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Primary Angioplasty for Treatment of Acute Myocardial Infarction

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This is to acknowledge that Dr. Keeley has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Keeley will be discussing off-label uses in her presentation.

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Clinical and research interests:

As an interventional cardiologist, my clinical interest is in percutaneous revascularization treatments of acute coronary syndromes, particularly catheter-based reperfusion strategies for the treatment of ST segment elevation myocardial infarction. My research interests include studying the role of inflammation in acute coronary syndromes, and the genetic predispositions that result in these syndromes.

Introduction. In the late 1970's, acute myocardial infarction (AMI) was determined to be, in nearly all cases, the result of a ruptured atherosclerotic plaque causing thrombosis and occlusion of the coronary artery (1). Soon thereafter, the reperfusion era was ushered in with the use of intracoronary, and later intravenous, thrombolysis. The widespread use of thrombolytic therapy in the early 1980's revolutionized the management of AMI from mostly supportive to one of active intervention directed at restoring antegrade blood flow in the infarct-related artery, salvaging myocardium, and decreasing mortality (2). Percutaneous transluminal coronary angioplasty (PTCA) as reperfusion therapy for AMI also had its origin in the early 1980's and became popular in the 1990's. Although this strategy is not as widely available as intravenous thrombolytic therapy, it provides an alternative for patients who are not suitable candidates for thrombolysis and is the preferred treatment strategy in several patient populations. The ultimate goal of therapy for AMI is to 1) provide aspirin, and 2) achieve rapid re-establishment of blood flow in the infarct-related artery either by administering thrombolytic therapy or by performing primary PTCA. The topic of this discussion will be primary PTCA. Primary PTCA is defined as balloon angioplasty undertaken as the primary reperfusion strategy for AMI without prior or concomitant thrombolytic therapy.

Pathophysiology of AMI. Coronary atherosclerosis progresses in a linear fashion over a period of many years (3). Rapid growth of coronary lesions is largely due to thrombosis that occurs at sites of plaque rupture. Even though severely stenotic lesions are more likely, over time, to progress to total occlusion, the majority of AMI evolve from coronary arteries that were deemed to have only mild to moderate, non-flow-limiting stenoses.

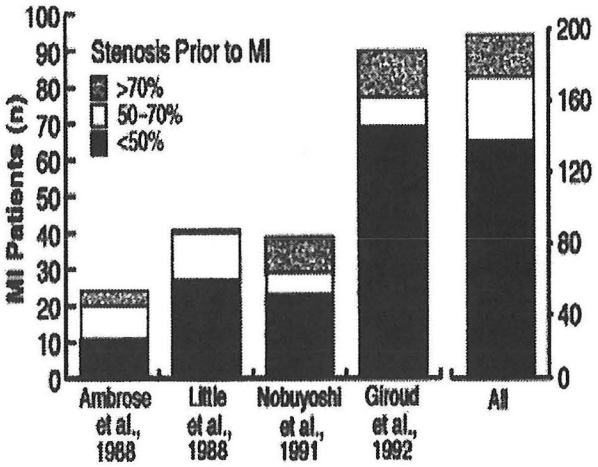

Figure 1. Moderate arterial stenoses are more likely associated with AMI (3).

Slowly developing high-grade stenoses of coronary arteries may progress to complete occlusion without precipitating AMI, because they stimulate the development of a rich collateral network over time. The rapid transition of a mildly stenotic lesion to total occlusion, however, results in a clinical event because protective collaterals do not have time to develop. During the development of an atherosclerotic plaque, an abrupt transition may occur, characterized by plaque rupture. Histological studies have

demonstrated certain characteristic features which make plaques more vulnerable to disruption. Compared with stable plaques, vulnerable plaques have: 1) a large, soft lipid core, 2) a thinned-out fibrous cap, 3) active infiltration by inflammatory cells into the plaque and fibrous cap, and 4) increased neovascularization (4).

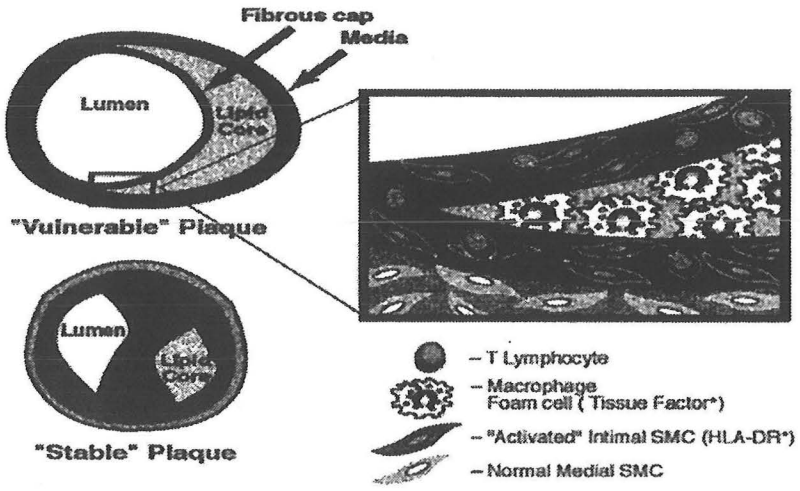

Figure 2. Features of the vulnerable plaque (3)

Inflammatory cells, such as macrophages, mast cells, and T-lymphocytes cause either decreased matrix synthesis or increased matrix degradation by macrophage-derived matrix metalloproteinases (4,5). The result is further thinning of the fibrous cap, which is more vulnerable to disruption. A variety of local mechanical and hemodynamic forces subject coronary plaques to constant stress that may "trigger" disruption of vulnerable plaques, particularly at their point of greatest weakness -- the shoulder region of the fibrous cap (6). After a plaque ruptures, the degree of thrombosis depends on the amount of stenosis caused by the disrupted plaque, the degree of endothelial dysfunction and blood flow disturbances, and the systemic thrombotic-thrombolytic milieu (4). At the site of rupture, platelets adhere to the arterial subendothelium and form a monolayer through the simultaneous interaction of von Willebrand factor protein and glycoprotein Ib that bind to collagen within the subendothelium (7). Binding to arterial subendothelium activates platelets. This leads to both a shape change from a smooth discoid form to a spiculated form, and degranulation of the alpha and dense granules, releasing platelet aggregatory and chemoattractant factors. The glycoprotein IIb/IIIa molecule is also activated, and undergoes a conformational change, developing a high affinity for fibrinogen (7). Fibrinogen facilitates platelet cross-linking, creating a growing platelet aggregate. Degranulated platelets release adenosine diphosphate (ADP), which binds to receptors on the surface of neighboring platelets, initiating an amplification process resulting in their activation and degranulation. Activation of cyclooxygenase in platelets converts arachidonic acid to thromboxane A2, which binds to receptors, and also activates neighboring platelets (5). The result of all these processes is the creation of platelet aggregates. Lastly, tissue factor, which is present in the lipid-rich core, initiates the

