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John N. Beattie
Henry Ford Health

Sandeep S. Soman
Henry Ford Health, SSOMAN1@hfhs.org

Keisha R. Sandberg
Henry Ford Health

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

Steven Borzak
Henry Ford Health

See next page for additional authors

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Authors

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Determinants of Mortality After Myocardial Infarction in Patients With Advanced Renal Dysfunction

John N. Beattie, MD, Sandeep S. Soman, MD, Keisha R. Sandberg, BS, Jerry Yee, MD, Steven Borzak, MD, Mukesh Garg, MD, and Peter A. McCullough, MD, MPH

• **Previous studies using administrative data have shown high mortality in patients with renal failure requiring dialysis after acute myocardial infarction (AMI). There has been little investigation into the mortality after AMI in those with advanced renal disease who are not on dialysis therapy. We analyzed a prospective coronary care unit registry of 1,724 patients with ST segment elevation myocardial infarction admitted over an 8-year period at a single tertiary-care center. Those not on chronic dialysis therapy were stratified into groups based on corrected creatinine clearance, with cutoff values of 46.2, 63.1, and 81.5 mL/min/72 kg. Dialysis patients (n = 47) were considered as a fifth comparison group. Older age, black race, diabetes, hypertension, previous coronary disease, and heart failure were incrementally more common across increasing renal dysfunction strata. There were also graded increases in the relative risk for atrial and ventricular arrhythmias, heart block, asystole, development of pulmonary congestion, acute mitral regurgitation, and cardiogenic shock. Primary angioplasty, thrombolysis, and β-blockers were used less often across the risk strata ($P < 0.0001$ for all trends). There was an early mortality hazard (age-adjusted relative risk, 8.76; $P < 0.0001$) for those with renal dysfunction but not on dialysis therapy for the first 60 months, followed by graded decrements in survival across increasing renal dysfunction strata. The excess mortality in this population appears to be mediated through arrhythmias, adverse hemodynamic events, and the lower use of mortality-reducing therapy.**

INDEX WORDS: Coronary care unit; renal failure; survival; arrhythmias; complications.

ADVANCED RENAL FAILURE requiring dialysis has been established as an independent predictor of mortality after acute myocardial infarction (AMI).[1-4] It has also been suggested that lesser degrees of renal failure, measured as serum creatinine (Cr) and blood urea nitrogen (BUN)l levels or corrected creatinine clearance (CorrCrCl), predict survival in patients with acute coronary syndromes, AMI, and after a variety of cardiovascular events.[2-8] However, knowledge of the determinants of mortality in these patient populations has been limited by previously used data collection methods and the routine exclusion of these patients from most large randomized AMI trials. Accordingly, we sought to evaluate the independent determinants of AMI mortality across the full spectrum of renal dysfunction.

METHODS

Setting, Data Collection, and Follow-Up

Henry Ford Hospital is a 903-bed tertiary care center located in Detroit, MI. The hospital receives patients whose care is provided primarily within the Henry Ford Health System, a vertically integrated, mixed-model, managed care organization with an advanced information technology infrastructure.[9,10] Methods of data collection used in the Henry Ford Hospital Cardiac Intensive Care Unit Database have been previously described.[11] In brief, this is a registry in which every admission to a 16-bed unit had clinical data (~250 discrete elements) prospectively recorded on case report forms by trained research assistants. Data collected from May 1, 1990, to August 22, 1998, included baseline demographics, laboratory values, and events occurring during the unit stay, such as revascularization and complications. The data collection period was stopped after discharge from the unit, either to another floor or to home.

Mortality during the unit stay was recorded prospectively. On an annual basis, vital status was tracked by ascertainment of future activity in the health system, confirmation of death by identification matching with the State of Michigan Death Certificate Registry, or record of a death on a later hospitalization within the health system corporate data stores. Finally, for those not identified with any of these means, the available Internet death identification service (www.ancestry.com) was used to confirm death primarily in a state other than Michigan. These data strategies yielded a 99% overall vital status ascertainment rate for patients followed up after

From the Department of Internal Medicine, Divisions of Cardiovascular Medicine and Hypertension and Nephrology, Henry Ford Hospital, Detroit, MI; and the Department of Internal Medicine, Cardiology Section, University of Missouri-Kansas City, Truman Medical Center, Kansas City, MO.

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Address reprint requests to Peter A. McCullough, MD, MPH, Department of Internal Medicine, Cardiology Section, Truman Medical Center, 2301 Holmes St, Kansas City, MO 64108. E-mail: mccullughp@umkc.edu

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the first admission longitudinally over 27 ± 28 months (minimum, 0 months; maximum, 100 months). The subset of 1,724 patients reported here from the 9,544-patient parent database was selected on the basis of the case report form indicating an ST segment elevation AMI defined as characteristic chest pain and ST segment elevation of 1 mm or greater in two or more contiguous leads on the initial electrocardiogram (ECG).

