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Risks Associated With Renal Dysfunction in Patients in the Coronary Care Unit

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OBJECTIVES The purpose of this study was to quantify the impact of baseline renal dysfunction on morbidity and mortality in patients in the coronary care unit (CCU).

BACKGROUND The presence of renal dysfunction is an established independent predictor of survival after acute myocardial infarction and revascularization procedures.

METHODS We analyzed a prospective CCU registry of 12,648 admissions by 9,557 patients over eight years at a single, tertiary center. Admission serum creatinine was available in 9,544 patients. Those not on long-term dialysis were classified into quartiles of corrected creatinine clearance, with cut-points of 46.2, 63.1 and 81.5 ml/min per 72 kg. Dialysis patients (n = 527) were considered as a fifth comparison group.

RESULTS Baseline characteristics, including older age, African-American race, diabetes, hypertension, previous coronary disease and heart failure, were incrementally more common across increasing renal dysfunction strata. There were graded increases in the relative risk for atrial and ventricular arrhythmias, heart block, asystole, development of pulmonary congestion, acute mitral regurgitation and cardiogenic shock across the risk strata. Survival analysis demonstrated an early mortality hazard for those with renal dysfunction, but not on dialysis, for the first 60 months, followed by graded decrements in survival across increasing renal dysfunction strata.

CONCLUSIONS Baseline renal function is a powerful predictor of short- and long-term events in the CCU population. There is an early hazard for in-hospital and postdischarge mortality for those with a corrected creatinine clearance <46.2 ml/min per kg, but not on dialysis. (J Am Coll Cardiol 2000;36:679–84) © 2000 by the American College of Cardiology

We and other investigators have shown a graded, independent risk of acute renal failure after a percutaneous coronary intervention, coronary artery bypass graft surgery and other cardiac events driven in part by baseline renal function, as measured in a variety of ways (1–5). The consequences of acute renal failure requiring dialysis include high rates of in-hospital mortality and shortened long-term survival, whether or not dialysis becomes permanent (2,6). In addition, baseline renal function measured as serum creatinine, blood urea nitrogen (BUN) or corrected creatinine clearance has been shown in multiple epidemiologic studies and clinical trials to be an independent predictor of survival in patients with acute myocardial infarction (AMI), acute coronary syndromes and a variety of other cardiovascular events (7–11). These investigations have been limited, however, by the exclusion of patients with more advanced renal insufficiency, including those receiving dialysis treatment. We sought to evaluate the independent risk of baseline renal dysfunction on outcomes in patients in the coronary care unit (CCU) across a broad range of cardiovascular diagnoses and the full spectrum of renal risk.

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METHODS

Setting, data collection and follow-up. The Henry Ford Hospital is a 903-bed tertiary-care center located in the urban core of the Detroit metropolitan area and 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 (12–14). The Henry Ford Hospital Cardiac Intensive Care Unit Database was a registry in which every admission to this 16-bed CCU 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 demographic data, 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 CCU stay was recorded prospectively. Vital status was tracked on an annual basis using a multilayered approach. This approach called for ascertainment of future activity in the health system by the patient, confirmation of death by identification matching with the State of Michigan Death Certificate Registry or record of a death on a later hospital admission within the health system corporate data stores. Finally, for those not identified with any of these means, the available internet death identification service was used to confirm death

Abbreviations and Acronyms

AMI = acute myocardial infarction
BUN = blood urea nitrogen
CHF = congestive heart failure
cCrCl = corrected creatinine clearance
CI = confidence interval
CCU = coronary care unit
ECG = electrocardiogram
LVH = left ventricular hypertrophy
RR = relative risk
UAP = unstable angina pectoris

primarily in a state other than Michigan. These data strategies yielded a 99% overall vital status ascertainment rate for patients followed after the first CCU admission longitudinally over 27 ± 28 months (minimum 0, maximum 100).

