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Routine Early Angioplasty after Fibrinolysis for Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Patients with a myocardial infarction with ST-segment elevation who present to hospitals that do not have the capability of performing percutaneous coronary intervention (PCI) often cannot undergo timely primary PCI and therefore receive fibrinolysis. The role and optimal timing of routine PCI after fibrinolysis have not been established.

METHODS

We randomly assigned 1059 high-risk patients who had a myocardial infarction with ST-segment elevation and who were receiving fibrinolytic therapy at centers that did not have the capability of performing PCI to either standard treatment (including rescue PCI, if required, or delayed angiography) or a strategy of immediate transfer to another hospital and PCI within 6 hours after fibrinolysis. All patients received aspirin, tenecteplase, and heparin or enoxaparin; concomitant clopidogrel was recommended. The primary end point was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days.

RESULTS

Cardiac catheterization was performed in 88.7% of the patients assigned to standard treatment a median of 32.5 hours after randomization and in 98.5% of the patients assigned to routine early PCI a median of 2.8 hours after randomization. At 30 days, the primary end point occurred in 11.0% of the patients who were assigned to routine early PCI and in 17.2% of the patients assigned to standard treatment (relative risk with early PCI, 0.64; 95% confidence interval, 0.47 to 0.87; $P=0.004$). There were no significant differences between the groups in the incidence of major bleeding.

CONCLUSIONS

Among high-risk patients who had a myocardial infarction with ST-segment elevation and who were treated with fibrinolysis, transfer for PCI within 6 hours after fibrinolysis was associated with significantly fewer ischemic complications than was standard treatment. (ClinicalTrials.gov number, NCT00164190.)

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*The Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) investigators are listed in the Appendix.

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P RIMARY PERCUTANEOUS CORONARY INTERVENTION (PCI) is an effective treatment for myocardial infarction with ST-segment elevation when it can be performed rapidly.¹ However, primary PCI is performed at less than 25% of acute care hospitals in the United States.^{2,3} Many patients with myocardial infarction with ST-segment elevation present to hospitals that do not have the capability of performing PCI and therefore cannot undergo PCI within the timelines recommended in the guidelines⁴; instead, they receive fibrinolysis as the initial reperfusion therapy. Although the proportion of such patients has decreased in recent years, 27.6% of the patients in the National Registry of Myocardial Infarction received fibrinolytic therapy in 2006.⁵

The advisability of transferring such patients to a PCI center immediately after fibrinolysis for routine early PCI remains unclear. Initial studies of this issue did not show a clinical benefit of routine early PCI after fibrinolysis.^{6,7} More recent studies, performed in the era of coronary stenting and contemporary pharmacotherapy, have been more encouraging but have not been adequately powered to definitively establish the safety and efficacy of this approach.⁸⁻¹¹ We therefore performed a large, randomized trial to compare a strategy of routine transfer and PCI within 6 hours after fibrinolysis with a standard strategy of transfer and PCI only in cases in which fibrinolytic therapy has failed.

METHODS

STUDY DESIGN

The details of the trial design have been published previously.^{12,13} The Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) was a randomized, nonblinded trial performed at 52 sites in three provinces (Ontario, Manitoba, and Quebec) in Canada. The protocol was designed by the authors and approved by the local institutional research ethics committees at all participating hospitals. Data collection, site management, and data analysis were carried out at the Canadian Heart Research Centre.

The study was sponsored by the Canadian Institutes of Health Research, Roche Canada, and Abbott Vascular Canada; the sponsors had no involvement in the study design, data analysis, or

manuscript preparation. The authors vouch for the accuracy and completeness of the data and the analyses.

STUDY POPULATION

Patients with myocardial infarction with ST-segment elevation who presented within 12 hours after the onset of symptoms to participating centers that did not have the capability of performing PCI and who were treated with tenecteplase were screened for eligibility. Participants were eligible for inclusion in the study either if they had ST-segment elevation of 2 mm or more in two anterior leads or if they had ST-segment elevation of 1 mm or more in two inferior leads and at least one of the following high-risk characteristics: systolic blood pressure of less than 100 mm Hg, heart rate of more than 100 bpm, Killip class II or III, ST-segment depression of 2 mm or more in the anterior leads, or ST-segment elevation of 1 mm or more in right-sided lead V₄ (V₄R), which is indicative of right ventricular involvement. Key exclusion criteria included cardiogenic shock before randomization, PCI within the previous month, previous coronary-artery bypass surgery, and the availability of primary PCI with an anticipated door-to-balloon time of less than 60 minutes. All participants provided written informed consent.

INTERVENTIONS

All patients received tenecteplase, aspirin, and unfractionated heparin or enoxaparin in the emergency department. The protocol was amended in April 2005 to strongly recommend concomitant treatment with clopidogrel at the time of fibrinolysis (at an initial dose of either 300 mg for participants 75 years of age or younger or 75 mg for participants older than 75 years of age). Patients older than 75 years of age did not receive enoxaparin.

Patients were randomly assigned to either the group that received routine early PCI (hereinafter termed the early-PCI group) or the group that received standard treatment. Randomization was performed by the coordinating center (or in the case of Manitoba, by a physician delegated by the coordinating center) and was stratified according to the referring site and the patient's age (older than 75 years of age vs. 75 years of age or younger). Patients who were assigned to the early-PCI group were then transferred urgently to a PCI cen-

ter with the goal of performing coronary angiography and PCI of the infarct-related artery within 6 hours after fibrinolysis. PCI was performed when persistent occlusion or substantial stenosis of the infarct-related artery (either stenosis of 70% or more of the diameter of the artery or stenosis of 50 to 70% with thrombus, ulceration, or spontaneous dissection) was present.

Among patients assigned to the standard-treatment group, 12-lead electrocardiography was repeated 60 to 90 minutes after randomization; patients with persistent ST-segment elevation (i.e., a decrease in ST-segment elevation of less than 50%) and chest pain or with hemodynamic instability were transferred to another hospital for rescue PCI. All other patients in the standard-treatment group remained at their presenting hospital for at least 24 hours. It was recommended that patients undergo cardiac catheterization within 2 weeks after randomization, an approach that is consistent with the standards of practice at participating sites.

