

TREATMENT OF ACUTE MYOCARDIAL INFARCTION AND 30-DAY MORTALITY AMONG WOMEN AND MEN

SANDRA C. GAN, M.D., SHELLI K. BEAVER, M.S., PETER M. HOUCK, M.D., RICHARD F. MACLEHOSE, M.S.,
HERSCHEL W. LAWSON, M.D., AND LEIGHTON CHAN, M.D., M.P.H.

ABSTRACT

Background Previous studies have suggested that women with acute myocardial infarction receive less aggressive therapy than men. We used data from the Cooperative Cardiovascular Project to determine whether women and men who were ideal candidates for therapy after acute myocardial infarction were treated differently.

Methods Information was abstracted from the charts of 138,956 Medicare beneficiaries (49 percent of them women) who had an acute myocardial infarction in 1994 or 1995. Multivariate analysis was used to assess differences between women and men in the medications administered, the procedures used, the assignment of do-not-resuscitate status, and 30-day mortality.

Results Among ideal candidates for therapy, women in all age groups were less likely to undergo diagnostic catheterization than men. The difference was especially pronounced among older women; for a woman 85 years of age or older, the adjusted relative risk was 0.75 (95 percent confidence interval, 0.68 to 0.83). Women were somewhat less likely than men to receive thrombolytic therapy within 60 minutes (adjusted relative risk, 0.93; 95 percent confidence interval, 0.90 to 0.96) or to receive aspirin within 24 hours after arrival at the hospital (adjusted relative risk, 0.96; 95 percent confidence interval, 0.95 to 0.97), but they were equally likely to receive beta-blockers (adjusted relative risk, 0.99; 95 percent confidence interval, 0.95 to 1.03) and somewhat more likely to receive angiotensin-converting-enzyme inhibitors (adjusted relative risk, 1.05; 95 percent confidence interval, 1.02 to 1.08). Women were more likely than men to have a do-not-resuscitate order in their records (adjusted relative risk, 1.26; 95 percent confidence interval, 1.22 to 1.29). After adjustment, women and men had similar 30-day mortality rates (hazard ratio, 1.02; 95 percent confidence interval, 0.99 to 1.04).

Conclusions As compared with men, women receive somewhat less aggressive treatment during the early management of acute myocardial infarction. However, many of these differences are small, and there is no apparent effect on early mortality. (N Engl J Med 2000;343:8-15.)

©2000, Massachusetts Medical Society.

CORONARY artery disease is the leading cause of death among women over 65 years of age in the United States.¹ In 1992 it accounted for more than 45 percent of all deaths in women, which is more than the proportion due to all forms of cancer combined.² Case fatality rates after hospitalization for acute myocardial infarction decreased for both women and men from 1987 through 1994.³ However, several studies have found that women receive less aggressive in-hospital therapy for acute myocardial infarction than do men,⁴⁻¹⁵ even though studies have reported that the beneficial effects of thrombolytic agents, aspirin, beta-blockers, and invasive cardiac procedures on morbidity and mortality are equal in women and men.¹⁶⁻²¹ It is not clear whether there are sex differences in short-term mortality after acute myocardial infarction. Some groups report higher mortality among women,²²⁻²⁶ and others do not.²⁷⁻²⁹

We analyzed data from Medicare's Cooperative Cardiovascular Project to determine whether there were differences between the sexes in the treatment and short-term mortality of Medicare beneficiaries hospitalized with acute myocardial infarction. Other investigators³⁰⁻³⁶ have used this data base for studies of the treatment of acute myocardial infarction, but sex differences in care have not been evaluated. We used these data for two reasons. First, the data base includes information on virtually all Medicare patients with fee-for-service coverage who were hospitalized for acute myocardial infarction during a specific time period, and its findings are therefore representative of the treatment given to hospitalized Medicare beneficiaries in 1994 and 1995. Second, the data are rich in clinical detail, enabling us to control for the severity of illness and to account for an important confounding factor not addressed in previous studies of this type — the suitability of the patient for treatment.

METHODS

Study Population

The Medicare National Claims History File was used to identify the study population. This file includes all Medicare benefi-

From the Department of Cardiology, Swedish Medical Center, Seattle (S.C.G.); the Division of Clinical Standards and Quality, Health Care Financing Administration, Region 10, Seattle (S.K.B., P.M.H., R.F.M., H.W.L., L.C.); the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta (H.W.L.); and the Department of Rehabilitation Medicine, University of Washington, Seattle (L.C.). Address reprint requests to Dr. Gan at the Department of Cardiology, Swedish Medical Center, 515 Minor Ave., Suite 300, Seattle, WA 98104.

Dr. Gan and Ms. Beaver contributed equally to the article.

ciaries hospitalized for an initial episode of care (i.e., not a follow-up episode) with a principal diagnosis of acute myocardial infarction (code 410.x1 of the *International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM]³⁷). Virtually all acute care hospitals in 46 states and Puerto Rico (4303 hospitals) contributed data to the project for 8 consecutive months during the 18-month period from February 1, 1994, through July 31, 1995. Data from states in the Cooperative Cardiovascular Project pilot study (Alabama, Connecticut, Iowa, and Wisconsin) were not available for this analysis. A complete description of the sampling methods, methods of data collection, and quality-control methods has been published previously.^{30,31} Dates of death were taken from the Medicare Enrollment Database obtained from the Social Security Administration.

