RISK STRATIFICATION OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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CASE PRESENTATION

J. B. first presented to PMH in April of 1993 at the age of 57 with extertional chest pain, left arm numbness, and increasing dyspnea on exertion. Risk factors for premature coronary artery disease included hypertension, diabetes mellitus, tobacco use, and a low HDL (18 mg/dl) with a normal LDL cholesterol (97 mg/dl). He was evaluated in the ambulatory care clinic and scheduled for an outpatient exercise echocardiogram. The baseline echocardiogram revealed preserved left ventricular systolic function with inferior hypokinesis. He exercised for 9 minutes on a standard Bruce protocol, the test was terminated for fatigue. During exercise he developed lateral ST segment depression, worsening inferior hypokinesis and lateral hypokinesis consistent with provoked ischemia in the absence of chest pain. He was treated with aspirin and a calcium channel blocker, and did well until October of 1994 when he was involved in a MVA. An MRI, CXR, and spine films were performed at an outside hospital and reported as "negative". After he was discharged form the hospital he began to have more frequent chest pain, new dyspnea on exertion, and orthopnea. He presented to PMH in November of 1994 and was admitted with new congestive heart failure. In retrospect, it was hypothesized that his sudden change in symptoms was due to an undiagnosed myocardial infarction in October. He ruled out for a myocardial infarction during the November admission, was diuresed, and referred for an echocardiogram to re-evaluate his left ventricular systolic function. The technical quality of this echocardiogram was limited, however the report indicated that J.B. had a dilated left atrium and globally depressed left ventricular systolic function. The physicians taking care of J.B. decided to complete his work-up as an outpatient and he was scheduled for an ETT Thallium. He exercised for 9 minutes on a standard Bruce protocol, increasing his heart rate from 84 to 124 bpm and systolic blood pressure from 150 to 175 mm Hg, achieving a RPP of 21,700 before the test was terminated for fatigue. He developed nondiagnostic ECG changes in the absence of chest pain, and perfusion imaging revealed a fixed posterior/inferior and posterior/septal defect with a small amount of peri-infarct reversibility consistent with borderzone ischemia. He was also noted to have significantly depressed left ventricular function on gated images. He was continued on medical therapy including aspirin, nitrates, an ACE inhibitor, and furosemide.

He was readmitted to PMH in February of 1995 and after reassessing his left ventricular systolic function by echocardiography it he was referred for catheterization to evaluate his coronary anatomy anticipating that if he had 3 vessel disease that he would derive a survival benefit from coronary artery bypass grafting. Cardiac catheterization revealed severely depressed left ventricular systolic function with an ejection fraction of 0.23 (normal $\geq$ 0.50) with anterior akinesis, apical dyskinesis, inferior hypokinesis and severe three vessel coronary artery disease. He was recommended for bypass surgery but unfortunately, developed overt heart failure 24 hours after the catheterization, ruled in for a myocardial infarction, and expired that evening from refractory ventricular arrhythmias.

INTRODUCTION

Acute myocardial infarction is a common manifestation of atherosclerotic coronary artery disease, accounting for more than 750,000 hospital admissions annually in the United States [1]. Although the vast majority, 80 to 95%, of those admitted to the hospital survive to be discharged [1], mortality in the first year approaches 10%, with an annual mortality of 2 to 5% in subsequent years [1-5]. Most mortal events, 50 to 75% [1,5,6], occur in the first 6 months, with the highest incidence in the first 6 weeks after an acute MI [1,5,6]. As a result, a structured attempt to identify patients at high risk for death or re-infarction---*risk stratification*---after an acute MI has become a standard part of their medical care in the hope that intervention in these patients will improve their prognosis.

Previous studies have associated death and/or re-infarction in the first 2 years after infarction with 1) the extent of myocardial necrosis [7-11], 2) symptoms of congestive heart failure [11-15], 3) evidence of spontaneous or provoked myocardial ischemia [8-10,16,17], and 4) electrical instability as measured by the severity of ambient ventricular ectopy [7,9-11,16], late potentials on a signal-averaged electrocardiogram (SAECG) [18-20], or altered autonomic tone resulting in reduced heart rate variability [21-23]. Furthermore, the risk of mortality for post-MI patients increases commensurate with the number of these risk factors present at the time of hospital discharge (Table 1), so that the 2 year mortality for patients with 1 risk factor is 4 to 9% while patients with all 4 risk factors have a two year mortality of 40 to 60% [24].

Table 1. Variables Associated with Increased Mortality Risk in the First 2 Years After a Myocardial Infarction

Variable	Odds Ratio	95% CI
Variables associated with the amount of myocardial damage (pre-existent and related to the index event)		
Symptoms > 1 month	2.2	1.3 to 3.6
Ejection fraction < 0.40	4.2	2.3 to 7.6
Rales above the bases	7.6	4.4 to 12.9
Congestion on chest radiograph	6.0	3.5 to 10.4
Previous myocardial infarction	1.8	1.1 to 3.1
Variables associated with residual ischemia		
Angina before discharge	1.3	0.76 to 2.2
Angina on exercise test	2.5	1.2 to 5.5
Variables associated with electrical instability		
More than 10 VPC/hour	2.7	1.4 to 1.5
Abnormal signal-averaged ECG (QRS > 114 ms, RMS < 20 μV, LAS > 38 ms)	8.0	
Heart rate variability (SDNN < 50 ms)	3.8	2.2 to 6.3

CI = confidence intervals calculated using Mantel-Haenszel estimates; VPC = ventricular premature complexes; ms = milliseconds RMS = root mean square; μV = microvolt; LAS = low-amplitude signals; SDNN = standard deviation of normal beat cycle lengths.
Krone RJ. Ann Intern Med 1992; 116:223-237.

The majority of studies that address post-MI risk stratification are based on data obtained prior to the routine use of agents known to reduce infarct mortality, including ACE-inhibitors, aspirin, ß-blockers, and thrombolytic therapy. Consequently, these studies must be considered in the context of the treatments contemporary for the time period in which they were performed. More recent studies have analyzed the outcomes of patients enrolled

in thrombolytic trials. Unfortunately, these patients represent a selected population, since they generally have fewer comorbidities, less advanced coronary disease (Figure 1) [25], higher ejection fractions, fewer late potentials on SAECG, and are younger than infarct populations as a whole.

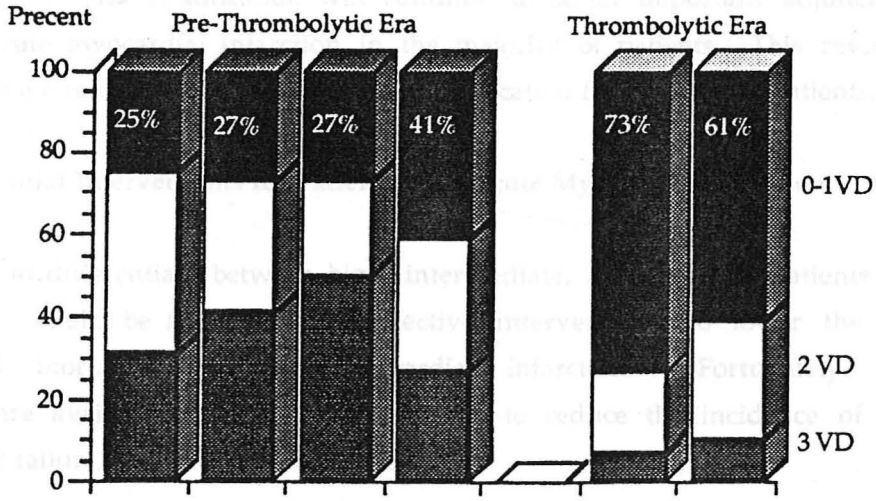


Figure 1. Difference in Severity of Coronary Artery Disease (VD = vessel disease) in the Pre-Thrombolytic and Thrombolytic Eras. Roger WJ, et al. J Am Coll Cardiol 1991:1007-16

Furthermore, these trials have been performed during the "interventional era", when patients are generally treated more aggressively for recurrent ischemia. As a result, the patients that undergo predischarge evaluation are highly selected, and their risk of post-MI complications is relatively low. Despite these differences, variables that identify patients as *high risk* for morbid and mortal events appear similar in both the "prethrombolytic and reperfusion eras".

Over the past twenty years post-MI treatment strategies have changed considerably. Even before the thrombolytic era, patients were mobilized sooner, shortening their length of hospitalization. Recently, the ability to limit myocardial necrosis through the use of direct angioplasty has stimulated investigators to reassess post-MI management and consider early discharge without risk stratification for low risk patients. It is likely that a similar approach

can and will be evaluated in low risk patients treated with thrombolytic agents. While this is a provocative concept, and will certainly attract great interest from health care reform advocates, currently only 18% of hospitals in the United States have cardiac catheterization laboratories, fewer have the capability of performing emergent angioplasty, and only one third of patients admitted to the hospital with an acute infarct are treated with thrombolytic therapy. Therefore, risk stratification will continue to be an important adjunct to the treatment of acute myocardial infarction in the majority of patients. This review will attempt to outline a reasonable approach to risk stratification for all post-MI patients.

Potential Interventions for Patients with Acute Myocardial Infarction

The ability to differentiate between high, intermediate, and low risk patients — risk stratification — would be futile without effective interventions to lower the risk of morbidity and mortality following myocardial infarction. Fortunately, several interventions are available that have been shown to reduce the incidence of angina, congestive heart failure, and sudden cardiac death.

Revascularization by Angioplasty

Thrombolytic therapy is limited by 1) unsuccessful in lysis of the occlusive thrombus in 10 to 25% of patients [26-28], suboptimal antegrade flow in approximately 25% in whom thrombolysis is successful (Table 2) [29], and 3) the presence of a severe residual coronary stenosis in many that successfully reperfuse [30]. In addition, many patients have a contraindication to receiving thrombolytic therapy. Consequently, several studies have assessed the role of angioplasty in patients with evolving myocardial infarctions. In the immediate period following the onset of infarction, angioplasty has been proposed and used (a) instead of thrombolytic therapy to restore antegrade flow in the infarct artery, "primary" angioplasty, (b) to restore antegrade coronary flow in the patient in whom thrombolytic therapy is unsuccessful, "rescue" angioplasty, or (c) in the asymptomatic patient who has a high-grade residual stenosis of the infarct artery after successful thrombolysis.

Table 2. Patency of the Infarct-Related Artery, According to Treatment Group

Patency	Streptokinase + SC Heparin	Streptokinase + IV Heparin	Accelerated t-PA	t-PA + Streptokinase
Open vessels, TIMI 2 and 3				
At 90 minutes, %	54	60	81*†	73
At 180 minutes, %	73	74	76	85
At 24 hours, %	77	80	86	94
At 5-7 days, %	72	84	84	80
Complete reperfusion, TIMI 3				
At 90 minutes, %	29	32	54†¶	38
At 180 minutes, %	35	41	43	53
At 24 hours, %	51	41	45	60
At 5-7 days, %	51	58	58	55

*P = 0.032 for the comparison of this group with the group given t-PA with streptokinase.
†P < 0.001 for the comparison of this group with the groups given streptokinase with subcutaneous or intravenous heparin.
¶P < 0.001 for the comparison of this group with the group given t-PA with streptokinase.
The GUSTO Angiographic Investigators. N Engl J Med 1993: 329:1615-22.

Primary Angioplasty For Acute Myocardial Infarction

Primary angioplasty should be considered in all patients presenting with acute myocardial infarction. However, caution must be exercised in patients with bleeding as a contraindication to thrombolytic therapy, since angioplasty mandates the aggressive use of heparin in the peri-procedural period [31]. Antiplatelet therapy is also required in the periprocedural period to reduce the risk of acute closure and their use may be contraindication in patients with bleeding disorders.

The merits of angioplasty as an alternative to thrombolytic therapy in the patient with acute myocardial infarction [32], have been closely examined [33,34]. Primary angioplasty in selected infarct patients restores antegrade flow in the occluded infarct artery in > 90%, accomplishing this more quickly than thrombolytic therapy, and is associated with a 1 year

survival of 90 to 96% [35-38]. However, primary angioplasty for acute myocardial infarction may be less successful in patients with depressed left ventricular function, three vessel coronary artery disease, or a tortuous infarct artery [39].