coagulation cascade and thrombin generation when extruded into circulating blood at the time of plaque rupture (8). The end product is a coronary thrombus consisting of aggregated platelets, cross-linked fibrin strands, and entrapped red blood cells (9). The enlarging thrombus may interrupt blood flow and lead to an imbalance between oxygen supply and demand and, if this imbalance is severe and persistent, to myocardial infarction and necrosis.

The reperfusion era. The reperfusion era began more than 20 years ago with the seminal work of Rentrop and colleagues in 1979 (10), who demonstrated that an occlusive thrombus in a coronary artery could be managed successfully by using the combination of a guidewire (a thin, 0.014" stainless steel wire advanced into the coronary artery over which a balloon catheter may be passed to perform balloon angioplasty) to mechanically initiate coronary blood flow and the intracoronary infusion of the thrombolytic agent, streptokinase, to restore complete flow.

The recognition that prompt resolution of the thrombus salvages myocardium, reduces infarct size, and prolongs life has been the driving force behind a large number of clinical trials evaluating thrombolytic therapy for AMI. The results of these trials, performed in the early 1980's and involving tens of thousands of patients, consistently and unequivocally showed that thrombolytic therapy resulted in preserved left ventricular function and decreased mortality in patients with AMI. While mortality rates in patients with AMI have fallen primarily due to the use of thrombolytic therapy, earlier diagnosis and treatment, improved management of complications such as recurrent ischemia, heart failure, and arrhythmias, the increased use of adjunctive pharmacologic therapy such as aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors have also played significant roles.

Limitations of thrombolytic therapy. Although thrombolytic therapy has been the mainstay of treatment for AMI, it has well-documented limitations. *First*, there are both absolute and relative contraindications to administering thrombolytic therapy. Due to these actual or perceived contraindications, most patients who present with AMI do not, in practice, receive thrombolytic therapy.

These "ineligible" patients are disproportionately women and the elderly who have a history of prior MI, multivessel coronary disease, and lower ejection fractions (11). As expected, these patients have significantly higher in-hospital mortality rates.

Second, with current thrombolytic regimens, coronary artery patency is restored in about 85% of patients with AMI, with only half of these patients

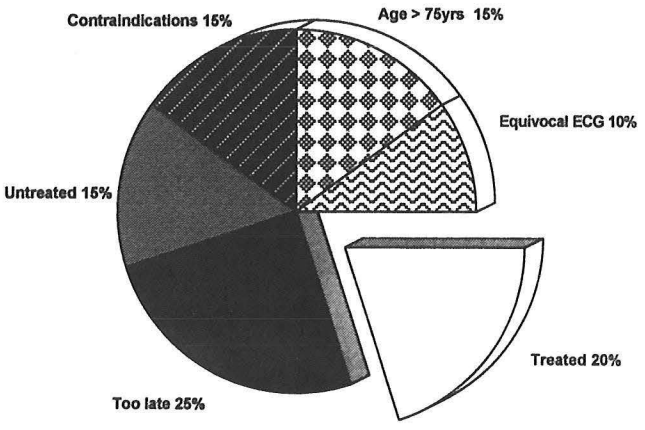

Figure 3. Eligibility for thrombolytic therapy

actually achieving complete myocardial reperfusion, angiographically defined as Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery. The TIMI flow grading system, devised in the TIMI 1 trial (12), is defined as the following:

TIMI grade 0	complete occlusion of the infarct-related artery
TIMI grade 1	some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed
TIMI grade 2	perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery
TIMI grade 3	full perfusion of the infarct vessel with normal flow

Table 1: Definition of TIMI flow (12)

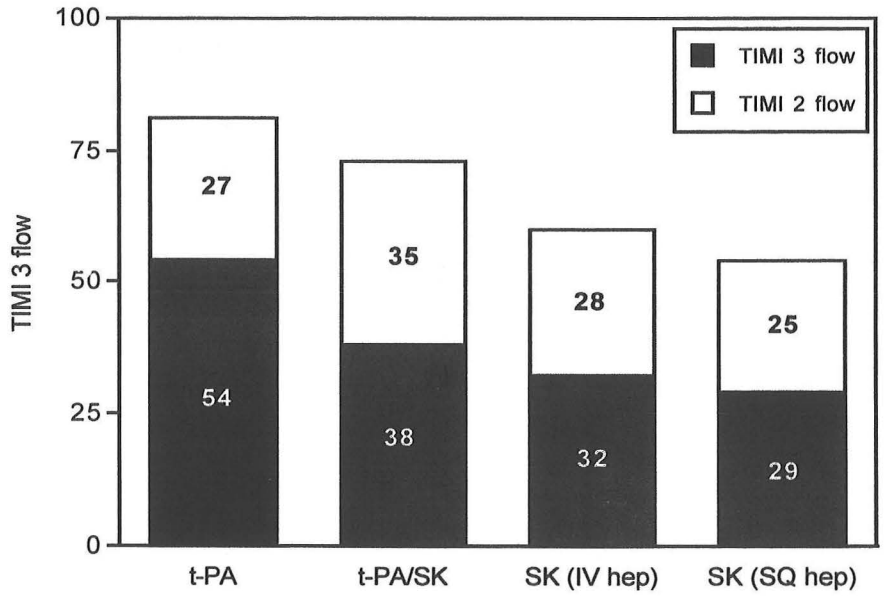

Figure 4. TIMI flow rates achieved by different reperfusion therapies (44)

The achievement of TIMI grade 3 flow is important because greater myocardial salvage and improved short- and long-term survival have been observed in patients with documented TIMI grade 3 flow compared to lesser degrees of TIMI flow.

