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Effect of Age on Outcome With Primary Angioplasty Versus Thrombolysis

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OBJECTIVES The purpose of this study was to determine how risks associated with increasing age differed in patients treated with percutaneous transluminal coronary angioplasty versus thrombolysis.

BACKGROUND Advancing age is a risk factor for adverse outcome in patients with acute myocardial infarction. Primary angioplasty has been thought to be particularly beneficial in higher risk patients including the elderly. There is, however, limited data on any differential incremental benefit of angioplasty compared with thrombolysis in candidates for either treatment.

METHODS In the GUSTO-IIb angioplasty substudy, 1,138 patients were randomized to receive primary angioplasty or accelerated tissue-type plasminogen activator (t-PA). The effect of age on outcome was assessed as a discrete and continuous variable for each treatment group. Models using age as a linear factor as well as cubic spline transformations were used for the major end points of 30-day death or disabling stroke; death or reinfarction; and death, reinfarction or disabling stroke.

RESULTS For each 10-year patient group, outcome was improved with angioplasty (n = 565) compared with t-PA (n = 573). Irrespective of treatment, however, risk increased with age. After adjusting for baseline characteristics, each increment of 10 years of age increased the risk of death or myocardial infarction by 1.32 (95% confidence interval 1.04 to 1.76, p = 0.022). For all adverse outcomes, this incremental effect of increasing age was constant.

CONCLUSIONS Advancing age is associated with worse outcomes, and the risks increase in proportion to age. Although primary angioplasty improves outcomes over thrombolysis, it does not appear to be more beneficial in older than in younger patient groups. The incremental adverse effect of age does not vary by treatment strategy. (J Am Coll Cardiol 1999;33:412–9) © 1999 by the American College of Cardiology

The treatment of acute myocardial infarction in older patients remains problematic. Older patients have been found to be at increased risk for adverse events, a result of several factors including the presence of more comorbid conditions, more advanced multivessel disease and longer times between the onset of symptoms and presentation for evaluation and treatment (1–9). In the Global Utilization of Streptokinese and t-PA for Occluded Coronary Arteries—I (GUSTO-I) study (10), which compared four different thrombolytic regimens, older patients had a higher mortality and morbidity despite aspirin, beta-adrenergic blocking agent and thrombolytic therapy. In that trial, 30-day mortality was 3.0% for patients <65 years of age, 9.5% for those aged 65 to 74 years, 19.6% for 75 to 84 years and 30.3% for patients over 85 years. Each 10-year increment of age was associated with a doubling of the odds of 30-day mortality.

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Primary angioplasty has been felt to be particularly beneficial in higher risk patient subsets including the elderly (11–14). This conclusion has been based primarily on observational data sets rather than randomized trials. The Global Use of Strategies to Open Occluded Coronary Arteries—II (GUSTO-IIb) angioplasty substudy randomized 1,138 patients to either primary angioplasty or thrombolytic therapy (15). It was the purpose of this study to analyze the effect of age on 30-day outcome in the GUSTO-IIb substudy to see if the incremental risks associated with increasing age were present to the same degree in patients treated with percutaneous transluminal coronary angioplasty compared with thrombolysis.

METHODS

GUSTO-IIb. The results of the GUSTO-IIb trial, a comparison of the effectiveness of hirudin versus heparin in over 12,000 patients with acute coronary syndromes, have been published (16); patients randomized to hirudin had a small improvement in the primary end point of death, nonfatal myocardial infarction or reinfarction at 30 days

Abbreviations and Acronyms

CI	=	95% confidence interval
GUSTO-I	=	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries—I
GUSTO-II	=	Global Use of Strategies to Open Occluded Coronary Arteries—II
IV	=	intravenous
TIMI	=	Thrombolysis in Myocardial Infarction
t-PA	=	tissue-type plasminogen activator

over patients randomized to heparin ($p = 0.058$). The effect was predominantly in the nonfatal myocardial infarction component of the composite.

Angioplasty substudy. The GUSTO-IIb primary angioplasty substudy has been previously reported (15); it recruited 1,138 patients at 57 hospitals in nine countries using an Institutional Review Board–approved protocol after obtaining informed consent. Eligibility criteria required that patients present within 12 h after onset of chest pain lasting at least 20 min accompanied by electrocardiographic changes of >0.2 mV ST segment elevation in two or more contiguous leads.

