

## **Pharmacologic and clinical characteristics of thrombolytic agents.**

**Deitcher SR, Jaff MR.**

**A**rterial and venous thromboembolic events, including myocardial infarction, ischemic stroke, peripheral arterial thrombosis, deep venous thrombosis, and pulmonary embolism are common and potentially life-, organ-, and limb-threatening vascular diseases. Anticoagulant therapy is recommended in these settings to prevent further thrombosis pending gradual clearance of the thrombotic occlusion by the endogenous fibrinolytic system. Recognition of the importance of the fibrinolytic system in thrombus resolution has resulted in the development of pharmacologic fibrinolytic (thrombolytic) agents to facilitate rapid restoration of vascular patency. Several plasminogen activator (PA) thrombolytic agents with different pharmacokinetic and pharmacodynamic properties have been developed to treat thrombotic disease. Newer PAs have been developed as "fibrin-specific," bolus-administration drugs to primarily treat acute coronary syndromes. Continuous infusions of these fibrin-specific PAs have become popular for the lysis of relatively larger peripheral vascular thromboses. Loss of coveted fibrin specificity due to the generation of fragment X during the continuous infusion of newer tissue-type plasminogen activator-based PAs may result in an increased risk of bleeding, including intracranial hemorrhage. Currently available data fail to provide compelling evidence that newer PAs offer significantly greater efficacy and safety than well-established agents like urokinase when used to treat peripheral vascular thrombosis.

## **Prognosis in the thrombolysis in myocardial ischemia III registry according to the Braunwald unstable angina pectoris classification.**

**Scirica BM, Cannon CP, McCabe CH, Murphy SA, Anderson HV, Rogers WJ, Stone PH, Braunwald E; Thrombolysis in Myocardial Ischemia III Registry Investigators.**

The unstable angina pectoris (UAP) classification proposed by Braunwald in 1989, although often used, has never been validated in a large, prospective multicenter study in which all subgroups of patients were included. Patients with UAP or non-ST-elevation myocardial infarction (NSTEMI) were enrolled in the Thrombolysis In Myocardial Ischemia III Registry and classified according to the Braunwald classification for UAP. Clinical end points were compared at 6 weeks and 1 year. Of 3,318 patients, those with primary UAP had lower rates of recurrent myocardial infarction (MI) or death when compared with patients with secondary UAP and post-MI UAP at 6 weeks (4.1% vs 6.4% vs 13.4%  $p < 0.001$ ) and 1 year (9.7% vs 16.7% vs 19.7%  $p < 0.001$ ). Recurrent ischemia at 6 weeks followed the same gradient (13.2% vs 18.5% vs 20.8%  $p < 0.001$ ). Patients with secondary UAP had similar extent of disease at angiography as primary UAP. Patients with nonresting UAP had lower rates of death or MI than patients with UAP at rest (3.0% vs 5.6%,  $p = 0.011$  at 6 weeks, and 8.2% vs 12.5%,  $p = 0.004$  at 1 year). Patients with ST-segment deviation and those who had received prior antianginal medical treatment also had worse outcomes. Thus, the Braunwald classification of UAP predicts prognosis with secondary UAP, post-MI UAP, and patients with pain at rest who have a higher risk for death or recurrent cardiac events. Given their high risk for adverse events, patients with secondary UAP should be treated aggressively.

## Thrombolytic therapy.

**Baker WF Jr.**

The therapeutic use of thrombolytic agents is the natural result of the increasing understanding of the pathophysiologic mechanisms underlying normal and deranged thrombosis and fibrinolysis. Plasminogen activators capable of increasing the production of plasmin exhibit considerable efficacy in the treatment of a variety of arterial and venous thrombotic disorders. The ideal thrombolytic agent has yet to be developed but the desired clinical result of rapid opening of the thrombosed vessel without reocclusion, without activation of systemic fibrinogenolysis, and without a risk of hemorrhage is well defined. Clinical studies clearly demonstrate that the addition of a variety of adjunctive agents to the available thrombolytics enhances benefit without inordinate risk. The addition of intravascular angioplasty and stenting to thrombolysis increases the potential long-term benefit. Newer thrombolytic agents and new protocols for the use of existing therapies offer the promise of saving many who would otherwise succumb to coronary or cerebral arterial thrombosis or to venous thromboembolism.

## **Outcome of acute myocardial infarction in patients with prior coronary artery bypass grafting treated with combination reduced fibrinolytic therapy and abciximab.**

**Mukherjee D, Gurm H, Tang WH, Roffi M, Wolski K, Moliterno DJ, Guetta V, Ardissinio D, Bode C, Steg G, Lincoff AM, Topol EJ.**

**S**T-segment elevation acute myocardial infarction (AMI) in patients who have undergone previous coronary artery bypass grafting (CABG) is associated with low reperfusion rates and poor outcome after fibrinolytic therapy. The efficacy of a combination strategy (reduced fibrinolytic plus platelet glycoprotein IIb/IIIa agent) in this setting is unknown. In the Global Use of Streptokinase and TPA for Occluded coronary arteries V (GUSTO V) trial, 553 patients with a history of CABG were treated with standard-dose reteplase (n = 273), or half-dose reteplase and full-dose abciximab (n = 280) in the first 6 hours of evolving ST-segment elevation MI. Mortality at 30 days was significantly higher in patients who underwent prior CABG compared with patients with no prior CABG (odds ratio [OR] 1.64, 95% confidence interval [CI] 1.21 to 2.24, p = 0.001). In patients who underwent prior CABG, mortality at 7 days was reduced 15% with combination therapy compared with reteplase alone, which was not statistically significant (OR 0.85, 95% CI 0.40 to 1.81, p = 0.66). Patients who underwent prior CABG treated with the combination therapy had fewer episodes of recurrent ischemia (OR 0.60, 95% CI 0.37 to 0.96, p = 0.02), high degree atrioventricular block (OR 0.17, 95% CI 0.02 to 0.82, p = 0.01), and ventricular tachycardia (OR 0.29, 95% CI 0.07 to 0.96, p = 0.04). There was a trend toward reduced urgent revascularization (OR 0.61, 95% CI 0.36 to 1.03, p = 0.06) but no significant difference in reinfarction (OR 0.61, 95% CI 0.31 to 1.52, p = 0.40). In the GUSTO V trial, patients who underwent prior CABG had significantly higher event rates compared with patients without CABG. As in the overall trial, combination therapy in patients who underwent prior CABG led to a consistent reduction in key secondary complications of AMI, including recurrent ischemia and a trend toward reduced urgent revascularization.

## **Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy.**

**Angeja BG, de Lemos J, Murphy SA, Marble SJ, Antman EM, Cannon CP, Braunwald E, Gibson CM; TIMI Study Group. Thrombolysis In Myocardial Infarction.**

**B**ACKGROUND: Patients with diabetes are at increased risk of death after acute myocardial infarction, independent of other baseline risk factors and more severe coronary artery disease. We studied the angiographic and electrocardiographic responses to thrombolytic agents in patients with diabetes; in particular ST-segment resolution as a measure of microvascular flow.

**METHODS:** Angiography was performed in 2588 patients at 90 minutes after thrombolytic agent administration as well as after percutaneous coronary intervention (PCI) in the Thrombolysis In Myocardial Infarction (TIMI) 4, 10A, 10B, and 14 trials. Electrocardiographic parameters were assessed at baseline and at 90 minutes in the TIMI 14 trial.

**RESULTS:** Compared with those without diabetes, patients with diabetes (347/2588 [13.4%]) were older, more often female, heavier, and less often smokers, and they had higher systolic blood pressure on admission. At angiography, they more frequently had 3-vessel disease, well-developed collateral vessels, more distal culprit lesions, and smaller reference segment diameters. In the infarct-related artery, there was no relationship between diabetes and TIMI 3 flow at 90 minutes (55.4% vs 59.0% without diabetes) or after PCI, (83.7% vs 84.2%, both  $P = \text{NS}$ ). Corrected TIMI frame counts were also similar at both time points. However, there was less frequent complete ST-segment resolution among diabetic patients after thrombolysis (38.6% vs 49.2%, adjusted  $P = .04$ ).

**CONCLUSION:** Thrombolysis and adjunctive/rescue PCI achieved equal rates of epicardial flow in patients with and without diabetes. However, diabetic patients had less complete ST-segment resolution, suggesting impaired microvascular flow. Abnormal microvascular flow may contribute at least in part to the poorer outcomes observed in patients with diabetes and acute myocardial infarction.

**A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COMbining Monteplase with Angioplasty (COMA) trial.**

Inoue T, Yaguchi I, Takayanagi K, Hayashi T, Morooka S, Eguchi Y.

**B**ACKGROUND: Both thrombolytic therapy and coronary angioplasty have been inconsistent together for primary acute myocardial infarction (AMI) therapy, because conventional thrombolytic agents accelerate plasminogen activator inhibitor-1 (PAI-1) activity. However, combining newly developed mutant tissue-type plasminogen activators with coronary angioplasty should be reconsidered.

**METHODS:** This study was designed to investigate clinical usefulness of such an agent, monteplase, for treatment of AMI in light of PAI-1 kinetics. One hundred fifty-four consecutive patients with AMI were randomly assigned to receive direct coronary angioplasty (Group I) or coronary angioplasty after pretreatment with intravenous monteplase (Group II). In 90 of these patients, total PAI-1 antigen levels were serially measured.

**RESULTS:** Baseline PAI-1 levels at admission were higher in patients with occluded infarct-related arteries than in patients with patent arteries in Group I (39 +/- 4 vs 20 +/- 2 ng/mL,  $P < .01$ ) and in Group II (36 +/- 3 vs 27 +/- 2 ng/mL,  $P < .05$ ). In the high PAI-1 level subgroup ( $> \text{ or } = 27 \text{ ng/mL}$ ,  $n = 53$ ), Group II showed a higher patency rate than Group I (56 vs 18%,  $P < .01$ ). Multiple logistic regression analysis indicated that patency could be predicted by the PAI-1 level in Group I (Wald  $\chi^2 = 3.94$ ,  $P = .02$ , odds ratio 0.924, 95% CI 0.855-0.999), but not in Group II. Serial change patterns in the PAI-1 level were identical in Group I and Group II.

**CONCLUSION:** Because monteplase can be used independently of PAI-1 kinetics, a combination of monteplase administration at a community hospital with prompt transfer to a tertiary center for coronary intervention may be a powerful strategy for AMI.

**Acute cardiogenic shock immediately after successful intervention for failed thrombolysis.**

Constantinides S, Wong P, Shiu MF.

We report the case of a 60-year-old female with a history of hypertension who was admitted with an acute inferior myocardial infarction. She received rescue percutaneous transluminal coronary angioplasty/stenting of an occluded right coronary artery for failed thrombolysis with a good initial result. However, this was immediately complicated by cardiogenic shock characterized by left ventricular outflow tract (LVOT) gradient. She was treated with intravenous fluids and adrenaline. PredischARGE echocardiography showed no LVOT gradient and features of left ventricular hypertrophy that mainly affected the septum.

## **Glycoprotein IIb/IIIa receptor inhibitor–thrombolytic combination therapy for acute myocardial infarction.**

**Maranian AM, Steinhubl SR.**

Over the past two decades, we have witnessed a large decrease in the death and complication rate of patients experiencing acute myocardial infarction (MI), due to our ability to restore blood flow to infarct-related arteries. Therapies include strategies to inhibit platelet function and induce fibrinolysis, and mechanical reperfusion with percutaneous intervention. Despite decreases in morbidity and mortality with thrombolytic therapy, reperfusion rates remain less than optimal. With standard fibrinolytic therapy in combination with aspirin, it is thought that thrombolytic-induced platelet activation may be an important reason for failure to induce perfusion, or maintain reperfusion in the infarct-related artery. In the past 10 years we have moved from platelet inhibition with aspirin to newer, more potent platelet inhibitors such as glycoprotein (GP) IIb/IIIa antagonists. Recent trials have evaluated the efficacy and safety of combining thrombolytic drugs with GP IIb/IIIa receptor antagonists. Future trends may use combination therapy as a part of a mechanical strategy, using these medications to induce early reperfusion as the patient is prepared for percutaneous intervention. This review summarizes recently published trials using combination thrombolytic and GP IIb/IIIa receptor inhibitor therapy in the treatment of acute MI.

## **The thrombolysis in myocardial infarction risk score in unstable angina/non-ST-segment elevation myocardial infarction.**

**Sabatine MS, Antman EM.**

**R**isk stratification in unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI) can provide an estimate of a patient's prognosis and optimize clinical choices. The Thrombolysis In Myocardial Infarction (TIMI) risk score for UA/NSTEMI is an integrated approach that uses baseline variables that are part of the routine medical evaluation to identify patients at high risk for death and other major cardiac ischemic events. Using multivariable logistic regression, seven independent predictor variables were identified: age  $\geq 65$  years,  $\geq 3$  risk factors for coronary artery disease (CAD), known CAD (stenosis  $\geq 50\%$ ), severe anginal symptoms ( $\geq 2$  anginal events in preceding 24 h), use of aspirin in the last seven days, ST-segment deviation  $\geq 0.05$  mV, and elevated serum cardiac markers of necrosis. Each predictor carried similar prognostic weight; therefore, a risk score was constructed as the simple arithmetic sum of the number of predictors. The rate of death, MI, or urgent revascularization significantly increased as the TIMI risk score increased, ranging from  $<5\%$  for patients with a risk score of 0 or 1 to  $>40\%$  for patients with a risk score of 6 or 7. The risk score has been validated in several other trials of UA/NSTEMI. In addition, using the risk score to categorize patients also effectively defines a gradient for benefit with specific treatments such as low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, and an early invasive strategy.

**A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COMbining Monteplase with Angioplasty (COMA) trial.**

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**CONCLUSION:** Because monteplase can be used independently of PAI-1 kinetics, a combination of monteplase administration at a community hospital with prompt transfer to a tertiary center for coronary intervention may be a powerful strategy for AMI.

## THROMBOLYTIC THERAPY

1. Pharmacologic and clinical characteristics of thrombolytic agents.

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Rev Cardiovasc Med 2002;3 Suppl 2:S25-33

2. Prognosis in the thrombolysis in myocardial ischemia III registry according to the Braunwald unstable angina pectoris classification.

Scirica BM, Cannon CP, McCabe CH, Murphy SA, Anderson HV, Rogers WJ, Stone PH, Braunwald E; Thrombolysis in Myocardial Ischemia III Registry Investigators.

Am J Cardiol 2002 Oct 15;90(8):821-6

3. Thrombolytic therapy.

Baker WF Jr.

4. Outcome of acute myocardial infarction in patients with prior coronary artery bypass grafting treated with combination reduced fibrinolytic therapy and abciximab.

Mukherjee D, Gurm H, Tang WH, Roffi M, Wolski K, Moliterno DJ, Guetta V, Ardissinio D, Bode C, Steg G, Lincoff AM, Topol EJ.

Am J Cardiol 2002 Dec 1;90(11):1198-203

5. Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy.

Angeja BG, de Lemos J, Murphy SA, Marble SJ, Antman EM, Cannon CP, Braunwald E, Gibson CM; TIMI Study Group. Thrombolysis In Myocardial Infarction.

Clin Cardiol 2002 Nov;25(11 Suppl 1):I23-6

6. A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COMbining Monteplase with Angioplasty (COMA) trial.

Inoue T, Yaguchi I, Takayanagi K, Hayashi T, Morooka S, Eguchi Y.

Am Heart J 2002 Oct;144(4):E5

7. Acute cardiogenic shock immediately after successful intervention for failed thrombolysis.

Constantinides S, Wong P, Shiu MF.

J Interv Cardiol 2002 Feb;15(1):19-21

8. Glycoprotein IIb/IIIa receptor inhibitor-thrombolytic combination therapy for acute myocardial infarction.

Maranian AM, Steinhubl SR.

Curr Cardiol Rep 2002 Jul;4(4):313-9

9. The thrombolysis in myocardial infarction risk score in unstable angina/non-ST-segment elevation myocardial infarction.

Sabatine MS, Antman EM.

J Am Coll Cardiol 2003 Feb 19;41(4 Suppl S):S89-95

10. A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COMbining Monteplase with Angioplasty (COMA) trial.

Inoue T, Yaguchi I, Takayanagi K, Hayashi T, Morooka S, Eguchi Y.

Am Heart J 2002 Oct;144(4):E5

**Am Heart J, 2001 ;141(4):592-8**

**Abciximab and early adjunctive percutaneous coronary intervention are associated with improved ST-segment resolution after thrombolysis: Observations from the TIMI 14 Trial.**

de Lemos JA, Gibson CM, Antman EM, Murphy SA, Morrow DA, Schuhwerk KC, Schweiger M, Coussement P, Van de Werf F, Braunwald E; TIMI 14 Investigators.

**BACKGROUND:** Percutaneous coronary intervention (PCI) improves clinical outcomes in selected patients with failed thrombolysis but has not been proven to benefit patients who achieve a patent infarct-related artery. Even after successful epicardial reperfusion, myocardial perfusion may be inadequate. We sought to evaluate whether a strategy that uses a reperfusion regimen containing abciximab and a reduced-dose thrombolytic agent (combination therapy), followed by early adjunctive PCI, would result in improved myocardial perfusion, as assessed by ST-segment resolution.

**METHODS:** ST resolution from 90 to 180 minutes after therapy was calculated for all 410 patients from the TIMI 14 trial who had evaluable electrocardiograms at both time points and who were treated with alteplase or reteplase. Patients were grouped according to whether they were treated with combination therapy or full-dose thrombolytic agent alone and whether they underwent PCI between the 90- and 180-minute electrocardiographic measurements.

**RESULTS:** Among 105 patients who underwent adjunctive PCI between 90 and 180 minutes, mean ST resolution from 90 to 180 minutes was significantly greater in those who had received combination therapy versus those who had received full-dose thrombolytic alone (54% vs 8%;  $P = .002$ ). Among 241 patients with TIMI grade 3 flow in the infarct-related artery at 90 minutes, adjunctive PCI significantly improved mean ST resolution in patients who had been treated with combination therapy (57% [PCI] vs 24% [no PCI];  $P = .006$ ), but

PCI did not have this effect in patients who had received thrombolytic therapy alone (1% [PCI] vs 10% [no PCI];  $P = .70$ ). In a multivariate model controlling for factors that would be expected to independently influence 90- to 180-minute ST resolution, abciximab treatment remained significantly associated with greater ST resolution ( $P = .008$ ).

**CONCLUSIONS:** A strategy that uses a combination reperfusion regimen that includes abciximab, followed by early adjunctive PCI, is associated with greater ST-segment resolution, which may reflect enhanced tissue level and microvascular perfusion. Future studies should evaluate prospectively the clinical efficacy of this strategy.

Am Heart J 2001 Apr;141(4):559-65

Recurrent ischemia after thrombolysis for acute myocardial infarction.

Pilote L, Miller DP, Califf RM, Topol EJ; Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) Investigators.

**BACKGROUND:** Reliable predictors have yet to be found for recurrent ischemia after thrombolysis for acute myocardial infarction (AMI), nor do we know whether early angiography can herald recurrent ischemia. This study sought to investigate the relationship between recurrent ischemia and cardiac procedures after thrombolysis for AMI.

**METHODS:** The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial prospectively studied recurrent ischemia, which was defined as the presence of angina and changes in hemodynamics or the electrocardiogram. Cox regression analysis was used to identify predictors of recurrent ischemia. Other variables examined included time to coronary angiography and revascularization.

**RESULTS:** Of 21,772 US GUSTO-I patients, 6313 (29%) had recurrent ischemia before discharge. Women (hazard ratio [HR] 1.25, 95% confidence interval [CI] 1.17-1.33) and patients with hypercholesterolemia (HR 1.14, 95% CI 1.07-1.22) or prior angina (HR 1.40, 95% CI 1.32-1.49) had a higher likelihood of recurrent ischemia. Current smoking and hours to thrombolysis were inversely related to recurrent ischemia (HR 0.86, 95% CI 0.81-0.92, HR 0.97, 95% CI 0.95-0.99, respectively). Patients who underwent angiography before recurrent ischemia had a marginally increased risk of ischemia within 12 hours after angiography (HR 1.2, 95% CI 1.1-1.4);

ultimately, they had a considerably lower risk 1 week after angiography than did patients without angiography (HR 0.57, 95% CI 0.45-0.72).

**CONCLUSIONS:** Female sex, hypercholesterolemia, prior angina, and nonsmoking status weakly predict recurrent ischemia. Early coronary angiography reduces recurrent ischemia, probably because high-risk patients are identified and revascularized

J Intern Med 2001 ;249(6):527-37

**Risk assessment in patients with acute myocardial infarction treated with thrombolytic therapy.**

Jensen-Urstad M, Samad BA, Jensen-Urstad K, Hulting J, Ruiz H, Bouvier F, Hojer J.

**OBJECTIVE:** Several noninvasive methods have prognostic information regarding mortality and new coronary events after an acute myocardial infarction (AMI). The practical for clinical decision-making in the immediate postmyocardial infarction (MI) period is, however, less evident. We investigated consecutive patients with AMI treated with thrombolysis to further clarify this issue.

**DESIGN:** A total of 100 patients (27% women) aged 64 +/- 9 years (mean +/- SD) were studied. Risk assessment based on a clinical score system, myocardial perfusion scintigraphy single photon emission computed tomography (SPECT) at rest and during adenosine stress, echocardiography, radionuclide angiography, symptom-limited exercise stress test, and 24-h Holter ECG recording with ST-analysis and analysis of heart rate variability (HRV) were performed 5-8 days after hospital admission. Mortality, nonfatal reinfarction, and the need for revascularization were followed during 12 months. **SETTING:** A university hospital.