Thrombolytic therapy's suboptimal ability to provide TIMI grade 3 flow is due, in part, to its mechanism of action: The term "thrombolytic" is, in fact, a misnomer, since it implies dissolution of the thrombus (a platelet aggregate stabilized by fibrin with entrapped red blood cells). A better description is "fibrinolytic", since the principal mechanism is the lysis of fibrin (9). When this occurs, the exposed thrombin not only

promotes the formation of more thrombin, but it is the most potent stimulus for platelet aggregation.

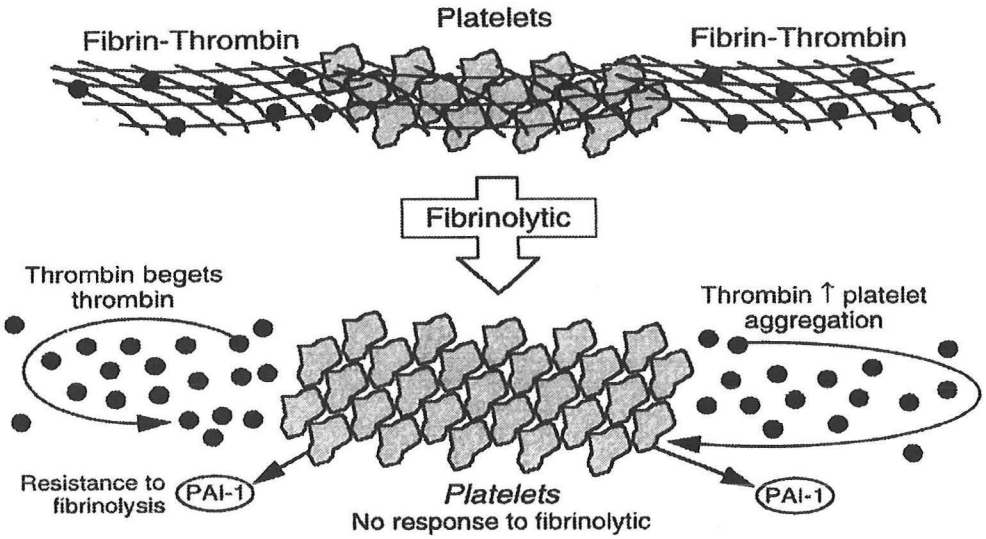

Figure 5. Prothrombotic effects of fibrinolytic therapy (9).

The platelet aggregate at the core of a coronary thrombus is resistant to thrombolytic therapy, and is one possible explanation as to why patients who present later after the onset of symptoms (who are more likely to have large platelet aggregates within the core of the thrombus) are relatively resistant to thrombolytic agents.

Third, patients who receive thrombolytic therapy have a 30% incidence of infarct-related artery reocclusion, reinfarction, or both within the subsequent three months. These major adverse cardiac events are associated with increased mortality (13).

Fourth, thrombolytic therapy is associated with increased risk of bleeding complications, including intracranial hemorrhage, which ranges from 0.3% to 2.0% in major randomized trials resulting in death or disabling stroke (2).

Age (yrs)	Number of patients	Major bleeding	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%

Table 2. Rate of bleeding complications in thrombolytic therapy (2)

In summary, the limitations of thrombolytic therapy include:

1) "Ineligibility" due to actual or perceived contraindications to its administration
2) Suboptimal patency rates and achievement of TIMI grade 3 flow
3) Risk of recurrent occlusion of the infarct-related artery and recurrent infarction
4) Risk of intracranial bleeding, particularly in the elderly population

Early work. It is because of these shortcomings primary PTCA has been studied and popularized. O'Keefe and colleagues in Kansas City, Missouri were the initial group credited with applying primary PTCA for AMI (14). Their results were excellent, but it was realized early on that the majority of patients with AMI do not present to hospitals that have an emergency on-call team to perform primary PTCA. Therefore, it seemed that initial thrombolysis followed by immediate PTCA would be a reasonable combined strategy. After encouraging pilot studies, randomized trials showed higher mortality rates, increased reinfarction rates, and increased need for emergency bypass surgery with this combination approach (15-17). The reasons were unclear at the time, but the discrepant findings compared with primary PTCA alone (without antecedent thrombolytic therapy) raised the possibility that thrombolysis itself lead to a prothrombotic state making PTCA in this milieu unfavorable. This set the stage for the randomized trials directly comparing thrombolytic therapy to primary PTCA.

Randomized trials of primary PTCA versus thrombolytic therapy. Primary PTCA has been compared to thrombolytic therapy in 10 randomized trials of AMI. I will review the three largest trials in detail, and then discuss results of a meta-analysis comparing all 10 trials.

Grines and colleagues (18), in the first Primary Angioplasty in Myocardial Infarction (PAMI-1) trial, randomized 395 patients within 12 hours of the onset of AMI to primary PTCA (195 patients) or conventional t-PA (200 patients). The primary endpoint was recurrent ischemia, death and serious bleeding complications. A post-hoc analysis grouped patients according to "low risk" or "not low risk" (defined as those with an anterior infarction, > 70 years old, or a heart rate > 100 beats per minute). After randomization, it required an average of 32 +/- 22 minutes to start the t-PA infusion and 60 +/- 41 minutes to perform angiography and subsequent PTCA (p=0.001). The two groups were closely matched in terms of baseline characteristics. The angioplasty success rate was 97%, and no patient required emergent coronary artery bypass surgery because of a failed PTCA. Intracranial bleeding occurred more frequently among patients who received t-PA than those who underwent PTCA (2.0% versus 0.0% p=0.05).

By six months, death had occurred in 3.7% of patients treated with PTCA and 7.9% in those treated with t-PA (p=0.08), and either death or nonfatal reinfarction had occurred in 8.5% and 16.8%, respectively (p=0.02). Compared to t-PA therapy for AMI, primary PTCA reduced the combined occurrence of nonfatal reinfarction or death, and was associated with a lower rate of intracerebral hemorrhage.

