Controversies in Clinical Cardiology

Primary PTCA or Thrombolytic Therapy: A Debate on the Preferred Therapy of Acute MI

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THROMBOLYSIS: THE PREFERRED THERAPY FOR ACUTE MI

Thrombolytic Therapy Exerts a Profoundly Beneficial Influence on Patient Survival.

Over the past 10 to 15 years, reperfusion therapy of acute ST elevation myocardial infarction (MI) -- accomplished with intravenously administered thrombolytic therapy -- has been shown convincingly to exert a markedly beneficial effect on (a) myocardial infarct size, (b) left ventricular performance, and -- most importantly -- (c) patient survival. In placebo-controlled, randomized trials involving almost 60,000 subjects, thrombolytic therapy alone has been shown to reduce short-term mortality by 15 to 20%, and **thrombolytic therapy in conjunction with aspirin has been shown to lower 35-day mortality by almost 40%** (Table 1).

Table 1: 35-day Mortality in ISIS-2

Treatment	35-day Mortality
Standard	13.2%
IV Streptokinase (1.5 mu in 1 hour)	10.4%
Oral Aspirin (160 mg QD)	10.7%
IV Streptokinase + Oral Aspirin	8.0%

From reference # 1

Thrombolytic therapy is particularly efficacious in patients to whom it can be administered early in the course of their evolving MI. For example, in those in whom treatment can be initiated within 60 minutes of the onset of chest pain, thrombolytic therapy saves 35 lives per 1000 patients treated. As the elapsed time from onset of chest pain to initiation of therapy lengthens, the magnitude of benefit with reperfusion therapy declines (Table 2).

Table 2: Time-Dependence of Reperfusion Therapy

Hours From Pain Onset to Rx	# Lives Saved/1000 Pts
0-1	35
2-3	25
4-6	19
7-12	16
13-24	5

From reference # 2

Based on these data, **a great deal of effort should be directed at initiating reperfusion therapy promptly and without delay.**

Thrombolytic therapy is especially salutary in patients who are in the midst of having a large MI. The subjects who derive the maximal benefit from thrombolytic therapy are those whose initial ECG shows (a) bundle branch block (BBB) or (b) ST elevation in the anterior leads -- i.e., electrocardiographic evidence of a large MI. In ISIS-2 [1], a streptokinase-aspirin combination reduced 35-day mortality by 50% in comparison to standard therapy in patients whose initial ECG showed BBB or anterior ST segment elevation. The data were similar in the Collaborative Trialists' analysis of all randomized trials (Table 3).

Table 3: Magnitude of Benefit of Thrombolytic Therapy as a Function of the Initial ECG

Initial ECG	# Lives Saved/1000 Pts
BBB	49
Anterior ST elevation	37
Inferior ST elevation	8
ST depression	-14

From reference # 2

Thrombolytic therapy is widely available and can be administered easily and quickly. It can be given by a physician, nurse, physician's assistant, or technician in the hospital or even before the patient arrives at the hospital (i.e., in the physician's office or in route to the Emergency Department via ambulance). It is equally effective whether given in a small rural hospital or a large metropolitan medical center. In short, thrombolytic therapy should and can be initiated within minutes of the patient's presentation [3].

Despite its proven efficacy in tens of thousands of patients with acute MI, **thrombolytic therapy has limitations**. Many subjects are considered to be ineligible for thrombolysis because of (a) contraindications, (b) late presentation (> 12 hours after onset of chest pain), or (c) nondiagnostic electrocardiographic abnormalities. The most serious and dreaded complication of thrombolytic therapy is **intracranial hemorrhage, which may occur in up to 0.7% of subjects** [4] (Table 4). Of those given thrombolytic therapy, 10 to 15% have persistent occlusion or reocclusion of the infarct-related artery [5].

Table 4: Incidence of Intracranial Hemorrhage in "Megatrials" of Thrombolytic Therapy

Trial	Agent Used	% Intracranial Bleed
GISSI-1 [6]	SK (n = 5,860)	0.2
ISIS-2 [1]	SK (n = 8,592)	0.1
GISSI-2 [7]	SK (n = 10,385)	0.3
	tPA (n = 10,364)	0.4
ISIS-3 [8]	SK (n = 12,848)	0.3
	tPA (n = 12,841)	0.7
	APSAC (n = 12,885)	0.6
GUSTO [4]	SK (n = 20,023)	0.5
	tPA (n = 10,268)	0.7

In summary, promptly administered intravenous thrombolytic therapy -- irrespective of the specific agent selected -- has been shown to be highly effective in reducing mortality in trials involving tens of thousands of patients with acute MI. These agents can be given without delay by physicians or support personnel irrespective of location. The risk of a serious adverse event (specifically, intracranial hemorrhage) is well below 1%.

PRIMARY PTCA: THE PREFERRED THERAPY FOR THE ACUTE MI

Limitations of Thrombolytic Therapy

The optimal method of reestablishing coronary patency in patients with acute MI is controversial. Clinical trials involving over 100,000 patients with evolving Q-wave MI have shown that intravenous thrombolytic therapy is effective in restoring antegrade coronary blood flow, improving left ventricular function, and reducing mortality. Nevertheless, thrombolytic therapy has several limitations. Studies have shown that only 20 to 30% of patients with acute MI receive a thrombolytic agent (Figure 1)[9].

