Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Relation Between Mild Renal Dysfunction and Outcomes After Coronary Artery Bypass Grafting

Rosita Zakeri, Nick Freemantle, Vivian Barnett, Graham W. Lipkin, Robert S. Bonser, Timothy R. Graham, Stephen J. Rooney, Ian C. Wilson, Robert Cramb, Bruce E. Keogh and Domenico Pagano

Circulation 2005;112;I-270-I-275
DOI: 10.1161/CIRCULATIONAHA.104.522623
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Relation Between Mild Renal Dysfunction and Outcomes After Coronary Artery Bypass Grafting

Rosita Zakeri, MB, ChB; Nick Freemantle, MA, PhD; Vivian Barnett; Graham W. Lipkin, MD, FRCP; Robert S. Bonser, FRCS, FRCP; Timothy R. Graham, FRCS; Stephen J. Rooney, FRCS; Ian C. Wilson, MD, FRCS; Robert Cramb, FRCPath; Bruce E. Keogh, MD, FRCS; Domenico Pagano, MD, FRCS

Background**—**Risk stratification algorithms for coronary artery bypass grafting (CABG) do not include a weighting for preoperative mild renal impairment defined as a serum creatinine 130 to 199 μmol/L (1.47 to 2.25 mg/dL), which may impact mortality and morbidity after CABG.

Methods and Results**—**We reviewed prospectively collected data between 1997 and 2004 on 4403 consecutive patients undergoing first-time isolated CABG with a preoperative serum creatinine <200 μmol/L (2.26 mg/dL)] in a single institution. The in-hospital mortality was 2.5% (112 of 4403), the need for new dialysis/hemofiltration was 1.3% (57 of 4403), and the stroke rate was 2.5% (108 of 4403). There were 458 patients with a serum creatinine 130 to 199 μmol/L or 1.47 to 2.25 mg/dL (mild renal dysfunction group) and 3945 patients with a serum creatinine <130 μmol/L (<1.47 mg/dL). Operative mortality was higher in the mild renal dysfunction group (2.1% versus 6.1%; $P<0.001$) and increased with increasing preoperative serum creatinine level. New dialysis/hemofiltration (0.8%versus 5.2%; $P<0.001$) and postoperative stroke (2.2% versus 5.0%; $P<0.01$) were also more common in the patients with mild renal impairment. Multivariate analysis adjusting for known risk factors confirmed preoperative mild renal impairment (creatinine 130 to 199 μmol/L or 1.47 to 2.25 mg/dL; odd ratio, 1.91; 95% CI, 1.18 to 3.03; $P=0.007$) or glomerular filtration rate estimates <60 mL/min per 1.73 m^2, derived using the Cockroft-Gault formula, (odds ratio, 1.98; 95% CI, 1.16 to 3.48; $P=0.015$) as independent predictors of in-hospital mortality. Preoperative mild renal dysfunction adversely affected the 3-year survival probability after CABG (93% versus 81%; $P<0.001$).

Conclusions**—**Mild renal dysfunction is an important predictor of outcome in terms of in-hospital mortality, morbidity, and midterm survival in patients undergoing CABG. **(*Circulation*. 2005;112[suppl I]:I-270–I-275.)**

Key Words: coronary artery bypass grafting ■ coronary disease ■ renal dysfunction

Mild renal dysfunction is an adverse prognostic indicator in patients with coronary artery disease.[1] In patients undergoing coronary artery bypass grafting (CABG), moderate (serum creatinine >200 μmol/L or >2.26 mg/dL) or end-stage renal dysfunction are recognized risk factors for increased perioperative mortality and are accounted for in the commonly used cardiac risk stratification scoring systems.[2,3] In addition, severe preoperative renal disease is associated with a higher incidence of morbidity, need for dialysis, and length of hospital stay after CABG.[4,5] Limited information exists on the influence of mild to moderate nondialysis-dependent renal disease on the immediate postoperative mortality and long-term survival of patients undergoing isolated first-time CABG. The aim of this study was to investigate the impact of mild renal dysfunction on the outcome of patients undergoing isolated first-time CABG at our institution.

Methods

Patient Selection.