Randomization and treatment. Eligible patients were randomized to either primary angioplasty or accelerated tissue-type plasminogen activator (t-PA) (15-mg bolus followed by 0.75 mg/kg over 30 min not to exceed 50 mg, then 0.5 mg/kg for 60 min not to exceed 35 mg for a maximum total of 100 mg). As has been reported, the first 1,012 patients were also randomized in a 2×2 factorial design to intravenous (IV) heparin or IV hirudin; angioplasty was performed by experienced interventional cardiologists with the primary goal of restoring flow in the infarct-related artery as quickly as possible. The infarct-related artery was the only target except in patients who had hemodynamic deterioration despite restoration of patency. In patients with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow at the time of angiography, the individual operator decided whether to proceed with angioplasty. Adjunctive medications included chewable aspirin. Other cardiac medications were used according to the pattern of care of the primary physician. Follow-up evaluation and treatment were also at the discretion of the attending physician, although angiography within 3 days of study entry was discouraged in patients randomized to t-PA except for the treatment of refractory ischemia or hemodynamic deterioration.

End points. The primary end point of the GUSTO-IIb trial was a composite of death or nonfatal reinfarction at 30 days. Secondary end points included death, myocardial infarction or disabling stroke at 30 days and recurrent medically refractory ischemia at 30 days and 6 months. Recurrent ischemia was defined as symptoms of ischemia with ST segment deviation or definite T wave inversion, occurring more than 12 h after enrollment and lasting for at least 10 min despite the use of nitrates and either beta-blockers or calcium channel blocking agents, and not fulfilling criteria for myocardial infarction.

Statistical methods. The effect of age on outcome was assessed as a continuous variable for the patients treated with primary angioplasty compared with thrombolysis. Patients were also arbitrarily divided into 10-year age groups, and the specific outcome was measured by treatment group. The actual rates of each outcome by age grouping and by treatment were generated. These rates were used to describe the differences in effects of specific age groups within each of the two treatment arms.

Logistic regression models using continuous age were used to describe the overall effect of increases in age on outcome. These models were also used to evaluate the overall significance of age in predicting each outcome.

Models using age as a linear factor versus cubic spline transformations were compared to evaluate the nature of the relationship between age and each outcome (17,18). If the models appeared comparable in predictive information and the plot of the spline transformation appeared fairly linear, then the relationship was assumed to be linear. If, however, the relationship appeared nonlinear, the plot was examined to determine the best transformation for age with respect to that outcome.

Two logistic models were run for each of the major end points of death or disabling stroke, death or reinfarction and death, reinfarction, or disabling stroke. These models tested whether age is a predictor of outcome after adjusting for the treatment received, and whether this relationship is different for patients receiving primary angioplasty and for patients receiving thrombolysis. The models consisted of: outcome = treatment + age; and outcome = treatment + age + treatment–age interaction.

There were no differences in primary end points in the GUSTO-IIb angioplasty (15) substudy between heparin and hirudin, so these groups were combined for this analysis. Two multivariable logistic models were created to evaluate the prognostic information contained in age after first adjusting for other potentially important baseline factors. The events for these two models were 30-day mortality or myocardial infarction and 30-day mortality, myocardial infarction or disabling stroke. The baseline factors included were race, U.S. versus non-U.S. site of treatment, hypercholesterolemia, family history of coronary artery disease, prior myocardial infarction, prior angina, prior congestive heart failure, weight, height, gender, diabetes mellitus, hypertension, smoking status, systolic and diastolic blood pressures, prior cerebrovascular disease, prior coronary bypass graft surgery, heart rate, peripheral vascular disease, diagnosed cancer, Killip class and angioplasty versus t-PA.

