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CLINICAL RESEARCH **Clinical Trials**

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.