Coronary perfusion during acute myocardial infarction with a combined therapy of coronary angioplasty and high-dose intravenous streptokinase

RICHARD S. STACK, M.D., CHRISTOPHER M. O'CONNOR, M.D., DANIEL B. MARK, M.D., M.P.H., TOMOAKI HINOHARA, M.D., HARRY R. PHILLIPS, M.D., MYOUNG M. LEE, M.D., PH.D., NORMAN M. RAMIREZ, M.D., WILLIAM G. O'CALLAGHAN, M.D., CHARLES A. SIMONTON, M.D., ERIC B. CARLSON, M.D., KENNETH G. MORRIS, M.D., VICTOR S. BEHAR, M.D., YIHONG KONG, M.D., ROBERT H. PETER, M.D., AND ROBERT M. CALIFF, M.D.

ABSTRACT Two hundred and sixteen patients with acute myocardial infarction were treated with immediate infusion of high-dose (1.5 million units) intravenous streptokinase followed by emergency coronary angioplasty. The infarct lesion was crossed and dilated in 99% and persistent coronary perfusion after the procedure was achieved in 90% (including 3% with significant residual stenosis). Total in-hospital mortality was 12%. Multivariable analysis showed a higher hospital mortality with cardiogenic shock (41% vs 5% without shock), older age, lower left ventricular ejection fraction, and female sex. Final patency of the infarct-related vessel was determined by follow-up in-hospital cardiac catheterization. Coronary reocclusion occurred in 11% (symptomatic in 7%, treated with emergency angioplasty or bypass surgery; silent in 4%, treated medically). Of the surviving patients with successful initial establishment of infarct vessel patency, 94% were discharged from the hospital with an open infarct artery or a bypass graft to the infarct vessel. There was significant improvement in both ejection fraction (44% to 49%; $p < .0001$) and regional wall motion in the infarct zone (-3.0 SD to -2.4 SD; $p < .0001$) among patients with persistent coronary perfusion and insignificant residual stenosis at the time of the follow-up cardiac catheterization. Thus, a treatment strategy for acute myocardial infarction that includes immediate administration of streptokinase followed by emergency coronary angioplasty, and coronary bypass surgery when necessary, results in a high rate of early and sustained patency of the infarct-related vessel.
Circulation 77, No. 1, 151–161, 1988.

EXPERIMENTAL STUDIES in both animals and man have demonstrated that jeopardized myocardium can be salvaged if coronary blood flow is reestablished early after coronary occlusion.[1–3] Recently, several large randomized controlled trials have shown significant improvement in survival among patients treated with intravenous streptokinase.[4–6] Experience from the Western Washington trial has shown that survival may be closely related to the patency status of the infarct-related vessel.[7, 8] A striking improvement in 1 year survival was observed in patients who were successfully perfused, even in the absence of improvement in left ventricular performance.[9] Newer thrombolytic agents, such as tissue-type plasminogen activator (t-PA), hold promise for a further reduction in mortality rates by achieving a higher incidence of early patency of the infarct-related vessel.[10, 11]

Two important limitations exist to the use of even the best available thrombolytic agents as sole therapy in acute myocardial infarction. First, at least 25% of treated patients are not reperfused within 4 to 6 hr of chest pain by thrombolytic therapy alone; unfortunately, there is no accurate noninvasive method available to identify these.[12] Second, even after successful thrombolytic therapy, most patients are left with a

From the Interventional Cardiac Catheterization Program and the Duke Cardiovascular Disease Databank, Division of Cardiology, Department of Medicine, Duke University Medical Center, and the VA Medical Center, Durham, NC.

Supported by NRSA training grant 5T 32 HL07101-09 from the NIH: research grants HS-03834, HS-04873, and HS-05635 from the National Center for Health Services Research; research grant HL-17670 from the National Heart, Lung, and Blood Institute; training grant LM-07003 and grant LM-03373 from the National Library of Medicine; and a grant from the Andrew W. Mellon Foundation, New York, NY.

Address for correspondence: Richard S. Stack, M.D., Director, Interventional Cardiac Catheterization Program, Box 3111, Duke University Medical Center, Durham, NC 27710.

Received June 11, 1986; revision accepted Sept. 24, 1987.

high-grade residual stenosis and an associated increased risk of reinfarction and limiting angina.[13, 14]

Use of emergency percutaneous transluminal coronary angioplasty (PTCA) as a method of overcoming the major limitations of thrombolytic therapy is increasing. To date, however, reported experience with emergency PTCA in acute myocardial infarction has been limited to small series. Furthermore, the protocols used in these studies have varied considerably, so that some patients have received PTCA alone while others in the same series have also been given either intracoronary or low-dose intravenous streptokinase. Importantly, only one previous study has described the use of high-dose intravenous streptokinase followed by emergency PTCA.[14] Yet this approach has the potential advantage of maximizing early coronary perfusion with initiation of thrombolytic therapy at the community hospital followed by transport to a referral center for more definitive revascularization by emergency PTCA.

The present report has three goals. First, we describe our results in achieving patency of the infarct-related vessel and minimizing the residual stenosis by a protocol of combined high-dose (1.5 million units) intravenous streptokinase and emergency PTCA in 216 patients with acute myocardial infarction. Second, we describe the final predischarge outcome of these patients as determined at follow-up cardiac catheterization. Third, we use multivariable statistical methods to identify the major independent factors related to hospital outcome in this population.

Methods

Patient population. The population for this study consisted of 216 patients with acute myocardial infarction referred to Duke University Medical Center between March 1984 and August 1986 who were enrolled consecutively in a protocol of prompt treatment with high-dose intravenous streptokinase followed by emergency coronary angioplasty. Protocol entry criteria were: (1) continuous chest pain consistent with myocardial infarction of 6 or fewer hours duration accompanied by ST segment elevation of 1 mm or greater in two or more electrocardiographic leads, or (2) intermittent ("stuttering") chest pain of 6 to 24 hr duration with both pain and ST segment elevation present on arrival at Duke. Patients meeting the entry criteria were excluded from the protocol if they had a contraindication to streptokinase: (1) recent history of gastrointestinal bleeding, stroke, major surgery, or trauma (including prolonged cardiopulmonary resuscitation), (2) history of a bleeding diathesis, (3) proliferative diabetic retinopathy, or (4) severe uncontrolled hypertension.

