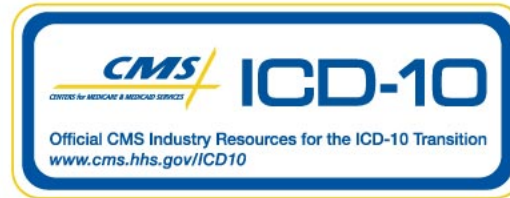


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CLINICAL STUDIES

Myocardial Infarction

Thrombolytic Therapy in Older Patients

Alan K. Berger, MD,* Martha J. Radford, MD, FACC,*†‡ Yun Wang, MS,†‡
Harlan M. Krumholz, MD, FACC*†‡§

New Haven and Middletown, Connecticut

OBJECTIVES	We compared outcomes following thrombolytic therapy and primary angioplasty with no reperfusion therapy in a population-based cohort of older patients presenting with acute myocardial infarction (AMI) and indications for acute reperfusion.
BACKGROUND	Evidence supporting the efficacy of acute reperfusion (thrombolytic therapy or primary angioplasty) in the elderly with suspected AMI is not as strong as it is in younger groups.
METHODS	From a national cohort of Medicare beneficiaries with AMI, we identified 37,983 patients age 65 or older who presented within 12 h of symptom onset with ST elevation or left bundle branch block. A total of 14,341 (37.8%) received thrombolytic therapy and 1,599 (4.2%) underwent primary angioplasty within 6 h of hospital arrival.
RESULTS	After adjustment for demographic, clinical, hospital and physician factors, and co-interventions, thrombolytic therapy was not associated with a better 30-day survival (odds ratio [OR] 1.01; 95% confidence interval [CI]: 0.94 to 1.09) compared with no therapy, whereas primary angioplasty was (OR 0.79; 95% CI: 0.66 to 0.94). At one year, both thrombolytic therapy (OR 0.84; 95% CI: 0.79 to 0.89) and primary angioplasty (OR 0.71; 95% CI: 0.61 to 0.83) were associated with a survival benefit.
CONCLUSIONS	In this national sample of older patients, those who received thrombolytic therapy or primary angioplasty had lower mortality at one year compared with those who did not receive a reperfusion strategy. However, only primary angioplasty was associated with better survival at 30 days. Our findings should heighten interest in further investigating the best approach to the treatment of older patients with suspected AMI and ST segment elevation or left bundle branch block. (<i>J Am Coll Cardiol</i> 2000;36:366-74) © 2000 by the American College of Cardiology

Clinical practice guidelines issued by the American College of Cardiology (ACC) and the American Heart Association (AHA) strongly endorse the use of reperfusion therapy for the treatment of patients without contraindications who present within 12 h of the onset of chest pain and have ST-segment elevation or left bundle branch block (LBBB) (1). The recommendation for early thrombolytic therapy is based on evidence from the more than 60,000 patients who

have been studied in placebo-controlled randomized trials (2). The more recent recommendation of primary angioplasty as an alternative to thrombolytic therapy comes from a series of randomized clinical trials comparing these two reperfusion therapies (3). As a result, the use of reperfusion therapy for appropriate patients is considered an indicator of the quality of care (4).

The efficacy of thrombolytic therapy in elderly patients has not been evaluated to the same extent as it has in younger groups. Early thrombolytic trials enrolled relatively few older patients and demonstrated a relatively small benefit. Pooled data from the large clinical trials showed that the 35-day mortality of patients 75 years of age and older was 24.3% for those treated with thrombolytic therapy and 25.3% for the placebo group (2). Although recent analyses comparing primary angioplasty with thrombolytic therapy among the elderly have suggested a survival benefit with early coronary intervention, these studies have not included comparison to a group that did not receive reperfusion therapy (3,5). Thus, even though evidence is accumulating that angioplasty may offer an alternative to thrombolytic therapy, it remains unclear whether any reperfusion therapy is more effective than no reperfusion therapy in older patients. This issue is particularly important given that the use of thrombolytic therapy in the elderly is increasing (6), and prompt angioplasty is not an option in many hospitals (6). In recognition of this limited evidence, the

From the *Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, †Yale-New Haven Hospital Center for Outcomes Research and Evaluation, New Haven, Connecticut; ‡Qualidigm®, Middletown, Connecticut; and §Section of Chronic Disease Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut. Dr. Krumholz is a Paul Beeson Faculty Scholar (The John A. Hartford Foundation, The Commonwealth Fund and the Alliance for Aging Research, New York, NY). The analyses upon which this publication is based were performed under Contract Number 500-96-P549, entitled "Utilization and Quality Control Peer Review Organization for the State of Connecticut," sponsored by the Health Care Financing Administration, Department of Health and Human Services. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The authors assume full responsibility for the accuracy and completeness of the ideas presented. This article is a direct result of the Health Care Quality Improvement Program initiated by the Health Care Financing Administration, which has encouraged identification of quality improvement projects derived from analysis of patterns of care, and therefore required no special funding on the part of this Contractor. Ideas and contributions to the author concerning experience in engaging with issues presented are welcomed.