A final separate analysis evaluated the relationship be-

Table 1. Baseline Patient Characteristics

	t-PA	Angioplasty
Total	573	565
Age (yr)	61.9 (CI 52.0, 70.1)	63.5 (CI 52.5, 71.0)
>75 yr old	79 (13.8%)	82 (14.5%)
Female	121 (21.5%)	139 (24.6%)
Current smoker	349 (44.5%)	361 (41.6%)
Diabetes	77 (13.5%)	99 (17.6%)
Heart rate (beats/min)	74.5 (CI 62, 86)	75 (CI 63, 87)
Hypertension	218 (38.2%)	225 (39.9%)
Killip class		
I	524 (91.8%)	507 (90.4%)
II	41 (7.2%)	47 (8.4%)
III	4 (0.7%)	2 (0.4%)
IV	2 (0.4%)	5 (0.9%)
Prior bypass surgery	16 (2.8%)	12 (2.1%)
Prior myocardial infarction	85 (14.9%)	73 (12.9%)
Prior angioplasty	28 (4.9%)	29 (5.1%)
Systolic blood pressure (mm Hg)	130 (CI 116, 148)	130 (CI 116, 147)
Time to hospital (h)*	1.8 (1.0, 3.1)	1.9 (1.1, 3.0)
Time to treatment (h)*	3.0 (2.0, 4.3)	3.8 (3.0, 5.3)
Weight (kg)	76 (CI 68, 86)	75 (CI 67, 86)

*Median (25th and 75th percentile) from symptom onset.
CI = 95% confidence interval.

tween TIMI flow and percent stenosis pre- and postprocedure in the angioplasty patients.

Continuous data are summarized as medians with 25th and 75th percentiles, and categorical factors are described as frequencies and percentages. Odds ratios with 95% confidence intervals (CIs) were used to compare treatments. Logistic regression models both unadjusted and adjusted were used to illustrate the effect of age on outcome. All tests of significance were two tailed, and the treatments were compared according to the intention-to-treat principle.

RESULTS

There were a total of 1,138 patients in the angioplasty substudy; 565 were randomized to angioplasty and 573 to t-PA; 170 (29.7%) patients in the t-PA arm underwent angioplasty for recurrent ischemia during the index hospitalization. As previously reported, the patient groups were similar with regard to their baseline characteristics (Table 1). The age distribution of patients in each group was also similar (Fig. 1). The most common 10-year age interval was 60 to 69 years; approximately 30% of each treatment group fell into this age range followed by the fifth and then seventh interval.

The effect of age on the primary end point and its components can be seen in Figure 2. As previously reported, patients treated with angioplasty in general had lower overall rates of mortality and/or reinfarction by 30 days than thrombolysis patients, but the difference was not statistically significant (Fig. 2, A). Thirty-day mortality for angioplasty ranged from 0% to 27.3%, and for lytic therapy it varied from 1.1% to 26.7%, with the highest mortality being seen in both treatment groups in patients older than 80 years of age (Fig. 2, B). At 6 months, the rate of death and nonfatal reinfarction ranged from a low of 6.4% in the 40 to 49 age group to 37.2% among those older than 80 years.

Reinfarction rates were somewhat less variable and ranged from 0 to 9.1% for angioplasty and from 2.3% to 11.1% for thrombolysis (Fig. 2, C). As previously reported, angioplasty patients had less reinfarction, but this difference was not statistically significant ($p = 0.183$).

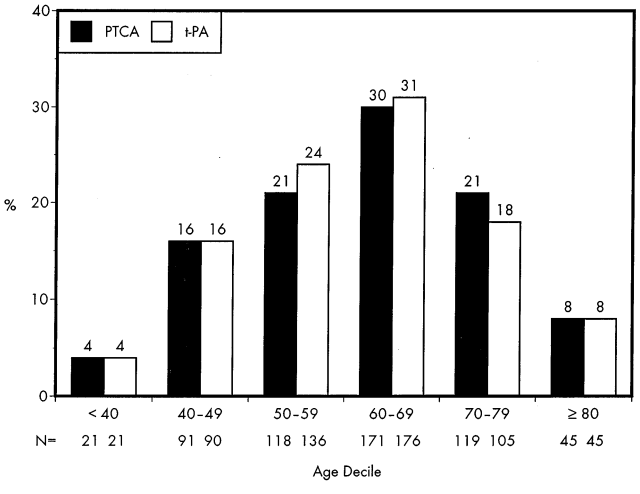

Figure 1. Age distribution of patients in the percutaneous transluminal coronary angioplasty (PTCA) substudy, by treatment group (angioplasty or tissue-type plasminogen activator [t-PA]) and by age decile.