During the same time period, 1111 patients were treated in the Duke University cardiac care unit for acute myocardial infarction. Six hundred and fifteen of these patients received no intravenous fibrinolytic therapy or PTCA because they either were referred to Duke beyond the time limit of our protocol and did not show evidence of ischemic but viable myocardium or they had a contraindication to interventional therapy. One hundred and ten patients received streptokinase alone and were found to have a patent infarct-related vessel at cardiac catheterization but were not believed to be appropriate candidates for PTCA. Fifty-one patients received only intracoronary or low-dose intravenous streptokinase and PTCA. One hundred and two patients were treated with t-PA and were randomly assigned to early or late angioplasty under a separate research protocol. Seventeen patients who presented within the protocol time limits were treated with PTCA alone because of contraindications to thrombolytic therapy.

Data collection. Baseline data regarding the pertinent history, physical examination, laboratory studies, chest x-ray, and electrocardiogram were collected prospectively for each patient, as were details of the interventional catheterization procedure and results. In-hospital complications were determined by retrospective review of each patient's chart.

Definitions. Cardiogenic shock was defined as sustained hypotension (systolic pressure of 90 mm Hg or less lasting for $\geq$1 hr) and evidence of peripheral vasoconstriction (Killip class IV).[15] Persistent patency of the infarct-related vessel was considered to be present if the vessel was completely perfused at the end of the procedure (Thrombolysis in Myocardial Infarction trial [TIMI] grade 2 or 3).[16] The coronary angioplasty were defined as successful ($\leq$50% residual stenosis), persistently perfused with residual subtotal stenosis (>50% residual stenosis), or unsuccessful with no persistent perfusion. Myocardial infarction location was described as anterior (ST elevation in I, aVL, V_1-V_6) or inferior (ST elevation in II, III, aVF). Groin hematoma was any hematoma occurring at the catheterization site. Gastrointestinal bleeding was any gastrointestinal blood loss noted by the cardiac care unit housestaff or nursing staff.

Interventional catheterization protocol. Each patient was treated with intravenous streptokinase administered as a single bolus of 1.5 million units in 250 ml of D5W given over 30 min as soon as the presumptive diagnosis of myocardial infarction was established. Four patients were unable to tolerate the full dose of streptokinase because of hypotension (three patients) or severe bradycardia (one patient). One hundred and ten (51%) of the 216 study patients were transported to Duke via the Duke emergency helicopter service.[17]

Patients were treated routinely with intravenous diphenhydramine as prophylaxis against allergic reactions to iodinated contrast and with intravenous lidocaine for prophylaxis against ventricular arrhythmias. Steroid pretreatment was not routinely given. Aspirin was begun either in the emergency room or immediately after PTCA in the cardiac care unit.

Each PTCA procedure was performed by a team of two senior staff cardiologists and a cardiology fellow. Introducer sheaths (No. 8F) were placed in the right femoral artery and vein. A No. 5F balloon-directed temporary pacemaker was inserted to the level of the inferior vena cava; it was advanced to the right ventricle if conduction disturbances or bradyarrhythmias occurred during this procedure. Heparin was administered as a 10,000 unit bolus at the beginning of the procedure, followed by a bolus of 2000 units each hour during prolonged procedures.

The noninfarct-related coronary artery was injected first to assess the degree of collateral circulation to the infarct region. The infarct-related artery was then injected in multiple views. A biplane left ventriculogram was obtained. Coronary angioplasty was performed with a No. 8F thin-wall guiding catheter and a low-profile balloon catheter (Hartzler LPS in 85% of cases, Simpson Robert in 15%, ACS). Multiple dilatations were often required to minimize the residual luminal diameter narrowing. Results were assessed with high-resolution video fluoroscopy; coronary stenosis gradients were not measured. If patients had multiple lesions in the infarct-related vessel, all those believed to be hemodynamically significant were dilated if possible. If patients had multivessel disease, only the infarct-related artery was dilated in the acute setting; lesions in other vessels believed

to be prognostically important were subsequently approached by either PTCA or surgery on an elective basis.

After the procedure, a Swan-Ganz catheter was inserted and the patient was sent to the cardiac care unit for observation. Heparin was infused continuously to maintain the partial thromboplastin time more than 2 × normal for at least 24 hr, but if a major coronary dissection occurred or the residual stenosis was 75% to 95%, heparin was continued for 2 to seven days.

Routine cardiac care unit management included bedside hemodynamic monitoring for 24 hr or until the patient was considered stable. Diltiazem, 30 to 90 mg qid, was started immediately after the procedure; if a contraindication to diltiazem existed, nifedipine was used. A β-blocker was given to achieve a heart rate less than 70 beats/min, unless a hemodynamic contraindication was present. The β-blocker, calcium-channel blocker, and antiplatelet therapy with aspirin and persantine were continued throughout the period of hospitalization. The hematocrit was carefully monitored and packed red blood cells were generally transfused if the value fell below 30.

Electrocardiographic monitoring was continued for 72 to 96 hr and patients were constantly observed for signs or symptoms of recurrent ischemia. When there was clinical evidence suggesting restenosis or reocclusion (generally recurrent ST segment elevation and/or chest pain), patients underwent emergency repeat angiography.

Surgical backup was available for each patient undergoing angioplasty. Patients who were initially perfused by PTCA but who subsequently developed abrupt reclosure accompanied by recurrent pain and ST elevation and were refractory to repeat PTCA were referred for emergency coronary artery bypass surgery (CABG). Since January 1985, these patients have been managed with use of the "transluminal reperfusion catheter" (ACS), a 4.5F passive perfusion stenting device used to maintain coronary blood flow.[18] The reperfusion catheter is preflushed with heparin (1000 units/ml) and streptokinase solution (6000 units/ml) and inserted over a guidewire across the total coronary obstruction. Blood from the aorta and proximal coronary artery passes through sideholes into the catheter, through the obstruction, and out through distal sideholes, resulting in continuous coronary perfusion and relief of myocardial ischemia. Patients are then transported directly to the operating room for definitive revascularization.

Follow-up catheterization and angiographic interpretation. To critically evaluate the final patency status of the infarct-related coronary artery, repeat cardiac catheterization was sought before hospital discharge as part of the study protocol in surviving patients not referred for CABG (n = 170). Patients with medical contraindications (n = 1) and surviving non-CABG patients in whom initial angioplasty failed (n = 11) were excluded. Of the remaining 158 patients, 144 (91%) underwent repeat cardiac catheterization.

