Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality

C. Michael Gibson, Duane S. Pinto, Sabina A. Murphy, David A. Morrow, Hans-Peter Hobbach, Stephen D. Wiviott, Robert P. Giugliano, Christopher P. Cannon, Elliott M. Antman, Eugene Braunwald, and TIMI Study Group

J. Am. Coll. Cardiol. 2003;42;1535-1543
doi:10.1016/j.jacc.2003.06.001

This information is current as of February 10, 2010

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://content.onlinejacc.org/cgi/content/full/42/9/1535

JACC
JOURNAL *of the* AMERICAN COLLEGE *of* CARDIOLOGY

Downloaded from content.onlinejacc.org by on February 10, 2010

Journal of the American College of Cardiology
Vol. 42, No. 9, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)01067-2
Published by Elsevier Inc.
© 2003 by the American College of Cardiology Foundation

CLINICAL RESEARCH **Prognostic Markers Following Infarction or Surgery**

Association of Creatinine and Creatinine Clearance on Presentation in Acute Myocardial Infarction With Subsequent Mortality

C. Michael Gibson, MS, MD,* Duane S. Pinto, MD,† Sabina A. Murphy, MPH,* David A. Morrow, MD, MPH,* Hans-Peter Hobbach, MD,‡ Stephen D. Wiviott, MD,* Robert P. Giugliano, MD, SM,* Christopher P. Cannon, MD,* Elliott M. Antman, MD,* Eugene Braunwald, MD,* for the TIMI Study Group

Boston, Massachusetts; and Siegen, Germany

OBJECTIVES We hypothesized that impaired renal function would also be associated with poorer clinical outcomes among patients with ST-segment elevation myocardial infarction (STEMI) treated with fibrinolysis.

BACKGROUND Previous studies have demonstrated that impaired renal function is associated with poorer clinical outcomes in the setting of unstable angina and non-STEMI and after percutaneous coronary intervention.

METHODS Data were drawn from the Thrombolysis In Myocardial Infarction (TIMI)-10, TIMI-14, and Intravenous nPA for the Treatment of Infarcting Myocardium Early (InTIME-II) trials.

RESULTS Within each TIMI risk score (TRS) for STEMI category (0 to 2, 3 to 4, ≥5), 30-day mortality increased stepwise among patients with normal (creatinine [Cr] ≤1.2 mg/dl), mildly (Cr >1.2 to 2 mg/dl), and severely (Cr >2.0 mg/dl) impaired renal function ($p < 0.001$) and in patients with normal (creatinine clearance [CrCl] ≥90 ml/min), mildly (60 to <90 ml/min), moderately (30 to <60 ml/min), and severely (<30 ml/min) impaired CrCl ($p < 0.001$). Impaired renal function was associated with increased mortality after adjusting for previously identified correlates of mortality (using Cr: odds ratio [OR] for mild impairment 1.52, 95% confidence interval [CI] 1.30 to 1.77, $p < 0.001$; OR for severe impairment 3.73, 95% CI 2.55 to 5.45, $p < 0.001$; using CrCl: OR for mild impairment 1.38, 95% CI 1.10 to 1.73, $p = 0.006$; OR for moderate impairment 2.06, 95% CI 1.59 to 2.66, $p < 0.001$; OR for severe impairment 3.81, 95% CI 2.57 to 5.65, $p < 0.001$).

CONCLUSIONS In the setting of STEMI, elevated Cr and/or impaired CrCl on presentation is associated with increased mortality, independent of other conventional risk factors and TRS. This association does not appear to be mediated by reduced fibrinolytic efficacy among patients with impaired renal function or by the presence of congestive heart failure on presentation. (J Am Coll Cardiol 2003;42:1535–43) © 2003 by the American College of Cardiology Foundation

Previous studies have demonstrated that impaired renal function is associated with poorer clinical outcomes in the setting of unstable angina and non–ST-segment elevation myocardial infarction (STEMI) and after a percutaneous coronary intervention (PCI) as well as coronary artery bypass graft surgery (1–8). The goal of the present study was to extend these observations to examine the association of baseline creatinine (Cr) and creatinine clearance (CrCl) with subsequent clinical outcomes after fibrinolytic administration among patients with STEMI who received optimal reperfusion therapy. We hypothesized that impaired renal function (elevated Cr and impaired CrCl) would be associated with poorer clinical outcomes after fibrinolytic administration. We also sought to examine the relation between Cr and CrCl with epicardial flow and myocardial perfusion.

See page 1544

METHODS

Clinical and angiographic data were pooled from the Thrombolysis In Myocardial Infarction (TIMI) trial-10A, -10B, and -14 trials. The TIMI-10A trial was a nonrandomized, open-label, dose-escalation study of eight ascending doses of tenecteplase, a mutant of recombinant tissue plasminogen activator, in 113 patients (9). The TIMI-10B trial was a randomized trial of 880 patients comparing 30, 40, and 50 mg tenecteplase versus front-

From the *TIMI Study Chairman's Office, Department of Medicine, Brigham and Women's Hospital, Boston; †Department of Medicine, Cardiovascular Division, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and ‡St. Marienkrankenhaus Siegen, Siegen, Germany. This study was supported in part by a grant from Genentech, Inc. and Boehringer-Ingelheim, South San Francisco, California and Rheimberg, Germany (TIMI 10A and B); Centocor and Eli Lilly Inc., Malvern, Pennsylvania and Indianapolis, Indiana (TIMI 14); and Bristol-Myers Squibb, New York, New York (InTIME-II).

Manuscript received April 18, 2003; revised manuscript received June 4, 2003, accepted June 9, 2003.