We reviewed data from the computerized cardiac surgical database, which holds clinical information on all of the patients undergoing cardiac surgery at our unit since 1997. These data are acquired prospectively as part of the patients' pathway and is based on the Society of Cardiothoracic Surgeons of Great Britain and Ireland minimal dataset, with some customized additions. We analyzed data on all of the patients undergoing isolated first-time CABG with no history of renal disease or dialysis and with a preoperative serum creatinine <200 μmol/L (2.26 mg/dL) (4403 patients) between January 1997 and March 2004. For the purpose of this study, the serum creatinine before surgery was used as a baseline. A baseline creatinine of 130 μmol/L or 1.47 mg/dL was used as the threshold to define renal dysfunction.[6] We stratified patients into the following 2 groups: (1) mild renal dysfunction group (serum creatinine 130 to 199 μmol/L or 1.47 to 2.25 mg/dL; 458 patients); and (2) a reference group without evidence of renal impairment (serum creatinine <130 μmol/L or 1.47 mg/dL; 3945 patients). A total of 4385 (99.5%) patients underwent CABG on cardiopulmonary bypass, and 18 patients (0.5%) were off-pump. The patients' glomerular filtration

From the Cardiothoracic Surgical Unit (R.Z., V.B., R.S.B., T.R.G., S.J.R., I.C.W., B.E.K., D.P.), the Department of Primary Care and General Practice (N.F.), the Department of Nephrology (G.W.L.), and Clinical Chemistry (R.C.), University Hospital Birmingham, Edgbaston, United Kingdom.

Correspondence to Dr D. Pagano, University Hospital Birmingham, Edgbaston B15 2 TH, United Kingdom. E-mail domenico.pagano@uhb.nhs.uk

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.104.522623**

TABLE 1. Preoperative Patient Characteristics

Characteristics	Reference Group (n=3945)	Renal Group (n=458)	*P* Value
Age (years±SD)	62.8±9.1	68.1±7.9	<0.001
Female gender (%)	22.2	10.9	0.254
Body mass index (±SD)	27.3±4.3	26.9±4.0	0.060
Unstable angina (%)	33.1	43.2	<0.001
Previous MI (%)	49.2	62.7	<0.001
LVEF<0.30 (%)	6.3	13.8	<0.001
Diabetes mellitus (%)	19.3	27.3	<0.001
Hypertension (%)	58.1	66.8	<0.001
Hypercholesteroleamia (%)	74.6	74.5	0.964
Previous stroke (%)	5.0	10.9	<0.001
Respiratory disease (%)	8.9	11.1	<0.001
Smokers (%)	71.9	76.6	0.033
Urgent operation (%)	32.4	44.1	<0.001
Mean CPB time (min±SD)	78±29	77±28	0.315
Mean clamp time (min±SD)	43±18	42±18	0.277
Median no. grafts (range)	3 (1–5)	3 (1–5)	0.890

MI indicates myocardial infarction; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; min, minutes.

rate (GFR) was estimated using the Cockroft-Gault formula[7] and adjusted for each 1.73 m^2 of body surface area. Renal dysfunction was defined as GFR<60 mL/min per 1.73 m^2 in accordance with the U.S. National Kidney Foundation guidelines.[8]

Study End Points.

The end points of the study were in-hospital death from any cause and long-term survival in which follow-up information from the postdischarge period was also included. We also describe the need for postoperative dialysis/hemofiltration and the incidence of new stroke (transient or permanent). New stroke was defined as nonfatal stroke, transient ischemic attack, or stupor /coma at the time of discharge (Type 1 neurological deficit).[9] Postdischarge survival data were obtained from the U.K. National Office of Statistics.

Statistical Analysis

The risk faced by cardiac surgery is commonly assessed using the European Risk Stratification Score System (EuroSCORE).[2] We developed prognostic models to examine whether there was an additional effect of renal function on all-cause mortality in cardiac surgery in the immediate in-hospital period after surgery. We also examined the importance of renal function on all-cause mortality in long-term follow-up. Thus, our analyses examined whether a preoperative measure of renal function could provide additional information regarding the operative risk faced by the patient, having accounted for known risk factors. In order to assess the effect of renal function on all-cause in hospital mortality, we used generalized linear models with logit link and binomial error.[10] Because of the limited number of in-hospital deaths, we implemented a reduced model in which myocardial infarction was combined with unstable angina, and diabetes was combined with hypertension to avoid overfitting.[11] In this model, we did not include surgeon level factor. In order to assess the effect of renal function on all-cause mortality in-hospital and at long-term follow-up, we fitted a Cox proportional hazard model, accounting for each item of the EuroSCORE and surgeon. The addition of surgeon stratification did not result in different outcomes of the models. In all of the models, mild renal dysfunction was defined as creatinine ≥130 μmol/L (≥1.47 mg/dL) or GFR <60 mL/min per 1.73 m^2. In addition, we fitted a cubic spline to GFR accounting for the potential nonlinear predictive value of these measures in order to describe the predictive value of different values and explore appropriate clinical thresholds.[11]