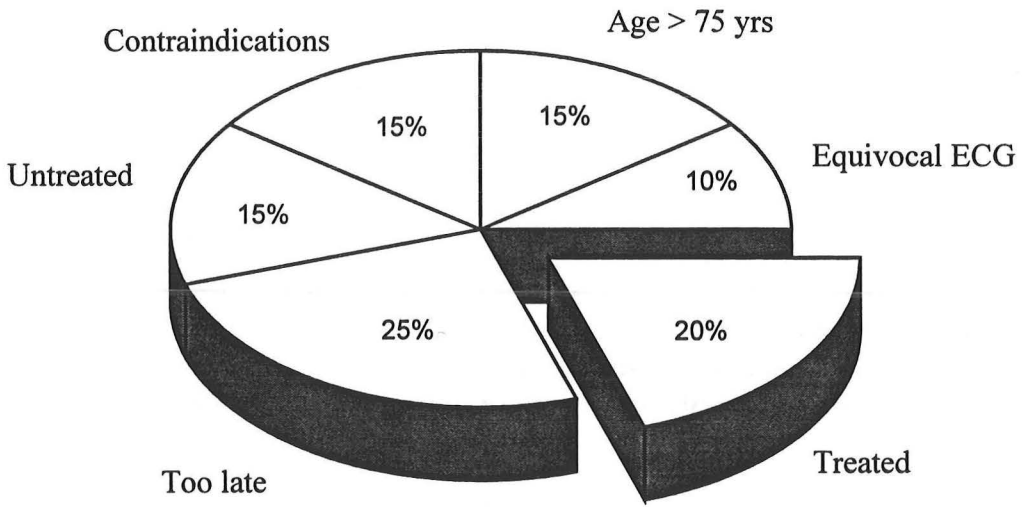


Figure 1: The proportion of patients eligible and ineligible for thrombolysis according to current recommendations and practices. Of an estimated 700,000 patients admitted to US hospitals annually with a diagnosis of acute MI, only 20 to 30% currently receive thrombolytic therapy [9].

Many patients with acute MI are not treated with a thrombolytic agent, because they have a contraindication to its administration (Table 5, next page).

Table 5. Contraindications to Thrombolytic Therapy

Absolute
- Previous hemorrhagic stroke at any time
- Cerebrovascular event within 1 year
- Known intracranial neoplasm
- Active internal bleeding
- Suspected aortic dissection

Relative
- Severe uncontrolled hypertension (> 180/100 mm Hg) on presentation
- History of prior cerebrovascular event or arteriovenous malformation
- Anticoagulation use
- Recent trauma (within 2 to 4 weeks), including prolonged CPR
- Puncture of a noncompressible vessel
- Recent (within 2 to 4 weeks) internal bleeding
- Pregnancy
- For streptokinase, prior exposure (within 5days to 2 years) or prior allergic reaction
- Active peptic ulcer
- History of chronic severe hypertension

Additionally, thrombolysis is reserved for patients with acute MI who have ST segment elevation or a left bundle branch block on the initial electrocardiogram [1,6]; those with classic symptoms who have enzymatic evidence of infarction (e.g., creatine kinase-MB or troponin I) but equivocal electrocardiographic changes on presentation (i.e., those with occlusion of the circumflex coronary artery) are not offered a thrombolytic agent. Hemorrhagic complications or stroke occur with thrombolysis, especially in elderly patients or those with hypertension (Table 6) [2,4].

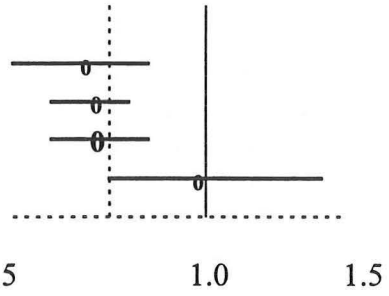
Table 6. Incidence of In-Hospital Stroke With Thrombolysis By Patient Age [2]

Age (yrs)	No. pts	Major bleed	Stroke
<55	6441	0.7%	0.3%
55-64	7727	1.4%	1.1%
65-74	6310	1.3%	1.4%
>75	2359	1.4%	2.0%

Furthermore, analysis of the major randomized thrombolytic trials [2] has cast doubt on whether thrombolytic therapy is beneficial in elderly patients with acute MI (Figure 2).

Figure 2. Proportional Effects of Thrombolytic Therapy on Early (Days 0-35) Mortality According to Patient Age [2]

Age	Early Mortality		Odds ratio & CI
	Control	Thrombolytics	
< 55	3.4%	4.6%	
55-64	8.9%	7.2%	
66-74	16.1%	13.5%	
75+	25.3%	24.3%	



The recent Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial evaluated the relative efficacy of intravenous streptokinase and/or a "front-loaded" dose of tissue plasminogen activator in 41,021 patients with evolving MI. This trial [10] showed that 20 to 40% of patients who receive thrombolytic therapy fail to achieve early coronary artery reperfusion (Figure 3).

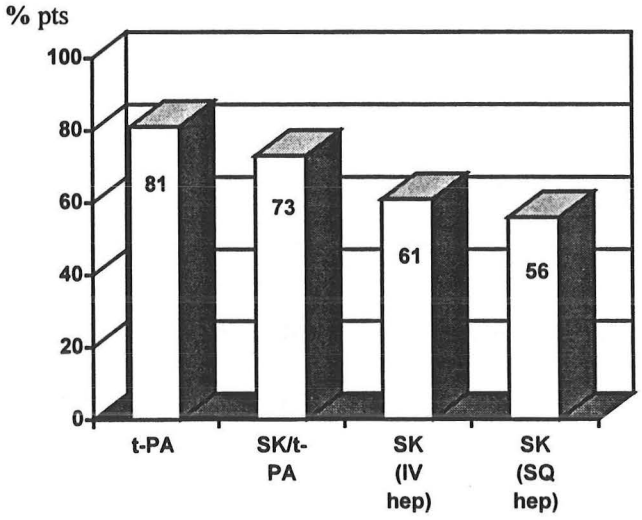


Figure 3. Infarct-Related Artery Patency (TIMI Grade 2 or 3 Flow) 90 Minutes After Thrombolytic Therapy [10]

Unfortunately, clinical markers of reperfusion (i.e., normalization of electrocardiographic changes, resolution of chest pain, and the appearance of reperfusion arrhythmias) are unreliable in identifying those in whom thrombolytic therapy has not reestablished coronary flow. Furthermore, normal coronary flow (grade 3, according to the system used in the

Thrombolysis in Myocardial Infarction [TIMI] trial) flow is achieved in only 30 to 55% of patients treated with thrombolytic therapy (Figure 4) [10], and it is well established that normal coronary flow is an important determinant of survival (Figure 5) [11].

