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Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI Study)

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OBJECTIVES We compared a strategy of tenecteplase (TNK)-facilitated angioplasty with one of TNK alone in patients presenting with high-risk ST-segment elevation myocardial infarction (STEMI).

BACKGROUND Previous trials show that thrombolysis followed by immediate angioplasty for the treatment of STEMI does not improve ischemic outcomes compared with thrombolysis alone and is associated with excessive bleeding complications. Since the publication of these trials, however, significant pharmacological and technological advances have occurred.

METHODS We randomized 170 patients with high-risk STEMI to treatment with TNK alone (84 patients) or TNK-facilitated angioplasty (86 patients). The primary end point was a composite of death, reinfarction, recurrent unstable ischemia, or stroke at six months.

RESULTS At six months, the incidence of the primary end point was 24.4% in the TNK-alone group versus 11.6% in the TNK-facilitated angioplasty group ($p = 0.04$). This difference was driven by a reduction in the rate of recurrent unstable ischemia (20.7% vs. 8.1%, $p = 0.03$). There was a trend toward a lower reinfarction rate with TNK-facilitated angioplasty (14.6% vs. 5.8%, $p = 0.07$). No significant differences were observed in the rates of death or stroke. Major bleeding was observed in 7.1% of the TNK-alone group and in 8.1% of the TNK-facilitated angioplasty group ($p = 1.00$).

CONCLUSIONS In patients presenting with high-risk STEMI, TNK plus immediate angioplasty reduced the risk of recurrent ischemic events compared with TNK alone and was not associated with an increase in major bleeding complications. (J Am Coll Cardiol 2005;46:417–24) © 2005 by the American College of Cardiology Foundation

Early, complete, and sustained reperfusion of the infarct-related artery (IRA) improves survival in patients presenting with ST-segment elevation myocardial infarction (STEMI) (1–3). Reperfusion with thrombolysis or percutaneous coronary intervention (PCI) is the current standard of care for STEMI (4). The advantages of the former are ease of administration and widespread availability. Although fibrin-specific thrombolytic agents can achieve early patency of the IRA, complete flow is restored in only 60% of patients (5). Angioplasty accomplishes this in up to 95% of patients and is associated with a lower rate of re-occlusion (5); however, delays associated with patient transfer and catheterization team mobilization, plus the limited accessibility to catheterization facilities, might significantly prolong the time to mechanical reperfusion.

Combining these strategies has the potential to provide the speed of pharmacological reperfusion with the more complete and sustained reperfusion provided by PCI. Although previous trials found this approach was complicated by increased bleeding, with no apparent clinical benefit compared with thrombolysis alone (6–8), these were performed without weight-adjusted bolus thrombolytic agents or coronary stents. These pharmacological and technological advances could alter the clinical outcomes. Therefore, we conducted a randomized multi-center trial, comparing thrombolysis alone to thrombolysis with immediate transfer for PCI.

METHODS

Patient selection. The study was conducted in four Ottawa hospitals, with the interventional facility located at the University of Ottawa Heart Institute. Patients presenting ≤6 h of the onset of chest discomfort of ≥30 min duration and having ≥1 mm ST-segment elevation in two or more contiguous leads or left bundle branch block on a 12-lead electrocardiogram were eligible if they had one of the

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Abbreviations and Acronyms

ACT = activated clotting time
ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent
CABG = coronary artery bypass graft surgery
IRA = infarct-related artery
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
TNK = tenecteplase