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
ACC	= American College of Cardiology
AHA	= American Heart Association
CABG	= coronary artery bypass surgery
CCP	= Cooperative Cardiovascular Project
CI	= confidence interval
GUSTO	= Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
ICD-9-CM	= International Classification of Diseases, 9th Revision, Clinical Modification
LBBB	= left bundle branch block
OR	= odds ratio
PT	= prothrombin time
ROC	= receiver operating characteristics
tPA	= tissue plasminogen activator

ACC/AHA guidelines initially suggested that the treatment of older patients was not strongly indicated, and even now do not endorse it with the same enthusiasm that they do for younger patients (1).

We undertook this study to assess the effectiveness of thrombolytic therapy in the elderly using the Cooperative Cardiovascular Project (CCP), a Health Care Financing Administration initiative to improve the quality of care for Medicare beneficiaries with acute myocardial infarction (AMI). Our primary aim was to determine if thrombolytic therapy is associated with a better outcome than no reperfusion therapy. We also included comparisons with patients who underwent primary angioplasty. As a secondary objective, we sought to identify whether there were specific subgroups in which thrombolytic therapy provided a survival benefit.

METHODS

Study sample. The patient cohort in this study is derived from the CCP national sample. The CCP database contains detailed clinical data on 234,769 patients with a principal discharge diagnosis of AMI (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 410) between January 1994 and February 1996 (7).

We restricted the study sample to patients who were 65 years of age or older who had clinical and electrocardiographic features upon presentation, making them appropriate for consideration for acute reperfusion: they presented directly to the index hospital within 12 h of symptom onset with ST-segment elevation of at least 1 mm in at least 2 contiguous leads or LBBB (1). We restricted the study sample to the first AMI admission for any given individual in the CCP cohort and excluded patients who were transferred into the hospital.

The primary cohort consisted of patients without any absolute contraindications to thrombolytic therapy: active bleeding on arrival, a history of bleeding disorder, stroke within the past year (see following text) or terminal illness.

We derived an ideal subgroup of patients for reperfusion therapy by further restricting the primary cohort to patients presenting within 6 h of symptom onset and having no absolute or relative contraindications to thrombolytic therapy. Relative contraindications included prior internal bleeding, recent trauma or surgery, recent cardiopulmonary resuscitation, any prior stroke, blood pressure >180/110 on arrival, patient or physician refusal of thrombolytic therapy, current use of warfarin with an International Normalized Ratio >2 or a prothrombin time (PT) >16 s. Patients with cancer or dementia, those admitted from a nursing home and those with a do-not-resuscitate order on arrival were also excluded from the ideal group to eliminate patients at high risk of mortality from competing comorbidity. Finally, we excluded from the ideal cohort patients with cardiogenic shock, a group in which the decision-making process is somewhat more complex and controversial (8).

Data source. The data elements collected as part of the CCP have been reported previously (7) and included more than 140 variables for each patient. Trained medical record reviewers abstracted patient demographics, past cardiac and noncardiac history, admission characteristics, diagnostic test results (including measurement of ST elevation for each electrocardiographic lead) and information on in-hospital events and procedures. The high reliability of the abstraction process has been reported (9). Documentation of angioplasty required that a coronary intervention had been attempted; cardiac catheterizations without associated coronary interventions did not qualify. Stroke during the year before discharge was identified by merging the CCP records with Medicare Part A hospital claims, and searching the UB-92 principal and secondary diagnosis codes (ICD-9-CM codes 430, 431, 432.1, 432.9, 436).

Hospital characteristics, including annual volume of AMI and the ability to perform on-site coronary angioplasty, were obtained from the American Hospital Association database (10). The attending physician was identified from Medicare Part A hospitalization claims; specialty was determined through linkage with the American Medical Association Physician Masterfile. Dates of death in the Medicare Enrollment Database were derived from the discharge dates of billing records indicating a discharge disposition of death and from the Master Beneficiary Record. The use of the Medicare Enrollment Database to establish the time of death has been validated (11).

Statistical analysis. The primary cohort, consisting of patients without absolute contraindications to thrombolytic therapy, was divided into three subgroups on the basis of primary reperfusion strategy. The cohort receiving thrombolytic therapy included patients who received this agent within 6 h of arrival at the hospital. The cohort undergoing primary angioplasty included patients who received angioplasty as the first reperfusion strategy within 6 h of hospital arrival. For the 1.5% of patients who underwent both thrombolytic therapy and angioplasty, cohort assignment

was based on the first treatment. The remaining patients, including those who had not received reperfusion therapy within 6 h of hospital arrival, constituted the reference group. The 6-h limit for door-to-therapy time was designed to select patients who were most likely treated as part of an initial clinical strategy and not as a response to a change in clinical status.