**RESULTS:** A total of 6 patients died, seven had a nonfatal reinfarction, and 23 were revascularized. Inability to perform an exercise test ( $P = 0.004$ ) and an ejection fraction (EF)  $< 40\%$  ( $P = 0.002$ ) were the only parameters separating those who died from the survivors. No method could predict a nonfatal reinfarction. Patients suffering either death or nonfatal reinfarction had a clinical risk assessment score 2 points higher (8.8 vs. 6.7,  $P = 0.05$ ) than the group without such events. A positive symptom-limited exercise stress test ( $P = 0.027$ ), ST-depressions on Holter ECG ( $P = 0.04$ ), and reversibility on myocardial perfusion scintigraphy ( $P = 0.029$ ) predicted the need for revascularization.

**CONCLUSION:** Risk assessment based on clinical information, exercise stress testing, and an estimate of left ventricular function (e.g. via echocardiography) contribute with prognostic information in thrombolysed MI-patients. Additional noninvasive investigations such as adenosine-SPECT, analysis of HRV, and Holter-monitoring do not add to these commonly available tools in risk stratification of subjects at low to medium risk.

Eur Heart J 2001;22(13):1128-35

**Outcome after combined reperfusion therapy for acute myocardial infarction, combining pre-hospital thrombolysis with immediate percutaneous coronary intervention and stent.**

Loubeyre C, Lefevre T, Louvard Y, Dumas P, Piechaud JF, Lanore JJ, Angellier JF, Le Tarnec JY, Karrillon G, Margenet A, Pougès C, Morice MC.

**BACKGROUND:** Primary therapies in acute myocardial infarction (thrombolysis and angioplasty) have inherent limitations which may be overcome by combining them. So far, no trial has demonstrated a clinical benefit in combining mechanical and pharmacological treatment strategies.

**METHODS:** From January 1995 to December 1999, out of 1010 patients admitted to our institution for acute myocardial infarction, 148 had received pre-hospital full dose thrombolysis within 12 h of onset. One hundred and thirty-one patients were included and underwent immediate angioplasty and stenting when suitable, independent of the infarct-artery patency (TIMI grade flow 0-3). In-hospital outcome was assessed and clinical information was collected for a mean ( $\pm$ SD) of 2 $\pm$ 1 years.

**RESULTS:** Ninety-minute angiography revealed a patent (TIMI grade 3) infarct artery in 65 patients (49%). Immediate angioplasty was performed in 119 patients (91%) with stent implantation in 114 (96%). Angioplasty achieved TIMI 2, 3 flow in 98%, and complete patency (TIMI 3 flow) in 92%. Six other patients underwent deferred revascularization (surgery in one patient, angioplasty in five) and six received medical treatment. Stent thrombosis and reinfarction occurred in three patients (2.3%). In-hospital death occurred in six patients (4.6%), including four patients presenting with cardiogenic shock. Major bleeding was observed in 2.3% of cases. No patient had emergency surgery. Freedom from death and reinfarction at 2 years was 90% and freedom from death, reinfarction and target vessel revascularization was 83%.

**CONCLUSION:** A strategy of combined reperfusion using full dose pre-hospital thrombolysis and immediate angioplasty with stent implantation in a non-selected acute myocardial infarction population is safe and achieves high and early patency rates. This preliminary experience suggests that a combined strategy in acute myocardial infarction may have a significant impact on both early and long-term outcomes.

Am J Cardiol , 2001 ;88(4):353-8

Early noninvasive detection of failed epicardial reperfusion after fibrinolytic therapy.

de Lemos JA, Morrow DA, Gibson CM, Murphy SA, Rifai N, Tanasijevic M, Giugliano RP, Schuhwerk KC, McCabe CH, Cannon CP, Antman EM, Braunwald E; TIMI 14 Investigators. Thrombosis In Myocardial Infarction.

Available noninvasive techniques for identifying patients with failed epicardial reperfusion after fibrinolytic therapy are limited by poor accuracy. It is unknown whether combining multiple noninvasive predictors would improve diagnostic accuracy and facilitate identification of candidates for rescue percutaneous coronary intervention. In the Thrombolysis In Myocardial Infarction (TIMI) 14 trial, we evaluated the ability of ST-segment resolution (n = 606), chest pain resolution (n = 859), and the ratio of 60-minute/baseline serum myoglobin (n = 308) to identify patients with angiographic evidence of failed reperfusion 90 minutes after fibrinolysis. Three criteria were prospectively defined: <50% ST resolution at 90 minutes, presence of chest pain at the time of angiography, and myoglobin ratio <4. Patients who met any individual criterion were more likely to have less than TIMI 3 flow and an occluded infarct-related artery (TIMI 0/1 flow) than those who did not meet the criterion (p <0.005 for each). When the 3 criteria were used together (n = 169), patients who satisfied 0 (n = 29), 1 (n = 68), 2 (n = 51), or 3 (n = 21) of the criteria had a 17%, 24%, 35%, and 76% probability of failing to achieve TIMI 3 flow (p <0.0001 for trend), a 0%, 6%, 18%, and 57% probability of an occluded infarct-related artery (p <0.0001 for trend), and a 0%, 1.5%, 2.0%, and 9.5% rate of 30-day mortality (p = 0.05 for trend), respectively. Use of the criteria in combination increased positive predictive values without decreasing negative predictive values. In conclusion, ST-segment resolution, chest pain resolution, and early washout of serum myoglobin can be used in combination to aid in the early noninvasive identification of candidates for rescue percutaneous coronary intervention.

J Am Coll Cardiol 2001 ;38(2):472-7

Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction.

Iwakura K, Ito H, Kawano S, Shintani Y, Yamamoto K, Kato A, Ikushima M, Tanaka K, Kitakaze M, Hori M, Higashino Y, Fujii K.

**OBJECTIVES:** We sought to elucidate the clinical factors related to the development of no-reflow phenomenon after successful coronary reperfusion in patients with an acute myocardial infarction (AMI). **BACKGROUND:** Myocardial contrast echocardiography revealed that the no-reflow phenomenon is observed in some patients with a reperfused AMI, and those patients usually have poor functional and clinical outcomes. It is still unknown what clinical factors are related to the development of the no-reflow phenomenon.

**METHODS:** Myocardial contrast echocardiography was performed 15 min after successful coronary reperfusion therapy in 199 patients with an anterior wall AMI who underwent successful coronary reperfusion with primary coronary angioplasty within 24 h after the onset of AMI. Multiple logistic regression analysis was used to identify independent predictors of the no-reflow phenomenon.

**RESULTS:** Seventy-nine patients showed the no-reflow phenomenon. Univariate analysis indicated that pre-infarction angina within 48 h before symptom onset, Killip class, Thrombolysis in Myocardial Infarction flow grade 0 on the initial coronary angiogram, the number of abnormal Q-waves and the wall motion score (WMS) on the echocardiogram obtained at hospital admission are related to the no-reflow phenomenon. Multivariate logistic regression analysis revealed that all of these factors, except for Killip class, are independent predictive factors of the no-reflow phenomenon.

**CONCLUSIONS:** Development of the no-reflow phenomenon is related to the severity of myocardial damage (number of Q-waves), the size of the risk area (WMS) and the occlusion status of infarct-related artery. In addition, ischemic preconditioning (pre-infarction angina) seems to be the factor that attenuates the no-reflow phenomenon.

Circulation, 2001;104(6):648-52

Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II).

Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, de Jong E, Coyne K; HART II Investigators.

**BACKGROUND:** Adjunctive unfractionated heparin (UFH) during thrombolytic therapy for acute myocardial infarction (AMI) promotes the speed and magnitude of coronary artery recanalization and reduces reocclusion. Low-molecular-weight heparins offer practical and potential pharmacological advantages over UFH in multiple applications but have not been systematically studied as adjuncts to fibrinolysis in AMI.

**METHODS AND RESULTS:** Four hundred patients undergoing reperfusion therapy with an accelerated recombinant tissue plasminogen activator regimen and aspirin for AMI were randomly assigned to receive adjunctive therapy for at least 3 days with either enoxaparin or UFH. The study was designed to show noninferiority of enoxaparin versus UFH with regard to infarct-related artery patency. Ninety minutes after starting therapy, patency rates (thrombolysis in myocardial infarction [TIMI] flow grade 2 or 3) were 80.1% and 75.1% in the enoxaparin and UFH groups, respectively. Reocclusion at 5 to 7 days from TIMI grade 2 or 3 to TIMI 0 or 1 flow and TIMI grade 3 to TIMI 0 or 1 flow, respectively, occurred in 5.9% and 3.1% of the enoxaparin group versus 9.8% and 9.1% in the UFH group. Adverse events occurred with similar frequency in both treatment groups.

**CONCLUSIONS:** Enoxaparin was at least as effective as UFH as an adjunct to thrombolysis, with a trend toward higher recanalization rates and less reocclusion at 5 to 7 days.

Am Heart J , 2001;142(2):244-7

A randomized trial confirming the efficacy of reduced dose recombinant tissue plasminogen activator in a Chinese myocardial infarction population and demonstrating superiority to usual dose urokinase: the TUCC trial.

Ross AM, Gao R, Coyne KS, Chen J, Yao K, Yang Y, Qin X, Qiao S, Yao M; The TUCC Investigators.

**BACKGROUND:** Reports from Japan suggest effective myocardial infarction (MI) treatment in Asian patients with much lower doses of tissue plasminogen activators (tPA) than used in European and American regimens. Because increasing doses of fibrinolytics lead to increased bleeding complications, identification of patients who respond to reduced doses is of importance. We conducted a trial in the People's Republic of China in which reduced-dose recombinant tPA was compared with the standard local therapy, urokinase.

**METHODS:** Four hundred patients with acute MI within 12 hours of symptom onset were to be randomized to an 8-mg bolus of recombinant tPA followed by a 42-mg 90-minute infusion or 1.5 million units of urokinase as a 30-minute infusion. Patients received aspirin and heparin and underwent angiography to determine infarct artery patency 90 minutes after the start of therapy.

**RESULTS:** The Data and Safety Monitoring Board recommended premature termination after 342 patients were recruited. Infarct artery patency (grade 2 or 3) occurred in 79% of patients receiving recombinant tPA and in 53% of patients receiving urokinase ( $P < .001$ ); Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was 48% and 28%, respectively ( $P < .001$ ). The higher-patency-rate recombinant tPA group had better posttreatment left ventricular ejection fractions, 58.6% versus 54.7%,  $P < .01$ . Adverse events were infrequent and not significantly different in the 2 groups.

**CONCLUSIONS:** This study confirms that a substantially lower dose of recombinant tPA is effective in Asian patients compared with that required in Western patients even after consideration of body weight. Specific dose-response studies should be performed with fibrinolytic regimens to avoid overdosage with its attendant risks of excess bleeding.

*Am Heart J*, 2001;142(2):237-43

Randomized comparison of a novel anticoagulant, vasoflux, and heparin as adjunctive therapy to streptokinase for acute myocardial infarction: results of the VITAL study (Vasoflux International Trial for Acute Myocardial Infarction Lysis).

Peters RJ, Spickler W, Theroux P, White H, Gibson M, Molhoek PG, Anderson HV, Weitz JI, Hirsh J, Weaver WD.

**BACKGROUND:** Vasoflux is a low-molecular-weight heparin derivative that inhibits factor IXa activation of factor X and catalyzes fibrin-bound thrombin inactivation by heparin cofactor II. We studied whether vasoflux improves the results of thrombolysis with streptokinase for acute myocardial infarction.

**METHODS AND RESULTS:** We randomized 277 patients with acute myocardial infarction to standard intravenous unfractionated heparin (UFH) or intravenous vasoflux 1, 4, 8, or 16 mg/kg as a bolus followed by 1, 4, 8, or 16 mg/kg per hour infusion, on top of streptokinase and aspirin, until angiography at 90 minutes. Patency and corrected Thrombolysis in Myocardial Infarction (TIMI) frame count were studied at 60 and 90 minutes. Rates of TIMI grade 3 flow with vasoflux at any dose (35% to 42%) were not different from UFH (41%) at either time point, nor was the corrected TIMI frame count. However, there was an excess of bleeding in the patients randomized to vasoflux 8 or 16 mg/kg: 78% and 71%, compared with 53% for UFH (P =.004 and .043, respectively). Major bleeding was observed in 13% and 28% at these vasoflux doses compared with 8% with UFH (P =.558 and .01, respectively).

**CONCLUSION:** At doses that increase the risk of bleeding, the addition of vasoflux to streptokinase and aspirin did not lead to improved patency rates compared with UFH. Targeting factor IXa and heparin cofactor II may not be a useful adjunct to thrombolysis.

Am J Cardiol , 2001 ;88(8A):25K-29K

Use of coronary revascularization in patients with unstable and non-ST-segment elevation acute myocardial infarction.

Popma JJ, Suk J.

Percutaneous coronary intervention can be safely performed in patients with acute coronary syndromes (ACS), including those with non-ST-segment elevation myocardial infarction (MI), and unstable angina. Although there remains debate about whether an aggressive strategy involving early coronary arteriography and

revascularization should be routinely performed in patients who present with non-ST-segment elevation MI and unstable angina, recent clinical trials suggest that an aggressive approach should be taken in both intermediate- and high-risk patients with ACS. There have been 4 clinical trials that have compared the outcomes of patients presenting with non-ST-segment elevation MI or unstable angina who were assigned to invasive or conservative strategies. The Thrombolysis in Myocardial Infarction (TIMI) IIIb trial and the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial failed to demonstrate a reduction in death or MI in patients assigned to an invasive approach, but it did demonstrate an important reduction in the frequency of rehospitalization. However, these studies were performed before the availability of coronary stents or the use of glycoprotein IIb/IIIa inhibitors. In contrast, the Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC) II and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trials demonstrated significant improvements in the rates of death or MI in patients with non-ST-segment elevation MI or unstable angina assigned to an invasive strategy. Event reductions were greatest in patients with non-ST-segment elevation MI or unstable angina at intermediate or high risk for an adverse outcome. Understanding that these subgroups comprise approximately 75% of patients presenting with non-ST-segment elevation MI or unstable angina, we believe that an invasive approach is indicated in most patients who develop non-ST-segment elevation MI or unstable angina. Regardless of the strategy used in ACS patients, lipid-lowering therapy is necessary to reduce recurrent ischemia events at the site of plaque instability and in atherosclerotic disease remote to the target lesion.

Am J Cardiol , 2001 ;88(8):842-7

Comparison of primary coronary angioplasty versus thrombolysis in patients with ST-segment elevation acute myocardial infarction and grade II and grade III myocardial ischemia on the enrollment electrocardiogram.

Birnbaum Y, Goodman S, Barr A, Gates KB, Barbash GI, Battler A, Barbagelata A, Clemmensen P, Sgarbossa EB, Granger CB, Califf RM, Wagner GS.

We investigated the impact of primary angioplasty compared with thrombolysis in 894 patients with ST elevation acute myocardial infarction and electrocardiographic grades II and III ischemia on enrollment. Patients were divided into 2 groups based on the enrollment electrocardiogram-grade III: (1) absence of an S wave below the isoelectric baseline in leads that usually have a terminal S configuration (leads V(1) to V(3)), or

(2) ST J-point amplitude  $\geq$  50% of the R-wave amplitude in all other leads. To be included in the grade III group, grade III criteria in  $\geq$  2 adjacent leads were required. Patients with ST elevation but without grade III criteria were classified as having grade II. In-hospital mortality was 3.2% and 6.8% in the grade II (n = 616) and grade III (n = 278) groups, respectively (p = 0.016). In the grade II group, in-hospital mortality was similar in the thrombolysis and angioplasty subgroups (3.2% and 3.3%, p = 0.941). In patients with grade III, in-hospital mortality was 6.4% and 7.3%, respectively (p = 0.762). The odds ratio for the grade III group for death with thrombolysis was 2.06 (95% confidence intervals [CI] 0.82 to 5.19; p = 0.125); the odds ratio for primary angioplasty was 2.30 (95% CI 0.93 to 5.66; p = 0.07). In the thrombolysis group, reinfarction occurred in 3.3% and 6.5% of the grade II and grade III subgroups (p = 0.137). In the angioplasty group, reinfarction occurred in 1.3% and 4.4%, respectively (p = 0.239). Grade III ischemia on admission was associated with higher in-hospital and 30-day mortality and a higher rate of reinfarction. There was no difference in mortality between primary angioplasty and thrombolysis in the grade II and grade III ischemia patients.

Am J Cardiol, 2001 ;88(8):831-6

Early coronary intervention following pharmacologic therapy for acute myocardial infarction (the combined TIMI 10B-TIMI 14 experience).

Schweiger MJ, Cannon CP, Murphy SA, Gibson CM, Cook JR, Giugliano RP, Changezi HU, Antman EM, Braunwald E; TIMI 10B and TIMI 14 Investigators.

Earlier studies have suggested that immediate percutaneous coronary intervention (PCI) following thrombolytic therapy for acute myocardial infarction (AMI) is associated with an increase in adverse events and that routine PCI in this setting has offered no advantage over a conservative strategy. To reassess this issue in a more recent era, we evaluated 1,938 patients from the Thrombolysis in Myocardial Infarction (TIMI) 10B and 14 trials of AMI. Patients in TIMI 10B were randomized to receive tissue plasminogen activator or TNK tissue plasminogen activator, whereas patients in TIMI 14B trial were randomized to receive thrombolytic therapy with or without abciximab. All patients underwent angiography 90 minutes after receiving pharmacologic therapy. Patients who underwent PCI were classified as having undergone a rescue procedure (TIMI 0 or 1 flow at 90 minutes), an adjunctive procedure (TIMI 2 or 3 flow at 90 minutes), or a delayed procedure (performed  $>$ 150 minutes after symptom onset, median of 2.75 days). Among patients with TIMI 0 or 1 flow, there was a trend for lower 30-day mortality among patients who underwent rescue PCI than among

those who did not (6% vs 17%,  $p = 0.01$ , adjusted  $p = 0.28$ ). Patients who underwent adjunctive PCI had similar 30-day mortality and/or reinfarction as those who underwent delayed PCI. In a multivariate model both had lower 30-day mortality and/or reinfarction than patients with “successful thrombolysis” (i.e., TIMI 3 flow at 90 minutes) who did not undergo revascularization ( $p = 0.02$ ). Thus, early PCI following AMI is associated with excellent outcomes. Randomized trials of an early invasive strategy following thrombolysis are warranted

Eur Heart J, 2001;22(22):2104-15

Availability of on-site catheterization and clinical outcomes in patients receiving fibrinolysis for ST-elevation myocardial infarction.

Llevadot J, Giugliano RP, Antman EM, Wilcox RG, Gurfinkel EP, Henry T, McCabe CH, Charlesworth A, Thompson S, Nicolau JC, Tebbe U, Sadowski Z, Braunwald E; InTIME (Intravenous nPA for Treatment of Infarcting Myocardium Early) II Investigators.

AIMS: To compare management and clinical outcomes in hospitals stratified by the availability of on-site catheterization in InTIME-II, a multicentre trial comparing alteplase with lanoteplase for acute myocardial infarction.

METHODS AND RESULTS: We studied 15,078 patients enrolled in 35 countries and 855 hospitals. Thirty-one percent of hospitals had 24-h, 25% day-only, and 44% no on-site catheterization facilities. Rates of cardiac angiography (57%, 38%, 26%) and revascularization (37%, 21%, 17%) were higher in hospitals with increasing access to on-site facilities ( $P < 0.0001$ ). The presence of a 24-h on-site facility was the strongest predictor of angiography during the index admission (odds ratio 4.17, 95% CI 3.85-4.54). There were no major differences in patient outcomes at 30 days when hospitals were stratified by availability of on-site catheterization. Adjusted 1-year mortality was similar between groups of hospitals (odds ratio for day-only 0.94 [0.80-1.09] and odds ratio for no availability 0.95 [0.83-1.10] compared to hospitals with 24-h facilities).

CONCLUSIONS: There is a marked variation in procedure use by the availability of on-site catheterization with no major differences in patient outcomes. There is a need for additional randomized trials in the current era to address both the appropriate selection of patients and timing of invasive procedures in ST-elevation acute myocardial infarction.

Am J Cardiol , 2001 ;88(12):1358-63

Predictive value of markers of myocardial reperfusion in acute myocardial infarction for follow-up left ventricular function.

Lepper W, Sieswerda GT, Vanoverschelde JL, Franke A, de Cock CC, Kamp O, Kuhl HP, Pasquet A, Voci P, Visser CA, Hanrath P, Hoffmann R.

This study evaluated recently suggested invasive and noninvasive parameters of myocardial reperfusion after acute myocardial infarction (AMI), assessing their predictive value for left ventricular function 4 weeks after AMI and reperfusion defined by myocardial contrast echocardiography (MCE). In 38 patients, angiographic myocardial blush grade, corrected Thrombolysis In Myocardial Infarction frame count, ST-segment elevation index, and coronary flow reserve (n = 25) were determined immediately after primary percutaneous transluminal coronary angioplasty (PTCA) for first AMI, and intravenous MCE was determined before, and at 1 and 24 hours after PTCA to evaluate myocardial reperfusion. Results were related to global wall motion index (GWMI) at 4 weeks. MCE 1 hour after PTCA showed good correlation with GWMI at 4 weeks ( $r = 0.684$ ,  $p < 0.001$ ) and was in an analysis of variance the best parameter to predict GWMI 4 weeks after AMI. The ST-segment elevation index was close in its predictive value. Considering only invasive parameters of reperfusion myocardial blush grade was the best predictor of GWMI at 4 weeks ( $R(2) = 0.3107$ ,  $p < 0.001$ ). A MCE perfusion defect size at 24 hours of  $>$  or  $=50\%$  of the MCE perfusion defect size before PTCA was used to define myocardial nonreperfusion. In a multivariate analysis, low myocardial blush grade class was the best predictor of nonreperfusion defined by MCE. Thus, intravenous MCE allows better prediction of left ventricular function 4 weeks after AMI than other evaluated parameters of myocardial reperfusion. Myocardial blush grade is the best predictor of nonreperfusion defined by MCE and is the invasive parameter with the greatest predictive value for left ventricular function after AMI. Coronary flow parameters are less predictive.

