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# Effectiveness of Thrombolytic Therapy for Acute Myocardial Infarction in the Elderly

## *Cause for Concern in the Old-Old*

Stephen B. Soumerai, ScD; Thomas J. McLaughlin, ScD; Dennis Ross-Degnan, ScD; Cindy L. Christiansen, PhD; Jerry H. Gurwitz, MD

**Background:** National guidelines have encouraged increased use of thrombolytic therapy for elderly patients with acute myocardial infarction (AMI). However, evidence supporting thrombolytic therapy in patients 75 years and older is lacking. In a retrospective cohort study of 2659 elderly AMI patients, we determined the association between thrombolytic use and in-hospital mortality by age and among patients with or without absolute or relative contraindications to thrombolytic treatment.

**Methods:** We abstracted the medical records of 2659 elderly patients admitted with AMI at 37 Minnesota community hospitals between 1992 and 1996. The main outcome measure was in-hospital mortality, controlling for demographic, clinical, comorbidity, and severity-of-illness variables.

**Results:** Sixty-three percent of 719 eligible patients received thrombolytic therapy. Twenty-seven percent of thrombolytic recipients had absolute contraindications to treatment. Patients receiving thrombolytic agents had fewer and less

severe comorbidities than those not receiving thrombolytic therapy. There was a 4% increase in the odds of death for every 1-year increase in age for all thrombolytic recipients vs nonrecipients (odds ratio [OR], 1.04 per year; 95% confidence interval [CI], 1.01-1.08;  $P = .03$ ). Among patients with 1 or more contraindication, the OR for death associated with thrombolytic use was 1.57 (95% CI, 1.03-2.40;  $P = .04$ ). The adjusted odds of death among eligible thrombolytic recipients (vs nonrecipients) increased significantly with age (OR, 1.08 per year; 95% CI, 1.02-1.14;  $P = .008$ ). Among eligible patients aged 80 to 90 years, the predicted odds of death among thrombolytic recipients vs nonrecipients was 1.4. Among eligible patients younger than 80 years, thrombolytic use was associated with reduced mortality.

**Conclusions:** Our findings suggest the need for more research on the effectiveness of thrombolytic therapy for AMI patients 75 years and older and for more careful selection of elderly patients for this treatment.

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**L**ARGE randomized clinical trials<sup>1-10</sup> involving about 60 000 patients worldwide have confirmed that thrombolytic therapy can substantially increase survival among patients with acute myocardial infarction (AMI), reducing absolute mortality by 20 to 30 per thousand treated.<sup>10</sup> As a result, many national treatment guidelines and quality assurance programs have strongly recommended use of these agents among younger and elderly AMI patients.<sup>11-14</sup>

Although the population benefits of thrombolytic therapy outweigh the risks in eligible middle-aged AMI patients and those aged 65 to 74 years, the evidence supporting use of thrombolytic therapy for patients 75 years and older is less clear. A systematic overview of 9 large trials of thrombolytic treatment in AMI cases showed that fewer than 10% of patients were 75 years or older,<sup>10</sup> although this

group experiences in-hospital mortality rates almost 10 times higher than among patients younger than 65 years (non-elderly).<sup>15</sup> Moreover, the pooled effect of thrombolytic therapy on survival among patients 75 years and older was not statistically significant.<sup>10</sup>

Despite the substantial rise in use of thrombolytic therapy among elderly patients ( $\geq 65$  years) since 1990,<sup>16</sup> many physicians are still reluctant to prescribe them for the oldest patients and for those with severe comorbidities because of the risks of bleeding and hemorrhagic stroke.<sup>14,17</sup> Several mechanisms could justify such caution in the old-old ( $\geq 80$  years): (1) the likelihood of delay from initial symptoms to hospital arrival ( $\geq 6$  hours) is increased in this group<sup>18</sup>; such delay is associated with substantially reduced survival benefits of thrombolysis<sup>11,19</sup>; absolute or relative contraindications are more likely in elderly patients<sup>12</sup>; and the

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## SUBJECTS AND METHODS

### STUDY SAMPLE

The data for this study were drawn from medical records for a previous study of patients admitted with AMI to 37 Minnesota hospitals during the periods October 1, 1992, to July 31, 1993, and July 1, 1995, to April 30, 1996 (before and after an educational intervention that did not affect thrombolytic use).<sup>14,17,18,24</sup> The study hospitals represented more than 80% of all community hospital beds and more than half of all AMI cases statewide. Only 2 of the hospitals were academic centers, 17 were in rural communities, 19 had fewer than 100 beds, and 2 had more than 500 beds.