Three randomized trials using contemporary angioplasty equipment and techniques have compared these approaches [40-42], and the results are summarized in Table 3. In these studies, angioplasty successfully restored antegrade coronary flow in approximately 95% in whom it was attempted. In the study by Zijlstra et al [40], follow-up angiography weeks after infarction showed that the infarct artery was patent in 91% of those who had angioplasty angioplasty and in only 68% of those who received thrombolysis ($p = 0.001$). The residual infarct artery stenosis was also less in those who underwent angioplasty (36% vs 76%, $p < 0.001$). As a result, those who underwent primary angioplasty had fewer in-hospital adverse events (non-fatal reinfarction or death) and were less likely to have recurrent ischemia or require coronary revascularization over the follow-up period.

Gibbons et al [41] also found that those who underwent primary angioplasty were less likely to require coronary artery revascularization for recurrent ischemia over a 6 month follow-up period than those treated with thrombolysis. Nevertheless, the two groups had a similar left ventricular ejection fraction, incidence of recurrent myocardial infarction, and survival.

These findings were confirmed by the Primary Angioplasty in Myocardial Infarction (PAMI) investigators [42], who found that angioplasty offered a clear advantage in "high risk" patients (i.e., > 65 years old, anterior infarction, or tachycardia on presentation). Mortality in these patients was 2% for those who underwent angioplasty and 10% for those who received thrombolysis ($p = 0.01$) (Table 3). The apparent survival benefit of angioplasty is, at least in part, due to the fact that the thrombolytic group had an excessive incidence of cerebrovascular hemorrhage (with death); cardiac related deaths were similar in the 2 groups. These investigators also found that recurrent ischemia was significantly less in the group undergoing primary angioplasty.

Table 3. Effect of MI Location on In-Hospital Endpoints in PAMI, by Treatment (%)

	Anterior MI			Non-Anterior MI		
	PTCA (n=71	tPA (n=67)	P value	PTCA (n=124)	tPA (n=133)	P value
Death	1.4	11.9	0.02	3.2	3.8	NS
Reinfarction	0	6.0	0.04	4.0	6.8	NS
Death or reinfarction	1.4	18.0	0.0009	7.3	9.0	NS
Recurrent ischemia	11.3	28.4	0.01	9.7	27.8	0.0002
Stroke	0	6.0	0.037	0	2.2	NS
Ventricular Fibrillation	1.4	1.5	NS	9.7	2.3	0.01

NS = not significant

The finding that patients presenting with anterior infarction benefited most from early infarct artery patency demonstrates the importance of the mass of jeopardized myocardium [43]. Limiting necrosis in the anterior wall has a profound effect on overall left ventricular systolic function (Table 4) and is associated with reduced post-MI morbidity and mortality [44].

Table 4. Global Left Ventricular Systolic Function According to the Site of Infarct-Related Occlusion

Location	Number of patients	Ejection fraction %
Proximal LAD artery	68	41.3 +10.7*
Middle LAD artery	30	51.0+11.4
Proximal RCA	104	53.3+10.0
Proximal circumflex artery	17	48.4+11.0

LAD = left anterior descending; RCA = right coronary artery; * $p < 0.0001$.
Stadius et al. Circulation 1985;72:292-301.

A recent angiographic substudy of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial enrolled 2431 patients and demonstrated the importance of establishing early infarct artery patency and restoring normal antegrade, TIMI 3, blood flow [29]. Patients were randomized to receive one of four thrombolytic + heparin regimens, (1) streptokinase + subcutaneous heparin, (2) streptokinase + intravenous heparin, (3) accelerated t-PA + intravenous heparin, or (4) t-PA + streptokinase + intravenous heparin. Patients were then subjected to coronary angiography at 90 minutes, 180 minutes, 24 hours, or 5 to 7 days. While patients treated with the most effective regimen, accelerated tPA and IV heparin, had an infarct artery patency of 81% at 90 minutes, only 54% had normal, TIMI 3, coronary blood flow. Establishing *normal antegrade blood flow* by 90 minutes resulted in a significant preservation of left ventricular systolic performance when measured by end-systolic volume index and ejection fraction (Table 5).

Table 5. Effect of Early Patency on Ventricular Function at Follow-up, According to TIMI Grade

Variable	TIMI 0	TIMI 1	TIMI 2	TIMI 3
At 90 minutes	N = 233	N = 84	N = 275	N = 370
Ejection Fraction %	55±15	55±15	56±15	62±14*¶
ESVI (ml/M^2)	31±17	33±21	29±14	26±14*¶
At 5 to 7 days	N = 171	N = 63	N = 212	N = 284
Ejection Fraction %	56±14	54±12	56±14	61±14
ESVI (ml/M^2)	32±16	34±13	30±13	26±14

N = number of patients; ESVI = end-systolic volume index
*P < 0.001 for the comparison of this group with the groups with TIMI grades 0 and 1.
¶ P < 0.001 for the comparison of this group with the group with TIMI 2.
The GUSTO Angiographic Investigators. N Engl J Med 1993: 329:1615-22.

The GUSTO Angiographic Investigators. N Engl J Med 1993: 329:1615-22.

Survival at hospital discharge was greatest in those patients that received thrombolytic therapy early after the onset of infarction (figure 2) and had a better left ventricular ejection fraction (figure 3) [29].

Figure 2. Effect of Early Thrombolytic Therapy on Mortality

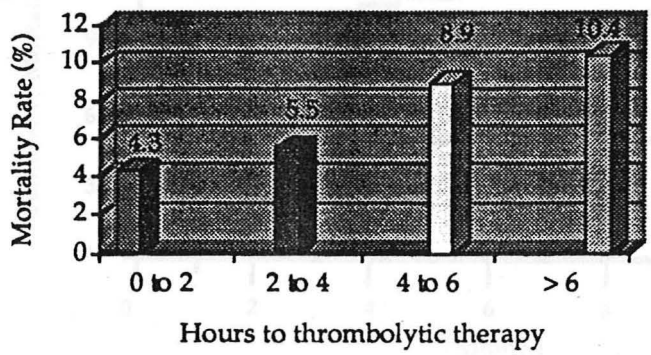
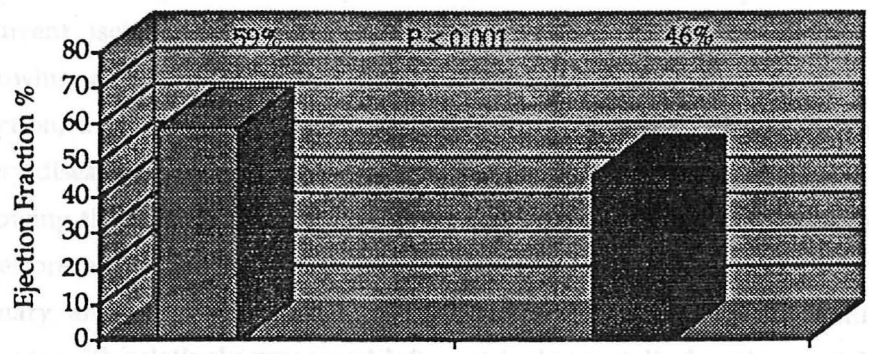


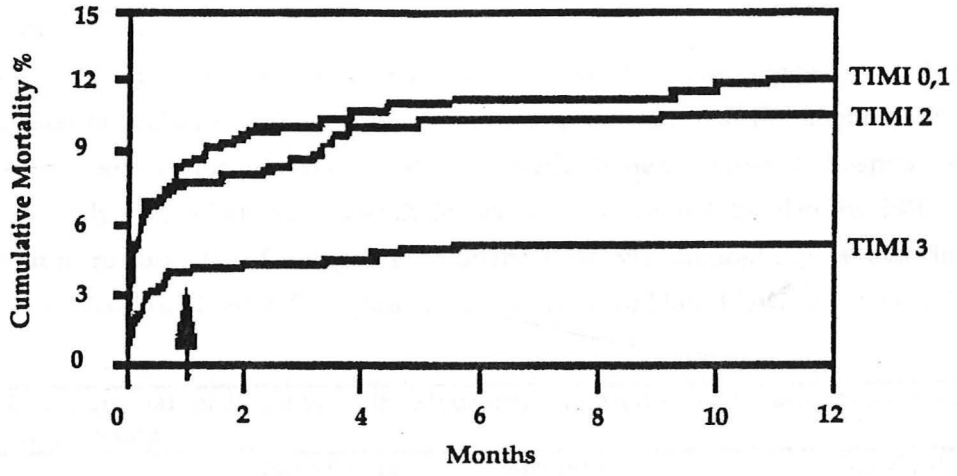
Figure 3. Effect of Ejection Fraction on Survival



The GUSTO Investigators. N Engl J Med 1993: 329:673-82.

At one year, the survival advantage for TIMI 3 blood flow compared to TIMI 1 or 2 flow increased to 54% (figure 4) [45].

Figure 4. Mortality Reduction Associated with Early TIMI 3 Blood Flow



Ross AM, et al. J Am Coll Cardiol 1995; 25:6A.

In comparison to thrombolytic therapy, primary angioplasty reduces the incidence of subsequent hospital morbidity, readmission, and follow-up costs, largely by reducing recurrent ischemia following intervention. Predictors of improved long-term survival following angioplasty for acute myocardial infarction include preserved left ventricular function, a patent infarct artery at discharge, early reperfusion, and single vessel coronary artery disease [36,37,46]. These same variables also predict an excellent long-term survival following thrombolysis for acute myocardial infarction [29], tPA, however is much less likely to restore normal perfusion early, or result in a patent infarct artery at discharge. Finally, primary angioplasty may change our approach to post-MI risk stratification. For those patients with relatively preserved left ventricular systolic function and 1 or 2 vessel disease, it is unlikely that additional testing will alter post-MI management, in the absence of spontaneous recurrent ischemia or evidence of ventricular arrhythmias. Recently, the preliminary results from the PAMI II trial were reported and suggest that patients presenting with an acute MI treated with successful angioplasty and classified as low risk (≤ 70 years of age, 1 or 2 vessel disease, ejection fraction > 45, and no malignant arrhythmias) do

not require intensive care monitoring and can be safely discharged at 3 days without additional risk stratification [47]. Confirmation of these findings in a larger trial could dramatically alter acute and post-MI management and result in a substantial reduction in health care costs.

Recent nonrandomized and retrospective studies have suggested that mechanical reperfusion of occluded coronary arteries may improve survival in patients with myocardial infarction and cardiogenic shock [48-53]. Such patients have a hospital survival of approximately 20% when treated with intravenous thrombolytic therapy [54]. In contrast, mechanical restoration of antegrade coronary flow via angioplasty is associated with a hospital survival of about 70% in these patients (Table 6) [55]. However, data collection on

TABLE 6. Survival of Patients With Myocardial Infarction and Cardiogenic Shock Treated With Angioplasty

Study	Number of Patients	Survival with successful angioplasty	Survival with unsuccessful angioplasty
Ellis SE, et al. J Am Coll Cardiol 1989; 13: 1251-9.	61	86%	32%
Lee L, et al. Circulation 1988; 78: 1345-51.	24	77%	18%
Lee L, et al. J Am Coll Cardiol 1991; 17: 599-603.	69	69%	20%
Moosvi AR, et al. J Am Coll Cardiol 1992; 19: 907-14.	38	56%	8%
Gacioch GM, et al. J Am Coll Cardiol 1992; 19: 647-53.	68	61%	7%
Hibbard MD, et al. J Am Coll Cardiol 1992; 19: 639-46.	45	71%	29%

Landau C et al. Coronary angioplasty in patients with acute myocardial infarction. Am J Med 1994; 96:536-42.

the 251 patients in the SHOCK Pre-Study Registry strongly suggest that patients with the worst prognosis are not undergoing cardiac catheterization and implies that results of

nonrandomized trial may be confounded by selection bias [56]. The SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) trial is an international randomized trial of emergency PTCA/CABG versus initial medical stabilization, including thrombolysis and aggressive hemodynamic support, designed to identify which patients benefit from emergent revascularization in the setting of cardiogenic shock.