Stents were implanted during PCI whenever technically possible, and the use of Multi-Link Vision and Multi-Link Mini Vision cobalt chromium bare-metal stents, provided free of charge by Abbott Vascular Canada, was encouraged. The protocol allowed for the use of glycoprotein IIb/IIIa antagonists during PCI and for 12 hours (if abciximab was the agent used) or 18 hours (if eptifibatid was used) after PCI at the discretion of the interventional cardiologist.

END POINTS

The primary end point of the study was the combined incidence of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days. Secondary end points included death or reinfarction at 6 months and the incidence of bleeding complications, classified with the use of both the Thrombolysis in Myocardial Infarction (TIMI) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) severity scales.^{14,15}

During the first 18 hours after enrollment, reinfarction was diagnosed on the basis of recurrent ST-segment elevation and recurrent chest pain lasting at least 30 minutes. After 18 hours, the diagnosis of reinfarction required that there be an elevation in the MB fraction of creatine kinase to

higher than the upper limit of the normal range (more than three times the upper limit of normal after PCI and more than five times the upper limit of normal after coronary-artery bypass surgery) or new Q waves. Recurrent ischemia was defined as chest pain lasting 5 minutes or longer associated with ST-segment or T-wave changes. New or worsening heart failure was defined as heart failure that required treatment 6 hours or more after enrollment and either pulmonary edema on a chest radiograph, rales, or a pulmonary-capillary wedge pressure greater than 18 mm Hg. A diagnosis of cardiogenic shock was made when the systolic blood pressure remained at less than 90 mm Hg without inotropic support or when inotropic support was required to maintain systolic blood pressure above 90 mm Hg and there was clinical evidence of hypoperfusion. All non-fatal components of the primary end point were adjudicated by a clinical events committee whose members were unaware of treatment-group assignments.

STATISTICAL ANALYSIS

Assuming an event rate for the primary end point of 21% with the standard-treatment strategy and a 5% loss to follow-up, we estimated that a sample size of 1200 patients would be needed for the study to have 80% power to show a relative risk reduction of 30% with the early-PCI strategy, at an alpha level of 0.05. However, in November 2007, the steering committee decided to stop enrollment at the end of December 2007 owing to slowing enrollment, lack of additional funding, and loss to follow-up that was lower than anticipated.

An interim safety analysis was performed by the data safety and monitoring committee on data from the first 536 patients, and the committee identified no safety concerns. No interim efficacy analysis was performed.

All comparisons between the two treatment groups are based on the intention-to-treat principle. All statistical tests were performed at a significance level of 0.05 (two-sided) and have not been adjusted for multiple testing. Categorical variables are summarized with the use of absolute frequencies and percentages, and numerical variables with the use of medians and interquartile ranges. Between-group comparisons of the baseline characteristics and of the pretreatment evaluations were made to assess the similarity of the

two treatment groups. Categorical variables were compared with the use of the Pearson chi-square test (Fisher's exact test was applied if the number of observations per cell was fewer than five). After assessment of normality with the Kolmogorov–Smirnov test, nonparametric tests (Wilcoxon rank-sum tests) were performed for the comparison of numerical variables between the two treatment groups.

Between-group comparisons of the cumulative

event rate at 30 days for the primary combined end point and its components were performed with the Pearson chi-square test or Fisher's exact test. The time to the primary combined end point was analyzed with the use of the Kaplan–Meier method. The cumulative rates of death and of death or reinfarction at 6 months were compared between the treatment groups with the use of the chi-square test. The time to these end points was analyzed with the use of the Kaplan–Meier meth-

Table 1. Baseline Characteristics of the Two Groups.*

Variable	Standard Treatment (N=522)	Routine Early PCI (N=537)	P Value
Age — yr			
Median	56	57	0.45
Interquartile range	50–66	51–66	
Age >75 yr — no. (%)	46 (8.8)	52 (9.7)	0.62
Female sex — no. (%)	105 (20.1)	111 (20.7)	0.82
Prior congestive heart failure — no. (%)	11 (2.1)	3 (0.6)	0.03
Prior myocardial infarction — no. (%)	51 (9.8)	59 (11.0)	0.52
Prior PCI — no. (%)	22 (4.2)	34 (6.3)	0.12
Prior stroke or transient ischemic attack — no. (%)	5 (1.0)	16 (3.0)	0.02
History of smoking — no./total no. (%)	316/519 (60.9)	332/533 (62.3)	0.64
Hypertension — no. (%)	178 (34.1)	173 (32.2)	0.52
Dyslipidemia — no. (%)	149 (28.5)	147 (27.4)	0.67
Diabetes — no. (%)	80 (15.3)	79 (14.7)	0.78
Weight — kg†			
Median	80	80	0.68
Interquartile range	70–91	70–90	
Blood pressure — mm Hg‡			
Systolic			
Median	145	145	0.67
Interquartile range	130–160	130–164	
Diastolic			
Median	84	84	0.85
Interquartile range	74–96	73–95	
Heart rate — bpm§			
Median	77	74	0.06
Interquartile range	66–90	63–88	
Killip class — no./total no. (%)			0.39
I	480/522 (92.0)	488/535 (91.2)	
II	37/522 (7.1)	36/535 (6.7)	
III	4/522 (0.8)	6/535 (1.1)	
IV	1/522 (0.2)	5/535 (0.9)	

Table 1. (Continued.)

Variable	Standard Treatment (N = 522)	Routine Early PCI (N = 537)	P Value
ST-segment elevation — no. (%)			
Anterior	271 (51.9)	302 (56.2)	0.16
Inferior¶	250 (47.9)	236 (43.9)	0.20
With systolic BP <100 mm Hg	48 (9.2)	52 (9.7)	0.79
With heart rate >100 bpm	29 (5.6)	28 (5.2)	0.81
With Killip class II or III	17 (3.3)	13 (2.4)	0.41
With ≥2-mm ST depression in the anterior leads	162 (31.0)	157 (29.2)	0.52
With ≥1-mm ST elevation in lead V ₄ R	101 (19.3)	96 (17.9)	0.54
Time from symptom onset to administration of tenecteplase — min			
Median	115	113	0.72
Interquartile range	75–191	74–182	
Time from hospital presentation to administration of tenecteplase — min‡			
Median	25	27	0.07
Interquartile range	16–41	17–44	

* BP denotes blood pressure, PCI percutaneous coronary intervention, and V₄R right-sided lead V₄.