Circulation, 2001;104(23):2778-83

Double-blind, randomized trial of an anti-CD18 antibody in conjunction with recombinant tissue plasminogen activator for acute myocardial infarction: limitation of myocardial infarction following thrombolysis in acute myocardial infarction (LIMIT AMI) study.

Baran KW, Nguyen M, McKendall GR, Lambrew CT, Dykstra G, Palmeri ST, Gibbons RJ, Borzak S, Sobel BE, Gourlay SG, Rundle AC, Gibson CM, Barron HV; The Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) Study Group.

**BACKGROUND:** Inhibition of leukocyte adhesion can reduce myocardial infarct size in animals. This study was designed to define the safety and efficacy of a recombinant, humanized, monoclonal antibody to the CD18 subunit of the beta2 integrin adhesion receptors (rhuMAb CD18), in reducing infarct size in patients treated with a thrombolytic agent.

**METHODS AND RESULTS:** The Limitation of Myocardial Infarction following Thrombolysis in Acute Myocardial Infarction Study (LIMIT AMI) was a randomized, double-blind, placebo-controlled, multicenter study conducted in 60 centers in the United States and Canada. A total of 394 subjects who presented within 12 hours of symptom onset with ECG findings (ST-segment elevation) consistent with AMI were treated with recombinant tissue plasminogen activator and were also given an intravenous bolus of 0.5 or 2.0 mg/kg rhuMAb CD18 or placebo. Coronary angiography was performed at 90 minutes, 12-lead ECGs were obtained at baseline, 90, and 180 minutes, and resting sestamibi scans were performed at  $\geq 120$  hours. Adjunctive angioplasty and use of glycoprotein IIb/IIIa antiplatelet agents at the time of angiography were discretionary. There were no treatment effects on coronary blood flow, infarct size, or the rate of ECG ST-segment elevation resolution, despite the expected induction of peripheral leukocytosis. A slight trend toward an increase in bacterial infections was observed with rhuMAb CD18 (P=0.33).

**CONCLUSIONS:** RhuMAb CD18 was well tolerated but not effective in modifying cardiac end points.

Circulation , 2002 ;105(2):157-61

Determination of successful reperfusion after thrombolysis for acute myocardial infarction: a noninvasive method using ultrasonic tissue characterization that can be applied clinically.

Hancock JE, Cooke JC, Chin DT, Monaghan MJ.

**BACKGROUND:** The aim of the present study was to determine the use of cyclic variation in ultrasonic integrated backscatter (IBS), which is reduced in ischemic myocardium, to predict an occluded infarct-related artery (IRA) after thrombolysis for acute myocardial infarction (AMI). This is important, because patency of the IRA 90 minutes after thrombolysis has been shown to predict outcome.

**METHODS AND RESULTS:** One hundred thirteen patients with AMI had peak-to-peak cyclic IBS measured in the myocardial territory supplied by their IRA as well as a remote territory with normal function from the parasternal long- or short-axis view. This analysis took 5 to 10 minutes. Wall motion score index was assessed, and coronary angiography, to determine patency of the IRA, was performed in all patients. Cyclic IBS in the IRA territory was much lower in segments supplied by an occluded IRA (3.3 versus 4.6 dB,  $P < 0.00001$ ). Using a difference in cyclic IBS between infarcted and normal segments of 15% (or 1.5 dB) as a cutoff, the sensitivity, specificity, positive and negative predictive values to determine an occluded IRA were 92%, 75%, 81%, and 89%, respectively.

**CONCLUSIONS:** The difference in cyclic IBS between IRA and remote normal segments, which can be analyzed rapidly, can be used to predict patency of the IRA in patients with AMI. This provides a noninvasive method to determine those patients who may require urgent invasive investigation.

Circulation, 2002 ;105(3):279-81

Proteolysis of tissue factor pathway inhibitor-1 by thrombolysis in acute myocardial infarction.

Ott I, Malcouvier V, Schomig A, Neumann FJ.

**BACKGROUND:** In acute myocardial infarction (AMI), surface-bound tissue factor pathway inhibitor-1 (TFPI-1) inhibits an increased monocyte procoagulant activity. In addition, TFPI-1 is released from microvascular endothelial cells after treatment with heparin and thereby contributes to its antithrombotic properties.

**METHODS AND RESULTS:** We examined 19 patients in a randomized study comparing intravenous fibrinolysis with alteplase (n=9) and revascularization by stent placement with additional abciximab treatment (n=10). We obtained blood samples for analysis of monocytic TFPI-1 surface expression by flow cytometry and

plasma TFPI-1 concentrations by immunoassay before and after therapy. We found a significant decrease in surface TFPI-1 on circulating monocytes 24 hours after thrombolysis (P=0.006) that was not observed after stenting. Systemic plasma TFPI-1 concentrations increased immediately after stenting by 71+/-14% (P=0.008), whereas after thrombolysis, a decrease in TFPI-1 plasma concentrations of 21+/-11% was observed (P=0.075). In vitro experiments confirmed that plasmin decreased TFPI-1 surface expression dose-dependently.

**CONCLUSIONS:** Activation of the fibrinolytic system by alteplase in AMI decreases surface-associated TFPI-1 on circulating monocytes and plasma TFPI-1. Reduced TFPI-1 may contribute to thrombotic complications after fibrinolysis in AMI.

Am Heart J, 2002 ;143(1):106-10

Relationship of creatine kinase-myocardial band release to Thrombolysis in Myocardial Infarction perfusion grade after intracoronary stent placement: an ESPRIT substudy.

Gibson CM, Murphy SA, Marble SJ, Cohen DJ, Cohen EA, Lui HK, Young J Jr, Kitt MM, Lorenz TJ, Tchong JE.

**BACKGROUND:** The etiology of creatine kinase-myocardial band (CK-MB) release after percutaneous coronary intervention (PCI) remains unclear. The goal of this study was to evaluate the relationship of both epicardial and tissue level perfusion at the completion of stent placement to CK-MB release after the procedure. Given the high rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow after PCI, we hypothesized that abnormalities in tissue level perfusion would instead explain CK-MB release.

**METHODS:** Data were drawn from the angiographic substudy of the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial of eptifibatid versus placebo in patients undergoing planned coronary stent implantation. In the substudy, cinefilms of 65 patients were analyzed by an angiographic core laboratory blinded to enzymatic and clinical outcomes. **RESULTS:** The release of CK-MB was not associated with TIMI grade 3 flow or the corrected TIMI frame count; 100% of patients had TIMI grade 3 flow at the completion of PCI. In contrast, tissue level perfusion using the TIMI myocardial perfusion grade (TMPG) was related to postintervention CK-MB release: patients with a closed myocardium (TMPG 0/1) or delayed myocardial perfusion (TMPG 2) had an average CK-MB release 2.2 +/- 2.7 times the upper limit of normal (n = 34), whereas those patients with normal myocardial perfusion (TMPG 3, n = 24) had CK-MB 0.8 +/-

0.6 times the upper limit of normal ( $P = .01$ ). Although no patients with TMPG 3 sustained death/myocardial infarction/urgent target vessel revascularization or thrombotic bailout, 17.7% of patients with TMPG 0/1/2 did by 48 hours ( $P = .037$ ).

**CONCLUSIONS:** Impaired tissue level perfusion as assessed by the TMPG and not epicardial coronary blood flow is associated with CK-MB elevation after PCI. These data provide a pathophysiologic link between impaired tissue level perfusion, post-PCI infarction, and adverse clinical outcomes.

Am J Cardiol , 2002 ;89(4):381-

Timing of aspirin administration as a determinant of survival of patients with acute myocardial infarction treated with thrombolysis.

Freimark D, Matetzky S, Leor J, Boyko V, Barbash IM, Behar S, Hod H.

Unlike thrombolytic agents, there are conflicting data regarding the time-dependent effect of aspirin treatment on outcome in acute myocardial infarction (AMI). We sought to evaluate the impact of timing of aspirin administration (before vs after thrombolysis) on mortality of patients with AMI. Our study included 1,200 patients with ST elevation AMI treated with thrombolysis. Early ( $n = 364$ ) versus late ( $n = 836$ ) users were defined as those receiving emergency aspirin before versus after initiation of thrombolysis, respectively. Time (median) from symptom onset to initiation of aspirin treatment was significantly shorter in early versus late users (1.6 vs 3.5 hours;  $p < 0.001$ ). There were no significant differences between the 2 groups with respect to baseline clinical characteristics. Early aspirin users were more likely to develop reischemia, to be treated with beta blockers, to be referred to coronary angiography, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery. Early users experienced lower mortality at 7 days (2.5% vs 6.0%,  $p = 0.01$ ), 30 days (3.3% vs 7.3%,  $p = 0.008$ ), and 1 year (5.0% vs 10.6%,  $p = 0.002$ ) than late users. This survival benefit persisted for patients with and without previous aspirin therapy or revascularization and after adjustment for baseline characteristics and therapies at 7 days (odds ratio 0.36, 95% confidence interval 0.15 to 0.79), at 30 days (odds ratio 0.39, 95% confidence interval 0.17 to 0.82), and at 1 year (odds ratio 0.41, 95% confidence interval 0.21 to 0.74). Our study proposes a time-dependent benefit from aspirin in patients with AMI treated with thrombolysis.

J Am Coll Cardiol 2002 ;39(3):377-86

Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial.

Brener SJ, Zeymer U, Adgey AA, Vrobel TR, Ellis SG, Neuhaus KL, Juran N, Ivanc TB, Ohman EM, Strony J, Kitt M, Topol EJ.

**OBJECTIVES:** This study was designed to test the hypothesis that eptifibatide and reduced-dose tissue plasminogen activator (t-PA) will enhance infarct artery patency at 60 min in patients with acute myocardial infarction (AMI).

**BACKGROUND:** Combination fibrin and platelet lysis improves epicardial and myocardial reperfusion in AMI.

**METHODS:** Patients were enrolled in a dose finding (Phase A, n = 344) followed by a dose confirmation (Phase B, n = 305) protocol. All patients received aspirin and weight-adjusted heparin and underwent angiography at 60 and 90 min. In Phase A, eptifibatide in a single or double bolus (30 min apart) of 180, 180/90 or 180/180 microg/kg followed by an infusion of 1.33 or 2.0 microg/kg per min was sequentially added to 25 or 50 mg of t-PA. In Phase B, patients were randomized to: 1) double-bolus eptifibatide 180/90 (30 min apart) and 1.33 microg/kg per min infusion with 50 mg t-PA (Group I); 2) 180/90 (10 min apart) and 2.0 g/kg per min with 50 mg t-PA (Group II); or 3) full-dose, weight-adjusted t-PA (Group III).

**RESULTS:** In Phase A, the best rate of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 was achieved using 180/90/1.33 microg/kg per min eptifibatide with 50 mg t-PA: 65% and 78% at 60 and 90 min, respectively. In Phase B, the incidence of TIMI flow grade 3 at 60 min was 42%, 56% and 40%, for Groups I through III, respectively (p = 0.04, Group II vs. Group III). The median corrected TIMI frame count was 38, 33 and 50, respectively (p = 0.02). TIMI major bleeding was reported in 8%, 11% and 6%, respectively; intracranial hemorrhage occurred in 1%, 3% and 2% of patients (p > 0.5 for both). The incidences of death (4%, 5% and 7%), reinfarction or revascularization at 30 days were similar among the three treatment groups.

**CONCLUSIONS:** In comparison with standard t-PA regimen, double-bolus eptifibatide (10 min apart) with a 48-h infusion and half-dose t-PA (Group II) is associated with improved quality and speed of reperfusion. The safety profile of this therapy is similar to that of other combination regimens.

Journal of the American College of Cardiology, 32:641-647

Clinical predictors of early infarct-related artery patency following thrombolytic therapy: importance of body weight, smoking history, infarct-related artery and choice of thrombolytic regimen: the GUSTO-I experience

Conor F. Lundergan, Jonathan S. Reiner, William F. McCarthy, Karin S. Coyne, Robert M. Califf, Allan M. Ross for the GUSTO-I Angiographic Investigators

**Objectives.** The purpose of this study was to determine patient characteristics that are a priori predictors of early infarct related artery patency following thrombolytic therapy, and to provide a paradigm which may identify patients who would be most likely to achieve restoration of normal (TIMI 3) coronary flow in response to thrombolytic therapy.

**Background.** Restoration of infarct-related artery perfusion in acute myocardial infarction is necessary for preservation of ventricular function and mortality reduction. Clinical variables that are a priori predictors of early patency with currently available thrombolytic regimens have not been fully characterized.

**Methods.** The probability of early infarct-related artery patency (TIMI 3 flow) was determined by multivariable logistic regression. We determined a reduced (parsimonious) model for predicting early (90 min) infarct-related artery patency (TIMI grade 3) based on data from 1,030 patients in the GUSTO-I Angiographic study.

**Results.** Predictors of 90 min TIMI 3 flow are use of an accelerated t-PA regimen (vs. streptokinase containing regimens) ( $X^2 = 39.1$ ;  $p \leq 0.0001$ ), infarct related artery (RCA/Lcx vs. LAD) ( $X^2 = 12.7$ ;  $p = 0.0004$ ), body weight ( $X^2 = 10.3$ ;  $p = 0.001$ ) and history of smoking ( $X^2 = 7.4$ ;  $p = 0.007$ ). Time from symptom onset to treatment was not significant ( $p = 0.71$ ).

**Conclusions.** The efficacy of currently available thrombolytic regimens is chiefly dependent on choice of thrombolytic regimen, body weight, infarct-related coronary artery and smoking history. Clinical variables alone correctly predict a priori TIMI 3 flow in the infarct-related artery 64% of the time. Patients with body weights greater than 85 kg are at a significant disadvantage with regard to achieving successful thrombolysis compared to those with lesser body weights.

Journal of the American College of Cardiology, 32:1326-1330

The distinction between coronary and myocardial reperfusion after thrombolytic therapy by clinical markers of reperfusion

Shlomi Matetzky, Dov Freimark, Pierre Chouraqui, Ilya Novikov, Oren Agranat, Babeth Rabinowitz, Elieser Kaplinsky, Hanoch Hod

**Objectives.** We sought to examine the hypothesis that rapid resolution of ST-segment elevation in acute myocardial infarction (AMI) patients with early peak creatine kinase (CK) after thrombolytic therapy differentiates among patients with early recanalization between those with and those without adequate tissue (myocardial) reperfusion.

**Background.** Early recanalization of the epicardial infarct-related artery (IRA) during AMI does not ensure adequate reperfusion on the myocardial level. While early peak CK after thrombolysis results from early and abrupt restoration of the coronary flow to the infarcted area, rapid ST-segment resolution, which is another clinical marker of successful reperfusion, reflects changes of the myocardial tissue itself.

**Methods.** We compared the clinical and the angiographic results of 162 AMI patients with early peak CK ( $\leq 12$  h) after thrombolytic therapy with (group A) and without (group B) concomitant rapid resolution of ST-segment elevation.

**Results.** Patients in groups A and B had similar patency rates of the IRA on angiography (anterior infarction: 93% vs. 93%; inferior infarction: 89% vs. 77%). Nevertheless, group A versus B patients had lower peak CK (anterior infarction:  $1,083 \pm 585$  IU/ml vs.  $1,950 \pm 1,216$ ,  $p < 0.01$ ; and inferior infarction:  $940 \pm 750$  IU/ml vs.  $1,350 \pm 820$ ,  $p = 0.18$ ) and better left ventricular ejection fraction (anterior infarction:  $49 \pm 8$ , vs.  $44 \pm 8$ ,  $p < 0.01$ ; inferior infarction:  $56 \pm 12$  vs.  $51 \pm 10$ ,  $p = 0.1$ ). In a 2-year follow-up, group A as compared with group B patients had a lower rate of congestive heart failure (1% vs. 13%,  $p < 0.01$ ) and mortality (2% vs. 13%,  $p < 0.01$ ).

**Conclusions.** Among patients in whom reperfusion appears to have taken place using an early peak CK as a marker, the coexistence of rapid resolution of ST-segment elevation further differentiates among patients with an opened culprit artery between the ones with and without adequate myocardial reperfusion.

JACC, 1998;32:596-605

**A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy : Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial**

Peter A. McCullough, William W. O'Neill, Mariann Graham, Robert J. Stomel, Felix Rogers, Shukri David, Ali Farhat, Rasa Kazlauskaitė, Majid Al-Zagoum and Cindy L. Grines

**Objectives.** The purpose of this study was to determine if early triage angiography with revascularization, if indicated, favorably affects clinical outcomes in patients with suspected acute myocardial infarction who are ineligible for thrombolysis.

**Background.** The majority of patients with acute myocardial infarction and other acute coronary syndromes are considered ineligible for thrombolysis and therefore are not afforded the opportunity for early reperfusion.

**Methods.** This multicenter, prospective, randomized trial evaluated in a controlled fashion the outcomes following triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Eligible patients (n = 201) with <24 h of symptoms were randomized to early triage angiography and subsequent therapies based on the angiogram versus conventional medical therapy consisting of aspirin, intravenous heparin, nitroglycerin, beta-blockers, and analgesics.

**Results.** In the triage angiography group, 109 patients underwent early angiography and 64 (58%) received revascularization, whereas in the conservative group, 54 (60%) subsequently underwent nonprotocol angiography in response to recurrent ischemia and 33 (37%) received revascularization (p = 0.004). The mean time to revascularization was  $27 \pm 32$  versus  $88 \pm 98$  h (p = 0.0001) and the primary endpoint of recurrent ischemic events or death occurred in 14 (13%) versus 31 (34%) of the triage angiography and conservative groups, respectively (45% risk reduction, 95% CI 27-59%, p = 0.0002). There were no differences between the groups with respect to initial hospital costs or length of stay. Long-term follow-up at a median of 21 months revealed no significant differences in the endpoints of late revascularization, recurrent myocardial infarction, or all-cause mortality.

**Conclusions.** Early triage angiography in patients with acute coronary syndromes who are not eligible for

thrombolytics reduced the composite of recurrent ischemic events or death and shortened the time to definitive revascularization during the index hospitalization. Despite more frequent early revascularization after triage angiography, we found no long-term benefit in cardiac outcomes compared with conservative medical therapy with revascularization prompted by recurrent ischemia.

Circulation, 1998 98; 2659-2665.

#### Ten-Year Follow-Up of the First Megatrial Testing Thrombolytic Therapy in Patients With Acute Myocardial Infarction : Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 Study

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**Background-**We conducted a 10-year follow-up of the 11 712 patients with acute myocardial infarction randomized in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 study, the first large trial assessing thrombolytic therapy.

**Methods and Results-**Information on survival at 10 years was obtained for the 93% of all randomized patients through the census offices of their towns of residence. The difference in survival produced by streptokinase and sustained up to 1 year was still significant at 10 years (log-rank test,  $P=0.02$ ), with the absolute benefit of 19 (95% CI 1 to 37) lives saved per 1000 patients treated. The time dependence of the extent of the benefit was confirmed, as the higher mortality rate reductions found in patients treated earlier were still present at 10 years. In the overall population, most of the benefit was obtained before hospital discharge (RR 0.81, 95% CI 0.72 to 0.90), since no difference in survival between thrombolyzed and control patients discharged alive was found at 10 years (RR 0.98, 95% CI 0.90 to 1.06). However, a slight albeit nonsignificant divergence of the survival curves of patients randomized within the first hour was observed [90 (95% CI 34 to 146) lives saved per 1000 at 10 years versus 72 (95% CI 37 to 107) lives saved at hospital discharge].

**Conclusions-**The benefits of a single intravenous infusion of 1.5 million units of streptokinase in prolonging survival of patients with acute myocardial infarction is sustained up to 10 years, with a still-evident trend in favor of the patients admitted earlier.

Circulation , 1998;98: 2117-2125

## Evaluation of a Weight-Adjusted Single-Bolus Plasminogen Activator in Patients With Myocardial Infarction : A Double-Blind, Randomized Angiographic Trial of Lanoteplase Versus Alteplase

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**Background-**Lanoteplase (nPA) is a rationally designed variant of tissue plasminogen activator with greater fibrinolytic potency and slower plasma clearance than alteplase.

**Methods and Results-**InTIME (Intravenous nPA for Treatment of Infarcting Myocardium Early), a multicenter, double-blind, randomized, double-placebo angiographic trial, evaluated the dose-response relationship and safety of single-bolus, weight-adjusted lanoteplase. Patients (n=602) presenting within 6 hours of acute myocardial infarction were randomized and treated with either a single-bolus injection of lanoteplase (15, 30, 60, or 120 kU/kg) or accelerated alteplase. The primary objective was to determine TIMI grade flow at 60 minutes. Angiographic assessments were also performed at 90 minutes and on days 3 to 5. Follow-up was continued for 30 days. Lanoteplase achieved its primary objective, demonstrating a dose-response in TIMI grade 3 flow at 60 minutes (23.6% to 47.1% of subjects,  $P<0.001$ ). Similar results were observed at 90 minutes (26.1% to 57.1%,  $P<0.001$ ). At 90 minutes, coronary patency (TIMI 2 or 3) increased across the dose range up to 83% of subjects at 120 kU/kg lanoteplase compared with 71.4% with alteplase. Thus, at this dose, lanoteplase was superior to alteplase in restoring coronary patency (difference, 12%; 95% CI, 1% to 23%). The early safety experience in this study suggests that lanoteplase was well tolerated at all doses with safety comparable to that of alteplase.