We evaluated the bivariate association between each reperfusion strategy and the demographic, clinical, hospital, physician and co-intervention variables. Categorical characteristics were compared with the chi-square test and continuous values were compared using the Wilcoxon rank-sum test. The results are reported as means \pm standard deviation.

We developed a series of logistic models to determine the association of thrombolytic therapy and primary angioplasty, compared with the no-reperfusion strategy, with both 30-day and one-year mortality. The initial model examined the unadjusted risks of early thrombolytic therapy and primary angioplasty, with the no-reperfusion subgroup serving as the reference. Demographic characteristics, including age, race, and gender, were then included in the next model. Adjustment for imbalances in other patient characteristics was performed by adding covariates from the previously published Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) mortality model (systolic blood pressure at admission, pulse, location of AMI, Killip class, height, weight, history of infarction, history of bypass surgery, smoking status, and the presence or absence of diabetes, hypertension and cerebrovascular disease) to the logistic model (12). As a surrogate for myocardium at risk, we identified the number of leads with ST elevation and calculated the sum of ST elevation in all leads (except AVR) of the initial electrocardiogram. We also included in our candidate model variables additional clinical characteristics associated with mortality in older, sicker cohorts: impaired mobility, serum creatinine, urinary incontinence, dementia, cancer, chronic obstructive pulmonary disease, do-not-resuscitate status on arrival, and admission from a nursing home. We then expanded the model to incorporate hospital and physician characteristics including physician specialty, annual hospital AMI volume and interventional facilities. In the final model, we included the use of aspirin and beta-blockers on arrival to adjust for co-interventions that may have had a beneficial impact on mortality. In each step, all the covariates were forced into the model.

We repeated the logistic models after stratifying the cohort by age, gender, the extent of ST-segment elevation and hospitalization at a facility with on-site angioplasty. Then, using the criteria outlined above, we evaluated the effect of the reperfusion strategies on a very restricted group of patients without absolute or relative contraindications to thrombolytic therapy and with minimal comorbidity (the "ideal cohort").

Next, we developed a multivariate logistic regression

model with thrombolytic therapy as the dependent variable to estimate the propensity of receiving thrombolytic therapy (13). The demographic, clinical, hospital and co-intervention variables were added in a stepwise fashion with an entry and exit significance level of 0.0001. The strict entry criteria were used because of the large size of the study sample and the number of variables examined. With this model, patients were ranked by their likelihood of receiving thrombolytic therapy. Patients in the lowest quintile constituted the "lowest-likelihood" group, whereas those in the highest quintile represented the "highest-likelihood" group. We then evaluated the outcomes following thrombolytic therapy, primary angioplasty, or neither within both the "lowest-likelihood" and "highest-likelihood" groups.

Finally, we investigated the influence of the type of thrombolytic agent and the delay in thrombolytic treatment (door-to-therapy time). For type of agent, we report the results for streptokinase and tissue plasminogen activator (tPA), the two most commonly used thrombolytic agents. For the delay analysis we used the ACC/AHA guidelines to define "delay" as the administration of thrombolytic therapy more than 30 min after arrival at the hospital (1).

For all models, calibration was evaluated by comparing fitted probabilities of thrombolytic therapy with observed use within quintiles of likelihood (14). Discrimination was evaluated by calculating an area under the receiver operating characteristic curve for each model (15). The statistical analyses were performed with the SAS 6.12 software package (16).

RESULTS

Baseline Characteristics. From among the 234,769 patients in the CCP database, 40,563 (17.2%) were at least 65 years old, presented directly to the index hospital within 12 h of the onset of chest pain and had ST-segment elevation or LBBB. After exclusion of patients for whom the time of therapy was not recorded, 39,212 patients remained for analysis. From this group, 1,229 patients were excluded because of the presence of at least one absolute contraindication to thrombolytic therapy, leaving a sample size of 37,983 patients (Table 1).

Among the study sample, 14,341 (37.8%) patients received thrombolytic therapy and 1,599 (4.2%) underwent primary angioplasty; 22,043 (58.0%) patients did not undergo reperfusion therapy. The mean times to thrombolytic treatment and primary angioplasty after reaching the hospital were 62 (\pm 48) min and 131 (\pm 60) min, respectively. Table 2 reports the comparison of the treatment groups. Patients not receiving reperfusion therapy were older, more likely to be female, and more likely to have a history of hypertension, diabetes, AMI, heart failure, prior coronary artery bypass surgery and noncardiac comorbidity. Patients not receiving thrombolytic therapy or primary angioplasty were more likely to have LBBB and nonanterior location of infarction, and less likely to have dramatic ST elevation.