In summary, primary angioplasty for acute myocardial infarction should be considered for all acute myocardial infarctions provided it can be performed expeditiously. Patients that will derive the largest mortality benefit from primary angioplasty, compared to thrombolytic therapy, are those with an anterior myocardial infarction. Patients that have contraindications to thrombolytic therapy should be referred for primary angioplasty provided they do not have bleeding as a contraindication and they can be instrumented within 12 hours of infarction. This strategy must be temporized by the realization that only 18% of hospitals in the United States have cardiac catheterization laboratories and even fewer have the capability of performing emergent angioplasty [55]. Although the transfer of patients with myocardial infarction to facilities that can perform angioplasty is possible, the obligate delay in achieving reperfusion may outweigh the potential benefits. Finally, since 5% of patients initially referred for angioplasty required emergent coronary artery bypass surgery, primary angioplasty should be performed only in centers with experienced and immediately available cardiac surgeons [57].

"Rescue" Angioplasty of a Persistently Occluded Infarct Artery for Failed Thrombolysis

Several studies have demonstrated the marked beneficial effect of infarct artery patency (obtained via endogenous, pharmacologic, or mechanical recanalization) on survival in patients with acute myocardial infarction [58-61]. Survivors of myocardial infarction with a patent infarct artery have an improved long-term outcome in comparison to those whose infarct artery is occluded, even though left ventricular systolic function is similar [61,62]. In the 10 to 25% of patients in whom thrombolytic therapy fails to restore antegrade coronary flow, recanalization of the infarct artery via angioplasty has been advocated to rescue ischemic (but viable) myocardium, and to improve long-term survival. Recently, Ellis et al [63] reported the results of a multicenter trial that randomized 151 patients, with occluded left anterior descending arteries despite receiving thrombolytic therapy, to a rescue angioplasty or continued medical therapy. Entry criteria included 1) ECG evidence of an

anterior infarct, 2) cardiac catheterization within 8 hours of the onset of chest pain, 3) treatment with any acceptable intravenous thrombolytic regimen, 4) age 21 to 79, 5) TIMI flow grade 0-1 in the left anterior descending artery at least 90 minutes after thrombolytic administration, and 6) ability to give informed consent. Patients with cardiogenic shock, history of a prior MI, and left main stenosis were excluded. Procedural success was achieved in 92% of interventions. Baseline patient characteristics are presented in table 7. The trial

Table 7. Baseline Characteristics for Patient in the Rescue Trial

	Angioplasty	Conservative
No. of patients	78	73
Age, years	59±11	59±11
Gender, % male	79	85
Diabetes, %	16	11
Smoking, %	44	56
Time from MI, hours	4.5±1.9	4.5±1.9
Systolic BP, mm HG	126±23	135±26
Heart rate, bpm	84±15	83±17
Killip class ≥2, %	21	26
Multivessel disease, %	34	40
Ongoing angina at the time of catheterization, %	81	67
Proximal occlusion site, %	46	51
TIMI 1 flow, %	36	37
Angiographic collaterals, %	32	37

P > 0.05 for all variables; MI = myocardial infarction; BP = blood pressure; and bpm = beats per minute.
Ellis SG, et al. Circulation 1994; 90:2280-2284.

demonstrated a significant reduction in the primary endpoint, death or CHF, in the angioplasty group, as well as an improved exercise ejection fraction, compared to the conservative group (Table 8).

Table 8. Procedural and 30-Day Outcomes for Rescue Angioplasty

	Angioplasty	Conservative	P
PTCA success, %	92	50*	-
Late in-hospital PTCA or CABG, %	9	14	NS
30-day LVEF, %			
Resting	40±11	39±12	NS
Exercise	43±15	38±13	0.04
30-day outcomes, %			
Death	5	10	NS
Severe CHF	1	7	NS
Nonfatal VT	12	12	NS
Death or CHF	6	17	0.05
Any of the above	18	28	NS

*Of two patients that "crossed over" to urgent angioplasty.
Ellis SG, et al. Circulation 1994; 90:2280-2284.

Infarct artery patency is an important predictor of mortality in survivors of myocardial infarction [60,61,64-67]. In comparison to those with a patent infarct artery, survivors of infarction with an occluded artery have (a) increased left ventricular dilatation [68], (b) a greater incidence of spontaneous and inducible ventricular arrhythmias [69], and (c) a poorer prognosis [65]. In survivors of myocardial infarction, the incidence of left ventricular aneurysm formation is higher in patients with an occluded infarct-related artery [70-72]. Forman et al [71] studied 79 survivors of myocardial infarction and noted that 48% of those with a persistently occluded left anterior descending coronary artery developed left

ventricular aneurysms, whereas this occurred in only 15% of patients with a patent left anterior descending coronary artery. Similarly, Jeremy et al [68] measured left ventricular volumes by radionuclide ventriculography in 40 patients 48 hours and 1 month after their first myocardial infarction. Left ventricular volumes increased in all 14 patients with an occluded infarct artery but in only 2 of the 26 patients with a patent artery. In addition, Lamas et al [73] reported that patients with a persistently occluded infarct-related artery have marked abnormalities in ventricular size, function, and shape when compared to those with similar sized infarcts and a patent infarct vessel. Thus, infarct artery patency substantially influences left ventricular remodeling over the days to months after myocardial infarction. In survivors of infarction, infarct artery patency may favorably influence left ventricular remodeling and electrical stability even if accomplished at a time when rescue of ischemic myocardium is unlikely (i.e., hours to days after unsuccessful thrombolysis) [64].

In summary, successful rescue angioplasty in patients with an occluded left anterior descending artery reduces the incidence of death or CHF and results in an improved exercise ejection fraction. It may also confer long-term mortality and morbidity advantages compared to patients with a persistently occluded infarct-related artery.

The major impediment to rescue angioplasty is the timely and accurate identification of patients in whom thrombolytic therapy has failed to reestablish antegrade coronary flow. Rescue of ischemic myocardium is unlikely unless unsuccessful thrombolysis is recognized and reperfusion is established in 8 to 12 hours of the onset of symptoms. Unfortunately, noninvasive methods of determining infarct artery patency are not yet widely applicable to patients with an evolving infarct [74-76], and clinical markers of reperfusion (relief of chest pain, resolution of ST segment elevation, and reperfusion arrhythmias) have limited predictive value in identifying failure of thrombolysis [77]. Immediate catheterization of *all* patients following thrombolytic therapy to identify those with an occluded infarct artery is impractical, costly, and may be associated with a high incidence of bleeding complications [26,27].

Currently, there are insufficient data to recommend widespread use of rescue angioplasty; Ellis et al [63] enrolled only patients with anterior infarcts, angioplasty may be ineffective in reestablishing antegrade coronary flow in approximately 8 to 15% of patients, and reocclusion of the infarct artery may occur in 9 to 20% of those that are successfully dilated [40,59]. Furthermore, although infarct artery patency 90 minutes after thrombolytic therapy is only 65 to 81%, it rises to 90% by 24 hours [28,29]. Such "late" reperfusion may improve survival without the risk of invasive procedures coupled with thrombolytic therapy [60,61,78-80].

Routine Angioplasty of Asymptomatic Patients Following Successful Thrombolytic Therapy

Following successful fibrinolysis, platelet aggregation and thrombus formation may recur at the site of arterial injury and lead to reocclusion, especially if a flow limiting stenosis is present [81]. Therefore, several randomized trial have examined whether attempting angioplasty of a severe residual stenosis in the infarct-related artery within hours [26,27,82], 2 days [83-85], or up to 2 weeks [86,87] after thrombolytic therapy prevents reocclusion, reinfarction, and/or death. Briefly, these trials have failed to show benefits attributable to routine angioplasty of asymptomatic patients with a stenotic infarct artery following thrombolytic therapy. Such a strategy does not appear to rescue myocardium or prevent reinfarction or death. On the contrary, patients subjected to this approach appear to have an *increased* incidence of adverse events, including bleeding, recurrent ischemia, emergent coronary artery bypass surgery, and death [27,88]. The increase in recurrent ischemia, need for emergent coronary artery bypass surgery, and death may in part be explained by the excessive hemorrhage into the vessel wall that occurs when these treatments are combined [89,90].

In short, routine angioplasty of the stenotic infarct artery in asymptomatic patients during the hours, days, or weeks following thrombolytic therapy exerts no benefit and may be harmful in comparison to conservative management. Therefore, an invasive strategy should be reserved for survivors of infarction who manifest ischemia at rest or with provocation.

Revascularization by Coronary Artery Bypass Grafting

Coronary artery bypass surgery is an excellent treatment for angina and improves long-term survival in selected patients. Data in support of the latter goal comes from three randomized trials, the VA Cooperative Study of CABG [91], the Coronary Artery Surgery Study (CASS) [92,93], and the European Coronary Surgery Study Group [94].

The VA Cooperative Study of CABG enrolled 686 men with stable angina for > 6 months (patients were excluded if they had had a MI within 6 months of randomization, refractory hypertension i.e. diastolic blood pressure > 100 mm Hg, unstable angina, LV aneurysm, decompensated congestive heart failure, severe comorbid disease, or EF < 0.25) and randomly assigned them to the medical (n = 354) or surgical (n = 332) therapeutic arms. The perioperative mortality for the entire surgical group was 5.8% with a 9.9% incidence of perioperative Q wave infarction. Survival (based on intention to treat) of patients with 1, 2 or 3 vessel disease and normal left ventricular function was similar for medical and surgical treatment. Of the 686 enrolled into the trial, 168 patients had depressed left ventricular systolic function (EF > 0.25 < 0.50) and 3 vessel coronary artery disease. Patients that were randomized to surgery derived a survival benefit compared to medically treated patients (Table 10) [91].

The CASS trial enrolled 780 patients (704 men, 76 women, age ≤ 65 years) and randomized them to medical or surgical treatment. Patients were eligible for randomization if they had Class I or II angina, with or without a history of an antecedent MI greater than 3 weeks prior to entering the study. Patients were excluded if the had more severe angina, Class III or IV congestive heart failure, severe comorbid disease, or could not be completely revascularized. The perioperative mortality for the entire CASS registry (6630 patients) was only 1.9%. Similar to the VA trial, patients with normal left ventricular systolic function did equally well regardless of whether they were treated medically or with surgery. However, the 160 patients with 3 vessel coronary artery disease and depressed left ventricular systolic function (EF > 0.34 < 0.50), derived a survival benefit from CABG as compared to medical therapy at 7 and 10 year follow-up (Table 10) [92,93].

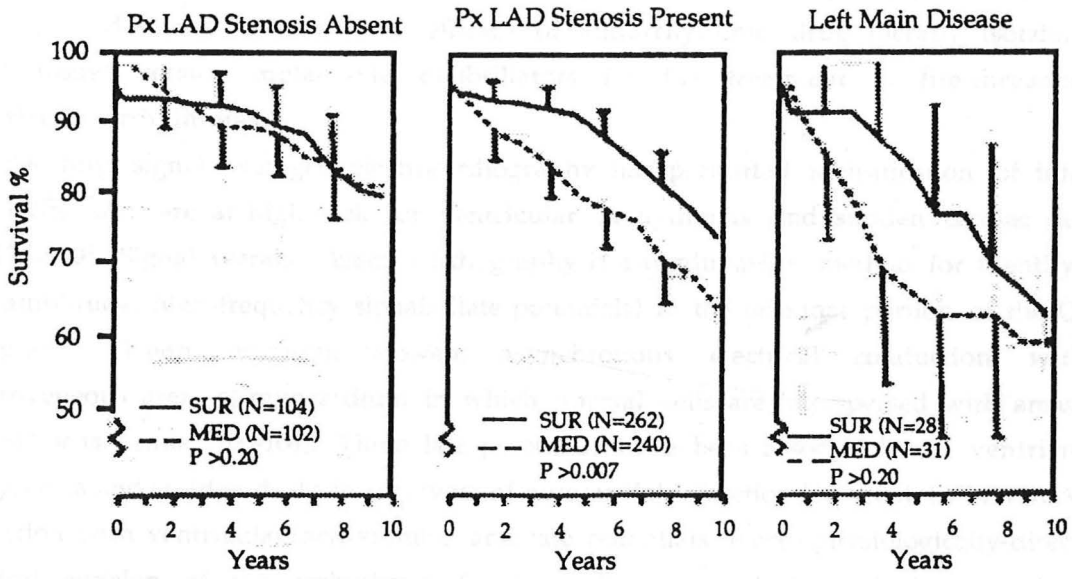
Table 10. Cumulative survival of patients with 3 vessel coronary artery disease and a depressed ejection fraction, < 0.50.