Figure 4. 90 Minute Patency Rate of Infarct-Related Arteries in Patients Treated With Thrombolysis in The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)Trial [10]

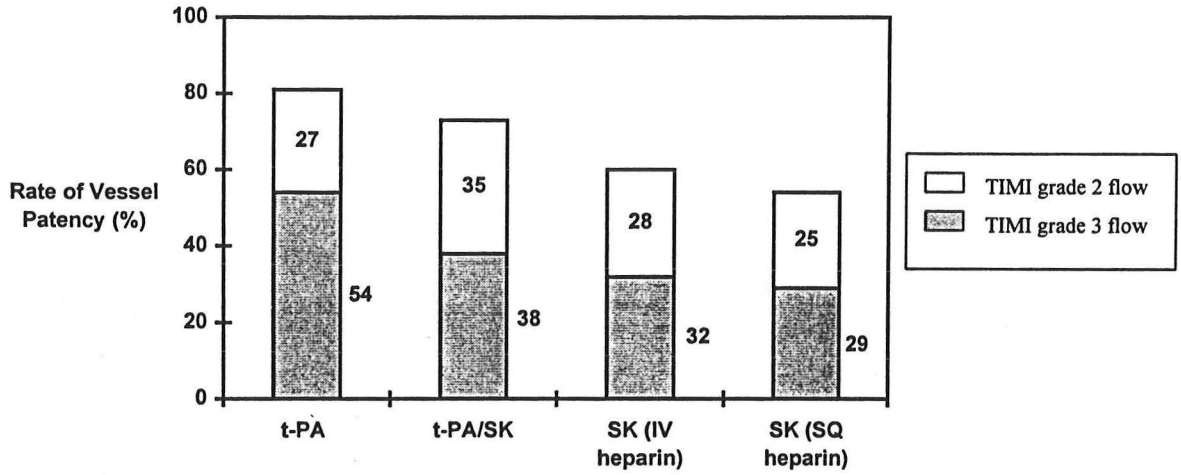
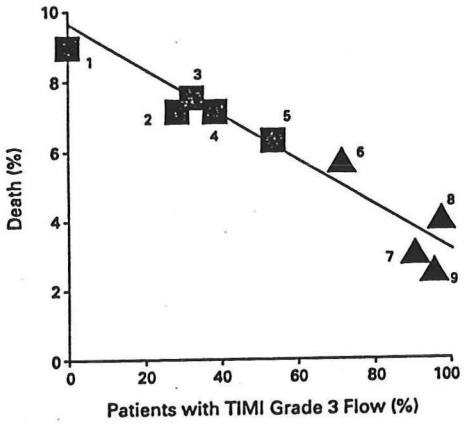


Figure 5. Early Mortality in Relation to the Proportion of Patients With TIMI Grade 3 Flow After Thrombolysis (Squares) or Primary PTCA (Triangles) [11]



GUSTO Study of Thrombolysis
1 Occluded arteries (all patients)
2 Patients given subcutaneous streptokinase and heparin
3 Patients given intravenous streptokinase and heparin
4 Patients given streptokinase plus t-PA
5 Patients given accelerated t-PA

Studies of Primary PTCA
6 GUSTO IIb[7]
7 PAMI-1[4]
8 PAR[3]
9 PAMI-2[5]

Data on PTCA are from Ellis (GUSTO IIb), Grines et al (PAMI 1), Brodie et al (PAR) and Brodie et al (PAMI-2). Abbreviations: GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; PAMI = Primary Angioplasty in Myocardial Infarction; PAR = Primary Angioplasty Registry.

Early reocclusion of the coronary artery after thrombolysis occurs in 5 to 10% of patients (Table 7) and increases the risk of MI, congestive heart failure, and death [10]. Following successful thrombolysis, late (3 month) reocclusion occurs in approximately 30% of patients [12].

Table 7. In-hospital Incidence of Recurrent Ischemia and Reinfarction in Thrombolytic Treated Patients in the GUSTO Trial [4]).

Thrombolytic Therapy	Recurrent Ischemia	Reinfarction
t-PA	16%	4%
t-PA/SK	15%	4%
SK (IV heparin)	16%	4%
SK (SQ heparin)	16%	3%

Finally, those with MI and cardiogenic shock have a substantial peri-infarction mortality, that is not improved with thrombolytic therapy (Table 8) [6].

Table 8. Mortality Rates With And Without Thrombolytic Therapy According to Killip Class at Entry in the GISSI-1 Trial [6].

		Killip I	Killip II	Killip III	Killip IV
Hospital mortality rate (%)					
	SK	5.9*	16.1*	33.0	69.9
	Placebo	7.3	19.9	39.0	70.1
1-year mortality rate (%)					
	SK	10.6*	26.6	50.3	76.6
	Placebo	11.9	28.9	53.3	72.4

* $p < 0.05$, SK = Streptokinase

Consequently, there has been great interest in performing immediate cardiac catheterization and percutaneous transluminal coronary angioplasty (PTCA) in patients with evolving MI (so called "primary PTCA"). There are several advantages of this approach.

First, primary angioplasty can be performed in most patients with MI. This includes the 15-20% who have a contraindication to thrombolytic therapy as well as those who do not have an absolute contraindication but are thought to be at increased risk for a hemorrhagic or cerebrovascular complication (e.g., elderly patients). Second, in patients who have symptoms consistent with acute MI and equivocal electrocardiographic changes or a left bundle branch block of unknown duration, cardiac catheterization can confirm – or exclude -- coronary artery occlusion, so that reperfusion therapy can be applied (or withheld) . Third, with primary PTCA, one can immediately and reliably assess the success of reperfusion; residual coronary stenoses can be treated immediately with additional balloon inflations or intracoronary stenting. Fourth, catheterization of these patients provides prognostic information that may alter the early post MI treatment of the patient. For example, patients with left main coronary artery disease or three vessel disease and depressed left ventricular systolic function or involvement of the proximal left anterior descending coronary artery would be referred for coronary artery bypass grafting for a survival benefit.

The Case for Primary PTCA

Early observational studies of primary PTCA reported (a) high recanalization rates (>90%); (b) a low in-hospital mortality (approximately 8%); and (c) a favorable 1 year survival (>90%) (Table 9) [13-22], similar to that obtained with thrombolytic therapy.