† Data were calculated on the basis of 521 patients in the standard-treatment group and 536 in the early-PCI group.

‡ Data were calculated on the basis of 522 patients in the standard-treatment group and 536 in the early-PCI group.

§ Data were calculated on the basis of 521 patients in the standard-treatment group and 535 in the early-PCI group.

¶ To qualify for participation in the trial, patients presenting with inferior ST-segment elevation were required to have at least one of the following high-risk characteristics: systolic blood pressure less than 100 mm Hg, heart rate more than 100 bpm, Killip class II or III, ST-segment depression of 2 mm or more in the anterior leads, or ST-segment elevation of 1 mm or more in lead V₄R.

|| Data were calculated on the basis of 522 patients in the standard-treatment group and 535 in the early-PCI group.

od. The incidence of bleeding complications during the index hospitalization, as assessed according to the TIMI and GUSTO classifications of bleeding severity, was compared with the use of the Pearson chi-square test or Fisher's exact test.

RESULTS

PATIENTS

From July 10, 2004, through December 27, 2007, 1059 patients were randomly assigned to the standard-treatment group (522 patients) or the early-PCI group (537 patients). Baseline characteristics were well balanced between the two groups except that there was a higher prevalence of previous stroke or transient ischemic attack in the early-PCI group than in the standard-treatment group and a higher prevalence of previous congestive heart failure in the standard-treatment group than in the early-PCI group (Table 1).

PROCEDURES

Cardiac catheterization was performed in 88.7% of the patients in the standard-treatment group at a median of 32.5 hours after randomization and in 98.5% of the patients in the early-PCI group at a median of 2.8 hours after randomization (Table 2 and Fig. 1). PCI was performed in 67.4% of the patients in the standard-treatment group at a median of 21.9 hours after randomization and in 84.9% of the patients in the early-PCI group at a median of 3.2 hours after randomization.

Urgent catheterization was performed within 12 hours after fibrinolysis in 182 (34.9%) of the patients in the standard-treatment group (Fig. 1). The indications for urgent catheterization among these patients included reinfarction (20 patients), cardiogenic shock (7), new or worsening heart failure (2), recurrent ischemia (3), and persistent chest pain, ST-segment elevation, or both (131). In the case of the remaining 19 patients, the in-

dication for urgent catheterization was not documented.

Stents were implanted in 98.3% of the patients who underwent PCI, and glycoprotein IIb/IIIa antagonists were administered in 82.5%. Aside from a higher rate of clopidogrel use in the early-PCI group, the use of evidence-based medical therapy was similar between the treatment groups.

EFFICACY OUTCOMES

A follow-up evaluation at 30 days was completed for all patients in the standard-treatment group

and all but one patient in the early-PCI group (99.9% overall). The clinical end points are shown in Table 3. The primary end point occurred in 11.0% of the patients in the early-PCI group and in 17.2% of the patients in the standard-treatment group (relative risk with early PCI, 0.64; 95% confidence interval [CI], 0.47 to 0.87; $P=0.004$) (Fig. 2). There were also significantly lower rates in the early-PCI group than in the standard-treatment group of recurrent ischemia (0.2% vs. 2.1%) and new or worsening congestive heart failure (3.0% vs. 5.6%). Fewer episodes of reinfarction were seen

Table 2. Interventions Used in the Two Groups.*

Intervention	Standard Treatment (N=522)	Routine Early PCI (N=537)	P Value
Drug therapy			
Before admission or within the first 6 hr — no. (%)			
Aspirin	509 (97.5)	525 (97.8)	0.79
Clopidogrel	359 (68.8)	475 (88.5)	<0.001
With fibrinolysis — no. (%)			
Unfractionated heparin	239 (45.8)	266 (49.5)	0.22
Enoxaparin	282 (54.0)	269 (50.1)	0.20
At discharge — no./total no. (%) [†]			
Aspirin	468/506 (92.5)	487/513 (94.9)	0.11
Clopidogrel	412/506 (81.4)	463/513 (90.3)	<0.001
Beta-blocker	432/506 (85.4)	462/513 (90.1)	0.02
ACE inhibitor or angiotensin-receptor blocker	409/506 (80.8)	425/513 (82.8)	0.40
Statin	453/506 (89.5)	463/513 (90.3)	0.70
Cardiac catheterization			
Total — no. (%)	463 (88.7)	529 (98.5)	<0.001
Time from randomization to insertion of arterial sheath — hr [‡]			
Median	32.5	2.8	<0.001
Interquartile range	4.0–69.1	2.2–3.8	
Single-vessel coronary artery disease — no./total no. (%)	216/463 (46.7)	227/529 (42.9)	0.24
Infarct-related coronary artery — no./total no. (%)			
Left anterior descending	228/463 (49.2)	277/529 (52.4)	0.33
Right	163/463 (35.2)	190/529 (35.9)	0.82
Left circumflex	50/463 (10.8)	50/529 (9.5)	0.48
Left main	2/463 (0.4)	4/529 (0.8)	0.51
Baseline TIMI flow — no./total no. (%)			
0	83/405 (20.5)	88/511 (17.2)	
1	37/405 (9.1)	68/511 (13.3)	
2	56/405 (13.8)	89/511 (17.4)	
3	229/405 (56.5)	266/511 (52.1)	