Table 1. Derivation of Primary Cohort and Ideal Subgroup from CCP Population

Characteristic	N
CCP population	234,769
Repeat admissions	23,773
Patients transferred into index hospital	42,177
Symptom onset to presentation >12 h	35,226
Symptom onset to presentation unknown	76,025
Absence of ST elevation or LBBB	152,477
Time of thrombolytic therapy or PTCA not documented	1,349
CCP qualifying patients	39,212
Active bleeding on arrival	799
History of bleeding disorder	236
Stroke within past year	90
Terminal illness	132
Primary cohort (patients without absolute contraindications)	37,983
Symptom onset to presentation >6 h	4,793
Recent trauma	917
Recent surgery	913
Cardiopulmonary resuscitation	1,185
Prior stroke	4,610
BP >180/110	8,811
Use of warfarin with PT ≥16 or INR ≥2	1,167
Documentation of physician or patient refusal of treatment	4,183
Cardiogenic shock on arrival	908
Cancer	794
Nursing home resident	1,371
Dementia	1,665
Do-not-resuscitate order	3,042
Ideal subgroup (patients without absolute or relative contraindications)	16,305

Exclusion criteria from various cohorts are not mutually exclusive; patients may have more than one exclusion criterion.

BP = blood pressure; CABG = coronary artery bypass surgery; CCP = Cooperative Cardiovascular Project; INR = International Normalized Ratio; LBBB = left bundle branch block; PT = prothrombin time; PTCA = percutaneous transluminal coronary angioplasty.

Patients receiving primary angioplasty and thrombolytic therapy were more likely to have been cared for by a cardiologist and were more likely to be treated with aspirin and beta-blockers.

Patients who received thrombolytic therapy had an unadjusted 30-day mortality rate of 13.5% ($p = 0.001$) and patients who underwent primary angioplasty had a 30-day mortality rate of 13.0% ($p = 0.001$) compared with 20.6% for patients who did not receive reperfusion therapy (Table 3). Among patients who died within 30 days, treatment with thrombolytic therapy was associated with earlier mortality (median of two days for patients receiving thrombolytic therapy, three days for those undergoing primary angioplasty and four days for those not receiving either therapy). At one year, the unadjusted mortality rates were similar between patients undergoing primary angioplasty (19.3%, $p = 0.001$) and thrombolytic therapy (19.5%, $p = 0.001$), and significantly lower than for patients not receiving reperfusion (36.9%).

In contrast to patients not treated with reperfusion therapy, the risk of developing post-infarction angina or heart failure during index hospitalization was lower in

patients receiving thrombolytic therapy and primary angioplasty (Table 3). Patients receiving thrombolytic therapy had a higher rate of intracranial hemorrhage (1.5%, $p = 0.001$) and total stroke (3.1%, $p = 0.07$) than those not receiving reperfusion (0.1% and 2.7%, respectively). Patients who had thrombolytic therapy were more likely to have a subsequent cardiac catheterization, coronary angioplasty, and coronary artery bypass than patients who did not undergo early reperfusion therapy.

Multivariate analysis. The logistic models for mortality were adjusted for demographic, clinical, hospital and physician characteristics, medical history, electrocardiographic factors and co-interventions. These variables produced mortality models with good to excellent discrimination (area under the receiver operating characteristic (ROC) curve of 0.78 for the 30-day model and 0.79 for the one-year model). In assessing the goodness-of-fit in both models, there was a <1% difference between observed and expected mortality within each quintile of likelihood, though the difference between expected and observed mortality rates was significant because of the large numbers. After adjustment, thrombolytic therapy was no longer associated with a significant 30-day survival benefit (odds ratio [OR] 1.01; 95% confidence interval [CI]: 0.94 to 1.09), but primary angioplasty continued to be associated with lower mortality (OR 0.79; 95% CI: 0.66 to 0.94). At one year, both thrombolytic therapy (OR 0.84; 95% CI: 0.79 to 0.89) and primary angioplasty (OR 0.71; 95% CI: 0.61 to 0.83) were associated with lower mortality.

Subgroup analyses. In most of the stratified analyses, mortality following thrombolytic therapy and primary angioplasty was similar to the overall analysis. Patients treated with thrombolytic therapy did not have a lower 30-day mortality, adjusted for age, gender, electrocardiographic criteria and availability of on-site angioplasty (Fig. 1). On the other hand, younger patients, women, and patients with >6 mm ST elevation had a statistically significantly lower mortality with primary angioplasty. At one year, both thrombolytic therapy and primary angioplasty were associated with a significantly lower mortality rate, independent of age, gender, extent of ST elevation, and availability of on-site angioplasty (Fig. 2). The benefit of primary angioplasty was greater than thrombolytic therapy at one year in each stratum.

Patients with LBBB treated with reperfusion therapy had an increased risk of 30-day and one-year mortality independent of the reperfusion strategy. Because these patients were so strikingly overrepresented in the group that underwent no reperfusion (Table 2), we repeated the mortality outcome comparison after omitting patients with LBBB from all cohorts. Our results did not change appreciably.