Analysis was limited to patients admitted directly (not transferred) to the hospital with acute myocardial infarction confirmed by a creatine kinase MB fraction above 0.05 unit; a lactate dehydrogenase level more than 1.5 times the upper limit of normal, with the level of lactate dehydrogenase isoenzyme 1 greater than the level of lactate dehydrogenase isoenzyme 2; or the presence of at least two of the following: chest pain, doubling of the creatine kinase level, or electrocardiographic evidence of a new acute myocardial infarction. A total of 138,956 patients met these criteria.

For the calculation of rates of diagnostic catheterization, we restricted our study group to patients admitted to facilities capable of performing this procedure (97,928 patients). For the calculation of rates of revascularization (percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting), we restricted the analysis to patients who were hospitalized in facilities that had the capability of performing these procedures and who underwent catheterization (29,243 patients).

The analysis of the use of thrombolytic agents, aspirin, beta-blockers, and angiotensin-converting-enzyme (ACE) inhibitors included only patients ideally suited for treatment. For each of these clinical interventions, patients were categorized as "eligible" or "ideal" candidates. Eligible candidates met the minimal requirements for the intervention (e.g., to be eligible to be treated with aspirin at discharge, a patient had to be discharged alive and not transferred to another hospital). Ideal candidates were eligible patients with no documented contraindications to the intervention (e.g., an ideal candidate for aspirin at discharge was not allergic to aspirin, had no bleeding disorders, and was not receiving anticoagulant drugs). The criteria for ideal treatment status were developed in the Cooperative Cardiovascular Project pilot project,³⁰ and all are listed in Table 1.

Statistical Analysis

We analyzed patients' characteristics by univariate and bivariate chi-square tests and Student's *t*-tests, as appropriate. Means (\pm SD) are reported for continuous variables.

We used a generalized linear model for binomial distribution with log transformation to estimate an adjusted relative risk for women as compared with men with respect to the rates of treatment and of do-not-resuscitate (DNR) orders.³⁸ Specifically, binomial regression was used to assess sex differences in the use of thrombolytic agents, aspirin, beta-blockers, ACE inhibitors, diagnostic catheterization, revascularization, and DNR orders. Where appropriate, the models included terms for age; race (black or nonblack); severity of illness as defined by the Acute Physiology and Chronic Health Evaluation (APACHE II) score (higher scores indicate more severe illness)³⁹; geographic location of the admitting hospital (New England or outside New England); residence in a skilled-nursing facility; current smoking status; history with respect to myocardial infarction; and the presence or absence of coexisting conditions (diabetes mellitus, systemic hypertension, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, and cerebrovascular accident), adverse events in the hospital (pneumonia, deep-vein thrombosis, cerebrovascular accident, anoxic brain damage, cardiogenic shock, hypotension, bradycardia, hemorrhage, or reinfarction of current myocardial infarction), terminal illness (doc-

umentation of an underlying condition involving a stated life expectancy of less than six months), urinary incontinence, and dementia.

Age and APACHE II scores were included as continuous variables in all models, except in the model examining the DNR designation, in which age (<75 years vs. \geq 75 years) and quartiles of APACHE II scores were coded categorically. All other covariates were dichotomous (yes or no). The coexisting illnesses were entered individually into the models. Cox proportional-hazards models were used to analyze 30-day mortality among the 138,956 patients directly admitted with acute myocardial infarction. Analyses were conducted with Stata software (version 6.0).⁴⁰

All hazard ratios and relative risks are adjusted and are reported with 95 percent confidence intervals. Sex differences were considered to be statistically significant if the confidence intervals did not include 1.0 or if the two-tailed *P* values were less than 0.05.

RESULTS

Characteristics of the Patients

Of the 224,377 patients in the Cooperative Cardiovascular Project data base who were hospitalized with suspected acute myocardial infarction, 180,083 were confirmed as having an acute myocardial infarction. Among those, 138,956 had a documented acute myocardial infarction on arrival at the hospital and were not transferred from another facility. Their demographic and clinical characteristics are shown in Table 2. The women were significantly older and had more coexisting conditions than the men. Women were more likely to delay seeking treatment for symptoms of acute myocardial infarction and had a longer wait before undergoing electrocardiography once admitted. There were no significant differences between women and men in the severity of illness on arrival at the hospital, in the likelihood of undergoing intubation, or in the proportion with a documented terminal illness.

Indicators of the Quality of Treatment

Treatment rates are presented according to sex in Table 3. The interventions are described below.

Thrombolysis and Aspirin in the First 24 Hours

Less than 11 percent of all patients were ideal candidates for thrombolytic therapy — 9 percent of women and 12 percent of men. Although a large percentage of all ideal candidates were not treated with thrombolytic agents, ideal female candidates were 7 percent less likely than ideal male candidates to receive a thrombolytic agent within the first hour after arrival at the hospital (adjusted relative risk, 0.93; 95 percent confidence interval, 0.90 to 0.96) and 3 percent less likely to receive a thrombolytic agent at any time during hospitalization (adjusted relative risk, 0.97; 95 percent confidence interval, 0.94 to 0.99). Less than 60 percent of all patients were ideal candidates for receiving aspirin on arrival. Among these, women were 6 percent less likely than men to receive aspirin during the first 24 hours of hospitalization (adjusted rel-

TABLE 1. DEFINITIONS OF ELIGIBLE AND IDEAL CANDIDATES FOR VARIOUS TREATMENTS FOR ACUTE MYOCARDIAL INFARCTION.*

Thrombolytic therapy

Eligible patients

All patients with confirmed acute myocardial infarction on arrival who were not transferred from another hospital and who were hospitalized for more than 1 day (n=131,808).