Table 9. Observational Studies of Primary PTCA

Study	Study period	No. pts	In-hospital mortality
Flaker et al [13]	85-88	93	14%
Marco et al [14]	publ 87	43	14%
Ellis et al [15]	83-88	271	13%
Rothbaum et al [16]	82-86	151	9%
Brodie et al [17]	84-93	907	9%
Bittl [18]	89-90	20	9%
O'Keefe et al [19]	80-93	1000	8%
Beauchamp et al [20]	82-89	214	8%
Grines et al [21]	publ 91	58	5%
Williams et al [22]	publ 91	226	5%
	Total	2983	8%

Predictors of improved survival included preserved left ventricular function, a patent infarct artery at hospital discharge, early reperfusion (within 2 hours of pain onset), and single

vessel coronary artery disease [19,23]. Since both primary PTCA and thrombolysis are effective in recanalizing occluded infarct arteries and are associated with excellent in-hospital and long-term survival, the issue of which therapy is optimal for the patient with an evolving MI is controversial. Accordingly, 3 prospective, randomized studies comparing the 2 therapies have been completed [24-26] (Table 10).

Primary PTCA vs Thrombolysis: Randomized Trials

In each of the 3 randomized studies, patients presenting within 6 to 12 hours of the onset of acute MI were randomized to receive (a) intravenous thrombolytic therapy (streptokinase or tissue plasminogen activator) or (b) catheterization and PTCA at centers experienced with its use. Antegrade coronary flow was established quickly (60 minutes, average time from presentation to initial balloon inflation) in 93-99% of patients in whom primary PTCA was attempted and, more specifically, normal coronary flow was established in almost all patients. In comparing primary PTCA to thrombolytic therapy, several endpoints were evaluated, including assessment of time to treatment, mortality, myocardial salvage, infarct artery patency, incidence of recurrent ischemia, and hospital costs.

Table 10. Prospective, Randomized Trials of Primary PTCA versus Thrombolysis

Study	No. Pts	Thrombolytic Agent	PTCA Success	Endpoints
Netherlands Trial [24]	301	SK (1.5 mU/1h)	98%	Left ventricular function Coronary patency/stenosis Clinical events
Mayo Clinic Trial [25]	108	t-PA (0.6 mg/kg/4h)	93%	Myocardial salvage Hospital costs
PAMI Trial [26]	395	t-PA (100mg/3h)	99%	Left ventricular function Clinical events

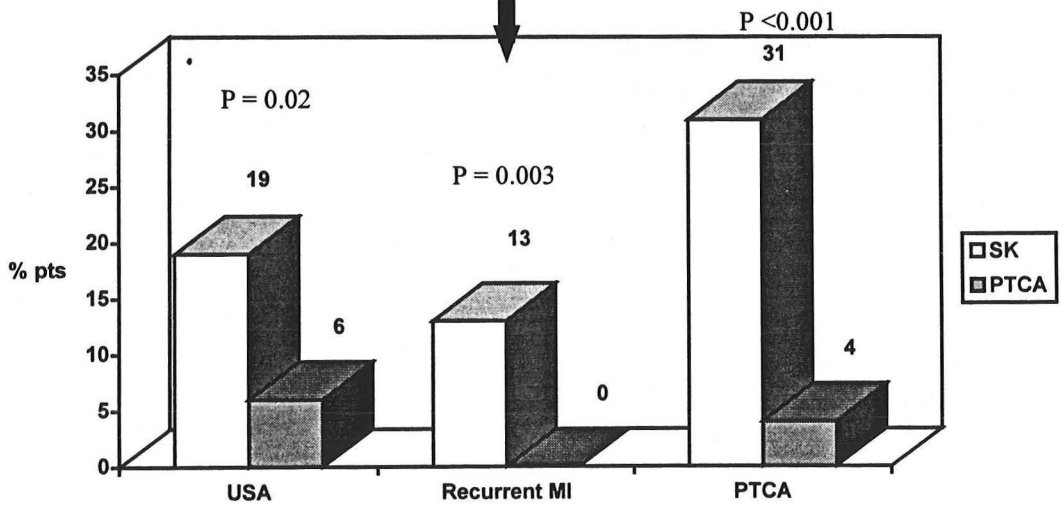
Abbreviations: PAMI = Primary Angioplasty in Myocardial Infarction; SK = streptokinase; t-PA = tissue plasminogen activator

Time to treatment: In all studies, thrombolytic therapy was initiated 30 to 60 minutes more rapidly than primary PTCA, even though PTCA was performed promptly (average time from randomization to PTCA, 60 minutes) at centers with experienced personnel who were immediately available. Since reperfusion of an occluded infarct artery typically occurs 20-60 minutes following initiation of a thrombolytic agent, the overall time required to restore antegrade coronary flow was probably similar for thrombolysis and primary PTCA (provided that the latter is performed expeditiously).

Infarct artery patency and recurrent ischemia: In the Netherlands trial, Zjilstra et al [24] performed catheterization 3 to 9 weeks after hospital discharge to assess the rate of infarct artery patency. The infarct-related vessel was patent in 68% of those who received thrombolytic therapy and 91% of those who had primary PTCA ($p = 0.001$). This translated into fewer episodes of unstable angina, recurrent MI, and unplanned angioplasties (Figure 6). Coronary artery patency following treatment was not assessed in the patients enrolled in the PAMI study; however, the incidence of recurrent ischemia was lower in those treated with primary PTCA (5.1% vs 23.5%, $p < 0.001$) [26].

Figure 6. Infarct Vessel Status at 3 Month Follow-up and Clinical Outcome in the Netherlands Trial [24].

	PTCA	SK	p value
% of infarct-related arteries patent	91	68	0.001
Severity of residual coronary stenosis (%)	36	76	<0.001



Abbreviations: MI = myocardial infarction; USA = unstable angina

Effect on mortality: In-hospital mortality was similar for the thrombolysis and angioplasty treated patients in the 2 smaller studies [24,25] (Table 11).

Table 11. In-Hospital Mortality in the Randomized Trials of Primary PTCA vs Thrombolysis

Study	No. Pts	In-Hospital Deaths: Primary PTCA	In-Hospital Deaths: Thrombolysis	p value
Netherlands Trial [24]	142	0 (0%)	4 (6%)	NS
Mayo Clinic Trial [25]	108	2 (4.3%)	2 (3.6%)	NS
PAMI Trial [26]	395	5 (2.6%)	13 (6.5%)	0.06

Abbreviations: PAMI = Primary Angioplasty in Myocardial Infarction

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The larger, multicenter study [26] showed a trend toward reduced in-hospital mortality with PTCA and a significant decrease in the combined endpoint of mortality and nonfatal reinfarction (Figure 7, next page). A post hoc analysis was performed, and the patients were classified as "not high risk" or "high risk," with the latter including those with anterior MI, age >70 years, or heart rate >100 beats/minute. Those at "high risk" had a significantly lower in-hospital mortality with primary PTCA (Figure 8, next page). The beneficial effects of primary PTCA were confirmed when the original Netherlands trial was extended from 142 to 301 patients followed for 18 months (mean; range 3-36 months) [27]. There was a marked difference in the combined endpoint of death from cardiac causes and non-fatal recurrent MI (6% versus 29% in PTCA and thrombolytic treated patients, respectively; $p < 0.001$) and in the incidence of cardiac death alone (4% vs 10% for the PTCA and thrombolytic treated patients, respectively; $p < 0.004$).