Table 2. (Continued.)			
Intervention	Standard Treatment (N = 522)	Routine Early PCI (N = 537)	P Value
PCI			
Total — no. (%)	352 (67.4)	456 (84.9)	<0.001
Time from randomization to first balloon inflation — hr [‡]			
Median	21.9	3.2	<0.001
Interquartile range	3.9–73.8	2.5–4.2	
Time from administration of tenecteplase to first balloon inflation — hr [¶]			
Median	22.7	3.9	<0.001
Interquartile range	4.5–74.3	3.1–4.9	
Access — no./total no. (%)			
Femoral	285/349 (81.7)	382/455 (84.0)	0.39
Radial	64/349 (18.3)	73/455 (16.0)	0.39
Thrombectomy — no./total no. (%)	11/352 (3.1)	19/456 (4.2)	0.44
Stent implanted — no./total no. (%)			
≥1 bare-metal	264/352 (75.0)	377/456 (82.7)	0.008
≥1 drug-eluting	97/352 (27.6)	80/456 (17.5)	<0.001
Glycoprotein IIb/IIIa inhibitor use — no. (%)	286/352 (81.2)	381/456 (83.6)	0.39
Time from administration of tenecteplase to infusion of glycoprotein IIb/IIIa inhibitor — hr			
Median	12.4	3.8	<0.001
Interquartile range	4.2–68.3	3.0–4.8	
Duration of glycoprotein IIb/IIIa inhibitor infusion — hr			
Median	13.8	12.1	<0.001
Interquartile range	12.0–18.1	11.9–16.8	
Final TIMI flow — no./total no. (%)			
0	3/339 (0.9)	2/451 (0.4)	0.58
1	3/339 (0.9)	4/451 (0.9)	
2	12/339 (3.5)	24/451 (5.3)	
3	321/339 (94.7)	421/451 (93.3)	
Coronary-artery bypass grafting — no. (%)	45 (8.6)	38 (7.1)	0.35

* ACE denotes angiotensin-converting enzyme, PCI percutaneous coronary intervention, and TIMI Thrombolysis in Myocardial Infarction.

[†] The total number represents the number of patients who were discharged alive.

[‡] Data were from 449 patients in the standard-treatment group and 528 in the early-PCI group.

[§] Data were from 348 patients in the standard-treatment group and 455 in the early-PCI group.

[¶] Data were from 348 patients in the standard-treatment group and 454 in the early-PCI group.

with routine early PCI than with standard treatment (3.4% vs. 5.7%), but this trend was not significant.

Information on death and reinfarction at 6 months was available for 1039 patients (98.1%). At 6 months, the rates of reinfarction and of death or reinfarction did not differ significantly between the two groups (Table 3 and Fig. 3).

ADVERSE EVENTS

Complications requiring treatment developed during transfer in 3.0% of the patients in the standard-treatment group who were transferred to a PCI facility and in 2.4% of the patients in the early-PCI group (all of whom were transferred to a PCI facility). The most common complication was hypotension. The only death that occurred during

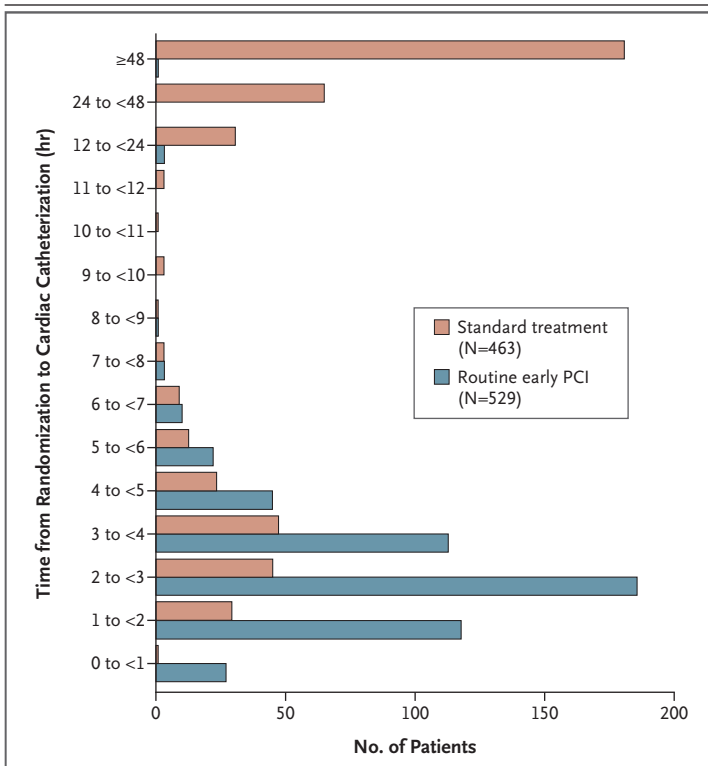


Figure 1. Time from Randomization to Cardiac Catheterization in the Two Treatment Groups.

PCI denotes percutaneous coronary intervention.

transfer was of a patient in the standard-treatment group who was being transferred for rescue PCI.

There were more mild bleeding events, as assessed according to the GUSTO criteria, with the early-PCI strategy than with the standard-treatment strategy (13.0% vs. 9.0%, $P=0.04$) but there were no significant differences in the rates of major or minor bleeding as assessed according to the TIMI criteria, moderate or severe bleeding as assessed according to the GUSTO criteria, transfusions, or intracranial hemorrhage. There were more deaths and episodes of cardiogenic shock at 30 days and more deaths at 6 months with the early-PCI strategy than with the standard-treatment strategy; however, the rates did not differ significantly.

DISCUSSION

In this trial, we compared a strategy of prompt interhospital transfer for early PCI after fibrinolysis with a standard strategy of transfer for PCI only in cases in which fibrinolytic therapy has

failed among 1059 patients presenting with ST-elevation myocardial infarction who could not undergo timely primary PCI. The primary end point, a composite of death, reinfarction, recurrent ischemia, congestive heart failure, or cardiogenic shock at 30 days, occurred significantly less frequently with early PCI than with standard therapy. No significant differences in the rates of major bleeding or transfusion were seen.

Trials of early PCI after fibrinolysis that were performed in the time before stents were used did not show a clinical benefit of this strategy and showed higher rates of major bleeding complications.¹⁶ In one trial, there was a trend to higher mortality with early PCI.⁶ One explanation that was proposed for the lack of benefit was that there is a risk of reocclusion after standard balloon angioplasty.¹⁷ The implantation of coronary stents and the use of glycoprotein IIb/IIIa antagonists and thienopyridines reduce the incidence of reocclusion after successful PCI.¹⁸⁻²⁰ It is also possible that higher rates of bleeding episodes with early PCI may have offset any benefit achieved with this intervention. Bleeding rates after PCI have been reduced with the use of smaller sheaths, earlier removal of sheaths, radial access, the administration of lower doses of anticoagulants, and the elimination of postprocedural heparin infusions.²¹ The use of highly fibrin-specific fibrinolytic agents such as tenecteplase is associated with lower rates of noncerebral bleeding.²² Furthermore, the rates of emergency coronary-artery bypass surgery after PCI have dropped dramatically since the use of coronary stents has become routine.²³ All these advances have made PCI safer and more effective when performed early after fibrinolysis.

