CORONARY ANGIOGRAPHY AND REVASCULARIZATION FOR ACUTE ISCHEMIC HEART DISEASE

FOR WHOM? WHEN? WHERE?

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Interests (1) Pathophysiology and Management of Ischemic Heart Disease

(2) Valvular Heart Disease

(3) Congenital Heart Disease in Adults

Over the past 15 to 20 years, clinical and pathological studies have examined the pathophysiology of the acute coronary syndromes: unstable angina pectoris, non-ST segment elevation myocardial infarction (MI), and ST segment elevation MI. In these conditions, rupture of a previously "stable" atherosclerotic plaque leads to varying amounts of platelet adhesion and aggregation, dynamic coronary arterial vasoconstriction, and the formation and/or sustenance of a partially or totally occlusive thrombus. Although the inhibition of platelet aggregation and thrombus formation and the restoration of antegrade flow in occluded coronary arteries improve survival and reduce the incidence of recurrent ischemia and infarction, a residual coronary arterial stenosis may lead to ischemia, recurrent infarction, or even death. As a result, there has been considerable interest in the **routine** use of coronary angiography and percutaneous revascularization in patients with these syndromes, in the hope of reducing the risk of subsequent adverse events [1].

The enthusiasm for -- and interest in -- routine coronary angiography, often in association with PTCA of coronary artery bypass grafting (CABG), are particularly strong in the United States. Yusuf et al [2] examined practice patterns in almost 8000 consecutive patients hospitalized with unstable angina pectoris or suspected non-ST segment elevation MI at 95 hospitals in 6 countries: the United States, Brazil, Canada, Australia, Hungary, and Poland. As the data in Table 1 (page 4) illustrate, coronary angiography and PTCA were performed frequently in the United States and Brazil. In contrast, they were somewhat less likely to be performed in Canada and Australia, and they were very unlikely to be performed in Hungary and Poland. At the same time, there were no significant differences among the 6 countries in the rates of cardiovascular death or MI, but the rates of stroke were higher in the United States and Brazil in comparison to the other 4 countries.

Why are coronary angiography and PTCA or CABG so often performed in patients with acute coronary syndromes in the United States, even without a clear indication? In my opinion, several factors may be responsible [1]. First, these procedures are frequently **patient-driven.** In an era in which invasive cardiac procedures are manifestations of high-technology, resource-intensive medical care, many patients and their family members expect and insist on an aggressive management strategy. Anything less projects the impression of obsolescence, inadequacy, and inferiority rather than of thoughtful reflection and the application of scientifically based, ischemia-guided therapy. In the event of an adverse outcome, the patient and his/her family may be more understanding and forgiving if an aggressive approach was pursued (i.e., if "everything possible was done"), even if such an approach contributes, directly or indirectly, to

Table 1: Rates of coronary angiography, PTCA, CABG, Cardiovascular Death or MI, and Stroke in Various Countries

Within 7 days of hospitalization

	Angiography	PTCA	CABG	CV Death/MI	Stroke
USA	58%	22%	14%	4%	0.8%
Brazil	60%	12%	10%	5%	0.3%
Canada	35%	9%	2%	5%	0.1%
Australia	22%	5%	1%	4%	0.2%
Hungary	15%	4%	3%	6%	0.2%
Poland	2%	0%	0%	6%	0.2%

Within 6 months of hospitalization

USA	65%	26%	22%	9%	2.0%
Brazil	72%	22%	27%	12%	1.6%
Canada	57%	22%	18%	12%	1.1%
Australia	41%	13%	16%	9%	1.2%
Hungary	32%	8%	17%	12%	1.3%
Poland	16%	4%	6%	11%	0.7%

From reference # 2

the adverse outcome. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial [3], which was performed in the United States and abroad, 4 thrombolytic regimens were compared in patients with ST segment elevation MI, after which each patient's management was determined by his or her own physician. In comparison to Canadian physicians, American physicians more often reported that requests by the patient or family members as well as concern about liability influenced them to pursue an aggressive management strategy.

Second, these procedures are often **physician-driven**. Many American physicians express skepticism about the applicability of the results of the various randomized trials to their patients. Of the physicians in the United

States who participated in the GUSTO trial, 54% said that they routinely recommend coronary angiography for survivors of uncomplicated MI, 71% do so for all patients receiving thrombolytic therapy, and 93% do so for survivors of MI who are < 45 years of age, even though these groups of patients have been shown to be at low risk for subsequent complications regardless of the manner in which they are managed.

