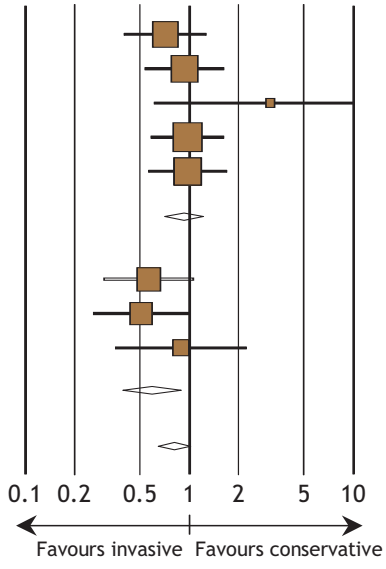

Fig. 3: Forest plot of odds ratios for combined death and myocardial reinfarction within 12 months (6 months, in the SIAM-3 trial). This plot shows a fixed-model analysis; similar numbers from a random-model analysis are included in an online version of Fig. 3 (available at www.cmaj.ca/cgi/content/full/173/12/1473/DC3).

there remains uncertainty about the role of routine transfer for immediate or early PCI after successful thrombolysis, transfer for immediate PCI is recommended for patients with cardiogenic shock, hemodynamic instability or persistent ischemic symptoms after thrombolysis.

Recommendations arising from the scientific evidence can be translated into guidelines for the management of STEMI in the emergency department. There are no indications for immediate transfer for PCI after successful thrombolysis. For patients with cardiogenic shock or failed thrombolysis, transfer should be arranged, with close monitoring of the patient. This approach requires developing a network of care with a tertiary care facility as well as an appropriate transport system. Recent studies showing a benefit from pharmaceutical agents (fibrinolytic agents or GP IIb/IIIa inhibitors) given en route to the catheterization laboratory to enhance the efficacy of PCI ("facilitated PCI") require confirmation in large, multicentre, randomized trials. This strategy remains investigational and cannot be currently recommended in emergency medicine practice.

This article has been peer reviewed.

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