Assessment of Baseline Renal Function

The database was augmented with merged data from laboratory tables to obtain complete renal function data, taken as the initial admission serum Cr level in millgrams per deciliter, for 9,544 patients (99.9%). Because weight was not available in the database, CorrCrCl was used as the best measure of baseline renal function as follows[12-15]:

$$\text{CorrCrCl}_{\text{male}} = (140 - \text{age}_{\text{y}})/72$$

$$\text{CorrCrCl}_{\text{female}} = 0.85[(140 - \text{age}_{\text{y}})/72]$$

CorrCrCl was found to be unimodal and normally distributed. Other epidemiological measures of renal function were considered, including 1/Cr and those formulas derived from patients without diabetes by Levey et al.[15] Given the advantages of correcting for age and sex, the high rates of diabetes in our population, and the performance of this measure in the parent database, which is substantially larger than that of previous studies, it was decided to retain CorrCrCl as the measure of interest.[11] Therefore, all 9,544 patients were divided into quartiles at the cutoff values of 46.2, 63.1, and 81.5 mL/min/72 kg. Quartile analysis of CorrCrCl was favored as an epidemiological tool over modeling CorrCrCl as a continuous variable because it allowed for analysis of trends by group and inclusion of dialysis patients. Patients on chronic dialysis therapy (n = 527) again were considered as a fifth comparison group. From this parent database, 1,723 consecutive patients with ST segment elevation AMI were evaluated on this study according to the strata of renal dysfunction described previously. We previously published the validation of 11 arrhythmic, hemodynamic, and fatal outcomes by blinded chart abstraction in which the mean percentage of agreement was 92.7% across the 11 outcomes.[11]

Statistical Analysis

Baseline characteristics are reported as mean ± SD or proportions with 95% confidence intervals (CIs), as appropriate, with exclusion of missing data points. Univariate comparisons were performed using analysis of variance or chi-square, as appropriate. Chi-square test for linear trend was used for comparisons of baseline characteristics across ascending levels of renal dysfunction. Multiple logistic regression was performed for the outcome of in-hospital death, with independent odds ratios (ORs) reported with 95% CIs. All models were tested for interactions. Variables in the causal pathway were included in the final models. Cox proportional hazards model was used to derive the independent hazard of estimated renal function with cumulative long-term survival. The log-rank test was used to evaluate the independent differences in survival across the strata. All P are two-tailed and considered significant at α less than 0.05.

RESULTS

Baseline Characteristics

Table 1 lists baseline characteristics of the patient groups stratified by renal risk. Overall mean age was 63.4 ± 13.8 years (range, 15 to 98 years). The mean age for women and men was similar at 63.6 ± 13.8 and 63.3 ± 13.7 years, respectively ($P = 0.22$). The overall woman-man ratio was 0.73, with men predominant in all groups. For the study group, 1,037 patients (60.1%) were white, 629 patients (36.5%) were black, and 57 patients (3.3%) were categorized as "other race." Black race increased in proportion from groups 1 to 4, but accounted for a smaller percentage of patients on dialysis therapy (40.4% versus 53.2%). Diabetes and hypertension were more common across the ascending risk groups 1 to 5 ($P < 0.0001$ for both trends). Conversely, smoking and hyperlipidemia were more common in the lower renal risk groups ($P < 0.0001$ for both trends). Previous coronary artery disease increased over the renal strata from 21.4% to 40.9% for a history of angina and 16% to 27.9% for a previous AMI ($P < 0.0001$ for both). Rates of prior coronary revascularization were similar among the groups. A history of congestive heart failure (CHF) also increased in frequency from 5.3% to 31.7% when comparing groups 1 to 5 ($P < 0.0001$). Rates of CHF medications, including angiotensin-converting enzyme inhibitors, diuretics, and digoxin, also increased over the strata, consistent with the frequencies of diabetes, CHF, and hypertension observed.

Admission Clinical Findings

Physical examination findings and baseline laboratory values are listed in Table 2. Patients were more likely to be admitted with CHF with the expected physical examination findings of an S_3, rales, and peripheral edema across the strata of increasing renal dysfunction. The clinical diagnosis of CHF and physical examination findings were separate variables on the case report form.

