

Use and Effectiveness of Intravenous Heparin Therapy for Treatment of Acute Myocardial Infarction in the Elderly

HARLAN M. KRUMHOLZ, MD, FACC,*†‡§ JOHN HENNEN, PhD,|| PAUL M. RIDKER, MD, FACC,¶
JAIME E. MURILLO, MD,* YUN WANG, MS,§ VIOLA VACCARINO, MD, PhD,†
EDWARD F. ELLERBECK, MD,# MARTHA J. RADFORD, MD, FACC§**

New Haven, Middletown and Farmington, Connecticut; Boston, Massachusetts; and Kansas City, Kansas

Objectives. We sought to determine the use and association with 30-day mortality of intravenous heparin for the treatment of acute myocardial infarction in elderly patients not treated with a reperfusion strategy and without contraindications to anticoagulation.

Background. The benefit of using full-dose intravenous heparin for the treatment of acute myocardial infarction in the elderly is not known.

Methods. We conducted a retrospective cohort study using hospital medical records of all Medicare beneficiaries admitted to the hospital with an acute myocardial infarction in Alabama, Connecticut, Iowa and Wisconsin from June 1992 through February 1993.

Results. Among the 6,935 patients ≥ 65 years old who had no absolute chart-documented contraindications to heparin, 3,227

(47%) received early full-dose intravenous heparin therapy. After adjustment for baseline differences in demographic, clinical and treatment factors between patients with and without heparin, the use of heparin (odds ratio 1.02, 95% confidence interval 0.87 to 1.18) was not associated with a significantly better 30-day mortality rate.

Conclusions. Although intravenous heparin was commonly used for treatment of acute myocardial infarction in the elderly, it was not associated with an improved 30-day mortality rate. Although the findings of this observational study must be interpreted with care, they lead us to question whether the prevalent use of intravenous heparin has therapeutic effectiveness in this population.

(J Am Coll Cardiol 1998;31:973-9)

©1998 by the American College of Cardiology

Despite the widespread use of intravenous heparin for the treatment of acute myocardial infarction (1), its value in this setting is controversial (2), especially among patients who do

not receive a primary reperfusion strategy. Early trials of full-dose heparin supported its use for the treatment of acute myocardial infarction, but they were conducted before the routine use of aspirin and included very few elderly patients (3-5). A recent systematic overview of 26 randomized trials of anticoagulant therapy for suspected acute myocardial infarction concluded that the clinical evidence does not justify the routine use of heparin in the treatment of acute myocardial infarction (6). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines (7) for the treatment of acute myocardial infarction state that, "in patients who will not be given thrombolytic therapy, there is little evidence about the benefit of heparin in the modern era, in which aspirin, [beta]-adrenoceptor blockers, nitrates and ACE [angiotensin-converting enzyme] inhibitors are routinely available." The guidelines do not endorse the use of full-dose intravenous heparin for the treatment of patients who do not receive a primary reperfusion strategy.

We sought to examine the use and effectiveness of heparin in clinical practice among elderly patients with an acute myocardial infarction. To address this issue, we made use of a population-based, observational study design that included a

From the *Section of Cardiovascular Medicine, Yale School of Medicine; †Section of Chronic Disease Epidemiology, School of Epidemiology and Public Health, Yale University; and ‡Yale-New Haven Hospital Center for Outcomes Research and Evaluation, New Haven, Connecticut; §Connecticut Peer Review Organization, Middletown, Connecticut; ||Department of Psychiatry, Harvard Medical School and ¶Divisions of Preventive Medicine and Cardiology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; #Department of Preventive Medicine, University of Kansas School of Medicine, Kansas City, Kansas; and **Cardiology Division, Department of Medicine, University of Connecticut Medical School, Farmington, Connecticut. This study was supported in part by the Patrick and Catherine Weldon Donaghue Medical Research Foundation, Hartford, Connecticut. Dr. Krumholz is a Paul Beeson Faculty Scholar. The analyses on which this publication is based were performed under Contract Number 500-96-P549, titled, "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 authors concerning experience in engaging with issues presented are welcomed.