The results of each PTCA and follow-up procedure were evaluated by consensus of a panel of at least three angiographers. Coronary luminal diameter narrowing was graded on an ordinal scale (i.e., 0%, <25%, 25%, 50%, 75%, 95%, 100%), as previously described.[19] The coronary angiographic methods used in this study have been validated in a previous angiographic-pathologic study.[20]

Ventriculographic analysis. Biplane left ventriculography was performed in the 30 degree right anterior oblique and 60 degree left anterior oblique projections during the acute and predischarge cardiac catheterization studies. Of the 144 patients who underwent repeat cardiac catheterization, 106 (74%) were judged to have technically adequate ventriculograms allowing regional wall motion analysis on both the acute and follow-up catheterization studies. All ventriculograms were recorded with a 35 mm camera at 60 frames/sec.

Regional wall motion was analyzed in the right anterior oblique projection by the centerline method of Sheehan et al.[21] The left ventricular silhouette was projected onto a rear projection screen and was traced onto clear plastic sheets by an observer who was blinded to the results of the intervention. Tracings were then digitized by a second blinded observer using a sonic digitizing device interfaced to a VAX computer for analysis of regional and global left ventricular performance. The jeopardized region was determined by averaging the motion of chords lying in the most abnormally contracting 50% of the territory supplied by the infarct-related artery. The abnormal chord motion in this zone was then compared with the chord motion in the same region at the time of the predischarge study.

Data analysis. Group data were summarized with medians and interquartile ranges (25th and 75th percentiles). Changes over time in global and regional left ventricular function were tested with the Wilcoxon sign-rank test. Univariable and multivariable analyses of factors predicting in-hospital death in the study group were performed with the logistic regression model.[22]

Results

Baseline characteristics. The baseline characteristics of the 216 study patients are listed in tables 1 and 2. The median age was 57 years and 79% of the patients were men. There was a slight preponderance of inferior wall infarctions (56%). Thirty-seven percent of patients had one or more complications of their infarction before arrival in the Interventional Catheterization Laboratory. Cardiogenic shock was present in 15%. Preprocedural complications in patients transported by helicopter were successfully managed on board and there were no deaths during transport.

The median time from onset of pain to administration of streptokinase was 3.0 hr, while the median

TABLE 1
Baseline clinical characteristics

Clinical variables	
Age (median, 25th to 75th percentile)	57 years (49–65)
Males	79
Anterior MI	44
Inferior MI	56
Complications before PTCA	
Ventricular tachycardia	13
Ventricular fibrillation	7
Cardiac arrest requiring CPR	4
Respiratory arrest	3
Cardiogenic shock	15
Severe bradycardia or asystole	17
Pulmonary edema	7
None of the above	63
Time intervals	
Time interval from pain onset to administration of SK (median, 25th to 75th percentile)	3 hr (1.8–4.7)
Time interval from pain onset to arrival in ICC lab (median, 25th to 75th percentile)	4.5 hr (3.0–6.3)

Values are percentages unless indicated otherwise.
MI = myocardial infarction; CPR = cardiopulmonary resuscitation, SK = streptokinase; ICC = interventional cardiac catheterization.

TABLE 2
Baseline angiographic characteristics

Infarct-related artery	
LAD	43
LCX	8
RCA	46
Bypass graft	2
Total occlusion of infarct vessel on first angiogram	56
Ejection fraction (median, 25th to 75th percentile)	44 (37–54)
LV end-diastolic pressure (median, 25th to 75th percentile)	22 mm Hg (17–28)
Number of diseased vessels (≥75% stenosis)	
One vessel	47
Two vessels	38
Three vessels	14
Left main disease	1

Values are percentages unless indicated otherwise.
LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; LV = left ventricular.

interval from onset of pain to arrival in the interventional laboratory was 4.5 hr. Forty-seven percent of patients had one-vessel disease, while 15% had three-vessel or left main disease. The median ejection fraction for the group was 44%, and one-third had an ejection fraction less than 40%.

Coronary angioplasty. The infarct-related artery was patent on the initial coronary angiogram in 44% (95/216) of patients. After further injections of contrast into the vessel and intracoronary nitroglycerin, an additional 9% (19/216) of infarct-related vessels became patent. The lesion was successfully crossed with a balloon catheter in 99% (214/216) and persistent perfusion (TIMI Grade 2 or 3) was established by both streptokinase and PTCA without CABG in 90% (194/216). Successful PTCA (residual stenosis ≤50%) was achieved in 87% (188/216). The median residual stenosis before PTCA was 100%; after the procedure, it was 25%. Multiple lesions in the same vessel were dilated in 20%. Procedural success rates did not vary significantly on univariable analysis with location of infarction, presence or absence of cardiogenic shock, sex, age, or time from pain onset to administration of streptokinase.

Thirteen percent of all patients underwent an unsuccessful PTCA procedure, including 3% who had greater than 50% but less than 100% residual stenosis after PTCA with resolution of ischemic symptoms. These patients were treated medically. Four percent had abrupt reclosure with recurrent ischemic symptoms after initially successful PTCA; these patients were sent for emergency bypass surgery with the reperfusion catheter persistently maintaining coronary blood flow. The remaining 6% of patients with failed PTCA had coronary occlusion after PTCA but were asymptomatic and were believed to have a completed infarction. These patients were transferred to the coronary care unit for routine postinfarction care.

TABLE 3
Complications during PTCA

None	70
Ventricular tachycardia	6
Ventricular fibrillation	5
Severe bradycardia or asystole	10
Cardiac arrest requiring CPR	2
Respiratory arrest	2
Persistent cardiogenic shock (onset pre-PTCA)	9
New onset cardiogenic shock	4
Emergency CABG	5
Stroke	0.5
Death	0.5

Values are percentages.
CPR = cardiopulmonary resuscitation.

Thirty percent of patients had complications during the PTCA procedure (table 3). Of the patients who had experienced no complications before the procedure (n = 138), 18% had at least one complication during the procedure. In contrast, of the 78 patients who had a preprocedure complication, 52% also had a complication during the PTCA. Cardiogenic shock was the most common complication (persistent from pre-PTCA in 9%, new onset in 4%), followed by severe bradycardia or asystole (10%), ventricular tachycardia (6%), and ventricular fibrillation (5%). There was one death in the laboratory from persistent cardiogenic shock and refractory ventricular fibrillation in a patient with successful complete dilatation.

Hospital course. The most common in-hospital complication (55% of patients) was development of a groin hematoma at the site of catheterization (table 4). A drop

TABLE 4
In-hospital complications[A]

Groin hematoma	55
Drop in hematocrit to <30%[B]	41
Transfusion of red blood cells[B]	40
Gastrointestinal bleeding	14
Femoral vascular surgery	3
Cardiac arrest with successful resuscitation and survival to hospital discharge	3
Nonfatal stroke	1
Death	12

Values are percentages.
[A]Does not include complications occurring during PTCA.
[B]Patients who had CABG are excluded from these totals.