The study population consisted of all elderly patients ( $\geq 65$  years) who were admitted with a diagnosis of AMI or suspected AMI and met at least 2 of the following criteria: (1) clinical symptoms typical of AMI (chest pain, arm or shoulder pain, diaphoresis, dyspnea, nausea or vomiting, or neck and/or jaw pain); (2) explicit medical record documentation by a physician that electrocardiographic findings were considered compatible with AMI (ie, new Q wave or ST segment depression or elevation  $\geq 1$  mm); and (3) elevated serum creatine kinase and MB fractions.<sup>14,24</sup> Patients were excluded if they died before admission, were transferred from a nonstudy hospital, or had an AMI in the previous 2 weeks. We also excluded 229 patients who received a revascularization procedure within 12 hours of admission, leaving a total study sample of 2659.

### DATA COLLECTION

As previously described,<sup>14,17,18,24</sup> trained nurses abstracted detailed medical record data on selected clinical variables, including AMI inclusion and exclusion criteria; medical history; admission data, including time to presentation; clinical and electrocardiographic findings at presentation and during the first 24 hours of hospitalization, and comorbidities at admission (based on the Greenfield Index of Coexistent Disease)<sup>25</sup>; indications and absolute or relative contraindications to thrombolytic therapy at presentation to the hospital, based on national evidence-based guidelines (**Table 1**)<sup>26</sup>; drugs administered in the first 48 hours, including during emergency transport and in the emergency department; time from hospital presentation to thrombolytic administration; complications during the first 72 hours, including significant bleeding (requiring a blood transfusion or other procedure) and hemorrhagic stroke; and whether discharged alive. Abstractors were required to demonstrate ongoing interrater agreement of 95% or higher with the criterion reviewer. The reviewers audited random samples of 10% of each abstractor's completed cases to ensure that this standard was met. In addition, the interpretations of electrocardiographic findings in the medical record correlated highly with the interpretations of 2 cardiologists.<sup>24</sup>

As described in other studies,<sup>14,17,18,24</sup> we determined eligibility for thrombolytic therapy based on the 1990 American College of Cardiology/American Heart Association guidelines<sup>26</sup> in effect during the observation period. Eligible patients were defined as having all indications for treatment and no absolute or relative contraindications (Table 1). All other patients had 1 or more absolute or relative contraindications.

risk of bleeding and hemorrhagic stroke is markedly increased among thrombolytic recipients 75 years and older.<sup>10,20,21</sup> Thus, the balance of risks and benefits of thrombolytic therapy may be different in the oldest age groups.<sup>22</sup> Increased comorbidity in this group may also adversely affect patient outcomes and has been demonstrated to affect clinical decision making relating to the use of thrombolytic therapy.<sup>17</sup>

Because of the relative exclusion of the oldest patients in the randomized clinical trials of thrombolytic therapy, the differences between results achieved in randomized clinical trials and community settings, and the likelihood that elderly patients in the community have more absolute or relative contraindications and comorbidities than participants in randomized clinical trials, it is important to study the appropriateness and outcomes of thrombolytic therapy in community populations.

Because the rapid application of thrombolytic eligibility criteria for elderly patients is challenging,<sup>23</sup> it is possible that some ineligible patients are receiving thrombolytic therapy, leading to suboptimal outcomes, but few data exist to address this issue. Therefore, we sought to answer the following specific questions using a large population-based sample of elderly AMI patients in the community: (1) What proportion of eligible and other patients (with absolute or relative contraindications) in community settings receive thrombolytic therapy? (2) Controlling for baseline risk status, demographic variables, and comorbidities, what is the association be-

tween thrombolytic use and in-hospital mortality by age and among patients with or without absolute or relative contraindications to thrombolytic treatment?