Figure 7. The Primary Angioplasty in Myocardial Infarction Study: Rates of Reinfarction, Mortality, and Both

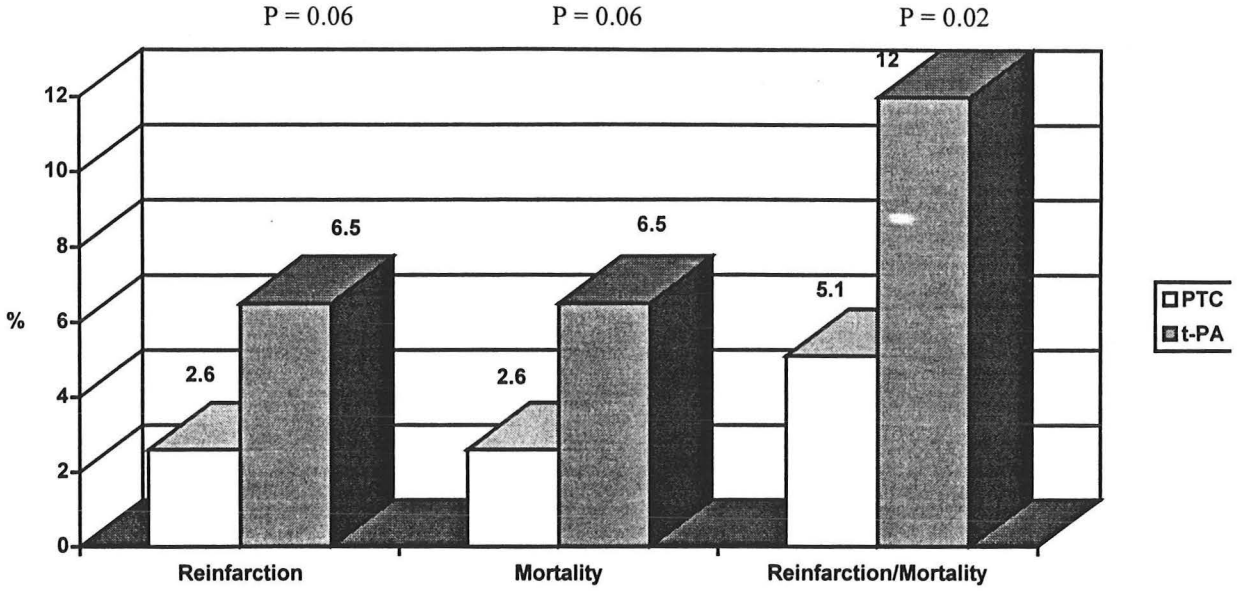
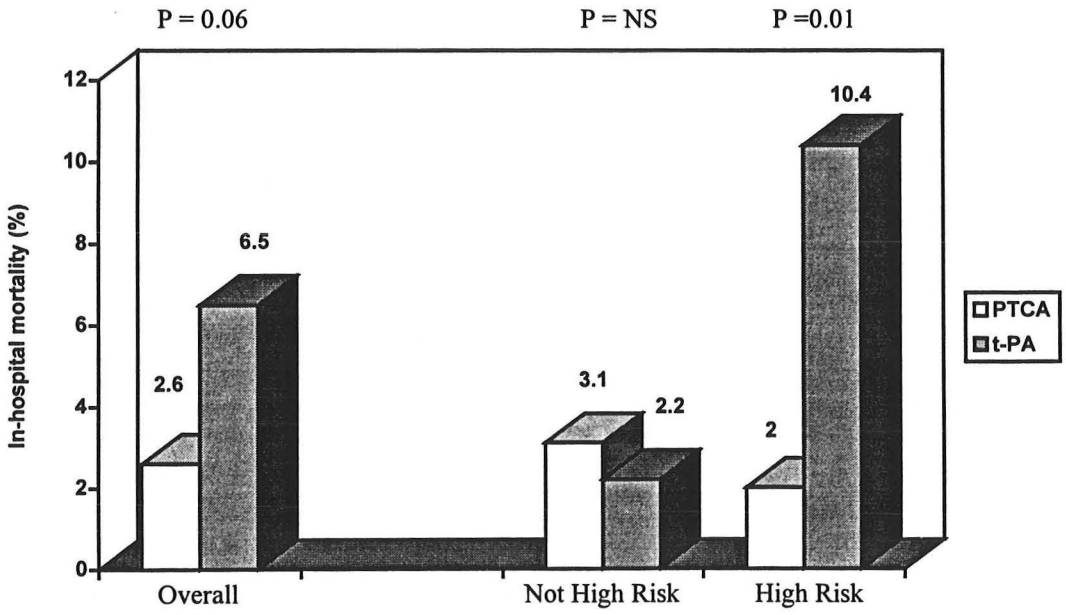


Figure 8. In-Hospital Mortality In The Primary Angioplasty Myocardial Infarction Study Sudivided Byto Patient Risk [26]



Cost of treatment: One [24] of the randomized studies reported hospital costs associated with primary PTCA and thrombolytic therapy and found no difference between the two treatment strategies as assessed at 12 month follow-up. More recently, primary PTCA has been associated with reduced costs -- in-hospital and at 2 year follow-up -- in patients "not at high risk," primarily because it results in reduced in-hospital adverse events, a shorter initial hospital stay, and fewer hospital readmissions than when thrombolysis is used [28].