**Conclusions-**Lanoteplase, a single-bolus, weight-adjusted agent, increased coronary patency at 60 and 90 minutes in a dose-dependent fashion. Coronary patency at 90 minutes was achieved more frequently with 120 kU/kg lanoteplase than alteplase. In this study, safety with lanoteplase and alteplase was comparable. InTIME-II, a worldwide mortality trial, will evaluate efficacy and safety with this promising new agent.

Journal of the American College of Cardiology, 31:7:1493-1498

Randomized Comparison of Direct Thrombin Inhibition Versus Heparin in Conjunction With Fibrinolytic Therapy for Acute Myocardial Infarction: Results From the GUSTO-IIb Trial

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**Objectives.** We sought to show that hirudin might interact differently with streptokinase (SK) and tissue-type plasminogen activator (t-PA), which could reduce the incidence of death or reinfarction at 30 days.

**Background.** In a large-scale trial of patients with acute coronary syndromes, hirudin provided modest benefit compared with heparin. However, the interaction with thrombolytic agents was not specifically assessed.

**Methods.** Patients with symptoms of acute myocardial infarction and electrocardiographic ST segment elevation were treated with thrombolytic therapy and randomly assigned to receive hirudin or heparin.

**Results.** A total of 2,274 patients received t-PA, and 1,015 received SK. Baseline characteristics were balanced by antithrombin assignment. Among SK-treated patients, death or reinfarction at 30 days occurred more often in those treated with adjunctive heparin (14.4%) rather than hirudin (8.6%, odds ratio [OR] 1.78, 95% confidence interval [CI] 1.20 to 2.66,  $p = 0.004$ ). Among t-PA-treated patients, the rates were 10.9% with heparin and 10.3% with hirudin (OR 1.06, 95% CI 0.81 to 1.38,  $p = 0.68$ ; for treatment heterogeneity: chi-square 4.20, degrees of freedom [df] 1,  $p = 0.04$ ). After adjustment for baseline differences between thrombolytic groups, the rates were 9.1% for SK with hirudin, 10.3% for t-PA with hirudin, 10.5% for t-PA with heparin and 14.9% for SK with heparin (for treatment heterogeneity: chi-square 4.5, df 1,  $p = 0.03$ ), suggesting that the beneficial treatment effect of hirudin was limited to the SK-treated patients.

**Conclusions.** Hirudin interacts favorably with SK but not t-PA, highlighting the importance of thrombin activity after SK therapy and the potential for simulating the effects of a more potent fibrinolytic agent through direct antithrombin therapy.

Journal of the American College of Cardiology, 31:7:1511-1517

Rescue Angioplasty After Failed Thrombolysis: Technical and Clinical Outcomes in a Large Thrombolysis Trial

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**Objectives.** We sought to assess the angiographic outcome, complication rates and clinical features of percutaneous transluminal coronary angioplasty (PTCA) after failed thrombolysis for acute myocardial infarction.

**Background.** “Rescue angioplasty” refers to mechanical reopening of an occluded infarct-related artery (IRA) after failed intravenous thrombolysis. Although the procedure is commonly performed, data describing its technical and clinical outcome are sparse. Early reports suggested that rescue PTCA is less often successful and produces more complications than primary PTCA. Other reports have described beneficial effects of successful rescue PTCA but adverse outcomes when PTCA is unsuccessful.

**Methods.** Using data from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) angiographic substudy, we compared clinical and angiographic outcomes of 198 patients selected for a rescue PTCA attempt with those of 266 patients with failed thrombolysis but managed conservatively and, for reference, with those of 1,058 patients with successful thrombolysis.

**Results.** Patients offered rescue PTCA had more impaired left ventricular function than those in whom closed vessels were managed conservatively. Rescue successfully opened 88.4% of closed arteries, with 68% attaining Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. The interventions did not increase catheterization laboratory or postprocedural complication rates. Multivariate analysis identified severe heart failure to be a determinant of a failed rescue attempt. Successful rescue PTCA resulted in superior left ventricular function and 30-day mortality outcomes, comparable to outcomes in patients with closed IRAs managed conservatively, but less favorable than in patients in whom thrombolytic therapy was initially successful. The mortality rate after a failed rescue attempt was 30.4%; however, five of the seven patients who died after failed rescue PTCA were in cardiogenic shock before the procedure.

**Conclusions.** Rescue PTCA tends to be selected for patients with clinical predictors of a poor outcome. It is effective in restoring patency. Patients who die after a failed rescue attempt are often already in extremis before the angioplasty attempt.

Circulation, 1998 ;98: 2805-2814

TNK-Tissue Plasminogen Activator Compared With Front-Loaded Alteplase in Acute Myocardial Infarction : Results of the TIMI 10B Trial

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**Background-**Bolus thrombolytic therapy is a simplified means of administering thrombolysis that facilitates rapid time to treatment. TNK-tissue plasminogen activator (TNK-tPA) is a highly fibrin-specific single-bolus thrombolytic agent.

**Methods and Results-**In TIMI 10B, 886 patients with acute ST-elevation myocardial infarction presenting within 12 hours were randomized to receive either a single bolus of 30 or 50 mg TNK-tPA or front-loaded tPA and underwent immediate coronary angiography. The 50-mg dose was discontinued early because of increased intracranial hemorrhage and was replaced by a 40-mg dose, and heparin doses were decreased. TNK-tPA 40 mg and tPA produced similar rates of TIMI grade 3 flow at 90 minutes (62.8% versus 62.7%, respectively,  $P=NS$ ); the rate for the 30-mg dose was significantly lower (54.3%,  $P=0.035$ ) and was 65.8% for the 50-mg dose ( $P=NS$ ). A prespecified analysis of weight-based TNK-tPA dosing using median TIMI frame count demonstrated a dose response ( $P=0.001$ ). Similar dose responses were observed for serious bleeding and intracranial hemorrhage, but significantly lower rates were observed for both TNK-tPA and tPA after the heparin doses were lowered and titration of the heparin was started at 6 hours.

**Conclusions-**TNK-tPA, given as a single 40-mg bolus, achieved rates of TIMI grade 3 flow similar to those of the 90-minute bolus and infusion of tPA. Weight-adjusting TNK-tPA appears to be important in achieving optimal reperfusion; reduced heparin dosing appears to improve safety for both agents. Together with the safety results from the parallel Assessment of the Safety of a New Thrombolytic: TNK-tPA (ASSENT I) trial, an appropriate dose of this single-bolus thrombolytic agent has been identified for phase III testing.

Journal of the American College of Cardiology, 32:3:620-628

Intravenous diltiazem in acute myocardial infarction : Diltiazem as adjunctive therapy to activase (DATA) trial

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**Objectives.** This study was defined as a pilot investigation of the usefulness and safety of intravenous diltiazem as adjunctive therapy to tissue plasminogen activator in acute myocardial infarction, followed by oral therapy for 4 weeks.

**Background.** Experimental studies have documented that calcium antagonists protect the myocardial cell

against the damage caused by coronary artery occlusion and reperfusion, yet no benefits have been conclusively demonstrated in acute myocardial infarction (AMI) in humans.

**Methods.** In this pilot study, 59 patients with an AMI treated with tissue-type plasminogen activator (t-PA) were randomized, double blinded, to intravenous diltiazem or placebo for 48 h, followed by oral therapy for 4 weeks. The primary objective was to detect an effect on indices of regional left ventricular function and perfusion. Patients were also closely monitored for clinical events, coronary artery patency and indices of infarct size and of left ventricular function.

**Results.** Creatine kinase elevation, Q wave score, global and regional left ventricular function and coronary artery patency at 48 h were not significantly different between the diltiazem and placebo groups. A greater improvement observed in regional perfusion and function with diltiazem was likely explained by initial larger defects. Diltiazem, compared to placebo, reduced the rate of death, reinfarction or recurrent ischemia at 35 days from 41% to 13% ( $p = 0.027$ ) and prevented the need for an urgent intervention. The rate of death or myocardial infarction was reduced by 65% ( $p = 0.15$ ). These benefits could not be explained by differences in baseline characteristics such as age, site and extent of infarction, time of inclusion or concomitant therapy. Heart rate and blood pressure were reduced throughout the study with active diltiazem treatment. Side effects of diltiazem were bradycardia and hypotension that required transient or permanent discontinuation of the study drug in 27% of patients, vs. 17% of patients with placebo.

**Conclusions.** A protective effect for clinical events related to early postinfarction ischemia and reinfarction was suggested in this study, with diltiazem administered intravenously with t-PA followed by oral therapy for 1 month, with no effect on coronary artery patency and left ventricular function and perfusion.

Journal of the American College of Cardiology, 1998;32:1326-1330

The distinction between coronary and myocardial reperfusion after thrombolytic therapy by clinical markers of reperfusion

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**Objectives.** We sought to examine the hypothesis that rapid resolution of ST-segment elevation in acute myocardial infarction (AMI) patients with early peak creatine kinase (CK) after thrombolytic therapy differentiates among patients with early recanalization between those with and those without adequate tissue

(myocardial) reperfusion.

**Background.** Early recanalization of the epicardial infarct-related artery (IRA) during AMI does not ensure adequate reperfusion on the myocardial level. While early peak CK after thrombolysis results from early and abrupt restoration of the coronary flow to the infarcted area, rapid ST-segment resolution, which is another clinical marker of successful reperfusion, reflects changes of the myocardial tissue itself.

**Methods.** We compared the clinical and the angiographic results of 162 AMI patients with early peak CK (12 h) after thrombolytic therapy with (group A) and without (group B) concomitant rapid resolution of ST-segment elevation.

**Results.** Patients in groups A and B had similar patency rates of the IRA on angiography (anterior infarction: 93% vs. 93%; inferior infarction: 89% vs. 77%). Nevertheless, group A versus B patients had lower peak CK (anterior infarction:  $1,083 \pm 585$  IU/ml vs.  $1,950 \pm 1,216$ ,  $p < 0.01$ ; and inferior infarction:  $940 \pm 750$  IU/ml vs.  $1,350 \pm 820$ ,  $p = 0.18$ ) and better left ventricular ejection fraction (anterior infarction:  $49 \pm 8$ , vs.  $44 \pm 8$ ,  $p < 0.01$ ; inferior infarction:  $56 \pm 12$  vs.  $51 \pm 10$ ,  $p = 0.1$ ). In a 2-year follow-up, group A as compared with group B patients had a lower rate of congestive heart failure (1% vs. 13%,  $p < 0.01$ ) and mortality (2% vs. 13%,  $p < 0.01$ ).

**Conclusions.** Among patients in whom reperfusion appears to have taken place using an early peak CK as a marker, the coexistence of rapid resolution of ST-segment elevation further differentiates among patients with an opened culprit artery between the ones with and without adequate myocardial reperfusion.

Lancet, 1998; 352: 1245 51

Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)

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**Background**

Thrombolysis for acute ischaemic stroke has been investigated in several clinical trials, with variable results. We have assessed the safety and efficacy of intravenous thrombolysis with alteplase (0.9 mg/kg bodyweight) within 6 h of stroke onset.

**Methods**

This non-angiographic, randomised, double-blind, trial enrolled 800 patients in Europe, Australia, and New Zealand. Computed tomography was used to exclude patients with signs of major infarction. Alteplase (n=409) and placebo (n=391) were randomly assigned with stratification for time since symptom onset (03 h or 36 h). The primary endpoint was the modified Rankin scale (mRS) at 90 days, dichotomised for favourable (score 01) and unfavourable (score 26) outcome. Analyses were by intention to treat.

#### Findings

165 (40.3%) alteplase-group patients and 143 (36.6%) placebo-group patients had favourable mRS outcomes (absolute difference 3.7%,  $p=0.277$ ). In a post-hoc analysis of mRS scores dichotomised for death or dependency, 222 (54.3%) alteplase-group and 180 (46.0%) placebo-group patients had favourable outcomes (score 02; absolute difference 8.3%,  $p=0.024$ ). Treatment differences were similar whether patients were treated within 3 h or 36 h. 85 (10.6%) patients died, with no difference between treatment groups at day  $90 \pm 14$  days (43 alteplase, 42 placebo). Symptomatic intracranial haemorrhage occurred in 36 (8.8%) alteplase-group patients and 13 (3.4%) placebo-group patients.

#### Interpretation

The results do not confirm a statistical benefit for alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increased risk of intracranial haemorrhage, thrombolysis with alteplase at a dose of 0.9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome.

Journal of the American College of Cardiology, 1998;32:634-640

Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience

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**Objectives.** We assessed the use and effects of acute intravenous and later oral atenolol treatment in a prospectively planned post hoc analysis of the GUSTO-I dataset.

**Background.** Early intravenous beta blockade is generally recommended after myocardial infarction, especially for patients with tachycardia and/or hypertension and those without heart failure.

**Methods.** Besides one of four thrombolytic strategies, patients without hypotension, bradycardia or signs of

heart failure were to receive atenolol 5 mg intravenously as soon as possible, another 5 mg intravenously 10 min later and 50 to 100 mg orally daily during hospitalization. We compared the 30-day mortality of patients given no atenolol (n = 10,073), any atenolol (n = 30,771), any intravenous atenolol (n = 18,200), only oral atenolol (n = 12,545) and both intravenous and oral drug (n = 16,406), after controlling for baseline differences and for early deaths (before oral atenolol could be given).

**Results.** Patients given any atenolol had a lower baseline risk than those not given atenolol. Adjusted 30-day mortality was significantly lower in atenolol-treated patients, but patients treated with intravenous and oral atenolol treatment vs. oral treatment alone were more likely to die (odds ratio, 1.3; 95% confidence interval, 1.0 to 1.5; p = 0.02). Subgroups had similar rates of stroke, intracranial hemorrhage and reinfarction, but intravenous atenolol use was associated with more heart failure, shock, recurrent ischemia and pacemaker use than oral atenolol use.

**Conclusions.** Although atenolol appears to improve outcomes after thrombolysis for myocardial infarction, early intravenous atenolol seems of limited value. The best approach for most patients may be to begin oral atenolol once stable.

The American Journal of Cardiology, 1998;81:3:282-287

#### Benefit of Early Sustained Reperfusion in Patients With Prior Myocardial Infarction (The GUSTO-I Trial)

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The primary objective of this study was to characterize a large cohort of patients receiving thrombolytic therapy for acute myocardial infarction with respect to the group with a prior event. Patients were randomly assigned to 1 of 4 thrombolytic strategies. Baseline characteristics, 30-day outcomes, and 1-year mortality were compared between patients with (n = 6,704) and without (n = 34,143) prior myocardial infarction. Patients with prior myocardial infarction presented to the hospital earlier than those having their first event, but institution of thrombolytic therapy was delayed. Mortality at 30 days (11.7% vs 5.9%, p = 0.001) and 1 year (17.3% vs 8.2%, p < 0.001) was greater among patients with prior infarction, and independent of other demographic variables. Accelerated alteplase was more effective than streptokinase or combination therapy (30-day mortality 10.4% vs 12.2%, p = 0.012; 1-year mortality 15.9% vs 17.8%, p = 0.041). Infarct vessel patency did not differ between those

with and without prior myocardial infarction (67.3% vs 67% at 90 minutes,  $p = 0.92$ ); however, recurrent ischemia was more common in patients with prior myocardial infarction. Patients with healed myocardial infarction should be educated to ensure early hospital admission if they develop symptoms suggestive of acute infarction, and upon hospital arrival should be promptly triaged to receive reperfusion therapy with accelerated alteplase.

Journal of the American College of Cardiology, 1998;31:2:338-343

### Tissue-Type Plasminogen Activator Therapy Versus Primary Coronary Angioplasty: Impact on Myocardial Tissue Perfusion and Regional Function 1 Month After Uncomplicated Myocardial Infarction

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#### Objectives.

This study sought to compare the impact of primary coronary angioplasty and thrombolytic therapy for acute myocardial infarction (AMI) on 1-month infarct size and microvascular perfusion.

**Background.** The effect of the reperfusion strategies of primary coronary angioplasty and thrombolytic therapy on microvascular integrity still remains to be determined.

#### Methods.

Sixty-two consecutive patients with a first AMI, undergoing intravenous tissue-type plasminogen activator (t-PA) therapy (32 patients, Group I) or primary angioplasty (30 patients, Group II), were studied. Only patients with 1-month Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 were selected for the study. Patients in whom primary angioplasty was unsuccessful or those with clinical evidence of failed reperfusion were excluded. Microvascular perfusion was assessed at 1 month by intracoronary injection of sonicated microbubbles. Contrast score index (CSI) and wall motion score index (WMSI) were derived using qualitative methods.

#### Results.

At baseline there were no significant differences between groups for age, risk factors, time to hospital presentation, Killip class on admission, prevalence of multivessel disease or anterior infarct site, infarct area extension before reperfusion, peak creatine kinase levels and postinfarction treatment. Conversely, significant differences between groups were found at follow-up for percent residual infarct related-artery (IRA) stenosis

( $70 \pm 12$  vs  $36 \pm 14$  [mean  $\pm$  SD],  $p = 0.0001$ ), CSI ( $1.02 \pm 0.4$  vs.  $1.49 \pm 0.5$ ,  $p = 0.0003$ ) and WMSI ( $1.67 \pm 0.3$  vs.  $1.45 \pm 0.3$ ,  $p = 0.015$ ). In particular, in the subset of patients with TIMI grade 3 flow, a perfusion defect occurred in one or more segments subtended by the IRA in 72% of Group I versus 31% of Group II patients ( $p < 0.00001$ ) and in 27% of Group I versus 8% of Group II segments ( $p < 0.00001$ ).

#### Conclusions.

The present study shows, in a highly selected cohort with successful IRA recanalization, that primary angioplasty is more effective than thrombolysis in preserving microvascular flow and preventing extension of myocardial damage at 1-month after AMI.

N Engl J Med , 1997;337:1124-30.

### A Comparison of Continuous Infusion of Alteplase with Double-Bolus Administration for Acute Myocardial Infarction

The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators

**Background.** Accelerated infusion of alteplase (tissue plasminogen activator) over a period of 90 minutes induces more rapid lysis of coronary-artery thrombi than a 3-hour infusion. With two bolus doses of alteplase, further shortening the duration of administration, complete reperfusion was achieved in more than 85 percent of the patients in initial angiographic studies. We tested the hypothesis that double-bolus alteplase is at least as effective as accelerated infusion.

**Methods.** In 398 hospitals, 7169 patients with acute myocardial infarction were randomly assigned to weight-adjusted, accelerated infusion of 100 mg of alteplase or to a bolus of 50 mg of alteplase over a period of 1 to 3 minutes followed 30 minutes later by a second bolus of 50 mg (or 40 mg for patients who weighed less than 60 kg). The primary end point was death from any cause at 30 days. The trial was stopped prematurely because of concern about the safety of the double-bolus injection.

**Results.** Thirty-day mortality was higher in the double-bolus group than in the accelerated-infusion group: 7.98 percent as compared with 7.53 percent. The absolute difference was 0.44 percent, with a one-sided 95 percent upper boundary of 1.49 percent, which exceeded the prespecified upper limit of 0.40 percent to indicate equivalence in 30-day mortality between the two regimens. The respective rates of any stroke and of hemorrhagic stroke were 1.92 and 1.12 percent after double-bolus alteplase, as compared with 1.53 and 0.81 percent after an accelerated infusion of alteplase ( $P = 0.24$  and  $P = 0.23$ , respectively).

**Conclusions.** Double-bolus alteplase was not shown to be equivalent, according to the prespecified criteria, to

accelerated infusion with regard to 30-day mortality. There was also a slightly higher rate of intracranial hemorrhage with the double-bolus method. Therefore, accelerated infusion of alteplase over a period of 90 minutes remains the preferred regimen.

Circulation, 1999 ;99: 2892-2900.

### Clinical Significance of Thrombocytopenia During a Non-ST-Elevation Acute Coronary Syndrome : The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Experience

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**Background-**The significance of thrombocytopenia in patients experiencing an acute coronary syndrome (ACS) has not been examined systematically. We evaluated this condition in a large non-ST-elevation ACS clinical trial, with particular interest paid to its correlation with clinical outcomes.

**Methods and Results-**Patients presenting without persistent ST elevation during an ACS were randomized to receive a double-blind infusion of the platelet glycoprotein (GP) IIb/IIIa inhibitor eptifibatide or placebo in addition to other standard therapies including heparin and aspirin. The primary end point was death/nonfatal myocardial infarction (MI) at 30 days, whereas bleeding and stroke were the main safety outcomes. Thrombocytopenia (nadir platelet count  $<100 \times 10^9/L$  or  $<50\%$  of baseline) occurred in 7.0% of enrolled patients. The time to onset was a median of 4 days in both treatment arms. Patients with thrombocytopenia were older, weighed less, were more likely nonwhite, and had more cardiac risk factors. These patients experienced significantly more bleeding events: they were more than twice as likely to experience moderate/severe bleeding after adjustment for confounders. Univariably, ischemic events (stroke, MI, and death) occurred significantly ( $P < 0.001$ ) more frequently in patients with thrombocytopenia; multivariable regression modeling preserved this association with death/nonfatal MI at 30 days. Neither the use of heparin or eptifibatide was found to independently increase thrombocytopenic risk.