following high-risk criteria: 1) anterior infarction with ST-segment elevation ≥2 mm in each of two contiguous precordial leads; 2) extensive non-anterior infarction: eight or more leads with ≥1 mm ST-segment elevation or depression or both, or the sum of ST-segment elevation >20 mm; 3) Killip class 3; or 4) systolic blood pressure <100 mm Hg. The criteria for exclusion were active bleeding, history of stroke, or central nervous system damage, major surgery or trauma within three months, uncontrolled hypertension (systolic blood pressure ≥200 mm Hg and/or diastolic blood pressure ≥120 mm Hg), prolonged (>10 min) cardiopulmonary resuscitation, a blood coagulation disorder, current warfarin treatment, previous coronary artery bypass graft surgery (CABG), PCI within six months, glycoprotein IIb/IIIa inhibitors within seven days, ≥5,000 IU of unfractionated heparin within 6 h, a therapeutic dose of any low molecular weight heparin within six h, intolerance to aspirin, other illness likely to result in death within 12 months, pregnancy, a creatinine >300 μmol/l (3.40 mg/dl), cardiogenic shock, and severe contrast allergy. The protocol was approved by the institutional review board at each hospital; all patients provided informed consent.

Study design. All patients received 160 mg of chewable aspirin immediately, and aspirin 325 mg daily thereafter. Eligible patients were randomized to tenecteplase (TNK) alone or TNK followed by immediate transfer for PCI. All patients received weight-adjusted TNK and weight-adjusted unfractionated heparin as reported in the Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT)-3 trial (9).

In patients assigned to TNK-facilitated PCI, heparin was stopped upon arrival at the catheterization laboratory, and coronary angiography was performed as soon as possible. Angioplasty was performed unless angiography identified diffuse disease not amenable to revascularization or the IRA had Thrombolysis In Myocardial Infarction (TIMI) (10) flow grade 3 and <70% stenosis at the culprit site. Coronary stenting was performed using ACS Multilink Penta or Zeta stents (Guidant, Advanced Cardiovascular Systems Inc., Temecula, California). Angioplasty with balloon alone was performed if the IRA was small or if technical difficulties prevented delivery of a stent. Glycoprotein IIb/IIIa inhibitors were not routinely used. Bolus doses of heparin were used, targeting an activated clotting time (ACT) of 250 s. Heparin was not routinely reinitiated after the procedure. Patients received clopidogrel 300 mg as a single dose and 75 mg daily for at least one month. The femoral arterial approach without any closure device was used for cardiac catheterization and femoral sheaths were removed 8 to 12 h after the TNK bolus.

In patients assigned to TNK alone, indications for acute angiography were persistent chest pain and ST-segment elevation ≥90 min after initiation of thrombolysis or deteriorating hemodynamic status.

All patients had radionuclide ventriculography scheduled at one week and at 30 days, and exercise testing (Bruce protocol) at 30 days after randomization.

End points and definitions. The primary end point was a composite of death, recurrent myocardial infarction, recurrent unstable ischemia, or stroke at six months after randomization. Reinfarction was defined as recurrent ischemic symptoms at rest lasting ≥30 min and accompanied by: 1) new or recurrent ST-segment elevation of ≥1 mm in any contiguous leads; 2) new left bundle branch block; or 3) re-elevation in serum creatine kinase level to greater than twice the upper limit of normal and ≥50% above the lowest level measured after infarction. If reinfarction occurred within 18 h, enzyme criteria were not used. Recurrent unstable ischemia was defined as recurrent symptoms of ischemia at rest associated with new ST-segment or T-wave changes, hypotension, or pulmonary edema. Stroke was defined as a focal neurological deficit, compatible with damage in the territory of a major cerebral artery with signs or symptoms persisting for >24 h and was classified as hemorrhagic or non-hemorrhagic according to computerized tomography. Congestive heart failure was documented when any two of the following were present: 1) dyspnea; 2) pulmonary venous congestion with interstitial or alveolar edema on chest radiograph; 3) crackles greater than or equal to one-third of the way up the lung fields; and 4) third heart sound associated with tachycardia. Cardiogenic shock was defined as systolic blood pressure <80 mm Hg not responding to fluid expansion and requiring intravenous inotropic support or intra-aortic balloon counterpulsation. Episodes of bleeding were classified as minor or major according to the TIMI criteria (10). An independent monitor verified all data entry into the case-report forms against the patient's medical records. A blinded, independent clinical event committee adjudicated all possible events related to primary outcome, congestive heart failure, and shock. The Data Safety Monitoring Committee reviewed the data at regular intervals.