REBUTTAL

THE REAL TRUTH ABOUT PRIMARY PTCA

There is a **huge** difference in the number of subjects enrolled in the various randomized trials of thrombolytic therapy and primary PTCA. Thrombolytic therapy has been shown to be superior to placebo in trials involving roughly **60,000** subjects, and various thrombolytic agents and regimens have been compared in trials involving **> 100,000** patients. In contradistinction, **the 4 randomized comparisons of thrombolytic therapy and primary PTCA enrolled a total of 745 subjects -- only 362 of whom underwent primary PTCA** (Table 12). In short, the results of the 4 randomized trials comparing thrombolysis and primary PTCA are very preliminary. Even if they suggest a benefit of 1 over the other, they must be confirmed in substantially larger trials.

Table 12: Number of Subjects in the 4 Randomized Comparisons of Thrombolytic Therapy and Primary PTCA

Authors	# Pts Enrolled	# Pts Having Primary PTCA
Grines [26]	395	195
Zijlstra [24]	142	70
Gibbons [25]	108	47
Ribeiro [29]	100	50
TOTAL	**745**	**362**

The observational study of Every et al [30], though not strictly a randomized comparison of thrombolysis and primary PTCA, provides very useful information. Of 12,331 consecutive subjects with acute MI admitted to 19 Seattle area hospitals between 1988 and 1994, 2095 received thrombolytic therapy (approximately 2/3 tPA, 1/3 streptokinase), and 1050 were treated with primary PTCA. The 2 groups were similar in all baseline variables. **There was no difference in mortality during hospitalization or long-term (3-4 year) follow-up between the groups** (Table 13).

Table 13: Mortality in the study of Every et al [30]

Mortality	Thrombolytic Rx	Primary PTCA
In-hospital	5.6%	5.5%
At 4 years	15.5%	16.0%

In the study of Every et al [30], patients given thrombolytic therapy were hospitalized an average of 1.1 days longer than those having primary PTCA. However, those receiving thrombolysis had lower average hospital costs (Table 14), and this continued to be true 3 years after randomization (Table 14).

Table 14: Average costs in the study of Every et al [30]

Cost	Thrombolytic Rx	Primary PTCA
In-hospital	$16,838	$19,702
At 3 years	$22,163	$25,459

In the PAMI study [26], Grines et al suggested that primary PTCA reduced mortality in comparison to thrombolysis, with a p value of 0.06 (Table 15).

Table 15: Mortality in the PAMI study [26]

Treatment	# Pts	# Deaths
tPA	200	13
PTCA	195	5

p = 0.06

Of the 13 deaths in the tPA group, 4 were the result of intracranial hemorrhage, **an incidence of 2%.** As shown in Table 4, the incidence of intracranial bleeding in all large thrombolytic trials has ranged from only 0.1 to 0.7%; in none of the large trials has it even approached 2%. For the sake of discussion, if we assume that the incidence of fatal intracranial hemorrhage in PAMI should have been only 0.5% (i.e., 1 patient rather than 4), then the total number of deaths among the 200 patients who received tPA would have been 10, not 13. If one then compares a mortality of 10/200 in the tPA group and 5/195 in the primary PTCA group, the p value is 0.34. **In short, PAMI suggested that primary PTCA reduced mortality in comparison to thrombolytic**

therapy, in large part because the incidence of intracranial bleeding in those receiving tPA was inordinately high -- 3 to 4 times higher than that reported in the large thrombolytic trials.

Less than 20% of hospitals in the United States and 10% in Europe have facilities for PTCA, and even fewer perform emergency PTCA. As a result, most patients with acute MI present to hospitals where PTCA is not available. Transfer to another facility for PTCA would unnecessarily delay reperfusion; remember that **the benefit of reperfusion therapy is critically dependent on the elapsed time from onset of chest pain to reperfusion** (Table 2). The withholding of thrombolysis in order to transfer the patient to a facility with PTCA capability would be deleterious.

In centers with extensive experience with emergency PTCA and immediately available catheterization facilities and support personnel (such as those of Grines et al [26], Zijlstra et al [24], and Gibbons et al [25]), primary PTCA can be performed quickly (within 60 to 80 minutes of presentation). Such prompt and expert PTCA may not be possible in most hospitals. In the study of Every et al [30], the average time from presentation to PTCA was 102 minutes. **At the participating hospitals that were said to have a low PTCA volume, the elapsed time from presentation to PTCA averaged 138 minutes.** In short, even if certain highly efficient centers can perform primary PTCA quickly and expertly, their results may not be applicable to the average patient who presents to the average hospital.

Primary PTCA is said to be indicated in the patient with evolving MI in whom thrombolytic therapy is contraindicated (because of a bleeding diathesis or late presentation). Although, in fact, primary PTCA may be the treatment of choice for such patients, their prognosis is much more guarded than those who are thrombolytic-eligible but for whom primary PTCA is elected. In fact, observational studies suggest that patients with acute MI who are deemed thrombolytic-ineligible have a high short-term mortality (19 to 24%) [9,31], even if they receive primary PTCA (14 to 27%) [17,19].

Finally, in comparison to standard management, thrombolytic therapy appears to be largely ineffective in improving survival in subjects with **cardiogenic shock**. As a result, there has been enthusiasm for performing primary PTCA in these patients. Although preliminary data suggested that PTCA was superior to thrombolysis in this patient population, these data are clouded by substantial selection bias concerning who undergoes PTCA and who is deemed "too sick" for mechanical intervention and, therefore, is managed "conservatively" (i.e., with thrombolytic therapy). The ongoing SHOCK trial -- a multicenter randomized comparison of primary PTCA and thrombolysis in patients with cardiogenic shock -- is designed to address the question of how these subjects should be managed.

Rebuttal

The Truth, The Whole Truth, and Nothing But The Truth (About Primary PTCA)

What do prospective, randomized trials offer that observational studies do not? The ability to compare treatment options without regard to the bias of the treating physician. Since physicians have a tendency to treat the sickest patients most aggressively and to use primary PTCA when the risks of thrombolytic therapy are increased, the results of the Every study [30] must be interpreted cautiously. For example, in contrast to the findings of Every et al, no randomized trial comparing the two therapies has reported that primary PTCA is associated with increased costs or subsequent procedure utilization. In addition, the in-hospital mortality rate for thrombolytic treated patients (5.6%) is lower in their study than that reported in other large thrombolytic trials (i.e., GUSTO) [4], suggesting that their sickest patients did not receive thrombolytic therapy. Since they did not provide data showing why a particular treatment was selected, it is not possible to assess if physician treatment bias affected the results of the study.