Downloaded from content.onlinejacc.org by on February 10, 2010

JACC Vol. 42, No. 9, 2003
November 5, 2003:1535–43

Abbreviations and Acronyms

CHF	= congestive heart failure
Cr(Cl)	= creatinine (clearance)
CTFC	= corrected TIMI frame count
ICH	= intracranial hemorrhage
MI	= myocardial infarction
OR	= odds ratio
PCI	= percutaneous coronary intervention
STEMI	= ST-segment elevation myocardial infarction
TIMI	= Thrombolysis In Myocardial Infarction
TRS	= TIMI risk score

loaded recombinant tissue plasminogen activator (10). Data from 1,187 patients enrolled in the TIMI-14 trial comparing fibrinolytic versus abciximab plus a reduced dose fibrinolytic were also included (11,12). Angiography was performed at 60, 75, and 90 min after thrombolytic administration (9–12). Nitroglycerin (intravenous or sublingual) was administered every 15 min if the systolic blood pressure (BP) exceeded 110 mm Hg (9–12). Clinical data were also pooled from the Intravenous nPA for the Treatment of Infarcting Myocardium Early (InTIME-II) trial, which compared the thrombolytics n plasminogen activator versus tissue-type plasminogen activator in 15,078 STEMI patients (13). The distribution of the TIMI risk score (TRS) for STEMI, as previously reported (14), was used to assess the association of Cr and CrCl with mortality in low-risk (TRS 0 to 2), intermediate-risk (TRS 3 to 4), and high-risk (TRS ≥5) patients. Creatinine clearance was divided into four categories: normal (≥90 ml/min) and mildly (60 to <90 ml/min), moderately (30 to <60 ml/min), and severely impaired (<30 ml/min), as defined by the Kidney Disease Outcome Quality Initiative (15).

Angiographic analysis methods. Angiographic outcomes were assessed at the TIMI Angiographic Core Laboratory by a single observer (Dr. Gibson), who was blinded to the clinical outcomes and drug assignment. The TIMI flow grade (16), corrected TIMI frame count (CTFC) (17–20), and TIMI myocardial perfusion grade (21) were assessed as previously defined. The optimal single-plane projection was selected that identified the stenosis in its greatest severity with minimal foreshortening or overlapping of branches, and end-diastolic frames were chosen for quantitative angiographic analysis (22).

Statistical analysis. All analyses were performed using Stata version 7.0 (Stata Corp., College Station, Texas). All continuous variables are reported as the mean ± SD. Analysis of variance was used for the analysis of continuous variables. The non-parametric Kruskal-Wallis test was used for the CTFC analysis when data were imputed to an occluded vessel. The chi-square test was used for the analysis of categorical variables. A test for trend across ordered groups was performed for the three Cr groups and four CrCl groups (Stata version 7.0). A multivariate logistic regression model was used for the analysis of 30-day mortality, adjusting for age, pulse, BP, history of congestive heart failure (CHF), Killip class II to IV on presentation, gender, history of diabetes, previous MI, history of hypertension, time to treatment, and anterior myocardial infarction (MI). Kaplan-Meier curves were generated for mortality through two years of follow-up. The log-rank test was used to test the equality of the

Table 1. Baseline Characteristics by Creatinine Group

	Normal Cr ≤1.2 mg/dl (n = 12,377)	Mild Renal Impairment Cr >1.2–2.0 mg/dl (n = 4,126)	Severe Renal Impairment Cr >2.0 mg/dl (n = 207)	p Value for Trend
Gender (% male)	71.8%	86.7%	75.9%	< 0.01
Age (yrs)	59.8 ± 11.8	63.5 ± 11.9	67.1 ± 11.6	< 0.01
Race (% white)	93.1%	93.2%	86.5%	0.15
Weight (kg)	77.6 ± 14.6	80.2 ± 14.2	77.2 ± 14.5	< 0.01
Cigarette smoking	48.5%	37.6%	30.2%	< 0.01
Previous MI	14.0%	20.3%	23.9%	< 0.01
History of diabetes	13.7%	14.2%	30.6%	< 0.01
History of CHF	2.1%	5.0%	14.2%	< 0.01
History of hypertension	28.7%	36.2%	58.1%	< 0.01
Previous PCI	4.7%	5.8%	5.3%	0.01
Previous CABG	2.4%	3.4%	5.7%	< 0.01
Admission SBP (mm Hg)	139.3 ± 21.3	136.9 ± 22.8	137.3 ± 27.7	< 0.01
Admission DBP (mm Hg)	82.2 ± 13.6	81.3 ± 14.2	79.6 ± 16.1	< 0.01
Admission pulse (per min)	75.7 ± 17.3	76.3 ± 19.6	79.6 ± 22.4	0.15
Killip class II–IV	10.4%	16.4%	27.6%	< 0.01
Anterior MI	41.8%	40.3%	39.7%	0.08
Median time (h) from symptom onset to treatment (IQ range)	2.9 (2.0–4.1)	2.75 (1.9–3.9)	3.45 (2.3–4.6)	< 0.01
Hypercholesterolemia*	24.7%	27.6%	33.3%	0.16

*Not collected in the Intravenous nPA for the Treatment of Infarcting Myocardium Early (InTIME-2) trial. Data are presented as the percentage of subjects or mean value ± SD, unless otherwise indicated.

CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; Cr = creatinine; DBP = diastolic blood pressure; MI = myocardial infarction; PCI = percutaneous coronary intervention; IQ = interquartile; SBP = systolic blood pressure.