TABLE 5
Global and regional left ventricular performance

Patency status of infarct-related vessel	LV function	Acute[A]	Follow-up[A]	p value
Insignificant	Regional[B]	−3.0 (−3.6 to −2.0)	−2.4 (−3.1 to −1.6)	.0001
stenosis (n = 78)	Global[C]	44% (36% to 53%)	49% (41% to 56%)	.0001
Significant	Regional[B]	−3.3 (−3.9 to −2.9)	−3.1 (−3.6 to −2.5)	.84
stenosis (n = 18)	Global[C]	43% (35% to 46%)	45% (39% to 48%)	.60
Total	Regional[B]	−3.4 (−3.7 to −3.1)	−3.2 (−3.6 to −2.7)	.68
occlusion (n = 10)	Global[C]	46% (43% to 52%)	49% (43% to 56%)	.91

LV = left ventricular.
[A]Median (25th to 75th percentiles in parentheses).
[B]Regional wall motion as measured by standard deviation per chord.
[C]LV ejection fraction.

in hematocrit to less than 30% was also common (41%) after interventional catheterization and packed red cells were frequently transfused (40%). Gastrointestinal bleeding was seen in 14% of patients. A total of 72% of all patients had some evidence of bleeding during the period of hospitalization. All of the bleeding episodes were managed successfully without resulting mortality.

Twenty-five patients (12%) died in-hospital after the initial procedure; two underwent intervening CABG. An additional 3% of patients had a cardiac arrest and were successfully resuscitated and 1% had a nonfatal stroke.

One hundred and forty-four of 158 eligible patients (91%) underwent follow-up cardiac catheterization. In most cases (85%), the second study was performed 7 days after the initial PTCA. Five percent of patients underwent recatheterization at 24 hr and an additional 10% underwent emergency recatheterization for recurrent symptoms before the scheduled 1 week study. Of the 14 patients who were eligible but did not undergo a restudy, none had evidence of angina pectoris or new electrocardiographic changes before discharge.

Changes in left ventricular performance between the acute and predischarge study are shown in table 5. A significant improvement in both regional and global contractile performance was observed in the group of patients who were successfully treated with immediate PTCA and who were found to have insignificant stenosis (≤50% luminal diameter narrowing) on predischarge arteriography. No improvement was observed in either the global ejection fraction or in the infarct zone among patients with significant stenosis (>50% but <100%) or occlusion (100%) at the time of follow-up study.

Figure 1 shows the final hospital outcome in the study population. Silent reocclusion was diagnosed at the time of predischarge cardiac catheterization in 4% (8/194) of patients who had initial patency of the infarct-related vessel after PTCA. These patients were treated medically. Symptomatic reocclusion before discharge occurred in 7% of patients (14/194) and was managed with repeat PTCA (11 patients; successful in 82%) or CABG (three patients). In patients with a successful initial PTCA, restenosis without reocclusion occurred in 12%. Conversely, in patients with an unsuccessful initial PTCA but sustained patency of the infarct-related vessel, the residual lesion was 50% or less at the time of discharge in 28%.

A policy of aggressive management to produce sustained myocardial perfusion was maintained throughout the period of hospitalization. Patients with symptomatic reocclusion of the infarct-related vessel were managed with repeat PTCA or CABG. Patients were managed with medical therapy alone only in the event that reocclusion of the infarct vessel was no longer associated with evidence of ischemia. Thus, by this combined treatment strategy, 94% of all surviving patients in the study population who had sustained perfusion after the initial catheterization (with PTCA, or with a reperfusion catheter and CABG) were also discharged from the hospital with an open infarct-related vessel or a bypass graft to the infarct artery. Rates of restenosis or reocclusion did not vary significantly on univariable analysis with infarct location, age, sex, presence or absence of cardiogenic shock, or time from onset of pain to administration of streptokinase.

Identification of clinical factors related to outcome. The strongest prognostic factor in the study population was cardiogenic shock (table 6). Forty-one percent of patients with shock died in-hospital compared with 5% of patients without it. Age was also an important factor: 31% of patients older than 65 years died compared with

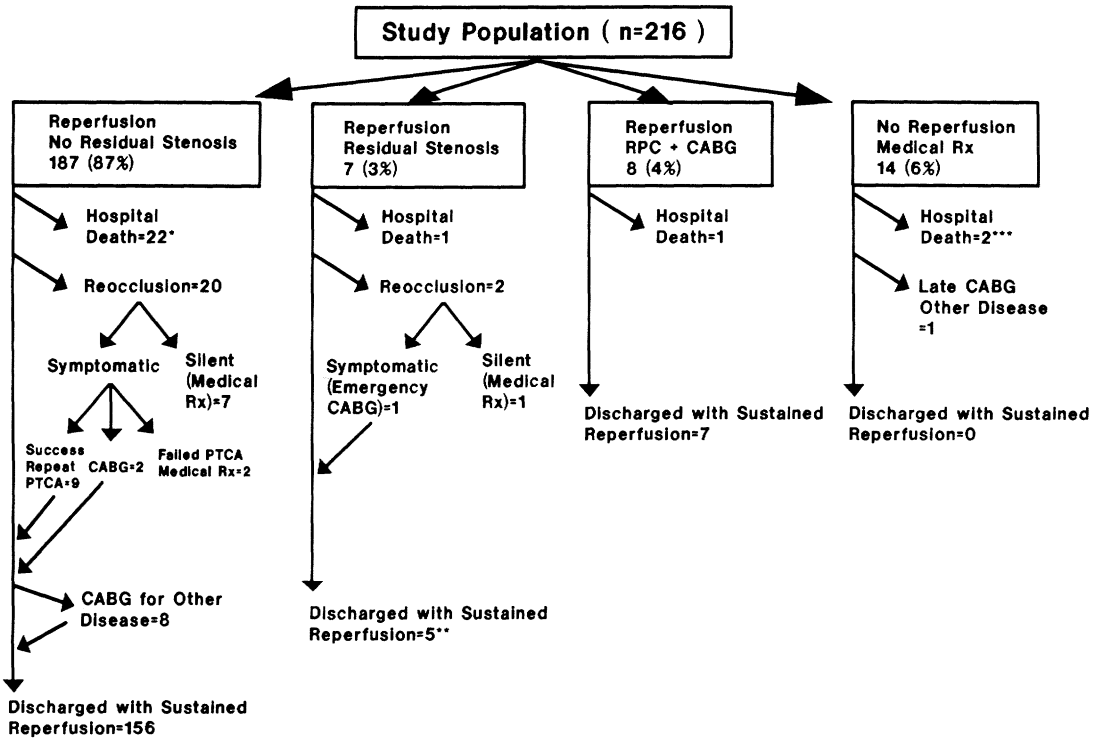

FIGURE 1. Outcome after emergency PTCA. *Includes one procedural death and one death after reocclusion and successful repeat PTCA. **Includes two patients found to have 50% or less stenosis on repeat catheterization. ***Includes one patient who died after CABG for other disease. Medical Rx = medical therapy; RPC = reperfusion catheter.