Results

The preoperative serum creatinine for the 4403 patients was normally distributed. The mean creatinine (±SD) was 106.2 μmol/L (±19.1). A total of 3945 (89.6%) patients had a serum creatinine <130 μmol/L (<1.47 mg/dL), and 458 patients (10.4%) had a serum creatinine between 130 and 199 μmol/L (1.47 to 2.25 mg/dL). There were 2003 patients with an estimated GFR <60 mL/min per 1.73 m^2 and 2400 patients at ≥60 mL/min per 1.73 m^2. The baseline characteristics of the 2 patient groups are illustrated in Table 1.

In-Hospital Outcomes

There were 112 in-hospital deaths (overall all-cause mortality 2.5%). The cause of death was recorded as cardiovascular in 96 patients, sepsis in 5 patients, adult respiratory distress syndrome in 5 patients, and other causes in 6 patients. Fifty-four patients (1.2%) required postoperative dialysis/hemofiltration, and 108 (2.5%) patients suffered a perioperative new stroke. The mean length of hospital stay was 13.9 days (interquartile range 7 to 15 days), and 465 patients (10.6%) required a hospital stay >14 days.

TABLE 2. Postoperative Complications Profile in the 2 Patient Groups

Complications	Reference Group (n=3945)	Renal Group (n=458)	*P* Value
Death (no. of patients)	84 (2.1%)	28 (6.1%)	<0.001
Dialysis/hemofiltration (no. of patients)	33 (0.8%)	24 (5.2%)	<0.001
Stroke (no. of patients, %)	85 (2.2%)	23 (5.0%)	<0.005
Ventilation (days±SD)	3.7 (±8.0)	5.9 (±6.3)	0.016
ITU stay (days±SD)	2.5 (±4.5)	4.5 (±9.9)	<0.001
Pulmonary complications (no. of patients)	412 (10%)	84 (18%)	<0.001
Infective complications (no. of patients)	317 (8.0%)	55 (12%)	<0.004
Reoperation (no. of patients)	287 (7.2%)	37 (8.0%)	0.509
Arrhythmia (no. of patients)	1157 (29%)	177 (39%)	<0.001
Inotrope/IABP use (no. of patients)	1286 (32%)	221 (48%)	<0.001
Hospital stay (no. >14 days)	378 (9.5%)	87 (19%)	<0.001

ITU intensive intensive therapy unit; IABP, intraaortic balloon pump (exclude prophylactic use).