Downloaded from content.onlinejacc.org by on February 10, 2010

Table 2. Baseline Characteristics by CrCl Group

	Normal CrCl ≥90 ml/min (n = 6,062)	Mild Renal Impairment CrCl 60 to <90 ml/min (n = 6,795)	Moderate Renal Impairment CrCl 30 to <60 ml/min (n = 3,514)	Severe Renal Impairment CrCl <30 ml/min (n = 264)	p Value for Trend
Gender (% male)	87.6%	77.1%	54.4%	39.8%	< 0.01
Age (yrs)	52.1 ± 9.6	62.3 ± 9.2	71.7 ± 8.6	76.0 ± 10.7	< 0.01
Race (% white)	92.5%	93.0%	94.3%	90.5%	0.014
Weight (kg)	87.2 ± 14.3	76.2 ± 11.0	67.8 ± 11.4	62.6 ± 14.1	< 0.01
Cigarette smoking	60.6%	42.5%	27.5%	21.0%	< 0.01
Previous MI	12.2%	16.2%	20.1%	24.0%	< 0.01
History of diabetes	13.8%	13.5%	15.1%	18.6%	0.03
History of CHF	1.2%	2.3%	5.9%	16.0%	< 0.01
History of hypertension	26.0%	30.3%	38.8%	52.5%	< 0.01
Previous PCI	5.2%	5.2%	4.1%	5.3%	0.06
Previous CABG	1.9%	3.0%	3.4%	4.1%	< 0.01
Admission SBP (mm Hg)	140.3 ± 20.7	138.4 ± 21.7	136.7 ± 22.8	134.8 ± 26.7	< 0.01
Admission DBP (mm Hg)	84.2 ± 13.5	81.7 ± 13.6	79.1 ± 13.8	77.1 ± 15.4	< 0.01
Admission pulse (per min)	76.3 ± 16.8	75.0 ± 17.7	76.4 ± 19.9	80.6 ± 23.3	0.23
Killip class II–IV	8.0%	11.2%	19.5%	26.4%	< 0.01
Anterior MI	39.9%	42.0%	42.8%	41.4%	< 0.01
Median time (h) from symptom onset to treatment (IQ range)	2.8 (2–4)	2.8 (2–4)	3 (2.2–4.2)	3.6 (2.5–4.8)	< 0.01
Hypercholesterolemia*	25.6%	25.1%	26.0%	16.7%	0.83

*Not collected in InTIME-2. Data are presented as the percentage of subjects or mean value ± SD, unless otherwise indicated.
CrCl = creatinine clearance; other abbreviations as in Table 1.

survivor function across groups, and the test for trend of the survivor function was performed across the ordered groups.

RESULTS

Baseline characteristics. There were 12,377 patients (74.1%) with normal Cr (≤1.2 mg/dl), 4,126 patients (24.7%) with mild renal impairment (Cr >1.2 to 2.0 mg/dl), and 207 patients (1.2%) with severe renal impairment (Cr >2.0 mg/dl). Normal CrCl ≥90 ml/min was present in 6,062 patients (36.4%), mild impairment (60 to <90 ml/min) in 6,795 patients (40.9%), moderate impairment (30 to <60 ml/min) in 3,514 patients (21.2%), and severe renal impairment or failure (<30 ml/min) in 264 patients (1.6%).

There was a stepwise increase in co-morbidities among patients with normal, mildly impaired, and severely impaired renal function (Tables 1 and 2). Patients with mildly and severely impaired renal function were older, and the frequency of previous MI, diabetes, CHF, hypertension, and the incidence of previous coronary artery bypass graft surgery was increased among these patients. Patients with severe renal impairment were more often of a non-white race. Cigarette smoking was less frequent among patients with mild and severe renal impairment. At presentation, patients with mildly or severely impaired renal function were more often tachycardic and in Killip class II to IV heart failure. The duration of symptoms before presentation was longer among patients with severe renal impairment.

Angiographic findings (TIMI flow grade, TIMI frame count, TIMI myocardial perfusion, minimum lumen diameter, or percent diameter stenosis) after thrombolytic administration in the TIMI-10A, -10B and -14 angiographic trials were not associated with Cr or CrCl (Tables 3 and 4).

Clinical outcomes. There was a stepwise increase in mortality among patients with normal, mildly, and severely impaired renal function ($p < 0.0001$ for each) and among

Table 3. Angiographic Characteristics by Creatinine Group*

	Normal Cr ≤1.2 mg/dl (n = 1,565)	Mild Renal Impairment Cr >1.2–2.0 mg/dl (n = 401)	Severe Renal Impairment Cr >2.0 mg/dl (n = 13)	p Value for Trend
TFG 2/3 at 90 min (%)	81.0 (1,268/1,565)	80.1 (321/401)	100 (12/12)	0.89
Median CTFC at 90 min (IQ range)	35 (23–70.6) (n = 1,537)	35 (24–78) (n = 390)	29.5 (17.5–34) (n = 12)	0.83
TMPG 2/3 at 90 min (%)	35.1 (276/787)	32.0 (66/206)	45.5 (5/11)	0.68
Stenosis at 90 min (%)	70.9 ± 19.5 (n = 1,533)	72.7 ± 17.2 (n = 390)	65.8 ± 9.15 (n = 12)	0.44
MLD at 90 min (mm)	0.86 ± 0.63 (n = 532)	0.86 ± 0.58 (n = 390)	1.10 ± 0.29 (n = 12)	0.21
Thrombus present (%)	29.4 (458/1,560)	31.0 (123/397)	30.8 (4/13)	0.53

*TIMI-10A, TIMI-10B, and TIMI-14 only. Data are presented as the percentage of subjects, median value (interquartile [IQ] range), or mean value ± SD.
Cr = creatinine; CTFC = corrected TIMI frame count; MLD = minimum lumen diameter; TFG = TIMI flow grade; TMPG = TIMI myocardial perfusion grade.