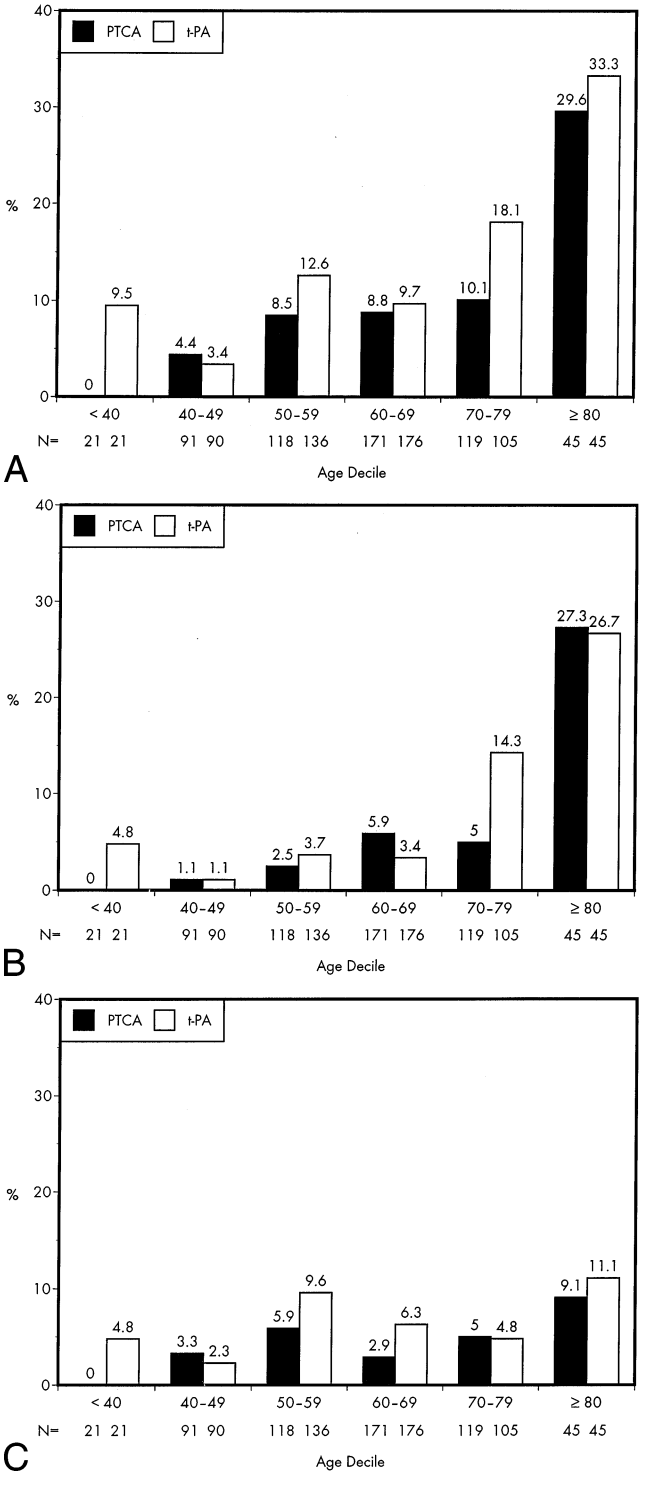

Figure 2. The primary outcome, 30-day mortality and/or reinfarction **(A)**, and its components, 30-day mortality **(B)** and 30-day reinfarction **(C)**, by treatment group and by age decile. Abbreviations as in Figure 1.

There tended to be an increase in reinfarction with increasing age; there was, however, no age-related trend in the time to reinfarction (<70 years = 4 [1.5, 10] days; >70 years = 6 [5, 7] days).