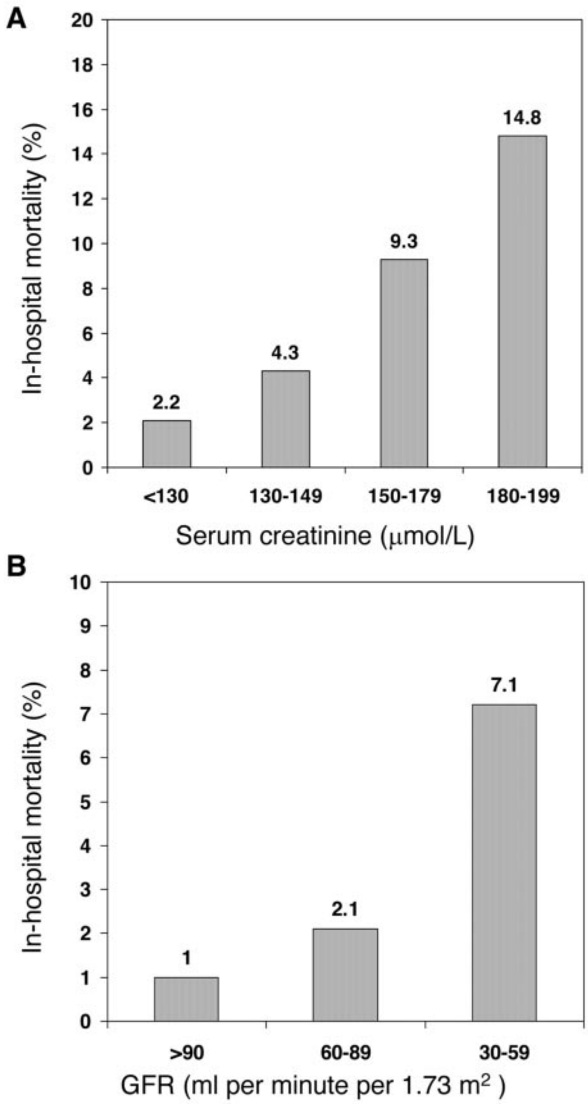


Figure 1. In-hospital mortality rates by (a) increasing serum creatinine and (b) decreasing estimated GFR. (a) Mortality rate for serum creatinine <130 μmol/L (<1.47 mg/dL): 2.2% (89 of 3945); creatinine 130 to 149 μmol/L (1.47 to 1.69 mg/dL): 4.3% (14 of 323); creatinine 150 to 179 μmol/L (1.70 to 2.02 mg/dL): 9.3% (10 of 108); creatinine 180 to 199 μmol/L (2.03 to 2.25 mg/dL): 14.8% (4 of 27). (b) Mortality rate for GFR ≥90 mL/min per 1.73 m^2: 1.0% (17 of 1707); GFR 60 to 89 mL/min per 1.73 m^2: 2.1% (40 of 1922); GFR 30 to 59 mL/min per 1.73 m^2: 7.1% (45 of 631).

The patients with a serum creatinine ≥130 μmol/L (≥1.47 mg/dL) had a higher rate of postoperative complications (Table 2), which included in-hospital mortality (2.1% versus 6.1%; $P<0.001$), greater need for postoperative dialysis/hemofiltration (0.8% versus 5.2%; $P<0.001$), strokes (2.2% versus 5.0%; $P<0.005$), and a prolonged length of hospital stay compared with the control group. Mortality increased with increasing preoperative serum creatinine levels and decreasing GFR estimates (Figure 1). Multivariate analysis identified preoperative creatinine ≥130 μmol/L or ≥1.47 mg/dL (odds ratio, 1.91; 95% CI, 1.18 to 3.03; $P=0.007$) or GFR <60 mL/min per 1.73 m^2 (odds ratio, 1.98; 95% CI, 1.16 to 3.48; $P=0.015$) as independent predictors of increased in-hospital mortality (Table 3).

TABLE 3. Multivariate Analysis of Risk of In-Hospital Death and Preoperative Variables

Variable	Odds Ratios	Lower 95% CI	Upper 95%CI	*P* Value
Age	1.07	1.04	1.1	<0.0001
Male gender	0.56	0.37	0.86	<0.001
Unstable angina/MI*	1.68	0.99	2.96	0.062
Creatinine ≥130 μmol/L	1.91	1.18	3.03	0.007
GFR<60 mL/min per 1.73 m^2	1.98	1.16	3.48	0.015
Respiratory disease	0.89	0.44	1.62	0.715
Diabetes/hypertension*	0.94	0.63	1.44	0.787
Urgent surgery	1.57	1.04	2.37	0.003
LVEF <0.30	3.91	2.41	6.18	<0.0001

MI indicates previous myocardial infarction; LVEF, left ventricular ejection fraction.

*Patients with 1 or both risk factors.

Serum creatinine data during the in-hospital postoperative period was available on 4001 (91%) patients (407 patients in the renal dysfunction and 3594 patients in the reference group). The mean (±SD) peak postoperative creatinine rise was 36 μmol/L (±69) in the renal dysfunction group and 11 μmol/L (±34) in the reference group ($P<0.0001$). A rise in creatinine >50 μmol/L was detected in 104 of 407 patients in the renal dysfunction group and 200 of 3594 patients in the reference group ($P<0.0001$).