Assessment of baseline renal function. The data base was augmented with merged data from laboratory tables to obtain complete renal function data on 9,544 patients. Patients not on dialysis were initially classified into four quartiles based on serum creatinine in mg/dl (creatinine cut-points of 0.9 mg/dl [79.6 μmol/liter], 1.1 mg/dl [97.2 μmol/liter], and 1.5 mg/dl [132.6 μmol/liter]). Because of the rules needed to assign quartiles for ties, there were uneven numbers of patients in groups 1 to 4: n = 2,851; n = 1,945; n = 2,262; and n = 1,961, respectively. Patients on long-term dialysis (n = 527) were considered as a fifth comparison group. In an exploratory analysis, seven tables were created with these risk groups, and univariate and multivariate relative risks (RRs) were calculated for the renal risk quartiles by baseline serum creatinine. This analysis showed an exposure–response relation between serum creatinine and risk, therefore justifying further investigation with a better estimate of baseline renal function suitable for division into quartiles. Because weight was not available in the data base, the corrected creatinine clearance (cCrCl) was used as the best measure of baseline renal function, as follows (15):

$$cCrCl_{male} = (140 - age_{yrs})/72$$

$$cCrCl_{female} = 0.85\ ([140 - age_{yrs}]/72)$$

The cCrCl was found to be unimodal and normally distributed. Therefore, patients were classified into quartiles at the cut-points of 46.2, 63.1 and 81.5 ml/min per 72 kg. Patients on long-term dialysis (n = 527) were considered again as a fifth comparison group. Seven tables were again created with these groups as the column headings. There were no directional changes in the final calculated univariate and multivariate RRs. On the basis of the established validity of estimated creatinine clearance as a surrogate for glomerular filtration rate and its frequency distribution in this data set, the investigators decided to retain the cCrCl as the measure of baseline renal function throughout the analysis (16–18).

Admitting diagnoses. The admitting diagnosis categories were ranked according to their in-hospital mortality. The order, from highest to lowest mortality, was the following: coma, shock, noncardiac diagnoses, other cardiac diagnoses, congestive heart failure (CHF), AMI, arrhythmias and unstable angina pectoris (UAP). The diagnosis rank code was then used in multivariate modeling to account for the severity of illness on admission.

Outcome validation. Eleven arrhythmic, hemodynamic and fatal outcomes were selected for validation with blinded chart abstraction. A random sample (n = 20) from each outcome category was chosen, and each record was compared against chart abstraction for the development of the outcome during the CCU stay. Agreement statistics were computed for each outcome and then averaged over the 12 categories. The mean percent agreement was 92.7% across the eleven outcomes.

Statistical analysis. Baseline characteristics are reported as the mean value ± SD or as proportions with the 95% confidence interval (CI), as appropriate, with exclusion of missing data points. Univariate comparisons were done using analysis of variance or the chi-square test, as appropriate. The chi-square test for linear trend was used for comparisons of baseline characteristics across ascending levels of renal dysfunction. Multiple logistic regression analysis was performed for the outcomes of arrhythmic and hemodynamic complications, in-hospital death and cumulative death, with independent RR and 95% CIs. All models were tested for interactions. Variables in the causal pathway were included in the final models. The 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 values are two-tailed and considered significant at alpha <0.05.

RESULTS

Baseline characteristics. The overall mean age was 63.4 ± 13.8 years (range 15 to 98). The mean age for women and men was similar—63.6 ± 13.8 and 63.3 ± 13.7 years ($p = 0.22$). The overall female/male ratio was 0.73, with male gender predominant in all groups. For the study group as a whole, 5,080 (53.2%) were white; 4,189 (43.9%) were African-American; and 275 (2.9%) were categorized as "other race." African-American race increased in proportion from group 1 to 5, including 60% of those on long-term dialysis. Diabetes and hypertension were more common across the ascending risk groups 1 to 5 ($p < 0.0001$ for both trends). In contrast, smoking and hyperlipidemia were more common in the lower risk group ($p < 0.0001$ for both trends). Previous coronary artery disease increased only slightly over the renal strata, from 27% to 37% for a history of angina and from 20.6% to 31.7% for a previous AMI ($p < 0.0001$ for both). Rates of previous coronary revascu-

larization were similar among the groups. There was, however, a graded increase from 13.8% to 45.0% in the frequency of previous CHF from group 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 CHF and hypertension frequencies observed. A history of atrial fibrillation (either chronic or paroxysmal) was collected only in a later group of patients (n = 373), from April 1, 1997 to August 22, 1998, and the frequencies for renal risk groups 1 to 5 were 3.0% (4/130), 8.0% (6/75), 9.2% (7/76), 11.3% (9/80) and 12.5% (1/8) ($p = 0.26$ for group 1 vs. 5, $p = 0.05$ for trend).