Ideal patients

All eligible patients except those with one or more of the following contraindications: no ST-segment elevation on the first electrocardiogram; chest pain lasting <30 min, beginning more than 6 hr before arrival, or not adequately documented; chronic liver disease; history of bleeding or coagulopathy; peptic ulcer disease; history of gastrointestinal bleeding or surgery in the previous month; recent head trauma; intracranial neoplasm or recent cardiopulmonary resuscitation; suspected dissecting aneurysm, blood in stool on arrival, or hemorrhagic eye disorder; treatment with warfarin on arrival; history of stroke; uncontrolled hypertension; age >80 yr; documentation that thrombolysis was considered but the doctor or patient decided against it (n=14,198).

Outcome

Documented use of thrombolytic agents at any time or within 60 min after arrival at hospital.

Aspirin within 24 hr after arrival at hospital

Eligible patients

All patients with confirmed acute myocardial infarction on arrival who were not transferred from another hospital and who were hospitalized for more than 1 day (n=105,749).

Ideal patients

All eligible patients except those with one or more of the following contraindications: evidence of bleeding on arrival or during stay; chronic liver disease; history of bleeding or coagulopathy; platelet count <100,000/mm³; serum creatinine level >3 mg/dl (265 μmol/liter); history of peptic ulcer disease or discharge diagnosis of upper gastrointestinal disorder; hemoglobin level <100 g per liter or hematocrit <0.3; allergy to aspirin; treatment with warfarin on arrival; metastatic cancer or other terminal illness (n=60,968).

Outcome

Documented use of aspirin within 24 hr of arrival.

Aspirin prescribed at hospital discharge

Eligible patients

All patients with confirmed acute myocardial infarction on arrival who were discharged alive and not transferred to another acute care hospital (n=90,960).

Ideal patients

All eligible patients except those with one or more of the following contraindications: bleeding on arrival or during stay; chronic liver disease; history of bleeding or coagulopathy; platelet count <100,000/mm³; serum creatinine level >3 mg/dl (265 μmol/liter); history of peptic ulcer disease or discharge diagnosis of upper gastrointestinal disorder; hemoglobin level <100 g per liter or hematocrit <0.3; allergy to aspirin; treatment with warfarin on admission; metastatic cancer or other terminal illness (n=44,773).

Outcome

Documentation of a prescription for aspirin at discharge.

Beta-blocker prescribed at hospital discharge

Eligible patients

All patients with confirmed acute myocardial infarction on arrival who were discharged alive and not transferred to another acute care hospital (n=90,960).

Ideal patients

All eligible patients except those with one or more of the following contraindications: hypotension or shock during hospitalization or systolic blood pressure <100 mm Hg at discharge; history of asthma or chronic obstructive pulmonary disease; bradycardia or pulse <50 at discharge; diagnosis of depression or treatment with antidepressants; dementia; conduction disorder, including second- or third-degree heart block, bifascicular block, or trifascicular block; left ventricular ejection fraction <35%; pulmonary edema or congestive heart failure; very low risk of another infarction, as documented by all of the following: no recurrent chest pain, no arrhythmias, no previous acute myocardial infarction, normal stress-test results, and left ventricular ejection fraction ≥50%; treatment with insulin (n=10,344).

Outcome

Documentation of a prescription for a beta-blocker at discharge.

ACE inhibitor prescribed at hospital discharge

Eligible patients

All patients with confirmed acute myocardial infarction on arrival who were discharged alive and not transferred to another acute care hospital (n=90,960).

Ideal patients

All eligible patients except those with one or more of the following contraindications: aortic stenosis; allergy or intolerance to ACE inhibitors; serum creatinine level >2 mg/dl (176 μmol/liter); systolic blood pressure <100 mm Hg at discharge (n=12,760).

Outcome

Documentation of a prescription for an ACE inhibitor at discharge.

*Numbers in parentheses are the numbers of patients in the Medicare National Claims History File who met the definition. For thrombolytic therapy and aspirin within 24 hours, only patients for whom the time of administration was documented were included. ACE denotes angiotensin-converting enzyme.

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MEDICARE BENEFICIARIES ADMITTED TO THE HOSPITAL WITH CONFIRMED ACUTE MYOCARDIAL INFARCTION ON ARRIVAL, ACCORDING TO SEX.*

