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Thrombolysis or PTCA for Acute Transmural Myocardial Infarction

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Introduction

Early and sustained infarct related artery (IRA) patency contributes to improved left ventricular function and outcome after myocardial infarction.[1,2] Both thrombolysis and percutaneous transluminal coronary angioplasty (PTCA) are well documented to achieve IRA patency during acute myocardial infarction. Angiographic studies of tissue plasminogen activator (tPA) for acute myocardial infarction demonstrate IRA patency rates of up to 90%.[3,4,5] PTCA has been shown to substantially improve IRA patency and TIMI 3 flow with rates between 89-95%.

Early trials comparing primary PTCA with the use of thrombolysis for the treatment of acute myocardial infarction have shown superior IRA patency with PTCA, with reduced in-hospital and 6 week mortality and shorter hospital length of stay. Long-term mortality has not been adequately studied. A recent large scale retrospective analysis did not show any mortality benefit for primary PTCA over thrombolysis, both in-hospital and at long-term follow up of 3-4 years.[6] To achieve an understanding of which modality of achieving IRA patency is most beneficial, one must closely review the randomized control trials (RCT) that have been done to date.

Randomized Controlled Trials

Nine RCTs from 1986 to 1994 (two reported as abstract only) have addressed the issue of primary PTCA versus thrombolysis for the treatment of acute myocardial infarction, and are summarized in Table 1. The first study by O'Neill et al of 56 patients under 75 years of age who presented within 12 hours of chest pain onset, and at least 2mm of ST elevation were randomized to receive either intracoronary SK or primary PTCA.[7] Although the two groups angiographically had equal efficacy in achieving reperfusion, the PTCA group had a reduced

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number and extent of residual stenoses, less pre-discharge scintigraphic evidence of ischemia, and a greater improvement in ejection fraction by contrast ventriculography. However, the two groups had no difference in reinfarction rates, death, or post-MI angina. DeWood et al in 1989 studied 36 patients who presented with early Q-wave myocardial infarction less than 6 hours after chest pain onset and were randomized to receive either dual chained tPA or primary PTCA.[8] Although there was no difference in 90 minute patency rates, this study demonstrated a lesser degree of residual stenoses in the primary PTCA group. No difference was demonstrated in mortality or rest and peak ejection fraction 6 weeks after the initial event.

In the same issue, the New England Journal of Medicine published three well performed randomized trials of thrombolysis versus primary PTCA.[9,10,13] Gibbons et al randomized 108 patients with either ST elevation or at least 2mm of precordial ST depression within 12 hours of chest pain onset to either double chain tPA or primary PTCA.[9] There was no difference between the groups for the primary endpoint: myocardium at risk and final infarct size as assessed by nuclear imaging. As well, the secondary endpoints of left ventricular ejection fraction (LVEF), recurrent infarction, and six month mortality were not statistically different. However, there was a trend towards lower costs in the PTCA group attributed to shorter length of stay and fewer readmissions.

Zijlstra et al studied 142 patients less than 76 years of age who presented with ST elevation within 6 hours of chest pain onset (or 6-24 hours if there was evidence of ongoing ischemia).[10] These patients were randomized to either SK or primary PTCA. The PTCA group had lower rates of unstable angina and recurrent myocardial infarction and had higher LVEF at rest pre-discharge. Follow up angiography was performed in both groups and revealed a much higher patency rate in the angioplasty group (91% versus 68%, p=0.001). However, secondary endpoints of in-hospital mortality, stroke, and need for bypass surgery, were not different between the two groups. Thus, an additional 159 patients were

TABLE 1

	Short-term Mortality (%)		**Long-Term Mortality (%)**	
	PTCA	Thrombolysis	PTCA	Thrombolysis
O'Neill (n=56)	6.9	3.7	n/a	n/a
DeWood (n=90)	6.5		8.7	4.5
PAMI (Grines) (n=395)	2.6	6.5	14.4	21
Zijlstra/deBoer (n=301)	2	7	5	11
Gibbons (n=103)	4.3	3.6	6.4	3.6
Ribeiro (n=100)	6	2	6	4
Elizaga (n=100)	5.8	14.6	5.8	16.7
Gusto IIb (n=1138)	5.7	7	n/a	n/a
Every (n=3211)	5.5	5.6	13.6	12

randomized into this trial and the results were published in 1994.[11] This subsequent study showed a significant reduction of in-hospital and 31 month mortality as well as the combined endpoint of 31 month mortality and non-fatal myocardial infarction for the patients in the primary PTCA group.[12]