Statistical analysis. On the basis of previous reports (11–15), we anticipated that the occurrence of the primary end point would be 40% in the TNK alone group and 20% in the TNK-facilitated PCI group at six months (a 50% reduction). With a two-sided alpha of 5%, a power of 80%, and a non-adherence rate of 2% (14), a total of 170 patients (85 patients per group) were required. Statistical analysis was performed according to the intention-to-treat principle.

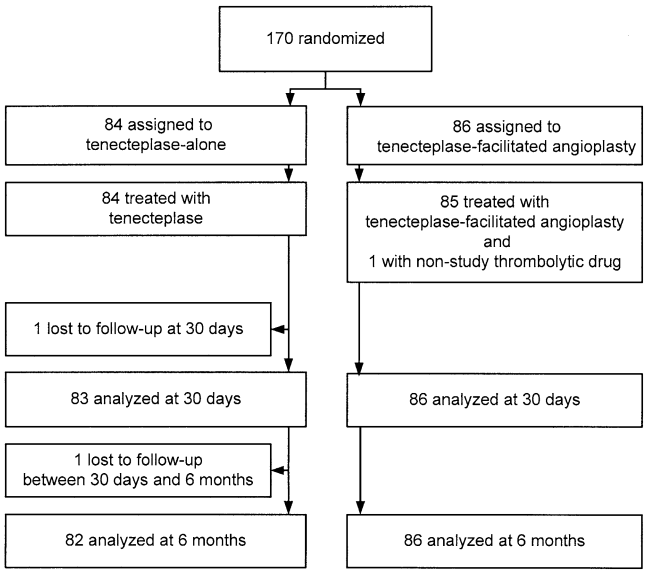

Figure 1. Randomization and disposition of patients.

Values for binary outcomes are reported as frequencies and percents with group comparisons using the Fisher exact test; values for continuous outcomes are reported as medians and interquartile ranges with group comparisons using the Mann-Whitney rank sum test; and time-to-event outcomes are reported using Kaplan-Meier curves with groups comparisons using the log-rank test. Two-sided tests and 95% confidence intervals were used. Analyses were performed with SAS statistical software (version 8.02, SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics of the patients. Between August 2001 and January 2004, 170 patients were enrolled: 84 were randomly assigned to TNK alone, and 86 to TNK-facilitated PCI. The details of randomization and disposition of the patients are outlined in Figure 1. The two treatment groups were well matched as to baseline characteristics (Table 1). The infarction location was anterior in 47.6% of patients assigned to TNK alone and anterior in 52.3% of the patients assigned to TNK-facilitated PCI.

Table 1. Baseline Characteristics of the Patients

	TNK-Alone Group (n = 84)	TNK-Facilitated Angioplasty Group (n = 86)	p Value
Age, yrs	58 (51, 66)	57 (50, 67)	0.82
Age ≥75 yrs	10.7	18.6	0.19
Male gender	76.1	75.6	1.00
Hypertension	44.0	44.2	1.00
Diabetes	11.9	20.9	0.15
Current smoking	63.1	54.7	0.28
Previous angina	16.7	23.2	0.34
Previous myocardial infarction	10.7	16.3	0.37
Previous angioplasty	3.6	5.8	0.72
Heart rate, beats/min	71 (60, 84)	73 (61, 85)	0.51
Systolic blood pressure, mm Hg	130 (119, 149)	128 (115, 148)	0.61
Diastolic blood pressure, mm Hg	80 (70, 91)	79 (65, 89)	0.16
Anterior index myocardial infarction	47.6	52.3	0.65
Killip class 1	79.8	79.1	1.00
Height, cm	173 (167, 178)	173 (165, 178)	0.25
Weight, kg	79 (67, 95)	80 (68, 91)	0.72
Critical time intervals, min			
Onset of symptoms to hospital arrival	64 (48, 141)	68 (45, 115)	0.68
Hospital arrival to randomization	37 (25, 54)	34 (22, 50)	0.48
Randomization to TNK bolus	5 (5, 6)	5 (5, 10)	0.12
Hospital arrival to TNK bolus	45 (34, 61)	43 (32, 55)	0.40
Onset of symptoms to TNK	120 (90, 208)	120 (90, 153)	0.61
Randomization to first balloon inflation		95 (73, 106)	
Randomization to first balloon inflation in transferred patients, n = 39		104 (95, 111)	
Randomization to first balloon inflation in non-transferred patients, n = 46		88 (63, 102)	
Hospital arrival to first balloon inflation		132 (113, 150)	
Onset of symptoms to first balloon inflation		204 (172, 250)	
Infarct-related artery			
Left anterior descending		52.3	
Left circumflex		11.6	
Right coronary		36.0	