**Conclusions-**Although causality between thrombocytopenia and adverse clinical events could not be established definitively, thrombocytopenia was highly correlated with both bleeding and ischemic events, and the presence of this condition identified a more-at-risk patient population.

Circulation, 1999 ;99: 299-304.

### The Contribution of Activated Factor XIII to Fibrinolytic Resistance in Experimental Pulmonary Embolism

Guy L. Reed and Aiilyan K. Houg

**Background-**The resistance of thrombi to fibrinolysis induced by plasminogen activators remains a major impediment to the successful treatment of thrombotic diseases. This study examines the contribution of activated factor XIII (factor XIIIa) to fibrinolytic resistance in experimental pulmonary embolism.

**Methods and Results-**The fibrinolytic effects of specific inhibitors of factor XIIIa-mediated fibrin-fibrin cross-linking and  $\alpha$ 2-antiplasmin-fibrin cross-linking were measured in anesthetized ferrets with pulmonary emboli. Five experimental groups were treated with heparin (100 U/kg) and/or tissue plasminogen activator (TPA, 1 mg/kg) and the percent (mean $\pm$ SD) lysis of emboli was determined: (1) control, normal factor XIIIa activity (14.1 $\pm$ 4.8% lysis); (2) inhibited factor XIIIa activity (42.7 $\pm$ 7.4%); (3) normal factor XIIIa activity+TPA (32.3 $\pm$ 7.7%); (4) inhibited factor XIIIa activity+TPA (76.0 $\pm$ 11.9%); and (5) inhibited  $\alpha$ 2-antiplasmin-fibrin cross-linking+TPA (54.7 $\pm$ 3.9%). Inhibition of factor XIIIa activity increased endogenous lysis markedly (group 1 versus 2; P<0.0001), to a level comparable to that achieved with TPA (group 2 versus 3; P<0.05). Among groups receiving TPA, selective inhibition of factor XIII-mediated  $\alpha$ 2-antiplasmin-fibrin cross-linking enhanced lysis (group 3 versus 5; P<0.0005). Complete inhibition of factor XIIIa also amplified lysis (group 3 versus 4; P<0.0001) and had greater effects than inhibition of  $\alpha$ 2-antiplasmin cross-linking alone (group 4 versus 5; P<0.0005). No significant fibrinogen degradation occurred in any group.

**Conclusions-**Factor XIIIa-mediated fibrin-fibrin and  $\alpha$ 2-antiplasmin-fibrin cross-linking both caused experimental pulmonary emboli to resist endogenous and TPA-induced fibrinolysis. This suggests that factor XIIIa may play a critical role in regulating fibrinolysis in human thrombosis.

Circulation, 1999; 99: 1945-1950

### Relationship Between TIMI Frame Count and Clinical Outcomes After Thrombolytic Administration

C. Michael Gibson, Sabina A. Murphy, Michael J. Rizzo, Kathryn A. Ryan, Susan J. Marble, Carolyn H. McCabe,

Christopher P. Cannon, Frans Van de Werf, and Eugene Braunwald

**Background-**The corrected TIMI frame count (CTFC) is the number of cine frames required for dye to first reach standardized distal coronary landmarks, and it is an objective and quantitative index of coronary blood flow.

**Methods and Results-**The CTFC was measured in 1248 patients in the TIMI 4, 10A, and 10B trials, and its relationship to clinical outcomes was examined. Patients who died in the hospital had a higher CTFC (ie, slower flow) than survivors ( $69.6 \pm 35.4$  [n=53] versus  $49.5 \pm 32.3$  [n=1195];  $P=0.0003$ ). Likewise, patients who died by 30 to 42 days had higher CTFCs than survivors ( $66.2 \pm 36.4$  [n=57] versus  $49.9 \pm 32.1$  [n=1059];  $P=0.006$ ). In a multivariate model that excluded TIMI flow grades, the 90-minute CTFC was an independent predictor of in-hospital mortality (OR=1.21 per 10-frame rise [95% CI, 1.1 to 1.3], an 0.7% increase in absolute mortality for every 10-frame rise;  $P<0.001$ ) even when other significant correlates of mortality (age, heart rate, anterior myocardial infarction, and female sex) were adjusted for in the model. The CTFC identified a subgroup of patients with TIMI grade 3 flow who were at a particularly low risk of adverse outcomes. The risk of in-hospital mortality increased in a stepwise fashion from 0.0% (n=41) in patients with a 90-minute CTFC that was faster than the 95% CI for normal flow (0 to 13 frames, hyperemia, TIMI grade 4 flow), to 2.7% (n=18 of 658 patients) in patients with a CTFC of 14 to 40 (a CTFC of 40 has previously been identified as the cutpoint for distinguishing TIMI grade 3 flow), to 6.4% (35/549) in patients with a CTFC >40 ( $P=0.003$ ). Although the risk of death, recurrent myocardial infarction, shock, congestive heart failure, or left ventricular ejection fraction 40% was 13.0% among patients with TIMI grade 3 flow (CTFC $\leq$ 40), the CTFC tended to segregate patients into lower-risk (CTFC $\leq$ 20, risk of adverse outcome of 7.9%) and higher-risk subgroups (CTFC >20 to  $\leq$  40, risk of adverse outcome of 15.5%;  $P=0.17$ ).

**Conclusions-**Faster (lower) 90-minute CTFCs are related to improved in-hospital and 1-month clinical outcomes after thrombolytic administration in both univariate and multivariate models. Even among those patients classified as having normal flow (TIMI grade 3 flow, CTFC $\leq$ 40), there may be lower- and higher-risk subgroups.

Circulation, 1999 ;99: 873-878

One-Year Survival Among Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock, and its Relation to Early Revascularization : Results From the GUSTO-I Trial

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**Background-**Although 30-day survival is increased in patients with acute myocardial infarction complicated by cardiogenic shock who undergo coronary revascularization, the longer-term outcome in such patients and the duration of benefit from revascularization are unknown.

**Methods and Results-**We analyzed 30-day survivors of acute myocardial infarction in the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial and identified 36 333 who had not had cardiogenic shock (systolic blood pressure <90 mm Hg for 1 hour, group 1) and 1321 patients who had shock (group 2). Group 2 patients were older and sicker. At 1 year, 97.4% of group 1 patients were alive versus 88.0% of group 2 (P=0.0001). Among group 2 patients, 578 (44%) had undergone revascularization within 30 days (group 2A) and 728 (56%) had not (group 2B). Revascularization was not required by protocol but was selected by the attending physicians. At 1 year, 91.7% of group 2A patients were alive versus 85.3% of group 2B (P=0.0003). With the use of multivariable logistic regression analysis to adjust for differences in baseline characteristics of shock patients alive at 30 days, revascularization within 30 days was independently associated with reduced 1-year mortality (odds ratio 0.6, [95% confidence interval 0.4, 0.9], P=0.007).

**Conclusions-**Most patients (88%) with acute myocardial infarction complicated by cardiogenic shock who are alive at 30 days survived at least 1 year. Shock patients who underwent revascularization within 30 days had improved survival at 1 year compared with shock patients who did not receive revascularization, even after adjustment for differences in baseline characteristics between the 2 groups.

The American Journal of Cardiology, 83:12:1623-1628

Low- versus high-dose recombinant urokinase for the treatment of chronic saphenous vein graft occlusion

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Recanalization of a totally occluded saphenous vein graft (SVG) using commercially available urokinase from human kidney cells has been shown to be effective, but the duration of infusion and complications such as allergic reactions, bleeding events, and non-Q-wave myocardial infarction have limited its acceptance. Recently, genetic engineering has allowed the synthesis of recombinant urokinase (r-UK). Patients with an occluded SVG

from 37 centers were randomized to receive a 6-hour infusion of either low-dose (125,000 IU/hour) or high-dose (350,000 IU/hour) r-UK followed by up to a maximum of 18 hours of r-UK (125,000 IU/hour) via a subselective catheter directly into the occluded vein graft. The primary study end point was final preintervention achievement of Thrombolysis In Myocardial Infarction (TIMI) flow  $\geq 2$  using core angiographic analysis. One hundred seven patients were randomized and 98 received the study drug (low dose 52 patients, high dose 46 patients). TIMI flow  $\geq 2$  after completion of the study drug was higher in the high-dose group (51% vs 24%,  $p = 0.019$ ). This difference narrowed, but a trend was still evident on the final angiogram after adjunctive mechanical intervention (72% vs 58%,  $p = 0.254$ ). Bleeding complications were frequent; severe or life-threatening bleeding occurred in 12% of patients on the low dose and 11% of patients on the high dose ( $p = \text{NS}$ ), including 2 intracerebral bleeds, both of which were fatal with 1 in each group. Thus, in patients with an occluded SVG, a randomized trial of direct low-dose versus high-dose r-UK infusion demonstrated increased recanalization rates (TIMI flow  $\geq 2$ ) in the high-dose arm. Percutaneous revascularization of SVG with r-UK can be accomplished with acceptable success rates, but complications are frequent.

Journal of the American College of Cardiology, 1999;33:479-487

Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists : Observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study

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**Objectives** The purpose of this study was to determine the incidence and demographic characteristics of patients experiencing cardiac rupture after thrombolytic and adjunctive anticoagulant therapy and to identify possible associations between the mechanism of thrombin inhibition (indirect, direct) and the intensity of systemic anticoagulation with its occurrence.

**Background** Cardiac rupture is responsible for nearly 15% of all in-hospital deaths among patients with myocardial infarction (MI) given thrombolytic agents. Little is known about specific patient- and treatment-related risk factors.

**Methods** Patients ( $n = 3,759$ ) with MI participating in the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9A and B trials received intravenous thrombolytic therapy, aspirin and either heparin (5,000 U bolus, 1,000 to 1,300 U/h infusion) or hirudin (0.1 to 0.6 mg/kg bolus, 0.1 to 0.2 mg/kg/h infusion) for at least 96 h. A

diagnosis of cardiac rupture was made clinically in patients with sudden electromechanical dissociation in the absence of preceding congestive heart failure, slowly progressive hemodynamic compromise or malignant ventricular arrhythmias.

**Results** A total of 65 rupture events (1.7%) were reported—all were fatal, and a majority occurred within 48 h of treatment. Patients with cardiac rupture were older, of lower body weight and stature and more likely to be female than those without rupture (all  $p < 0.001$ ). By multivariable analysis, age  $>70$  years (odds ratio [OR] 3.77; 95% confidence interval [CI] 2.06, 6.91), female gender (OR 2.87; 95% CI 1.44, 5.73) and prior angina (OR 1.82; 95% CI 1.05, 3.16) were independently associated with cardiac rupture. Independent predictors of nonrupture death included age  $>70$  years (OR 3.68; 95% CI 2.53, 5.35) and prior MI (OR 2.14; 95% CI 1.45, 3.17). There was no association between the type of thrombin inhibition, the intensity of anticoagulation and cardiac rupture.

**Conclusions** Cardiac rupture following thrombolytic therapy tends to occur in older patients and may explain the disproportionately high mortality rate among women in prior clinical trials. Unlike major hemorrhagic complications, there is no evidence that the intensity of anticoagulation associated with heparin or hirudin administration influences the occurrence of rupture.

The American Journal of Cardiology, 1999;83:1600-1605

Determinants of infarct size after thrombolytic treatment in acute myocardial infarction

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Both experimental and single-center clinical studies have shown that myocardium at risk, residual collateral flow, and duration of coronary occlusion are important determinants of final infarct size. The purpose of this study was to replicate these results on a multicenter basis to demonstrate that perfusion imaging using different camera and computer systems can provide reliable assessments of myocardium at risk and collateral flow. Sequential tomographic myocardial perfusion imaging with technetium-99 (Tc-99m) sestamibi was performed in 74 patients with first time myocardial infarction, who were enrolled in a multicenter, randomized, double-blind, placebo-controlled pilot study of poloxamer 188 as ancillary therapy to thrombolysis. All patients underwent thrombolysis within 6 hours of the onset of chest pain. Tc-99m sestamibi was injected intravenously at the initiation of thrombolytic therapy, and tomographic imaging was performed 1 to 6 hours later to assess myocardium at risk. Collateral flow was estimated noninvasively from the acute sestamibi images by 3

methods that assess the severity of the perfusion defect. Final infarct size was determined at hospital discharge by a second sestamibi study. Myocardium at risk ( $r = 0.61$ ,  $p < 0.0001$ ) and radionuclide estimates of collateral flow ( $r = 0.58$  to  $0.66$ , all  $p < 0.0001$ ) were significantly associated with final infarct size. These associations were independent of the treatment center. On a multivariate basis, myocardium at risk ( $p = 0.003$ ), the radionuclide estimate of collateral flow ( $p = 0.03$ ), and treatment arm ( $p = 0.04$ ) were all independent determinants of infarct size. Time to thrombolytic therapy showed only a trend ( $p = 0.10$ ). The treatment center was not significant ( $p = 0.42$ ). Myocardium at risk and collateral flow are important determinants of infarct size that are independent of treatment center. Tomographic imaging with Tc-99m sestamibi can provide noninvasive assessments of these parameters in multicenter trials of thrombolytic therapy.

Eur Heart J, 1999;20:128-35

Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction among patients receiving reteplase or alteplase. Results from GUSTO-III Conclusion

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**Aims** Reteplase has been reported to achieve better patency of the infarct artery than alteplase. As infarct artery patency is strongly associated with survival among patients with cardiogenic shock, we postulated that treatment with reteplase would improve outcomes among shock patients.

**Methods** We compared 30-day mortality rates among patients in GUSTO-III who either presented with shock or developed shock after enrolment; all patients received either front-loaded alteplase or reteplase (two bolus doses of 10 MU, 30 min apart).

**Results** Shock occurred in 260 (5.3%) of 4921 patients randomized to alteplase and 560 (5.5%) of 10 138 patients randomized to reteplase. Of these patients, 28 (10.8%) and 55 (9.8%) randomized to alteplase and reteplase, respectively, presented with shock. In-hospital, 35% and 37% of shock patients assigned to alteplase or reteplase, respectively, underwent coronary angiography, with similar rates of percutaneous (11-13%) or surgical (2-3%) revascularization procedures subsequently performed. Death within 30 days occurred in 169 (65%) and 353 (63%) shock patients randomized to alteplase and reteplase, respectively ( $P=0.59$ ). Of patients presenting with shock, 64% and 58% of patients randomized to alteplase or reteplase died within 30 days ( $P=0.59$ ).

Journal of the American College of Cardiology, 1999;33:3:627-633

Low molecular weight heparin (dalteparin) as adjuvant treatment to thrombolysis in acute myocardial infarction-a pilot study: Biochemical Markers in Acute Coronary Syndromes (BIOMACS II)

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**OBJECTIVES** This randomized, double blind, placebo-controlled pilot trial evaluated the effect of dalteparin as an adjuvant to thrombolysis in patients with acute myocardial infarction regarding early reperfusion, recurrent ischemia and patency at 24 h.

**BACKGROUND** Low-molecular-weight heparin, given subcutaneously twice daily without monitoring, might be an attractive alternative to conventional intravenous heparin in the treatment of acute myocardial infarction.

**METHODS** In 101 patients dalteparin/placebo 100 IU/kg was given just before streptokinase and a second injection 120 IU/kg after 12 h. Monitoring with continuous vector-ECG was done to obtain signs of early reperfusion and later ischemic episodes. Blood samples for myoglobin were obtained at start and after 90 min to evaluate signs of reperfusion. Coronary angiography was performed after 20-28 h to evaluate TIMI-flow in the infarct-related artery.

**RESULTS** Dalteparin added to streptokinase tended to provide a higher rate of TIMI grade 3 flow in infarct-related artery compared to placebo, 68% versus 51% ( $p = 0.10$ ). Dalteparin had no effects on noninvasive signs of early reperfusion. In patients with signs of early reperfusion, there seemed to be a higher rate of TIMI grade 3 flow, 74% versus 46% (myoglobin) ( $p = 0.04$ ) and 73% versus 52% (vector-ECG) ( $p = 0.11$ ). Ischemic episodes 6-24 h. after start of treatment were fewer in the dalteparin group, 16% versus 38% ( $p = 0.04$ ).

**CONCLUSIONS** When dalteparin was added as an adjuvant to streptokinase and aspirin, there were tendencies for less ECG monitoring evidence of recurrent ischemia and better patency at 24 h, warranting further study.

Journal of the American College of Cardiology, 1999;33:1879-1885

A multicenter, randomized study of argatroban versus heparin as adjunct to tissue plasminogen activator (TPA) in acute myocardial infarction: myocardial infarction with Novastan and TPA (MINT) study

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**OBJECTIVES** This study examined the effect of a small-molecule, direct thrombin inhibitor, argatroban, on reperfusion induced by tissue plasminogen activator (TPA) in patients with acute myocardial infarction (AMI).

**BACKGROUND** Thrombin plays a crucial role in thrombosis and thrombolysis. In vitro and in vivo studies have shown that argatroban has advantages over heparin for the inhibition of clot-bound thrombin and for the enhancement of thrombolysis with TPA.

**METHODS** One hundred and twenty-five patients with AMI within 6 h were randomized to heparin, low-dose argatroban or high-dose argatroban in addition to TPA. The primary end point was the rate of thrombolysis in myocardial infarction (TIMI) grade 3 flow at 90 min.

**RESULTS** TIMI grade 3 flow was achieved in 42.1% of heparin, 56.8% of low-dose argatroban ( $p = 0.20$  vs. heparin) and 58.7% of high-dose argatroban patients ( $p = 0.13$  vs. heparin). In patients presenting after 3 h, TIMI grade 3 flow was significantly more frequent in high-dose argatroban versus heparin patients: 57.1% versus 20.0% ( $p = 0.03$  vs. heparin). Major bleeding was observed in 10.0% of heparin, and in 2.6% and 4.3% of low-dose and high-dose argatroban patients, respectively. The composite of death, recurrent myocardial infarction, cardiogenic shock or congestive heart failure, revascularization and recurrent ischemia at 30 days occurred in 37.5% of heparin, 32.0% of low-dose argatroban and 25.5% of high-dose argatroban patients ( $p = 0.23$ ).

**CONCLUSIONS** Argatroban, as compared with heparin, appears to enhance reperfusion with TPA in patients with AMI, particularly in those patients with delayed presentation. The incidences of major bleeding and adverse clinical outcome were lower in the patients receiving argatroban.

Circulation, 1999 ;99: 2714-2716

Combined Thrombolytic and Platelet Glycoprotein IIb/IIIa Inhibitor Therapy for Acute Myocardial Infarction : Will Pharmacological Therapy Ever Equal Primary Angioplasty?

J. Ward Kennedy and Michael L. Stadius

The management of acute myocardial infarction (AMI) was altered dramatically with the introduction of intracoronary thrombolytic therapy in the late 1970s by Rentrop and others. The visualization of coronary artery occlusion by angiography performed during the first few hours of AMI and the removal of some of these thrombi at the time of emergent coronary artery bypass surgery convinced the medical community that AMI was, as was thought years earlier, due to “coronary thrombosis.” After the publication of a number of randomized clinical trials (RCTs) of intracoronary and intravenous lytic therapy, reperfusion of acutely occluded coronary artery beds with thrombolytic therapy became a standard treatment of AMI by the mid-1980s.

While thrombolytic therapy was gaining early acceptance as a means to achieve reperfusion, a parallel pathway for achieving reperfusion was developing with catheter-based techniques. Reports of PTCA for the management of AMI appeared in 1983. Soon a vigorous competition developed between pharmacological and mechanical methods of reperfusion. Important differences between these 2 competing approaches were apparent. Thrombolytic therapy could be initiated rapidly once the diagnosis was made, with treatment instituted in the emergency department or even before hospitalization, and it did not require the technical skills of a proceduralist for its implementation. However, because reperfusion did not occur until 60 to 90 minutes after the onset of treatment, the occurrence of successful reperfusion (or its failure) could not be ascertained with certainty by use of clinical markers, and there was an obligatory risk of intracranial hemorrhage (ICH) of 0.5% to 1.0%, with higher rates experienced in elderly patients. With PTCA, on the other hand, there was an obligatory delay between diagnosis and initiation of the procedure, and highly skilled procedural cardiologists and technical staff were required to be available 24 hours a day. Because a minority of hospitals had facilities for the support of primary PTCA, it was often necessary to transfer patients to a tertiary facility. This latter requirement markedly limited the availability of primary angioplasty. Once the emergent procedure was begun, however, some degree of reperfusion was usually achieved within a few minutes, the reperfusion status of the coronary artery was known with certainty, and the presence of severe disease best treated with emergency bypass surgery rather than angioplasty was defined. In addition, experience soon showed that there was virtually no risk of ICH and a low risk of other serious bleeding with this primary mechanical approach.

The most important difference between thrombolytic therapy and emergent PTCA, however, has to do with the achievement of acceptable reperfusion. From the earliest days of thrombolytic trials, it was known that the best clinical outcomes were associated with prompt restoration of normal or near-normal blood flow in the infarct-related artery. By the early 1990s, achievement of TIMI 3 (normal) flow through the infarct-related artery was recognized as the goal of reperfusion therapy because of the survival benefit associated with its occurrence. And there has been little doubt that mechanical reperfusion has been associated with better success at

establishing TIMI 3 reperfusion of infarct arteries than has thrombolytic therapy. The most successful thrombolytic regimen for establishing reperfusion, the front-loaded tissue plasminogen activator protocol, results in TIMI 3 reperfusion in 50% of treated arteries. Primary balloon angioplasty results in TIMI 3 flow in 46% to 97% of treated arteries, with most series reporting rates in excess of 70%. A meta-analysis of a number of small RCTs comparing PTCA with thrombolytic therapy indicated that there was a survival advantage for the mechanical reperfusion technique equal to 2 lives saved per 100 treated patients at 30 days after AMI. This result was confirmed in the large-scale, multicenter GUSTO IIB trial, in which primary PTCA was associated with a survival advantage of 1 life saved per 100 treated patients at 30 days. Most recently, mechanical reperfusion techniques have been further buttressed by the use of coronary stents, which appear to provide a small additional benefit compared with balloon angioplasty alone in terms of achieving complete reperfusion of the infarct-related artery bed. Although controversy persists, the playing field for these 2 competing reperfusion therapies had definitely shifted by the mid-1990s to favor mechanical techniques if the resources and technical skills that are its prerequisites were in place.