Grines et al published the PAMI (Primary Angioplasty in Myocardial Infarction) study,[13] the largest study at the time, randomizing 395 patients of all ages who presented with ST elevation within 12 hours of chest pain onset. Patients were randomized to either tPA or primary angioplasty. The success rate of angioplasty was 97%, not including 20 of 195 patients in the angioplasty arm who were excluded from receiving PTCA because of an unsuitable or high risk lesion. There was no difference between the two groups of patients in the development of congestive heart failure, hypotension, predischarge LVEF, or rate of coronary artery bypass surgery. The PTCA group had earlier resolution of chest pain (290min vs. 354min, p=0.004), less recurrent ischemia (10.3% vs. 28%, p<0.001), a trend towards reduced in-hospital mortality (2.6% vs. 6.5%, p=0.06), a reduction in the combined endpoint of non-fatal MI and death (5.1% vs. 12%, p=0.02), and reduced hospital length of stay (7.5d vs. 8.4d, p=0.03). Long-term results demonstrated a trend towards reduced 6 month (3.7% vs. 7.9% p=0.08) and 2 year (14.4% vs. 21%, p=0.07) mortality. Further substudies suggested that PTCA had a definite in-hospital survival benefit in patients presenting with anterior wall infarction (1.4% vs. 11.9%, p=0.01). Post-hoc stratification of patients into high risk and low risk groups based on presence of anterior infarction, age >70 years, and baseline heart rate >100 beats per minute, showed a substantial mortality reduction in the high risk population (2% vs. 10.4%, p=0.01).

A further trial of 100 patients (Ribeiro) under the age of 75 who presented with ST elevation within 6 hours of chest pain onset were randomized to SK versus primary PTCA, with angiography to follow 48 hours after the initial intervention.[14]

Angiography revealed no difference between the two groups in the achievement of TIMI 2 or 3 flow (74% vs. 80%). Analysis of secondary endpoints failed to show a difference between the two groups in mortality or improvement in LVEF.

A meta-analysis of the trials presented above was published by Michels and Yusuf in 1995.[15] They looked at crude data from 7 trials including abstracts and found that although there was a mortality reduction at 6 weeks for patients having primary PTCA (3.7% vs. 6.4%, odds ratio 0.56, 95% CI (0.33-0.94)), this mortality benefit was not persistent at 1 year (6.7% vs. 7.1%, odds ratio 0.91, 95% CI 0.42-2.0)). Additionally, primary PTCA did not show a reduction in the combined endpoint of non-fatal MI and death at 1 year (9.2% vs. 10.1%, odds ratio 1.00, 95% CI 0.14-7.[16])). Although the 1 year data was not optimal in all cases, this meta-analysis suggested that perhaps primary PTCA was not as superior to thrombolysis as once thought. Indeed, the authors concluded that evidence to support primary PTCA in all patients presenting with acute myocardial infarction was marginal at best. Additionally, these trials were performed in highly specialized centres, making generalizability of the results more difficult.

Does GUSTO IIb Answer the Question?

Obviously, one would hope that a large scale, multicentred, international trial of primary PTCA versus

thrombolysis would better answer the question of optimal intervention. The GUSTO IIb Angioplasty substudy analyzed data from 1138 patients who received either primary PTCA (565 patients) or tPA (573 patients). There was no difference between the groups for 30 day mortality (tPA 7%, PTCA 5.7%, p=0.37), or recurrent myocardial infarction (tPA 6%, PTCA 4.4%, p=0.24); however, an analysis of combined endpoints of death, recurrent MI, or stroke, showed a trend favoring primary PTCA (9.6% vs. 13.1%, p=0.06).

Retrospective Non-Randomized Data

A recently published retrospective analysis of 3211 patients treated with either thrombolysis or primary PTCA showed results quite different from those previously presented.[6] The patients were chosen from a registry of 12331 patients who presented to 19 hospitals in the Seattle, Washington area with acute myocardial infarction. Patients in the two groups were similar in all characteristics with the exception that those in the PTCA group had a higher incidence of prior gastrointestinal bleeding and coronary artery bypass surgery. Overall, there was no difference between the groups for in-hospital mortality. Despite a statistically significant shorter length of stay in the PTCA group (6.8d vs 7.9d), the cost of stay was significantly lower in the thrombolysis group. This finding is contrary to one other study which noted significantly lower costs to PTCA attributable to shorter length of stay.[9]