Third, studies that substantiate preconceived notions are likely to be embraced and their recommendations followed, whereas those that do not are often ignored. Many physicians in the United States, even today, continue to believe that all patients with acute coronary syndromes are best treated with prompt coronary angiography and revascularization, despite the absence of scientific support for such an approach.

Fourth, these procedures are often **facilities-driven.** In comparison to Canada and Europe, the United States has an abundance of (a) facilities for prompt angiography and revascularization, (b) physicians trained (and eager) to perform these procedures, and (c) monetary remuneration to the facilities and physicians. The combination of these factors encourages the use of angiography and revascularization without a clear indication. Physicians who work in hospitals with catheterization facilities are more likely to recommend coronary angiography than those without easy access to such a facility [4]. Cardiologists are more likely to recommend coronary angiography than internists, and cardiologists who perform angiography are even more likely than their colleagues who do not perform the procedure to recommend it [5].

At present, particularly in the United States, a substantial number of patients with acute coronary syndromes undergo coronary angiography and subsequent revascularization without a clear indication. Therefore, my purpose today is to review the indications for coronary angiography and revascularization in patients with acute ischemic heart disease. I shall concentrate my remarks on several distinct clinical scenarios:

1. ST Segment Elevation MI

    a. As an alternative to Thrombolytic Rx (so-called "Primary PTCA")

    b. As "salvage" or "rescue" Rx after presumably failed thrombolysis

c. As routine Rx after successful thrombolysis

1. within minutes to hours of thrombolysis
2. within hours to days of thrombolysis
3. within days to weeks of thrombolysis

2. Non-ST Segment Elevation MI

3. Unstable Angina Pectoris

ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

a. Angiography/PTCA as an Alternative to Thrombolytic Therapy (so-called "Primary PTCA")

In 5 randomized, prospective studies [6-10], patients presenting within 6 to 12 hours of the onset of acute MI were assigned to receive (a) intravenous thrombolytic therapy (streptokinase or tissue plasminogen activator) or (b) angiography and PTCA at centers experienced with its use. Only one of the studies used a "front loaded" or "accelerated" dose of tissue plasminogen activator, the regimen most successful in achieving early coronary arterial patency. Antegrade coronary arterial flow was established in 80 to 99% of patients in whom primary PTCA was attempted. Of note, PTCA was not attempted if coronary angiography demonstrated left main or severe 3 vessel coronary artery disease or a "high-risk" coronary arterial lesion. As a result, 4 to 7% of patients assigned randomly to receive primary PTCA underwent urgent coronary artery bypass grafting instead of PTCA. In comparing primary PTCA with thrombolytic therapy, several endpoints were evaluated, including (1) time to treatment, (2) mortality, (3) myocardial salvage, (4) infarct artery patency, (5) incidence of recurrent ischemia, and (6) hospital costs.

(1) Time to Treatment: In all studies, thrombolytic therapy was initiated 30 to 60 minutes more rapidly than primary PTCA, despite the fact that PTCA was performed promptly (mean time from randomization to PTCA = 60 to 78 minutes) at centers with experienced personnel who were "on site." Since reperfusion of an occluded infarct artery typically occurs 20 to 60 minutes after initiation of a thrombolytic agent, the overall time required to restore antegrade coronary flow was probably similar for thrombolysis and primary PTCA, **provided the latter is performed expeditiously.** Because the magnitude of mortality reduction is strongly influenced by the rapidity of

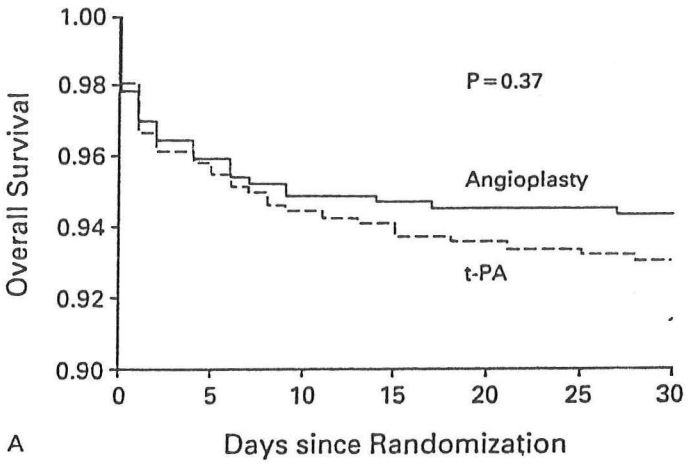
reperfusion [11,12], withholding thrombolysis to transport the patient to a facility for primary PTCA is probably deleterious.