CHARACTERISTIC	WOMEN (N=68,108)	MEN (N=70,848)	P VALUE
Age — yr	78.0±7.6	75.2±6.9	<0.001
Nonblack race — % (no.)†	93.3 (63,521)	95.4 (67,587)	<0.001
APACHE II score	10.1±4.5	10.1±4.5	0.66
DNR order — % (no.)	22.1 (15,025)	13.9 (9848)	<0.001
Coexisting conditions — % (no.)			
Diabetes	33.8 (23,003)	28.5 (20,197)	<0.001
Hypertension	68.0 (46,282)	55.9 (39,596)	<0.001
Congestive heart failure	25.4 (17,309)	18.9 (13,416)	<0.001
Cerebrovascular accident	14.3 (9757)	13.6 (9642)	<0.001
Peripheral vascular disease	9.9 (6763)	11.8 (8331)	<0.001
Previous acute myocardial infarction	27.5 (18,761)	34.6 (24,485)	<0.001
Chronic obstructive pulmonary disease	18.1 (12,347)	22.7 (16,071)	<0.001
Current smoking — % (no.)	13.2 (8993)	15.9 (11,240)	<0.001
Terminal illness — % (no.)	0.4 (258)	0.4 (268)	0.95
Intubation — % (no.)	12.1 (8272)	11.8 (8385)	0.075
Adverse in-hospital events — % (no.)			
Cardiogenic shock	7.8 (5329)	6.8 (4848)	<0.001
Pneumonia	9.2 (6267)	9.8 (6917)	<0.001
Cerebrovascular accident	3.2 (2171)	2.4 (1702)	<0.001
Reinfarction of current infarction	3.9 (2656)	3.7 (2650)	0.12
Time to ECG — min‡	37.2±50.0	33.5±48.9	<0.001
Chest pain >6 hr before arrival — % (no.)§	30.8 (16,877)	27.6 (16,694)	<0.001
Resident of skilled-nursing facility before admission — % (no.)	8.0 (5450)	3.2 (2254)	<0.001
Incontinence on arrival — % (no.)	10.2 (6957)	6.9 (4894)	<0.001
Dementia on arrival — % (no.)	7.6 (5194)	4.7 (3365)	<0.001
Length of stay — days	7.5±8.0	7.0±9.7	<0.001
Therapies for which patient is ideal candidate¶			
Thrombolytic agents	9.2 (5899)	12.3 (8299)	<0.001
Aspirin on arrival	58.8 (29,483)	56.6 (31,485)	<0.001
Aspirin at discharge	50.9 (22,998)	47.6 (21,775)	<0.001
Beta-blocker at discharge	11.8 (5346)	10.9 (4998)	<0.001
ACE inhibitor at discharge	13.2 (5957)	14.9 (6803)	<0.001

*Plus-minus values are means ±SD. APACHE II denotes Acute Physiology and Chronic Health Evaluation, DNR do not resuscitate, ECG electrocardiography, and ACE angiotensin-converting enzyme. Higher APACHE II scores indicate more severe illness.

†Data from persons of unknown race were excluded.

‡Patients with times greater than 360 minutes were excluded.

§Data are from patients with information on the duration of chest pain before admission.

¶Percentages are based on the numbers of eligible candidates; see Table 1 for definitions of eligible and ideal candidates.

ative risk, 0.94; 95 percent confidence interval, 0.92 to 0.95).

Diagnostic Catheterization and Revascularization

Seventy percent of the patients (97,928) were admitted to hospitals that performed coronary arteriography. Because age significantly affected the relation between sex and diagnostic catheterization ($P < 0.001$), the results were stratified according to age (65 through 69, 70 through 74, 75 through 79, 80 through 84, and 85 or more years). Women were significantly less likely than men to undergo catheterization in all age categories; however, this difference was more pronounced at older ages (adjusted rela-

tive risk at 65 though 69 years, 0.94; 95 percent confidence interval, 0.92 to 0.96; adjusted relative risk at 85 years of age or older, 0.75; 95 percent confidence interval, 0.68 to 0.83). After undergoing catheterization, women were referred for revascularization (either percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting) at the same rate as men (adjusted relative risk, 0.99; 95 percent confidence interval, 0.97 to 1.00).

Aspirin, Beta-Blockers, and ACE Inhibitors at Discharge

Less than 50 percent of all patients were ideal candidates for aspirin therapy at discharge. Among these, women were 5 percent less likely than men to be

TABLE 3. RATES OF USE OF INTERVENTIONS FOR ACUTE MYOCARDIAL INFARCTION IN WOMEN AND MEN.*

INTERVENTION	WOMEN	MEN	RELATIVE RISK (95% CI)
	%		
Thrombolytic therapy within 1 hr of arrival†	60.2	65.2	0.93 (0.90–0.96)
Thrombolytic therapy at any time during hospitalization	58.0	61.8	0.97 (0.94–0.99)
Aspirin within 24 hr of arrival	62.2	66.5	0.96 (0.95–0.97)
Diagnostic catheterization according to age‡			
65–69 yr	56.1	60.4	0.94 (0.92–0.96)
70–74 yr	50.3	55.4	0.91 (0.89–0.94)
75–79 yr	40.3	45.0	0.90 (0.87–0.93)
80–84 yr	24.7	29.8	0.83 (0.80–0.87)
≥85 yr	8.5	11.8	0.75 (0.68–0.83)
PTCA or CABG§	63.2	65.0	0.99 (0.97–1.00)
Aspirin at discharge	72.6	78.1	0.95 (0.94–0.96)
Beta-blocker at discharge¶	50.0	52.6	0.99 (0.95–1.03)
ACE inhibitor at discharge¶	62.0	57.7	1.05 (1.02–1.08)

*Except for catheterization and PTCA or CABG, only patients who were ideal candidates for the intervention in question were included in this analysis. Relative risks are for the use of the intervention in women as compared with men. All relative risks have been adjusted for age, race, severity of illness, and geographic region. CI denotes confidence interval, PTCA percutaneous transluminal coronary angioplasty, CABG coronary-artery bypass graft, and ACE angiotensin-converting enzyme.

†Percentages are based on the number of patients receiving thrombolytic therapy at any time during hospitalization.