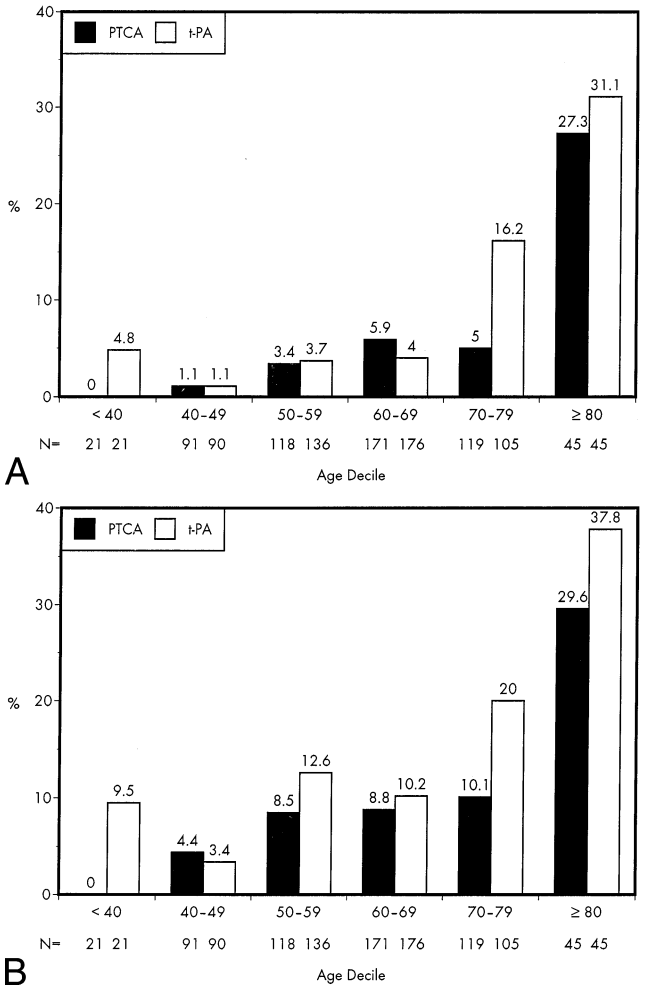

Figure 3. Thirty-day mortality or disabling stroke **(A)** and 30-day mortality, disabling stroke or reinfarction **(B)**, by treatment group and by age decile. Abbreviations as in Figure 1.

The secondary end points of death or disabling stroke (Fig. 3A), and of death, reinfarction or disabling stroke (Fig. 3B) also rose progressively with increasing age within each treatment group.

There was a significant difference in recurrent refractory ischemia between patients treated with angioplasty and those treated with thrombolysis; 3.9% of patients treated with angioplasty had refractory ischemia within 30 days of enrollment compared with 6.8% of patients treated with t-PA ($p = 0.031$). Recurrent ischemia occurred earlier in patients aged 70 years or older (3.4 [2.4, 5.6] days) than in patients <70 years (4.6 [1.0, 9.5] days).

Figure 4, A and B illustrate the 30-day probabilities of death and/or reinfarction and of death, reinfarction or disabling stroke, respectively. These plots are based on modeling age using cubic spline transformations, the treatment assigned (either angioplasty or t-PA) and the interaction of these two factors. For each 10 years of age, the likelihood of a cardiovascular event increased regardless of the method of reperfusion. Using the unadjusted

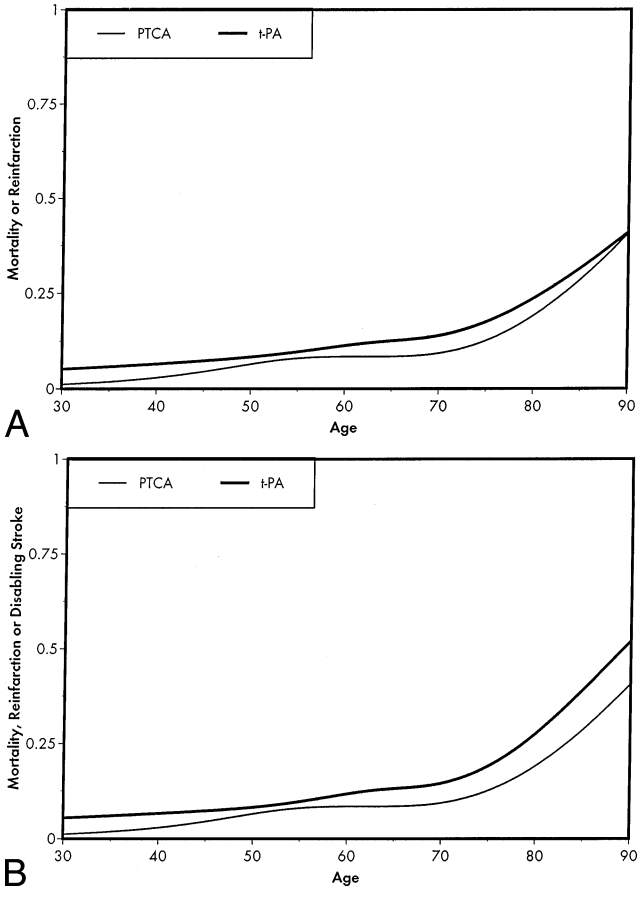

Figure 4. Probabilities of 30-day death and/or reinfarction **(A)** and of 30-day death, reinfarction or disabling stroke **(B)**. Abbreviations as in Figure 1.