Summary

There is no convincing evidence of a sustained long-term therapeutic benefit of primary PTCA. However, the use of aggressive heparin with monitoring of activated clotting time was not universally employed in many centres, and several trials did not include patients who had completely occluded arteries. Conversely, the ability to provide primary PTCA in as short amount of time as is possible with systemic thrombolysis is limited, even in very specialized centres. Since the benefit of opening an infarct vessel decreases with time, thrombolysis may be more beneficial because it can be delivered rapidly and easily. Perhaps the benefit of PTCA is limited to a certain subgroup of patients only – such as those with anterior myocardial infarction, advanced age, hemodynamic compromise or patients who are either not candidates for thrombolytic therapy, or who have a high risk of thrombolytic complications. Certainly, with the introduction of newer thrombolytic agents and adjuncts to thrombolysis such as hirudin, other heparin analogues, and glycoprotein IIb/IIIa inhibitors, the comparison of an invasive versus conservative approach to treatment of myocardial infarction becomes even more difficult. Preliminary studies of intracoronary stenting have been promising and randomized trials comparing traditional PTCA with intracoronary stenting are underway.[15]

The less than dramatic improvement of outcome with PTCA as compared to thrombolysis may be related to several factors: lack of generalizability of the technique to lower volume laboratories, delay in performing PTCA, reperfusion injury, and low use of aggressive anticoagulation. Perhaps as these difficulties are overcome, the obvious superiority of PTCA in opening occluded arteries will result in improved survival both in the short and long term.

References

1. Cigarroa RG, Lange RA, Hillis LD. Prognosis after myocardial infarction in patients with and without residual anterograde coronary blood flow. *Am J Cardiol* 1989;64:155-60.
2. Simes RJ. Topol EJ. Holmes DR Jr. et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation.* 1995,91(7):1923-8.
3. Carney RJ, Murphy GA, Brandt TR, et al. Randomized angiographic trial of recombinant tissue-type plasminogen activator (alteplase) in myocardial infarction. *J Am Coll Cardiol* 1992;20: 17-23.
4. Wall TC, Califf RM, George BS, et al. Accelerated plasminogen activator dose regimens for coronary thrombolysis. *J Am Coll Cardiol* 1992;19:482-9.
5. Bode C, Smalling RW, Berg G, et al. Thrombolysis Achieved With Double-Bolus Reteplase (Recombinant Plasminogen Activator) and Front-Loaded Accelerated Alteplase (Recombinant Tissue Plasminogen Activator) in Patients With Acute Myocardial Infarction. *Circulation* 1996;94(5):891-8.
6. Every NR. Parsons LS, Hlatky M, et al. A Comparison of Thrombolytic Therapy with Primary Coronary Angioplasty for Acute Myocardial Infarction. *N Engl J Med* 1996;335(17): 1253-60.
7. O'Neill W, Timmis GC, Bourdillon PD, et al. A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. *N Engl J Med* 1986;314:812-8.
8. DeWood MA, Fisher MJ. Direct PTCA Verses Intravenous r-tPA In Acute Myocardial Infarction: Preliminary Results From A Prospective Randomized Trial. *Circulation* Supplement II 1989;80(4):II-418.
9. Gibbons RJ, Holmes DR, Reeder GS, et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med* 1993;328:685-91.
10. Zijlstra F, deBoer MJ, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680-4.
11. deBoer MJ, Hoorntje JCA, Ottervanger JP, et al. Immediate coronary angioplasty versus intravenous streptokinase in acute myocardial infarction: left ventricular ejection fraction, hospital mortality and reinfarction. *J Am Coll Cardiol* 1994;23:1004-8.
12. Zijlstra F. deBoer MJ, Beukema WP, et al. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. *Eur Heart J* 1996;17:382-7.
13. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;328:673-9.
14. 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;22:376-80.
15. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. *Circulation* 1995;91:476-85.
16. Grines CL. Aggressive Intervention for Myocardial Infarction: Angioplasty, Stents, and Intra-aortic Balloon Pumping. *Am J Cardiol* 1996;78(suppl 3A) 29-34.

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Abstracts of Interest

Costs of Direct Angioplasty versus Thrombolysis for Acute Myocardial Infarction: Results from the GUSTO II Randomized Trial