‡Percentages are based on the number of patients hospitalized in facilities billing for at least four catheterizations in 1994. Data have been stratified according to age because age is a significant effect modifier and interaction term ($P < 0.01$).

§Percentages are based on the number of patients who were hospitalized in facilities billing for more than one PTCA or CABG in 1994 and who also underwent diagnostic catheterization.

¶The relative risk has been adjusted for age, race, severity of illness, geographic region, history of diabetes, and history of hypertension.

prescribed aspirin at discharge (adjusted relative risk, 0.95; 95 percent confidence interval, 0.94 to 0.96).

Twelve percent of patients were ideally suited for beta-blocker use at discharge. Although a smaller percentage of women than men in this category received a prescription for a beta-blocker at discharge (50 percent vs. 53 percent), the adjusted relative risk indicated that there was no significant sex difference in the use of this therapy (adjusted relative risk, 0.99; 95 percent confidence interval, 0.95 to 1.03).

Fourteen percent of patients were ideal candidates for an ACE inhibitor at discharge. Among these, women were 5 percent more likely than men to be discharged with a prescription for an ACE inhibitor (adjusted relative risk, 1.05; 95 percent confidence interval, 1.02 to 1.08).

DNR Status

Eighteen percent of patients had a DNR order in their medical records: 22 percent of the women and

TABLE 4. CHARACTERISTICS OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION GIVEN DO-NOT-RESUSCITATE ORDERS.*

CHARACTERISTIC	WOMEN (N=68,108)	MEN (N=70,848)	P VALUE
Age — yr	82.5±7.4	79.8±7.4	<0.001
APACHE II score	12.5±5.7	13.5±6.2	<0.001
Days from arrival to DNR order	1.9±3.8	2.6±4.5	<0.001
DNR status — % (no.)	22.1 (15,025)	13.9 (9848)	<0.001
Adjusted RR (95% CI)†	1.26 (1.22–1.29)	1.00	<0.001

*Plus-minus values are means ±SD. APACHE II denotes Acute Physiology and Chronic Health Evaluation, DNR do not resuscitate, RR relative risk, and CI confidence interval. Higher APACHE II scores indicate more severe illness.

†The relative risk has been adjusted for age (<75 vs. ≥75 years), APACHE II score (in quartiles), presence or absence of incontinence, presence or absence of dementia, and preadmission residence in a skilled-nursing facility. Men served as the reference group.

14 percent of the men. Ninety-nine percent of these orders were assigned after admission. The median day of assignment to DNR status was the day of admission for women and the day after admission for men. Among patients with a DNR order, the women were, on average, older and less ill (on the basis of their slightly lower mean APACHE II scores) (Table 4). After adjustment for demographic, clinical, and prognostic characteristics, women were 26 percent more likely to have a DNR order than men (adjusted relative risk, 1.26; 95 percent confidence interval, 1.22 to 1.29).

Mortality

The unadjusted 30-day mortality rates were 21 percent for women and 17 percent for men (unadjusted hazard ratio for death, 1.24; 95 percent confidence interval, 1.21 to 1.28) (Table 5). However, after adjustment for demographic characteristics, severity of illness, coexisting conditions, and adverse events in the hospital, the hazard ratio for death was reduced to 1.04 (95 percent confidence interval, 1.01 to 1.07), and after in-hospital interventions were added to the model, it was reduced slightly further (hazard ratio, 1.02; 95 percent confidence interval, 0.99 to 1.04).

DISCUSSION

Among the Medicare beneficiaries hospitalized for acute myocardial infarction, older women were less likely to undergo cardiac catheterization than men of similar age. However, the sex differences were smaller for other treatments, such as thrombolytic agents and aspirin. Women in this population had a 30-day mortality rate that was similar to that of men but were more likely to be assigned DNR status.

TABLE 5. 30-DAY MORTALITY AND HAZARD RATIO FOR DEATH AMONG WOMEN AND MEN WITH ACUTE MYOCARDIAL INFARCTION.*

VARIABLE	WOMEN (N=68,108)	MEN (N=70,848)
30-Day mortality — (no.)	21.0 (14,274)	17.2 (12,211)
Unadjusted HR (95% CI)	1.24 (1.21–1.28)	1.00
Adjusted HR (95% CI) in model not including treatments†	1.04 (1.01–1.07)	1.00
Adjusted HR (95% CI) in model including early treatments‡	1.02 (0.99–1.04)	1.00

*HR denotes hazard ratio, and CI confidence interval. In all analyses, men served as the reference group.

†The hazard ratio has been adjusted for age; race; severity of illness; history with respect to diabetes, hypertension, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, and cerebrovascular accident; current smoking status; presence or absence of intubation; presence or absence of the following during hospitalization: pneumonia, cerebrovascular accident, anoxic brain damage, cardiogenic shock, hypotension, bradycardia, hemorrhage; reinfarction of the current infarction; Q-wave infarction; anterior infarction; and residence in a skilled-nursing facility before admission.

‡The hazard ratio has been adjusted for age; race; severity of illness; history with respect to diabetes, hypertension, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, and cerebrovascular accident; current smoking status; presence or absence of intubation; presence or absence of the following during hospitalization: pneumonia, cerebrovascular accident, anoxic brain damage, cardiogenic shock, hypotension, bradycardia, hemorrhage; reinfarction of the current infarction; Q-wave infarction; anterior infarction; residence in a skilled-nursing facility before admission; receipt or nonreceipt of aspirin in first 24 hours; receipt or nonreceipt of thrombolytic therapy; catheterization; and receipt or nonreceipt of revascularization.