The PAMI investigators obtained clinical follow-up on all 395 patients at two years (19). Patients who underwent primary PTCA had less recurrent ischemia (36.4% versus 48%, p=0.026), lower reintervention rates (27.2% versus 46.5%, p<0.0001), and reduced hospital readmission rates (58.5% versus 69.0%, p=0.035). The combined

endpoint of death or reinfarction was 14.9% for primary PTCA versus 23% for t-PA (p=0.034). Multivariate analysis found primary PTCA to be independently predictive of a reduction in death, reinfarction or target vessel revascularization (p=0.0001). Thus, the initial benefit of primary PTCA performed by experienced operators was maintained over a 2 year follow-up period with improved infarct-free survival and reduced rates of reintervention.

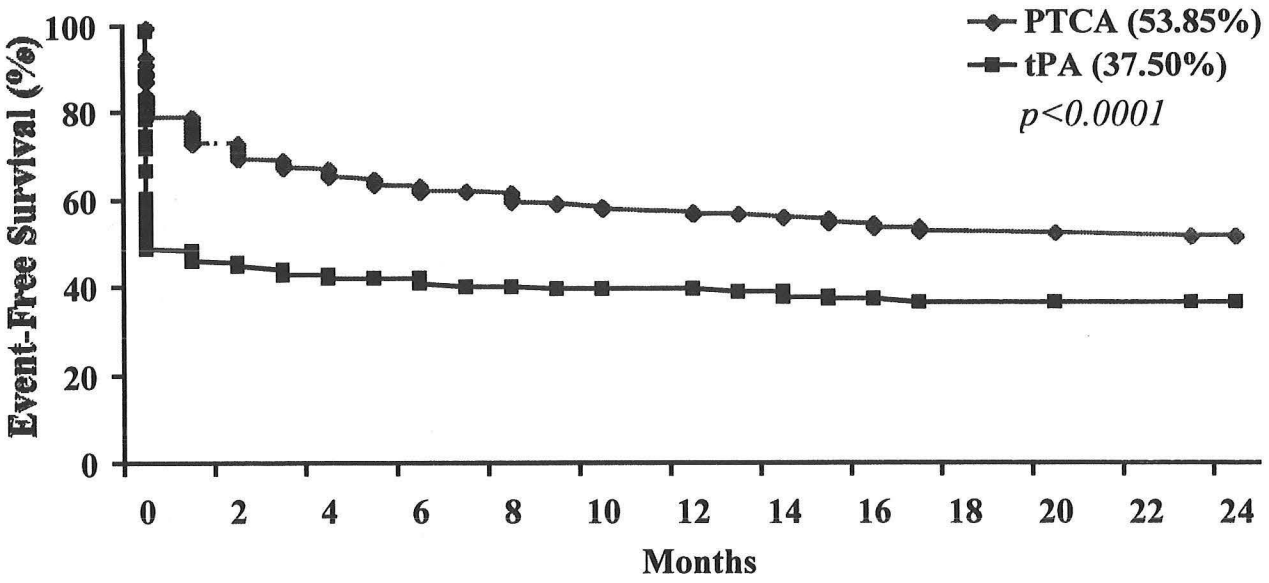

Figure 6. Long-term follow-up PAMI-1 trial (19)

During the same time period of the PAMI-1 trial, Zijlstra and colleagues from the Netherlands performed a prospective, randomized trial comparing primary PTCA with intravenous streptokinase in patients presenting with ST segment elevation within 6 hours of onset of symptoms (20). A total of 142 patients were randomized, 72 patients received streptokinase, and 70 patients underwent primary PTCA. The primary endpoint was rate of recurrent ischemia, left ventricular function and vessel patency. The mean time from admission to start of streptokinase infusion was 30 +/- 15 minutes. The mean time from admission to balloon inflation in those randomized to PTCA was 61 +/- 22 minutes. Success rate for primary PTCA was 98%. In-hospital recurrent ischemia occurred in 27 patients (38%) who received streptokinase, but in only 6 patients (9%) who underwent primary PTCA, p<0.001. Left ventricular ejection fraction was 45 +/-12 % in the streptokinase group and 51 +/- 11% in the primary PTCA group (p=0.004). At 2 month follow-up angiography, the infarct-related artery was patent in 68% of patients who received streptokinase and 91% of those randomized to primary PTCA (p=0.001).

In summary, these investigators showed that primary PTCA was associated with a higher patency rate, better left ventricular function, and less recurrent myocardial ischemia and infarction compared to streptokinase therapy.

These investigators continued to enroll patients in this study for an additional two years. Subsequently, they published a follow-up study consisting of a total of 395 patients randomized to either primary PTCA (194 patients) or streptokinase (201 patients) (21). The clinical characteristics of the two groups were similar with respect to age, gender, infarct location, presence or absence of a previous myocardial infarction, multivessel coronary artery disease, and diabetes. Patency of the infarct-related artery was analyzed in all patients who survived to the time of follow-up angiography: 191 in the PTCA group, and 196 in the streptokinase group. The infarct-related artery was patent in a greater proportion of patients in the primary PTCA group compared to the streptokinase group -- 90% in the primary PTCA group, versus 65% in those treated with streptokinase ($p<0.001$). The proportion of patients with depressed left ventricular ejection fractions of <40% was higher in the streptokinase group compared to the PTCA group (26% versus 14% respectively, $p=0.006$). At long-term follow-up, 5 +/- 2 years, overall survival was higher in those patient who underwent primary PTCA (=0.01), and the combined incidence of death and nonfatal reinfarction was lower in the PTCA group compared to the streptokinase group ($p<0.001$).