8% of patients from 45 to 65 years old and no patients under 45 years old. The death rate also increased with a lower ejection fraction (22% for patients with an ejection fraction of <40% vs 7% for patients with an ejection fraction ≥40%), female sex (27% death rate vs 8% for men), and an occluded infarct-related vessel on the initial coronary angiogram (17% death rate vs 7% in patients with an open vessel on the first angiogram). Factors not significantly related to in-hospital survival were number of diseased vessels, location of infarction, and time interval from onset of pain to administration of streptokinase. Logistic regression analysis showed that the independent predictors of in-hospital mortality were cardiogenic shock ($p < .0001$), older age ($p < .0001$), lower ejection fraction ($p = .005$), and female sex ($p = .009$).

Discussion

The results of this study demonstrate that early reestablishment of coronary perfusion can be achieved and sustained in a high proportion of patients with acute myocardial infarction with the use of a combination of high-dose intravenous streptokinase and emergency PTCA and, when necessary, emergency bypass surgery. The prognostic benefits of thrombolytic therapy have now been convincingly demonstrated by the GISSI trial and others.[4–6, 8] The addition of prompt mechanical dilatation to the interventional regimen overcomes the major limitations of isolated thrombolytic therapy by reducing the residual stenosis, thereby lowering the risk of in-hospital reocclusion. In addition, emergency repeat dilatation can be performed successfully in the great majority of those patients who develop symptomatic reocclusion, resulting in a high overall rate of sustained patency of the infarct-related artery at the time of hospital discharge.

TABLE 6
In-hospital prognosis

Variable	Univariable χ^2 [A]	Multivariable χ^2 [B]
Cardiogenic shock	32	15
Age	23	14
Ejection fraction	12	8
Sex	6	7
Infarct vessel open on initial angiogram	5	—
Number of diseased vessels	2	—
Anterior wall infarct	1	—
Time interval from pain onset to streptokinase administration	0	—

[A] χ^2 of 3.84 with 1 degree of freedom is equal to $p = .05$.
[B] Logistic regression analysis.

Although the evidence pointing to the major prognostic importance of an open infarct-related artery is growing, the pathophysiologic relationship of patency of the infarct-related vessel, left ventricular function, and long-term survival needs to be further elucidated. The rationale for an aggressive approach to early and complete revascularization of the infarct region has developed from both basic and clinical studies. A recurring finding in basic studies has been that myocardial salvage occurs when vessel patency can be established early after infarction.[1, 2] Human studies with thrombolytic therapy[3, 5, 23] or surgery[24] have consistently shown better left ventricular function in patients with patent infarct-related vessels. Several studies of thrombolytic therapy have found a close relationship between vessel patency and both early and late survival.[5, 8] These observations, coupled with the failure of intravenous thrombolytic therapy to reperfuse 25% to 50% or more of infarct-related vessels, led to the development of the current protocol.

Study population. The population in this study represents the broad spectrum of acute myocardial infarction seen in a referral center with a relatively large proportion of high-risk patients. Compared with populations in other recently reported trials of thrombolytic therapy, our patients had a much higher incidence of cardiogenic shock, cardiac arrest, and other complications before intervention. For example, cardiogenic shock was present in less than 4% of the GISSI population[6] and the Western Washington trial,[25] compared with 15% in our study. The larger number of critically ill patients in our study may have resulted from the tendency of community hospitals to refer their most complicated patients for more aggressive therapy.

The ability to provide access to mechanical recanalization to patients in community hospitals without cardiac catheterization facilities depends on safe and effective medical transportation. Half of our patients were transferred via the Duke emergency helicopter service, which provides a mobile intensive care unit environment and is staffed by two intensive care flight nurses. A physician is not routinely aboard, but constant radio contact with the interventional cardiologist and telemetric monitoring are maintained. No patients died en route despite the large number of patients with cardiogenic shock and ventricular arrhythmias.[17] A similarly effective result has been reported by Topol et al.[26]

Emergency cardiac catheterization and PTCA. Our initial angiographic findings underscore the importance of emergency diagnostic cardiac catheterization with immediate PTCA to reestablish blood flow in patients in whom thrombolytic therapy fails. Unfortunately, current noninvasive diagnostic techniques are not sufficiently accurate to assess coronary reperfusion reliably.[12] Although our study population is a subset of the overall patient group treated with thrombolytic therapy at our institution, the failure rate for streptokinase we observed (56%) is quite consistent with previous studies of thrombolytic therapy.[16, 27] With currently available thrombolytic agents, about half of patients will fail to reperfuse early. Initial studies with intravenous t-PA have reported reperfusion rates of 60% to 80%.[28] Thus, even with the most effective thrombolytic agent, therapy will fail in a significant number of patients.

Besides producing a higher rate of patency of the infarct-related vessel, PTCA also reduces the high-grade residual stenosis present in most patients. Reduction of the residual coronary stenosis may result in two important clinical outcomes: fewer recurrent ischemic events and enhanced recovery of myocardial function. In controlled randomized trials, the incidence of clinical reinfarction has been more than twice as high among patients successfully treated with streptokinase compared with control patients.[5, 6, 23] In the only controlled study of emergency PTCA vs thrombolytic therapy alone, O'Neill et al.[29] reported a reocclusion rate of 15% with intracoronary streptokinase, compared with 7% with PTCA. In the same study, patients treated with streptokinase had a mean residual stenosis on predischarge cardiac catheterization of 80% and showed only a modest improvement of regional wall motion and no significant change in ejection fraction. Patients treated with PTCA had a mean residual stenosis of 32% and showed significantly greater improvement in regional wall motion (change after PTCA = 1.32 SD vs streptokinase = 0.59 SD, $p < .05$) as well as a significantly greater improvement in ejection fraction (7% vs 2%, $p < .01$).

In our present study, regional and global left ventricular performance was analyzed as a function of the patency status of the infarct-related artery at the time of follow-up cardiac catheterization. Patients with insignificant residual stenosis showed improvement in both regional wall motion and ejection fraction. Patients with significant residual stenosis or total occlusion showed no change in either the infarct zone or the ejection fraction.