Downloaded from content.onlinejacc.org by on February 10, 2010

JACC Vol. 42, No. 9, 2003
November 5, 2003:1535–43

Table 4. Angiographic Characteristics by CrCl Group*

	Normal CrCl ≥90 ml/min (n = 890)	Mild Renal Impairment CrCl 60 to <90 ml/min (n = 789)	Moderate Renal Impairment CrCl 30 to <60 ml/min (n = 269)	Severe Renal Impairment CrCl <30 ml/min (n = 16)	p Value for Trend
TFG 2/3 at 90 min (%)	80.7 (718/890)	80.2 (633/789)	85.5 (230/269)	93.3 (14/15)	0.11
Median CTFC at 90 min (IQ range)	35.3 (23–75.9) (n = 869)	34.7 (24–785) (n = 775)	32.9 (24–50) (n = 265)	28.2 (18–34) (n = 15)	0.08
TMPG 2/3 at 90 min (%)	32.6 (141/433)	35.6 (142/397)	36.8 (56/152)	46.2 (6/13)	0.18
Stenosis at 90 min (%)	71.0 ± 18.8 (n = 871)	71.2 ± 19.7 (n = 774)	71.3 ± 18.1 (n = 263)	70.9 ± 12.6 (n = 15)	0.76
MLD at 90 min (mm)	0.89 ± 0.65 (n = 870)	0.84 ± 0.59 (n = 774)	0.84 ± 0.59 (n = 263)	0.91 ± 0.37 (n = 15)	0.16
Thrombus present (%)	31.5 (280/888)	29.9 (234/782)	20.8 (56/269)	31.3 (5/16)	< 0.01

*TIMI-10A, TIMI-10B, and TIMI-14 only. Data are presented as the percentage of subjects, median value (interquartile [IQ] range), or mean value ± SD.
CrCl = creatinine clearance; other abbreviations as in Table 3.

patients with normal, mildly, moderately, and severely impaired renal function by CrCl ($p < 0.001$) (Fig. 1). Kaplan-Meier curves show the mortality increased early during the follow-up and continued to separate up to two years of follow-up in the severely impaired renal function group ($p < 0.001$ for each) (Fig. 2). Within each TRS category (0 to 2, 3 to 4, ≥5), there was a stepwise increase in mortality among patients with normal, mildly, and severely impaired renal function ($p < 0.0001$ for each) (Fig. 3A) and among patients with normal, mildly, moderately, and severely impaired renal function by CrCl ($p < 0.001$) (Fig. 3B). Heart failure as a cause of death increased with increasing renal impairment: 24.6%, 35.9%, and 46.2% for normal, mildly, and severely impaired Cr, respectively ($p < 0.0001$ for trend), and 23.9%, 27.4%, 29.8%, and 48.2% for normal, mildly, moderately, and severely impaired CrCl, respectively ($p = 0.0014$ for trend).

In an analysis restricted to patients ≥65 years old, a similar stepwise increase in mortality was observed as renal impairment increased (Fig. 4). Both impaired Cr and CrCl were related to mortality in a stepwise fashion when stratified by the presence or absence of a history of CHF at baseline (Figs. 5A and 5B) and Killip class I and Killip class II to IV at presentation (Figs. 6A and 6B). Mildly and severely impaired renal function were associated with increased mortality in a multivariate model adjusting for age, pulse, BP, history of CHF, Killip class II to IV on presentation, gender, history of diabetes, previous MI, history of hypertension, time to treatment, and anterior MI (odds ratio [OR] for mild impairment 1.52, 95% confidence interval [CI] 1.30 to 1.77; $p < 0.001$; OR for severe impairment 3.73, 95% CI 2.55 to 5.45; $p < 0.001$). Likewise, mildly, moderately, and severely impaired renal function by CrCl was associated with increased mortality in a multivariate model (OR for mild impairment 1.38, 95% CI 1.10 to 1.73; $p = 0.006$; OR for moderate impairment 2.06, 95% CI 1.59 to 2.66; $p < 0.001$; OR for severe impairment 3.81, 95% CI 2.57 to 5.65; $p < 0.001$).

Intracranial hemorrhage (ICH) was associated with increased renal impairment: 0.9%, 1.1%, and 2.9% for normal,

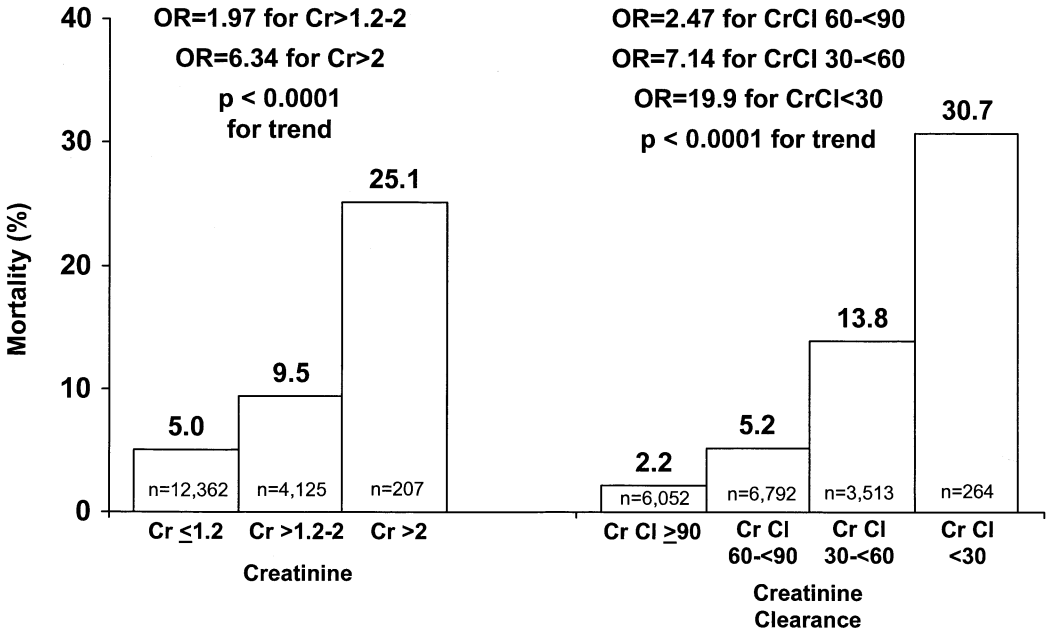

Figure 1. Mortality at 30 days according to baseline creatinine (Cr) and creatinine clearance (CrCl). OR = odds ratio.