Manuscript received May 28, 1997; revised manuscript received December 2, 1997, accepted December 23, 1997.

Address for correspondence: Dr. Harlan M. Krumholz, Yale University School of Medicine, 333 Cedar St., Post Office Box 208025, New Haven, Connecticut 06520-8025. E-mail: harlan.krumholz@Yale.edu.

Abbreviations and Acronyms

ACC/AHA	= American College of Cardiology/American Heart Association
aPTT	= activated partial thromboplastin time
CCP	= Cooperative Cardiovascular Project
CI	= confidence interval
CK	= creatine kinase
ECG	= electrocardiogram, electrocardiographic
HCFA	= Health Care Financing Administration
ICD-9-CM	= International Classification of Diseases, Ninth Revision, Clinical Modification
LDH	= lactic dehydrogenase
OR	= odds ratio

retrospective review of the complete hospital medical records for Medicare beneficiaries admitted to the hospital with an acute myocardial infarction in Alabama, Connecticut, Iowa and Wisconsin from June 1992 through February 1993. We focused on patients who had no contraindication for anticoagulation and were not treated with a primary reperfusion strategy.

Methods

Study sample. The study sample was derived from the Cooperative Cardiovascular Project (CCP) pilot, a Health Care Financing Administration (HCFA) initiative to improve the quality of care for Medicare beneficiaries with acute myocardial infarction (8). The sample included patients ≥ 65 years old with a principal discharge diagnosis of acute myocardial infarction [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM 410)] (9) in Alabama, Connecticut, Iowa, and Wisconsin between June 1, 1992 and February 28, 1993. We excluded admissions that were not related to the care of an acute myocardial infarction (the fifth digit of the ICD-9-CM code = 2) and other patients who did not have evidence of an acute myocardial infarction as documented by a peak creatine kinase, MB fraction (CK-MB) $>5\%$ or lactic dehydrogenase (LDH)-2 >1.5 times the normal value and LDH-1 $>$ LDH-2 or two of the three following criteria: chest pain, a twofold elevation of CK or new Q waves on the electrocardiogram (ECG). We excluded admissions in which patients were transferred from another acute care institution because the focus of this study was the treatment of acute myocardial infarction on initial presentation. For patients with more than one admission during the study period, we only included the first admission.

We restricted the cohort to patients who did not have a contraindication to heparin therapy and had no documented reason to receive limited treatment. Therefore, we excluded patients with active bleeding, a history of hemorrhagic stroke, a history of a bleeding disorder, thrombocytopenia (platelets $<100,000$), anemia (hematocrit $<30\%$ or hemoglobin <10 mg/dl), rectal bleeding, a prothrombin time >16 s, recent head

trauma or allergy to heparin. We also excluded patients if the medical record documented that they were terminally ill or had metastatic cancer, if the admission orders indicated that the patient should be given palliative care only or if a "do-not-resuscitate" order was written at the time of admission. To focus on patients who did not receive a primary revascularization strategy, we excluded patients who received thrombolytic therapy or underwent primary percutaneous coronary revascularization within the first 24 h.

Collection of data. The medical records for each admission were obtained from the acute care hospitals. Trained nurses and medical record technicians abstracted the hospital medical record and entered the information directly into a computerized database management system using the Uniform Clinical Data Set System (10). On-line data definitions and range checks were used to decrease errors and data entry variability. We reabstracted 594 charts to test the reliability of the data collection; for heparin received during the hospital stay, the kappa value was 0.94. The initial ECG for each patient in the Connecticut cohort was interpreted by a trained physician (J.M.) who was not aware of the study hypothesis. The medical charts of the Connecticut cohort were also reabstracted to determine the highest activated partial thromboplastin time (aPTT) within 24 h of the initiation of therapy. The source of the mortality data was the Medicare Beneficiary Record. This information is obtained from the Social Security Administration and is considered highly accurate.