Trials performed after widespread use of stents became routine have shown encouraging results for PCI performed early after fibrinolysis.^{8-10,24-26} Our results are consistent with those of smaller trials and meta-analyses of trials in which contemporary PCI techniques and pharmacotherapy were used.^{8-10,16,24-28} Our findings are similar to those seen in the recent Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction trial (CARESS-in-AMI; ClinicalTrials.gov number, NCT00220571), in which a half-dose of reteplase combined with abciximab was used as the initial reperfusion therapy.²⁶ The results of that trial, together with those of our study, suggest that, in order to be effective, such strategies would probably require adequate antiplatelet ther-

Table 3. Clinical End Points.*

End Point	Standard Treatment (N=522)	Routine Early PCI (N=536) [†]	Relative Risk with Routine Early PCI (95% CI)	P Value
Efficacy end points at 30 days — no. (%)				
Primary end point [‡]	90 (17.2)	59 (11.0)	0.64 (0.47–0.87)	0.004
Death	18 (3.4)	24 (4.5)	1.30 (0.71–2.36)	0.39
Reinfarction	30 (5.7)	18 (3.4)	0.57 (0.33–1.04)	0.06
Death or reinfarction	47 (9.0)	38 (7.1)	0.79 (0.52–1.19)	0.25
Recurrent ischemia	11 (2.1)	1 (0.2)	0.09 (0.01–0.68)	0.003
Death, reinfarction, or recurrent ischemia	58 (11.1)	39 (7.3)	0.65 (0.44–0.96)	0.03
New or worsening congestive heart failure	29 (5.6)	16 (3.0)	0.54 (0.30–0.98)	0.04
Cardiogenic shock	16 (3.1)	24 (4.5)	1.46 (0.79–2.72)	0.23
Efficacy end points at 6 mo — no./total no. (%)				
Death	23/511 (4.5)	30/528 (5.7)	1.27 (0.77–2.23)	0.39
Reinfarction	33/511 (6.5)	21/528 (4.0)	0.60 (0.34–1.05)	0.07
Death or reinfarction	54/511 (10.6)	47/528 (8.9)	0.83 (0.55–1.25)	0.36
Safety end points during index hospitalization — no. (%)				
Any bleeding	84 (16.1)	110 (20.5)	1.27 (0.98–1.65)	0.06
Intracranial hemorrhage	6 (1.1)	3 (0.6)	0.49 (1.22–1.93)	0.34
Bleeding at access site	18 (3.4)	27 (5.0)	1.46 (0.81–2.61)	0.20
TIMI bleeding				
Minor	17 (3.3)	26 (4.8)	1.49 (0.82–2.71)	0.19
Major	47 (9.0)	40 (7.4)	0.83 (0.55–1.24)	0.36
Major, non-CABG-related	25 (4.8)	18 (3.4)	0.70 (0.39–1.27)	0.24
GUSTO bleeding				
Mild	47 (9.0)	70 (13.0)	1.45 (1.02–2.05)	0.04
Moderate	29 (5.6)	34 (6.3)	1.14 (0.70–1.84)	0.59
Severe	8 (1.5)	6 (1.1)	0.73 (0.25–2.09)	0.55
Severe, non-CABG-related	7 (1.3)	5 (0.9)	0.69 (0.22–2.17)	0.53
Major TIMI or severe GUSTO bleeding	47 (9.0)	40 (7.4)	0.83 (0.55–1.24)	0.36
Transfusion	32 (6.1)	40 (7.4)	1.22 (0.78–1.90)	0.39

* CABG denotes coronary-artery bypass grafting, CI confidence interval, GUSTO Global Use of Strategies to Open Occluded Coronary Arteries, PCI percutaneous coronary intervention, and TIMI Thrombolysis in Myocardial Infarction.

[†] In this group, the efficacy end points were calculated on the basis of 536 patients because 1 patient was lost to follow-up at 30 days. The safety end points were calculated on the basis of all 537 patients in the group.

[‡] The primary end point was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days.

apy with either glycoprotein IIb/IIIa antagonists combined with reduced-dose fibrinolysis or clopidogrel combined with full-dose fibrinolysis and the liberal use of glycoprotein IIb/IIIa antagonists during PCI.

The strategy of PCI performed a few hours after fibrinolysis — which was evaluated in our

trial — should be distinguished from the strategy of PCI performed immediately after fibrinolysis, an approach that has been termed facilitated PCI.²⁹ Clinical trials of facilitated PCI have shown increased rates of bleeding and no clinical benefit with that strategy as compared with primary PCI alone.^{30,31} Although the reasons for these disap-