Downloaded from content.onlinejacc.org by on February 10, 2010

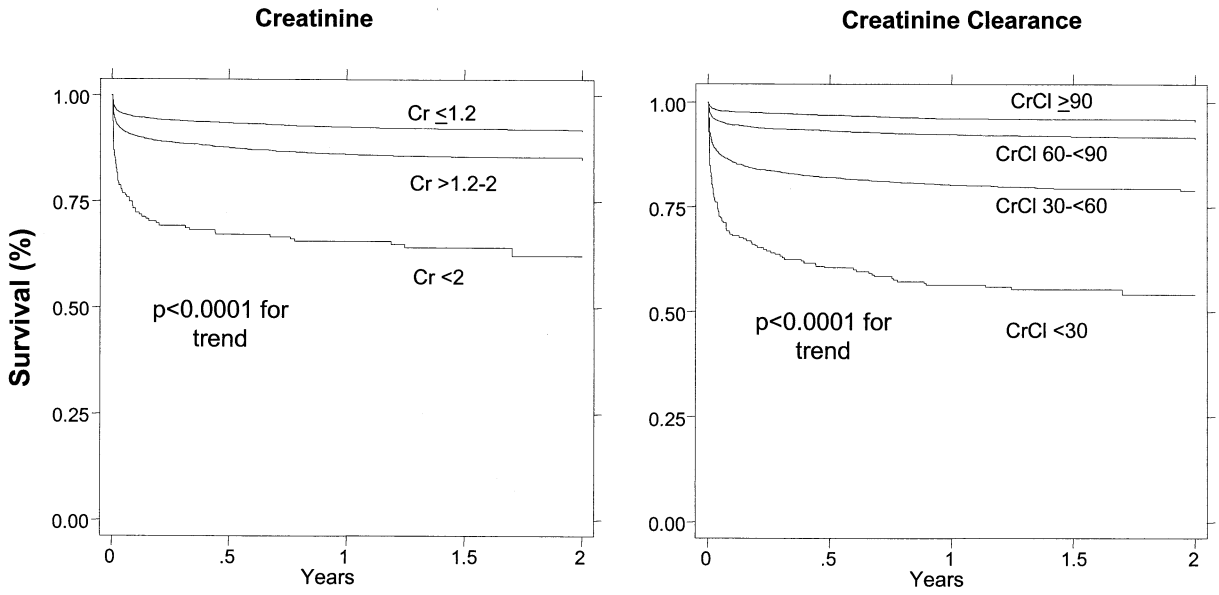

Figure 2. Kaplan-Meier survival curves through two years according to baseline Cr and CrCl. Data available through 30 days only in TIMI-10A and TIMI-14. Abbreviations as in Figure 1.

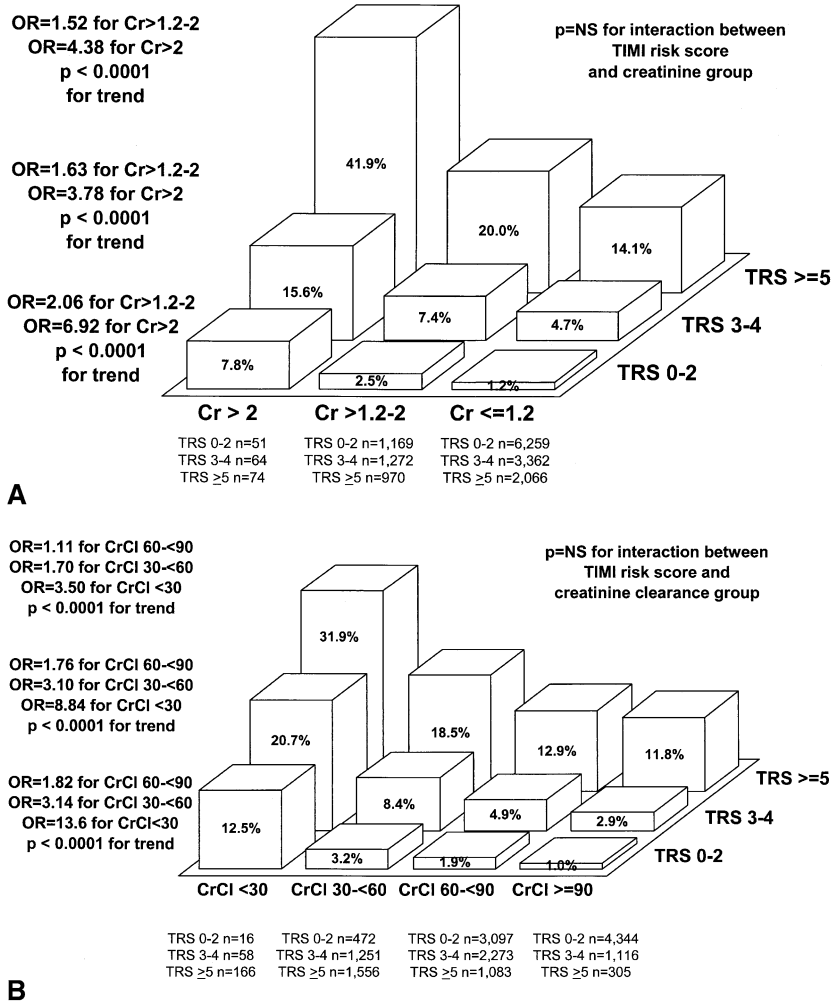

Figure 3. Mortality at 30 days according to baseline **(A)** Cr and **(B)** CrCl stratified by TIMI risk score (TRS). Abbreviations as in Figure 1.