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Previous small randomized trials have suggested that reperfusion with direct angioplasty (PTCA) may have better clinical outcomes and lower costs than thrombolysis. The GUSTO IIb randomized trial of PTCA versus accelerated t-PA found a trend for greater freedom from death, MI or non-fatal disabling stroke at 30 days with PTCA (p=.06). As part of the GUSTO II trial, we prospectively collected resource use and medical cost data on 374 of the 410 pts (91%) randomized in the U.S. Charges on hospital bills were converted to costs and MD fees were taken from the Medicare Fee Schedule. Total length of stay was slightly shorter for PTCA (7.0 vs 7.7 days, p=.0009). Catheterization and PTCA were both more frequent in the PTCA arm (98% vs 75%, p<.001; and 84% vs 40%, p<.001) while CABG was slightly less frequent (13% vs. 17% for t-PA, p=.25). Direct PTCA pts had lower mean hospital costs (13.337 vs 14,236, p=.004) and higher MD costs (3,912 vs 3,367, p=.001) so that the total cost difference for the initial hospitalization was 354 dollars lower with PTCA (p=.15). During follow-up to 6 months, rehospitalization (31% for PTCA vs 27% for t-PA) and repeat cardiac procedures (10% for PTCA vs 6% for t-PA) occurred approximately equivalently in the two arms. Cumulative 6 month medical costs were 18,643 for PTCA and 19,396 for t-PA (p=.19). Thus, the GUSTO IIb randomized trial demonstrates that along with nearly equivalent clinical outcomes, direct PTCA and accelerated t-PA have equivalent costs out to 6 months.

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The Central Unifying Concept of TIMI-3 Flow After Primary PTCA and Thrombolytic Therapy in Acute Myocardial Infarction

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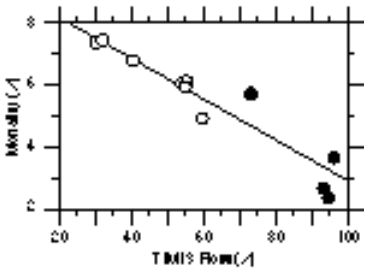
Whereas restoration of TIMI-3 flow has been established as the primary determinant of outcome after thrombolysis, little is known of the importance of TIMI-3 flow after primary PTCA in AMI. In the PAMI-1 and PAMI-2 trials, primary PTCA was performed in 1157 pts at 40 centers. TIMI-3 flow was restored in 1077 pts (93%). Compared to pts with TIMI Q-2 flow, pts with TIMI-3 flow had lower rates of death (2.1% vs 11.3%, p=.0002). CHF/hypotension (17% vs 34%, p=.0001), recurrent ischemia (11% vs 18%, p=.08) and a shorter hospital stay (7.8 ± 6.2 vs 9.2 ± 6.1 days, p=.05). The importance of TIMI-3 flow was further explored by plotting the short term mortality vs the % of pts in whom TIMI-3 flow was achieved from 11 studies of thrombolysis (open circles) and primary PTCA (closed circles). A strong linear relationship was present (r^2=.90, p<.0001), independent of reperfusion modality. Conclusions: The high rates of TIMI-3 flow achieved are responsible for the excellent outcomes after primary PTCA, and may explain the improved results of PTCA compared to thrombolysis in randomized trials.



Excerpted from *Circulation*, 1996;Vol 94, No 8:I-515.

Overview of the Randomized Trials of Primary PTCA and Thrombolysis in Acute Myocardial Infarction

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Primary PTCA is increasing in popularity as a treatment of MI. Several new trials have been reported, none large enough to show a significant reduction in mortality. To determine the relative benefits of primary PTCA vs thrombolysis we performed a meta-analysis of the nine trials of primary PTCA compared with intravenous thrombolysis. To date there have been 2,023 patients randomized to PTCA or thrombolytic therapy. The recently completed GUSTO IIb trial compared the accelerated t-PA regimen to PTCA in a wider community setting raising questions of including this trial; hence both analyses (with odds ratio (95%CI) & p-values) are presented. (Table) Studies used different definitions of MI and varying periods of follow-up for reported events. If the analysis was confined to time to discharge (5 trials available) rather than "end of study" the relative risk for mortality was 0.73 (95% CI 0.49-1.07) and for death+MI was 0.56 (0.41-0.77). Both the PAMI and GUSTO 2 trials showed an increase in hemorrhagic stroke rate (2% vs 0% and 1.4% vs 0%). An overview of total stroke intracranial hemorrhage and relative benefits of each treatment strategy will be presented. Recognizing the limitations of combining trials using various thrombolytics and varied trial designs, there is borderline statistically significant benefit favoring primary PTCA for mortality and a clearer effect on death and MI. The estimated risk reduction of PTCA in the GUSTO 2 trial is less than for the other studies, but there is not clear evidence of heterogeneity across studies.

Study Outcome	Death + MI			Mortality		
GUSTO 2	0.76	(0.52-1.11)	0.15	0.80	(0.50-1.29)	0.36
All other studies	0.46	(0.30-0.74)	0.001	0.54	(0.33-0.91)	0.02
Combined	0.62	(0.47-0.82)	0.001	0.67	(0.47-0.95)	0.02

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