Variables. Patients were classified in the heparin group if they received intravenous heparin within the first 2 hospital days. The 2-day period was chosen to allow for the possibility that some patients might have presented late on the day of admission and received heparin the next day after presentation. We also repeated the study after classifying patients in the heparin group only if the medication was initiated on the day of presentation. We did not consider patients to be in the heparin therapy group if they received heparin subcutaneously or received a dose more appropriate for prophylaxis of venous thrombosis ($\leq 10,000$ U/day) than systemic anticoagulation.

To evaluate the use and effectiveness of heparin we made use of the following variables: age, gender, race, medical history (hypertension, diabetes, smoking, myocardial infarction, congestive heart failure, coronary revascularization, stroke), medications on admission (beta-adrenergic blocking agents, digoxin, loop diuretic drugs), vital signs on admission (pulse, systolic blood pressure, respiratory rate), clinical condition on admission (congestive heart failure, renal dysfunction, shock, intubation and cardiac arrest) and cointerventions on admission (treatment with thrombolytic therapy or beta-blockers). Systolic blood pressure, pulse and respiratory rate were taken as the highest value recorded within 24 h after admission. Renal dysfunction was defined as blood urea nitrogen >40 mg/dl or creatinine >2.5 mg/dl. Of these variables, data were missing in $<3\%$ of cases. We evaluated these variables for collinearity and determined that the correlation between any pair of variables was <0.3 .

ECG variables abstracted by a physician were also available

only for the Connecticut cohort (n = 1,573). ECG variables in the Connecticut cohort were derived from the initial ECG and included the presence of ST segment elevation (≥ 2 mm in at least two contiguous leads) or Q waves not known to be old and the presence of left bundle branch block.

The principal end point for the outcome analysis was 30-day mortality. We also evaluated in-hospital hemorrhage, in-hospital transfusion, in-hospital strokes and 1-year mortality.

Statistical analysis. We evaluated the association of the use of heparin with demographic characteristics (age, gender and race), clinical characteristics (coronary artery disease risk factors, past medical history, admission cardiac medications, cardiac history, acuity of presentation, ECG presentation) and cointerventions (aspirin and beta-blockers). Then, using the variables from the bivariate analysis, we developed a multivariable logistic regression model by backward stepwise selection with the use of heparin as the dependent variable. Variables were dropped from the model at a significance level of $p < 0.01$.

Next, we determined whether the use of heparin was associated with better 30-day survival, after adjusting for potential confounders. To accomplish this objective, we developed a series of logistic regression models to predict 30-day mortality using the patients who did not receive heparin as the reference group. Demographic variables, clinical variables and cointerventions (beta-blockers, thrombolytic therapy) were added in sequential steps. For each model we calculated an odds ratio and a 95% confidence interval for patients who received heparin compared with those who did not. We also checked for interactions between heparin and the use of aspirin, the patient's age, the presence of heart failure, the presence of diabetes mellitus, the history of an acute myocardial infarction and the presence of chest pain, respectively.

Goodness of fit was evaluated by comparing fitted probabilities of 30-day mortality with observed 30-day mortality within deciles of risk and calculating the corresponding observed chi-square statistics (11). In addition, we calculated an area under the receiver operator curve for each model to evaluate the discriminating power of the fitted model (12).

To determine whether our results were sensitive to changes in our definition of the study sample or the timing of treatment, we repeated the final analysis after restricting the heparin group to those patients who had treatment initiated on the day of admission. We also repeated the mortality models with the Connecticut cohort, adding ECG variables that are only available in the Connecticut database to the final models. These variables, the presence of ST segment elevation and left bundle branch block were selected because they were known to be associated with 30-day mortality and were possible sources of residual confounding in the main analysis. Finally, we repeated the fully adjusted model to evaluate the association between the use of heparin and 1-year mortality.