Downloaded from content.onlinejacc.org by on February 10, 2010

JACC Vol. 42, No. 9, 2003
November 5, 2003:1535–43

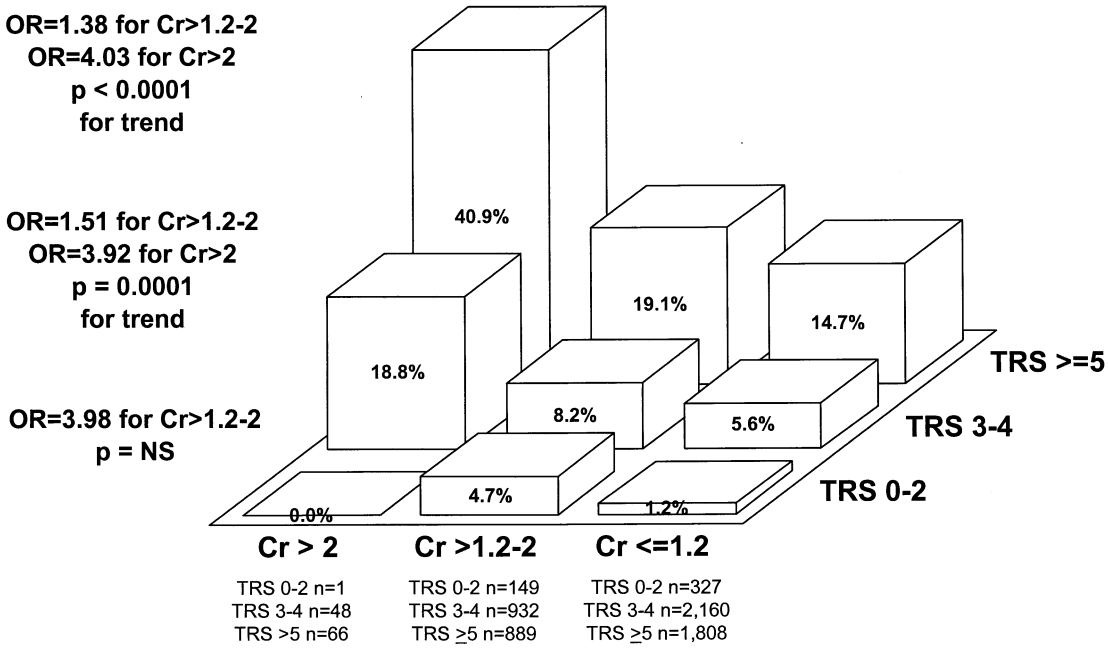

Figure 4. Mortality at 30 days according to baseline Cr stratified by TRS in patients over the age of 65 years. Abbreviations as in Figures 1 and 3.

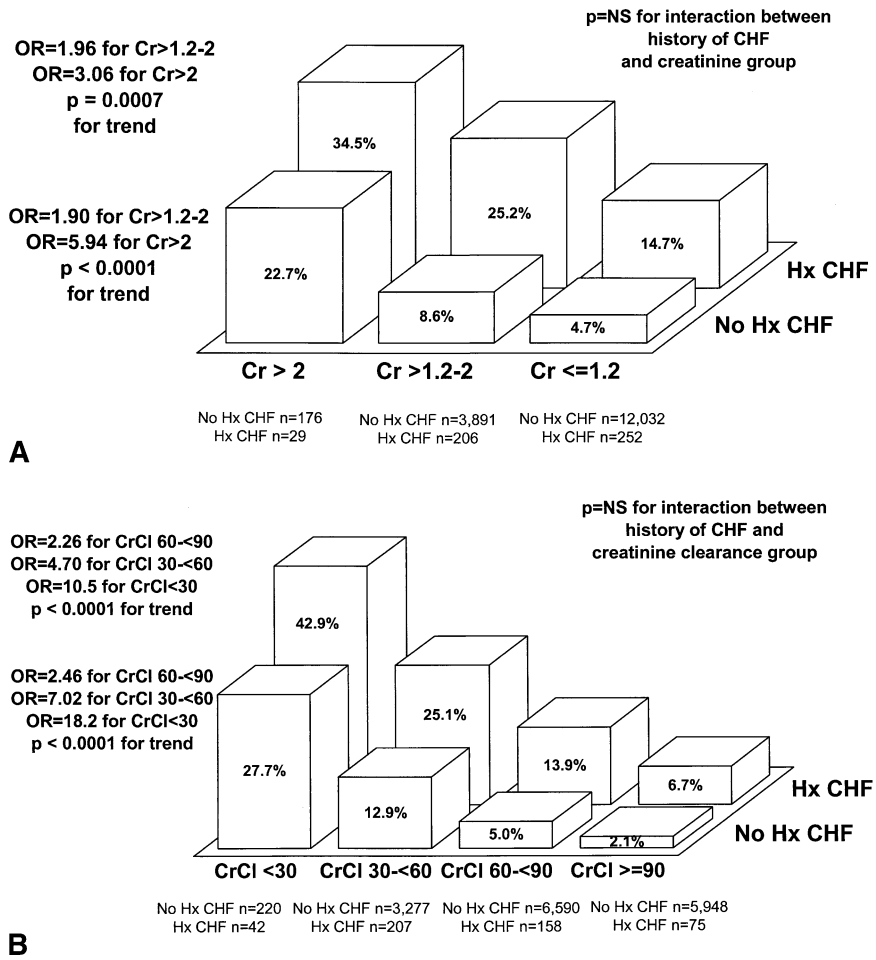

Figure 5. Mortality at 30 days according to baseline **(A)** Cr and **(B)** CrCl stratified by history (Hx) of congestive heart failure (CHF) at presentation. Abbreviations as in Figure 1.