Values are given as percentages or medians (25th, 75th percentiles).
TNK = tenecteplase.

Treatment received. All randomized patients were treated according to protocol except for one patient assigned to the facilitated PCI group who was treated with activase instead of TNK and transferred for angiography outside the prespecified 3-h window.

The median time from symptom onset to TNK administration was 120 min in both groups. Among the 86 patients assigned to TNK-facilitated PCI, 40 required ambulance transfer, and 85 (99%) had coronary angiography within 3 h from the time of randomization. Of the latter, 79 patients (91%) underwent PCI, with a median time from randomization to first balloon inflation of 95 min. Stents were implanted in 77 patients (89%), and PCI with balloon alone was performed in 2 patients (2.3%). Platelet glycoprotein IIb/IIIa inhibitors were prescribed in 12 patients (14%) and used only when the angiographic result was suboptimal. On the initial angiogram, a patent IRA (TIMI flow grade 2 or 3) was present in 84% of patients assigned to TNK-facilitated PCI, and TIMI flow grade 3 in 52%. After PCI, patency increased to 97%, with 89% having TIMI flow grade 3. Angiographic success (stenosis of <50% and TIMI flow grade 3) was observed in 92% of the 79 patients who underwent facilitated PCI. The median peak ACT during the procedure was 207 s (interquartile range, 180 to 228). No patient required emergency CABG.

The types of cardiac medication prescribed did not differ between the two groups except for clopidogrel, which was prescribed to 91% of patients assigned to TNK-facilitated PCI and to 57% of patients assigned to TNK alone ($p < 0.001$). At discharge, 96% of patients were prescribed aspirin, 93% beta-blockers, 90% angiotensin-converting enzyme inhibitors, and 92% lipid-lowering drugs. At six months, 96% of patients were taking aspirin, 84% beta-blockers, 84% angiotensin-converting enzyme inhibitors, and 91% lipid-lowering drugs.

Primary end point events. Complete data were available in all but one patient (99.4%) at 30 days and all but two patients (98.8%) at six months. Patients assigned to TNK-facilitated PCI experienced fewer primary end point events at 30 days (21.7% vs. 9.3%, $p = 0.03$) and at 6 months (24.4% vs. 11.6%, $p = 0.04$) (Table 2). A reduction in reinfarction and recurrent unstable ischemia accounted for the superiority of TNK-facilitated PCI over TNK alone, because there was no difference in either death or stroke between groups. The Kaplan-Meier curves for the cumulative rate of the primary end point indicate that the relative benefit of TNK-facilitated PCI occurred mostly within the first week after randomization (Fig. 2).

Bleeding. Major bleeding during hospitalization occurred in six patients (7.1%) in the TNK-alone group and in seven patients (8.1%) in the TNK-facilitated PCI group (relative risk, 1.14; 95% confidence interval, 0.40 to 3.25; $p = 1.0$) (Table 3). Blood transfusion was required in two patients (2.4%) assigned to TNK alone and in five patients (6.0%) assigned to TNK-facilitated PCI (relative risk, 2.44; 95% confidence interval, 0.49 to 12.25; $p = 0.44$). One patient in each group experienced a stroke due to intracranial hemorrhage.