## RESULTS

### CHARACTERISTICS OF SAMPLE AND USE OF THROMBOLYTIC THERAPY

Of the 2659 elderly patients who met study criteria, 735 patients (27.6%) received thrombolytic therapy. In general, patients receiving thrombolytic therapy had fewer comorbidities and risk factors than patients who did not receive a thrombolytic (**Table 2**). Patients who did not receive thrombolytic therapy were significantly more likely to have medical histories of previous AMI, angina, revascularization procedures, previous stroke, diabetes, and hypertension. Patients who did not receive thrombolytic therapy were almost twice as likely to have heart failure or pulmonary edema (31.5%) and a severe comorbidity (36.1%) at admission compared with thrombolytic recipients. Thrombolytic recipients were more likely to exhibit ST elevation and to have experienced anterior myocardial infarction. As expected, more than twice as many patients who did not receive thrombolytic therapy presented to the hospital more than 6 hours after symptoms (42.0% vs 15.8% for thrombolytic recipients).

Thrombolytic therapy recipients were significantly more likely than nonrecipients to have received aspirin

## PATIENT OUTCOMES AND INDEPENDENT VARIABLES

Our primary outcome of interest was short-term mortality, measured as death due to any cause during the AMI hospitalization. Demographic variables included age and female sex, which are associated with lower short-term survival after AMI<sup>27</sup> and reduced rates of thrombolytic use,<sup>24</sup> and race. We included relevant medical history variables, time to presentation, and clinical characteristics at admission (Table 1), which might predict AMI outcomes.<sup>27</sup> Also, we included variables identifying anterior location of myocardial infarction and the presence of a mild, moderate, or severe comorbidity (based on the Greenfield Index of Coexistent Disease),<sup>25</sup> both of which are associated with poorer AMI outcomes.<sup>10</sup> In addition, we included variables identifying patients receiving selected treatments during the first day of hospitalization (aspirin,  $\beta$ -blockers, and angiotensin-converting enzyme inhibitors) and several provider characteristics that could influence thrombolytic use or survival, such as the number of AMIs treated at the hospital<sup>28</sup> and availability of cardiac catheterization.

## STATISTICAL ANALYSIS

First, we compared the baseline demographic and clinical characteristics, time to presentation, medical histories, drug management in the first 24 hours, and provider characteristics of thrombolytic recipients vs nonrecipients using  $\chi^2$  statistics. Next, we conducted simple univariate comparisons of mortality among thrombolytic

recipients and nonrecipients stratified by age (65-74 years vs  $\geq 75$  years).

We first calculated propensity scores<sup>29</sup> to estimate the likelihood that a patient received thrombolytic therapy. These propensity scores were then used as control variables in analyses of the effects on mortality of actual use of thrombolytic therapy. Propensity scores are used in observational studies to reduce selection-to-treatment bias and to reduce to 1 value the differences in observed patient characteristics that affect treatment selection. Propensity of exposure to a thrombolytic agent was developed using logistic regression on all variables in Table 1 and interactions of these variables. To adjust maximally for potential confounding, we included in the final propensity model all variables associated with the likelihood of thrombolytic use with  $P < .30$ . A *c* statistic (area under a receiver operating characteristic curve) and Hosmer-Lemeshow goodness-of-fit test indicated that the propensity score model predicted thrombolytic use well.<sup>30,31</sup>

A logistic regression model, with patients' individual propensity scores as a control variable, was used to test the effect of age and thrombolytic use on mortality in all patients, while controlling for selection factors leading to thrombolytic use. In a separate model, we added an interaction term examining effect modification by age (continuous variable). In addition, patients were stratified into those eligible for thrombolytic therapy and all other patients with absolute or relative contraindications, and stratum-specific estimates of the effect of thrombolytic use on mortality were obtained and adjusted for propensity scores.

or  $\beta$ -blockers (89.4% vs 72.5% and 60.3% vs 42.3%, respectively) but were somewhat less likely to receive angiotensin-converting enzyme inhibitors (Table 2). In addition, those receiving thrombolytic therapy were somewhat more likely to be cared for by a cardiologist or at a hospital with a low volume of AMIs.

## THROMBOLYTIC USE BY ELIGIBILITY

Among 719 patients who were eligible for thrombolytic therapy, 455 (63.3%) received this treatment. However, among the remaining 1940 patients who had 1 or more absolute ( $n=1709$ ) or relative contraindications, 280 (14.4%) received a thrombolytic.

Among 280 thrombolytic recipients with contraindications, 71.0% had 1 or more absolute contraindication to thrombolysis. The most frequent reasons for ineligibility (Table 1) were presence of 1 or more medical contraindications (43.3%), absence of an ST segment elevation of 1 mm or more (25.3%), and delay greater than 12 hours (23.9%).