Downloaded from content.onlinejacc.org by on February 10, 2010

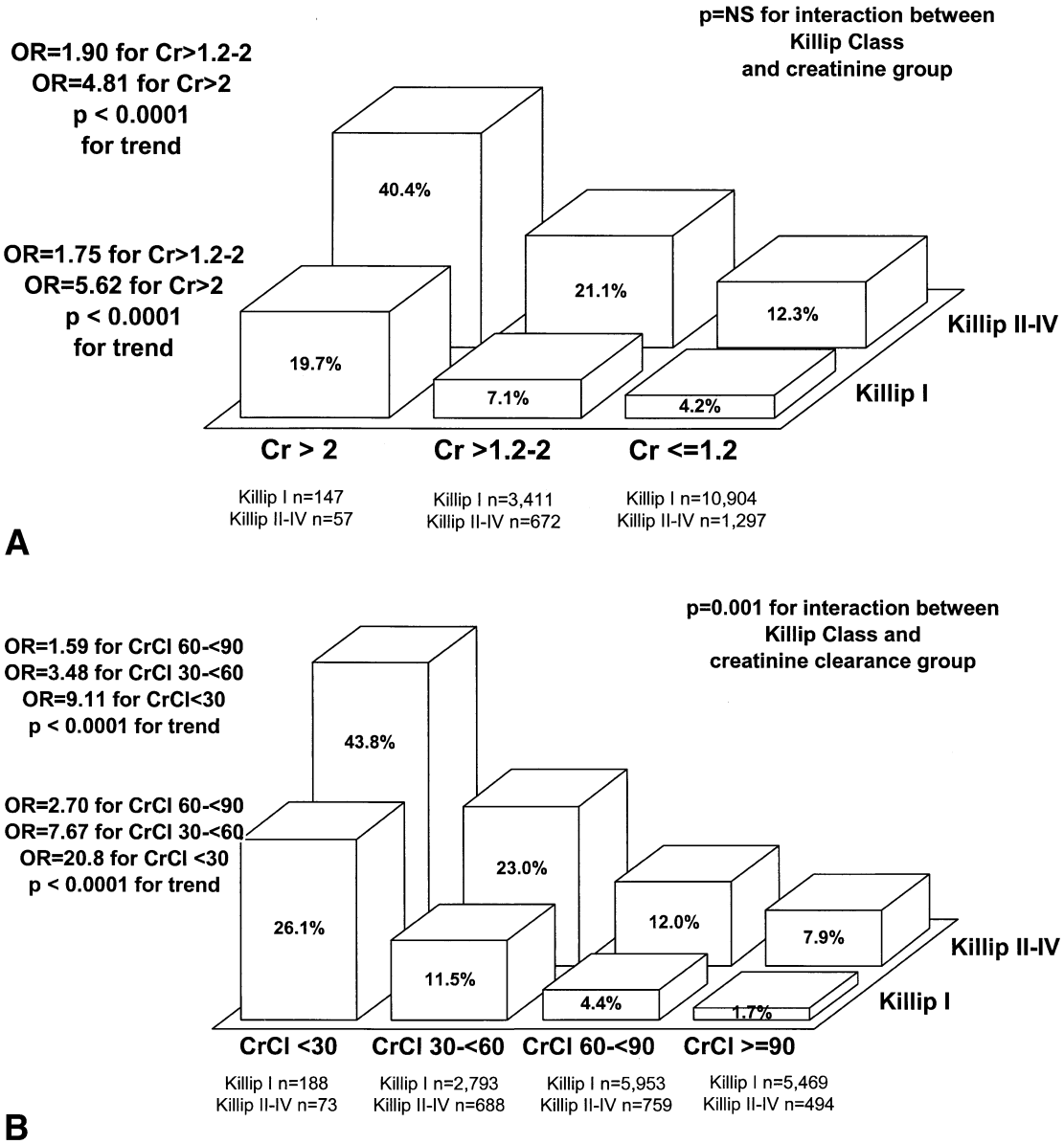

Figure 6. Mortality at 30 days according to baseline **(A)** Cr and **(B)** CrCl stratified by Killip class at presentation.

mildly, and severely impaired Cr, respectively ($p = 0.057$ for trend); and 0.6%, 0.8%, 1.8%, and 3.0% for normal, mildly, moderately, and severely impaired CrCl, respectively ($p < 0.0001$ for trend). Although the CrCl group was not significantly associated with ICH in a multivariate model adjusting for known correlates of ICH (age, gender, systolic and diastolic BP), severely impaired Cr tended to be associated with increased ICH (multivariate OR for severe impairment 2.31, 95% CI 0.99 to 5.37, $p = 0.053$).

DISCUSSION

This study extends previous observations regarding the association of renal dysfunction and adverse clinical outcomes among patients with coronary artery disease. In the presence of STEMI, elevated Cr and/or reduced CrCl on presentation are associated with increased mortality, independent of other conventional risk factors and TRS. Heart failure as the primary cause of death increased with increasing renal impairment. Retrospective analyses have demonstrated that renal dysfunction is associated with an increased risk of CHF and mortality after acute MI, and that while reperfusion therapy may improve outcomes, reperfusion therapy is less frequently administered to these patients (23,24). Elderly patients with renal dysfunction are less frequently treated with aspirin, beta-blockers, and fibrinolytic therapy, and they undergo angiography and angioplasty less frequently during the index hospitalization (25).

In contrast to previous observational studies suggesting lower rates of pharmacologic and interventional therapy

Downloaded from content.onlinejacc.org by on February 10, 2010

among patients with renal insufficiency, all patients (regardless of baseline Cr or CrCl) received reperfusion therapy for STEMI in the present study, including fibrinolytic and aspirin therapy within 6 to 12 h of symptom onset in all patients, beta-blocker therapy in a large proportion, and early PCI in many patients. Despite the facts that aggressive pharmacologic treatment was administered to all patients and the epicardial and myocardial reperfusion rates were equivalent, reduced renal function remained associated with impaired survival through up to two years of follow-up. This finding was also observed when the analysis was restricted to patients over the age of 65 years.

Elevated Cr on presentation was associated with increased ICH, independent of age, gender, and BP. Given these findings of increased ICH with increased renal impairment at presentation, physicians should exercise caution in administering fibrinolytics to patients with increased Cr; primary PCI may represent a favorable alternative therapy. However, the risk of ICH in primary PCI patients presenting with renal impairment has not been defined, and likewise may be associated with increased rates of ICH.