Trial	Follow-up Period years	Medical Treatment %	CABG %	P Value
VA Coop Study n = 168 (71 S & 97 M)				
	5	66	83	0.018
	7	52	76	0.002
	11	38	50	0.026
CASS n = 160 (78 S & 82 M)				
	7	65	88	0.009
	10	61	79	0.01

n = number of patients; S = surgically treated group; M = medically treated group.

The European Coronary Surgery Study Group randomized 767 men, age < 65 years with normal left ventricular systolic function, mild to moderate angina for ≥ 3 months, and 2, 3, or left main disease (≥ 50% < 75%) to early coronary bypass surgery or medial therapy. Survival was improved in the surgery group compared to the medical group at 5 years (p = 0.0001) and although the advantage declined with time, survival in the surgery group was still superior at 12 years (p = 0.04) [94]. Further analysis revealed that the survival advantage was related to the presence or absence of proximal left anterior descending arterial stenosis (Figure 5).

Figure 5. Ten-Year Cumulative Survival Rates with 95% Confidence Interval for the Surgically and Medically Treated Groups



Px = proximal; LAD = left anterior descending artery; SUR = surgery; MED = medicine.
Varnauskas E, et al. N Engl J Med 1988; 319:332-337.

Although the trial randomized patients with left main coronary artery stenosis, it was under-powered to demonstrate a difference in survival of patients.

Treatment of Ventricular Arrhythmias

The presence of complex ventricular ectopy following acute myocardial infarction is an established predictor of poor prognosis. The Cardiac Arrhythmia Suppression Trial (CAST), a randomized trial designed to assess the risk/benefit ratio of treating arrhythmias in asymptomatic patients clearly demonstrated an excess mortality associated with antiarrhythmic agents [95].

Although invasive electrophysiologic evaluations have demonstrated that patients at highest risk for clinically important arrhythmias, are inducible and have a left ventricular ejection fraction below 0.40, the optimal management of these patients is still being defined [98]. Two randomized trial are currently in progress that may provide additional insight into the management of post-MI patients with high grade ventricular ectopy. The Multicenter Unsustained Tachycardia Trial (MUSTT), an ongoing trial is designed to

nonsustained (3 beats to 30 seconds) ventricular tachycardia reduces sudden death and overall mortality [96]. The second trial, Antiarrhythmics Versus Implantable Defibrillators (AVID), is designed to assess the efficacy of antiarrhythmic drug therapy (sotalol or amiodarone) versus implantable defibrillators for the treatment of life-threatening ventricular arrhythmias.

Recently, signal averaged electrocardiography has permitted identification of infarct survivors who are at high risk for ventricular arrhythmias and sudden cardiac death [18,19,97-99]. Signal-averaged electrocardiography is a noninvasive method for identifying low-amplitude, high-frequency signals (late potentials) in the terminal portion of the QRS complex. These represent slowed, asynchronous electrical conduction within heterogeneous areas of myocardium in which normal cells are interspersed with areas of fibrosis or ischemia [100-104]. These late potentials have been associated with ventricular tachycardia and sudden death in survivors of myocardial infarction [105-106]. In survivors of infarction with ventricular arrhythmias and late potentials, electrophysiologically-directed surgical excision of the arrhythmia focus results in resolution of the ventricular arrhythmias and late potentials, and it improves survival [107]. Additionally, successful thrombolysis is associated with a reduction in the incidence of signal-averaged electrocardiographic late potentials [108]. In a pilot study, Boehrer et al [109] demonstrated that mechanical restoration of anterograde flow 1 to 2 weeks after acute myocardial infarction resolved late potentials in patients with an occluded infarct-related artery. Since patients with late potentials after infarction have an increased incidence of ventricular tachycardia and sudden death, establishing anterograde flow in the infarct artery, even late, may reduce the occurrence of these events. However, a large multicentered randomized trial will be required to determine whether abolishing late potentials in this patient population confers a survival benefit.

Prevention of Progressive Left Ventricular Dilatation

Left ventricular dilatation and impaired left ventricular systolic function after myocardial infarction are important predictors of a poor prognosis [9,11-15,110]. Dilatation of the infarct zone — infarct expansion — occurs within the first few days of infarction and results in an increase in ventricular diastolic volume due to altered left ventricular compliance and increased filling pressures. As a consequence, the left ventricular cavity

changes from its usual ellipsoid shape to a more spherical configuration. This change in ventricular geometry leads to increased regional wall stress, disruption of the normal myocyte architecture and worsened contractile dysfunction. Infarct expansion occurs in 35 to 45% of survivors of anterior myocardial infarctions and has been reported in up to 70% of those with fatal infarction [111]. With extensive infarct expansion, a left ventricular aneurysm may form with an associated one year mortality of 60 to 80% [112]. Thus, patients with infarct expansion after myocardial infarction have a higher mortality than those with similar sized infarcts without expansion. In addition to early infarct expansion, late remodeling of the ventricle occurs over the weeks to months after infarction. This is characterized by dilatation of the noninfarcted portion of the ventricle. This phenomenon also adversely affects prognosis in survivors of infarction. Recently, several large randomized trials have demonstrated that the use of ACE inhibitors in post-MI patients with reduced ejection fractions improves long-term survival and reduces hospital admissions for congestive heart failure (Table 11) [113-116].

Table 11. ACE Inhibitor Trial to Limit Ventricular Dilatation

	Consensus II	ISIS-4	SAVE	AIRE
Time to Randomization	Within 24 hours	Within 24 hours	3 to 16 days	3 to 10 days
LVEF	Unknown	Unknown	≤ 40%	Unknown
Drug	Enalapril	Captopril	Captopril	Ramipril
Presence of CHF	Possible	Possible	No overt CHF	Present, NYHA IV excluded
Follow-up	6 months	35 days	42 months	15 months
Endpoints	Mortality and morbidity	Mortality	Mortality and morbidity	Mortality and morbidity
Results	Survival not improved, treatment of CHF improved	Survival improved	Survival improved	Survival improved

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In short, patients with left ventricular systolic dysfunction following a myocardial infarction, symptomatic and asymptomatic, are benefited long-term by treatment with ACE inhibitors.

CONTEMPORARY RISK STRATIFICATION

Risk stratification is designed to identify patients at high risk of complications of an acute myocardial infarction so that they may be considered for "an intervention" to improve their outcome. Traditionally, this stratification has been based on review of the patient's clinical profile and noninvasive testing performed during the pre-discharge period. However, over the past 10 years the options for intervention early in the course of an acute myocardial infarction have flourished and contemporary risk stratification is best divided into 3 phases including, phase 1---presentation to the emergency room through the first 24 hours, phase 2---days 2 through 5, and phase 3---predischarge. While the goals and available options may differ at each phase, the prime concern of the physician is the same---weighing the risk/benefit ratios of intervention versus conservative therapy. The goals in phase 1 are to identify those patients for whom primary angioplasty would be most beneficial and those at high risk for whom rescue angioplasty would be beneficial in the event that thrombolysis fails. Phase 2 is a the period of watchful waiting ---the physician closely monitors the patient for evidence of recurrent ischemia, infarct extension, reinfarction, or mechanical complications such as pump failure, ischemic mitral valve disease, or myocardial rupture (septal or free wall). Finally, phase 3 is designed to identify those patients with poor left ventricular systolic function, severe arrhythmias, positive SAECG's, poor exercise capacity, or evidence of ischemia during provocative testing. In summary, contemporary management of patients with acute myocardial infarction entails continuos monitoring for signs and symptoms suggesting that a patient is in a high risk group and then weighing the risk versus benefit of a more aggressive management style.

Phase 1. Risk Stratification in the First 24 Hours of an Evolving Myocardial Infarction

The administration of thrombolytic therapy in combination with aspirin, heparin, and ß-blockers can save lives and is considered the standard of care for patients with an acute myocardial infarction [117]. However, the physician caring for the patient must quickly and

carefully determine that the risk/benefit ratio of providing this care is favorable for each individual patient. In some patients, primary angioplasty may be more appropriate than lytic therapy while others may be poor candidates for any form of reperfusion therapy.

FEATURES THAT PREDICT HIGH RISK AT THE TIME OF PRESENTATION

Patients that present with a history of preceding left ventricular systolic dysfunction, advanced age, prior myocardial infarction(s), diabetes mellitus, and female gender are at increased risk for death and morbid events, both from their infarct and from potential interventions [11-15,118-120]. Therefore all interventions must be thoughtfully considered in an expeditious manner. Kowalchuk and colleagues [119] evaluated the coronary anatomy in 84 consecutive octogenarians and found that 88% had coronary anatomy suitable for coronary artery bypass grafting (CABG), while only 31% were suitable for percutaneous transluminal coronary angioplasty. Elective CABG in this patient population was associated with a 16% mortality, whereas the mortality associated with angioplasty was 8%, 8 times the incidence for the general population. Furthermore, octogenarians undergoing an emergent CABG during an acute MI have a 20 to 25% perioperative mortality [121].

The presence of tachycardia, hypotension, pulmonary congestion, or shock on physical examination are important predictors of adverse short- and long-term outcomes. These clinical markers usually indicate severe left ventricular systolic dysfunction, and are associated with increased mortality and morbidity. In the setting of tachycardia, hypotension, and/or shock, volume depletion and right ventricular infarction must be considered and ruled out, as these processes may be easily corrected with volume expansion.

While the resolution or persistence of a patient's chest pain after thrombolytic therapy does not reliably predict infarct artery patency, continued chest pain has been associated with a worse prognosis. Herlitz et al [122] reported that patients requiring ≥ 3 injections of analgesic had an increased 2 year mortality [29% versus 16%, $p < 0.001$), greater incidence of in hospital ventricular fibrillation (10.3% compared to 2.7%, $p < 0.001$), and a 63.3% chance of developing congestive heart failure in the hospital compared to a 29.6% incidence ($p < 0.001$) in patients without prolonged pain.

Several electrocardiographic patterns present during infarction have been associated with a worse prognosis. Anterior ST elevation (V2 to V4) reflects occlusion of the left

anterior descending artery and identifies patients with a poorer prognosis compared to patients with other sites of infarction [123,124]. In fact, death from single vessel coronary artery disease is most commonly associated with involvement of the proximal left anterior descending artery [125]. Anterior infarction may be associated with inferior ST segment depression or elevation. This electrocardiographic finding is present when the left anterior descending artery wraps around the apex supplying a portion of the inferior ventricular septum or provides collateral flow to a severely diseased or occluded right coronary artery. Infarction in this distribution leads to an extensive area of myocardial necrosis with a in hospital mortality of 14.3% compared to 6.7% for anterior infarcts not involving the inferior wall [128]. Anterior and/or lateral ST segment depression in association with an inferior infarction, implies extension of the infarct from the inferior wall to the posterior and/or lateral left ventricular walls and this electrocardiographic pattern is also associated with a poor prognosis. Finally, patients that present with widespread ST segment depression or persistent ST segment depression have a worse prognosis [126-129]. Patients in the GISSI trial control group with widespread ST depression had an associated 16% mortality [127]. Raunio et al [128], in an autopsy series, found that widespread ST segment depression correlated with an 89% incidence of severe three-vessel coronary disease.

In summary, patients that present with preexisting left ventricular systolic dysfunction, advanced age, prior myocardial infarction(s), diabetes mellitus, female gender, anterior or extensive infarcts, and widespread ST segment depression are at increased risk for death and morbid events related to infarction. These patients need to be assessed quickly and strategies implemented to reestablish normal antegrade coronary blood flow early after identification.

Phase 2. Risk Stratification from day 2 through day 5

During this phase of care patients with suspected left ventricular systolic dysfunction should be identified so that ACE inhibitors can be started promptly to favorably influence infarct expansion and remodeling. Patients with anterior infarction, inferior-posterolateral infarction, or any infarct with pre-existing reduced myocardial performance are most likely to benefit from ACE inhibition.