Our results are consistent with those of numerous other studies comparing the treatment of acute myocardial infarction in women and in men.^{4-7,10,11,14,22,24,29} Our study extends these findings by controlling for contraindications to treatment with aspirin, thrombolytic agents, beta-blockers, and ACE inhibitors. A weakness of previous studies of the effect of patients' sex on the treatment of acute myocardial infarction is that variations in treatment may have been due to differences between women and men in eligibility for treatment. We addressed this limitation by restricting our comparisons to the men and women identified as ideal candidates for treatment.

Our finding that women were less likely than men to undergo diagnostic catheterization is consistent with the results of several other studies.^{6,11-13,15,23,29,41} However, we also found an interaction between age and sex: differences between women and men in the rate of diagnostic catheterization widened with increasing age. Women in the youngest age group (those 65 through 69 years old) were 6 percent less likely to undergo catheterization than men, and the difference increased to 25 percent in the oldest age group (those 85 years of age or older). Underuse of this diagnostic procedure in women is especially disconcerting, since failure to perform catheterization after

acute myocardial infarction has been associated with increased short-term mortality.^{15,25} In addition, as in other studies,²⁹ we found that women who underwent diagnostic catheterization subsequently underwent revascularization at rates equal to those of men. This suggests that although the decision to perform diagnostic catheterization is influenced by the patient's sex, the decision to perform revascularization is not.

Although women were significantly less likely than men to receive aspirin at discharge, the adjusted relative risk (0.95) was very close to 1.0. Perhaps of greater importance, however, is the fact that the overall rate of use of aspirin at discharge among both men and women who were ideal candidates for aspirin therapy was less than 80 percent. This underutilization was unfortunate, since aspirin is safe in ideal candidates and is an effective and inexpensive drug for the treatment of acute myocardial infarction. It is estimated that the appropriate use of aspirin by patients with acute myocardial infarction could prevent more than 3000 deaths among Medicare beneficiaries in the United States annually.³²

Women who were ideal candidates were 3 percent less likely than men to receive any thrombolytic therapy and 7 percent less likely to receive it within the first hour after admission. Although these are small differences, they are consistent with other evidence suggesting that myocardial infarction is recognized later in women than in men after their arrival at the hospital. For example, women in our study waited an average of 3.7 minutes longer than men to undergo electrocardiography. As with the use of aspirin, these results suggest the possibility of small sex differences in the use of thrombolytic therapy. However, perhaps more important is the finding that only approximately 60 percent of ideal candidates of either sex received thrombolytic therapy at any time during hospitalization. Studies have shown that local hospitals can improve essential elements of care, including shortening the time to treatment, by making an effort to recognize acute myocardial infarction earlier, especially in women patients.⁴²

Not all therapies were less likely to be administered to women than to men in our study. Among ideal candidates, after adjustment for patients' characteristics, women were as likely as men to be prescribed a beta-blocker at discharge. Women were 5 percent more likely than men to be prescribed an ACE inhibitor at discharge. This could be because more women had diabetic nephropathy or were already taking ACE inhibitors at admission, but we do not have enough information on renal function or preadmission medications to examine this issue.

Our study and that of Wenger et al.⁴³ found that women were more likely than men to have a DNR order recorded in their charts. Our results extend the findings of Wenger et al., because we were able to control for factors related to the severity of illness

that are potentially associated with DNR orders. There may be several explanations for the sex differences in DNR status. Women in our cohort may have requested a DNR order more frequently, or providers may have been more willing to recommend DNR status to them. In addition, unmeasured psychosocial or functional-status factors may explain these findings. Unfortunately, the Cooperative Cardiovascular Project does not include the data necessary to examine this important issue fully.

Our results are consistent with the findings of prior studies that adjustment for patients' characteristics and adverse events in the hospital reduces or eliminates differences in crude mortality rates between women and men.^{22,27,41,43-49} We calculated an unadjusted hazard ratio for death at 30 days of 1.24 for women. However, after adjustment for patients' characteristics, the hazard ratio for women as compared with men was reduced to nearly 1.0.

Our study has certain limitations. Because of the very large size of our sample, most differences we identified are statistically significant, but the clinical relevance of some of the differences is uncertain. In addition, relative risks can be affected by the manner in which variables are coded and entered into statistical models. Because many of the adjusted relative risks we calculated were near 1.0, they might not represent true differences in treatment based on sex. We therefore developed a series of models for each outcome, varying the manner in which variables such as age were coded (as continuous or categorical variables) and the way in which variables themselves were entered into the models. Throughout these analyses, our findings were quite robust. Although we did find small changes in the adjusted relative risks with different models, the direction and statistical significance of our findings were unchanged.

The data we analyzed were collected by retrospective chart review, and errors in abstraction were possible. However, validation studies suggest that the reliability of data from the Cooperative Cardiovascular Project is high.⁵⁰

Because our study was observational, the results may have been subject to uncontrolled confounding. For instance, we have only limited information on the extent of damage to the myocardium. Although we were able to control for the location of the infarct, we lacked complete information about its size and other prognostic indicators, such as the results of cardiac stress tests or tests of diastolic function, that might have affected mortality. A further limitation was the brief period for which data were collected by the Cooperative Cardiovascular Project and the fact that our results may not reflect long-term trends. Whether we could duplicate our findings in the current medical environment, with its focus on women's health care issues, is unknown.