JACC , 1999;34:62-69

Survival 12 years after randomization to streptokinase: the influence of thrombolysis in myocardial infarction flow at three to four weeks

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#### OBJECTIVES

The purpose of this study was to determine whether the mortality benefit of intravenous streptokinase administered within 4 h of the onset of acute myocardial infarction is maintained at 12 years, and whether Thrombolysis in Myocardial Infarction (TIMI) flow grades independently influence late survival.

#### BACKGROUND

Treatment with reperfusion therapies and achievement of TIMI 3 flow are associated with increased short- and medium-term survival after infarction. Whether infarct artery flow independently influences survival more than five years after infarction is unknown.

#### METHODS

The late survival of patients randomized to receive either streptokinase (1,500,000 IU over 30 to 60 min) or a

matching placebo within 4 h of symptom onset in 1984-1986 was determined. Angiography was performed in surviving patients at three to four weeks, and TIMI flow grades were assessed blind to randomization and outcomes. The late vital status was determined in 99% of patients.

#### RESULTS

Patients randomized to receive streptokinase (n = 107) had improved survival compared with those randomized to placebo (n = 112) at five years (84% vs. 70%; p = 0.023) and 12 years (66% vs. 51%; p = 0.022). At five years 94% of patients with TIMI grade 3 flow, 81% of those with TIMI grade 2 flow and 72% of those with TIMI grade 0-1 flow survived (p = 0.005). At 12 years 72% of patients with TIMI 3, 67% of those with TIMI 2 and 54% of those with TIMI 0-1 flow survived (p = 0.023). Multivariate analysis identified the ejection fraction (p = 0.014), exercise duration (p = 0.013) and TIMI 3 flow (p = 0.04 compared with TIMI 0-2 flow) as important factors for five-year survival. At 12 years multivariate predictors of late survival were the ejection fraction (p = 0.006), exercise duration (p = 0.003) and myocardial score (p = 0.013). The end-systolic volume index was similar to the ejection fraction as a predictor of survival at five and 12 years.

#### CONCLUSIONS

The survival benefits of streptokinase persist for 12 years after infarction. TIMI flow at three to four weeks is an independent predictor of five-year survival.

Am J Cardiol 1999 ;84(9):976-80

Weight-adjusted dosing of TNK-tissue plasminogen activator and its relation to angiographic outcomes in the thrombolysis in myocardial infarction 10B trial. TIMI 10B Investigators.

Gibson CM, Cannon CP, Murphy SA, Adgey AA, Schweiger MJ, Sequeira RF, Grollier G, Fox NL, Berioli S, Weaver WD, Van de Werf F, Braunwald E

Fixed doses of thrombolytic agents are generally administered to patients of varying body weights, and the dose-response relation may be confounded by the variability in patient weight. We hypothesized that higher doses of TNK-tissue plasminogen activator (tPA) per unit body weight would be related to improved flow at 90 minutes after thrombolytic administration. A total of 886 patients with acute myocardial infarction were randomized to receive either a single bolus of 30, 40, or 50 mg of TNK-tPA or front-loaded tPA in the Thrombolysis In Myocardial Infarction (TIMI) 10B trial. The dose of TNK-tPA administered was divided by the patient's weight to arrive at the TNK-tPA dose (mg) per unit body weight (kg), and patients were stratified into

tertiles based on mg/kg of TNK-tPA: low dose, 0.2 to 0.39 mg/kg; mid-dose, 0.40 to 0.51 mg/kg; high dose, 0.52 to 1.24 mg/kg. Flow in the culprit and nonculprit arteries was analyzed using the TIMI flow grades and the corrected TIMI frame count (CTFC). The median CTFC in culprit arteries differed between the tertiles (3-way  $p = 0.007$ ), with the CTFC being 7.2 frames faster in high-dose than in low-dose patients (43.1  $\pm$  30.1, median 31.2,  $n = 171$  vs 54.6  $\pm$  34.8, median 38.4,  $n = 166$ , 2-way  $p = 0.002$ ). Patients in the mid- and high-dose tertiles achieved patency more frequently (TIMI grade 2 or 3 flow) by 60 minutes ( $p = 0.02$ ), and the 90-minute percent diameter stenosis was less severe in patients in the high- versus low-dose tertile ( $p = 0.03$ ). In nonculprit arteries, the CTFC was faster in high- than in low-dose tertiles (29.6  $\pm$  13.4, median 26.9,  $n = 130$  vs 34.7  $\pm$  16.3, median 32.8,  $n = 108$ , 3-way  $p = 0.03$ , 2-way  $p = 0.008$ ). In patients who underwent percutaneous transluminal coronary angioplasty (PTCA), the CTFC in culprit arteries after PTCA was fastest in the high- and mid-dose tertiles than in those receiving low doses (2-way  $p = 0.05$ ). Thus, higher doses per unit body weight of TNK-tPA result in not only faster culprit artery flow, but also faster nonculprit, global, and post-PTCA flow, which may reflect earlier opening, reduced stunning, or improved microvascular function. The greater effectiveness of thrombolysis must be weighed against any increase in risk.

P=NS for all comparisons, CTFC: corrected TIMI frame counts

## Summary

J Am Coll Cardiol 1999 Nov 1;34(5):1403-12

Determinants of coronary blood flow after thrombolytic administration. TIMI Study Group. Thrombolysis in Myocardial Infarction.

Gibson CM, Murphy S, Menown IB, Sequeira RF, Greene R, Van de Werf F, Schweiger MJ, Ghali M, Frey MJ, Ryan KA, Marble SJ, Giugliano RP, Antman EM, Cannon CP, Braunwald E

**OBJECTIVES:** This study evaluated the determinants of coronary blood flow following thrombolytic administration in a large cohort of patients. **BACKGROUND:** Tighter residual stenoses following thrombolysis have been associated with slower coronary blood flow, but the independent contribution of other variables to delayed flow has not been fully explored. **METHODS:** The univariate and multivariate correlates of coronary blood flow at 90 min after thrombolytic administration were examined in a total of 2,195 patients from the Thrombolysis in Myocardial Infarction (TIMI) 4, 10A, 10B and 14 trials. The cineframes needed for dye to first

reach distal landmarks (corrected TIMI frame count, CTFC) were counted as an index of coronary blood flow. RESULTS: The following were validated as univariate predictors of delayed 90-min flow in two cohorts of patients: a greater percent diameter stenosis ( $p < 0.0001$  for both cohorts), a decreased minimum lumen diameter ( $p = 0.0003$ ,  $p = 0.0008$ ), a greater percent of the culprit artery distal to the stenosis ( $p = 0.03$ ,  $p = 0.02$ ) and the presence of any of the following: delayed achievement of patency (i.e., between 60 and 90 min) ( $p < 0.0001$  for both cohorts), a culprit location in the left coronary circulation (left anterior descending or circumflex) ( $p = 0.02$ ,  $p < 0.0001$ ), pulsatile flow (i.e., reversal of flow in systole, a marker of heightened microvascular resistance,  $p = 0.0003$ ,  $p < 0.0001$ ) and thrombus ( $p = 0.002$ ,  $p = 0.03$ ). Despite a minimal 16.4% residual stenosis following stent placement, the mean post-stent CTFC ( $25.8 \pm 17.2$ ,  $n = 181$ ) remained significantly slower than normal ( $21.0 \pm 3.1$ ,  $n = 78$ ,  $p = 0.02$ ), and likewise 34% of patients did not achieve a CTFC within normal limits (i.e.,  $<28$  frames, the upper limit of the 95th percent confidence interval previously reported for normal flow). Those patients who failed to achieve normal CTFCs following stent placement had a higher mortality than did those patients who achieved normal flow (6/62 or 9.7% vs. 1/118 or 0.8%,  $p = 0.003$ ). CONCLUSIONS: Lumen geometry is not the sole determinant of coronary blood flow at 90 min following thrombolytic administration. Other variables such as the location of the culprit artery, the duration of patency, a pulsatile flow pattern and thrombus are also related to slower flow. Despite a minimal 16% residual stenosis, one-third of the patients treated with adjunctive stenting still have a persistent flow delay following thrombolysis, which carries a poor prognosis.

#### Summary

1. Significant variables by univariate analysis: a greater % DS, a decreased MLD, a greater % of the culprit artery distal to the stenosis and the presence of any of the following: delayed achievement of patency, a culprit location in the left coronary circulation, pulsatile flow and thrombus
2. Patients failed to achieve normal CTFCs following stent placement: higher mortality ( $p = 0.003$ )

Am Heart J, 1999 ;138(3 Pt 1):518-24

Thrombolysis with saruplase versus streptokinase in acute myocardial infarction: five-year results of the PRIMI trial.

Spiecker M, Windeler J, Vermeer F, Michels R, Seabra-Gomes R, vom Dahl J, Kerber S, Verheugt FW, Westerhof PW, Bar FW, Nixdorff U, Barth H, Hopkins GR, von Fisenne MJ, Meyer J

**BACKGROUND:** Short-term safety and efficacy of thrombolysis with saruplase in acute myocardial infarction have been shown in several trials. To assess long-term outcome of patients treated with saruplase or streptokinase for myocardial infarction, a 5-year follow-up of patients included in the Pro-Urokinase in Myocardial Infarction Trial was performed. **METHODS AND RESULTS:** Follow-up data are available from 8 centers on 255 (92.4%) of 276 included patients. The 5-year mortality rate was comparable with 20.8% of patients in the saruplase group and 16.9% in the streptokinase group (odds ratio 1.29, 95% confidence interval 0.69 to 2.42). In both groups, a considerable number of fatal cardiovascular events occurred more than 1 year after study inclusion. Rates of percutaneous transluminal coronary angioplasty and coronary artery bypass grafting were comparable in both groups. Reinfarction within 5 years occurred in 19.0% of patients in the saruplase group and tended to be less frequent at 10.8% after streptokinase treatment (odds ratio 1.94, 95% confidence interval 0.98 to 3.84). In both groups, the majority of reinfarctions took place more than 3 months after study inclusion. The 5-year stroke rate was 3.6% and 7.2% in the saruplase and streptokinase groups, respectively (odds ratio 0.49, 95% confidence interval 0.16 to 1.47). Subjective symptoms of heart failure and angina pectoris were comparable in both groups. **CONCLUSIONS:** Our data are consistent with a similar long-term outcome for patients treated with saruplase or streptokinase. Despite the low-risk profile of the patient cohort, there were considerable adverse event rates over a 5-year period.

## Summary

Am Heart J, 1999 ;138(2 Pt 1):319-25

Increased thrombin activity correlates with increased ischemic event rate after percutaneous transluminal coronary angioplasty: lack of efficacy of locally delivered urokinase.

Wilensky RL, Pyles JM, Fineberg N

**BACKGROUND:** Angiographic thrombus is associated with increased coronary occlusion and restenosis rates after angioplasty. Administration of intracoronary urokinase decreases the incidence of thrombus but is associated with an increased periprocedural event rate, including stroke and myocardial infarction. An alternative approach is to deliver the agent directly into the arterial wall, thereby reducing the thrombotic substrate in the absence of a systemic effect of the delivered agent. **OBJECTIVE:** This randomized, double-blind,

prospective study correlated intracardiac fibrinopeptide A levels with the ischemic events after angioplasty and evaluated whether locally administered urokinase could reduce the event rate. METHODS: Fifty-four patients with acute coronary syndromes were randomly assigned to local delivery of urokinase or saline. Levels of fibrinopeptide A, a marker of thrombin activity, were obtained before and after administration of heparin, after 2 balloon inflations, and at the end of the procedure in 43 patients and were correlated with ischemic events within the 6-month follow-up period (death, myocardial infarction, or recurrent ischemia). RESULTS: Multivariate analysis revealed that an elevated fibrinopeptide A level before angioplasty significantly correlated with an increased likelihood of an adverse event over the 6-month clinical follow-up. A postangioplasty reduction in the fibrinopeptide A level was noted in control patients ( $P < .001$ ), but not after local urokinase administration, and the final fibrinopeptide A level was higher in the urokinase group ( $P = .02$ ). Urokinase had no effect on the procedural results. On follow-up more patients receiving urokinase (13 of 27) had ischemic events than did control patients (6 of 25,  $P = .04$ ). Most events were recurrent ischemia caused by restenosis. CONCLUSIONS: Heparin-resistant thrombin activity, as evidenced by an increased fibrinopeptide A level correlates with ischemic events on long-term follow-up. Local delivery of urokinase increased the event rate.

Figure. Association of fibrinopeptide A levels and ischemic events noted at 6-month follow-up.

Am J Cardiol ,1999 ;83(1):21-6

Early infarct artery collateral flow does not improve long-term survival following thrombolytic therapy for acute myocardial infarction.

Nicolau JC, Nogueira PR, Pinto MA, Serrano CV Jr, Garzon SA

It is known that acutely developed collaterals can prevent the onset of acute myocardial infarction (AMI) in the presence of a total coronary occlusion. However, there still is controversy concerning long-term follow-up of coronary collateral circulation to the infarct-related artery. In this study we analyze the prognostic role of collateral flow (degrees 0 to 3) as well as antegrade flow (degrees 0 to 3) in patients with AMI treated with thrombolytic therapy. Four hundred twenty-two patients (median age 57 years, 355 men) with AMI were treated with intravenous streptokinase and followed prospectively for up to 8 years. At the end of the study period, patients with collateral coronary flow 3 ( $n = 30$ ) and those with flow  $<3$  ( $n = 392$ ) at in-hospital coronary arteriography had survival rates of 66% and 85%, respectively ( $p < 0.12$ ). Meanwhile, patients with coronary

anterograde flow  $\geq 3$  (n = 189) and those with flow  $< 3$  (n = 233) had survival rates of 89% and 80%, respectively (p < 0.04). By censored regression analysis, a negative correlation was found between coronary collateral flow degree and survival (p = 0.0498) and, inversely, a positive correlation was found between coronary anterograde flow degree and survival (p = 0.0053). By Cox multivariate analysis, the following variables showed significant correlations with long-term survival: global left ventricular ejection fraction (p = 0.0003), anterograde flow degree (p = 0.0006), collateral flow degree (negative correlation, p = 0.0179), and medical treatment (negative correlation, p = 0.0464). Thus, patients treated with intravenous streptokinase during AMI and with adequate coronary collateral circulation had a worse prognosis than those who developed adequate anterograde flow, probably because of residual myocardial ischemia. Such patients may benefit from coronary revascularization (angioplasty or surgery) to restore anterograde blood flow and minimize myocardium at risk.

Circulation , 2000 ;102: 1761-1765

Survival Outcomes 1 Year After Reperfusion Therapy With Either Alteplase or Reteplase for Acute Myocardial Infarction : Results From the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) III Trial

Eric J. Topol, E. Magnus Ohman, Paul W. Armstrong, Robert Wilcox, Alan M. Skene, Philip Aylward, John Simes, Anthony Dalby, Amadeo Betriu, Christoph Bode, Harvey D. White, Judith S. Hochman, Hakan Emanuelson, Alec Vahanian, Shelly Sapp, Amanda Stebbins, David J. Moliterno, and Robert M. Califf

**Background**-New recombinant plasminogen activators have been developed to simulate the fibrinolytic action of the physiological serine protease tissue plasminogen activator (alteplase, t-PA), and have prolonged half-life features permitting bolus administration. One such activator, reteplase (r-PA), was compared with t-PA in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-III Trial.

**Methods and Results**-At 1-year follow-up, survival status was ascertained in 97.4% of the 15 059 patients enrolled in the GUSTO-III trial. At 1 year, the mortality rate for the t-PA-assigned group was 11.06%, and for r-PA it was 11.20% (P=0.77). The absolute mortality difference of 0.14% has 95% CIs of -1.21% to 0.93%. There were no significant differences in outcome by intention-to-treat for the 2 different plasminogen activators in the prespecified groups (age, infarct location, time-to-treatment). The absolute difference in mortality rates between t-PA and r-PA progressively narrowed over the predetermined observation times after random assignment; it was 0.31% at 24 hours, 0.26% at 7 days, 0.23% at 30 days, and 0.14% at 1 year. Of note, mortality rate in the trial between 30 days and 1 year in 13 883 patients was 4.02% and did not differ between the

treatment groups. However, this mortality rate was substantially greater than in GUSTO-I, in which mortality rate for t-PA versus streptokinase between 30 days and 1-year was 2.97% (heart rate 1.36, 95% CI 1.23, 1.50,  $P<0.001$ ).

**Conclusions**-The r-PA and t-PA strategies yielded similar survival outcomes after 30 days in this trial. The increase in mortality rate during extended follow-up compared with previous trials may reflect higher-risk patients and highlights the need for improved secondary prevention strategies.

Circulation 2000 102: 1766-1772.

### Polyethylene Glycol-Derivatized Cysteine-Substitution Variants of Recombinant Staphylokinase for Single-Bolus Treatment of Acute Myocardial Infarction

Desire Collen, Peter Sinnaeve, Eddy Demarsin, Huberte Moreau, Marc De Maeyer, Laurent Jespers, Yves Laroche, and Frans Van de Werf

**Background**-Thrombolytic therapy of acute myocardial infarction (AMI) is evolving toward bolus administration. Derivatization of proteins with polyethylene glycol (PEG) may reduce their clearance.

**Methods and Results**-A staphylokinase (SakSTAR) variant with 12 amino acid substitutions to reduce its antigenicity, SakSTAR (K35A, E65Q, K74R, E80A, D82A, T90A, E99D, T101S, E108A, K109A, K130T, K135R), and with Ser in position 3 mutated into Cys (code SY161), was derivatized with maleimide-PEG with Mr of 5000 (P5), 10 000 (P10), or 20 000 (P20). The PEGylated variants recognized only one third of the antibodies elicited with wild-type SakSTAR in AMI patients. In experimental animals, plasma clearances were reduced 2.5- to 5-fold with P5, 5- to 20-fold with P10, and 20-fold with P20, and bolus injection induced pulmonary plasma clot lysis at doses inversely related to their clearance. Intravenous bolus injection of 5 mg of the P5, P10, or P20 variants in AMI patients was associated with plasma half-lives ( $t_{1/2}$ ) of 13, 30, and 120 minutes and clearances of 75, 43, and 8 mL/min, respectively, compared with 3 minutes and 360 mL/min for SakSTAR. Injection of 5 mg P5 variant restored TIMI-3 flow within 60 minutes in 14 of 18 AMI patients (78%, 95% CI 55% to 91%) and of 2.5 mg in 7 of 11 patients (63%, 95% CI 35% to 85%), both in the absence of fibrinogen degradation. The immunogenicity of the variants was significantly ( $P<0.002$ ) reduced.

**Conclusions**-The staphylokinase variant SY161-P5, derivatized with one linear polyethylene glycol molecule of Mr 5000, is a promising fibrin-selective agent for single-bolus coronary thrombolysis.

N Engl J Med 2000;343:385-91

## Coronary Stenting plus Platelet Glycoprotein IIb/IIIa Blockade Compared with Tissue Plasminogen Activator in Acute Myocardial Infarction

Albert Schomig, Adnan Kastrati, Josef Dirschinger, Julinda Mehilli, Ullrich Schricke, Jurgen Pache, Stefan Martinoff, Franz-Josef Neumann, Markus Schwaiger, for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators

**Background.** Prevention of myocardial damage is the main goal of all reperfusion therapies in patients with acute myocardial infarction. The relative efficacy of various reperfusion strategies is under intensive investigation. We assessed whether coronary stenting combined with the blockade of platelet glycoprotein IIb/IIIa receptors produces a greater degree of myocardial salvage than fibrinolysis with an accelerated infusion of alteplase, a tissue plasminogen activator.

**Methods.** A total of 140 patients were enrolled in the randomized trial; 71 were assigned to receive a stent plus abciximab, and 69 to receive intravenous alteplase. The primary end point was the degree of myocardial salvage, determined by means of serial scintigraphic studies with technetium Tc 99m sestamibi. The secondary end point was a composite of death, reinfarction, and stroke within six months after randomization.

**Results.** In the group that received a stent plus abciximab, the median size of the final infarct was 14.3 percent of the left ventricle (25th and 75th percentiles, 6.8 and 24.5 percent), as compared with a median of 19.4 percent (25th and 75th percentiles, 7.9 and 34.2 percent) in the alteplase group ( $P=0.02$ ). This difference was due to the larger salvage index (the percentage of the left ventricle that was salvaged, divided by the percentage that was compromised by the initial perfusion defect) in the stent group: 0.57 (25th and 75th percentiles, 0.35 and 0.69), as compared with 0.26 (25th and 75th percentiles, 0.09 and 0.61;  $P<0.001$ ). The cumulative incidence of death, reinfarction, or stroke at six months was lower in the stent group than in the alteplase group (8.5 vs. 23.2 percent,  $P=0.02$ ; relative risk, 0.34; 95 percent confidence interval, 0.13 to 0.88).

**Conclusions.** In patients with acute myocardial infarction, coronary stenting plus abciximab leads to a greater degree of myocardial salvage and a better clinical outcome than does fibrinolysis with a tissue plasminogen activator.