Table 1. Baseline Clinical Characteristics of 1,724 Patients Admitted to a Coronary Care Unit With ST Segment Elevation Myocardial Infarction Stratified by Renal Risk Group

Characteristic	Group 1 CorrCrCl* > 81.5 mL/min/72 kg	Group 2 63.1 < CorrCrCl ≤ 81.5 mL/min/72 kg	Group 3 46.2 < CorrCrCl ≤ 63.1 mL/min/72 kg	Group 4 CorrCrCl ≤ 46.2 mL/min/72 kg Not on Dialysis	Group 5 Chronic Dialysis	*P* Group 1 *v* Group 5	*P* for Trend
No. of patients	524	421	421	310	47	—	—
Age (y)	54.4 ± 13.0	62.8 ± 12.2	69.8 ± 11.8	70.2 ± 12.9	64.9 ± 16.2	<0.0001	<0.0001
Women-men ratio	0.52	0.48	0.58	0.76	0.34		
Black	153 (29.2)	149 (35.4)	160 (38.0)	148 (47.7)	19 (40.4)	<0.0001	<0.0001
White	353 (67.4)	255 (60.6)	252 (59.9)	152 (49.0)	25 (53.2)	0.0001	<0.0001
Other race	18 (3.4)	17 (4.0)	9 (2.1)	10 (3.2)	3 (6.4)	0.53	0.27
Diabetes	124 (23.7)	111 (26.4)	124 (29.5)	118 (38.1)	19 (40.4)	0.01	<0.0001
Hypertension	269 (51.3)	228 (54.2)	252 (59.9)	235 (75.8)	30 (63.8)	0.10	0.23
Dyslipidemia	205 (39.1)	150 (35.6)	149 (35.4)	103 (33.2)	11 (23.4)	0.03	0.02
Tobacco use	345 (65.8)	248 (58.9)	222 (52.7)	158 (51.0)	28 (59.6)	0.001	<0.0001
Prior angina	109 (21.4)	101 (24.6)	115 (28.0)	100 (34.0)	18 (40.9)	0.003	<0.0001
Prior AMI	82 (16.0)	89 (21.9)	93 (22.4)	103 (34.7)	12 (27.9)	0.05	<0.0001
Any prior revascularization	58 (11.1)	35 (8.3)	40 (9.5)	33 (10.6)	7 (14.9)	0.43	0.84
Prior CHF	27 (5.3)	29 (7.2)	32 (7.9)	69 (23.2)	13 (31.7)	<0.0001	<0.0001
Aspirin	149 (30.0)	124 (31.2)	123 (30.8)	76 (27.7)	15 (39.5)	0.22	0.99
β-blockers	88 (17.6)	86 (21.3)	85 (21.0)	53 (19.2)	8 (20.5)	0.65	0.45
ACE inhibitor	61 (12.3)	60 (15.3)	65 (16.3)	71 (25.3)	8 (20.5)	0.14	<0.0001
Calcium channel blockers	98 (19.6)	77 (19.4)	74 (18.6)	88 (31.5)	14 (35.0)	0.02	<0.0001
Nitrates	67 (13.5)	67 (16.6)	91 (22.6)	73 (26.0)	18 (45.0)	<0.0001	<0.0001
Diuretics	62 (12.4)	56 (14.2)	85 (21.1)	97 (33.9)	22 (51.2)	<0.0001	<0.0001
Digitalis	15 (3.0)	18 (4.6)	28 (7.0)	40 (14.2)	10 (25.0)	<0.0001	<0.0001

NOTE. Only the first admission is counted in these comparisons. Values in parentheses are percentages.

Abbreviations: PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery; ACE, angiotensin-converting enzyme.

They showed significant clustering, thus supporting the diagnosis. There were increasing levels of blood pressure and heart rate across the renal risk strata. In addition, there were greater rates of atrial fibrillation, complete heart block, and left bundle-branch block on the admission ECG across the renal risk strata. Patients with advanced renal dysfunction were more likely to have a combination of infarct locations, including anteroseptal, lateral, and posterior walls ($P < 0.0001$). There was no difference in mean peak creatine kinase levels measured from groups 1 to 5 (mean creatine kinase: group 1, 1,917.6 ± 1,740.3 U/L; group 5, 1,715.6 ± 1,636.3 U/L; $P = 0.23$). Evidence for left ventricular dysfunction was more common in the higher renal risk strata; the majority of those in groups 4 and 5 had cardiomegaly on initial chest radiograph. Cardiomegaly was more than twice as common a radiographic finding in the highest versus lowest renal dysfunction group (group 1, 22.9%; group 5, 58.6%; $P < 0.0001$).