Left ventricular function. There was no difference between patients assigned to TNK alone or to TNK-facilitated PCI in the occurrence of congestive heart failure or cardiogenic shock (Table 3). There was no difference between groups in

Table 2. Occurrence of the Primary End Point*

	TNK-Alone Group (n = 84)	TNK-Facilitated Angioplasty Group (n = 86)	Relative Risk (95% Confidence Interval)	p Value
In-hospital				
Death	3 (3.6)	2 (2.3)	0.65 (0.11–3.80)	0.68
Reinfarction	11 (13.1)	3 (3.5)	0.27 (0.08–0.92)	0.03
Recurrent unstable ischemia†	15 (17.9)	5 (5.8)	0.33 (0.12–0.86)	0.02
Stroke	1 (1.2)	1 (1.2)	0.98 (0.06–15.36)	1.00
Death, reinfarction, or stroke	14 (16.7)	5 (5.8)	0.35 (0.13–0.93)	0.03
Primary end point	18 (21.4)	7 (8.1)	0.38 (0.17–0.86)	0.02
At 30 days				
Death	3 (3.6)	2 (2.3)	0.64 (0.11–3.75)	0.68
Reinfarction	11 (13.3)	4 (4.7)	0.35 (0.12–1.06)	0.06
Recurrent unstable ischemia†	15 (18.1)	6 (7.0)	0.39 (0.16–0.95)	0.04
Stroke	1 (1.2)	1 (1.2)	0.97 (0.61–15.18)	1.00
Death, reinfarction, or stroke	14 (16.9)	6 (7.0)	0.41 (0.17–1.03)	0.06
Primary end point	18 (21.7)	8 (9.3)	0.43 (0.20–0.93)	0.03
At 6 months				
Death	3 (3.7)	3 (3.5)	0.95 (0.20–4.59)	1.00
Reinfarction	12 (14.6)	5 (5.8)	0.40 (0.15–1.08)	0.07
Recurrent unstable ischemia†	17 (20.7)	7 (8.1)	0.39 (0.17–0.90)	0.03
Stroke	1 (1.2)	1 (1.2)	0.95 (0.60–14.99)	1.00
Death, reinfarction, or stroke	15 (18.3)	8 (9.3)	0.51 (0.23–1.14)	0.12
Primary end point	20 (24.4)	10 (11.6)	0.48 (0.24–0.96)	0.04

Values are given as number (percentages). *Death, reinfarction, recurrent unstable ischemia, or stroke. †Includes patients with reinfarction.
TNK = tenecteplase.