Am Heart J , 2000 ;139(2 Pt 2):S33-7

Combination therapy for acute myocardial infarction: fibrinolytic therapy and glycoprotein IIb/IIIa inhibition.

Califf RM

Reperfusion with a regimen of fibrinolytic therapy, aspirin, and unfractionated heparin is limited by a less than desirable reperfusion rate, an excessive reocclusion rate, a dose-limiting intracranial hemorrhage rate, and a competitive posture relative to direct coronary angioplasty. Only 50% to 60% of patients achieve early Thrombolysis in Myocardial Infarction grade 3 flow within 90 minutes with the most effective thrombolytic regimens. Even after initial reperfusion is achieved, transient and permanent reocclusion occurs too often and is associated with a high mortality rate. As more older patients are being treated, intracranial hemorrhage is becoming more common. Finally, the risk of bleeding and procedural failure has been high in patients who received an acute percutaneous interventional procedure shortly after treatment with fibrinolytic therapy. Early studies combining full-dose fibrinolytic treatment and glycoprotein IIb/IIIa inhibitors have been promising with regard to overcoming these limitations, but concern about bleeding has hindered this strategy. Several recent trials have evaluated full-dose abciximab with reduced-dose fibrinolytic therapy and have yielded promising results. The complementary nature of the results from different trials is striking, with substantial evidence that approximately half the conventional dose of fibrinolytic therapy combined with full-dose glycoprotein IIb/IIIa inhibition with abciximab achieves high rates of grade 3 flow and excellent clinical outcomes. This approach will now be tested in a large-scale mortality trial.

#### Summary

1. Effect of current thrombolytic regimen is not satisfactory.
2. Early studies combining full-dos fibrinolytic treatment and GpIIb/IIIa inhibitors - good, but with higher bleeding complications
3. Half-dose fibrinolytic + GpIIb/IIIa inhibitors - Promising, waiting the results of large scale studies

Catheter Cardiovasc Interv, 2000 ;49(1):113-6

Safety and efficacy of abciximab use in conjunction with intracoronary urokinase in patients requiring angioplasty.

Rashdan I, Schechter E

Abciximab decreases ischemic complications during angioplasty. Intracoronary urokinase lyses intracoronary thrombus. We studied the combination of both drugs. Twenty-six consecutive patients with acute coronary syndromes and intracoronary thrombus underwent intervention with abciximab and intracoronary urokinase. All received aspirin and IV heparin. The dose of abciximab was a weight-adjusted bolus and a 12-hr infusion. The dose of urokinase was 250,000 to 633,000 units. Hemorrhagic complications were classified according to the TIMI study group. Hemoglobin and platelet counts were measured before and 12 and 48 hr after the procedure. Procedural success was achieved in 24 patients. There were no deaths or repeat interventions. No patient had a major bleeding complication. Only two had minor complications. One patient needed blood transfusion. None had a stroke or thrombocytopenia. The use of abciximab and intracoronary urokinase in the presence of intracoronary thrombus is associated with encouraging efficacy and few complications

#### Summary

1. Procedural success: 92%
2. No deaths or repeat interventions.
3. No major bleeding complication, two minor complications.
4. No stroke or thrombocytopenia.

American Heart Journal, 2000 ;140(1):29-33

Hierarchy of risk based on history and location of prior myocardial infarction in the thrombolytic era. GUSTO-I Investigators.

Brieger DB, Mak KH, Miller DP, Califf RM, Topol EJ

**Background:** Among patients receiving thrombolytic therapy for myocardial infarction, the outcome for those with a history of infarction is dramatically worse than for those with their first event.

**Methods and Results:** We performed a post hoc analysis of patients with a history of myocardial infarction enrolled in the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO)-I trial, focusing on

the impact of the location of their current and prior events on mortality rates. Within the first 24 hours, mortality rate was greatest among patients with a current infarction in a territory remote from their previous event. By 48 hours after examination, mortality rates among patients with a second anterior infarct had overtaken that among patients with a current inferior/prior anterior infarct. This hierarchy of risk persisted at both 30 days and 1 year (mortality rate at 1 year: current anterior/prior inferior 23.2%  $\pm$  1.4%, current anterior/prior anterior 20%  $\pm$  1.5%, current inferior/prior anterior 17%  $\pm$  1.2%, current inferior/prior inferior 10.8%  $\pm$  0.9%).

**Conclusions:** In patients with ST-elevation myocardial infarction on a background of prior infarction, the location of current and prior events predicts a hierarchy of short- and long-term risk of death.

**Fig. 1.** Kaplan-Meier estimates of mortality rates within 24 hours of enrollment for patients with history of infarction based on location of current and prior MI. ANT/ant, Current anterior, prior anterior; ANT/inf, current anterior, prior inferior; INF/ant, current inferior, prior anterior; INF/inf, current inferior, prior inferior.

**Fig. 2.** Cumulative mortality rates of patients enrolled in GUSTO-I trial according to location of current MI and presence and location of prior MI. ANT/ant, Current anterior, prior anterior; ANT/inf, current anterior, prior inferior; INF/ant, current inferior, prior anterior; INF/inf, current inferior, prior inferior. Absolute mortality rates were significantly different ( $P < .05$ ) between all subgroups at both 30 days and 1 year except ANT/ant vs INF/ant at 30 days ( $P = .22$ ) and ANT/inf vs ANT/ant at 1 year ( $P = .1$ )

Journal of Internal Medicine. 2000 Aug;248(2):119-25

Diabetes mellitus is a strong negative prognostic factor in patients with myocardial infarction treated with thrombolytic therapy.

Strandberg LE, Ericsson CG, O'Konor ML, Bergstrand L, Lundin P, Rehnqvist N, Tornvall P

**Objectives.** To assess the long-term prognostic values of baseline demographic data, occurrence of vector-cardiographic signs of reperfusion, left ventricular function and coronary angiographic features.

**Design.** Longitudinal study of morbidity and mortality.

**Setting.** Coronary care unit at Danderyd Hospital, Stockholm, Sweden.

**Subjects.** A total of 222 patients (mean age 61 years) with a suspected acute myocardial infarction treated with thrombolysis were investigated and followed for 2-5 years (mean 1216 days).

**Main outcome measures.** Death or a new myocardial infarction.

**Results.** Age above 55 years ( $P < 0.05$ ), a previous diagnosis of diabetes mellitus ( $P < 0.005$ ), hypertension ( $P < 0.05$ ), heart failure ( $P < 0.001$ ) and myocardial infarction ( $P < 0.05$ ), a previous use of beta-blockers ( $P < 0.05$ ) and

an ejection fraction below 60% ( $P < 0.01$ ) were predictors for death or a new myocardial infarction in univariate analysis. Sex, a previous history of smoking or angina pectoris, vectorcardiographic signs of reperfusion or degree of coronary artery disease had no prognostic values. In multivariate analysis including age above 55 years, a previous diagnosis of diabetes mellitus, hypertension and myocardial infarction, and an ejection fraction below 60%, only age ( $P < 0.05$ ), diabetes mellitus ( $P < 0.01$ ) and ejection fraction ( $P < 0.05$ ) were predictors for death or a new myocardial infarction.

**Conclusions.** The results of the present study emphasize the importance of diabetes mellitus as a long-term prognostic risk factor in patients with myocardial infarction treated with thrombolysis. Further studies are needed to determine the mechanisms behind this increased risk.

**Fig. 1** Cumulative proportion surviving during follow-up (in days): 1, age < 56 years, EF > 60%, no diagnosis of diabetes mellitus; 2, age > 55 years, EF > 60%, no diagnosis of diabetes mellitus; 3, age > 55 years, EF < 60%, no diagnosis of diabetes mellitus; 4, age > 55 years, EF < 60%, a diagnosis of diabetes mellitus.

Heart, 2000 ;84(3):262-6

Improving door to needle times with nurse initiated thrombolysis.

Wilmshurst P, Purchase A, Webb C, Jowett C, Quinn T

**OBJECTIVE:** To evaluate the effect of nurse initiated thrombolysis on door to needle time (the interval between arriving at the hospital and starting thrombolytic treatment) in patients with acute myocardial infarction.

**DESIGN:** Comparison of door to needle times before and after the employment of nurses trained and approved to initiate thrombolysis without prescription by a doctor but with a protocol for rapid triage of patients with chest pain.

**SETTING:** A district general hospital.

**SUBJECTS:** All patients admitted with suspected myocardial infarction between April 1995 and March 1999.

**MAIN OUTCOME MEASURES:** Speed (door to needle time) and appropriateness of administration of thrombolytic drugs to patients with acute myocardial infarction who gave a characteristic history and had appropriate criteria on the admission ECG.

**RESULT:** During seven periods (each of four months) before the introduction of nurse initiated thrombolysis and a new chest pain triage protocol, the median door to needle time varied from 50-58 minutes. In four periods (each of 4-6 months) following the introduction of the changes, the median door to needle time was 25-30 minutes. The improvement was significant ( $p < 0.001$ ). Nurses trained to initiate thrombolysis currently provide cover for 66% of the time. Median door to needle time for nurses was 15 minutes. Median door to

needle time for junior doctors improved to 35 minutes. The median door to needle times when nurses initiated thrombolysis was significantly shorter than when doctors did so ( $p < 0.001$ ). There have been no inappropriate management decisions by nurses approved to initiate thrombolysis.

**CONCLUSIONS:** The use of nurse initiated thrombolysis has resulted in a clinically important reduction in the time taken for thrombolysis to be started in patients with acute myocardial infarction.

Figure 1. Door to needle times for cases of unequivocal myocardial infarct on admission during the seven audit periods before and the four audit periods after introduction of nurse initiated thrombolysis and a chest pain triage trolley

Am J Med, 2000;109(1):52-8

### Third-generation thrombolytic drugs

Verstraete M

Several third-generation thrombolytic agents have been developed. They are either conjugates of plasminogen activators with monoclonal antibodies against fibrin, platelets, or thrombomodulin; mutants, variants, and hybrids of alteplase and prourokinase (amediplase); or new molecules of animal (vampire bat) or bacterial (*Staphylococcus aureus*) origin. These variations may lengthen the drug's half-life, increase resistance to plasma protease inhibitors, or cause more selective binding to fibrin.

Compared with the second-generation agent (alteplase), third-generation thrombolytic agents such as monteplase, tenecteplase, reteplase, lanoteplase, pamiteplase, and staphylokinase result in a greater angiographic patency rate in patients with acute myocardial infarction, although, thus far, mortality rates have been similar for those few drugs that have been studied in large-scale trials. Bleeding risk, however, may be greater.

Figure. Recanalization rate of infarct-related arteries determined by coronary angiography before and at 15-minutes intervals after start of thrombolyte treatment. Circles indicate TIMI flow grade 3 in the monteplase group; triangles indicate TIMI flow grade 3 in the tisokinase (rt-PA) group. There were significant differences between the groups at 15 minutes ( $P < 0.01$ ), 30 minutes ( $P < 0.01$ ), 45 minutes ( $P < 0.01$ ), and 60 minutes ( $P < 0.05$ ). The numbers in parentheses are 95% confidence intervals

Lancet 2000 ;356(9228):449-54

## Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis

Mehta SR. Eikelboom JW. Yusuf S.

**Background:** Although thrombolytic therapy given by bolus injection seems to be as effective as infusion over 60-90 min, no single trial has been adequately powered to detect clinically important safety differences between the two strategies. We did a meta-analysis to find out whether bolus administration of thrombolytics is associated with an increased frequency of intracranial haemorrhage.

**Methods:** We identified randomised trials comparing bolus with infusion thrombolytic therapy by a search of electronic databases, reference lists, and conference proceedings. Odds ratios for primary intracranial haemorrhage, non-haemorrhagic stroke, mortality, and reinfarction were calculated for each trial and were combined in a fixed-effects model.

**Findings:** Seven trials, involving a total of 103 972 patients, met our inclusion criteria. Bolus treatment was associated with an increased risk of intracranial haemorrhage compared with infusion (0.8 vs 0.6%; odds ratio 1.25 [95% CI 1.08-1.45];  $p=0.003$ ). The increased risk was most striking in trials comparing bolus with infusion administration of the same agent (1.75 [1.32-2.33],  $p=0.0001$ ), but was also evident in trials comparing a newer generation bolus agent with standard infusion therapy (1.25 [1.03-1.50];  $p=0.02$ ). The rates of non-haemorrhagic stroke (0.94 [0.81-1.09]), 30-day mortality (1.01 [0.97-1.06]), or reinfarction (1.04 [0.97-1.11]) did not differ between the two strategies.

**Interpretation:** The increased risk of bolus thrombolytic treatment seems to be primarily associated with the method of administration rather than properties of the agents. Although the increased risk of intracranial haemorrhage is small, physicians should balance this risk against the putative benefits of easier administration with no difference in mortality or reinfarction.

**Figure 2:** Intracranial haemorrhage in trials of bolus versus infusion of thrombolytic agents\* $[\chi^2]$ -test for heterogeneity 8.78 (df6),  $p=0.27$

**Figure 3:** Odds ratios for clinical outcomes in trials of bolus versus infusion of thrombolytic agents $[\chi^2]$  values for heterogeneity: \*8.78 (df6),  $p=0.27$ ; †3.70 (df6)  $p=0.81$ ; ‡1.19 (df6)  $p=0.99$ ; §8.76 (df6)  $p=0.27$ .

Heart. 2000 Aug;84(2):142-8

The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. For the

CORE investigators

(Collaborative Organisation for RheothRx Evaluation).

Chareonthaitawee P. Gibbons RJ. Roberts RS. Christian TF. Burns R. Yusuf S

**OBJECTIVES:** To examine the impact of time to thrombolytic treatment on multiple acute outcome variables in a single trial of thrombolysis in acute myocardial infarction.

**DESIGN AND PATIENTS:** Mortality and reinfarction rate were measured in 2770 patients with acute myocardial infarction who received thrombolysis within 12 hours in CORE, an international, dose ranging trial of poloxamer 188. Tc-99m sestamibi infarct size and radionuclide angiographic ejection fraction substudies included 1099 and 1074 patients, respectively.

**RESULTS:** Time to thrombolysis, subgrouped by intervals (< 2, 2-4, >= 4-6, and >= 6 hours), was significantly associated with infarct size (median 15.0%, 18.5%, 22.0%, 18.5% of left ventricle;  $p = 0.033$ ), mean (SD) ejection fraction (51.5 (12.0)%, 48.3 (13.9)%, 48.2 (13.3)%, 48.2 (15.0)%;  $p = 0.006$ ), 35 day mortality (5.7%, 7.1%, 7.9%, 12.5%;  $p = 0.0004$ ), six month mortality (7.3%, 8.6%, 10.4%, 15.5%;  $p < 0.0001$ ), and 35 day reinfarction rate (6.1%, 3.2%, 4.0%, 0.9%;  $p = 0.0001$ ).

**CONCLUSIONS:** In this single large trial, the beneficial effect of time to thrombolysis on infarct size and ejection fraction was restricted to treatment given within two hours of symptom onset, while the effect on mortality was evident over all time intervals. Reinfarction rate was higher in patients treated with earlier thrombolysis.

Figure 3. Bar graph of the 35 day and six month cumulative mortality for the CORE thrombolysis population, for each time interval. (A) Patients without previous myocardial infarction. (B) Patients with previous myocardial infarction. (C) All patients. The significant association between the cumulative 35 day and six month mortality and time to thrombolysis is shown

Cardiovascular Drugs & Therapy, 2000;14(1):83-9

Efficacy of rescue thrombolysis in patients with acute myocardial infarction: preliminary findings

Sarullo FM, Americo L, Di Pasquale P, Castello A, Mauri F

Thrombolysis reduces mortality in patients with acute myocardial infarction (AMI) who are hospitalized within 6 hours from the onset of symptoms. AMIs involving a small area of myocardium show a lower mortality in comparison with AMI involving a large area. The present study was aimed at evaluating the safety and efficacy of rescue thrombolysis in patients with large AMI who had failed thrombolysis.

Ninety patients (69 Males and 21 Females), mean age  $56.7 \pm 9$  years, hospitalized for suspected AMI within 4 hours from the onset of symptoms, suitable for thrombolysis (First episode), and showing pain and persistent ST segment elevation 120 minutes after starting thrombolysis, were randomized (double-blind) into two groups. Group A (45 patients: 10 females and 35 males) received an additional thrombolytic treatment (rTPA 50 mg), 10 mg as bolus plus 40 mg in 60 minutes. Group B (45 patients: 11 females and 34 males) received placebo. Positive noninvasive markers were defined as follows: (1) resolution of chest pain, (2) >50% reduction in ST segment elevation, (3) double marker of creatine kinase (CK) and CK-MB activity 2 hours after the start of thrombolysis, and (4) occurrence of reperfusion arrhythmias within the first 120 minutes of thrombolytic therapy. Blood pressure, heart rate, and ECG were continuously monitored. An echocardiogram was carried out at entry, and before discharge, to control ejection fraction and segmentary kinetics. Adverse events such as death, re-AMI, recurrent angina, incidence of major and minor bleeding, and emergency CABG/ PTCA were checked.

The groups were similar in terms of age, sex, diabetes, smoking habits, hypertension, and adjuvant therapy (beta-blockers). No significant difference was observed between the two groups regarding the time elapsed from the onset of symptoms to thrombolysis and AMI localization.

Thirty-five patients (77.7%) showed reperfusion (10-50 minutes) after commencement of additional rTPA. Of the patients receiving placebo, 12 (26.6%) showed reperfusion within 35-85 minutes. Group A showed an earlier and lower CK and CK-MB peak than the control group, (respectively,  $p = 0.0001-0.009$  and  $0.002$ ). Mortality (17.7%, 16 patients) was higher in group B than in the additional rTPA group, i.e., 6.6% (3 patients) in group A versus 28.8% (13 patients) in Group B ( $p = 0.041$ ). Seven patients from group A showed nonfatal re-AMI. Angina was observed in 18 patients (40%) from group A and 3 (6.6%) from group B ( $p = 0.006$ ). Ten of these patients underwent urgent PTCA (9 from group A and 1 from group B), and 3 from group A underwent urgent CABG. Minor bleeding was higher in group A than in group B (44.4% versus 15.5%,  $p = 0.047$ ). Major bleeding was observed in group A (nonfatal stroke). At predischage, the echocardiogram ejection fraction was higher in group A than in group B ( $46 \pm 8\%$  versus  $38 \pm 7\%$ ,  $p = 0.0001$ ).

Our data suggest that an additional dose of thrombolytic drug in patients with unsuccessful thrombolysis is feasible and also that the bleeding increase is an acceptable risk in comparison with the advantages obtained in reducing AMI extension. Rescue thrombolysis can allow a gain in time to perform mechanical revascularization in patients admitted to hospital without an interventionist cardiology laboratory or in those who have to be referred to another hospital for urgent CABG.

American Journal of Cardiology, 2000 ;85(12):1409-13

Degree of residual stenosis in the culprit coronary artery after thrombolytic administration (Thrombolysis In Myocardial Infarction [TIMI] trials)

Llevadot J, Giugliano RP, McCabe CH, Cannon CP, Antman EM, Murphy S, Gibson CM

This study was undertaken to characterize residual stenosis after thrombolytic administration and to evaluate clinical and angiographic features and early outcomes of patients with mild residual obstruction after thrombolytic administration. Patients who underwent angiography at 90 minutes after thrombolytic administration in the Thrombolysis In Myocardial Infarction 4, 10A, 10B, and 14 trials were divided into 3 groups according to the degree of residual stenosis measured by quantitative coronary angiography: patients with a patent culprit artery with <50% stenosis, patients with patent arteries and residual stenosis  $\geq$ 50%, and patients with occluded arteries. Only 8.9% of the patients (188 of 2,119) had an infarct-related artery luminal diameter stenosis of <50% 90 minutes after thrombolysis. Compared with patients with patent arteries and  $\geq$ 50% stenosis, patients with mild residual obstruction were younger (56.8 vs 58.6 years;  $p = 0.03$ ), had fewer prior myocardial infarctions (6.9% vs 13.3%;  $p = 0.01$ ), fewer eccentric (19.8% vs 42.1%;  $p < 0.0001$ ), ulcerated (7.5% vs 13.2%;  $p = 0.03$ ), and collateralized (6.6% vs 13.2%,  $p = 0.01$ ) lesions, but a greater thrombus burden (29.7% vs 18.3%,  $p = 0.0002$ ). Among patients with patent arteries, a residual stenosis of <50% was associated with a significantly lower composite of in-hospital death, myocardial infarction, and congestive heart failure (2.8% vs 7.1%,  $p = 0.03$ ). Thus, a minority of patients have a mild residual obstruction at 90 minutes after thrombolytic administration. These patients have less complex lesions with greater thrombus burdens and better clinical outcomes.

TABLE III In-Hospital Clinical Outcomes

American Heart Journal, 2000 ;139(6):985-92

Factors associated with delay in reperfusion therapy in elderly patients with acute myocardial infarction: analysis of the cooperative cardiovascular project

Berger AK, Radford MJ, Krumholz HM

**Background:** Many elderly patients with an acute myocardial infarction (AMI) do not receive thrombolysis within 30 minutes of hospital arrival as recommended by the American College of Cardiology/American Heart Association Guidelines. We sought to identify factors associated with delay in administration of thrombolysis after arrival to the hospital in these patients and to determine whether this delay is associated with increased mortality rates.