(2) Mortality: In 4 of the 5 studies [7-10], mortality was similar for the thrombolysis- and PTCA-treated patients (Table 2 and Figure 1, below). One of the studies [6] showed a trend toward reduced in-hospital mortality with primary PTCA, in large part because the patients receiving thrombolysis had an incidence of stroke 2 to 3 times that expected; the incidence of cardiac death was similar for the 2 treatments. In a post-hoc analysis, the patients were classified as "low risk" or "not low risk," with the latter including those with (a) anterior MI, (b) age > 70 years, or (c) heart rate > 100 beats/minute. Those who were "not low risk" appeared to have a lower in-hospital mortality with primary PTCA. However, further analysis revealed that only the elderly benefited from PTCA; for those < 65 years of age, the incidence of in-hospital death and reinfarction was similar with thrombolysis and primary PTCA, regardless of heart rate or infarct location. In the largest study [10], the higher-risk patients did not gain greater benefit from primary PTCA.

Table 2: In-hospital mortality in the randomized trials of primary PTCA versus thrombolysis

Ref #	# pts	thrombolytic agent	in-hospital mortality PTCA	in-hospital mortality thrombolysis
6	395	t-PA	3%	7%
7	142	streptokinase	0%	6%
8	108	t-PA	4%	4%
9	100	streptokinase	6%	2%
10	1138	t-PA	6%	7%
TOTAL	1883		5%	7%

Figure 1: Survival in the 2 treatment groups within 30 days of randomization. From ref # 10.



(3) Myocardial Salvage: In one study [7], LV ejection fraction at hospital discharge was higher in patients who received primary PTCA than in those treated with streptokinase (average, 51% versus 45%, respectively). In the other studies [6,8,9], no significant difference was noted. Gibbons et al [8] assessed myocardial salvage by quantitating the change in size of the left ventricular perfusion defect by radionuclide tomographic imaging before and after reperfusion therapy; in this study, primary PTCA did not result in greater myocardial salvage than thrombolytic therapy.

(4) Infarct Artery Patency and Recurrent Ischemia: In 2 of the 5 trials, coronary arterial patency after treatment with thrombolysis or primary PTCA was a primary endpoint. Ribeiro et al [9] showed no difference in infarct artery patency at 48 hours among the primary PTCA and thrombolytic treated patients (74% versus 80%, respectively), and the incidence of recurrent ischemia was similar in the 2 groups (8% with PTCA, 10% with streptokinase). In contrast, Zijlstra et al [7] performed angiography 3 to 9 weeks after hospital discharge and showed that in comparison to streptokinase, primary PTCA was associated with increased infarct artery patency (91% versus 68%, respectively) as well as less severe residual stenosis in the infarct vessel (76% versus 36% coronary arterial luminal diameter narrowing, respectively). This translated into fewer episodes of unstable angina, recurrent MI, and unplanned PTCAs in those receiving primary PTCA. In contrast, in the Gusto IIb angiographic substudy, the incidence of recurrent ischemia or MI at 30 days was similar for the primary PTCA- and thrombolysis-treated patients.

(5) Monetary Costs: Reeder et al 13] reported hospital costs associated with primary PTCA and thrombolysis. They found no difference between the 2 treatment strategies as assessed at 12 month follow-up.

These previously described randomized trials were conducted in small numbers of patients at centers highly experienced with urgent angiography/PTCA, and long-term follow-up was lacking. Uncertainty has arisen regarding their applicability to the community hospital setting, where most patients with acute MI receive their care. Accordingly, 4 large observational studies [14-17] assessed the outcome of thrombolytic therapy or primary PTCA in > 54,000 thrombolytic-eligible patients treated in a community hospital setting. In 3 of these studies [14-16], data from patients of all ages were included, whereas the other analysis [17] included only data from those > 65 years of age. The results of the 3 studies which assessed patients of all ages are remarkably concordant (Table 3 and Figure 2,