Arrhythmic and Hemodynamic Complications

Table 3 lists the graded increases in univariate risk for developing atrial fibrillation, ventricular tachycardia, and ventricular fibrillation across the renal risk strata. There was a clear dose-response relation seen between level of renal dysfunction and development of complete heart block (Table 3). Table 3 lists univariate risks for hemodynamic complications occurring from the time of emergency department presentation through the coronary care unit course. These complications were defined on the case report form as having developed after hospital arrival, based on the clinical examination and supportive diagnostic testing. For example, acute mitral regurgitation was defined as the presence of a new or worsened murmur and the finding of new

Table 2. Physical Examination and ECG Findings and Laboratory Values for 1,724 Patients Admitted to a Coronary Care Unit With ST Segment Elevation AMI Stratified by Renal Risk Group

	Group 1 CorrCrCl > 81.5 mL/min/ 72 kg	Group 2 63.1 < CorrCrCl ≤ 81.5 mL/min/ 72 kg	Group 3 46.2 < CorrCrCl ≤ 63.1 mL/min/ 72 kg	Group 4 CorrCrCl ≤ 46.2 mL/min/ 72 kg Not on Dialysis	Group 5 Chronic Dialysis	*P* Group 1 *v* Group 5	*P* for Trend
No. of patients	524	421	421	310	47	—	—
Physical examination findings							
Heart rate (beats/min)	80.9 ± 18.6	83.0 ± 19.8	83.0 ± 21.6	87.1 ± 22.0	84.6 ± 22.0	0.003	<0.0001
SBP (mm Hg)	126.8 ± 22.6	129.0 ± 24.2	130.6 ± 26.1	130.4 ± 28.7	131.6 ± 3.7	0.17	0.02
DBP (mm Hg)	74.4 ± 15.5	76.1 ± 16.1	76.4 ± 15.8	74.3 ± 18.4	74.6 ± 22.7	0.27	0.77
Jugular venous distension (%)	34/508 (6.7)	38/406 (9.4)	38/412 (9.2)	45/293 (15.4)	9/43 (20.9)	<0.0001	<0.0001
Pulmonary rales	61/507 (12.0)	69/406 (17.0)	90/413 (21.8)	93/204 (31.3)	18/45 (40.0)	<0.0001	<0.0001
S_3	37/507 (7.3)	49/405 (12.1)	41/412 (10.0)	50/287 (17.4)	10/43 (23.3)	<0.0001	<0.0001
S_4	79/507 (15.6)	81/405 (20.0)	88/410 (21.5)	53/288 (18.4)	7/42 (16.7)	0.21	0.21
Hepatomegaly	10/501 (2.0)	8/403 (2.0)	5/410 (1.2)	12/288 (4.2)	3/44 (6.8)	0.03	0.05
Peripheral edema	26/500 (5.2)	32/404 (7.9)	32/410 (7.8)	46/287 (16.0)	7/44 (15.9)	<0.0001	<0.0001
Infarct location by ECG							
Anteroseptal	115 (21.9)	109 (25.9)	100 (23.8)	84 (27.1)	14 (29.8)	0.21	<0.0001
Anterior	53 (10.1)	57 (13.5)	44 (10.5)	37 (11.9)	7 (14.9)	0.44	0.35
Inferior	170 (32.4)	157 (37.3)	191 (45.4)	116 (37.4)	14 (29.8)	0.71	0.37
Lateral	47 (9.0)	50 (11.9)	44 (5.23)	51 (16.5)	13 (27.7)	0.0002	<0.0001
High lateral	22 (4.2)	31 (7.4)	23 (5.5)	21 (6.8)	9 (19.1)	<0.0001	<0.0001
Posterior	42 (8.0)	26 (6.2)	34 (8.1)	22 (7.9)	4 (8.5)	0.87	<0.0001
LBBB	3 (0.6)	8 (1.9)	7 (1.7)	12 (3.9)	2 (4.3)	0.99	0.01
Combination	0 (0.0)	17 (4.0)	22 (5.2)	33 (10.6)	17 (36.1)	<0.0001	<0.0001
Other ECG findings							
Atrial fibrillation/flutter	32 (6.1)	30 (7.1)	37 (8.8)	50 (16.1)	5 (10.6)	<0.0001	0.74
Complete heart block	6 (1.1)	15 (3.6)	23 (5.5)	19 (6.1)	3 (6.4)	0.0001	0.72
Laboratory values							
Sodium (mEq/L)	137.7 ± 5.8	138.0 ± 5.0	137.8 ± 5.9	136.9 ± 5.0	138.6 ± 7.7	0.21	0.37
Potassium (mEq/L)	4.2 ± 0.9	4.1 ± 0.7	4.2 ± 0.7	4.4 ± 0.9	4.5 ± 1.0	0.001	0.001
Hemoglobin (g/dL)	13.6 ± 2.0	13.7 ± 1.9	13.4 ± 2.1	12.7 ± 2.3	12.2 ± 2.7	<0.0001	<0.0001
Creatinine (mg/dL)*	0.8 ± 0.2	1.0 ± 0.2	1.2 ± 0.2	2.7 ± 2.6	3.3 ± 2.5	<0.0001	<0.0001
BUN (mg/dL)†	16.2 ± 18.3	16.0 ± 9.9	21.8 ± 24.5	28.5 ± 23.5	40.1 ± 25.2	<0.0001	<0.0001