The model developed to determine the likelihood of receipt of thrombolytic therapy had an area under the ROC curve of 0.77 and the goodness-of-fit statistic had a p-value of 0.97, indicating an excellent fit. Using this model, patients in the "highest-likelihood" quintile had a high

Table 2. Baseline Clinical and Hospital Characteristics of Patients Without Absolute Contraindications to Thrombolytic Therapy

Characteristic	No Reperfusion	Thrombolytic Therapy	p*	Primary PTCA	p†
N	22,043 (58.0%)	14,341 (37.8%)		1,599 (4.2%)	
Demographics					
Age (mean), years	77.7 ± 7.4	73.4 ± 6.1	0.001	73.7 ± 6.1	0.001
Median age (25 th , 75 th)	78 (72, 83)	73 (69, 77)		73 (69, 78)	
Female	50.4%	42.7%	0.001	43.0%	0.001
Caucasian	91.0%	92.7%	0.001	92.8%	0.02
Risk factors					
Hypertension	63.2%	56.1%	0.001	57.4%	0.001
Diabetes	32.2%	22.6%	0.001	21.7%	0.001
Smoker	12.8%	20.8%	0.001	20.4%	0.001
Cardiac history					
AMI	34.8%	20.6%	0.001	20.0%	0.001
Heart failure	26.9%	6.7%	0.001	6.3%	0.001
Bypass surgery	14.2%	7.2%	0.001	9.0%	0.001
Noncardiac history					
Stroke	15.8%	6.7%	0.001	10.2%	0.001
COPD	20.1%	15.8%	0.001	16.3%	0.001
Dementia	6.2%	2.0%	0.001	1.4%	0.001
Limited mobility	19.3%	7.6%	0.001	8.0%	0.001
Urinary incontinence	6.9%	2.6%	0.001	3.8%	0.001
Cancer	2.6%	1.3%	0.001	2.6%	0.93
Nursing home resident	5.6%	0.9%	0.001	0.9%	0.001
DNR on arrival	11.2%	3.7%	0.001	2.4%	0.001
Clinical presentation					
Symptom onset <6 h	84.1%	92.3%	0.001	89.4%	0.001
Mean time after arrival (min)	N/A	62 ± 48	N/A	131 ± 60	N/A
Early cardiac arrest	3.5%	2.5%	0.001	4.0%	0.27
Height (inches)	65.9 ± 4.2	66.5 ± 4.0	0.001	66.6 ± 4.1	0.001
Weight (lbs)	159.0 ± 35.8	167.7 ± 34.2	0.001	167.3 ± 33.2	0.001
Hypotension (SBP < 90)	1.5%	2.0%	0.001	2.8%	0.001
Bradycardia (HR < 60)	7.7%	17.9%	0.001	19.6%	0.001
Killip class					
1	45.4%	63.4%	0.001	61.9%	0.001
2	12.6%	14.6%	0.001	13.1%	0.52
3	39.6%	20.1%	0.001	19.1%	0.001
4	2.4%	2.0%	0.03	5.9%	0.001
Electrocardiographic features					
ST elevation ≥3 leads	73.2%	86.1%	0.001	86.1%	0.001
Sum ST elevation ≥6 mm	39.3%	55.9%	0.001	57.0%	0.001
Anterior location	48.7%	56.0%	0.001	56.9%	0.001
LBBB	23.4%	2.7%	0.001	3.9%	0.001
Serum creatinine (mg/dl)	1.4 ± 0.9	1.2 ± 0.5	0.001	1.2 ± 0.8	0.001
Hospital characteristics					
Annual AMI volume	201 ± 174	186 ± 155	0.001	316 ± 205	0.001
PTCA available	42.2%	38.9%	0.001	100%	0.001
Attending physician is cardiologist	25.0%	35.6%	0.001	59.1%	0.001
Admission therapies					
Aspirin	78.3%	93.2%	0.001	93.8%	0.001
Beta blocker	43.7%	61.1%	0.001	53.5%	0.001

*Comparison of thrombolytic therapy to no reperfusion. †Comparison of primary coronary angioplasty to no reperfusion.

AMI = acute myocardial infarction; COPD = chronic obstructive pulmonary disease; DNR = do-not-resuscitate; HR = heart rate; LBBB = left bundle branch block; PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic blood pressure.

probability of receiving thrombolysis, whereas those in the lowest were unlikely to receive thrombolysis. After adjustment for other factors, among patients in the “lowest-likelihood” quintile to receive thrombolytic therapy, reperfusion therapy was associated with a nonsignificantly higher 30-day mortality and no significant benefit for one-year

mortality. Among patients in the “highest-likelihood” quintile to receive thrombolytic therapy, reperfusion therapy was associated with a nonsignificantly lower 30-day and one-year mortality.

We repeated the logistic models for the 16,305 patients considered the most ideal for reperfusion therapy (Table 4).