## UNADJUSTED MORTALITY AND HEMORRHAGIC STROKE

In the overall study population, 13.1% died during the AMI hospitalization. The unadjusted mortality rate for thrombolytic recipients aged 65 to 74 years was 7.2%, slightly below the rate of 7.6% observed for nonrecipi-

ents (nonsignificant). However, among those 75 years or older, thrombolytic recipients experienced a somewhat higher unadjusted mortality rate than nonrecipients (20.1% vs 16.6%,  $P=.15$ ).

Overall, 0.6% of study patients experienced a fatal or nonfatal hemorrhagic stroke; among younger thrombolytic recipients (age,  $<75$  years), this rate was 1.4% compared with 0.2% among nonrecipients ( $P=.02$ ); among patients 75 years and older, hemorrhagic stroke occurred in 2.4% of thrombolytic recipients compared with 0.2% of nonrecipients ( $P<.001$ ).

## MULTIVARIATE ANALYSES

**Table 3** provides the results of the multiple logistic regression analyses of the odds of death for thrombolytic recipients vs nonrecipients for the entire sample and for subsets of the sample stratified by thrombolytic eligibility. Propensity scores (probability of receiving thrombolytic therapy) range between 0 and 1. As expected based on the lower baseline risk status of thrombolytic recipients compared with nonrecipients, the propensity score was strongly associated with a reduced odds of death in the overall sample (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.22-0.82;  $P=.01$ ) and among those with absolute or relative contraindications to thrombolytic therapy (OR, 0.23; 95% CI, 0.09-0.54;  $P=.001$ ).

The odds of death associated with thrombolytic use in all patients (Table 3) was 1.53 (95% CI, 1.13-2.08;

**Table 1. Eligibility and Contraindications for Thrombolytic Therapy\***

## Eligible population†

All patients with AMI or suspected AMI presenting within 12 h of onset of symptoms; ST-segment elevation  $\geq 1$  mm‡; no contraindications.

## Absolute contraindications

Active internal bleeding; suspected aortic dissection; prolonged or traumatic cardiopulmonary resuscitation; recent head trauma ( $\leq 2$  wk); intracranial neoplasm; hemorrhagic ophthalmic conditions; previous allergic reaction to the thrombolytic agent; sustained systolic blood pressure  $>180$  mm Hg or diastolic blood pressure  $>110$  mm Hg; any recorded blood pressure  $>200/120$  mm Hg on admission; trauma or surgery  $\leq 2$  wk; and AMI onset  $>24$  h.

## Relative contraindications

Major bleeding; recent trauma or surgery  $>2$  wk and  $<2$  mo; history of chronic severe hypertension with or without drug therapy; history of CVA; current use of warfarin anticoagulants; prior use of streptokinase or APSAC (if they are the agents of choice); significant liver dysfunction; active peptic ulcer; and AMI onset  $>12$  h.

\*AMI indicates acute myocardial infarction; CVA, cerebrovascular accident; and APSAC, anistreplase (anisoylated plasminogen streptokinase activator complex).

†Eligibility for thrombolytic therapy was defined as being in the eligible population and having no absolute or relative contraindications. Absence of ST-segment elevation greater than 1 mm was considered an absolute contraindication in analyses of patients with and without contraindications.

‡Based on physician documentation in the medical record.

$P = .006$ ), but this was strongly influenced by the large fraction (71.0%) of patients with 1 or more absolute or relative contraindication for whom the adjusted odds of death among thrombolytic recipients was 1.57 (95% CI, 1.03-2.40;  $P = .04$ ) compared with nonrecipients. For patients eligible for thrombolytic treatment, the odds of death were not significantly different between those patients receiving and not receiving the drug in the model without an interaction term (OR, 0.96; 95% CI, 0.58-1.58;  $P = .86$ ).

The significant interaction term for thrombolytic use with age for all patients (Table 3) indicates that the odds of death associated with thrombolytic use increased with age (OR, 1.04; 95% CI, 1.01-1.08;  $P = .03$ ). This indicates that there was a 4% increase in the odds of death for every 1-year increase in age for all thrombolytic recipients compared with nonrecipients. Like the overall cohort, mortality associated with thrombolytic use increased with age (OR, 1.08; 95% CI, 1.02-1.14;  $P = .008$ ) among patients eligible for thrombolytic therapy. However, thrombolytic therapy was associated with a survival benefit for eligible patients younger than 80 years. For all other patients with contraindications, the increased odds of death associated with thrombolytic use did not change with age (Table 3).