Although emergency PTCA for acute myocardial infarction was first reported in 1982, only a limited number of studies have examined the results of this approach (table 7).[14, 29–40] Because of the small number of patients in each series, the diversity of methods

TABLE 7
Emergency PTCA in patients with acute myocardial infarction

Study	SK	No. of patients[A]	% reper	% ≤50%
Meyer et al.[30]	IC	18	78	78
Hartzler et al.[31]	IC	26	88	88
	None	15	100	100
Serruys et al.[32]	IC	16	100	100
Hartzler et al.[33]	IC	41	95	95
	None	37	78	78
Gold et al.[34]	IC	28	79	61
Pepine et al.[35]	None	8	100	100
Holmes et al.[36]	IC	44	80	75
	None	11	91	91
Papapietro et al.[37]	IC	18	72	72
Prida et al.[38]	IC	16	81	81
	None	7	100	100
	IV	5	80	80
Kitazume et al.[39]	IC UK	22	90	90
O'Neill et al.[29]	None	29	83	79
Erbel et al.[40]	IV (low dose) + IC	69	[B]	65
Fung et al.[14]	IV	29	97	90

[A]Includes only those patients in each study who underwent emergency PTCA.

[B]PTCA was attempted only in patients successfully reperfused by SK.

SK = streptokinase; IC = intracoronary; IV = intravenous; UK = urokinase; % reper = percent of patients in whom reperfusion was successful; % ≤50% = percent of patients without significant residual stenosis.

used, and the wide variability in success rates, assessment of the relative efficacy of PTCA has been difficult. The most popular regimens have involved the use of intracoronary streptokinase followed by PTCA, with infarct-related artery patency rates ranging from 72% to 100%, or the use of primary PTCA without thrombolytic therapy, with infarct-related artery patency rates of 78% to 100%. The rates of successful dilatation (≤50% residual stenosis) have ranged from 61% to 100%. Predischarge angiography has been performed only sporadically, so that the prevalence of coronary patency 1 week or more after emergency PTCA remains uncertain. Although emergency PTCA is now commonly used after high-dose intravenous streptokinase, only one previous study has reported on the use of this combination.[14]

In the present study, the infarct lesion was successfully crossed with the PTCA balloon in 99% of patients, despite the high prevalence of total coronary occlusions. PTCA was successful in 87% of patients, and an additional 3% had persistent infarct-related vessel patency with a residual subtotal stenosis. Clinically evident reocclusion occurred in 7% and was treated with repeat PTCA or emergency CABG. Silent reocclusion was diagnosed on follow-up catheterization in 4% and was treated medically. Although the initial success rate was higher and the reocclusion rate was lower than the rates reported in patients treated with thrombolytic therapy alone, these results differ somewhat from the results obtained with PTCA under elective circumstances. In a recent study from our laboratory, the results of 269 PTCA procedures during acute myocardial infarction were compared with the results of 288 elective procedures performed during the same time period.[41] There was a significant difference in both initial success rates (87% vs 94%, $p < .01$) and clinical in-hospital reocclusion rates (9% vs 3%, $p < .01$) in patients with acute myocardial infarction vs those undergoing an elective procedure. This difference in clinical course after PTCA may result from instability of the endothelial surface of the infarct-related plaque or from the effects of thrombus in the vessel.[42] A difference in the response of the plaque to PTCA in these two clinical groups is further suggested by the occurrence in the present study of early restenosis (>75% but <100%) among 12% of patients who initially had 50% or less residual stenosis after the PTCA procedure. Importantly, 28% of patients with a subtotal stenosis after the initial PTCA (>50% stenosis) had spontaneous reduction of this critical stenosis by the time of the predischarge cardiac catheterization.

Complications. The use of emergency cardiac catheterization after high-dose intravenous thrombolytic therapy results in a high incidence of clinically evident bleeding. The 55% prevalence of hematoma in this study is comparable to the rates of 47% with streptokinase and 43% with t-PA in the TIMI trial.[16] The high rate of transfusion in the current study in part reflects our aggressive approach to augmentation of hematocrit; the risks and benefits of such an aggressive approach remain to be determined. No deaths were attributed to bleeding complications.

Rapid access to emergency surgical backup was necessary to provide revascularization for patients in whom PTCA failed and had evidence of continued jeopardized myocardium or hemodynamic compromise. The use of the transluminal reperfusion catheter allowed patients to go to the operating room with persistent coronary perfusion and a stable hemodynamic status. A significant amount of bleeding was experienced in the perioperative period, requiring large quantities of packed red blood cells (median transfusion requirement = 9 units) and fresh frozen plasma. Despite the increased need for intensive care in the

perioperative period, only two patients died, both as a result of persistent power failure.

Multivariable analysis of factors related to prognosis. Because of the extremely high mortality associated with cardiogenic shock, any series including a significant number of these patients will have a high overall mortality. Although our 41% in-hospital mortality rate for patients with cardiogenic shock remains much higher than the 5% in-hospital mortality rate of patients without cardiogenic shock, it is lower than mortality rates with traditional medical therapy. Killip et al.[15] reported an 81% mortality rate in patients with cardiogenic shock using the same clinical criteria as in the present study. A later clinical trial of intra-aortic balloon counterpulsation in cardiogenic shock reported an 83% mortality rate.[43] In contrast, DeWood et al.[24] found that use of an intra-aortic balloon pump followed by CABG within 24 hr of acute myocardial infarction was associated with a 28% hospital mortality in patients presenting with cardiogenic shock. A recent report of PTCA in cardiogenic shock has described a 27% mortality.[44] In the GISSI study, the mortality for patients with cardiogenic shock was 70% in both the patients treated with intravenous streptokinase and the control group; PTCA was not used in either group.[6]

Elderly patients remained at significantly increased risk of death in our study despite rates of early and persistent coronary patency equivalent to those in younger patients. Multiple studies of populations with acute myocardial infarction before thrombolytic therapy have identified age as a major independent prognostic factor. In the GISSI trial, the overall mortality rate was 6.7% in patients less than age 65, 17.4% in patients between 65 and 75 years of age, and 31% in patients over age 75.[6] Although a statistically significant benefit of streptokinase alone was not demonstrated in that study in patients over age 65, a trend toward benefit in this group was observed. Despite the continued identification of older age as a major adverse factor, the lack of a control group does not allow us to draw conclusions about whether elderly patients experience either disproportionate benefit or harm from this aggressive management strategy.