Table 3. In-Hospital Events and Mortality Rates for Patients Without Absolute Contraindications to Thrombolytic Therapy*

Characteristic	No Reperfusion	Thrombolytic Therapy	p†	Primary PTCA	p‡
N	22,043 (58.0%)	14,341 (37.8%)		1,599 (4.2%)	
Post-MI angina	31.5%	29.4%	0.001	23.6%	0.001
Heart failure	47.8%	29.4%	0.001	32.3%	0.001
Intracranial hemorrhage	0.1%	1.5%	0.001	0.1%	0.98
All strokes	2.7%	3.1%	0.07	2.1%	0.15
Hemorrhage	11.7%	22.5%	0.001	30.9%	0.001
Cardiac catheterization	23.3%	36.7%	0.001	100%	0.001
Coronary angioplasty	4.7%	10.0%	0.001	100%	0.001
Coronary artery bypass surgery	4.3%	6.0%	0.001	10.1%	0.001
Mortality					
30-day	20.6%	13.5%	0.001	13.0%	0.001
1-year	36.9%	19.5%	0.001	19.3%	0.001

*Reference group for statistical comparisons are patients not receiving reperfusion therapy. †Comparison of thrombolytic therapy with no reperfusion. ‡Comparison of primary angioplasty with no reperfusion.
 MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

In this subgroup, 8,487 (52.0%) of the patients received thrombolytic therapy, 700 (4.3%) received primary angioplasty, and 7,118 (43.7%) did not undergo reperfusion therapy. The 30-day and one-year mortality rates were lowest for patients undergoing primary angioplasty; patients receiving thrombolytic therapy had lower mortality than those not receiving reperfusion therapy. After adjusting for baseline characteristics, neither thrombolytic therapy nor angioplasty was associated with a significant survival advantage at 30 days. Both reperfusion strategies were associated with a lower risk of one-year mortality.

We repeated the analyses after stratifying the thrombolytic therapy group by door-to-therapy time and selection of

thrombolytic agent (Table 5). Administration of the thrombolytic agent within 30 min was associated with a trend toward decreased 30-day mortality. The benefit of early thrombolytic therapy was even more apparent at one year; compared with patients in the no-reperfusion group, patients treated with streptokinase had a nonsignificant decrease in mortality, while those treated with tPA had a significant reduction in mortality.

DISCUSSION

Previous studies. Our results provide new information about the use and effectiveness of thrombolytic therapy in

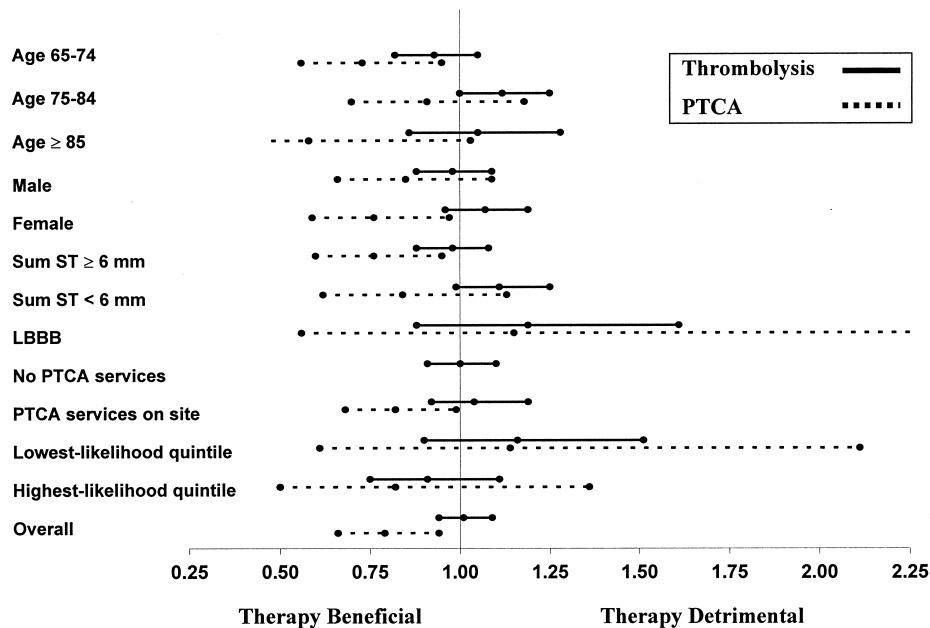


Figure 1. Thirty-day mortality model for patients without absolute contraindications to thrombolytic therapy, stratified by clinical and hospital characteristics. The odds ratio and 95% confidence intervals for thrombolysis (solid line) and primary angioplasty (dashed line) are compared with no reperfusion strategy at 30 days. The results are stratified by clinical and hospital characteristics and also demonstrated for the combined study sample. Points to the left of 1.00 indicate a benefit of the therapy whereas point estimates to the right of 1.00 indicate a detrimental effect.