The **Figure** shows the adjusted odds of death for thrombolytic recipients vs nonrecipients by age for the entire cohort, for eligible patients, and for all other patients with contraindications. For the entire cohort (Figure A), thrombolytic use for patients older than 70 years was associated with an increased odds of mortality compared with younger patients. For eligible patients younger than 80 years, thrombolytic use was associated with reduced mortality, but thrombolytic recipients older than 80 years experienced higher mortality rates than nonrecipients (predicted OR, 1.4 for patients aged 80-90 years). Age did not significantly modify the association between thrombolytic use and increased mortality among all other patients with absolute or relative contraindications (Figure B).

**COMMENT**

The findings of this observational study regarding the use of thrombolytic agents in a large community popu-

lation of AMI patients suggest that (1) in general, thrombolytic recipients have fewer comorbidities and risk factors than nonrecipients; (2) thrombolytic use is associated with reduced mortality among eligible patients younger than 80 years but increased mortality among the old-old; the oldest patients, even those without relative or absolute contraindications to therapy, experienced an excess risk of mortality compared with untreated patients (OR, 1.4 for thrombolytic recipients 80-90 years); and (3) the manner in which thrombolytic therapy is used in the community setting differs markedly from that observed in randomized clinical trials, where patients are selected for treatment using explicit and consistent criteria and agents are administered according to protocol. A substantial proportion of thrombolytic recipients in the study (38.0%) had relative and absolute contraindications to treatment, and this was strongly associated with an increased risk of mortality compared with such patients who did not receive thrombolytic therapy.

The current American College of Cardiology/American Heart Association practice guidelines for AMI assign a class IIa designation to the recommendation for use of thrombolytic therapy in persons older than 75 years, indicating that while the weight of evidence and expert opinion is in favor of the usefulness of treatment, there remains conflicting evidence or a divergence of opinion about whether the treatment is beneficial, useful, and effective.<sup>11</sup> While a large randomized trial focused exclusively on elderly AMI patients would produce the most valid information regarding the benefits vs risks of thrombolytic therapy, this approach has failed previously because of ethical difficulties inherent in randomization of AMI patients to placebo and in identifying and enrolling large enough numbers of patients without contraindications to therapy.<sup>32</sup> Analyses of combined data from the largest trials of thrombolytic agents in AMI have not demonstrated a significant survival benefit in patients older than 75 years. A systematic overview of 9 trials that randomized 58 600 patients with suspected AMI between thrombolytic therapy and control included 5754 participants 75 years or older.<sup>10</sup> Among this group, the mortality during the first 35 days was 24.3% for those treated with a thrombolytic agent compared with 25.3% for those

**Table 2. Baseline Demographic and Clinical Characteristics and Early Treatments According to Receipt of Thrombolytic Therapy**

Characteristic	Received Thrombolytic Therapy, % (n = 735)	Did Not Receive Thrombolytic Therapy, % (n = 1924)	P Value
Demographic characteristics			
Age ≥75 y	39.3	64.4	<.001
Female	42.9	51.5	<.001
Nonwhite race	9.5	9.6	.98
Medical history			
Previous myocardial infarction	21.6	35.3	<.001
Previous angina	31.8	40.2	<.001
Previous coronary bypass or angioplasty	11.0	15.0	.009
Previous stroke	7.2	15.6	<.001
Diabetes	22.2	27.9	.003
Hypertension	52.2	58.7	.003
Current smoker	16.6	10.6	<.001
Hypercholesterolemia	30.3	24.9	.004
Clinical characteristics at admission			
Severity index			
No heart failure	68.7	58.0	
Heart failure/pulmonary edema	18.4	31.6	<.001
Cardiogenic shock	12.9	10.4	
No chest pain	3.4	10.1	<.001
Index of Coexistent Disease category*			
No comorbidity present†	11.8	4.7	
Mild-to-moderate comorbidity present	69.3	59.2	<.001
Severe comorbidity present	18.9	36.1	
Body mass index‡			
<23	28.2	35.3	
23-28	35.4	32.4	<.002
>28†	36.4	32.2	
Systolic blood pressure, mm Hg			
>120†	72.5	76.6	
90-120	21.9	18.3	.08
<90	5.6	5.1	
Pulse >100 beats/min	13.2	28.3	<.001
Findings on initial electrocardiogram			
ST elevation	84.9	30.4	<.001
Anterior location of myocardial infarction	32.2	19.4	<.001
Time to presentation			
<2 h†	47.8	25.0	
2-6 h	36.4	33.0	<.001
>6 h	15.8	42.0	
Management in first 24 h			
Aspirin	89.4	72.5	
β-Blockers	60.3	42.3	<.001
Angiotensin-converting enzyme inhibitors	14.3	24.3	
Characteristics of providers			
Cardiologist attending or consultation	76.9	66.3	<.001
Nonurban hospital	21.0	20.6	.83
Availability of cardiac catheterization	56.6	56.9	.90
Low volume of acute myocardial infarctions at hospital (<1.4 per week)§	49.1	42.1	<.001