NOTE. Values in parentheses are percentages.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LBBB, left bundle-branch block.
*To convert to micromolar, multiply by 88.4.
†To convert to millimolar, multiply by 0.357.

or worsened mitral regurgitant flow on echocardiography. Likewise, new pulmonary edema was defined as the development of rales and/or a consistent chest radiograph with pulmonary edema. Cardiogenic shock was defined as hypotension (systolic blood pressure < 90 mm Hg or mean arterial pressure < 70 mm Hg) and inadequate perfusion attributable to a cardiac cause. In a graded fashion, group 5 had the greatest adjusted risk for developing acute mitral regurgitation, pulmonary edema, and cardiogenic shock compared with group 1.

Treatment Received

Unless there was an absolute contraindication, all patients were administered 162 mg of soluble aspirin according to the coronary care unit AMI admission orders. Figure 1 shows the decreasing

Table 3. Risks for Arrhythmic and Hemodynamic Complications Stratified by Renal Risk Group

	Group 1 CorrCrCl > 81.5 mL/min/72 kg	Group 2 63.1 < CorrCrCl ≤ 81.5 mL/min/72 kg	Group 3 46.2 < CorrCrCl ≤ 63.1 mL/min/72 kg	Group 4 CorrCrCl ≤ 46.2 mL/min/72 kg Not on Dialysis	Group 5 Chronic Dialysis
No.	524	421	421	310	47
Atrial fibrillation or atrial flutter					
OR	1.00	1.18	1.48	2.96	1.83
95% CI	—	0.71-1.98	0.91-2.42	1.85-4.72	0.68-4.95
P	—	0.53	0.12	<0.0001	0.22
Sustained ventricular tachycardia					
OR	1.00	1.60	1.34	2.21	2.31
95% CI	—	0.81-3.20	0.66-2.74	1.11-4.43	0.65-8.30
P	—	0.18	0.42	0.02	0.18
Ventricular fibrillation					
OR	1.00	2.35	1.92	4.17	2.95
95% CI	—	1.25-4.39	1.01-3.66	2.27-7.65	0.95-9.22
P	—	0.006	0.05	<0.0001	0.07
Complete heart block					
OR	1.00	3.19	4.99	5.64	5.88
95% CI	—	1.23-8.29	2.01-12.37	2.23-14.27	1.42-24.34
P	—	0.01	<0.0001	<0.0001	0.03
Asystole					
OR	1.00	7.31	5.10	15.23	11.84
95% CI	—	2.13-25.11	1.43-18.18	4.56-50.90	2.32-60.41
P	—	<0.0001	0.007	<0.0001	0.009
Pulmonary edema					
OR	1.00	1.51	1.79	3.36	4.41
95% CI	—	1.08-2.10	1.30-2.48	2.41-4.67	2.37-8.23
P	—	0.02	<0.0001	<0.0001	<0.0001
Acute mitral regurgitation					
OR	1.00	3.57	3.84	3.81	7.08
95% CI	—	1.28-10.00	1.38-10.62	1.31-11.10	1.64-30.60
P	—	0.02	0.006	0.02	0.02
Cardiogenic shock					
OR	1.00	1.48	1.87	3.57	4.09
95% CI	—	0.85-2.56	1.10-3.16	2.15-5.93	1.73-9.68
P	—	0.20	0.02	<0.0001	0.003

NOTE. Unadjusted odds ratios with 95% CIs and number per cell are given with Group 1 as the referent.
Abbreviation: OR, odds ratio.

rates of treatment with reperfusion (angioplasty or thrombolysis) and β-blocker use across the renal risk strata ($P < 0.0001$ for all trends). Of note, angioplasty proportions include primary angioplasty and treatment for failure of thrombolysis and recurrent ischemia after medical therapy. Additionally, 44 patients (2.6%) underwent coronary artery bypass surgery during the coronary care unit stay.