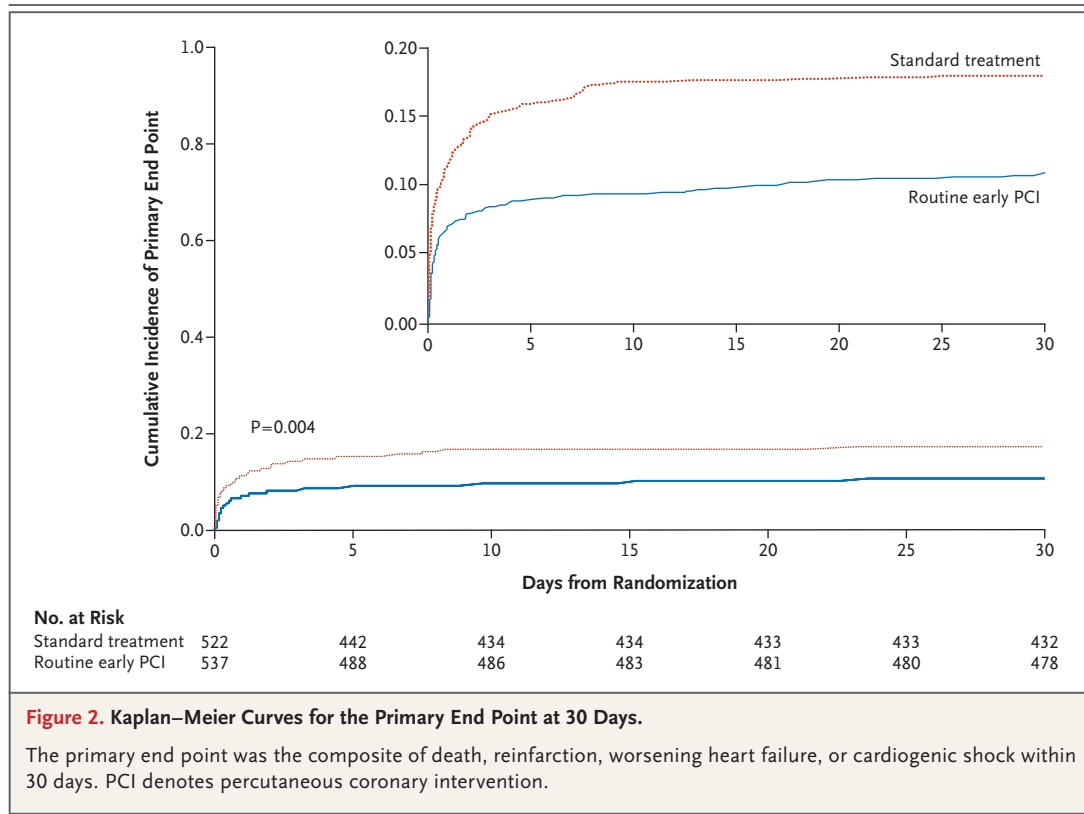


Figure 2. Kaplan–Meier Curves for the Primary End Point at 30 Days.

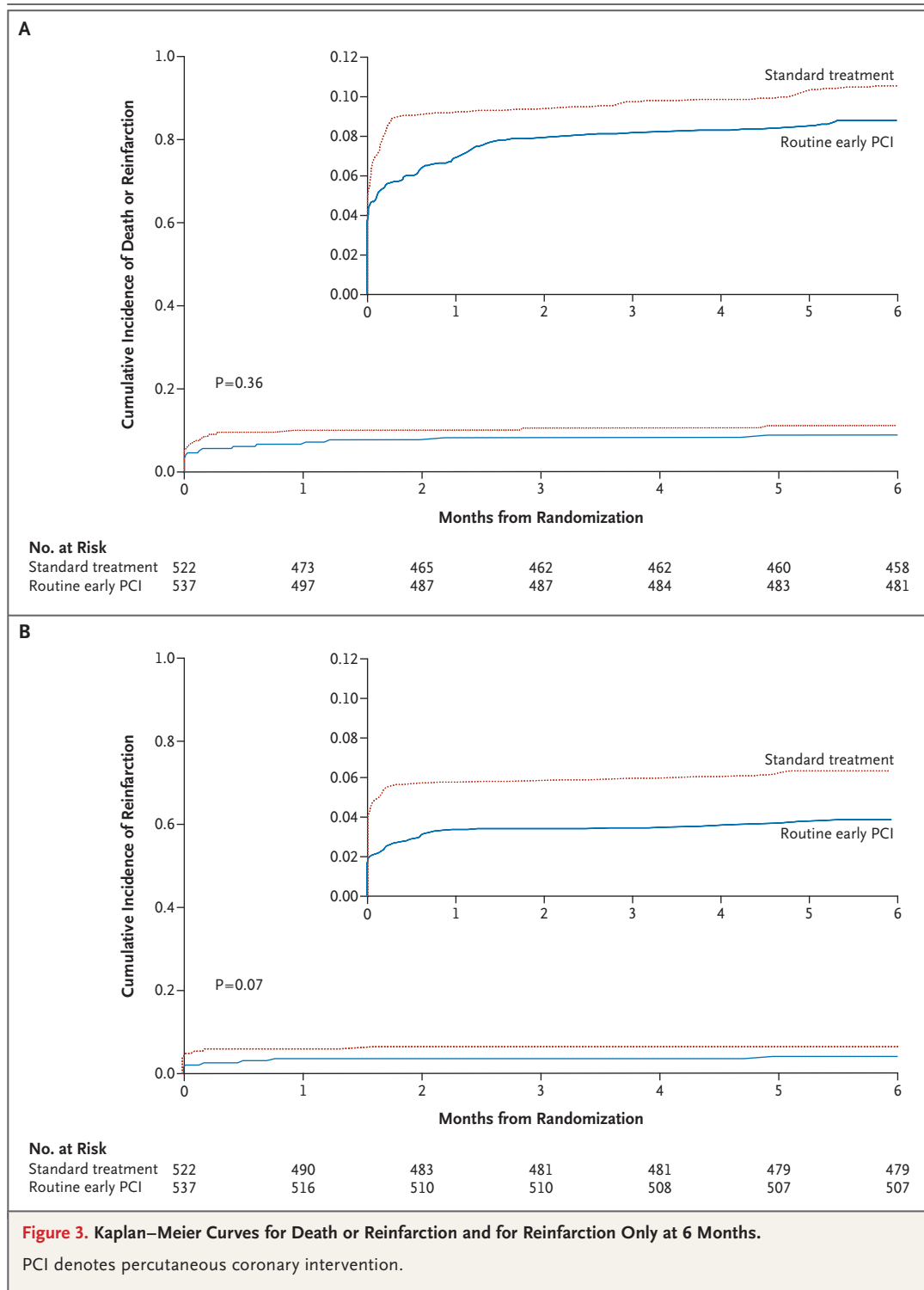
The primary end point was the composite of death, reinfarction, worsening heart failure, or cardiogenic shock within 30 days. PCI denotes percutaneous coronary intervention.

pointing findings remain speculative, it is possible that the time between fibrinolysis and PCI (median, 90 to 104 minutes) was too short in these trials, with the result that persistent fibrinolytic activity led to increased bleeding complications. The lack of adequate antiplatelet therapy in these trials may have also conferred a predisposition to thrombotic complications. Fibrinolysis is followed by increased platelet activation and aggregation, and stent implantation early after fibrinolysis without adequate antiplatelet therapy may be associated with increased rates of acute stent thrombosis.³² However, if the delay between fibrinolysis and PCI is too long, patients are exposed to the risk of reinfarction and recurrent ischemia while they await PCI, and patients in whom reperfusion after fibrinolysis is not successful may not be able to undergo rescue PCI quickly enough to salvage myocardium. Therefore, the goal in our trial was to perform catheterization and PCI within 6 hours after fibrinolysis; the actual median interval from lysis to balloon inflation in our study was 3.9 hours (interquartile range, 3.1 to 4.9).