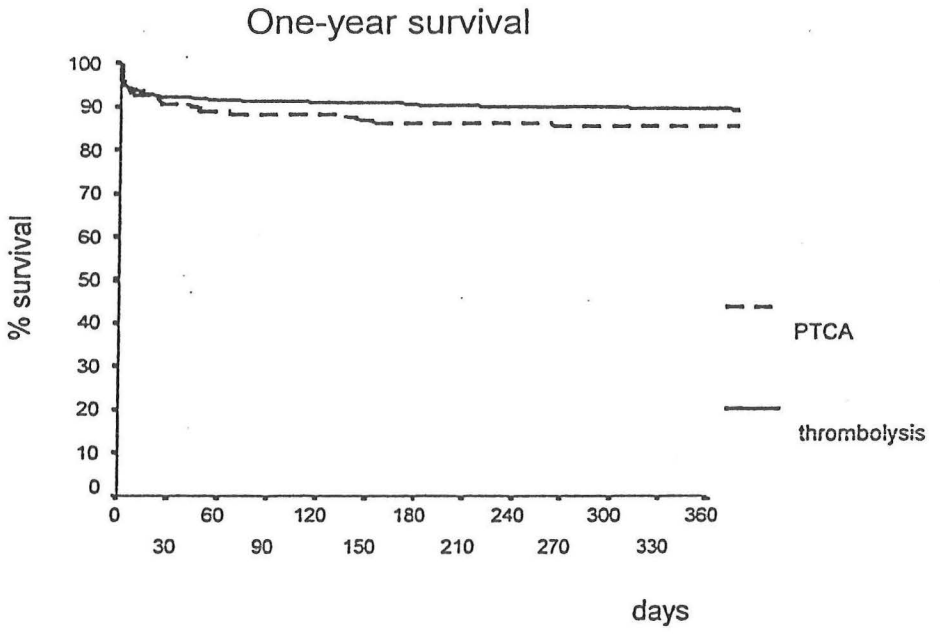
below). Patients treated with thrombolytic therapy had a higher incidence of stroke but similar in-hospital mortality as those treated with primary PTCA, and the incidence of the combined end-point of death and nonfatal stroke was similar for the 2 treatment modalities.

Table 3: Outcome of patients of all ages receiving thrombolytic therapy or primary PTCA in the community setting

Ref #	# pts	Stroke	In-hospital mortality
14			
thrombolysis	2,050	1.5%	6%
primary PTCA	1,095	0.7%*	6%
15			
thrombolysis	24,705	1.6%	5%
primary PTCA	4,939	0.7%*	5%
			One year mortality
16			
thrombolysis	569		10%
primary PTCA	152		14%

* $p < 0.05$ in comparison to thrombolysis

Figure 2: One-year survival in patients treated with primary PTCA or thrombolytic therapy. From ref # 16.



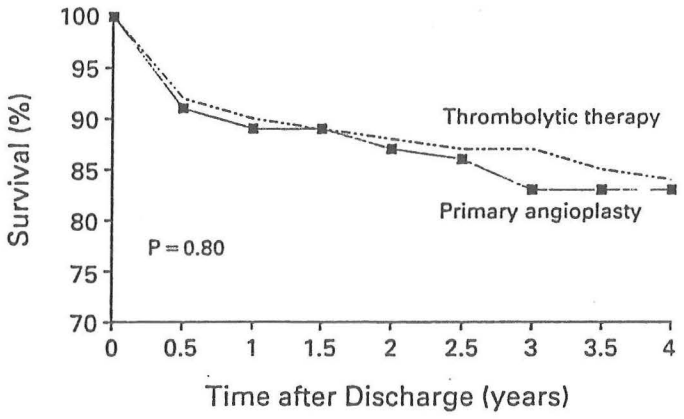
In the study of Every et al [14], 3-year follow-up data were obtained, which showed no difference in survival between the 2 treatment groups (Table 4 and Figure 3, below).

Table 4: Outcome of patients receiving thrombolytic therapy or primary PTCA in the community setting (from ref # 14)

	thrombolysis	primary PTCA
In-hospital		
mortality		
all patients	6%	6%
high-risk patients	8%	9%
pts at high volume PTCA centers	5%	5%
mean hospital costs ($)	16,838	19,702*
At 3 years		
mortality		
high-risk patients	18%	25%
pts at high volume PTCA centers	12%	13%
mean inpatient costs ($)	22,163	25,459*

* $p < 0.001$ in comparison to thrombolysis

Figure 3: Cumulative survival among 1050 patients in the primary PTCA group and 2095 patients given thrombolytic therapy. From ref # 14.



As noted previously, Grines et al [6] originally suggested that primary PTCA might be preferable to thrombolytic therapy in patients > 65 years of age, and a recently published observational analysis provides data that support this suggestion. Berger et al [17] analyzed data from a large cohort of Medicare beneficiaries diagnosed with acute