In spite of these shortcomings, the Cooperative

Cardiovascular Project has provided one of the largest and most comprehensive pictures of the care of elderly patients with acute myocardial infarction in the United States to date. The study has strengths related to its sampling strategy and the breadth of its clinical data.³⁵ By taking cases from the Medicare National Claims History File, we eliminated selection bias resulting from reliance on the voluntary participation of patients and medical facilities. The richness of the clinical data allowed us to adjust for suitability for treatment and other important variables not included in previous studies. Moreover, because only Medicare beneficiaries were included, the ability to pay for care was eliminated as a confounding factor.

Our results have several implications. Future studies of differences in treatment between women and men after acute myocardial infarction should consider eligibility for treatment in their design and analysis. They should also include a careful examination of how a patient's sex is related to the assignment of DNR status and how this factor affects treatment decisions and outcome. Moreover, health care providers should be made aware of potential sex differences in treatment, particularly with regard to the use of diagnostic catheterization in older patients. Finally, we found that overall compliance with the practice guidelines for the treatment of acute myocardial infarction was poor. More women and men should receive the recommended lifesaving therapies to reduce morbidity and mortality after myocardial infarction.

This study was performed in the Division of Clinical Standards and Quality, Health Care Financing Administration, Region 10, Seattle, as part of Medicare's Health Care Quality Improvement Program. The views expressed here are those of the authors and not necessarily those of the Health Care Financing Administration, the Swedish Medical Center, or the University of Washington.

We are indebted to Louise P. Roumagoux, M.S.N., M.P.H., Cecilia-Marina Praela, Pharm.D., Nathan Every, M.D., M.P.H., J. Randall Curtis, M.D., M.P.H., and Cassian Yee, M.D., for their assistance in this project.

REFERENCES

- 1997 Heart and stroke statistical update. Dallas: American Heart Association, 1996.
- Coronary heart disease incidence, by sex — United States, 1971–1987. *MMWR Morb Mortal Wkly Rep* 1992;41:526-9.
- Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med* 1998;339:861-7.
- Kober L, Torp-Pedersen C, Ottessen M, Rasmussen S, Lessing M, Skagen K. Influence of gender on short- and long-term mortality after acute myocardial infarction. *Am J Cardiol* 1996;77:1052-6.
- Yarzebski J, Col N, Pagely P, Savageau J, Gore J, Goldberg R. Gender differences and factors associated with the receipt of thrombolytic therapy in patients with acute myocardial infarction: a community-wide perspective. *Am Heart J* 1996;131:43-50.
- Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women. *Am J Cardiol* 1996;78:9-14.
- Maynard C, Althouse R, Cerqueira M, Olsufka M, Kennedy JW. Underutilization of thrombolytic therapy in eligible women with acute myocardial infarction. *Am J Cardiol* 1991;68:529-30.
- Maynard C, Beshansky JR, Griffith JL, Selker HP. Influence of sex on the use of cardiac procedures in patients presenting to the emergency de-