The peak incidence of mechanical complications occurs between days 3 and 5, therefore patients require vigilant monitoring during phase 2 for these complications of infarction. Since myocardial rupture only occurs in the presence of transmural infarction, any

intervention that limits infarction to the subendocardium or partial involvement of the myocardium may prevent this complication. Unfortunately, the administration of thrombolytic therapy late, > 11 hours, has been associated with an increased incidence (and earlier occurrence) of myocardial rupture [130]. This has been associated with the pathologic observation that thrombolytic therapy converts non-hemorrhagic infarcts to hemorrhagic infarcts [130]. Despite this increase in myocardial rupture, thrombolytic therapy administered late ≤ 12 hours results in a net clinical benefit with reduced mortality [130,131].

Patients with postinfarction angina and ST segment changes have a 10-fold higher inhospital mortality, and an increased 1-year mortality (20% versus 9%) and re-infarction rate (27% versus 18%) [132]. Similarly, episodic pulmonary edema identifies patients as high risk and may represent recurrent myocardial ischemia and or ischemic mitral regurgitation. In the prethrombolytic era, Dwyer and coworkers [133] demonstrated that patients with recurrent pulmonary congestion had a 1-year mortality of 28% compared with 5.5% in those without pulmonary edema.

Patients with depressed left ventricular systolic function following infarction are at high risk for ventricular arrhythmias, sudden cardiac death, and progressive heart failure. Both the VA Cooperative Study of CABG and CASS trial demonstrated that bypass surgery leads to a survival benefit for patients with 3 vessel coronary disease and depressed left ventricular systolic function, EF < 0.50, compared to medical therapy [91-93]. Therefore, patients with depressed left ventricular systolic function that lack severe comorbidities should be evaluated for the presence of three vessel coronary artery disease. Several studies, utilizing echocardiography [134-136], radionuclide ventriculography [137], or thallium perfusion imaging [137-140] have evaluated the ability of these tests to predict the presence of coronary artery disease in patients with depressed left ventricular systolic function. Unfortunately, noninvasive testing often provides nondiagnostic results and has limited sensitivity (≤ 85%) and specificity (44% to 90%) [141,142]. Additionally, since the decision to refer a patient to surgery will ultimately be based on the absence or presence of 3 vessel disease with suitable distal target vessel, these patients should be referred directly for catheterization rather than relying on noninvasive testing.

IDENTIFICATION OF HIGH RISK PATIENTS PREDISCHARGE

In the 1960s several investigators demonstrated that morbidity and mortality after acute myocardial infarction are closely related to historical, clinical, hemodynamic, and electrocardiographic variables that are often present at the time initial presentation [12-14]. Although thrombolytic therapy has profoundly altered the treatment of acute myocardial infarction and reduced mortality, the risk factors that predict post-infarct complications remain the same. This is evident by the striking similarity between the *coronary prognostic index* described by Peel et al [12] in 1962 (Table 12), and the risk factors that Hillis et al [15] identified from review of the 3,261 patients enrolled in the TIMI II trial (Table 13).

Table 12. Coronary Prognostic Index

	Score		Score
Gender and age:			
Men, 54 or under	0	Women, 64 or under	2
55-59	1	65 or over	3
60-64	2		
65 or over	3		
Previous History:			
Previous infarct			6
Other cardiovascular diseases or history of exertional dyspnea			3
Angina only			1
No cardiovascular disease			0
Shock:			
Absent			0
Mild---transient at onset			1
Moderate---present on admission but subsiding with rest and sedation			5
Severe---persisting despite rest and sedation			7
Congestive Heart Failure:			
Absent			0
Few basal rales only			1
Any one or more of the following: breathlessness; acute pulmonary edema; orthopnea or dyspnea; gallop rhythm; liver enlargement; edema; or jugular vein distention			4
Electrocardiogram:			
Normal QRS. Changes confined to R-T segment or T wave			1
QR complexes			3
QS complexes or bundle-branch block			4
Rhythm:			
Sinus			0
Any one or more of the following: Atrial fibrillation or flutter, paroxysmal tachycardia, persisting sinus tachycardia, frequent ectopic beats, nodal rhythm or heart block			4
Total Patient Score = Prognostic Index			

Patients with an index between 1 to 8 are at low risk with a 4 week mortality of under 5%.
Patients with an index over 17 are at high risk with a 4 week mortality of under 50%.

Peel AAF, et al. Br Heart J 1962; 24:745-60.

Table 13. Mortality at 6 Weeks for Each of the Risk Factors Identified in TIMI II

Risk Factor	No. of Patients with Risk Factor (%)	No. of Deaths in 6 Weeks (%)	P Value
Age ≥ 70 years	374 (11.5)	42 (11.2)	< 0.001
Previous infarction	456 (13.7)	36 (7.9)	0.002
Anterior infarction	1,681 (51.5)	94 (5.6)	< 0.001
Atrial fibrillation	66 (2.0)	7 (10.6)	0.062
Rales in more than one third of lung fields	105 (3,2)	13 (12.4)	0.012
Hypotension and sinus tachycardia	158 (4.8)	16 (10.1)	<0.001
Female gender	577 (17.7)	41 (7.1)	0.031
Diabetes mellitus	425 (13.0)	36 (8.5)	0.002

Hillis LD, et al. J Am Coll Cardiol 1990; 16:313-5.

Table 14. Mortality at 6 Weeks According to the Number of Risk Factors Present in TIMI II Trial

No. of Risk Factors	No. of Patients	No. of Deaths within 6 Weeks	Mortality Rate (%)
0	864	13	1.5
1	1,384	32	2.3
2	689	48	7.0
3	231	30	13.0
≥4	93	16	17.2

No. = number.
Hillis LD, et al. J Am Coll Cardiol 1990; 16:313-5.

The presence of increasing numbers of these clinical factors clearly identifies a gradient of risk for increased morbidity and mortality after infarction regardless of whether they receive thrombolytic therapy; therefore patients with 2 or more risk factors should be considered for coronary angiography.

Noninvasive Stress Testing

The utility of several noninvasive diagnostic tests have been evaluated in patients after myocardial infarction to determine which patients are at greatest risk for subsequent cardiac events. These tests rely on the occurrence of symptoms and/or objective evidence of provoked myocardial ischemia. Their sensitivity and specificity vary in accordance with patient characteristics including ability to exercise, gender, baseline electrocardiographic abnormalities, and the presence of other myopathic processes that result in myocardial scarring and wall motion abnormalities. The simplest and least costly is an exercise tolerance testing which can be safely performed early, between days 3 to 5 post-infarction. To maximize the sensitivity of exercise testing while maintaining safety, patients are exercised on a treadmill or bicycle ergometer until they achieve 70% of the maximal predicted heart rate, complete 5 METS, develop clinically important dyspnea or fatigue, experience typical chest pain accompanied by ST segment depression of ≥ 1 mm, or have 3 or

more consecutive ventricular ectopic beats [143]. Patients that exercise for > 9 minutes without evidence of ischemia or ventricular ectopy have an excellent one year mortality, < 2% [17]. Those that have a positive test or can not perform the test have a worse prognosis and should be considered for cardiac catheterization. Finally, inability to complete an exercise test and or the presence of baseline electrocardiographic abnormalities reduces its sensitivity and specificity. To overcome these limitations, tests that combine exercise or pharmacologic stress (adenosine, dipyridamole, or dobutamine intravenous infusions) with an imaging modality (echocardiography, myocardial perfusion imaging, or radionuclide ventriculography) have been used extensively [141,142,144,145]. Although these tests have a greater sensitivity and specificity for detecting ischemia than regular exercise testing, their specificity is limited by nonischemic myopathic processes [146]. Furthermore, until recently the utility of these tests for predicting prognosis after infarction had not been compared in the same patient. Olona et al [147] recently compared the utility of 1) exercise testing + echocardiography, 2) exercise testing + radionuclide ventriculography, 3) exercise thallium-201 + echocardiography, and 4) exercise thallium-201 + radionuclide ventriculography with cardiac catheterization for predicting the prognosis of patients after their first infarct. Over a 5 year follow-up period, 78 of 115 patients (68%) developed complications that were severe in 37 (32%). As illustrated in table 15 all test were similar in sensitivity and specificity. Combining any two of the test increased the predictive value, the combination of exercise testing thallium-201 scintigraphy and radionuclide ventriculography yielded the best results predicting 90% of the complications, provided both test were abnormal. Although combining these tests also improved the negative predictive value for severe complications (72 to 97%), the negative predictive value for no complications was still poor (55 to 83%).

Table 15. Sensitivity and Specificity of Cardiovascular Tests for Predicting Moderate and Severe Complications after Infarction.

	Sensitivity	Specificity
Complications		
Exercise testing	57%	74%
Thallium-201 scintigraphy	91%	50%
Radionuclide ventriculography	57%	71%
Two-dimensional echocardiography	60%	62%
Cardiac catheterization	36%	76%
Severe complications		
Exercise testing	60%	58%
Thallium-201 scintigraphy	65%	76%
Radionuclide ventriculography	55%	70%
Two-dimensional echocardiography	55%	80%
Cardiac catheterization	64%	63%

The following complications were identified over 5 years of follow-up: angina, new myocardial infarction, heart failure, coronary angioplasty, cardiac surgery, and death.
Patients were included in the severe complications group if they experienced severe angina (Canadian Cardiovascular Society functional class III or IV), severe heart failure (New York Heart Association functional classes III or IV), reinfarction, angioplasty, cardiac surgery, or death.
Olona M, et al. J Am Coll Cardiol 1995:815-22.

The determination of left ventricular systolic function also provides key prognostic information and can define a high risk patient population that should be considered for diagnostic coronary angiography [9,11-15,110].

Cardiac Catheterization

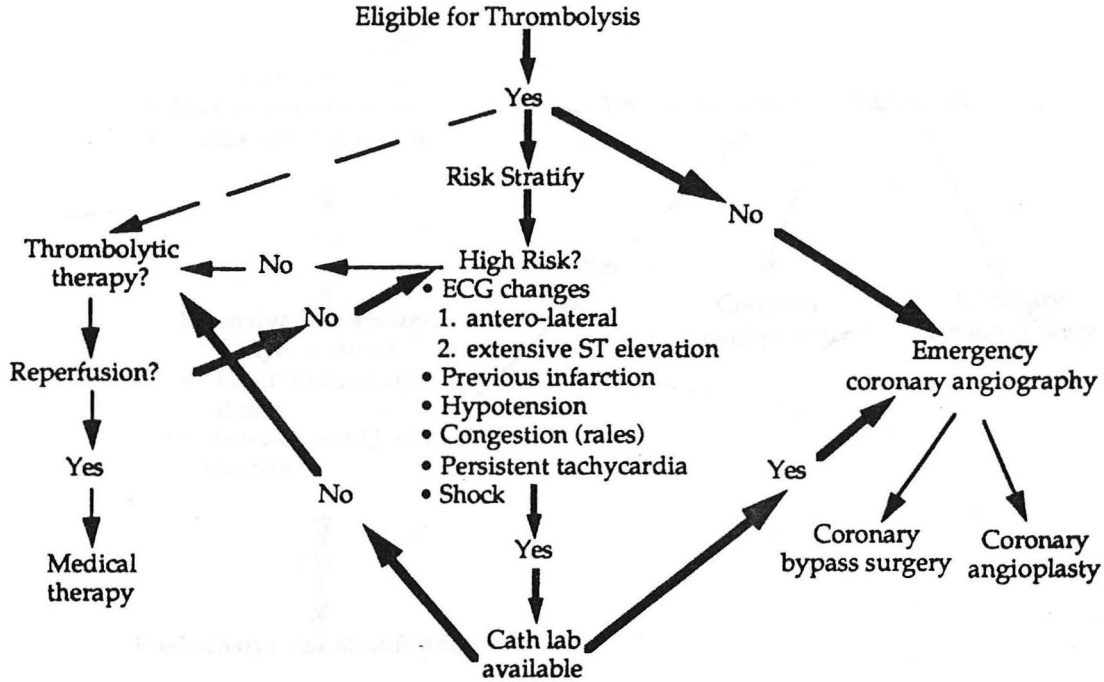
Performing cardiac catheterization on unselected patients following acute myocardial infarction has limited utility [148]. The mere presence of a residual high grade coronary stenosis in the infarct related artery or other stenoses does not predict the site of future infarction(s) or ischemic events. In fact, Little et al [149] and Nobuyoshi et al [150] have reported that serial angiograms demonstrated that 40 to 60% of future infarcts occur at the site of minimal lesions, < 50% diameter stenosis.