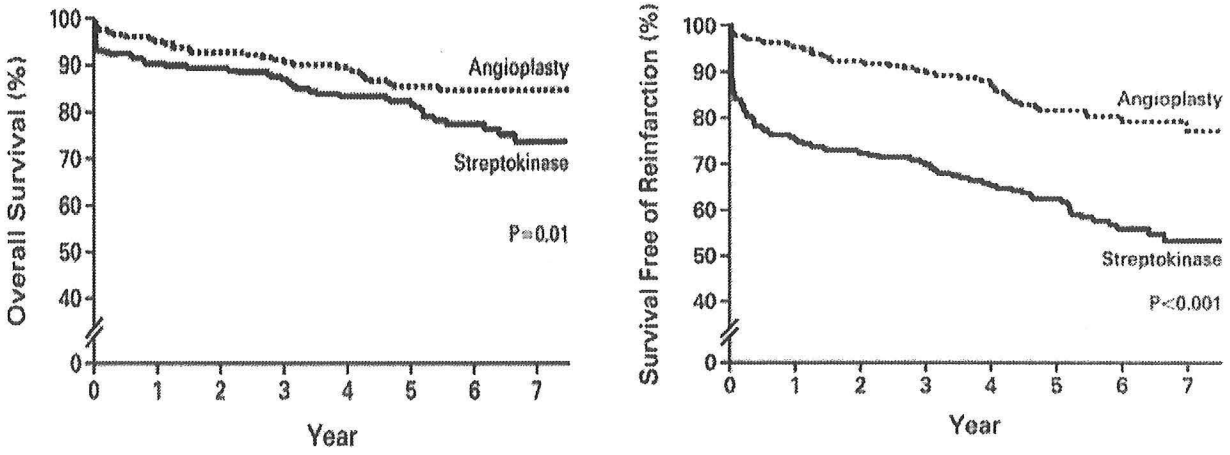

Figure 7. Long-term follow-up Netherlands trial (21).

The largest prospective, randomized trial of primary PTCA versus thrombolytic therapy for AMI was the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb substudy (22). In this study, 1,138 patients with ST segment elevation were randomized to either primary PTCA (573 patients) or accelerated, "front-loaded" t-PA (565 patients) within 12 hours after onset of symptoms. Patients who were randomized to PTCA underwent the first balloon inflation at a median of 80 minutes. The primary endpoint was a composite of death, nonfatal MI or nonfatal disabling stroke at 30 days. This endpoint was reached in 13.7% of the t-PA patients and 9.6% of the primary PTCA group ($p=0.03$). Intracranial bleeding occurred in 1.4% of the t-PA group and 0% of the

primary PTCA group (p=0.004). Overall, there was a benefit at 30 days with primary PTCA with respect to the primary combined endpoint of death, reinfarction and disabling stroke.

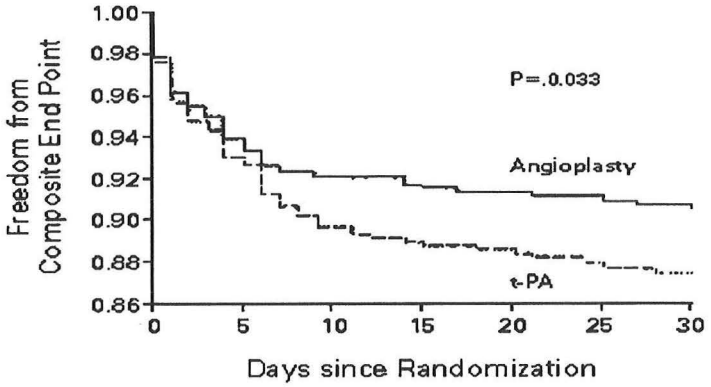

Figure 8. 30-day clinical outcome from the GUSTO IIb substudy (22).

In addition to these 3 large trials, 7 smaller studies have compared primary PTCA to thrombolytic therapy in the treatment of AMI. I will summarize the results of a meta-analysis of these 10 randomized trials (23). It must be noted that there was a marked heterogeneity in the designs of the various trials with respect to the thrombolytic agent used, the dosing of the thrombolytic agent, and the dosing and duration of concomitant heparin infusion. In addition, these trials are modest in size with the largest trial, as discussed above, GUSTO IIb substudy enrolling 1,138 patients. Because of the differences it is helpful to review the trials in three groupings, streptokinase, conventional t-PA, and accelerated t-PA. When considering death or nonfatal AMI, there was a gradient effect with an absolute risk reduction of 7.4% for streptokinase, 4.8% for conventional 3-hour t-PA, and 3.3% for accelerated t-PA. The overall reduction in the combination of death or nonfatal reinfarction was 11.9% for thrombolytic therapy versus 7.2% for primary PTCA (p<0.001). This gradient of benefit follows the established potency of the thrombolytics, with the least difference of primary PTCA versus accelerated, "front-loaded" t-PA. Mortality was decreased with primary PTCA (4.4% for primary PTCA versus 6.5% with thrombolytic therapy, p=0.02). Overall, this translated into an absolute benefit of two lives saved per 100 patients treated with primary PTCA compared with thrombolysis. In addition, primary PTCA was associated with a significant reduction in total stroke (2.0% with thrombolysis, 0.7% with primary PTCA, p=0.007), and hemorrhagic stroke (0.1% with primary PTCA versus 1.1% with thrombolysis, p<0.001). Based on the outcomes at hospital discharge or 30 days, primary PTCA was superior to thrombolytic therapy for treatment of patients with AMI.

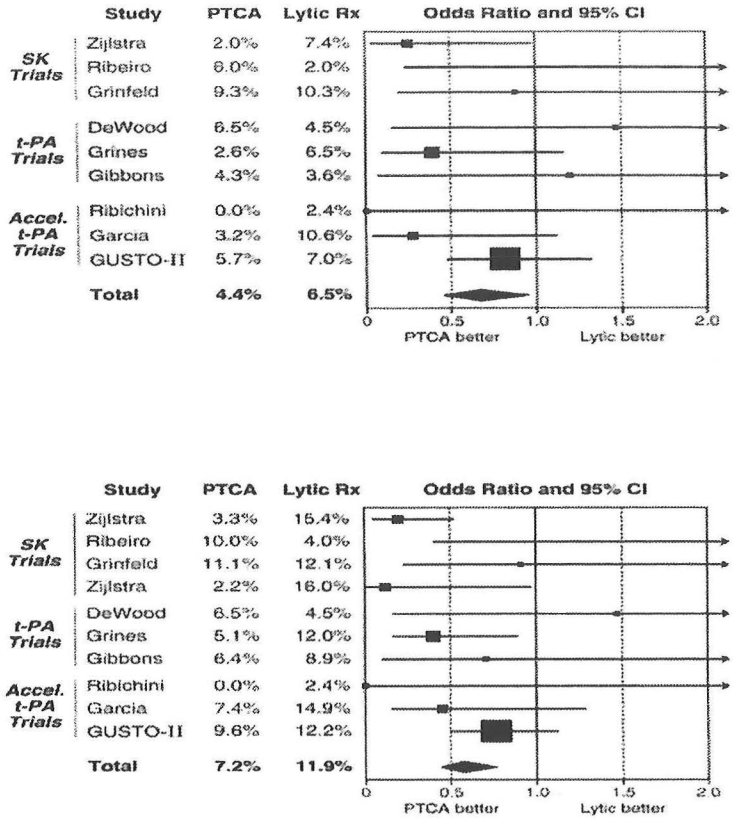

Figure 9. Results of a meta-analysis of major trials comparing primary PTCA with thrombolytic therapy in treatment of ST-elevation AMI (23). Top panel, mortality; bottom panel, mortality or non-fatal reinfarction.