Randomized trials comparing primary PTCA to thrombolytic therapy have convincingly demonstrated that the former is associated with (a) improved infarct-artery patency and flow; (b) a reduction in recurrent ischemic events; (c) a shorter hospital stay; and (e) reduced mortality, especially in "high risk" patients. It should not be surprising that the therapy that is most effective in restoring coronary flow and reducing residual coronary stenoses (e.g., primary PTCA) is associated with fewer episodes of recurrent ischemia and improved survival. The benefit may be even more marked when intracoronary stents and more effective antiplatelet agents (e.g., the glycoprotein IIb/IIIa receptor antagonists) are used adjunctively to PTCA. In contrast, more potent thrombolytic therapy or concomitant antithrombotic/antiplatelet therapy increases the rate of intracerebral stroke, bleeding complications, and mortality.

Should primary PTCA be limited to the "high risk" group of patients? This question was addressed in a recently published study by Zijlstra et al [32]. Patients presenting within 6 hours of the onset of acute MI were classified as low risk or high risk, with the latter having at least one of the following: (a) a contraindication to thrombolytic therapy; (b) an anterior MI; or (c) Killip class $\geq$ 2. All high risk patients received primary PTCA, and the low risk patients were randomized to receive thrombolytic therapy or primary PTCA. In comparison to the thrombolytic treated patients, the low risk patients treated with primary PTCA had a lower rate of adverse events at 6 months of follow-up at a similar hospital cost (Table 16).

Table 16. Thrombolysis vs PTCA in Low Risk Patients [32]

	Low Risk Group			High Risk Group
	PTCA (n=45)	p value	SK (n=50)	PTCA (n=145)
Revascularization Procedures				
CABG	6 (12%)	1	7 (14%)	23 (16%)
PTCA	9 (20%)	<0.001	30 (60%)	29 (14%)
Clinical outcome				
Death	1 (2%)	0.47	0 (0%)	16 (11%)
Stroke	1 (2%)	1	2 (4%)	0 (0%)
Reinfarction	0 (0%)	<0.001	8 (16%)	4 (3%)
Primary Endpoint	2 (4%)	< 0.02	10 (20%)	20 (14%)

Similar results were noted in a recent analysis of the cost and effectiveness of primary PTCA in the PAMI trial [28]. Compared with t-PA, primary PTCA resulted in reduced rates of in-hospital mortality, recurrent ischemia, and stroke in the "high risk" patients (i.e., those with age >70 years, admission heart rate >100 beats/min, or anterior MI location) (Table 17). But even in the "not high risk" group, primary PTCA resulted in reduced rates of recurrent ischemia, unplanned revascularization, hospital stay, and costs (Table 18).

Table 17. In-Hospital Outcomes and Charges Stratified by Therapy and Patient "Risk" [28]

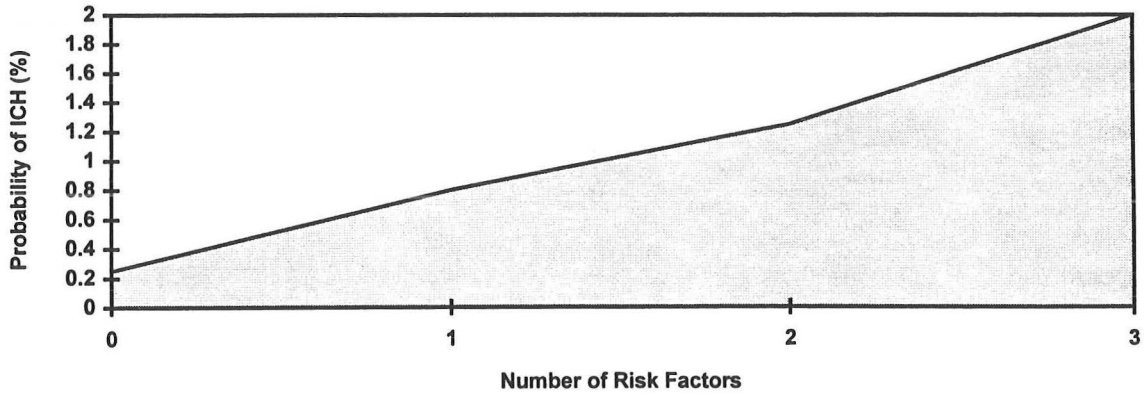
	High Risk Patients		
	PTCA (n=87)	t-PA (n=90)	p value
Death	2 (2%)	10 (11%)	0.01
Recurrent ischemia	11 (13%)	25 (28%)	0.01
Stroke	0 (0%)	6 (6.7%)	0.03
Nonprotocol cath	16 (18%)	59 (66%)	<0.0001
Nonprotocol PTCA	7 (8%)	32 (36%)	< 0.0001
Hospital Charges	$24,948	$27,412	0.57

Table 18. In-Hospital Outcomes and Charges Stratified by Therapy and Patient "Risk" [28]

	Not High Risk Patients		
	PTCA (n=90)	t-PA (n=91)	p value
Death	2 (2%)	3 (3%)	0.51
Recurrent ischemia	9 (10%)	27 (30%)	0.0007
Stroke	0 (0%)	1 (1%)	0.5
Nonprotocol cath	7 (8%)	55 (60%)	<0.0001
Nonprotocol PTCA	4 (4%)	33 (36%)	< 0.0001
Hospital stay (days)	7.0	8.3	0.03
Hospital Charges	$22,038	$26,413	0.025

The PAMI study has been criticized for the high rate of hemorrhagic cerebrovascular events (2%) in the thrombolytic treated patients. It is important to note that these events occurred in the "high risk" patients, and these patients are known to be at increased risk for such events (Figure 9) [33]. In patients with acute MI who are candidates for thrombolytic therapy, the following are known to be risk factors for increased intracranial hemorrhage: age > 65 years, weight < 70 kg, hypertension on admission, and use of t-PA. The more risk factors present, the higher the likelihood of an intracranial hemorrhage. The "high risk" patients in the PAMI trial had at least two risk factors (age and t-PA use).

Figure 9. Risk of Intracranial Hemorrhage (ICH) During Thrombolytic Therapy [32].