Our sample size was fixed by the size of the CCP pilot. We calculated that we would have $>90\%$ power to detect a three-point difference (15% vs. 18%) in 30-day mortality based on the sample.

Table 1. Study Sample

	No. of Subjects
Total sample	16,182
AMI confirmed	13,655
Exclusions*	
Age <65 yr	916
Transfer in/from emergency room	2,346
Terminal illness, metastatic cancer, recent trauma	1,218
PTCA within 6 h of admission	259
Thrombolytic therapy on admission	1,170
Heparin dose	547
Repeat admission	1,164
Total exclusions	7,744
Contraindications	
History of hemorrhagic stroke	21
Active bleeding at admission	94
Rectal blood	67
Allergy to heparin	4
History of bleeding disorder	37
Thrombocytopenia	57
Anemia	384
Prothrombin time >16 s	297
Study sample	6,935

*Categories can be mutually exclusive. AMI = acute myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

All calculations were performed using the software system STATA 5.0.

Results

Study sample. The study sample included 6,935 patients (Table 1). The study sample was elderly (mean age 76.3 ± 7.2 years) and had roughly equal proportions of men (52%) and women (48%).

Use of heparin. Among the patients in the study sample, 3,227 (47%) received full-dose intravenous heparin within the first 2 hospital days. The nonrandom allocation of patients among treatment groups is demonstrated by significant differences in the demographic and clinical characteristics among the two groups (Table 2). The patients who received heparin had a more favorable clinical profile as evidenced by their younger age, more favorable clinical history (lower prevalence of congestive heart failure, diabetes, stroke, chronic obstructive pulmonary disease, peptic ulcer disease, renal insufficiency, preadmission use of calcium-channel blocking agents, digoxin, angiotensin-converting enzyme inhibitors, loop diuretic drugs), better admission characteristics (lower prevalence of tachycardia, tachypnea, hypotension, intubation) and higher use of beta-blockers and aspirin. In the multivariable analysis (Table 3), the following variables were independently associated with the use of heparin: age, gender, comorbidity (stroke, chronic obstructive pulmonary disease, renal dysfunction), preadmission medications (digoxin, beta-blockers), history of percutaneous transluminal coronary angioplasty, presence and duration of chest pain and treatment with aspirin.

Table 2. Characteristics Associated With Patients Who Received Heparin

	Heparin (n = 3,227) [no. (%) of pts]	No Heparin (n = 3,708) [no. (%) of pts]	p Value
Age group			
65-74 yr	1,683 (52%)	1,339 (36%)	< 0.001
75-84 yr	1,250 (39%)	1,679 (45%)	< 0.001
≥85 yr	294 (9%)	690 (19%)	< 0.001
Female	1,404 (44%)	1,947 (53%)	< 0.001
White	3,044 (94%)	3,433 (93%)	< 0.01
Cardiac risk factor			
Hx of HTN	1,724 (53%)	1,887 (51%)	0.04
DM	863 (27%)	1,081 (29%)	0.03
Current smoker	491 (15%)	483 (13%)	0.01
Cardiac Hx			
MI	826 (26%)	973 (26%)	0.54
CHF	876 (27%)	1,420 (38%)	< 0.001
Angioplasty	212 (7%)	160 (4%)	< 0.001
Bypass surgery	450 (14%)	389 (10%)	< 0.001
Medical comorbidity			
Stroke	288 (9%)	455 (12%)	< 0.001
COPD	384 (12%)	544 (15%)	0.001
Peptic ulcer disease	124 (4%)	167 (5%)	0.17
Renal insufficiency*	147 (5%)	319 (9%)	< 0.001
Preadmission med			
Aspirin	1,086 (34%)	1,035 (28%)	< 0.001
Nitrates	1,058 (33%)	1,186 (32%)	0.48
BBs	584 (18%)	509 (14%)	< 0.001
CCBs	1,046 (32%)	1,222 (33%)	0.63
Digoxin	877 (27%)	1,308 (35%)	< 0.001
ACEI	503 (16%)	691 (19%)	< 0.001
Loop diuretic	974 (30%)	1,381 (51%)	< 0.001
Warfarin	128 (4%)	161 (4%)	0.44
Chest pain			
Present	2,836 (88%)	2,663 (72%)	< 0.001
Duration > 6 h	474 (15%)	344 (9%)	< 0.001
Vital signs			
Pulse >100 bpm	1,214 (38%)	1,667 (45%)	< 0.001
Resp rate > 30 breaths/min	417 (13%)	730 (20%)	< 0.001
SBP < 125 mm Hg	210 (7%)	287 (8%)	0.05
Shock within 24 h of admission	22 (1%)	29 (1%)	0.63
Intubation within 24 h of admission	148 (5%)	238 (6%)	< 0.001
CPR	73 (2%)	136 (4%)	< 0.001
Admission med			
Aspirin	2,400 (74%)	1,941 (52%)	< 0.001
BBs	1,277 (40%)	776 (21%)	< 0.001