\*Based on Greenfield's Index of Coexistent Disease.<sup>25</sup>

†Reference category.

‡Calculated as weight in kilograms divided by the square of height in meters.

§Data based on the study by Thiemann et al.<sup>28</sup>

who did not receive treatment. These findings have been interpreted by many authorities to indicate an absolute benefit of treatment of 10 lives saved per thousand patients treated among those 75 years or older. However, the 95% CI around this estimate is quite wide (-16.0 to 36.0), suggesting the potential for risk as well as benefit. The relative risk of death for patients in this older age group who received thrombolytic therapy compared with controls was 0.96 (95% CI, 0.88-1.05). Thus,

the limited data derived from clinical trials of thrombolytic therapy in elderly AMI patients suggest that the relative benefits from use of thrombolytic therapy experienced by this group is marginal at best. Given the low likelihood of mounting any new trials in the old-old, and a general consensus that eligible elderly AMI patients should have access to all available treatment modalities, it has become essential to examine the outcomes of these therapies in observational studies of community popu-

**Table 3. Multivariate Analysis of the Odds of In-Hospital Mortality\***

Variable	Odds of In-Hospital Death (95% Confidence Interval)	P Value
All patients (n = 2631)†		
Propensity score (to receive thrombolytics)‡	0.42 (0.22-0.82)	.01
Thrombolytic use§	1.53 (1.13-2.08)	.006
Interaction of thrombolytic use with age, y	1.04 (1.01-1.08)	.03
Eligible for thrombolytics (n = 719)		
Propensity score (to receive thrombolytics)‡	0.66 (0.21-2.07)	.48
Thrombolytic use§	0.96 (0.58-1.58)	.86
Interaction of thrombolytic use with age, y	1.08 (1.02-1.14)	.008
All other patients with contraindications (n = 1912)		
Propensity score (to receive thrombolytics)‡	0.23 (0.09-0.54)	<.001
Thrombolytic use§	1.57 (1.03-2.40)	.04
Interaction of thrombolytic use with age, y	1.02 (0.96-1.08)	.49

\*Adjusting for age and propensity score (probability of receiving thrombolytic therapy based on all other demographic and clinical predictors given in Table 2) in all models.

†There were 28 of 2659 patients with missing values in multivariate models.

‡Variables associated with thrombolytic use in the propensity score model were cardiogenic shock, delay time, ST depression, presence of cardiology consultation, female sex, high comorbidity, and absence of chest pain with significant interactions.

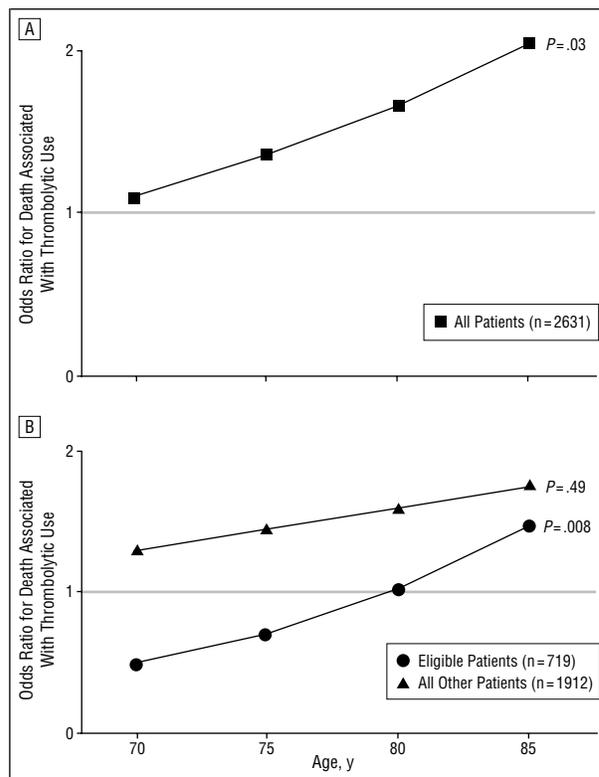
§Independent effect, not including interactions.