Our trial enrolled patients only at centers that did not perform PCI; these patients could not un-

dergo timely primary PCI and were therefore treated with fibrinolysis. The strategy of fibrinolysis followed by routine early PCI was not directly compared with the strategy of primary PCI in this trial. Current guidelines recommend primary PCI for patients who can undergo coronary intervention within 90 minutes after presentation.⁴

This trial was not powered to detect differences in mortality. There were six more deaths in the early-PCI group than in the standard-treatment group at 30 days, and seven more in the early-PCI group than in the standard-treatment group at 6 months, but the rates did not differ significantly. However, since five of the patients in the early-PCI group who died were in Killip class IV before randomization (despite the fact that cardiogenic shock was an exclusion criterion), this difference may have been due to a chance occurrence that there were more patients with cardiogenic shock before enrollment in the early-PCI group than there were in the standard-treatment group. A recent meta-analysis of contemporary trials (not including TRANSFER-AMI) has shown that there are significantly lower mortality and reinfarction rates with routine early PCI after fibrinolysis



than with a more conservative ischemia-guided approach.²⁷

Our trial was also underpowered to detect differences in the other individual components of the

primary end point. It could be argued that a reduction in the rate of recurrent ischemia alone does not necessarily justify the strategy of routine early PCI after successful fibrinolysis, since pre-

sumably a patient can be transferred for elective or urgent PCI if ischemia recurs. The benefit of routine early PCI with respect to new or worsening heart failure must be considered to be of uncertain significance, since new or worsening heart failure is only one of several secondary end points evaluated. The trend toward a reduction in the rate of reinfarction with routine early PCI was not significant.

An alternative to the approach used in this trial would be a strategy of prompt transfer to a PCI center after fibrinolysis, followed by the selective use of PCI for only those patients with failed reperfusion or subsequent ischemic complications. This strategy, which might be designated “transfer and wait,” was not studied in our trial. In our trial, nearly a third of the patients in the standard-therapy group underwent urgent catheterization within 12 hours after fibrinolysis, suggesting that a substantial number of patients for whom a transfer-and-wait strategy would be adopted (at least patients with a similar risk profile to that of our trial population) would require intervention.

In conclusion, among patients presenting with a myocardial infarction with ST-segment elevation who could not undergo timely primary PCI, we compared a strategy of prompt interhospital transfer for early PCI after fibrinolysis with a standard strategy of transfer for PCI only when fibrinolysis fails. The primary end point, a composite

of death, reinfarction, recurrent ischemia, congestive heart failure, or cardiogenic shock at 30 days, occurred significantly less frequently with the early-PCI strategy than with standard therapy.

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APPENDIX

The following investigators participated in the TRANSFER-AMI Trial: **Trial Organization:** Steering Committee: W. Cantor (principal investigator), S. Goodman (study chair), D. Fitchett, A. Langer, B. Borgundvaag, M. Heffernan, J. Ducas, E. Cohen, V. Dzavik, S. Mehta, C. Lazzam, L. Morrison, B. Schwartz; *Data Safety Monitoring Committee:* E.M. Ohman (chair), P. Berger, C. Buller, K. Pieper; *Clinical Events Committee:* D. Fitchett (chair), T. Charron, S. Jolly, S. Goodman, W. Cantor; *Trial Hotline Pager Coverage:* A. Bagnall, B. Borgundvaag, J. Burstein, W. Cantor, T. Charron, N. Fam, D. Fitchett, A. Georgescu, L. Goldman, S. Goodman, J. Graham, Q. Hassan, M. Heffernan, S. Kassam, H.H. Kim, M. Prabhakar, T. Sheth, J. Syed, A. Uxa, R. Vijayaraghavan, J. Wawrzyniak, H. Wijeyesundera, A. Yan. **Coodinating Center:** *Canadian Heart Research Centre:* M. Tan, G. Obispo, G. Escobilla, S. Francis, J. Wawrzyniak, A. Georgescu, Q. Hussan, D. Camara, P. Singh, A. Gebru, M. Oh, D. Minott, C. Spindler, M. Datoo, O. Kornilova, M. Dinulos. **Sponsors:** Canadian Institutes of Health Research (CIHR), Roche, Canada, Abbott Vascular Canada. **Participating Sites:** *PCI Sites:* St. Michael's Hospital: S. Goodman, W. Cantor, B. Zile, J. Wawrzyniak, A. Fry; *Trillium Health Centre:* C. Lazzam, A. Carter; *Sunnybrook Health Sciences Centre:* E. Cohen, L. Balleza, E. Hsu; *Saint Boniface Hospital:* J. Ducas, S.L. Aceves, A. Munoz; *Toronto General Hospital:* V. Dzavik, A. Patel, D. Atchison; *Southlake Regional Health Centre:* S. Miner, K. Robbins; *Rouge Valley Centenary:* S.A. Kassam, B. Hart, B. Bozek; *St. Mary's General Hospital:* H.H. Kim, I. Janzen; *Hamilton Health Sciences:* S.R. Mehta, S. Brons; *London Health Sciences Centre:* K. Sridhar, T. Oke; *Hôpital de Mont Laurier:* E. Schampaert, C. Mercure. **Referring Sites:** *Credit Valley Hospital:* P. Pageau, M. Maingi, R. Durdos; *St. Joseph's Health Centre:* R. Choi, M. Duic, C. Vardy, D. Wilkinson, A. Buss; *North York General Hospital:* B.J. Lubelsky, L. Sommer, J. Coldwell; *Rouge Valley Ajax Pickering Hospital:* J. Burstein, S. Dhingra, D. Hancock, C. Harrison, T. Eymann; *Scarborough General Hospital:* J.M. Cherry, G. Vertes, G. Pape, B. Ross, M. Tam; *Royal Victoria Hospital:* B. Burke, S. Snow; *Scarborough Grace Hospital:* W.H.P. Kong, J. Butchey, D. Hutton; *William Osler Health Centre Etobicoke:* A. Lee, D. Borts, M. Coons; *Lakeridge Health Centre Oshawa:* R. Bhargava, R. Vandersluis, T. Novak, J. Easton, J. Bouwmeester, L. Lafance; *William Osler Health Centre Brampton:* A. Lee, D. Borts, M. Kajil; *Oakville Trafalgar Memorial Hospital:* M. Heffernan, L. Martin, R. Franks; *Rouge Valley Scarborough Centenary:* S.A. Kassam, F. Moss, B. Hart, B. Bozak; *St. Catharines General Hospital:* S. Pallie, A. Sharma, S. Krekorian; *Toronto East General Hospital:* C. Lefkowitz, J. Tyberg, E. Klakowitz, N. Walters, M. Thornley; *Grace General Hospital:* J. Ducas, A. Munoz, S.L. Aceves; *Bluestar Health Sarnia General:* N. Ali, L. Robichaud; *Winnipeg Health Sciences Centre:* W. Palatnick, A. Munoz, S.L. Aceves; *Seven Oaks General Hospital:* R. de Faria, A. Munoz, S.L. Aceves; *Victoria General Hospital:* J. Ducas, A. Munoz, S.L. Aceves; *Ross Memorial Hospital:* N. Krishnan, C. McBride; *Notfolk General Hospital:* D. Kennedy, M. Robinson; *Huntsville District Memorial Hospital:* M. Mensour, S. Tumber; *Mount Sinai Hospital:* B. Borgundvaag, A. Barolet, M. Loftus; *Stratford General Hospital:* M. Mann, Y. Balmain, J. Gardiner; *Peterborough Regional Health Centre:* N.K. Greene, N. Turney; *West Haldimand General Hospital:* S. Chiu, K.J. Marshall; *Owen Sound Grey Bruce Health Services:* G. Kumar, M.