*Blood urea nitrogen >40 mg/dl or creatinine >2.5 mg/dl. ACEI = angiotensin-converting enzyme inhibitor; BBs = beta-blockers; bpm = beats/min; CCBs = calcium channel blockers; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; DM = diabetes mellitus; HTN = hypertension; Hx = history; med = medication; MI = myocardial infarction; pts = patients; Resp = respiratory.

The Connecticut cohort of the CCP pilot was used to evaluate whether heparin treatment achieved effective anticoagulation. Of the patients in whom intravenous heparin was started, 88% had an aPTT >46 s within 24 h of the initiation of therapy.

Complications. The use of heparin was associated with an increased risk of complications. The rate of a major hemorrhage during the hospital stay was higher among patients who received heparin than in those who did not (2.8% vs. 1.3%, $p < 0.001$). The rate of transfusions was also higher in patients who received heparin (11.6% vs. 5.6%, $p < 0.001$). The number of strokes was slightly higher in the heparin group (1.7% vs. 1.3%, $p = 0.2$).

Mortality. The 30-day mortality rate for the entire study sample was 16.2% (1,121 of 6,935). The 30-day mortality rate for the patients who received heparin was 13.4% (431 of 3,227) compared with 18.6% (690 of 3,708, $p < 0.001$) for those who did not receive heparin. To adjust for the baseline differences in risk, a sequence of multivariate logistic regression models was developed to test the association of the treatment groups and survival (Table 4).

In the model that adjusted for demographic and clinical variables, patients who received heparin did not demonstrate a significantly lower odds of 30-day mortality (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.80 to 1.07). After adding variables indicating the use of aspirin and beta-blockers, the patients who received heparin (OR 1.02, 95% CI 0.87 to 1.18) did not have a significantly lower odds of 30-day mortality than those who did not receive heparin. In this model, aspirin was associated with a significantly lower odds of 30-day mortality (OR 0.67, 95% CI 0.58 to 0.78). There was no evidence of a significant interaction between heparin and use of aspirin, patient age, presence of heart failure, presence of diabetes mellitus, history of an acute myocardial infarction and presence of chest pain, respectively. Heparin was not associated

Table 3. Factors Associated With Use of Heparin for Acute Myocardial Infarction, Based on Multiple Logistic Regression With Backward Stepwise Selection*