||Estimates the change in odds of death for thrombolytic recipient vs nonrecipient with each 1-year increase in age.

lations, which may provide more realistic information on effectiveness in a “real-world” setting.

The major challenge of this and other observational studies that attempt to assess therapeutic effectiveness is to overcome confounding caused by treatment decisions that are determined in a nonrandomized fashion.<sup>33</sup> Even after extensive statistical adjustments, it is difficult to control for the bias that elderly thrombolytic recipients have characteristics associated with better prognosis before treatment relative to nonrecipients. While underadjusting for this bias might lead to an exaggerated survival benefit in patients aged 65 to 74 years, it may also lead to an underestimation of the increased mortality found among the oldest thrombolytic recipients. The validity of our findings is further supported by the clear and predictable differences in survival between eligible thrombolytic recipients and patients with relative and absolute contraindications to therapy who received thrombolytic therapy.

There are additional limitations regarding the present study because of its observational nature. In our study, all thrombolytic agents were combined into a single category, and we did not assess issues relating to the specific agent used, dosing, or the timing of drug administration in our analyses. The rates of important adverse events of thrombolytic therapy, notably intracranial hemorrhage, have been shown to vary across agents<sup>34,35</sup>; however, agent-specific effects on mortality



Predicted odds of in-hospital mortality for thrombolytic recipients vs nonrecipients for different ages based on age interactions in multivariate models and stratified by thrombolytic eligibility. The logistic regression models controlled for age, propensity scores (to receive thrombolytic therapy), and interactions between age and thrombolytic use (see Table 3). P values denote significance of interaction of age and thrombolytic use as predictors of mortality.

could not be examined in the context of the present study owing to sample size limitations. Furthermore, the dose at which the thrombolytic agent is administered can have an impact on the occurrence of intracranial hemorrhage. Recent data from the National Registry of Myocardial Infarction 2 have demonstrated that AMI patients who received excessive tissue-type plasminogen activator doses, relative to the recommended weight-adjusted doses, had a significantly increased risk of having an intracranial hemorrhage.<sup>36,37</sup>

Another limitation of this study is the relatively small sample size of AMI patients from a single state. However, the sample size was sufficient to detect significant increases in the odds of dying among elderly thrombolytic recipients. Furthermore, patterns of use of thrombolytic agents for elderly AMI patients in Minnesota are similar to patterns observed in other studies.<sup>12,16</sup> Moreover, our findings of increased mortality among eligible, elderly thrombolytic recipients are similar to those of a recent study.<sup>22</sup>

In summary, the findings of this observational study confirm the benefits of thrombolytic treatment in the community setting among younger patients meeting eligibility criteria for treatment. However, our findings raise concerns about the benefits of this treatment in the old-old, even those who might be considered eligible for treatment according to current criteria. These results require confirmation using data derived from

other large observational studies of AMI patients that include meaningful numbers of the old-old. For the present, the findings of this study suggest a need to reassess our approach to the use of thrombolytic therapy in the treatment of AMI patients older than 75 years. Careful assessment for absolute and relative contraindications to thrombolytic therapy is critical in this group of patients. When such patients are considered eligible for treatment, the timing of treatment should be optimized,<sup>23</sup> and the agent must be administered at the correct dosage. The relative benefits of alternatives to thrombolytic therapy, such as primary coronary angioplasty, in the old-old require further assessment. Despite reservations about the true benefits of thrombolytic therapy in the oldest AMI patients, this vulnerable group will clearly benefit from increased adherence to guidelines regarding use of all available beneficial therapeutic modalities.<sup>38-42</sup>

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