In accordance with numerous trials examining post-MI risk stratification, the American College of Cardiology/American Heart Association Task Force has stated that diagnostic coronary angiography is indicated predischarge in patients, 1) with angina pectoris occurring at rest or with minimal activity; 2) that have heart failure during the evolving infarct, or a left ventricular ejection < 0.45; 3) with evidence of myocardial ischemia during stress testing with or without concomitant angina pectoris; and, 4) that have a non-Q wave myocardial infarction [151]. The first three groups of patients have well delineated reasons for diagnostic coronary angiography, and knowledge of their coronary anatomy will influence their management, however the recommendation to perform a cardiac catheterization on patients following a non-Q wave infarction is controversial. Cardiac catheterization is also indicated in patients known to be at increased risk based on the presence of two or more clinical risk factors (Tables 12 & 13), as many of these patients will have multi-vessel disease and or depressed left ventricular systolic function. However, patients that appear to be at low risk for recurrent infarction or sudden cardiac death should not routinely undergo cardiac catheterization for risk stratification.

Contemporary Treatment Strategies and Risk Stratification of Patients with Acute Myocardial Infarction.

Patients presenting within 12 hours of infarction should be considered for primary angioplasty or thrombolytic therapy based on the strategy outline in figure 6. Those patients

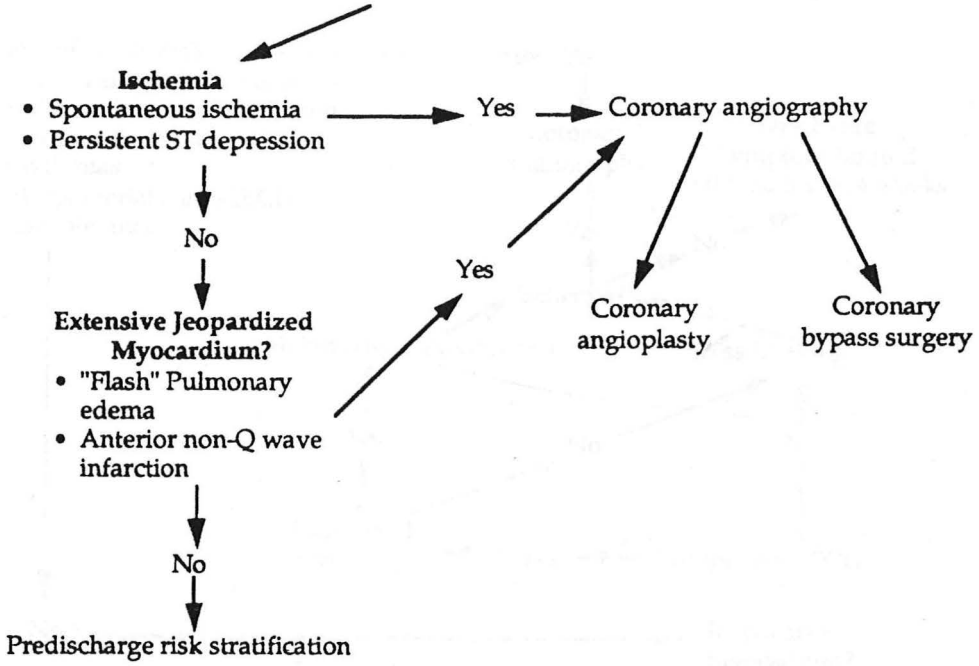
Figure 6. Treatment Strategies During an Evolving Myocardial Infarction



identified as high risk are likely to derive the greatest benefit from reestablishing TIMI 3 flow early. Based on currently available data, patients that undergo primary angioplasty are much more likely to achieve this goal than those that receive thrombolytic therapy. Patients with severe left main disease discovered at the time of coronary angiography should be considered for emergent CABG. Those patients with contraindications to thrombolytic therapy, except for those related to bleeding, should be considered for primary angioplasty.

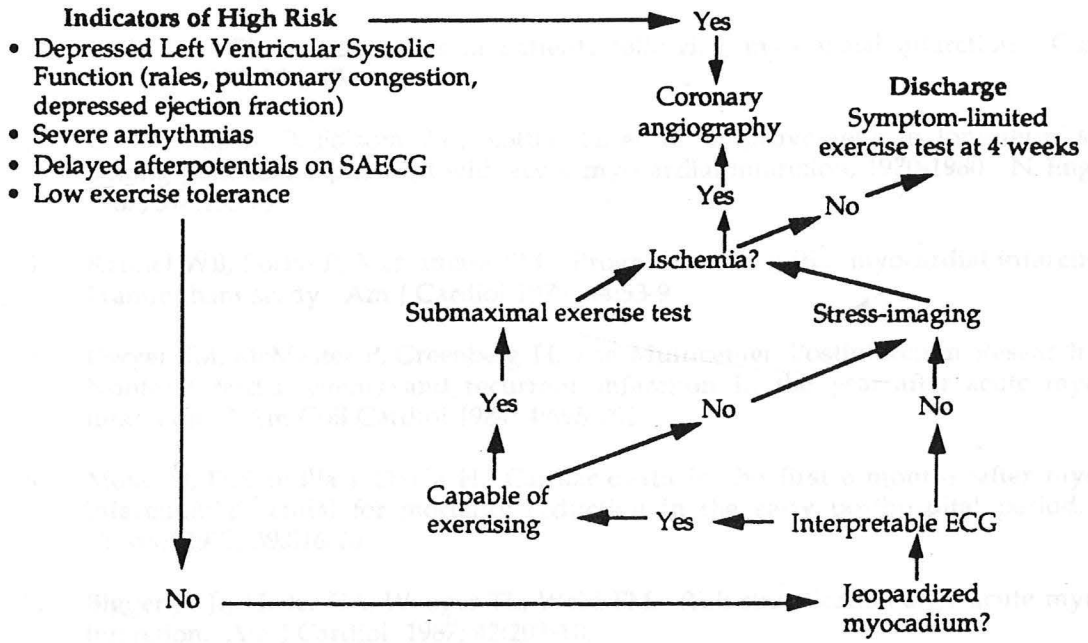
Currently there no reliable methods to detect failed reperfusion following thrombolytic therapy. Until such a method becomes available, it will be necessary to base the decision to perform emergent coronary angiography on clinical variables, including resolution of chest pain and ECG changes, and/or evidence clinical deterioration. During the early post-MI period, evidence of spontaneous ischemia, widespread persistently depressed ST segments or other markers of a poor prognosis, or evidence of a mechanical complication are compelling reasons to consider coronary angiography (Figure 7). Those patients with

Figure 7. Treatment Strategies in the Early Post-Infarct Period



left main, 3 vessel disease and depressed left ventricular systolic function, or mechanical complications derive a survival advantage from surgery. Finally, the remaining patients should be considered for elective cardiac catheterization if clinical variables indicate that they are in a high risk group or they have evidence of ischemia during provocative testing (Figure 8).

Figure 8. Risk Stratification: Predischarge



Concluding Remarks

The treatment of patients with evolving infarcts should be focused on obtaining TIMI 3 flow as quickly as possible using the most readily available method of reperfusion. Thereafter, patients should be managed based on persistent or recurrent symptoms, the presence of clinical characteristics that identify those patients at high risk, or evidence of ischemia during provocation.

References

1. Moss AJ. Prognosis after myocardial infarction. Am J Cardiol 1983; 52:667-6.

2. Kelly DT. Clinical decisions in patients following myocardial infarction. Curr Probl Cardiol 1985; 10:1-45.

3. Gomez-Marin O, Folsom AR, Kottke TE et al. Improvement in long-term survival among patients hospitalized with acute myocardial infarction, 1970-1980. N Engl J Med 1987; 316:1353-9.

4. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: The Framingham study. Am J Cardiol 1979; 44:53-9.

5. Dwyer EM, McMaster P, Greenberg H, The Multicenter Postinfarction Research Group. Nonfatal cardiac events and recurrent infarction in the year after acute myocardial infarction. J Am Coll Cardiol 1984; 4:695-702.

6. Moss AJ, DeCamilla J, Davia H. Cardiac death in the first 6 months after myocardial infarction: potential for mortality reduction in the early posthospital period. Am J Cardiol 1977; 39:816-20.

7. Bigger JT Jr, Heller CA, Wenger TL, Weld FM. Risk stratification after acute myocardial infarction. Am J Cardiol 1987; 42:202-10.

8. DeBusk RF. Specialized testing after recent acute myocardial infarction. Ann Intern Med 1989; 110:470-81.

9. Moss AJ, Benhorn J. Prognosis and management after a first myocardial infarction. N Eng J Med 1990; 322:743-53.

10. Ross J, Gilpin EA, Madsen EB, Henning H, Nicod P, Dittrich H, Engler R, Rittelmeyer J, Smith SC, Viquerat C. A decision scheme for coronary angiography after acute myocardial infarction. Circulation 1989; 79:292-303.

11. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983; 309:331-6.

12. Peel AAF, Semple T, Wang I, Lancaster WM, Dall JLG. A coronary prognostic index for grading the severity of infarction. Br Heart J 1962; 24:745-60.

13. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. Am J Cardiol 1967; 20:457-64.

14. Norris RM, Brandt PWT, Caughey DE, Lee AJ, Scott PJ. A new coronary prognostic index. Lancet 1969; 1:274-8.

15. Hillis LD, Forman S, Braunwald E, The Thrombolysis in Myocardial Infarction (TIMI) Phase II Co-Investigators. Risk stratification before thombolytic therapy in patients with acute myocardial infarction. J Am Coll Cardiol 1990; 16:313-5.

16. Krone RJ, Gillespie JA, Weld FM, Miller JP, Moss AJ, and the Multicenter Post-Infarction Research Group. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. Circulation 1985; 71:80-9.

17. DeBusk RF, Blomqvist CG, Kouchoukos NT, Luepker RV, Miller HS, Moss AJ, et al. Identification and treatment of low-risk patients after acute myocardial infarction and coronary-artery bypass graft surgery. N Engl J Med 1986; 314:161-6.

18. Gomes, JA, Winters SL, Martinson M, Machac J, Stewart D, Targonski A. The prognositic significance of quantitative signal-averaged variables relative to clinical variables, site of myocardial infarction, ejection fraction and ventricular premature beats: a prospective study. J Am Coll Cardiol 1989; 13:377-84.

19. Kuchar DL, Thorburn CW, Sammel NL. Prediction of serious arrhythmic events after myocardial infarction: signal-averaged electrocardiogram, holter monitoring and radionuclide ventriculography. J Am Coll Cardiol 1987; 9:531-8.

20. Cripps T, Bennett D, Camm J, Ward D. Prospective evaluation of clinical assessment, exercise testing and signal-averaged electrocardiogram in predicting outcome after acute myocardial infarction. Am J Cardiol 1988; 62:995-1004.

21. Kleiger RE, Miller JP, Bigger JT, Moss AJ, Multicenter Postinfarction research group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59:256-62.

22. Lombardi F, Sandrone G, Pernpruner S, Garimoldi M, Cerutti S, Baselli G, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. Am J Cardiol 1987; 60:1239-45.

23. Malik M, Camm AJ. Heart rate variability. Clin Cardiol 1990; 13:570-6.

24. Krone RJ. The role of risk stratification in the early management of a myocardial infarction. Ann Intern Med 1992; 116:223-37.

25. Rogers WJ, Babb JD, Baim DS, Chesebro JH, Gore JM, Roberts R, Williams DO, Frederick M, Passamani ER, Braunwald E. Selective versus routine predischarge coronary arteriography after therapy with recombinant tissue-type plasminogen activator, heparin and aspirin for acute myocardial infarction. J Am Coll Cardiol 1991; 17:1007-16.

26. The TIMI Research Group. Immediate vs. delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. JAMA 1988; 260: 2849-58.

27. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987; 317: 581-8.

28. Neuhaus KL, Von Essen R, Tebbe U, et al. Improved thrombolysis in acute myocardial infarction with front-loaded administration of altepase: Results of the rt-PA-APSAC patency study (TAPS). J Am Coll Cardiol 1992; 19: 885-91.

30. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction Trial, phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase - clinical findings through hospital discharge. Circulation 1987; 76: 142-54.

29. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329:1615-22.

31. McGarry TF Jr., Gottlieb RS, Morganroth J, et al. The relationship of anticoagulation level and complications after successful percutaneous transluminal coronary angioplasty. Am Heart J 1992; 1223: 1445-51.

32. Hartzler GO, Rutherford BD, McConahay DR, et al. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. Am Heart J 1983; 106: 965-73.

33. Meier B. Balloon angioplasty for acute myocardial infarction. Was it buried alive? Circulation 1990; 82: 2243-5.

34. Brundage BH. Because we can, should we? J Am Coll Cardiol 1990; 15: 544-5.

35. O'Keefe JH, Rutherford BD, McConahay DR, et al. Early and late results of coronary angioplasty without antecedent thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1989; 64: 1221-30.

36. O'Keefe JH, Rutherford BD, McConahay DR, et al. Myocardial salvage with direct coronary angioplasty for acute infarction. Am Heart J 1992; 123: 1-6.

37. Stone GW, Rutherford BD, McConahay DR, et al. Direct coronary angioplasty in acute myocardial infarction: Outcome in patients with single vessel disease. J Am Coll Cardiol 1990; 15: 534-43.

38. Kander NH, O'Neill WW, Topol EJ, et al. Long-term follow-up of patients treated with coronary angioplasty for acute myocardial infarction. Am Heart J 1989; 118: 228-33.

39. Ellis SG, Topol EJ, Gallison L, et al. Predictors of success for coronary angioplasty performed for acute myocardial infarction. J Am Coll Cardiol 1988; 12: 1407-15.

40. Zijlstra F, Jan de Boer M, Hoorntje JCA, et al. Comparison of direct coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med. 1993; 328: 680-4.

41. Gibbons RJ, Holmes DR, Reeder GS, et al. Randomized trial comparing immediate angioplasty to thrombolysis followed by conservative treatment for myocardial infarction. N Engl J Med. 1993; 328: 685-91.

42. Grines CL, Browne KF, Marco J, et al. A comparison of primary angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993; 328: 673-9.

43. Califf RM, Phillips HR, Hindman MC, Mark DB, Lee KL, Behar VS, Johnson RA, Pryor DB, Rosati RA, Wagner GS, Harrell FE. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985; 5:1055-63.

44. Stadius ML, Maynard C, Fritz JK, Davis K, Ritchie JL, Sheehan F, Kennedy JW. Coronary anatomy and left ventricular function in the first 12 hours of acute myocardial infarction: the Western Washington Randomized Intracoronary Streptokinase Trial. Circulation 1985; 72:292-301.

47. Brodie B, Grines CL, Spain M, Griffin J, Balestrini C, Stone GW, Costantini C, Esente P, Ayres M, Nobuyoshi M, Donohue B, Chelliah N, Rothbaum D, Wharton T Jr, Jones D, Mason D, Sachs D, O'Neill WW. A prospective, randomized trial evaluating early discharge (day 3) without non-invasive risk stratification in low risk patients with acute myocardial infarction: PAMI-2. J Am Coll Cardiol 1995; 25:5A.

45. Ross AM, Cho S, Lundergan C, Reiner J, Simoons M, Van de Werf F, Coyne K, Califf R, Topol E, and the GUSTO Angiographic Investigators. The Survival advantage of early grade 3 patency after thrombolysis for infarction increases over time. J Am Coll Cardiol 1995; 25:6A.

46. Baim DS, Diver DJ, Feit F, et al. Coronary angioplasty within the Thrombolysis in Myocardial Infarction II study. Circulation 1992; 85: 95-105.

48. Ellis SE, O'Neill WW, Bates R, et al. Implications for triage from survival and left ventricular functional recovery analyses in 500 patients treated with coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1989; 13: 1251-9.

49. Lee L, Bates ER, Pitt B, Walton, et al. Percutaneous coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. Circulation 1988; 78: 1345-51.

50. Lee L, Erbel R, Brown TM, Laufer N, et al. Multicenter registry of angioplasty therapy of cardiogenic shock: Initial and long-term survival. J Am Coll Cardiol 1991; 17: 599-603.

51. Moosvi AR, Khafa F, Villanueva L, et al. Early revascularization improves survival in cardiogenic shock complicating acute myocardial infarction. J Am Coll Cardiol 1992; 19: 907-14.

52. Gacioch GM, Ellis SG, Lee L, et al. Cardiogenic shock complicating acute myocardial infarction: The use of coronary angioplasty and the integration of the new support devices into patient management. J Am Coll Cardiol 1992; 19: 647-53.

53. Hibbard MD, Holmes DR, Bailey KR, et al. Percutaneous transluminal coronary angioplasty in patients with cardiogenic shock. J Am Coll Cardiol 1992; 19: 639-46.

54. Bates ER, Topol EJ. Limitations of thrombolytic therapy for acute myocardial infarction complicated by congestive heart failure and cardiogenic shock. J Am Coll Cardiol 1991; 18: 1077-84.

55. Landau C, Glamann DB, Willard JE, Hillis LD, Lange RA. Coronary angioplasty in patients with acute myocardial infarction. Am J Med 1994; 96:536-42.

56. Hochman JS, Boland J, Sleeper LA, Porway M, Brinker J, Col J, Jacobs A, Slater J, Miller D, Wasserman H, Menegus MA, Talley JD, McKinlay S, Sanborn T, LeJemtel T, and the SHOCK Registry Investigators. Current spectrum of cardiogenic shock and effect of early revascularization on mortality: results of an international registry. Circulation 1995; 91:873-81.

57. Ryan TJ, Bauman WB, Kennedy JW, Kereiakes DJ, King SB III, McCallister BD, Smith SC Jr, Ullyot DJ. ACC/AHA guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association task force on assessment of diagnostic and therapeutic cardiovascular procedures (committee on percutaneous transluminal coronary angioplasty). J Am Coll Cardiol 1993; 22:2033-54.

58. Califf RM, Topol EJ, George BS, et al. Characteristics and outcome of patients in whom reperfusion with intravenous tissue plasminogen activator fails: Results of the TAMI I trial. Circulation 1988; 77: 1090-9.

59. Abbotsmith CW, Topol EJ, George BS, et al. Fate of patients with patency of the infarct related vessel achieved with successful thrombolysis versus rescue angioplasty. J Am Coll Cardiol 1990; 16: 770-8.

60. Lange RA, Cigarroa RG, Hillis LD. Influence of residual antegrade coronary blood flow on survival after myocardial infarction in patients with multivessel coronary artery disease. Coronary Artery Dis 1990; 1: 59-63.

61. Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. Am J Cardiol 1989; 64: 155-60.

62. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983; 309: 1477-82.

63. Ellis SG, Ribeiro da Silva E, Heyndrickx G, Talley JD, Cernigliaro C, Steg G, Spaulding C, Nobuyoshi M, Erbel R, Vassanelli C, Topol EJ, for the RESCUE Investigators. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. Circulation 1994; 90:2280-4.

74. Krucoff MW, Wagner NB, Pope JE, et al. The portable programmable microprocessor-driven real-time 12 lead electrocardiographic monitor: A preliminary report of a new device for the noninvasive detection of successful reperfusion or silent coronary reocclusion. Am J Cardiol 1990; 65: 143-8.

75. Ellis AK, Little T, Masud ARZ, et al. Early noninvasive detection of successful reperfusion in patients with acute myocardial infarction. Circulation 1988; 78: 1352-7.

76. Hundley WG, Clarke GD, Landau C, Lange RA, Willard JE, Hillis LD, Peshock RM. Noninvasive determination of infarct artery patency by cine magnetic resonance angiography. 1994; (Submitted for publication).

77. Califf RM, O'Neill WW, Stack RS, et al. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. Ann Intern Med 1988; 108: 658-62.

78. Trappe HJ, Lichtlen PR, Klein H, et al. Natural history of single vessel disease. Risk of sudden coronary death in relation to coronary anatomy and arrhythmia profile. Eur Heart J 1989; 10:514-524.

79. Galvani M, Ottani F, Ferrini D, et al. Patency of the infarct-related artery and left ventricular function as the major determinants of survival after Q-wave acute myocardial infarction. Am J Cardiol 1993; 71:1-7.

80. Moliterno DJ, Lange RA, Willard JE, et al. Restoration of antegrade flow in the infarct-related coronary artery days to weeks after acute myocardial infarction improves long-term survival. Coronary Artery Disease 1992; 3:299-304.

81. Harrison DG, Ferguson DW, Collins SM, et al. Rethrombosis after reperfusion with streptokinase: Importance of geometry of residual lesions. Circulation 1984; 69: 991-9.

82. Simoons ML, Arnold AE, Betriu A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: No additional benefit from immediate percutaneous coronary angioplasty. Lancet 1988; 1: 197-203.

88. Arnold AER, Simoons ML, Van de Werf F, et al. Recombinant tissue-type plasminogen activator and immediate angioplasty in acute myocardial infarction. One -year follow-up. Circulation 1992; 86: 111-20.

89. Waller BF, Rothbaum DA, Pinkerton CA, et al. Status of the myocardium and infarct related coronary artery in 19 necropsy patients with acute recanalization using pharmacologic (streptokinase, r-tissue plasminogen activator), mechanical (percutaneous transluminal coronary angioplasty) or combined types of reperfusion therapy. J Am Coll Cardiol 1987; 9: 785-92.

90. Duber C, Jungbluth A, Rumpelt HJ, et al. Morphology of the coronary arteries after combined thrombolysis and percutaneous coronary angioplasty for acute myocardial infarction. Am J Cardiol 1986; 58: 698-703.

83. SWIFT Trial Study Group. SWIFT trial of delayed elective intervention v. conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. Br Med J 1991; 302: 555-60.

84. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the TIMI phase II trial. N Engl J Med 1989; 320: 618-27.

85. Williams DO, Braunwald E, Knatterud G, et al. One-year results of the TIMI phase II trial. Circulation 1992; 85: 533-42.

86. Barbash GI, Roth A, Hod H, et al. Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. Am J Cardiol 1990; 66: 538-45.

87. Ellis SG, Mooney MR, George BS, et al. Randomized trial of late elective angioplasty versus conservative management for patients with residual stenosis after thrombolytic treatment of myocardial infarction. Circulation 1992; 86: 1400-6.

65. Stadius ML, Davis K, Maynard C, et al. Risk stratification for one year survival based on characteristics identified in the early hours of acute myocardial infarction. Circulation 1986; 74: 703-11.

66. Dalen JE, Gore JM, Braunwald E, and the TIMI Investigators. Six and twelve month follow-up of the phase I Thrombolysis in Myocardial Infarction (TIMI) trial. Am J Cardiol 1988; 62: 179-85.

67. Ohman EM, Califf RM, Topol EJ, et al. Characteristics and importance of reocclusion following successful reperfusion therapy in acute myocardial infarction. Circulation 1990: 82: 781-91.

68. Jeremy RW, Hackworthy RA, Bautovich G, et al. Infarct artery perfusion and changes in left ventricular volume in the month after acute myocardial infarction. J Am Coll Cardiol 1987; 9: 989-95.

69. Kersschot IE, Brugada P, Ramentol M, et al. Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation: A prospective, randomized study. J Am Coll Cardiol 1986; 7: 1234-42.

64. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival. Should the paradigm be expanded? Circulation 1989; 79: 441-4.

70. Meizlish JL, Berger HJ, Plankey M, et al. Functional left ventricular aneurysm formation after acute anterior transmural myocardial infarction: incidence, natural history, and prognostic implications. N Engl J Med 1984; 311:1001-1006.

71. Forman MB, Collins HW, Kopelman HA, et al. Determinants of left ventricular aneruysm formation after anterior myocardial infarction: a clinical and angiographic study. J Am Coll Cardiol 1986; 8:1256-1262.

72. Hirai T, Fujita M, Nakajima H, et al. Importance of collateral circulation for prevention of left ventricular aneurysm formation in acute myocardial infarction. Circulation 1989; 79:791-796.

73. Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular thrombus formation after first anterior wall acute myocardial infarction. Am J Cardiol 1988; 62:31-35.

91. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the veterans administration randomized trial of coronary bypass surgery for stable angina. N Engl J Med 1984; 311:1333-9.