The higher mortality in women seen in our study was also reported in the GISSI study and other studies in the untreated postmyocardial infarction population. In the Framingham study, 30 day mortality after acute myocardial infarction was 16% for men and 28% for women.[45]

Significance of an open vessel and "sustained" reperfusion. In a previous study, we reported that improvement in regional left ventricular function and reduction of infarct size were limited to those patients with early sustained reperfusion during acute myocardial infarction and were absent in patients with a closed vessel. There was no improvement in patients who had late opening (at 24 hr catheterization) after initial failure of reperfusion during the first 6 hr after the onset of symptoms.[3]

A recent report on risk stratification from the Western Washington trial used multivariable analysis to examine the relationship between a completely reperfused infarct-related artery and 1 year survival.[8] A dramatic improvement in survival was found among patients with an open vessel and that survival benefit was further magnified as baseline left ventricular function decreased. Patients with unsuccessful or "partial" reperfusion showed no improvement when compared with untreated control patients.

In the present study, reduction of the infarct lesion to an insignificant residual stenosis was achieved in 87% of our patients by use of streptokinase followed by PTCA. Importantly, by use of repeat PTCA or CABG in patients with symptomatic reocclusion, 94% of all surviving patients who had sustained reperfusion after the initial procedure were discharged from the hospital with an open infarct-related artery or a bypass graft to the infarct-related artery. Approaches using thrombolytic therapy alone will almost certainly result in a lower rate of early and sustained myocardial perfusion. Adoption of this more aggressive approach to treatment of acute myocardial infarction, however, will substantially increase the cost of initial therapy. If the superior rate and degree of vessel patency translates into a major beneficial impact on patient survival, these costs will be well justified.

We gratefully acknowledge the leadership of Dr. Joseph C. Greenfield, Jr., M.D., Chairman of the Department of Medicine, who established and developed the Interventional Cardiac Catheterization Program at Duke for the purpose of exploring the value and limitations of new interventional techniques designed to improve the treatment of patients with cardiovascular disease. We also wish to thank Ms. Patricia Hoffman, ICC Research Co-ordinator, and David B. Pryor, M.D., Director of the Duke Cardiovascular Disease Database. We also express our appreciation to Dr. Mark Hlatky for critical review of the manuscript and to Ms. Renee Story and Ms. Cristy Vollmar for their secretarial assistance.

References

1. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB: The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation **56:** 786, 1977
2. Theroux P, Ross J, Franklin D, Kemper WS, Sasayama S: Coronary arterial reperfusion. III. Early and late effects on regional myocardial function and dimensions in conscious dogs. Am J Cardiol **38:** 599, 1976
3. Stack RS, Phillips HR, Grierson DS, Behar VS, Kong Y, Peter RH, Swain JL, Greenfield JC: Functional improvement of jeopardized