**Methods and Results:** By using the Cooperative Cardiovascular Project database, we identified patients who received thrombolysis for an AMI. The patients were stratified into groups by time to thrombolysis after hospital arrival. Among a cohort of 17,379 patients, 22.2% received thrombolysis in the first 30 minutes after hospital arrival. Patients treated after the first 30 minutes were more likely to be older, be female, be diabetic, have a history of hypertension or heart failure, and have less marked ST elevation. They were also more likely to be admitted to smaller hospitals with a lower volume of AMIs and to hospitals without a cardiac catheterization laboratory. The 30-day mortality rate was significantly lower for patients treated within the first 30 minutes. After adjustments were made for clinical and hospital characteristics, delays in therapy beyond 30 and 90 minutes were associated with an increase in 1-year mortality rates of 9% and 27%, respectively, compared with delays for patients treated within 30 minutes.

**Conclusions:** After hospital arrival, time to treatment with thrombolytic therapy is longer than recommended in a significant proportion of patients. Clinical characteristics and institutional factors are associated with the delay in treatment. The more rapid treatment of appropriate elderly patients with an AMI probably will reduce mortality rates.

Table III. Independent correlates of delay in thrombolytic therapy administration

Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences.

Ellis SG, Da Silva ER, Spaulding CM, Nobuyoshi M, Weiner B, Talley JD

**Background:** Prompt restoration of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow improves survival in patients with acute ST-segment elevation myocardial infarction (MI). Fibrinolytic therapy fails to restore TIMI 3 flow within 90 minutes in 40% to 50% of patients. Because the results of percutaneous coronary intervention (PCI) for MI seem to be improving, a reevaluation of the role of PCI after fibrinolytic therapy for MI appears to be warranted.

**Methods and Results:** Data from all 9 randomized controlled trials (including new data from 4 trials) of rescue percutaneous transluminal coronary angioplasty (PTCA) versus conservative therapy after fibrinolytic therapy (1456 patients), 4 contemporary registries of PCI in this setting (977 patients), and other germane studies are reviewed. PTCA after failed fibrinolysis (TIMI 0 to 1 flow) appears to reduce early severe heart failure (3.8% vs 11.7%,  $P = .04$ ) and improve survival over 1 year in patients with moderate to large MI (92% vs 87%,  $P = .001$ ) and possibly reduces early repeat MI (4.3% vs 11.3%,  $P = .08$ ). Assessment of the possible benefit of PTCA for TIMI 2 flow is hampered by the small number of patients randomly assigned. Repeat MI may be decreased and left ventricular functional recovery enhanced. PTCA early after successful fibrinolysis is nearly always technically successful and may reduce repeat MI and hospital length of stay. However, it must be recalled that randomized trials from the 1980s suggested increased mortality rates with PTCA after restoration of TIMI 2 to 3 flow with fibrinolysis. Data from contemporary randomized studies of stents and glycoprotein IIb/IIIa inhibitors suggest that PCI as performed today may yield better results than those reviewed.

**Conclusions:** These data suggest a probable benefit of rescue PTCA in several distinct scenarios and that the pivotal mid-1980s studies suggesting no benefit or harm for PTCA after fibrinolytic therapy may no longer be relevant. The role of mechanical intervention in the treatment of patients treated in these settings should be reassessed

Fig. 1. Kaplan-Meier survival curves for patients randomly assigned to rescue PTCA or conservative treatment in the only two RCTs with available long-term follow-up. demonstrating survival advantage with rescue PTCA

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)

Coulter SA. Cannon CP. Ault KA. Antman EM. Van de Werf F. Adgey AA. Gibson CM. Giugliano RP. Mascelli MA. Scherer J. Barnathan ES. Braunwald E. Kleiman NS

**Background:** We evaluated platelet activation and aggregation in patients with acute myocardial infarction (AMI) treated with thrombolytic therapy alone or with reduced-dose thrombolysis and concomitant abciximab. **Methods and Results:** The study was performed in 20 control subjects and 51 patients with AMI before and after reperfusion with either alteplase or reteplase or reduced doses of these agents with concomitant abciximab. Platelet activation was assayed by platelet surface expression of P-selectin. Turbidometric platelet aggregation in response to ADP was measured in patients before thrombolytic therapy and 90 minutes and 24 hours after the beginning of thrombolytic therapy. P-selectin expression was greater at baseline in patients than normal control subjects (30.4% versus 9.8%,  $P < 0.0001$ ) but was identical between the 2 groups after stimulation with ADP (64.4% versus 69.3%,  $P = 0.37$ ). However, at 24 hours, basal P-selectin expression declined in patients ( $P = 0.0025$  versus baseline), whereas ADP-stimulated P-selectin expression was lower in patients than in control subjects (48% versus 69%,  $P = 0.0004$ ). When combined with reduced doses of either alteplase or reteplase, abciximab achieved 91% and 83% inhibition of 5 and 20  $\mu\text{mol/L}$  ADP-induced platelet aggregation, which decreased to 46% and 40%, respectively, at 24 hours. No appreciable difference in the platelet inhibition profile of abciximab was observed between the 2 thrombolytics.

**Conclusions:** Platelet activation and aggregation are heightened in the setting of thrombolysis for AMI. Despite this enhanced level of platelet activation, abciximab, combined with a reduced-dose thrombolytic, inhibited platelet aggregation similarly to the level reported in elective settings.

JAMA, 2000 ;283(20):2686-92

Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis

Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ

**Context:** Early administration of thrombolysis for acute myocardial infarction (AMI) may improve survival if safely and appropriately delivered. No systematic reviews that have comprehensively examined this topic exist in the literature.

**Objective:** To perform a meta-analysis of randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI measuring in-hospital mortality.

**Data Sources:** The Cochrane search strategy was used to search MEDLINE, EMBASE, and the Science Citation Index (1982-1999); Dissertation Abstracts (1987-1999); and Current Contents (1994-1999) for the terms thrombolysis, thrombolysis therapy, prehospital, and acute myocardial infarction. In addition, text and journal article bibliographies were hand searched, the National Institutes of Health Web site was reviewed, and primary authors and thrombolytic drug manufacturers were contacted for unpublished studies.

**Study Selection:** Randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI measuring all-cause hospital mortality were included. Two authors independently reviewed 175 citations by title, abstract, or complete article. After exclusion of 30 duplicate citations, 145 studies remained, of which 6 studies and 3 follow-up studies met the inclusion criteria.

**Data Extraction:** Independent data abstraction by 2 reviewers blinded to the journal, title, and author was confirmed by consensus. Trial quality was independently assessed by 2 other coauthors, blinded to the author, title, journal, introduction, and discussion.

**Data Synthesis:** The results of the 6 randomized trials (n=6434) were pooled and indicated significantly decreased all-cause hospital mortality among patients treated with prehospital thrombolysis compared with in-hospital thrombolysis (odds ratio, 0.83; 95% confidence interval, 0.70-0.98). Results were similar regardless of trial quality or training and experience of the provider. Estimated (SE) time to thrombolysis was 104 (7) minutes for the prehospital group and 162 (16) minutes for the in-hospital thrombolysis group (P=.007).

**Conclusions:** Our meta-analysis suggests that prehospital thrombolysis for AMI significantly decreases the time to thrombolysis and all-cause hospital mortality.

**Figure 2. Results of Randomized Trials of Prehospital Thrombolysis on Hospital Mortality** Panel A, z score=-2.14; P=.03. Panel B, z score=-2.06; P=.04. Panel C, z score=-1.73; P=.08. OR indicates odds ratio; CI, confidence interval; EMIP, The European Myocardial Infarction Project; and GREAT, Grampian Region Early Anistreplase Trial

American Heart Journal, 2000 ;139(5):820-3

Collaborative angiographic patency trial of recombinant staphylokinase (CAPTORS)

Armstrong PW, Burton JR, Palisaitis D, Thompson CR, Van de Werf F, Rose B, Collen D, Teo KK.

**Background:** We undertook an angiographic, dose-finding study of staphylokinase (SAK42D variant) to evaluate its efficacy and safety in patients with acute ST-segment myocardial infarction.

**Methods and Results:** Patients were studied within 6 hours of symptom onset and received SAK42D as a 30-minute infusion with 20% of the total dose given as a bolus. Eighty-two patients with a median age of 60 years (interquartile range 52 to 69 years), 84% male and 43% with an anterior myocardial infarction, were studied at a median time from symptom onset of 2.7 hours. There was a high degree of Thrombolysis in Myocardial Infarction (TIMI) 3 flow achieved with 15 mg of SAK42D, that is, 62%. Therefore after 21 patients had been studied at this dose the next dose of 30 mg was used and 65% TIMI 3 patency was achieved. At the peak dose of 45 mg, TIMI 3 90-minute patency was 63%. There were no allergic reactions, and no patient had intracranial hemorrhage. Four patients had major and 9 moderate bleeding during the study; 2 of the major and 5 of the moderate bleeding events occurred within 48 hours of commencement of treatment. The majority (62%) of these were related to vascular instrumentation, and there was no relation between the extent of bleeding and dose of SAK42D used. Forty-five minutes after cessation of SAK42D, there were small percent decrements in plasma fibrinogen and plasminogen levels that did not reach statistical significance. However, there were dose-related changes in [alpha]2 anti-plasmin that revealed a borderline significant reduction that was dose related (P = .053).

**Conclusion:** These data revealed similar fibrinolytic efficacy across a 3-fold increment in dose, indicating that this study operated on a flat portion of the dose-response curve. The favorable efficacy/safety profile achieved with staphylokinase is encouraging, and further investigation is warranted

**Fig. 1.** Ninety-minute TIMI perfusion grades according to dose. TIMI 3 patency 95% confidence intervals were 39% to 85% at 15 mg, 47% to 82% at 30 mg, and 45% to 82% for 45 mg.

Heart, 2000 ;84(2):157-63

Changing the site of delivery of thrombolytic treatment for acute myocardial infarction from the coronary care unit to the emergency department greatly reduces door to needle time.

Hourigan CT. Mountain D. Langton PE. Jacobs IG. Rogers IR. Jelinek GA. Thompson PL.

**OBJECTIVE:** To quantify the change in door to needle time when delivery of thrombolytic treatment of acute myocardial infarction was changed from the coronary care unit to the emergency department.

**DESIGN:** A comparative observational study using prospectively collected data.

**SETTING:** Coronary care unit and emergency department of an Australian teaching hospital.

**PARTICIPANTS:** 89 patients receiving thrombolysis in coronary care unit between June 1994 and January 1996, and 100 patients treated in the emergency department between April 1997 and May 1998.

**INTERVENTIONS:** From April 1997, by agreement between cardiology and emergency medicine, all patients with acute myocardial infarction receiving thrombolysis were treated by emergency physicians in the emergency department.

**MAIN OUTCOME MEASURE:** Door to needle time measured from time of arrival at the hospital to start of thrombolysis. Other outcomes included pain to needle time and mortality.

**RESULTS:** Median door to needle times were less for patients treated in the emergency department than in the coronary care unit (37 minutes, 95% confidence interval (CI) 33 to 44 v 80 minutes, 95% CI 70 to 89, respectively;  $p < 0.0001$ ). Door to needle time was under 60 minutes in 83% of emergency department patients and 26% of coronary care unit patients (57% difference, 95% CI 45% to 69%;  $p < 0.0001$ ). Median pain to needle time was less for emergency department patients than for coronary care unit patients (161 minutes, 95% CI 142 to 177 v 195 minutes, 95% CI 180 to 209;  $p = 0.004$ ); times of less than 90 minutes occurred in 18% of emergency department patients v 1% of coronary care unit patients (17% difference, 95% CI 9% to 25%;  $p < 0.05$ ). Overall mortality was similar in patients treated in the emergency department and the coronary care unit.

**CONCLUSIONS:** With a collaborative interdepartmental approach, thrombolytic treatment of acute myocardial infarction was more rapid in the emergency department, without compromising patient safety. This should improve the outcome in patients with infarcts treated with thrombolytic agents.

Figure 2. Comparison of numbers of patients from the emergency department (ED) versus the coronary care unit (CCU), with door to needle times in four 30 minute frames.

J Am Coll Cardiol , 2000 ;36(2):366-74,

Thrombolytic therapy in older patients.

Berger AK. Radford MJ. Wang Y. Krumholz HM.

**OBJECTIVES:** We compared outcomes following thrombolytic therapy and primary angioplasty with no reperfusion therapy in a population-based cohort of older patients presenting with acute myocardial infarction (AMI) and indications for acute reperfusion.

**BACKGROUND:** Evidence supporting the efficacy of acute reperfusion (thrombolytic therapy or primary angioplasty) in the elderly with suspected AMI is not as strong as it is in younger groups.

**METHODS:** From a national cohort of Medicare beneficiaries with AMI, we identified 37,983 patients age 65 or older who presented within 12 h of symptom onset with ST elevation or left bundle branch block. A total of 14,341 (37.8%) received thrombolytic therapy and 1,599 (4.2%) underwent primary angioplasty within 6 h of hospital arrival.

**RESULTS:** After adjustment for demographic, clinical, hospital and physician factors, and co-interventions, thrombolytic therapy was not associated with a better 30-day survival (odds ratio [OR] 1.01; 95% confidence interval [CI]: 0.94 to 1.09) compared with no therapy, whereas primary angioplasty was (OR 0.79; 95% CI: 0.66 to 0.94). At one year, both thrombolytic therapy (OR 0.84; 95% CI: 0.79 to 0.89) and primary angioplasty (OR 0.71; 95% CI: 0.61 to 0.83) were associated with a survival benefit.

**CONCLUSIONS:** In this national sample of older patients, those who received thrombolytic therapy or primary angioplasty had lower mortality at one year compared with those who did not receive a reperfusion strategy. However, only primary angioplasty was associated with better survival at 30 days. Our findings should heighten interest in further investigating the best approach to the treatment of older patients with suspected AMI and ST segment elevation or left bundle branch block.

Table 3. In-Hospital Events and Mortality Rates for Patients Without Absolute Contraindications to Thrombolytic Therapy

Table 5. Thirty-Day and One-Year Mortality Models Stratified by Thrombolytic Therapy Characteristics

Am Heart J, 2000 ;139(6):1096-100

Reduction of congestive heart failure symptoms by very early fibrinolytic therapy in acute myocardial infarction: a long-term follow-up.

Gilon D. Leitersdorf I. Gotsman MS. Zahger D. Sapoznikov D. Weiss AT.

**Background:** In patients with acute myocardial infarction (MI), early fibrinolytic therapy results in improved survival and preservation of ventricular function. The purpose of the study was to determine whether very early treatment also reduces the development of congestive heart failure.

**Methods and Results:** During the years 1984 to 1989, 358 consecutive patients with acute MI were treated with streptokinase, 161 within the first 1.5 hours from the onset of chest pain (group A) and 197 within 1.5 to 4.0

hours (group B). In 68, fibrinolysis was initiated in the prehospital setting pioneered by our group. Symptoms related to heart failure including dyspnea on exertion, fatigue, orthopnea, paroxysmal nocturnal dyspnea, nocturia, and peripheral edema, in addition to pulmonary edema events, were assessed during 5 years of follow-up. The evaluation was based on medical records and a detailed questionnaire, which was filled in by the investigators. A favorable significant effect of very early thrombolysis on the development of most of these limiting symptoms appeared 3 months after hospital discharge and persisted thereafter ( $P < .05$ ). During hospitalization, pulmonary edema attacks occurred less frequently in patients from group A (23% vs 36.5%,  $P < .01$ ). This difference persisted during 4 years of follow-up (13% vs 36%,  $P < .001$ ).

Conclusions: Our data demonstrate that very early fibrinolytic therapy results in a significant long-term reduction of congestive heart failure-related symptoms and thereby improves the quality of life in patients after MI.

Fig. 1. Four-year follow-up on presence of grade III to IV dyspnea on exertion (DOE) severity by New York Heart Association (NYHA) classification. Group A, Streptokinase administration within 1.5 hours after onset of pain (open bars); group B, streptokinase administration at 1.5 to 4.0 hours from onset of pain (solid bars).

New Engl J Med, 2000;343(1):8-15

Treatment of acute myocardial infarction and 30-day mortality among women and men..

Gan SC. Beaver SK. Houck PM. MacLehose RF. Lawson HW. Chan L

Background: Previous studies have suggested that women with acute myocardial infarction receive less aggressive therapy than men. We used data from the Cooperative Cardiovascular Project to determine whether women and men who were ideal candidates for therapy after acute myocardial infarction were treated differently.

Methods: Information was abstracted from the charts of 138,956 Medicare beneficiaries (49 percent of them women) who had an acute myocardial infarction in 1994 or 1995. Multivariate analysis was used to assess differences between women and men in the medications administered, the procedures used, the assignment of do-not-resuscitate status, and 30-day mortality.

Results: Among ideal candidates for therapy, women in all age groups were less likely to undergo diagnostic catheterization than men. The difference was especially pronounced among older women; for a woman 85 years of age or older, the adjusted relative risk was 0.75 (95 percent confidence interval, 0.68 to 0.83). Women were somewhat less likely than men to receive thrombolytic therapy within 60 minutes (adjusted relative risk, 0.93; 95 percent confidence interval, 0.90 to 0.96) or to receive aspirin within 24 hours after arrival at the

hospital (adjusted relative risk, 0.96; 95 percent confidence interval, 0.95 to 0.97), but they were equally likely to receive beta-blockers (adjusted relative risk, 0.99; 95 percent confidence interval, 0.95 to 1.03) and somewhat more likely to receive angiotensin-converting-enzyme inhibitors (adjusted relative risk, 1.05; 95 percent confidence interval, 1.02 to 1.08). Women were more likely than men to have a do-not-resuscitate order in their records (adjusted relative risk, 1.26; 95 percent confidence interval, 1.22 to 1.29). After adjustment, women and men had similar 30-day mortality rates (hazard ratio, 1.02; 95 percent confidence interval, 0.99 to 1.04).

Conclusions: As compared with men, women receive somewhat less aggressive treatment during the early management of acute myocardial infarction. However, many of these differences are small, and there is no apparent effect on early mortality.

#### Table 5. 30-Day Mortality and Hazard Ratio for Death among Women and Men with Acute Myocardial Infarction

Circulation 2000 20;101(24):2788-94

Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Strategies for Patency Enhancement in the Emergency Department .  
(SPEED) Group.

Background: Low-dose alteplase with standard-dose abciximab enhances reperfusion 90 minutes after acute myocardial infarction (MI). We combined standard-dose abciximab with low-dose reteplase for acute MI in 2 phases. Two heparin doses were also explored.

**Methods and Results:** Phase A patients were randomized 4:1 to receive an abciximab bolus with infusion alone (n=63) or with 5 U, 7.5 U, 10 U, 5 U+2.5 U, or 5 U+5 U of reteplase (total n=241). Phase B tested the best phase A strategy (abciximab plus 5 U+5 U reteplase, expressed as abciximab-reteplase 5+5 U; n=115) against 10 U+10 U reteplase alone (n=109). The primary end point was Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow at 60 to 90 minutes. In phase A, 62% of the abciximab-reteplase 5+5 U group had TIMI grade 3 flow versus 27% of the abciximab-only patients (P =0.001). In phase B, 54% of the abciximab-reteplase 5+5 U group had grade 3 flow versus 47% of the reteplase-only patients (P =0.32). Grade 3 flow rates were 61% for a 60 U/kg heparin bolus and abciximab-reteplase 5+5 U, 51% for a 40 U/kg heparin bolus and abciximab-reteplase 5+5 U (P =0.22), and 47% for reteplase alone (P =0.05 versus the 60 U/kg heparin group). Major bleeding rates in phase A were 3.3% for abciximab alone and 5.3% for abciximab-reteplase 5+5 U; rates in phase B were 9.8% for abciximab-reteplase 5+5 U and 3.7% for reteplase alone. Major bleeding was similar with standard- or low-dose heparin (6.3% versus 10.5%, P =0.30).

**Conclusions:** In this phase II trial, adding reteplase to abciximab treatment of acute MI versus reteplase alone enhanced the incidence of early complete reperfusion after the initiation of therapy in the emergency department.

J Am Coll Cardiol, 2000 ;35(1):136-43

Predictors of cardiogenic shock after thrombolytic therapy for acute myocardial infarction.

Hasdai D. Califf RM. Thompson TD. Hochman JS. Ohman EM. Pfisterer M. Bates ER. Vahanian A. Armstrong PW. Criger DA. Topol EJ. Holmes DR Jr.

**OBJECTIVES:** This study characterized clinical factors predictive of cardiogenic shock developing after thrombolytic therapy for acute myocardial infarction (AMI). **BACKGROUND:** Cardiogenic shock remains a common and ominous complication of AMI. By identifying patients at risk of developing shock, preventive measures may be implemented to avert its development. **METHODS:** We analyzed baseline variables associated with the development of shock after thrombolytic therapy in the Global Utilization of Streptikinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial. Using a Cox proportional hazards model, we devised a scoring system predicting the risk of shock. This model was then validated in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) cohort. **RESULTS:** Shock developed in 1,889 patients a median of 11.6 h after enrollment. The major factors associated with increased adjusted risk

of shock were age (chi2 = 285, hazard ratio [95% confidence interval] 1.47 [1.40, 1.53]), systolic blood pressure (chi2 = 280), heart rate (chi2 = 225) and Killip class (chi2 = 161, hazard ratio 1.70 [1.52, 1.90] and 2.95 [2.39, 3.63] for Killip II versus I and Killip III versus I, respectively) upon presentation. Together, these four variables accounted for >85% of the predictive information. These findings were transformed into an algorithm with a validated concordance index of 0.758. Applied to the GUSTO-III cohort, the four variables accounted for > 95% of the predictive information, and the validated concordance index was 0.796. CONCLUSIONS: A scoring system accurately predicts the risk of shock after thrombolytic therapy for AMI based primarily on the patient's age and physical examination on presentation.

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