Admission clinical findings and diagnoses. Patients in group 5 were more likely to be admitted with CHF (23%), with the expected physical examination findings of an S_3 (22.0%), rales (38.9%) and peripheral edema (21.8%). There were increasing levels of blood pressure and heart rate across the renal risk strata (both $p < 0.0001$). In addition, there were higher rates of atrial fibrillation, complete heart block and bundle branch blocks on the admission electrocardiogram (ECG) across the renal risk strata (all $p < 0.0001$). Left ventricular hypertrophy (LVH) by ECG criteria was present in 18.5% of group 5 as compared with 7.1% of group 1 ($p < 0.0001$), consistent with the prevalence of hypertension across these groups. Finally, as expected, there were higher levels of baseline potassium, serum creatinine and BUN on admission laboratory tests across the groups (mean serum creatinine levels for groups 1 to 5: 0.8 ± 0.2, 1.0 ± 0.2, 1.2 ± 0.2, 3.0 ± 2.8 and 4.9 ± 3.7 mg/dl, (respectively). Hemoglobin was found to be significantly lower across the groups, with a mean hemoglobin level of 10.6 ± 2.3 g/dl in the group on long-term dialysis.

Myocardial injury and left ventricular impairment. Confirmed myocardial infarction was less common in the higher renal risk groups—44.2% of all patients with confirmed AMI in group 1 versus 21.8% of those in group 5 ($p < 0.0001$). For those who had myocardial injury, the mean peak creatine kinase values were lower in group 5 versus group 1—$845.3 \pm 1{,}242.3$ versus $1{,}188.3 \pm 1{,}527.4$ U/liter ($p < 0.0001$). Evidence for left ventricular dysfunction was more common in the higher renal risk strata, with the majority of those in groups 4 and 5 having cardiomegaly and reduced left ventricular function as measured by echocardiography or radionuclide ventriculography. These observed proportions are higher than the expected values, given the fact that left ventricular function measurement was more likely to be performed in those with clinical CHF or suspected left ventricular dysfunction.

Tachyarrhythmias. There were graded increases in the adjusted risk for atrial fibrillation, accelerated idioventricular rhythm, sustained ventricular tachycardia and ventricular fibrillation across the groups. There was no clear risk pattern seen for levels of renal dysfunction and nonsustained ventricular tachycardia.

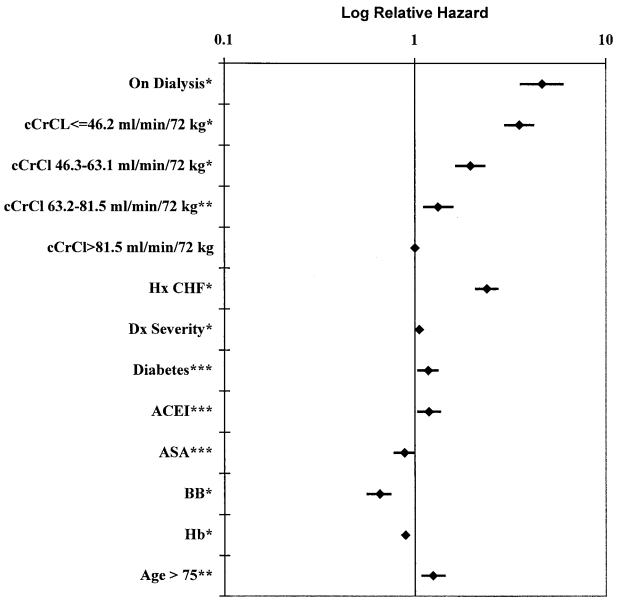

Figure 1. Relative hazard for cumulative death after discharge from a coronary care unit. A history (Hx) of heart failure is the greatest independent hazard among dichotomous variables. The level of renal function risk is the most important independent factor. *$p < 0.00001$. **$p = 0.0001$. ***$p < 0.03$. ACEI = angiotensin-converting enzyme inhibitor use before admission; ASA = aspirin use before admission; BB = beta-blocker use before admission; Dx severity = cardiac intensive care unit admission diagnosis severity rank; Hb = hemoglobin in g/dl.

Bradyarrhythmias. There was a clear relation seen between the level of renal dysfunction and the development of complete heart block (adjusted RRs for groups 2 to 5: 1.73, 2.73, 2.82 and 3.64, respectively, $p < 0.0001$). A similar pattern was seen for the level of renal dysfunction and the development of asystole (adjusted RRs for groups 2 to 5: 1.75, 1.57, 2.80 and 2.36, respectively, $p = 0.05$).