Factor	OR (95% CI)	p Value
Age 75-84 yr	0.67 (0.60-0.75)	< 0.001
Age ≥ 85 yr	0.43 (0.36-0.50)	< 0.001
Female gender	0.80 (0.72-0.89)	< 0.001
Hx of PTCA	1.28 (1.02-1.60)	0.03
Stroke	0.78 (0.66-0.92)	< 0.01
COPD	0.85 (0.73-0.99)	0.04
Chest pain present	2.04 (1.77-2.34)	< 0.001
Duration > 6 h	1.29 (1.10-1.51)	< 0.01
Resp rate > 30 breaths/min	0.79 (0.69-0.92)	< 0.002
Preadmission digoxin	0.82 (0.73-0.91)	< 0.001
Preadmission BBs	1.86 (1.66-2.04)	< 0.001
Renal insufficiency	0.72 (0.58-0.90)	< 0.01
Aspirin	2.14 (1.92-2.38)	< 0.001
Intubation	1.28 (1.01-1.61)	0.04

*Adjusted odds ratios (ORs) were derived from a multiple logistic regression analysis in which each odds ratio was adjusted for all other factors listed; an odds ratio <1 indicates that patients with the characteristic have a lower likelihood of receiving heparin than those without the characteristic; an odds ratio >1 indicates that patients with the characteristic have a higher likelihood of receiving heparin than those without the characteristic. CI = confidence interval; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 2.

Table 4. Odds of 30-Day Mortality of Patients Treated With Heparin Compared With Patients Not Treated With Heparin*

Heparin Group	Unadjusted Model	Adjusted Models		
		Demographic Factors	Demographic and Clinical Factors	Demographic, Clinical and Treatment Factors
OR	0.67	0.78	0.92	1.02
95% CI	0.59-0.77	0.68-0.89	0.80-1.07	0.87-1.18

*Demographic characteristics included age, gender, race; clinical characteristics included preadmission use of aspirin, preadmission use of nitrates, preadmission use of beta-blockers, preadmission use of digoxin, preadmission use of loop diuretic agents, history of diabetes, smoking, myocardial infarction, hypertension, coronary revascularization, congestive heart failure, pulse >100 beats/min, systolic blood pressure <125 mm Hg, respiratory rate >30 breaths/min, congestive heart failure on admission, shock on admission, resuscitation on admission, intubation on admission, chest pain on admission, duration of chest pain >6 h and renal dysfunction; treatment variables included admission use of aspirin and beta-blockers. Abbreviations as in Table 3.

with a survival benefit in any of these subgroups. The analyses were repeated after restricting the heparin group to those patients who received the medication on the first hospital day, and there was no substantial change in the odds ratio (OR 0.96, 95% CI 0.82 to 1.12).

When data from the Connecticut cohort were used, heparin was not associated with a survival benefit even if the analysis was restricted to patients who had an aPTT >46 s within 24 h of the initiation of therapy. Moreover, the addition of ST segment elevation and left bundle branch block to the model did not substantially change the result. Finally, using 1-year mortality after admission as the outcome, heparin therapy was not associated with a significant survival benefit (OR 1.04, 95% CI 0.91 to 1.19).

Graphic displays of partial residual plots from these models did not reveal any problems with our model assumptions. The chi-square goodness of fit statistic for the final model with demographic, clinical and treatment variables had a p value of 0.10, indicating that the fitted model was acceptable. Goodness of fit statistics for models based on demographic variables only and for demographic and clinical variables were also not significant, indicating acceptable model fits. The final models had areas under the receiver operating characteristic curves that exceeded 75%, indicating good model discrimination.

Discussion

We report that heparin therapy is widely used for the treatment of acute myocardial infarction in the vast majority of elderly patients who are not treated with a primary reperfusion therapy. However, we could not demonstrate that the use of heparin was associated with a significantly lower 30-day mortality, after adjusting for baseline differences in the treatment groups. The present study supports the recommendations of the ACC/AHA guidelines (7) and raises the possibility that the widespread use of heparin (1) may not provide an important benefit for elderly patients with an acute myocardial infarction.

Previous studies. The appropriate role of heparin for the treatment of acute myocardial infarction is not well established in the current era of treatment (2). Older studies have suggested that heparin is associated with a 10% to 30% reduction in short-term mortality after acute myocardial infarction (13,14). However, these trials were performed before the current era of treatment, leading experts to discount their relevance to contemporary management (7).