- partment: a prospective multicenter study. *Circulation* 1996;94:Suppl II:II-93-II-98.
9. McLaughlin TJ, Soumerai SB, Willison DJ, et al. Adherence to national guidelines for drug treatment of suspected acute myocardial infarction: evidence for undertreatment in women and elderly. *Arch Intern Med* 1996;156:799-805. [Erratum, *Arch Intern Med* 1996;156:1920.]
 10. Chu P-H, Chiang C-W, Cheng N-J, et al. Gender differences in baseline variables, therapies and outcomes in Chinese patients with acute myocardial infarction. *Int J Cardiol* 1998;65:75-80.
 11. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. *Arch Intern Med* 1998;158:981-8.
 12. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. *N Engl J Med* 1991;325:221-5.
 13. Giles WH, Anda RF, Casper ML, Escobedo LG, Taylor HA. Race and sex differences in rates of invasive cardiac procedures in US hospitals: data from the National Hospital Discharge Survey. *Arch Intern Med* 1995;155:318-24.
 14. Tsuyuki RT, Teo KK, Ikuta RM, Bay KS, Greenwood PV, Montague T. Mortality risk and patterns of practice in 2,070 patients with acute myocardial infarction, 1987-92: relative importance of age, sex, and medical therapy. *Chest* 1994;105:1687-92.
 15. Kostis JB, Wilson AC, O'Dowd K, et al. Sex differences in the management and long-term outcome of acute myocardial infarction: a state-wide study. *Circulation* 1994;90:1715-30.
 16. Manson JE, Stampfer MJ, Colditz GA, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA* 1991;266:521-7.
 17. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22. [Erratum, *Lancet* 1994;343:742.]
 18. Viscoli CM, Horwitz RI, Singer BH. Beta-blockers after acute myocardial infarction: influence of first-year clinical course on long-term effectiveness. *Ann Intern Med* 1993;118:99-105.
 19. Woodfield SL, Lundergan CF, Reiner JS, et al. Gender and acute myocardial infarction: is there a different response to thrombolysis? *J Am Coll Cardiol* 1997;29:35-42.
 20. Krumholz HM, Murillo JE, Chen J, et al. Thrombolytic therapy for eligible elderly patients with acute myocardial infarction. *JAMA* 1997;277:1683-8.
 21. Harpaz D, Benderly M, Goldbourt U, Kishon Y, Behar S. Effect of aspirin on mortality in women with symptomatic or silent myocardial ischemia. *Am J Cardiol* 1996;78:1215-9.
 22. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med* 1999;341:217-25.
 23. Demirovic J, Blackburn H, McGovern PG, Luepker R, Sprafka JM, Gilbertson D. Sex differences in early mortality after acute myocardial infarction (the Minnesota Heart Survey). *Am J Cardiol* 1995;75:1096-101.
 24. Marrugat J, Sala J, Masia R, et al. Mortality differences between men and women following first myocardial infarction. *JAMA* 1998;280:1405-9.
 25. Jenkins JS, Flaker GC, Nolte B, et al. Causes of higher in-hospital mortality in women than in men after acute myocardial infarction. *Am J Cardiol* 1994;73:319-22.
 26. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction: comparison with 4,315 men. *Circulation* 1991;83:484-91.
 27. Dittrich H, Gilpin E, Nicod P, Cali G, Henning H, Ross J Jr. Acute myocardial infarction in women: influence of gender on mortality and prognostic variables. *Am J Cardiol* 1988;62:1-7.
 28. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991: presentation, diagnosis, treatment and 28-day case fatality of 3991 events in men and 1551 events in women. *Circulation* 1996;93:1981-92.
 29. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction: results from the Myocardial Infarction Triage and Intervention Registry. *Arch Intern Med* 1992;152:972-6.
 30. Ellerbeck EF, Jencks SF, Radford MJ, et al. Quality of care for Medicare patients with acute myocardial infarction: a four-state pilot study from the Cooperative Cardiovascular Project. *JAMA* 1995;273:1509-14.
 31. O'Connor GT, Quinton HB, Traven ND, et al. Geographic variation in the treatment of acute myocardial infarction: the Cooperative Cardiovascular Project. *JAMA* 1999;281:627-33.
 32. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin for secondary prevention after acute myocardial infarction in the elderly: prescribed use and outcomes. *Ann Intern Med* 1996;124:292-8.
 33. Krumholz HM, Chen J, Murillo JE, Cohen DJ, Radford MJ. Clinical correlates of in-hospital costs for acute myocardial infarction in patients 65 years of age and older. *Am Heart J* 1998;135:523-31.
 34. Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA* 1998;280:623-9. [Erratum, *JAMA* 1999;281:37.]
 35. Every NR, Frederick PD, Robinson M, Sugarman J, Bowlby L, Barron HV. A comparison of the National Registry of Myocardial Infarction 2 with the Cooperative Cardiovascular Project. *J Am Coll Cardiol* 1999;33:1886-94.
 36. Krumholz HM, Chen J, Wang Y, Radford MJ, Chen YT, Marciniak TA. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation* 1999;99:2986-92.
 37. International classification of diseases, 9th rev., clinical modification: ICD-9-CM. Los Angeles: Practice Management Information, 1999.
 38. Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. *Am J Epidemiol* 1986;123:174-84.
 39. Ludwigs U, Hulting J. Acute Physiology and Chronic Health Evaluation II scoring system in acute myocardial infarction: a prospective validation study. *Crit Care Med* 1995;23:854-9.
 40. Stata, version 6.0. College Station, Tex.: Stata, 1999 (software).
 41. Udvarhelyi IS, Gatsonis C, Epstein AM, Pashos CL, Newhouse JP, McNeil BJ. Acute myocardial infarction in the Medicare population: process of care and clinical outcomes. *JAMA* 1992;268:2530-6.
 42. Cannon CP, Johnson EB, Cermignani M, Scirica BM, Sagarin MJ, Walls RM. Emergency department thrombolysis critical pathway reduces door-to-drug times in acute myocardial infarction. *Clin Cardiol* 1999;22:17-20.
 43. Wenger NS, Pearson ML, Desmond CA, Brook RH, Kahn KL. Outcomes of patients with do-not-resuscitate orders: toward an understanding of what do-not-resuscitate orders mean and how they affect patients. *Arch Intern Med* 1995;155:2063-8.
 44. Fiebach NH, Viscoli CM, Horwitz RI. Differences between women and men in survival after myocardial infarction: biology or methodology? *JAMA* 1990;263:1092-6.
 45. Gottlieb S, Moss AJ, McDermott M, Eberly S. Comparison of posthospital survival after acute myocardial infarction in women and men. *Am J Cardiol* 1994;74:727-30.
 46. Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI. Sex differences in mortality after myocardial infarction: is there evidence for an increased risk for women? *Circulation* 1995;91:1861-71.
 47. Bueno H, Vidan MT, Almazan A, Lopez-Sendon JL, Delcan JL. Influence of sex on the short-term outcome of elderly patients with a first acute myocardial infarction. *Circulation* 1995;92:1133-40.
 48. Lincoff AM, Califf RM, Ellis SG, et al. Thrombolytic therapy for women with myocardial infarction: is there a gender gap? *J Am Coll Cardiol* 1993;22:1780-7.
 49. Malacrida R, Genoni M, Maggioni AP, et al. A comparison of the early outcome of acute myocardial infarction in women and men. *N Engl J Med* 1998;338:8-14.
 50. Huff ED. Comprehensive reliability assessment and comparison of quality indicators and their components. *J Clin Epidemiol* 1997;50:1395-404.