In-Hospital Death and Long-Term Survival

Figure 2 shows age- and sex-adjusted risks for in-hospital death stratified by renal risk group. Of note, those in group 4 with advanced renal dysfunction but not on dialysis therapy had the greatest risk for in-hospital death (age-adjusted relative risk, 8.76; $P < 0.0001$). Figure 3 shows the adjusted relative hazard for cumulative death over long-term follow-up. Groups 3 through 5 had worsened survival compared with groups 1 and 2 ($P < 0.05$ by log rank). Group 4 had the worst survival for the first 60 months until its survival curve was crossed by group 5, patients on chronic dialysis therapy, who showed an overall mortality rate of 60% during the follow-up period.

DISCUSSION

This study has shown that baseline renal function, measured as CorrCrCl in milliliters per

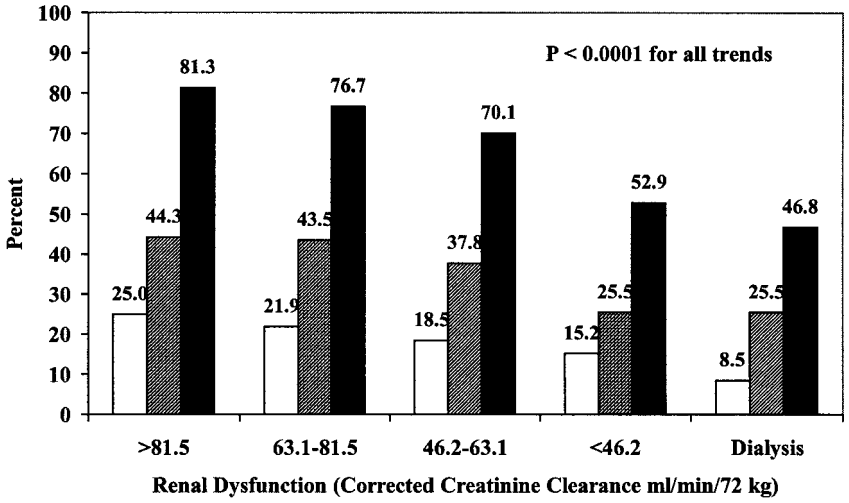

Fig 1. Treatment received for AMI stratified by renal dysfunction group. (□) Angioplasty; (▨) thrombolysis; (■) beta blockers.

minute per 72 kg, accurately stratifies patients entering the coronary care unit with an AMI with respect to in-hospital complications and long-term survival. Through a range of normal serum Cr levels, 0.8 ± 0.2 mg/dL (70.7 ± 17.7 μmol/L) to 1.2 ± 0.2 mg/dL (106.1 ± 17.7 μmol/L) in groups 1 through 3, there are measurable graded increases in risk. At the highest level of renal dysfunction not yet requiring dialysis (Cr, 2.7 ± 2.6 mg/dL [238.1 ± 229.3 μmol/L]), the risk appears to be the greatest for several adverse outcomes.

There were significant ethnic differences across the renal risk groups, with a greater proportion of blacks in the higher risk groups, including 40.4% of those on chronic dialysis therapy compared with 29.2% of those in the lowest risk group. The impact of baseline comorbidities across the renal strata was evident. Those patients on chronic dialysis therapy had, as expected, significantly greater rates of diabetes, hypertension, and CHF. Measurement of left ventricular function was not performed routinely on patients. However, when it was assessable by such indices as cardiothoracic ratio, it was lower in the higher risk strata, consistent with greater rates of prior CHF.

Our study found the rates of mortality-reducing therapy, including angioplasty, thrombolysis, and β-blocker use, were all reduced at progressively lower levels of renal function. This indicates a treatment bias in favor of those with less baseline comorbidity and is consistent with the