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REFERENCES

- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. *Lancet* 2003;361:13-20.
- Nallamothu BK, Bates ER, Herrin J, et al. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRM)-3/4 analysis. *Circulation* 2005;111:761-7.
- Bates ER, Nallamothu BK. Commentary: the role of percutaneous coronary intervention in ST-segment-elevation myocardial infarction. *Circulation* 2008;118:567-73.
- Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008;51:210-47. [Erratum, *J Am Coll Cardiol* 2008;51:977.]
- Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 2008;156:1035-44.
- Simoons ML, Arnold AE, Bietri A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1988;1:197-203.
- The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction — results of the Thrombolysis in Myocardial Infarction (TIMI) phase II trial. *N Engl J Med* 1989;320:618-27.
- Scheller B, Hennen B, Hammer B, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:634-41.
- Fernandez-Avilés F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomized controlled trial. *Lancet* 2004;364:1045-53.
- Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). *J Am Coll Cardiol* 2005;46:417-24.
- Armstrong PW, WEST Steering Committee. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. *Eur Heart J* 2006;27:1530-8.
- Cantor WJ, Fitchett D, Borgundvaag B, et al. Rationale and design of the Trial of Routine ANgioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI). *Am Heart J* 2008;155:19-25.
- Cantor WJ, Choi R, Heffernan M, et al. Transfer for urgent percutaneous coronary intervention immediately after thrombolysis for ST-elevation myocardial infarction: the Transfer-AMI pilot feasibility study. *Can J Cardiol* 2006;22:1121-6.
- Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;115:256-65.
- The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.
- Cantor WJ, Brunet F, Ziegler CP, Kiss A, Morrison LJ. Immediate angioplasty after thrombolysis: a systematic review. *CMAJ* 2005;173:1473-81.
- Arnold AE, Serruys PW, Rutsch W, et al. Reasons for the lack of benefit of immediate angioplasty during recombinant tissue plasminogen activator therapy for acute myocardial infarction: a regional wall motion analysis. *J Am Coll Cardiol* 1991;17:11-21.
- Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.
- Schömig A, Kastrati A, Mudra H, et al. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. *Circulation* 1994;90:2716-24.
- De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 2005;293:1759-65.
- Cantor WJ, Mahaffey KW, Huang Z, et al. Bleeding complications in patients with acute coronary syndrome undergoing early invasive management can be reduced with radial access, smaller sheath sizes, and timely sheath removal. *Catheter Cardiovasc Interv* 2007;69:73-83.
- Van de Werf F, Barron HV, Armstrong PW, et al. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: a comparison of TNK-tPA and rt-PA. *Eur Heart J* 2001;22:2253-61.
- Yang EH, Gumina RJ, Lennon RJ, Holmes DR Jr, Rihal CS, Singh M. Emergency coronary artery bypass surgery for percutaneous coronary interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. *J Am Coll Cardiol* 2005;46:2004-9.
- Fernández-Avilés F, Alonso JJ, Peña G, et al. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. *Eur Heart J* 2007;28:949-60.
- Bednár F, Widimský P, Krupicka J, Groch L, Aschermann M, Zelizko M. Interhospital transport for primary angioplasty improves the long-term outcome of acute myocardial infarction compared with immediate thrombolysis in the nearest hospital (one-year follow-up of the PRAGUE-1 study). *Can J Cardiol* 2003;19:1133-7.
- Di Mario C, Dudek D, Piscione F, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 2008;371:559-68.
- Wijesundera HC, You JJ, Nallamothu BK, Krumholz HM, Cantor WJ, Ko DT. An early invasive strategy versus ischemia-guided management after fibrinolytic therapy for ST-segment elevation myocardial infarction: a meta-analysis of contemporary randomized controlled trials. *Am Heart J* 2008;156:564-72.
- Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 2006;48:1326-35.
- Keeley EC, Boura JA, Grines CL. Com-

- parison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006; 367:579-88. [Erratum, *Lancet* 2006;367:1656.]
- 30.** Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;367:569-78.
- 31.** Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008;358:2205-17.
- 32.** Coulter SA, Cannon CP, Ault KA, et al. High levels of platelet inhibition with abciximab despite heightened platelet activation and aggregation during thrombolysis for acute myocardial infarction: results from TIMI (Thrombolysis In Myocardial Infarction) 14. *Circulation* 2000; 101:2690-5.

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