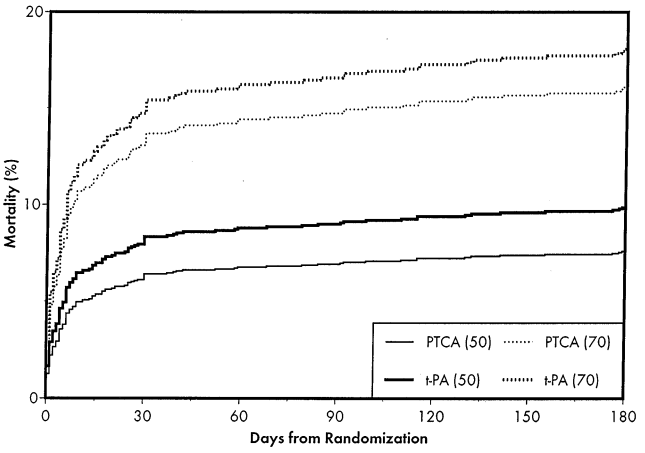

Figure 5. Mortality rates over 6 months for 50-year old patients and for 70-year old patients, by treatment group. Abbreviations as in Figure 1.

model and death and/or myocardial infarction as the end point, the odds ratio for each 10-year increment in age was 1.54 (CI 1.31 to 1.81, p = 0.001). After adjusting for other baseline characteristics, each increment of 10 years increased the risk of death or myocardial infarction by 1.32 (CI 1.04 to 1.67, p = 0.02). Similarly using death, reinfarction or disabling stroke as the end point, in either the unadjusted or adjusted model, older patients did significantly worse.

The increase in the odds of having an adverse outcome remained constant with increasing age (p > 0.20 for death and/or myocardial infarction, death or disabling stroke, and the combined end point of death, myocardial infarction or disabling stroke for the interaction of age with treatment). This increase in odds was true irrespective of the treatment to which the patient was allocated. For example, the odds of death or myocardial infarction for a 50-year old versus a 40-year old patient are similar to those for a 70-year old versus a 60-year old patient. The age effect on each of these three composite outcomes was not statistically significantly different for percutaneous transluminal coronary angioplasty compared with thrombolysis (all p > 0.60). Figure 5 demonstrates 6-month mortality rates for 50-year old patients treated with primary angioplasty or with thrombolysis and for 70-year old patients treated similarly, again illustrating that increasing age is associated with increased mortality, but the two treatments are similar with regard to mortality.

In the angioplasty patients, there was a significant difference in age for patients with TIMI 2 or 3 flow at baseline (p = 0.037) (Table 2), with younger patients more frequently having TIMI 2 or 3 flow at baseline than older patients. Following angioplasty there was no significant difference in TIMI 2 or 3 flow by age (p = 0.378). Similarly, there was a significant effect on baseline diameter stenosis by age (p = 0.018); this difference was not significant postprocedure (p = 0.710) (10).

DISCUSSION

Age and short-term outcome. This international substudy of primary angioplasty versus thrombolytic therapy for acute myocardial infarction documents the previously known adverse effect of increasing age on short-term outcome (1,6,19,20). The most important new observation is that the log-linear relationship between age and the probability of reaching an adverse end point is similar for patients treated with primary angioplasty as it is for patients treated with thrombolysis, that is, although older patients are at higher risk from myocardial infarction, primary angioplasty does not blunt the relationship between age and outcome. There does not appear to be a particular age cohort who would have a greater relative benefit from receiving angioplasty over thrombolytic agents.

Primary angioplasty versus thrombolysis. The relative merits of primary angioplasty versus thrombolytic therapy have been debated extensively (10). A recent meta-analysis of eight randomized trials documented that primary angio-

Table 2. Extent of Stenosis Before and After Angioplasty

	Patient Age (yr)					
	<40 (n = 21)	40 to 49 (n = 91)	50 to 59 (n = 118)	60 to 69 (n = 171)	70 to 79 (n = 119)	≥80 (n = 45)
Baseline TIMI flow						
0	56%	65%	76%	70%	72%	71%
1	19%	6%	10%	14%	12%	9%
2	6%	13%	6%	7%	9%	12%
3	19%	16%	8%	9%	6%	9%
Procedure TIMI flow						
0	0	4%	0	4%	2%	6%
1	0	0	2%	4%	0	0
2	0	5%	4%	7%	14%	6%
3	100%	91%	94%	85%	84%	88%
Baseline TIMI 2/3	25%	29%	14%	16%	15%	21%
Postangioplasty TIMI 2/3	100%	100%	98%	92%	98%	94%
Pretreatment % stenosis (CI)	100 (90, 100)	100 (95, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (99, 100)
Posttreatment % stenosis (CI)	25 (20, 30)	25 (10, 30)	25 (20, 30)	20 (10, 30)	20 (10, 30)	23 (15, 30)