Several more recent trials have evaluated the benefit of heparin in the treatment of unstable angina and non-Q wave myocardial infarction (15-20). Four trials found no significant benefit of heparin beyond that provided by aspirin (15-17,19). One study (18), by investigators from the Montreal Heart Institute, reported that treatment with heparin was associated with the development of significantly fewer myocardial infarctions than treatment with aspirin. The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial (20) found that heparin and warfarin plus aspirin were more effective than aspirin alone in the prevention of recurrent ischemic events in the early phase of unstable angina.

A meta-analysis of these studies (21) has found that, when taken together, there is a borderline significant trend toward a benefit for patients treated with aspirin plus heparin compared with those treated with aspirin alone. The relevance of these trials to the current study is not clear. These studies focused predominately on patients without an acute myocardial infarction, and few included substantial numbers of elderly patients. Collins et al. (6) recently performed a systematic overview of all 26 unconfounded randomized trials of anticoagulant therapy for suspected acute myocardial infarction. They found that heparin was only beneficial in this group in the absence of aspirin therapy. They concluded that the clinical evidence from the trials does not justify the routine use of heparin for the treatment of suspected acute myocardial infarction.

Use of heparin. Despite the lack of evidence to support the use of heparin, almost half of our cohort received it. These findings are consistent with the report of the National Registry of Myocardial Infarction (1), which found that >50% of 240,989 patients admitted to the hospital across the United States with an acute myocardial infarction received intravenous heparin. The frequent use of heparin highlights the need for studies to determine whether this clinical strategy has therapeutic effectiveness in the current era.

Our analysis also demonstrated the impact of the nonrandom allocation of patients to the various treatment groups. Although the data do not reveal why physicians choose a particular antithrombotic regimen, they do reveal certain treatment patterns. Younger patients were much more likely to have heparin included in their treatment regimen. The lowest risk patients, based on admission characteristics, were most likely to receive heparin. The difference in risk among the treatment groups occurred even though patients with any contraindication for heparin therapy or with a terminal illness or preference for limitation of treatment had been excluded from the analysis.

Heparin and mortality. The observation that patient characteristics were strongly related to the choice of heparin therapy highlights the importance of using multivariable methods in the mortality analysis. With the more favorable clinical profile of the heparin-treated patients, the unadjusted 30-day mortality rate was lower. As expected, on the basis of the bivariate analyses, the sequential adjustment for demographic, clinical and treatment variables in the multivariable models attenuated the decreased odds of 30-day mortality in the heparin group. In the final model, patients who received heparin did not have a significantly lower odds of 30-day mortality. Although we cannot exclude the possibility that unmeasured factors contributed to the appearance of no difference between the groups, there is no indication that heparin provided an important benefit to these patients.

To explore the possibility that heparin was providing a benefit for a specific subgroup of patients, we evaluated the interaction of heparin with aspirin, age and chest pain, respectively. There was no significant interaction of heparin among these subgroups. To further test our conclusions, we determined whether our results were sensitive to changes in the definition of the study sample or in the length of follow-up. None of these changes in the study sample affected our principal finding.

Limitations and strengths. The most important limitation of our observational study is the nonexperimental allocation of treatment strategy. To address this issue, we restricted the study sample to patients who were eligible for heparin therapy and collected detailed clinical information from the medical records to adjust for differences among the treatment groups in their initial risk of 30-day mortality. We previously used these methods in a similar study sample (22) to evaluate the association of the acute use of aspirin and 30-day mortality and found that the use of aspirin was associated with an adjusted odds reduction in mortality of 22%, a figure that was very close to the 23% odds reduction reported by the International Study of Infarct Survival (ISIS)-2 trial.

In contrast, a major strength of our study is that it reflects the experience of the entire spectrum of patients and hospitals in four diverse states. This design avoids the problem of selection bias by including the experience of hospitals outside the sphere of the tertiary care hospitals, a class of institutions that is disproportionately represented in published reports (23). Our study design also has the strength of using data abstracted from the hospital medical record, thereby avoiding strict reliance on administrative data with its inherent limitations (24).