Because Cr levels were measured at presentation, which was in general within 3 h of symptom onset, these Cr levels likely reflect renal status near the time of onset of the event and less likely reflect changes in renal hemodynamics due to impaired systemic perfusion (26). Although other biomarkers reflect activation of inflammation (high-sensitivity C-reactive protein, sCD40 ligand, interleukin-6), necrosis (troponin, creatine kinase), the presence of a "metabolic syndrome" (glycosylated hemoglobin, microalbuminuria), or activation of the neuroendocrine system (brain natriuretic peptide), it could be speculated that Cr and CrCl are integrative markers of metabolic abnormalities, neuroendocrine activation, and end-organ damage due to several cardiac risk factors, including hypertension, dyslipidemia, diabetes, and vascular disease in general.

Study limitations. This analysis is a non-randomized, retrospective analysis, and as such, it is possible that both identified and unidentified confounders may have influenced the outcomes. Strict enrollment criteria are used in clinical trials, and the results observed herein may not be applicable to all patients in clinical practice.

Conclusions. In the setting of STEMI, elevated Cr and/or impaired CrCl on presentation is associated with increased mortality, independent of other conventional risk factors and TRS. This association does not appear to be mediated by reduced fibrinolytic efficacy among patients with impaired renal function.

Reprint requests and correspondence: Dr. C. Michael Gibson, Director TIMI Data Coordinating Center, 350 Longwood Avenue, First Floor, Boston Massachusetts 02115. E-mail: mgibson@timi.org.

REFERENCES

1. Januzzi JL, Cannon CP, DiBattiste PM, Murphy S, Weintraub W, Braunwald E. Effects of renal insufficiency on early invasive management in patients with acute coronary syndromes: the TACTICS-TIMI 18 trial. Am J Cardiol 2002;90:1246–9.
2. Al Suwaidi J, Reddan DN, Williams K, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation 2002;106:974–80.
3. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–9.
4. Rao V, Weisel RD, Buth KJ, et al. Coronary artery bypass grafting in patients with non-dialysis-dependent renal insufficiency. Circulation 1997;96 Suppl II:II38–45.
5. Liu JY, Birkmeyer NJ, Sanders JH, et al., the Northern New England Cardiovascular Disease Study Group. Risks of morbidity and mortality in dialysis patients undergoing coronary artery bypass surgery. Circulation 2000;102:2973–7.
6. Anderson RJ, O'Brien M, MaWhinney S, et al. Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery: VA Cooperative Study no. 5. Kidney Int 1999;55:1057–62.
7. Hirose H, Amano A, Takahashi A, Nagano N. Coronary artery bypass grafting for patients with non-dialysis-dependent renal dysfunction (serum creatinine ≥2.0 mg/dl). Eur J Cardiothorac Surg 2001;20:565–72.
8. Nakayama Y, Sakata R, Ura M, Itoh T. Long-term results of coronary artery bypass grafting in patients with renal insufficiency. Ann Thorac Surg 2003;75:496–500.
9. Cannon CP, McCabe CH, Gibson CM, et al. TNK-tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 10A dose-ranging trial. Circulation 1997;95:351–6.
10. Cannon CP, Gibson CM, McCabe CH, et al., the Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Circulation 1998;98:2805–14.
11. Antman EM, Gibson CM, de Lemos JA, et al., the Thrombolysis in Myocardial Infarction (TIMI) 14 Investigators. Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14. Eur Heart J 2000;21:1944–53.
12. Antman EM, Giugliano RP, Gibson CM, et al., the TIMI 14 Investigators. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial. Circulation 1999;99:2720–32.
13. The InTIME-II Investigators. Intravenous nPA for the Treatment of Infarcting Myocardium Early (InTIME-II): a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. Eur Heart J 2000;21:2005–13.
14. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031–7.
15. National Kidney Foundation Kidney Disease Outcome Quality Initiative Advisory Board. Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39 Suppl:S1–246.
16. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932–6.
17. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
18. Gibson CM, Murphy SA, Rizzo MJ, et al., the Thrombolysis In Myocardial Infarction (TIMI) Study Group. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Circulation 1999;99:1945–50.
19. Al-Mousa EN, Dodge JT, Jr., Rizzo M, et al. Thrombolysis in Myocardial Infarction frame count in saphenous vein grafts. Am Heart J 1998;135:323–8.

Downloaded from content.onlinejacc.org by on February 10, 2010

20. French JK, Ellis CJ, Webber BJ, et al. Abnormal coronary flow in infarct arteries 1 year after myocardial infarction is predicted at 4 weeks by corrected Thrombolysis in Myocardial Infarction (TIMI) frame count and stenosis severity. Am J Cardiol 1998;81:665–71.
21. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125–30.
22. Gibson CM, Sandor T, Stone PH, Pasternak RC, Rosner B, Sacks FM. Quantitative angiographic and statistical methods to assess serial changes in coronary luminal diameter and implications for atherosclerosis regression trials. Am J Cardiol 1992;69:1286–90.
23. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. Ann Intern Med 2002;137:563–70.
24. Hillege HL, van Gilst WH, van Veldhuisen DJ, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomized trial. Eur Heart J 2003;24:412–20.
25. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555–62.
26. Hallynck T, Soep HH, Thomis J, et al. Prediction of creatinine clearance from serum creatinine concentration based on lean body mass. Clin Pharmacol Ther 1981;30:414–21.

Downloaded from content.onlinejacc.org by on February 10, 2010

Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality

C. Michael Gibson, Duane S. Pinto, Sabina A. Murphy, David A. Morrow, Hans-Peter Hobbach, Stephen D. Wiviott, Robert P. Giugliano, Christopher P. Cannon, Elliott M. Antman, Eugene Braunwald, and TIMI Study Group

J. Am. Coll. Cardiol. 2003;42;1535-1543
doi:10.1016/j.jacc.2003.06.001

This information is current as of February 10, 2010

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/42/9/1535
References	This article cites 24 articles, 16 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/42/9/1535#BIBL
Citations	This article has been cited by 24 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/42/9/1535#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl

Downloaded from content.onlinejacc.org by on February 10, 2010