CI = 95% confidence interval; TIMI = Thrombolysis in Myocardial Infarction.

plasty is associated with improved short-term outcome in comparable patients (21). Primary angioplasty has been felt to be particularly beneficial in higher risk patients, including the elderly.

Adverse characteristics of older myocardial infarction patients. The relationships among age, treatment received and outcome of myocardial infarction have been previously studied (1–9,22). Older patients constitute a significant percentage of infarction populations; in GUSTO-I, 12.1% were older than 75 years. Weaver et al. (8) reported that 28% of an infarction population was >75 years. Several characteristics of older patients contribute to increased adverse events with thrombolytic therapy including 1) the likelihood that they will present later than younger patients (10,23) (in GUSTO-I [10], patients over 65 years arrived at the hospital 20 to 40 min later than younger patients); 2) the presence of more comorbid disease and possibility of relative contraindications to thrombolytic therapy; and 3) the increased incidence of noncardiac complications including stroke. It must be remembered that even though treated with thrombolytic therapy, older patients have increased mortality. Because of the higher absolute event rate, more older patient lives may be saved per 1,000 patients treated (24).

Age and extent of stenosis. Another important factor in the relationship between age and outcome may be the severity of stenosis and impairment of TIMI flow at baseline. In the angioplasty group reported here, older patients more frequently had TIMI 0 or 1 flow and a more severe stenosis at baseline than younger patients. This higher rate of failure to reperfuse may reflect differences in pathology and could account for some of the increasing mortality in older patients.

Previous studies of primary angioplasty in the elderly. For the above reasons, primary angioplasty has been felt to be particularly attractive in older patients. There are limited data upon which to draw this conclusion (11–14). Several smaller series have looked at age as a discrete variable. In these series of older patients (11–14,17), mortality has been variable from 5.7% to 34%. Of importance is the fact that initial angiographic success may not directly translate into improved in-hospital outcome. Whether the outcome of these patients treated with angioplasty is improved compared to similar patients treated with thrombolytic therapy is difficult to determine. The current study documented the effect of age as a continuous variable on outcome. There was a significant log-linear relationship between age and the probability of reaching an adverse end point. Even adjusting for a large number of other variables, each 10 years of age was associated with a 1.32 times greater risk of dying or having recurrent infarction within 30 days. With the combined end point of disabling stroke, myocardial infarction or death, the adjusted risk ratio was 1.38 ($p = 0.007$). In general within each age group dilation was association with improved outcome.

Effect of treatment assignment in older patients in GUSTO-IIb. The most important finding is that the log-linear relationship between age and outcome is the same irrespective of whether the patient is treated with primary angioplasty or thrombolytic therapy. Although as a whole,

in GUSTO-IIb, primary angioplasty was associated with an improved combined primary end point of death or infarction or disabling stroke (9.6% vs. 13.7%, odds ratio 0.67, $p = 0.033$), this effect was not just the result of disproportionately improving outcome in the higher risk older patients. Indeed, tests for interaction between patient age and specific treatment selected (angioplasty vs. thrombolysis) were nonsignificant.

Limitations. Although this study has the advantage of examining the effect of age on outcome in a large number of patients eligible for either angioplasty or thrombolysis, it has limitations. As a substudy, it was not specifically designed to evaluate this question. However, given the large number of patients and the use of age as a continuous variable, this study offers a possibility of evaluating this relationship not previously possible in observational studies of primary angioplasty in older patients. Older patients may have relative or absolute contraindications to thrombolytic therapy making angioplasty the only practical means of achieving reperfusion. In these patients, even though primary angioplasty was associated with increased mortality, it did result in improved outcomes compared with non–reperfusion, conservative strategies.

Conclusions. Advancing age was associated with increasing adverse outcomes after acute myocardial infarction; the risks were increased proportionally to advancing age. Although primary angioplasty was found to have improved outcomes compared with thrombolysis, primarily angioplasty did not change the relationship between incremental risk and age. For all adverse outcomes, the incremental effect of increasing age was constant and did not vary irrespective of whether the patient was treated with angioplasty or thrombolysis.