myocardium following intracoronary streptokinase infusion in acute myocardial infarction. J Clin Invest **72:** 84, 1983
4. Yusuf S, Collins R, Peto R, Furberg C, Stampfer MJ, Goldhaber SZ, Hennekens CH: Intravenous and intracoronary fibinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side effects from 33 randomized controlled trials. Eur Heart J **6:** 556, 1985
5. Simoons ML, V'D Brand M, DeZwaans C, Verheugt FWA, Remme WJ, Serruys PW, Bars F, Rest J, Krauss XH, Vermeer F, Lubsen J: Improved survival after early thrombolysis in acute myocardial infarction. A randomized trial by the Interuniversity Cardiology Institute in the Netherlands. Lancet **2:** 578, 1985
6. Gruppo Italiano Per Lo Studio Della Streptochinasi Nell'Infarto Miocardico (GISSI): Effectiveness of intravenous thombolytic treatment in acute myocardial infarction. Lancet **1:** 397, 1986
7. Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz JK: The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12-month follow-up report. N Engl J Med **312:** 1073, 1985
8. Stadius ML, Davis K, Maynard C, Ritchie JL, Kennedy JW: Risk stratification for 1 year survival based on characteristics identified in the early hours of acute myocardial infarction. Circulation **74:** 703, 1986
9. Ritchie JL, Davis KB, Williams DL, Caldwell J, Kennedy JW: Global and regional left ventricular function and tomographic radionuclide perfusion: The Western Washington Intracoronary Streptokinase in Myocardial Infarction Trial. Circulation **70:** 867, 1984
10. Williams DO, Borer J, Braunwald E, Chesebro JH, Cohen LS, Dalen J, Dodge HT, Francis CK, Knatterud G, Ludbrook P, Markis JE, Mueller H, Desvigne-Nickens P, Passamani ER, Powers ER, Rao AK, Roberts R, Ross A, Ryan TJ, Sobel BE, Winniford M, Zaret B: Intravenous recombinant tissue-type plasminogen activator in patients with acute myocardial infarction: a report from the NHLBI thrombolysis in myocardial infarction trial. Circulation **73:** 338, 1986
11. Gold HK, Leinbach RC, Garabedian HD, Yasuda T, Johns JA, Grossbard EB, Palacios I, Collen D: Acute coronary reocclusion after thrombolysis with recombinant human tissue-type plasminogen activator: prevention by a maintenance infusion. Circulation **73:** 347, 1986
12. Kircher BJ, Topol EJ, O'Neill WW, Pitt B: Prediction of infarct coronary artery recanalization after intravenous thrombolytic therapy. Am J Cardiol **59:** 513, 1987
13. Harrison DG, Ferguson DW, Collins SM, Skorton DJ, Ericksen EE, Kioschos JM, Marcus ML, White CW: Rethrombosis after reperfusion with streptokinase: importance of geometry of residual lesions. Circulation **69:** 991, 1984
14. Fung AY, Lai P, Topol EJ, Bates ER, Bourdillon PDV, Walton JA, Mancini GBJ, Kryski T, Pitt B, O'Neill WW: Value of percutaneous transluminal coronary angioplasty after unsuccessful intravenous streptokinase therapy in acute myocardial infarction. Am J Cardiol **58:** 686, 1986
15. Killip T, Kimball JT: Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol **20:** 457, 1967
16. The TIMI Study Group: The thrombolysis in myocardial infarction (TIMI) trial. N Engl J Med **312:** 932, 1985
17. Bellinger RL, Califf RM, Mark DB, Weber RA, Collins P, Stone J, German L, Stack RS: Helicopter transport of patients during acute myocardial infarction. Am J Cardiol (in press)
18. Hinohara T, Simpson JB, Phillips HR, Behar VS, Peter RH, Kong Y, Carlson EB, Stack RS: Transluminal catheter reperfusion: a new technique to reestablish blood flow after coronary occlusion during PTCA. Am J Cardiol **57:** 684, 1986
19. Harris PJ, Harrell FE, Lee KL, Behar VS, Rosati RA: Survival in medically treated coronary artery disease. Circulation **60:** 1259, 1979
20. Trask N, Califf RM, Conley MJ, Kong Y, Peter RH, Lee KL, Hackel D, Wagner GS: Accuracy and interobserver variability of coronary cineangiography: a comparison with postmortem evaluation. J Am Coll Cardiol **3:** 1145, 1984
21. Sheehan FH, Bolson EL, Dodge HT, Mathey DG, Schofer J, Woo HW: Advantages and applications of the centerline method for characterizing regional ventricular function. Circulation **74:** 293, 1986
22. Harrell FE: The LOGIST procedure. *In* SAS Institute, Inc: SUGI supplemental library user's guide, 1983 edition. Cary, NC, 1983, SAS Institute, Inc., p 181
23. The I.S.A.M. Study Group: A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.): mortality, morbidity, and infarct size at 21 days. N Engl J Med **314:** 1465, 1986
24. DeWood MA, Spores J, Berg, Kendall RW, Grunwald RP, Selinger SL, Hensley GR, Sutherland KI, Shields JP: Acute myocardial infarction: decade of experience with surgical reperfusion in 701 patients. Circulation **68**(suppl II): II-8, 1983
25. Kennedy JW, Ritchie JL, Davis KB, Fritz JK: Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med **309:** 1477, 1983
26. Topol EJ, Fung AY, Kline E, Kaplan L, Landis D, Strozeski M, Burney RE, Pitt B, O'Neill WW: Safety of helicopter transport and out-of-hospital intravenous fibrinolytic therapy in patients with evolving myocardial infarction. Cathet Cardiovasc Diag **12:** 151, 1986
27. Tennant SN, Dixon J, Venable TC, Page HL, Roach A, Kaiser AB, Frederiksen R, Tacogue L, Kaplan P, Babu NS, Anderson EE, Wooten E, Jennings HS, Breinig J, Campbell WB: Intracoronary thrombolysis in patients with acute myocardial infarction: comparison of the efficacy of urokinase with streptokinase. Circulation **69:** 756, 1984
28. Topol EJ, Califf RM: The role of tissue plasminogen activator in myocardial infarction. *In* Califf RM, Wagner GS, editors: Acute coronary care. Boston, 1987, Martinus Nijhoff Publishing, p 73
29. O'Neill WW, Timmis GC, Bourdillon PD, Lai P, Ganghadarhan V, Walton J, Ramos R, Laufer N, Gordon S, Schork MA, Pitt B: A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. N Engl J Med **314:** 812, 1986
30. Meyer J, Merx W, Schmitz H, Erbel R, Kiesslich T, Dorr R, Lambertz H, Bethge C, Krebs W, Bardos P, Minale C, Messmer BJ, Effert S: Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. Circulation **66:** 905, 1982
31. Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, McCallister BD, Cura GM, Conn RC, Crockett JE: Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. Am Heart J **106:** 965, 1983
32. Serruys PW, Wijns W, Van Den Brand M, Ribeiro V, Fioretti P, Simoons ML, Kooijman CJ, Reiber JHC, Hugenholtz PG: Is transluminal coronary angioplasty mandatory after successful thrombolysis? Quantitative coronary angiographic study. Br Heart J **50:** 257, 1983
33. Hartzler GO, Rutherford BD, McConahay DR: Percutaneous transluminal coronary angioplasty: application for acute myocardial infarction. Am J Cardiol **53:** 117C, 1984
34. Gold HK, Cowley MJ, Palacios IF, Vetrovec GW, Akins CW, Block PC, Leinbach RC: Combined intracoronary streptokinase infusion and coronary angioplasty during acute myocardial infarction. Am J Cardiol **53:** 122C, 1984
35. Pepine CJ, Prida X, Hill JA, Feldman RL, Conti CR: Percutaneous transluminal coronary angioplasty in acute myocardial infarction. Am Heart J **107:** 820, 1984
36. Holmes DR, Smith HC, Vlietstra RE, Nishimura RA, Reeder GS, Bove AA, Bresnahan JF, Chesebro JH: Percutaneous transluminal coronary angioplasty, alone or in combination with streptokinase therapy, during acute myocardial infarction. Mayo Clin Proc **60:** 449, 1985
37. Papapietro SE, MacLean WAH, Stanley AWH, Hess RG, Corley N, Arcinigas JG, Cooper TB: Percutaneous transluminal coronary angioplasty after intracoronary streptokinase in evolving acute myocardial infarction. Am J Cardiol **55:** 48, 1985
38. Prida XE, Holland JP, Feldman RL, Hill JA, MacDonald RG, Conti CR, Pepine CJ: Percutaneous transluminal coronary angioplasty in evolving acute myocardial infarction. Am J Cardiol **57:** 1069, 1986
39. Kitazume H, Iwama T, Suzuki A: Combined thrombolytic therapy and coronary angioplasty for acute myocardial infarction. Am Heart J **111:** 826, 1986
40. Erbel R, Pop T, Henrich KJ, von Olshausen K, Schuster CJ,

Rupprecht HJ, Steuernagel C, Med C, Meyer J: Percutaneous transluminal coronary angioplasty after thrombolytic therapy: a prospective controlled randomized trial. J Am Coll Cardiol **8:** 485, 1986

41. Ramirez N, Califf RM, O'Callaghan WG, Hinohara T, Mark D, Morris KG, Peter RH, Behar VS, Kong Y, Phillips HR, Stack RS: Does clinical indication for coronary angioplasty affect outcome? J Am Coll Cardiol **9:** 182A, 1987
42. Sherman CT, Litvack F, Grundfest W, Lee M, Hickey A, Chaux A, Kass R, Blanche C, Matloff J, Morgenstern L, Ganz W, Swan HJC, Forrester J: Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med **315:** 913, 1986
43. Scheidt S, Wilner G, Mueller H, Summers D, Tesch M, Wolff G, Krakauer J, Rubenfire M, Fleming P, Noon G, Oldham N, Killip T, Kantrowitz A: Intra-aortic balloon counterpulsation in cardiogenic shock. Report of a cooperative clinical trial. N Engl J Med **288:** 979, 1973
44. O'Neill W, Erbel R, Laufer N, Walton J, Bates E, Topol E, Bourdillon D, Meyer J, Pitt B: Coronary angioplasty therapy of cardiogenic shock complicating acute myocardial infarction. Circulation **72**(suppl III): III-309, 1985
45. Kannel WB, Sorlic P, McNamara PM: Prognosis after initial myocardial infarction: The Framingham Study. Am J Cardiol **44:** 53, 1979