Hemodynamic complications and death. In a graded fashion, group 5 had the highest adjusted risk of developing acute mitral regurgitation and pulmonary edema, as compared with group 1 (adjusted RR 3.80, 95% CI 1.78 to 8.14, $p = 0.0006$). However, with cardiogenic shock and in-hospital death, there was increased risk from groups 1 to 4 (adjusted RR 2.61, 95% CI 1.69 to 4.03, $p < 0.0001$), and then a much lower adjusted risk in the group on long-term dialysis (adjusted RR 1.70, 95% CI 0.84 to 3.46, $p = 0.14$). Patients with AMI, heart failure or arrhythmia as the principal diagnosis displayed relations of risk across the renal strata (all $p < 0.05$). Only group 4 displayed an increased risk of death in unstable angina and shock (RR 3.40, 95% CI 1.49 to 7.77, $p = 0.003$ and RR 5.29, 95% CI 1.40 to 20.02, $p = 0.009$). Risk assessments could not be made for other cardiac diagnoses or coma because of small cell sizes.

Long-term survival. Figure 1 displays the adjusted relative hazard of cumulative death over long-term follow-up. Patients on dialysis had the greatest adjusted risk over the follow-up period. Again, there was a clear, graded and independent relation between the calculated cCrCl strata on

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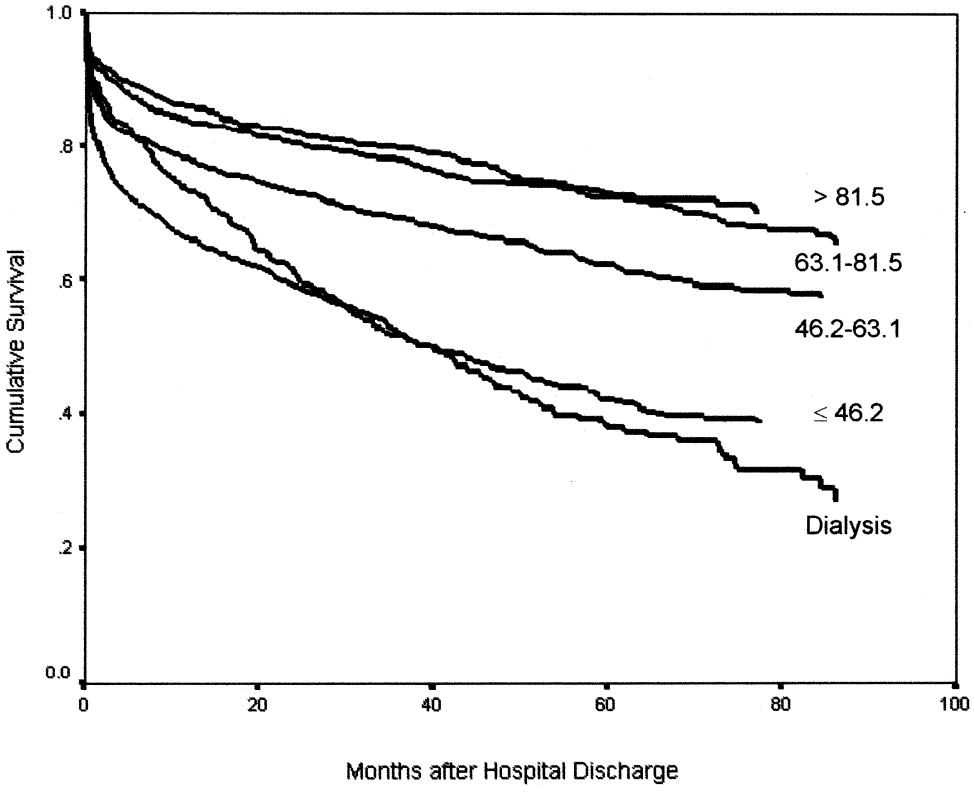

Figure 2. Survival analysis of 9,544 consecutive patients admitted to a CCU and stratified by baseline cCrCl in ml/min per 72 kg. Proportional hazards have been adjusted for age, gender, race, admission diagnosis, history of heart failure, previous aspirin, beta-blocker and angiotensin-converting enzyme inhibitor use, diabetes and baseline hemoglobin in g/dl. This demonstrates an early mortality hazard within five years after discharge for individuals with cCrCl ≤46.2 ml/min per 72 kg but not on dialysis, as compared with those on dialysis ($p < 0.05$ for comparisons of groups 3 to 5 versus groups 1 and 2).

CCU admission and long-term death. A history of heart failure had the single greatest risk as a binary predictor variable. Previous use of aspirin and beta-blockers had a protective effect. A higher baseline hemoglobin level (g/dl) was also independently associated with a reduced risk of death over the long term.