In summary, to overcome the limitations of thrombolytic therapy, primary PTCA has been introduced as an alternative for the treatment of ST segment elevation AMI. Results of 10 prospective randomized trials performed by different investigators in different countries showed that compared with thrombolytic therapy, primary PTCA results in reduced rates of mortality, reinfarction, stroke, and more frequent restoration of TIMI grade 3 flow.

Selected patient populations. There are two subgroups of patients in whom primary PTCA has been shown to be superior to thrombolytic therapy:

1) Cardiogenic shock. In cardiogenic shock mortality exceeds 80% without reperfusion treatment. The recently published Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial was an unblinded, randomized controlled trial which enrolled patients with AMI who developed cardiogenic shock due to left ventricular failure within 36 hours of diagnosis of AMI (24). A total of 302 patients were randomized to emergency revascularization (152 patients) or "initial medical stabilization" (150 patients). Patients were randomly assigned to undergo emergency revascularization with either PTCA or coronary artery

bypass surgery, or to thrombolysis, and intra-aortic balloon counterpulsation. Emergency revascularization resulted in a 39% improvement in 1-year survival compared with aggressive medical stabilization. This translated into an absolute benefit of 132 lives saved for every thousand patients treated. The higher 1-year survival with emergency revascularization was consistent among subgroups with one notable exception. Patients < 75 years old derived a large benefit from early revascularization, in contrast to an apparent lack of benefit for those > 75 years or older. Based on the results of the SHOCK trial, the American College of Cardiology/American Heart Association revised guidelines to recommend emergency revascularization for patients younger than 75 years with cardiogenic shock within 36 hours of AMI (25).

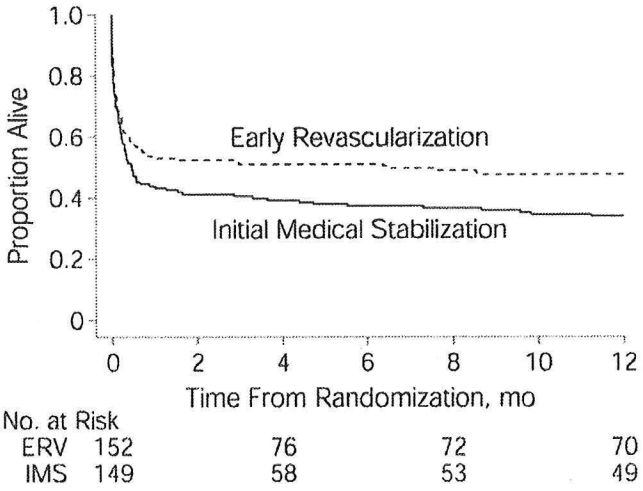

Figure 10. Survival rates for early revascularization vs. initial medical stabilization strategies for treatment of cardiogenic shock (24).

*2) **Elderly.*** The results of randomized clinical trials may be difficult to extrapolate to elderly patients, who are more likely to have extensive coronary artery disease, and comorbid conditions that may influence decisions about the appropriate reperfusion strategy. In the absence of conclusive evidence from randomized trials, data from observational studies reflect general practice in the community rather than care provided in highly specialized centers. The Cooperative Cardiovascular Project (CCP) was initiated by the Health Care Financing Administration as an ongoing national program to improve the quality of care for Medicare beneficiaries with ST segment elevation AMI. From this database, Berger et al analyzed the 30-day and 1-year survival of these patients (26). A total of 80,456 patients arrived within 12 hours of symptom onset and were eligible for reperfusion therapy. Of this cohort, 18,645 (23.2%) received thrombolytic therapy, 2,038 (2.5%) underwent primary PTCA, 59,673 (74.2%) did not receive reperfusion therapy within the first 6 hours, and 54,989 (68.4%) did not receive reperfusion therapy at any time. Berger's analysis included the 20,683 patients who received either form of reperfusion therapy, primary PTCA or thrombolytic therapy. Patients who underwent primary PTCA, in comparison with those who received thrombolytic therapy, had lower 30-day and 1-year mortality rates after adjustments for baseline characteristics. The lower mortality rates were observed in all subgroup

analyses, in both men and women, and independent of the hospital's volume of primary PTCA cases. Therefore, the survival advantage was not solely due to its performance in hospitals with clinical excellence in the management of AMI.

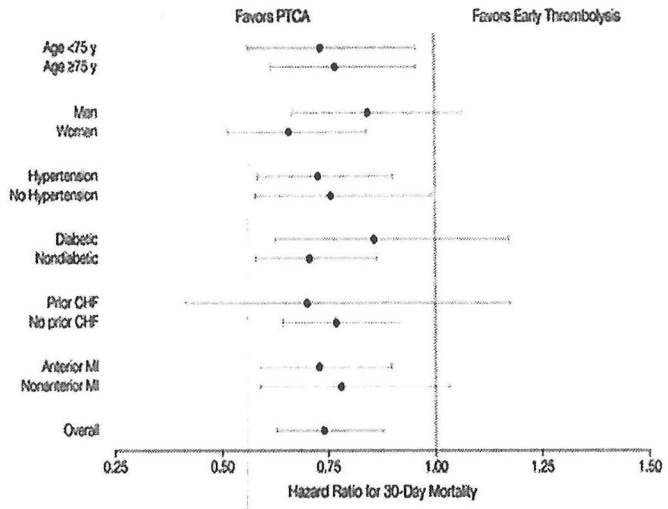

Figure 11. Benefit of primary PTCA on 30-day mortality according to subgroup (26).