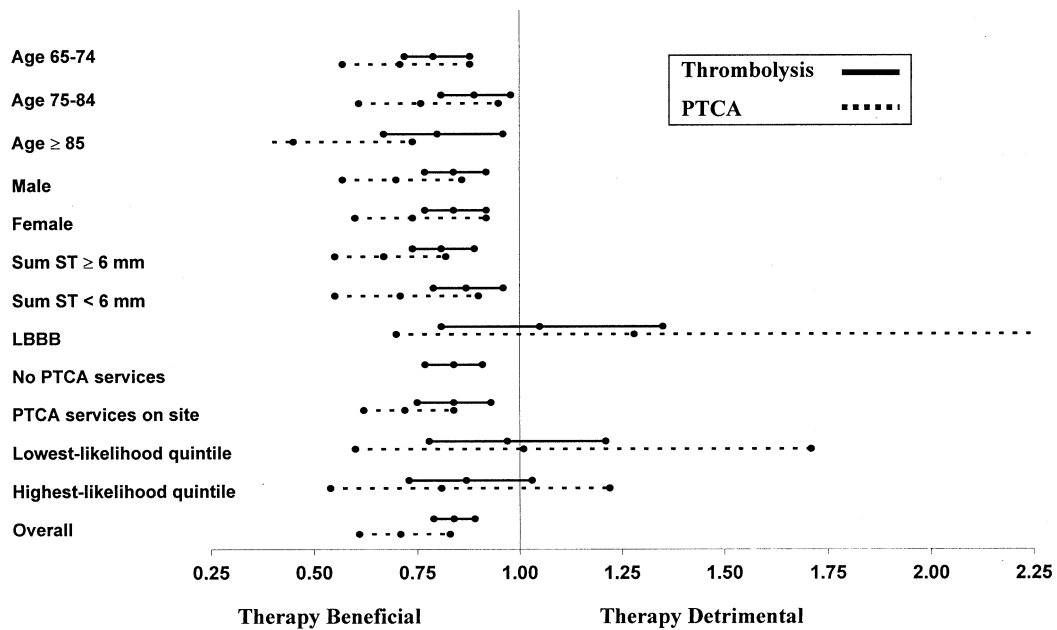


Figure 2. One-year mortality model for patients without absolute contraindications to thrombolytic therapy, stratified by clinical and hospital characteristics. The odds ratio and 95% confidence intervals for thrombolysis (solid line) and primary angioplasty (dashed line) are compared with no reperfusion strategy at one year. The results are stratified by clinical and hospital characteristics and also demonstrated for the combined study sample. Points to the left of 1.00 indicate a benefit of the therapy whereas point estimates to the right of 1.00 indicate a detrimental effect.

actual clinical practice among older patients hospitalized with an AMI. Unlike the randomized controlled trials, thrombolytic therapy in this community-based cohort was not associated with significant or substantial benefit at 30 days when compared with no treatment. Our findings were consistent across subgroups—including strata of age, gender, electrocardiographic features and hospital on-site angioplasty—and were evident among a restricted cohort of patients considered “ideal” for therapy, a group that might have been expected to be most similar to the cohort enrolled in the trials.

Although the randomized clinical trials demonstrated a benefit with thrombolytic therapy, the magnitude of the benefit was smaller among older patients. In pooled analyses there was a marked diminution of relative benefit associated with thrombolytic therapy in the oldest age groups. Among the 5,754 patients who were 75 years of age and older, the relative reduction in mortality was roughly 4%, with an absolute reduction of 1% (2). This mortality difference was not statistically significant. The lack of benefit that we

observed in the patients who were 65 to 74 years of age does contrast with the pooled result of a 16% relative reduction and an absolute reduction of 2.6%. The difference in outcomes between these randomized clinical trials and our observational nationwide study likely reflects, in part, the strict selection criteria of the clinical trials relative to clinical practice. In addition to explicit study inclusion criteria (clinical trials are, in general, designed to enroll patients with the most favorable expected benefit-to-risk ratio), there is clinical judgment applied in the decision to even consider patients for enrollment in trials. This pre-randomization patient selection is likely responsible for the small numbers of elderly individuals enrolled in acute reperfusion trials, and raises questions about how representative of their age cohort they are.

However, thrombolytic therapy was associated with an improved long-term prognosis. The reason for a benefit of thrombolytic therapy at one year that was not present at 30 days remains less clear. Prior studies demonstrate that the significant short-term benefit of thrombolysis persists

Table 4. Unadjusted and Adjusted Mortality Rates of Patients Ideal for Reperfusion Therapy*

Characteristic	No Reperfusion	Thrombolytic Therapy	p†	Primary PTCA	p‡
N	7,118 (43.7%)	8,487 (52.0%)		700 (4.3%)	
Unadjusted mortality rates					
30-day	14.8%	10.6%	0.001	8.9%	0.001
1-year	29.4%	15.8%	0.001	13.1%	0.001
Adjusted mortality rates					
30-day	1.00	1.05 (0.93, 1.19)‡		0.78 (0.58, 1.05)	
1-year	1.00	0.85 (0.77, 0.94)		0.63 (0.49, 0.81)	

*Reference group for odds ratios are patients who did not receive early reperfusion therapy. †Comparison of thrombolytic therapy to no reperfusion. ‡Comparison of primary coronary angioplasty to no reperfusion.