Figure 2 displays the adjusted survival curves stratified by renal dysfunction. Groups 3 to 5 had worsened survival as compared with groups 1 and 2 ($p < 0.05$, by the log-rank test). Group 4 had the worst survival for the first 60 months until its survival curve is crossed by group 5 (patients on long-term dialysis), who displayed an overall mortality rate of 60% during the follow-up period. Mortality rates for the subgroup of patients with a discharge diagnosis of AMI (Q wave and non–Q wave combined), over a mean follow-up period of 27.1 months ($n = 4,035$), were 14.6%, 22.7%, 30.5%, 54.3% and 65.0% for groups 1 to 5, respectively ($p < 0.0001$).

DISCUSSION

Renal dysfunction as a risk for morbidity and mortality. This study has shown that a surrogate for baseline renal function—cCrCl in ml/min per 72 kg—stratified patients entering the CCU with a variety of diagnoses, with respect to in-hospital complications and long-term survival. Through a range of "normal" serum creatinine levels—0.8 ± 0.2 mg/dl (70.7 ± 17.7 μmol/liter) to 1.2 ± 0.2 mg/dl (106.1 ± 17.7 μmol/liter) in groups 1 to 3, there are measurable, graded increases in risk. At the highest level of renal dysfunction not yet requiring dialysis, the risk appears to be the greatest for many adverse outcomes.

There were significant ethnic differences across the renal risk groups, with higher proportions of African-Americans in the higher risk groups—60% on long-term dialysis versus 37.6% in the lowest risk group. The impact of baseline comorbidities across the renal strata was evident. Those patients on long-term dialysis had, as expected, significantly higher rates of diabetes, hypertension and CHF. Patients with renal dysfunction were more likely to be admitted with CHF than with acute ischemic syndromes. Although measurement of left ventricular function was not done routinely in patients, when it was evaluable by indexes such as cardiothoracic ratio, echocardiography, or radionuclide ventriculography, it was lower in the higher risk strata, consistent with higher rates of a history and admission diagnosis of CHF. The multivariate analysis, however, indicates that not all the risk observed in the upper strata can be explained by decreased left ventricular function alone. Another confounder—baseline hemoglobin—was found to be lower as renal failure advanced across the groups. This finding

is consistent with the anemia associated with renal dysfunction and was appropriately accounted for in all of the multivariate analyses of this group. We did not record the rates of transfusions in each group, as this would have been unlikely to affect overall mortality rates (19).

Potential mediators of renal risk. This study suggests that there are other unmeasured intermediate factors present that mediate risk for arrhythmias, hemodynamic problems and death. Candidate biologic and clinical mechanisms include the presence of LVH, diastolic dysfunction, adverse pharmacologic interactions, endothelial dysfunction, chronic volume overload and more aggressive atherosclerosis related to increases in serum homocysteine (20–23).

Impact of dialysis. We found an early hazard with respect to survival for those with a reduced cCrCl <46.2 ml/min per 72 kg, but not yet on dialysis. This suggests that dialysis therapy, whether by selection or biologic action, has at least a stabilizing effect on mortality in the first five years after discharge. In the AMI subset of patients on dialysis, our observed mortality rate at two years of 65% was consistent with the results recently reported by Herzog et al. from the U.S. Renal Data System (24).

Study limitations. We and other investigators have shown the extraordinary high risk of in-hospital death for those placed on short-term dialysis therapy after a percutaneous intervention or open-heart surgery and in the medical intensive care unit (2–5). This risk is almost certainly mediated by multiorgan system failure and not by the dialysis therapy alone (2). Although initiation of dialysis was not an event captured in our registry, we expect this factor may have influenced group 4, a predialysis group, but not the other groups, where new dialysis was an unlikely clinical issue.

In-hospital mortality rates do not reflect deaths in the emergency room or in patients who were transferred to long-term care facilities where the intent was terminal care. In addition, we did not capture the advanced directives of the patients in the data base, hence variations in the frequency and determinants of in-hospital mortality are inherent in this study.

Finally, we did not perform a detailed analysis of the interactions between renal risk and complications related to in-hospital procedures or other forms of therapy. These interactions are known to be clinically important and deserve future epidemiologic and prospective investigation.

Conclusions. Baseline cCrCl derived from serum creatinine, age and gender is a significant, independent risk factor for acute arrhythmic and hemodynamic complications during CCU stays. 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 comorbidities, including diabetes, age and CHF. We conclude that renal function is integrally related to survival after a variety of cardiac events and that further research into the clinical and biologic mechanisms for this relation is warranted.

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