Recently, another study using data from the CCP database comparing clinical outcomes following thrombolytic therapy, primary PTCA, or no reperfusion therapy for AMI was published (27). The cohort consisted of 37,983 patients 65 years or older who presented within 12 hours of symptom onset with ST segment elevation or left bundle branch block. A total of 14,341 (37.8%) received thrombolytic therapy and 1,599 (4.2%) underwent primary PTCA. After adjustment for demographic, clinical, hospital, and physician factors, primary PTCA was associated with a better 30-day survival rate compared to no reperfusion therapy, whereas thrombolytic therapy was not associated with a better 30-day survival compared with no therapy.

A retrospective study by Thiemann et al (28) analyzed 7,864 Medicare patients age 65 to 86 years who were admitted with AMI and were eligible for thrombolytic therapy. For patients 65 to 75 years old, thrombolytic therapy was associated with a survival benefit. Among patients 76 to 86 years old, however, thrombolytic therapy was associated with a 30-day mortality hazard ratio of 1.38 (C.I. 1.12 to 1.71, p=0.003). Thrombolytic therapy for patients > 75 years old did not confer a survival advantage.

Lastly, pooled data from two large registries from German prospective, multicenter, observational studies of the treatment of patients with ST segment elevation AMI-the Maximal Individual Therapy in Acute Myocardial Infarction trial (MITRA) and the Myocardial Infarction Registry (MIR) were analyzed to determine the value of primary PTCA compared to thrombolytic therapy in different subgroups of patients (29). A total of 9,906 lytic-eligible patients with AMI presenting within 12 hours of symptoms were treated with either primary PTCA (1,327 patients) or thrombolytic therapy (8,579 patients). They found that primary PTCA was superior to thrombolytic therapy across all subgroups: 6.4% mortality for primary PTCA versus 11.3% for thrombolytic therapy.

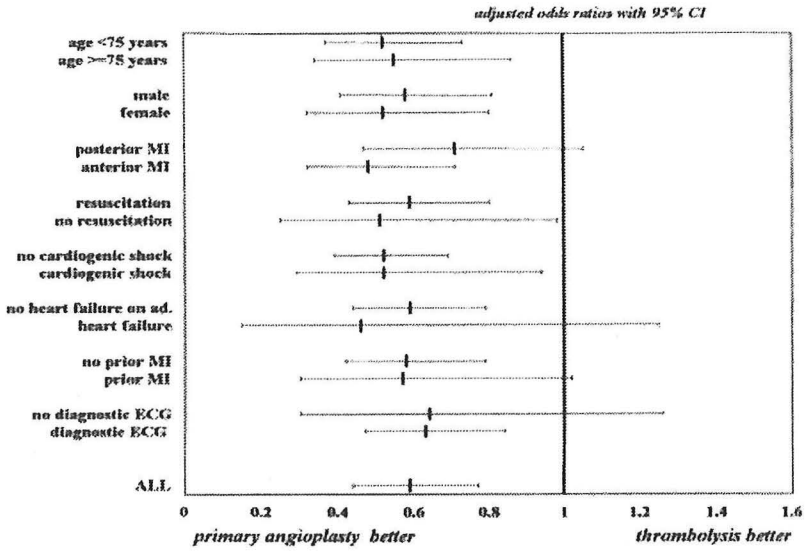

Figure 12. Multivariate analysis of hospital mortality for primary PTCA and thrombolytic therapy according to patient subgroups (29).

Other advantages of primary PTCA. In addition to its wider applicability, greater achievement of TIMI grade 3 flow, decreased reinfarction and reocclusion rates, and decreased incidence of intracranial bleeding, primary PTCA offers several additional advantages.

1) Primary PTCA affords the opportunity to assess coronary anatomy and obtain hemodynamic data. Patient management is facilitated by the knowledge of the coronary anatomy, allowing identification of a subgroup of patients that can be discharged within 3 days after the acute event (30), as well as the 5-10% of patients who have an indication for coronary artery bypass grafting, such as severe left main disease, or three vessel disease involving the proximal left anterior descending artery. Patients who should not undergo reperfusion therapy can quickly be identified by angiography; for example, patients with spontaneous reperfusion of the infarct-related coronary artery, or those with coronary vasospasm or a non-coronary condition such as myocarditis, that may mimic an AMI. Finally, patients with aortic dissection or coronary anatomy unsuitable for angioplasty can be considered for acute surgical intervention. These patients are few in number, but this treatment strategy has a disproportionate impact on their clinical outcome.

2) Primary PTCA is cost-effective. Analysis of detailed hospital charge data from the PAMI-1 trial showed that compared with t-PA, primary PTCA resulted in a shorter hospital stay (7.6 +/- 3.3 days versus 8.4 +/- 4.7 days, p=0.04). Despite the initial costs of cardiac catheterization in all patients with the invasive strategy, total mean hospital charges were $3,436 lower per patient treated with primary PTCA compared to those treated with t-PA ($23,468 +/- $13,410 versus $26,904 +/- $18,246, p=0.04). Since professional fees were higher after primary PTCA ($4,185 +/- 3,183 versus $3,322 +/- 2,728, p=0.001), however, the overall total costs were similar ($27,653 +/- 13,709 versus $30,227 +/- 18,903, p=0.21) (18).

The Netherlands investigators also analyzed the total medical charges per patient. Their cost analysis included the initial hospital stay, readmissions, procedures, physician charges, and medications. The costs in this study were similar as well ($16,090 in the primary PTCA group, and $16,813 in the streptokinase group, p=0.05) (21).

The second Primary Angioplasty in Myocardial Infarction (PAMI-2) trial evaluated the hypothesis that primary PTCA with subsequent discharge from the hospital 3 days later is safe and cost-effective in low-risk patients (30). Low risk patients (defined as age <70 years, left ventricular ejection fraction > 45%, one- or two-vessel disease, successful PTCA, no persistent arrhythmias) were randomized to receive either accelerated care (237 patients) with admission to a non-intensive care unit, and day #3 hospital discharge without noninvasive testing, or traditional care (234 patients) with monitoring in the coronary care unit, and pre-discharge stress-testing. Patients who received accelerated care had similar rates of mortality, recurrent ischemia, reinfarction, stroke, congestive heart failure, or their combined occurrence compared to those who received traditional care. Therefore, early identification of low risk patients with AMI allowed omission of the traditional intensive care phase and pre-discharge noninvasive testing, and a 3 day hospital discharge strategy. This resulted in substantial cost saving. Patients who received accelerated care were discharged three days earlier (4.2 +/- 2.3 versus 7.1 +/- 4.7 days, p=0.0001) and had lower hospital costs ($9,658 +/- 5,287 versus $11,604 +/- 6,125, p=0.002) compared to patients who received traditional care.