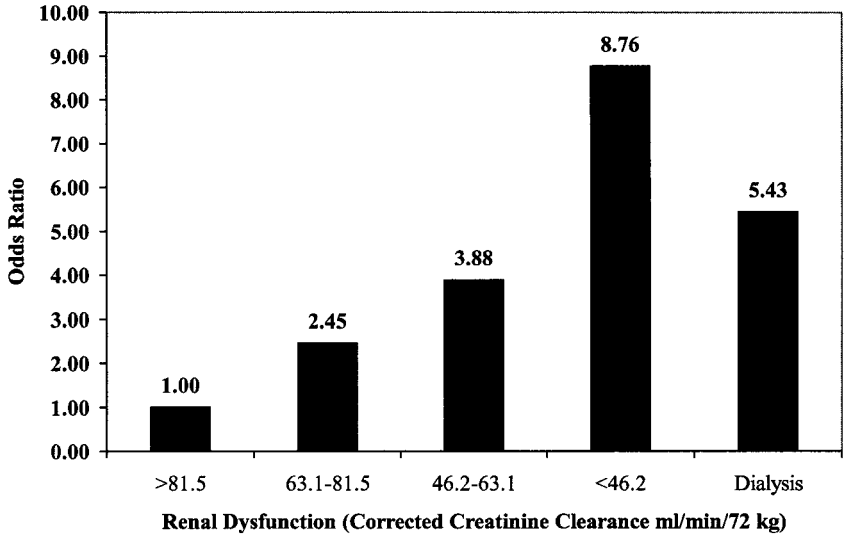

Fig 2. Age- and sex-adjusted risks for in-hospital death in 1,724 patients admitted to a coronary care unit with ST segment elevation AMI stratified by renal risk group. For groups 2 through 5, *P* < 0.0001.

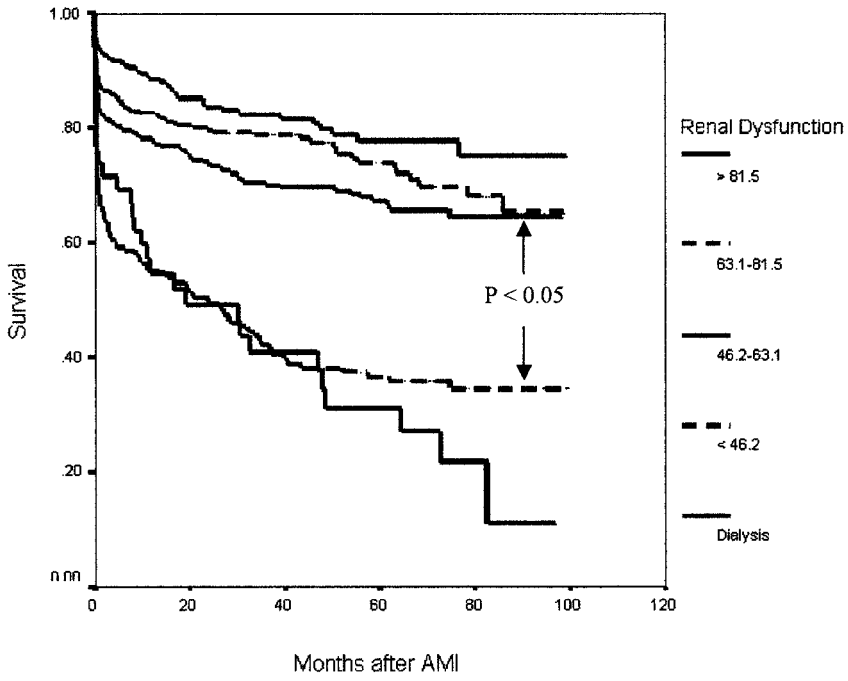

Fig 3. Survival analysis of 1,724 consecutive patients admitted to a coronary care unit stratified by baseline serum Cr level. Proportional hazards have been adjusted for age and sex. The overall model found CorrCrCl statistically significant ($P < 0.0001$). This shows an early mortality hazard within 5 years after discharge for individuals with CorrCrCl of 46.2 mL/min/72 kg or less but not on dialysis therapy (group 4) compared with those on dialysis therapy (group 5). $P < 0.05$ for comparisons of groups 3 through 5 versus 1 and 2.

findings of other investigators.[1] The reduced rates of percutaneous intervention (15.2% of those with CorrCrCl < 46.2 mL/min/72 kg) can be understood in light of the increased risk for contrast nephropathy and its related mortality.[5] However, the lower rates of thrombolysis and β-blocker use can only be partially explained by increased rates of hemodynamic complications. This implies that considerable progress can be made in AMI mortality by the extension of reperfusion and β-blockers to those with advanced renal dysfunction.[16]

This study suggests other unmeasured intermediate factors are present that mediate risk for arrhythmias, hemodynamic problems, and death. Candidate biological and clinical mechanisms include the presence of LVH, diastolic dysfunction, volume overload, adverse pharmacological interactions, endothelial dysfunction, and more aggressive atherosclerosis related to increases in serum homocysteine level.[17-20] The increases in hypertension and ECG voltage criteria for left ventricular hypertrophy (LVH) seen across the strata are suggestive that left ventricular mass index, although poorly correlated with ECG LVH, if measured, would be more common in the higher risk groups.[21-23] Evidence from the literature exists to expect a high rate of LVH in the predialysis and dialysis populations.[24] In these groups, LVH has been related to greater rates of asymptomatic ventricular arrhythmias, stroke, and cardiac events, including AMI, revascularization, CHF, and cardiac death.[25-28] Diastolic dysfunction commonly occurs in patients with end-stage renal disease with LVH and is a likely mechanism for the development of pulmonary edema.[29,30] Volume overload is anticipated in groups 4 and 5, with the distinct possibility that the volume excess is better handled by dialysis than high-dose diuretics in those with significant impairment in renal function. This may explain in part the plateau in risk seen in group 4 for many of the adverse outcomes. Adverse drug interactions, or at least more problematic administration of such commonly used drugs as digitalis, diuretics, angiotensin II–converting enzyme inhibitors, and antiarrhythmics, would be expected in groups 4 and 5 and may have contributed to poor outcomes.