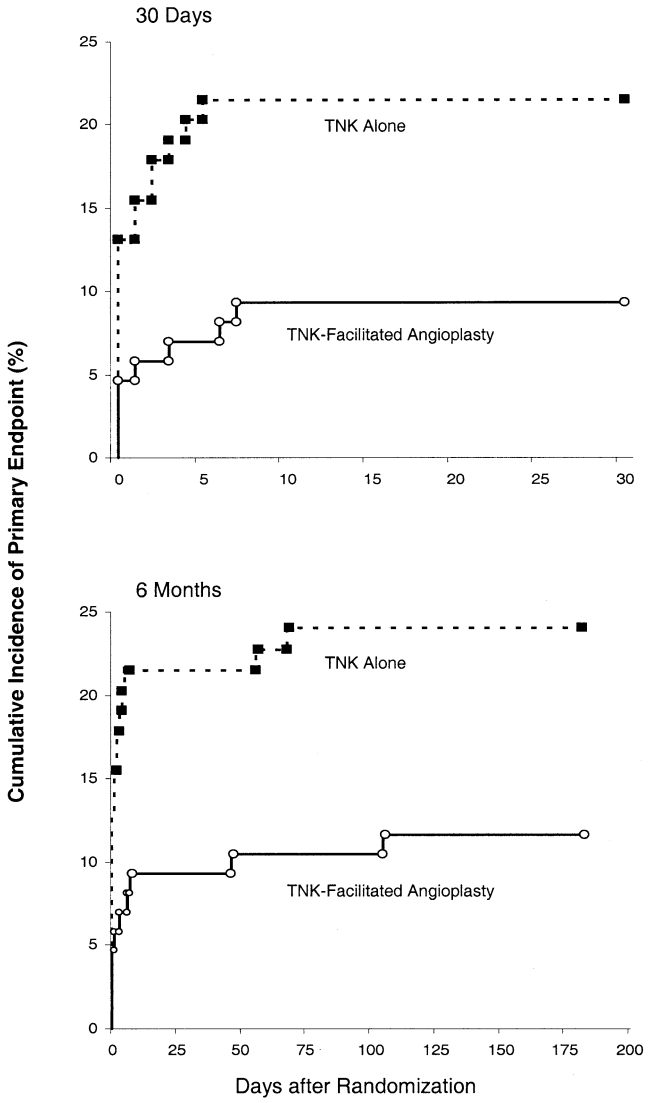

Figure 2. Kaplan-Meier curves showing the cumulative incidence of the primary end point at 30 days and at six months. The primary end point was a composite of death, reinfarction, recurrent unstable ischemia, or stroke after random assignment to treatment with tenecteplase (TNK) alone or TNK-facilitated angioplasty. In the TNK-facilitated angioplasty group, there was a 58% relative reduction in the risk of the primary end point at 30 days (log-rank p = 0.03) **(top)**. At six months, there was a 53% reduction in the risk of the primary end point in the TNK-facilitated angioplasty group (log-rank p = 0.03) **(bottom)**.

the left ventricular ejection fraction measured at one week and 30 days, and in treadmill exercise duration measured at 30 days.

Unscheduled cardiac procedures. During the index hospitalization, non-protocol catheterization was performed in 56 patients assigned to TNK alone (66.7%) versus 12 patients assigned to TNK-facilitated PCI (14.0%; $p < 0.001$) (Table 4). Among patients assigned to TNK-alone, the indication for catheterization was recurrent ischemia in 39.3% and failure of thrombolysis (rescue) in 9.5%. Non-protocol PCI was performed in 42 patients in the TNK-alone group (50.0%), compared with 12 patients in the TNK-facilitated PCI group (14.0%; $p < 0.001$). In 7 of these 12 patients, the reason for unscheduled catheterization was PCI involving a coronary artery other than the IRA performed.

At six months, 53.7% of patients assigned to TNK alone required unscheduled revascularization versus 16.3% of patients assigned to TNK-facilitated PCI ($p < 0.001$). Only two patients required CABG, both in the TNK-alone group.

DISCUSSION

This trial assessed the effectiveness and safety of full-dose weight-adjusted TNK followed by immediate transfer for facilitated PCI in patients presenting with high-risk STEMI. Compared with TNK alone, this strategy was associated with a significant reduction in the combined end point of death, reinfarction, recurrent unstable ischemia, or stroke, at 30 days and at 6 months, and was not associated with an increase in major bleeding. These results suggest that a strategy of full-dose thrombolysis followed by immediate transfer for PCI might be safe and might be superior to thrombolysis-alone.

Facilitated PCI combines the early reperfusion associated with immediate pharmacological therapy with the completeness and sustainability of reperfusion provided by PCI. In addition to limiting myocardial necrosis, successful reperfusion before PCI simplifies the technical performance of the procedure by allowing better visualization of the IRA and its branches. Previous trials failed to show any clinical benefit of immediate PCI after full-dose thrombolysis, and bleeding complications increased (6–8); however, since the publication of these trials, significant advances have occurred in pharmacological therapy and PCI technology. The recent introduction of the highly fibrin-specific, weight-adjusted, single-bolus tissue plasminogen activator TNK simplifies the administration of thrombolysis and is associated with fewer major bleeding complications when coupled with a reduced dose of heparin (11). Aspirin is now given immediately to all patients to prevent re-occlusion, whereas in the TIMI IIa study, aspirin was given to only one-third of the patients on the first day of hospitalization (6). The current widespread use of stents with primary PCI yields superior clinical outcomes over those previously obtained with balloon alone (16). During PCI, heparin dosing is now guided by the ACT, and the addition of thienopyridines has reduced the incidence of abrupt vessel closure after PCI (17). Taken together, these advances provide a plausible explanation of why thrombolysis-facilitated PCI might now be safe and effective.