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REFERENCES

1. Gurivitz JH, Goldberg RJ, Chen Z, et al. Recent trends in hospital mortality of acute myocardial infarction—the Worcester Heart Attack Study: have improvements been realized for all age groups? Arch Intern Med 1994;154: 2202–8.
2. Daida H, Kottke TE, Backes RJ, et al. Are coronary unit changes in therapy associated with improved survival of elderly patients with acute infarction? Mayo Clin Proc 1997;72: 1014–21.
3. Calle P, Jordaens L, De Buyzere M, et al. Age related differences in presentation, treatment, and outcome of acute myocardial infarction. Cardiology 1994;85:111–20.
4. Califf RM, Lee KL, Granger CB, Ohman EM. Predictors of outcome of reperfusion therapy. Eur Heart J 1997;18: 728–35.
5. Forman DE, Rich NW. Management of acute myocardial infarction in the elderly. Drugs Aging 1996;8:358–77.
6. Paul SD, O'Gara PT, Mahjoub ZA. Geriatric patients with acute myocardial infarction: cardiac risk factor profiles, presentations, thrombolysis, coronary interventions and prognosis. Am Heart J 1996;131:710–5.
7. Hillis LD, Forman S, Braunwald E, et al. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. J Am Coll Cardiol 1990;15:313–5.
8. Weaver WD, Litwin PE, Martin JS, et al. Effect of age on use of thrombolytic therapy and mortality in acute myocardial infarction. J Am Coll Cardiol 1991;18:657–62.
9. Aguirre FV, McMahon RP, Mueller H, et al. Impact of age on clinical outcome and post lytic management strategies in patients treated with intravenous thrombolytic therapy: results from the TIMI II study. Circulation 1994;90:78–86.
10. White HD, Barbash GI, Califf RM, et al. Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial. Circulation 1996;94:1826–33.
11. Lee TC, Laramee LA, Rutherford BD, et al. Emergency percutaneous transluminal coronary angioplasty for acute myocardial infarction in patients 70 years of age and older. Am J Cardiol 1990;66:663–7.
12. Brodie BR, Weingraub RA, Stuckey TD, et al. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non candidates for thrombolytic therapy. Am J Cardiol 1991;67:7–12.
13. Stone GW, Grines CL, Browne KF, et al. Predictors of in-hospital and 6-month outcome after acute myocardial infarction in the reperfusion era: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. J Am Coll Cardiol 1995;25:370–7.
14. Stone GW, Grines CL, Browne K, et al. Outcome of different reperfusion strategies in patients with former contraindications to thrombolytic therapy: a comparison of primary angioplasty and tissue plasminogen activator. Primary Angioplasty in Myocardial Infarction (PAMI) investigators. Cathet Cardiovasc Diagn 1996;39:333–9.
15. The GUSTO IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–8.
16. The GUSTO IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775–82.
17. Stone CJ, Koo CY. Additive splines in statistics. Proc Stat Comp Section, Am Stat Assoc 1985;45–8.
18. Walker SH, Duncan DB. Estimation of the probability of an event as a function of several independent variables. Appl Stat 1967;37:87–94.
19. Holland KJ, O'Neill WW, Bates ER, Pitt B, Topol EJ. Emergency percutaneous transluminal coronary angioplasty during acute myocardial infarction for patients more than 70 years of age. Am J Cardiol 1989;63:399–403.
20. Mickelson JK, Blum CM, Geraci JM. Acute myocardial infarction: clinical characteristics management and outcome in a metropolitan Veterans Affairs Medical Central teaching hospital. J Am Coll Cardiol 1997;29:915–25.
21. Weaver WD, Simes RJ, Betriu A, et al. Comparison of

primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–8.
22. Chandra H, Yarzebski J, Goldberg RJ, et al. Age related trends (1986–1993) in the use of thrombolytic agents in patients with acute myocardial infarction. Arch Intern Med 1997;157:741–6.
23. 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 randomized trials of more than 1000 patients. Lancet 1994;343:311–22.
24. Krumholz HM, Pasternak RC, Weinstein MC. Cost-effectiveness of thrombolytic therapy with streptokinase in elderly patients with suspected acute myocardial infarction. N Engl J Med 1992;327:7–13.