92. Alderman EL, Bourassa MG, Cohen LS, Davis KB, Kaiser GG, Killip T, Mock MB, Pettinger M, Robertson TL, for the CASS Investigators. Ten-year follow-up of survival and myocardial infarction in the randomized coronary artery surgery study. Circulation 1990; 82:1629-46.

93. Passamani E, Davis KB, Gillespie MJ, Killip T, and the CASS Principal Investigators and Their Associates. A randomized trial of coronary artery bypass surgery: survival of patients with a low ejection fraction. N Engl J Med 1985; 312:16665-71.

94. Varnauskas E, and the European Coronary Surgery Study Group. Twelve-year follow-up of survival in the randomized European coronary surgery study. N Engl J Med 1988; 319:332-7.

95. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trialor arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321:406-12.

96. Buxton AE, Fisher JD, Josephson ME, et al. Prevention of sudden death in patients with coronary artery disease: the multicenter unsustained tachycardia trial (MUSTT). Prog Cardiovasc Dis 1993; 36:215-26.

97. Kersschot IE, Brugada P, Ramentol M, et al. Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation: A prospective, randomized study. J Am Coll Cardiol 1986; 7:1234-1242.

98. Denniss AR, Richards DA, Cody DV, et al. Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on signal-averaged electrocardiograms of survivors of acute myocardial infarction. Circulation 1986; 74:731-745.

99. Kuchar DL, Thorburn CW, Sammel NL. Prediction of serious arrhythmic events after myocardial infarction: Signal-averaged electrocardiogram, Holter monitoring and radionuclide ventriculography. J Am Coll Cardiol 1987; 9:531-538.

100. Simson MB, Untereker WJ, Spielman SR, et al. Relation between late potentials on the body surface and directly recorded fragmented electrograms in patients with ventricular tachycardia. Am J Cardiol 1983; 51:105-112.

101. El-Sherif N, Scherlag BJ, Lazzara R. Electrode catheter recordings during malignant ventricular arrhythmia following experimental acute myocardial ischemia. Evidence for re-entry due to conduction delay and block in ischemic myocardium. Circulation 1975; 51:1003-1014.

102. Winters SL, Stewart D, Targonski A, et al. Role of signal-averaging of the surface QRS complex in selecting patients with nonsustained ventricular tachycardia and high grade ventricular arrhythmias for programmed ventricular stimulation. J Am Coll Cardio 1988; 12:1481-1487.

103. Gardner PI, Ursell PC, Fenoglio JJ, et al. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985; 72:596-611.

104. Breithardt G, Borggrefe M. Pathophysiologic mechanisms and clinical significance of ventricular late potentials. Eur Heart J 1986; 7:364-385.

105. Gomes JA, Mehra R, Barreca P, et al. Quantitative analysis of the high-frequency components of the signal-averaged QRS complex in patients with acute myocardial infarction: A prospective study. Circulation 1985; 72:105-111.

106. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: Natural history and prognostic significance. Circulation 1986; 74:1280-1289.

107. Denniss AR, Johnson DC, Richards DA, et al. Effect of excision of ventricular myocardium on delayed potentials detected by the signal-averaged electrocardiogram in patients with ventricular tachycardia. Am J Cardiol 1987; 59:591-595.

108. Gang ES, Lew AS, Hong M, et al. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. N Engl J Med 1989; 321:712-716.

109. Boehrer JD, Glamann DB, Lange RA, et al. Effect of coronary angioplasty on late potentials 1 to 2 weeks after acute myocardial infarction. Am J Cardiol 1992; 70:1515-1519.

110. White HD, Norris RM, Brown MA, Takayama M, Maslowski A, Bass NM, Ormiston JA, Whitlock T. Effect of intravenous streptokinase of left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987; 317:850-5.

111. Hutchins GM, Bulkley BH. Infarct expansion versus extension: two different complications of acute myocardial infarction. Am J Cardiol 1978; 41:1127-1132.

112. Meizlish JL, Berger HJ, Plankey M, et al. Functional left ventricular aneurysm formation after acute anterior transmural myocardial infarction: incidence, natural history, and prognostic implications. N Engl J Med 1984; 311:1001-1006.

113. Swedberg K, Held P Kjekshus J, et al. Effects on the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 1992; 327:678-84.

114. Sleight P. Vasodilators after myocardial infarction-ISIS IV. Am J Hypertension 1994; 7:102S-5S.

115. Pfeffer MA, Braunwald E, Moye L, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992; 327:669-77.

116. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342:821-8.

117. ACC/AHA Task Force on assessment of diagnostic and therapeutic cardiovascular procedures. Guidelines for the early management of patients with acute myocardial infarction. Circulation 1990; 82:664-707.

118. Montague NT, Kouchoukos NT, Wilson TAS, Bennett AL, Knott HW, Lochridge SK et al. Morbidity and mortality of coronary bypass grafting in patients 70 years of age and older. Ann Thorac Surg 1985; 39:552-7.

119. Kowalchuk GJ, Siu SC, Lewis SM. Coronary artery disease in the octogenarian: angiographic spectrum and suitability for revascularization. Am J Cardiol 1990; 66:1319-23.

120. Jackman JD, Navetta FI, Smith JE, Tcheng JE, Davidson CJ, Phillips HR, et al. Percutaneous transluminal coronary angioplasty in octogenarians as an effective therapy for angina pectoris. Am J Cardiol 1991; 68:116-9.

121. Freeman WK, Schaff HV, O'Brien PC, Orzulak TA, Naessens JM, Tajik AJ. Cardiac surgery in the octogenarian: perioperative out-come and clinical follow-up. J Am Coll Cardiol 1991; 18:29-35.

122. Herlitz J, Hjalmarson A, Holmberg S, Ryden L, Swedberg K, Waagstein F, et al. Variability, prediction and prognostic significance of chest pain in acute myocardial infarction. Cardiology 1986; 73:13-21.

123. Bär FW, Vermeer F de Zwaan C, Ramentol M, Braat S, Simoons MI, et al. Value of the admission electrocardiogram in predicting outcome of thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1987; 59:6-13.

124. Greenberg H, Gillespie J, Dwyer EM Jr. A new electrocardiographic classification for post-infarction clinical trials. The Multicenter Post-Infarction Research Group. Am J Cardiol 1987; 59:1057-63.

125. Schuster EH, Griffith LS, Bulkley BH. Preponderance of acute proximal left anterior descending coronary artery lesions in fatal myocardial infarction: a clinicopathologic study. Am J Cardiol 1981; 47:1189-96.

126. Willems JL, Willems RJ, Willems GM, Arnold AER, Van de Werf F, Verstraete M, et al. Significance of intiial ST segment elevation and depression for the management of thrombolytic therapy in acute myocardial infarction. Circulation 1990; 82:1147-58.

127. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986; 1:397-402.

128. Raunio H, Rissanen V, Helin M, Rehnbert S, Romppanen T, Janatuinen E. Early pronounced ST segment depression with marked J point decline heralding acute lethal clinical myocardial infarction: necropsy-electrocardiographic correlative study. Am Heart J 1982; 103:32-7.

129. Schechtman KB, Capone RJ, Kleiger RE, Gibson RS, Schwartz DJ, Roberts R, et al. Risk stratification of patients with non-Q wave myocardial infarction: the critical role of ST segment depression. Circulation 1989; 80:1148-58.

130. Honan MB, Harrell FE Jr, Reimer KA, Califf RM, Mark DB, Pryor DB, Hlatky MA. Cardiac rupture, mortality and the timing of thrombolytic therapy: a meta-analysis. J Am Coll Cardiol 1990; 16:359-67.

131. Gertz SD, Kragel AH, Kalan JM, Braunwald E, Roberts WC, and the TIMI Investigators. Comparison of coronary and myocardial morphologic findings in patients with and without thrombolytic therapy during fatal first acute myocardial infarction. Am J Cardiol 1990;66:904-9.

132. Gibson RS, Young PM, Boden WE, Schechtman K, Roberts T. Prognostic significance and beneficial effect of diltiazem on the incidence of early recurrent ischemia after non-Q wave myocardial infarction: results from the multicenter diltiazem reinfarction study. The Diltiazem Reinfarction Group. Am J Cardiol 1987; 60:203-9.

133. Dwyer EM Jr, Greenberg HM, Steinberg G. Clinical characteriistics and natural history of survivors of pulmonary congestion during acute myocardial infarction. The Multicenter Postinfarction Research Group. Am J Cardiol 1989; 63:1423-8.

134. Chen Y, Sherrid MV, Dwyer EM. Value of two-dimensional echocardiography in evaluating coronary artery disease: A randomized blinded analysis. J Am Coll Cardiol 1985;5:911-7.

135. Medina R, Panidis IP, Morganroth J, Kotler MN, Mintz GS. The value of echocardiographic regional wall motion abnormalities in detecting coronary artery disease in patients with or without a dilated left ventricle. Am Heart J 1985;109:799-803.

136. Sawada SG, Ryan T, Segar D. Distinguishing ischemic cardiomyopathy from nonischemic dilated cardiomyopathy with coronary echocardiography. J Am Coll Cardiol 1992;19:1223-8.

137. Glamann DB, Lange RA, Corbett JR, Hillis LD. Utility of various radionuclide techniques for distinguishing ischemic from nonischemic dilated cardiomyopathy. Arch Intern Med 1992;152:769-72.

138. Bulkley BH, Hutchins GM, Bailey I, Strauss HW, Pitt B. Thallium 201 imaging and gated cardiac blood pool scans in patients with ischemic and idiopathic congestive cardiomyopathy. Circulation 1977;55:753-60.

139. Saltissi S, Hockings B, Croft DN, Webb-Peploe MM. Thallium-201 myocardial imaging in patients with dilated and ischaemic cardiomyopathy. Br Heart J 1981;46:290-5.

140. Dunn RF, Uren RF, Sadick N, et al. Comparison of thallium-201 scanning in idiopathic dilated cardiomyopathy and severe coronary artery disease. Circulation 1982;66:804-10.

141. DeBusk RF. Specialized testing after recent acute myocardial infarction. Ann Intern Med 1989; 110:470-81.

142. Kotler TS, Diamond GA. Exercise thallium-201 scintigraphy in the diagnosis and prognosis of coronary artery disease. Ann Int Med 1990. 113:684-702.

143. Waters DD, Bosch X, Bouchard A, et al. Comparison of clinical variables and variables derived from a limited predischarge exercise test as predictors of early and late mortality after myocardial infarction. J Am Coll Cardiol 1985; 5:1-8.

144. Gibson RS, Watson DD, Craddock GB, Crampton RS, Kaiser DL, Denny MJ, Beller GA. Prediction of cardiac events after uncomplicated myocardial infarction: a perspective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. Circulation 1983; 68:321-36.

145. Corbett JR, Dehmer GJ, Lewis SE, et al. The prognositc valve of submaximal exercise testing with radionuclide ventriculography before hospital discharge in patients with recent myocardial infarction. Circulation 1981; 64:535-44.

146. Glamann DB, Lange RA, Corbett JR, Hillis LD. Utility of various radionuclide techniques for distinguishing ischemic from nonischemic dilated cardiomyopathy. Arch Intern Med 1992;152:769-72.

147. Olona M, Candell-riera J, Permanyer-Miralda G, Castell J, Barrabés JA, Domingo E, Rosselló J, Vaqué J, Soler-Soler J. Strategies for prognostic assessment of uncomplicated first myocardial infarction: 5-year follow-up study. J Am Coll Cardiol 1995:815-22.

148. Rogers WJ, Babb JD, Baim DS, Chesebro JH, Gore JM, Roberts R, Williams DO, Frederick M, Passamani ER, Braunwald E, for the TIMI II Investigators. Selective versus routine predischarge coronary arteriography after therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. J Am Coll Cardiol 1991; 17:1007-16.

149. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988; 78:1157-66.

150. Nobuyoshi M, Tanaka M, Nosaka H, Kimura T, Yokoi H, Hamasaki N, Kim K, Shindo T, Kimura K. Progression of coronary atherosclerosis: is coronary spasm related to progression? J Am Coll Cardiol 1991; 18:904-10.

151. ACC/AHA Task Force on assessment of diagnostic and therapeutic cardiovascular procedures. Guidelines for coronary angiography. J Am Coll Cardiol 1987; 10:935-50.