Retrospective studies suggest that an open artery before primary PCI portends a better prognosis (18–20). In one study, a patent IRA at initial angiography correlated with less cardiogenic shock, a higher left ventricular ejection fraction, and better survival (18–20). Two other studies found that pre-procedural TIMI flow grade 3 was an independent predictor of late survival (19,20). The Primary

Table 3. Occurrence of Secondary End Points

	TNK-Alone Group (n = 84)	TNK-Facilitated Angioplasty Group (n = 86)	p Value
Bleeding with initial treatment			
Baseline hemoglobin per patient, g/l	151 (141, 157)	148 (141, 159)	0.73
Nadir hemoglobin per patient, g/l	125 (115, 136)	129 (111, 137)	0.94
Average drop in hemoglobin per patient, g/l	22 (15, 29)	22 (15, 33)	0.53
Transfusion required	2 (2.4)	5 (6.0)	0.44
Major bleeding	6 (7.1)	7 (8.1)	1.00
Minor bleeding	11 (13.1)	20 (23.3)	0.11
Congestive heart failure*			
At 30 days	10 (12.1)	11 (12.8)	1.00
At 6 months	12 (14.6)	12 (14.0)	1.00
Cardiogenic shock			
At 30 days	3 (3.6)	4 (4.7)	1.00
At 6 months	3 (3.7)	4 (4.7)	1.00
Left ventricular ejection fraction	n = 60	n = 75	
At 1 week	53 (46, 58)	49 (41, 55)	0.09
At 30 days	55 (50, 61)	52 (45, 59)	0.08
Difference	3 (−1, 7)	2 (−2, 8)	0.74
Exercise test at 30 days	n = 53	n = 59	
Duration, min	6.8 (6.0, 9.0)	6.4 (4.6, 8.7)	0.33
Length of stay (index hospitalization)	6.0 (5.5, 8.0)	5.0 (4.0, 7.0)	0.02
Re-hospitalization per patient	12 (14.5)	15 (17.9)	0.83

Values are given as number (percentages) or medians (25th, 75th percentiles). *Includes patients with cardiogenic shock.
TNK = tenecteplase.

Angioplasty Combined with Thrombolysis (PACT) study showed that pre-treatment with half-dose tissue-plasminogen activator appears to be safe and achieves higher pre-procedural TIMI flow grade 3 compared with placebo, 33% versus 15% (21). In our study, full-dose TNK-facilitated PCI was associated with pre-procedural TIMI flow grade 3 in 52% of patients at a median of 95 min. These results are similar to those achieved in the TIMI 10b study (22) and in marked contrast to the TIMI flow grade 3 of <20% reported at the time of primary PCI (20,23).

Significant delays associated with transfer to the catheterization facility remain an important drawback to primary PCI (24). Our results indicate that TNK-facilitated PCI can bridge the time gap between diagnosis and balloon

Table 4. Unscheduled Cardiac Procedures

Cardiac Procedure	TNK-Alone Group (n = 84)	TNK-Facilitated Angioplasty Group (n = 86)	p Value
During index hospitalization			
Coronary angiogram	56 (66.6)	12 (14.0)	<0.001
Time to angiography, days	2.5 (0, 6.0)	3.5 (1.5, 6.0)	
Indication			
Recurrent ischemia	33 (39.3)	5 (5.8)	
Failed thrombolysis	8 (9.5)	—	
Congestive heart failure/shock	2 (2.4)	0 (0)	
Ventricular tachycardia	3 (3.6)	0 (0)	
Physician preference	8 (9.5)	0 (0)	
Other	2 (2.4)	7 (8.1)*	
PCI	42 (50.0)	12 (14.0)	<0.001
Time to PCI, days	2.0 (0, 5.0)	3.5 (1.5, 6.0)	
CABG	2 (2.4)	0 (0.0)	0.24
At 30 days			
Coronary angiogram	56 (67.5)	12 (13.9)	<0.001
PCI	42 (50.6)	12 (13.9)	<0.001
CABG	2 (2.4)	0 (0.0)	0.24
At 6 months			
Coronary angiogram	60 (73.2)	14 (16.3)	<0.001
PCI	44 (53.7)	14 (16.3)	<0.001
CABG	2 (2.4)	0 (0.0)	0.24