Table 5. Thirty-Day and One-Year Mortality Models Stratified by Thrombolytic Therapy Characteristics

Logistic Model Features	Neither	30-Day Mortality		1-Year Mortality	
		Thrombolytic Therapy	PTCA	Thrombolytic Therapy	PTCA
Early thrombolytic therapy (≤ 30 min)	1.00	0.93 (0.85, 1.01)	0.79 (0.67, 0.94)	0.77 (0.71, 0.83)	0.71 (0.62, 0.83)
Later thrombolytic therapy		1.27 (1.16, 1.39)		1.01 (0.93, 1.09)	
Streptokinase	1.00	1.20 (1.07, 1.34)	0.80 (0.68, 0.96)	0.99 (0.90, 1.09)	0.72 (0.62, 0.83)
tPA		1.03 (0.95, 1.12)		0.83 (0.77, 0.89)	

PTCA = percutaneous transluminal coronary angioplasty; tPA = tissue plasminogen activator.

through one year and may even be present as far as 10 years after the AMI (17-19), but that the benefit does not increase over time. Our results may reflect an early hazard of thrombolysis, an attenuated early benefit of thrombolysis among older patients or a selection effect for which we were unable to adjust. The early hazard of thrombolytic therapy, particularly stroke and hemorrhage, is higher among older patients, thereby reducing the potential 30-day benefit. Alternatively, the benefit of an "open artery" resulting from thrombolysis may not be limited to myocardial salvage and may occur later as a result of improved left ventricular modeling. More likely, the results reflect the absence of a true benefit of thrombolytic therapy in older patients and a tendency to administer thrombolytic agents to healthier patients. Although we adjusted for many prognostic factors and comorbid conditions, there may have been residual confounders.

In contrast, primary angioplasty was associated with an improved survival at both 30 days and one year. In a recent investigation using the same database, we found that patients treated with primary angioplasty had a moderate improvement in survival compared with patients treated with thrombolytic therapy (5). In an ideal restricted cohort, the magnitude of benefit was small and not statistically significant. In that investigation we did not include an assessment of the "no-treatment" strategy. The current study suggests that primary angioplasty, in contrast to thrombolytic therapy, may be associated with an early survival benefit. Although both reperfusion strategies were associated with improved one-year survival, the benefit of primary angioplasty was greater than that of thrombolytic therapy, particularly in patients over age 85. Our results are consistent with a recent meta-analysis of randomized trials of angioplasty versus thrombolysis showing a modest benefit of primary angioplasty over thrombolytic therapy in the management of AMI (3). It is interesting that analyses of other observational databases that examined younger cohorts (median age 60 years) suggest that the outcomes of both strategies may be similar (20,21). The improved survival associated with primary angioplasty in the CCP cohort (median age 75 years) may reflect a greater benefit of this reperfusion strategy among older patients.

Another important finding in this study is the low utilization of reperfusion therapy in older Americans. Among patients without absolute contraindications to thrombolytic therapy, only 42% received either thrombolytic therapy or primary angioplasty. Even after restricting the

cohort to a subgroup of patients considered ideal for thrombolytic therapy, the proportion of patients receiving reperfusion therapy remained low (56.3%). Although there may have been factors for which we could not account, it is unclear why so many otherwise eligible and appropriate patients did not receive reperfusion therapy.

Study limitations. The most important limitation of this study is the nonrandom assignment of treatment strategy. Consequently, we cannot exclude the possibility that unmeasured selection factors influenced our results. To address this issue, we used methods that minimize the problems inherent to drawing inferences from observational data (22). For other studies in which we applied this methodology, aspirin and beta-blockers were found to be associated with a similar relative risk reduction in a population-based sample of older patients as in the randomized trials (23,24).

Conclusions. We found evidence supporting the one-year, but not 30-day, benefit of thrombolytic therapy for patients 65 years of age and older. These findings are surprising and not entirely consistent with the randomized trials. In contrast, the results with primary angioplasty are consistent with previous findings. The results can be interpreted as indicating that older patients benefit from thrombolytic therapy in the long run. On the other hand, it may be that the intervention is not as effective, on average, in the older population as it is in younger patients, and that the long-term benefit is the result of residual confounding associated with treating patients who have less comorbidity and better long-term prognosis. Thus, the effectiveness of thrombolytic therapy and the role of primary angioplasty in the very elderly remain somewhat uncertain. Overall, our findings generally support the current ACC/AHA guidelines that reflect the absence of a consensus opinion in administering thrombolytic therapy to older patients. Our findings also indicate a need for further investigation to determine the best approach to the treatment of older patients with suspected AMI and ST-segment elevation or LBBB.

Reprint requests and correspondence: Dr. Harlan M. Krumholz, Yale University School of Medicine, 333 Cedar St., P.O. Box 208025, New Haven, Connecticut 06520-8025. E-mail: harlan.krumholz@yale.edu.

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Alan K. Berger, Martha J. Radford, Yun Wang, and Harlan M. Krumholz
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