Intracoronary stenting in AMI. Coronary stenting is superior to conventional PTCA for the majority of patients with stable or unstable angina, and it is playing an increasing role in the treatment of patients with AMI (31). With improved stent deployment and use of oral antiplatelet agents including aspirin in conjunction with ADP antagonists such as clopidogrel, the risk of stent thrombosis in the setting of AMI has been substantially reduced

Several randomized trials (32-35) have been published evaluating the role of stenting in AMI, the largest of which is the Primary Angioplasty in Myocardial Infarction (PAMI) Stent Trial (36). This trial randomized 900 patients with an infarct-related native coronary artery suitable for stenting to PTCA or to PTCA followed by intracoronary stenting. At 6 months the composite endpoint of death, nonfatal AMI, disabling stroke, or target vessel revascularization was lower for the stent group, entirely driven by the decreased restenosis rates in the stent group. At 1-year, the composite endpoint remained significantly lower in the stent group.

The complementary effects of glycoprotein IIb/IIIa inhibition and stenting have been shown in elective percutaneous coronary interventions. Whether this combination is also beneficial in the AMI setting is an area of active research (37-40).

Current research in primary PTCA. In a recent paper by Stone and colleagues, the importance of achieving TIMI grade 3 flow is re-emphasized (41). Analyzing data from 2327 patients enrolled in 4 PAMI trials, the authors compared those who had spontaneous reperfusion with documented TIMI grade 3 flow on the angiogram before primary PTCA (375 patients) with those who had TIMI grade 0 to 2 flow (1,952 patients). Despite relatively similar baseline characteristics, those with spontaneous TIMI grade 3 flow had improved left ventricular function, lower rates of congestive heart failure, and lower mortality compared to those with lesser TIMI flows. In

addition, they observed that the procedural success was higher in patients with baseline TIMI 3 flow. Their observations reinforce the central goal of achieving TIMI grade 3 flow as early as possible in ST segment elevation AMI. Several trials have been published demonstrating the efficacy and safety of pharmacologically mediated reperfusion before percutaneous intervention (42-45). This strategy aims to achieve the earliest possible reperfusion, while maintaining the benefits of primary PTCA (46).

Institutional and operator volume. The results of primary PTCA are in part dependent on the setting in which it is performed, and therefore, the results from various hospitals may differ considerably. There is an inverse relationship between institutional volume and door to balloon time. More experienced sites and operators are more rapid in performing primary PTCA. Magid and colleagues compared outcomes among patients with AMI treated with primary PTCA versus thrombolytic therapy at hospitals with varying levels of experience with primary PTCA using the National Registry of Myocardial Infarction (NRMI) database (47). A total of 62,299 patients received reperfusion therapy (21,973 in the primary PTCA group, and 40,326 in the thrombolytic therapy group). At intermediate- and high- volume hospitals (defined as 17-48 primary PTCA's, and >49 primary PTCA's per year, respectively) mortality was lower among patients who received primary PTCA compared with those who received thrombolytic therapy. In contrast, the risk of death among patients treated with primary PTCA and thrombolysis at low-volume hospitals (defined as <16 primary PTCA's per year) was similar. However, patients treated with primary PTCA were less likely to have a nonfatal stroke or to undergo subsequent revascularization compared with those treated with thrombolytic therapy.

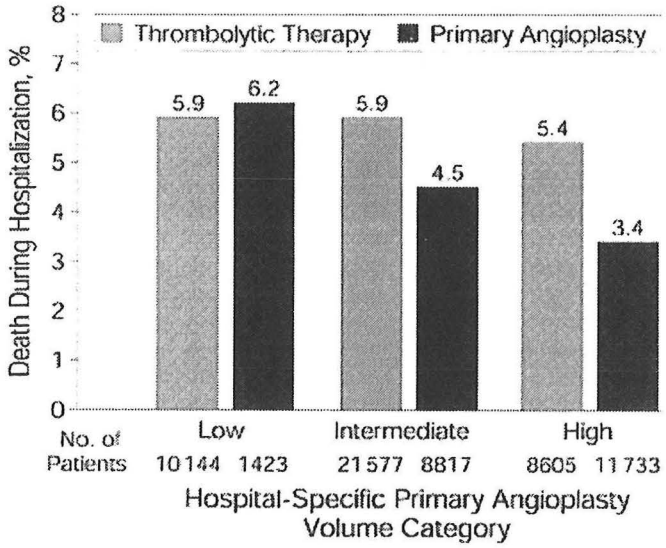

Figure 13. Association between reperfusion strategy and hospital primary PTCA volume (47).

In 1999, the American College of Cardiology/American Heart Association Guidelines on the Management of Acute Myocardial Infarction (25) stated that in institutions performing primary PTCA the following guidelines should be met:

1) Balloon dilation should occur within 90 +/- 30 minutes of the diagnosis of AMI,
2) TIMI 2 or 3 flow should be established in >90% of patients,
3) Emergency CABG rates should be <5%,
4) Primary PTCA should be performed in >85% of patients with an AMI brought to the catheterization laboratory with this diagnosis, and
5) Mortality rates should be <12%

Conclusions. The primary goal in treating patients with ST segment elevation AMI is achieving TIMI grade 3 flow as quickly as possible. All patients should be treated with aspirin followed by reperfusion therapy -- either thrombolytic therapy or primary PTCA. Primary PTCA, when available and performed by experienced operators, provides the following advantages over thrombolysis in all patients with ST segment elevation AMI:

- higher patency rates and TIMI 3 flow,
- less recurrent ischemia and infarction,
- less intracranial bleeding,
- earlier triage of patients to surgery when necessary,
- earlier hospital discharge,
- fewer hospital readmissions,
- similar or reduced cost.

In addition, primary PTCA reduces mortality in the elderly and in patients with cardiogenic shock.

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