Values are given as number (percentages) or medians (25th, 75th percentiles). *Staged angioplasty procedures.
CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; TNK = tenecteplase.

inflation. Although the time window in which facilitated PCI confers benefit is unknown, we found that the Kaplan-Meier curves separate within the first 24 h, suggesting that the observed benefits are attenuated by delaying coronary angiography. Conversely, in settings where door-to-balloon intervals are very short, the benefits of facilitated PCI might be less because restoration of blood flow to the IRA before PCI will occur in fewer patients.

It is plausible that TNK-facilitated PCI will be superior to primary PCI because of the benefits provided by earlier reperfusion, particularly in settings where transportation time and logistics might delay PCI, although this has yet to be proven. The ongoing ASSENT-4 trial is comparing TNK-facilitated PCI with primary PCI and will test this hypothesis directly.

Glycoprotein IIb/IIIa inhibitors were used sparingly to avoid bleeding complications that might otherwise have arisen by combining these drugs with full-dose thrombolytic therapy. A systematic overview of abciximab in primary PCI suggests that it might be an important adjunct (25), and one randomized trial has reported superior clinical outcomes with abciximab-facilitated PCI compared with primary PCI alone (26). Larger trials addressing the role of pharmacologic reperfusion therapy with abciximab alone or in combination with reduced-dose reteplase, followed by PCI, are currently underway (27,28).

Our results complement two recently published studies that support early intervention after thrombolysis (29,30). The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) randomly assigned 163 patients initially treated with thrombolysis to immediate stenting or to elective stenting after two weeks. Immediate stenting performed <6 h after thrombolysis was associated with a significant reduction of the six-month composite of death, reinfarction, target lesion revascularization, and ischemic events (25.6% vs. 50.6%) (29). The Grupo de Análisis de la Cardiopatía Isquémica Aguda-1 (GRACIA-1) randomly assigned 500 patients after thrombolytic therapy to a routine invasive strategy within 24 h of thrombolysis versus an ischemia-guided approach (30). The composite of death, reinfarction, or revascularization at one year was lower in the early invasive group (9% vs. 21%).

The percent risk reduction achieved with TNK-facilitated PCI compared with TNK alone was as predicted, although primary end point events were fewer than expected. Several factors might have contributed to this, including relatively short symptom-onset to treatment times (1), aggressive revascularization during the index hospitalization (31), and rigorous application of practice guidelines in prescribing beta-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs (32).

Study limitations. Our study of a small, but well-defined cohort is the first contemporary randomized control trial to rigorously assess the merits of TNK-facilitated PCI against TNK alone. Lower rates of recurrent unstable ischemia and reinfarction with TNK-facilitated PCI compared with TNK alone accounted for lowering the rate of occurrence of the primary end point. Although our study was not powered to detect differences in mortality, larger studies indicate that recurrent ischemia or reinfarction occurring after thrombolysis are associated with increased morbidity, mortality, and resource utilization (33–35). Regarding major bleeding, our study is too small to provide reliable estimates of the relative safety.

Conclusions. This study shows that a strategy of TNK-facilitated angioplasty for patients presenting with high-risk STEMI appears to be safe and reduces the risk of recurrent ischemic events compared with TNK alone. Larger randomized trials, including comparison with primary PCI alone and studies evaluating the cost-effectiveness of TNK-facilitated PCI, will further define its role.

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APPENDIX

For a list of the CAPITAL AMI Trial Organization and investigators, please see the online version of this article.