Several lines of evidence suggest that worsened renal clearance is associated with endothelial dysfunction, which probably has a role in the development of pulmonary edema.[31,32] However, it is not known which process is first, cardiac or renal dysfunction, as the inciting factor for endothelial dysfunction. It has been hypothesized that the candidate factor related to a more aggressive coronary atherosclerotic diathesis in patients with

renal failure is homocysteine. Serum homocysteine level has been found to track with levels of serum creatinine and BUN and be markedly elevated in those on chronic dialysis therapy.[33-35] Recent data from stable patients and those with acute coronary syndromes suggest graded increases in risk for future cardiac events through the range of normal serum homocysteine levels.[36,37] Other putative atherosclerosis risk factors in patients with renal failure include elevations of serum fibrinogen and lipoprotein(a) levels.[38] In addition, there are undoubtedly hundreds of factors, including advanced glycation and lipoxidation end products in patients with renal failure, that may have a role in atherogenesis, but these are in the early stages of scientific investigation.[39,40]

We found an early hazard with respect to survival for those with reduced CorrCrCl less than 46.2 mL/min/72 kg but not yet on dialysis therapy. This suggests that dialysis therapy, whether by selection or biological action, has at least a stabilizing effect on mortality in the first 5 years after discharge. Our observed mortality rate at 2 years of 65.0% was consistent with the results recently reported by Herzog et al[41] from the US Renal Data System.

Like all retrospective studies of prospectively collected data, our study is subject to the threats to validity posed by missing data. In addition, the single measure of renal function, initial serum Cr level, undoubtedly was influenced by the degree of hydration, renal perfusion, and, in some cases, possibly acute renal failure. Ejection fraction was not captured in the data registry; however, it is expected that lower mean ejection fractions would have been recorded in the higher renal dysfunction strata consistent with the rates of prior CHF and in-hospital hemodynamic complications. Outpatient medications were not captured in the data collection; thus, the influence of lipid-reducing agents, aspirin, β-blockers, and angiotensin-converting enzyme inhibitors were not taken into account after hospital discharge. The initiation of dialysis therapy also was not captured in our registry. We expect this was rare and may have influenced group 4, a predialysis group, but not the other groups, in which new dialysis was an unlikely clinical issue.[5,6]

In-hospital mortality rates do not reflect deaths in the emergency department or in patients who were transferred to long-term care facilities with the intent of terminal care. In addition, we did not capture the advanced directives of patients in the database; therefore, variation in the frequency and determinants of in-hospital mortality are inherent in this study.

The results of this study are more applicable to urban tertiary hospitals with greater proportions of blacks and the expected comorbidities of diabetes, hypertension, and CHF. Practice settings and clinical trials that care for and include primarily lower risk patients may not be able to replicate the important relationship between renal dysfunction and outcomes observed in this study.

This study points out four fundamental mechanisms for the observed cardiorenal risk: (1) uncontrolled confounding, (2) therapeutic nihilism, (3) adverse effects of conventional therapy, and (4) special biological processes. Mechanisms 2 through 4 should be systematically approached from a clinical and research standpoint. Clearly, the more equitable use of proven therapies should be a goal of those treating patients with AMI and renal dysfunction. The safety and efficacy of reperfusion and antithrombotic therapy in those with renal dysfunction should be systematically addressed with randomized trials. Last, the special biological effects of the renal dysfunction state on the pathogenesis of atherosclerosis, heart failure, arrhythmias, and conduction disturbances should be studied in great detail given the generalizability to our aging US population.

In conclusion, baseline CorrCrCl derived from serum Cr level, age, and sex is a significant independent risk factor for acute arrhythmic and hemodynamic complications after AMI. Furthermore, renal risk stratification can identify groups with high rates of in-hospital death and poor long-term survival. This risk is only partially explained by such comorbidities as diabetes, age, CHF, and treatment received. We conclude that renal function is integrally related to survival after a variety of cardiac events and that further research into the clinical and biological mechanisms for this relation are warranted.

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