Although thrombolytic therapy is more widely available than primary PTCA, a minority of patients with acute MI are considered suitable candidates to receive it. In contrast, 80% of the US population resides within 30 minutes of a cardiac catheterization laboratory, and almost all can be treated with primary PTCA.

Both primary PTCA and intravenous thrombolytic therapy are effective in achieving reperfusion in the patient with coronary artery occlusion and acute MI. Prospective, randomized trials have established that primary PTCA is the preferred therapy when it can be administered quickly by experienced operators. Under such conditions, it results in improved infarct artery patency and coronary flow and a reduced incidence of reinfarction and mortality than that observed with thrombolytic therapy and at a similar or lower cost.

Concluding Remarks

In the latest ACC/AHA Guidelines for Treatment of Acute MI [33] (written by a distinguished panel of so-called experts in the field), primary PTCA is said to be "an acceptable alternative to thrombolytic therapy only if performed in a timely fashion by individuals skilled in the procedure and supported by experienced personnel in high-volume centers." The panel then goes on to express "serious concern that a routine policy of primary PTCA for patients with acute MI will result in unacceptable delays in achieving reperfusion in a substantial number of cases and less than optimal outcomes if performed by less experienced operators. Strict performance criteria must be mandated for primary PTCA programs so that such delays in revascularization and performance by low-volume operators/centers do not occur. Interventional cardiologists and centers must operate within a specified 'corridor of outcomes' to include (a) balloon dilation within 60 to 90 minutes of diagnosis of acute MI; (b) documented clinical success rate with TIMI II or III flow attained in > 90% of patients without emergency CABG, stroke, or death; (c) emergency CABG rate < 5% among all patients undergoing the procedure; (d) actual performance of PTCA in a high percentage (85%) of patients brought to the laboratory; and (e) mortality rate < 12%. Otherwise, the focus of treatment should be the early use of thrombolytic therapy."

References

1. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349-360.

2. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343:311-22.

3. Berger PB, Bell MR, Holmes DR Jr, Gersh BJ, Hopfenspirger M, Gibbons R. Time to reperfusion with direct coronary angioplasty and thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1994; 73:231-236.

4. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329:673-682.

5. Lange RA, Hillis LD. Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? Thrombolysis -- the preferred treatment. N Engl J Med 1996; 335:1311-1312.

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

7. Grupo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Lancet 1990; 336:65-71.

8. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group: ISIS-3. A randomized comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992; 339:753-770.

9. Muller DWM, Topol EJ. Selection of patients with acute myocardial infarction for thrombolytic therapy. Ann Intern Med 1990; 113: 949-60.

10. 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.

11. Grines CL. Primary angioplasty - the strategy of choice. N Engl J Med 1997; 335:1313-5.

12. Meijer A, Verheugt FWA, Werter CJPJ, Lie KI, van der Pol JMJ, van Eenige MJ. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study; results of the APRICOT Study. Circulation 1993;87:11524-30.

13. Flaker GC, Webel RR, Meinhardt S, Anderson S, Santolin C, Artis, et al. Emergency angioplasty in acute anterior myocardial infarction. Am Heart J 1989; 118:1154-60.

14. Marco J, Caster L, Szatmary LJ, Fajadet J. Emergency percutaneous transluminal coronary angioplasty without thrombolysis as initial therapy in acute myocardial infarction. Int J Cardiol 1987; 15:55-63.

15. Ellis SG, O'Neill WW, Bates ER, Walton JA JR, Nabel EG, Werns SW, et al. Implications for patient 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.

16. Rothbaum DA, Linnemeier TJ, Landin RJ, Steinmetz EF, Hillis JS, Hallam CC, et al. Emergency percutaneous transluminal coronary angioplasty in acute myocardial infarction: A 3 year experience. J Am Coll Cardiol 1987; 10:264-72.

17. Brodie BR. Primary angioplasty in a community hospital in the USA: insights into advantages and limitations. Br Heart Jl 1995;73:411-3.

18. Bittl JA. Indications, timing, and optimal technique for diagnostic angiography and angioplasty in acute myocardial infarction. Chest 1991; 99:150S-6S.

19. O'Keefe JH JR, Bailey WL, Rutherford BD, Hartzler GO. Primary angioplasty for acute myocardial infarction in 1000 consecutive patients: results in an unselected population and high-risk subgroups. Am J Cardiol 1993;72:107G-15G..

20. Beauchamp GD, Vacek JL, Robuck W. Management comparison for acute myocardial infarction: Direct angioplasty versus sequential thrombolysis angioplasty. Am Heart J 1990; 120:237-42.

21. Grines CK, Meany TB, Weintraub R, Strzelecji M, Cragg DR, Timmis GC, et al. Streptokinase angioplasty myocardial infarction trial: Early and late results [abstr]. J Am Coll Cardiol 1991; 17:336A.

22. Williams DO, Holubkov AL, Detre KM, Hommes DR, Kent KM. Impact of pretreatment by thrombolytic therapy upon outcome of emergent direct coronary angioplasty for patients with acute myocardial infarction [abstr]. J Am Coll Cardiol 1991; 17:337A.

23. 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.

24. Zijlstra F, Jan de Boer M, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata. Comparison of direct coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med. 1993; 328: 680-4

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

26. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al. A comparison of primary angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993; 328: 673-9.

27. Zijlstra F, Jan de Boer M, Ottervanger JP, Liem AL, Hoorntje JCA, Suryapranata H. Primary coronary angioplasty versus intravenous streptokinase in acute myocardial infarction: differences in outcome during a mean follow-up of 18 months. Cor Art Dis 1994;5:707-12.

28. Stone GW, Grines CL, Rothbaum D, et al. Analysis of relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: The Primary Angioplasty in Myocardial Infarction (PAMI) trial. J Am Coll Cardiol 1997; 29:901-7.

29. Ribeiro EE, Silva LA, Carneiro R, et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1993; 22:376-380.

30. Every NR, Parsons LS, Hlatky M, Martin JS, Weaver WD, for the Myocardial Infarction Triage and Intervention Investigators. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. N Engl J Med 1996; 35:1253-1260.

31. Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. Ann Intern Med 1991; 115:173-177.

32. Zijlstra F, Beukema WP, van't Hof AWJ, Liem A, Reiffers S, Hoorntje JCA, Suryapranata H, de Boer M-J. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908-12.

33. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. J Am Coll Cardiol 1996; 29:1328-428.