Conclusions. This investigation was a result of a HCFA-based initiative to improve health care for Medicare patients admitted with acute myocardial infarction. We used data developed within this initiative to evaluate the pattern of use and therapeutic effectiveness of intravenous heparin for the treatment of acute myocardial infarction. The data indicate that more than half of elderly patients receive intravenous heparin in the acute phase of admission for an acute myocardial infarction. Our inability to find a mortality benefit associ-

ated with the use of heparin leads us to question the prevalent belief that intravenous heparin has therapeutic effectiveness in this population. These results suggest a need for more studies to define the best antithrombotic regimen for selected groups of elderly patients.

We are indebted to the members of the Peer Review Organizations from Alabama, Connecticut, Iowa and Wisconsin and to all the other individuals, hospitals and organizations who contributed to the development and implementation of the Cooperative Cardiovascular Project.

References

1. Rogers WJ, Bowly LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993). *Circulation* 1994;90:2103-14.
2. Ridker PM, Hebert PR, Fuster V, Hennekens CH. Are both aspirin and heparin justified as adjuncts to thrombolytic therapy for acute myocardial infarction? *Lancet* 1993;341:1574-7.
3. Anticoagulants in acute myocardial infarction: results of a cooperative clinical trial. *JAMA* 1973;225:724-30.
4. Drapkin A, Merskey C. Anticoagulant therapy after acute myocardial infarction: relation of therapeutic benefit to patient's age, sex and severity of infarction. *JAMA* 1972;222:541-8.
5. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council. Assessment of short-term anticoagulant administration after cardiac infarction. *BMJ* 1981;1:335-42.
6. Collins R, MacMahon S, Flather M, et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996;313:652-9.
7. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996;28:1328-428.
8. Ellerbeck EF, Jencks SF, Radford MJ, et al. Treatment of Medicare patients with acute myocardial infarction: report on a four state pilot of the Cooperative Cardiovascular Project. *JAMA* 1995;273:1509-14.
9. International Classification of Diseases, Ninth Revision, Clinical Modification. Washington (DC): Public Health Service, U.S. Department of Health and Human Services, 1988.
10. Audet AM, Scott HD. The Uniform Clinical Data Set: an evaluation of the proposed national database for Medicare's Quality Review Program. *Ann Intern Med* 1993;119:1209-13.
11. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: Wiley, 1989.
12. Hanley J, McNeil BJ. The meaning and use of the area under the receiver operating characteristic (ROC) curve. *Radiology* 1992;143:29-36.
13. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease—I: treatments following myocardial infarction. *JAMA* 1988;260:2088-93.
14. Chalmers TC, Matt RJ, Smith H, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med* 1977;297:1091-6.
15. Gurfinkel EP, Manos EJ, Mejail RI, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol* 1995;26:313-8.
16. RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-30.
17. Theroux P, H Ouimet, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
18. Theroux P, Waters D, Qiu S, McCans J, de Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993;88:2045-8.
19. Cohen M, Adams PC, Hawkins L, Bach M, Fuster V. Usefulness of antithrombotic therapy in resting angina pectoris or non-Q wave myocardial infarction in preventing death and myocardial infarction. *Am J Cardiol* 1990;66:1287-92.

20. Cohen M, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q wave infarction in nonprior aspirin users. *Circulation* 1994;89:81-8.
21. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. *JAMA* 1996;276:811-5.
22. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries: patterns of use and outcomes. *Circulation* 1995;92:2841-7.
23. White KL, Williams TF, Greenberg BG. The ecology of medical care. *N Engl J Med* 1961;265:885-92.
24. Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muhlbaier LH, Mark DB. Discordance of databases designed for claims payment versus clinical information systems. *Ann Intern Med* 1993;119:844-50.