Survival Analysis

The median follow-up after CABG was 889 days (interquartile range 8 to 1761 days). Kaplan-Meier estimates of 30-day and 3-year post-CABG survival were 98% and 93%, respectively, for the patients with a preoperative creatinine <130 μmol/L (<1.47 mg/dL) and 93% and 81%, respectively ($P<0.001$) (Figure 2, Table 4), for those with a creatinine ≥130 μmol/L (≥1.47 mg/dL). Decreasing estimated GFRs were associated with increasing mortality rates (Figure 3). The hazard ratio for the effect of GFR <60 mL/min per 1.73 m^2 on survival was 1.56 (95% CI, 1.14 to 2.13; $P=0.006$). The risk of death increased sharply with GFR <60 mL/min per 1.73 m^2 having accounted for EuroSCORE and surgeon (Figure 4). GFR had a substantially better predictive power than creatinine alone (comparison of model fit between GFR and creatinine $P=5\times10^{-13}$).

Discussion

Effects of Preoperative Renal Dysfunction on In-Hospital Outcomes

Moderate or end-stage renal dysfunction is known to be an important predictor of morbidity and mortality after CABG.[5,6,12] The 2 most common risk stratification scoring systems, used to estimate perioperative mortality, give a weighting factor only for advanced renal disease, that is, creatinine ≥200 μmol/L or dialysis dependency.[2,3] Our study suggests that patients with mild renal dysfunction are at risk of increased perioperative mortality and morbidity. This is in accordance with a previous smaller report.[6] The accuracy of serum creatinine as a marker of renal dysfunction has been an

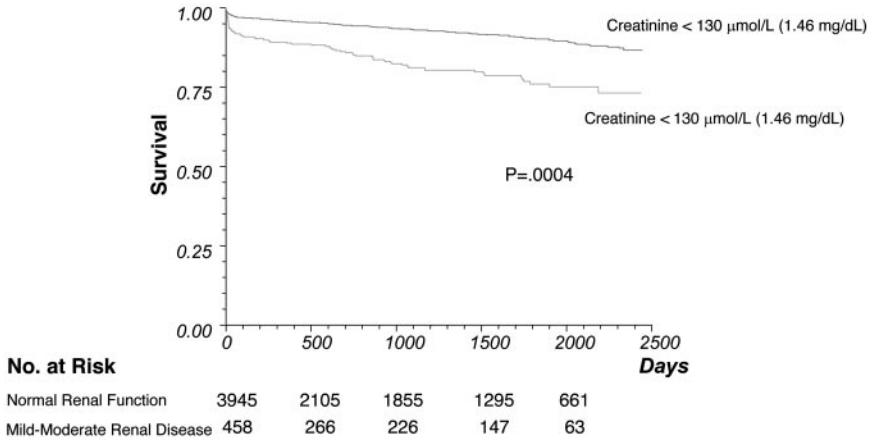


Figure 2. Kaplan-Meier estimated survival according to preoperative serum creatinine level. Cox proportional hazard probability value <0.001.

object of criticism because of its nonlinear association with GFR. In our study, preoperative serum creatinine was a very powerful predictor of in-hospital outcome, and the use of GFR estimates at the threshold used did not add additional accuracy to this prediction model. The in-hospital mortality of patients with a mildly elevated serum creatinine was 3-fold that of the control group, and multivariate analysis identified it as the third most important adverse factor after age and severe left ventricular dysfunction. The mechanism by which renal dysfunction contributes to perioperative mortality is unknown. In our study, patients with mild renal dysfunction had a high prevalence of traditional cardiovascular risk factors, and this is in accordance with other reports.[1,13] Most perioperative deaths (86%) were attributable to cardiovascular causes. It is possible, therefore, that elevated serum creatinine is merely a marker of more advanced and generalized disease, which identifies patients less likely to endure the surgical insult. However, a raised serum creatinine or a reduced estimated GFR were both independent and strong predictors for adverse outcomes. Patients with mild renal dysfunction were also more likely to develop postoperative complications. The need for postoperative dialysis/hemofiltration in the entire study population was 1.3%, but it was 4-fold more likely to be needed in those patients with preoperative renal dysfunction. These findings are in accordance with previous reports.[4] Some studies have suggested that intraoperative factors, such as a prolonged cardiopulmonary bypass time and aortic cross clamp time, are important contributors to postoperative renal dysfunction.[4] This was not the case in this study.

We did not collect data on type II neurological deficit[9] or neuropsychometric outcome on the patients included in this study; however, the incidence of type I neurological deficit was >2-fold higher in the group with mild renal dysfunction. To the best of our knowledge, this is a new finding.

TABLE 4. Hazard Ratios for Effect of Preoperative Risk Factors on Mortality

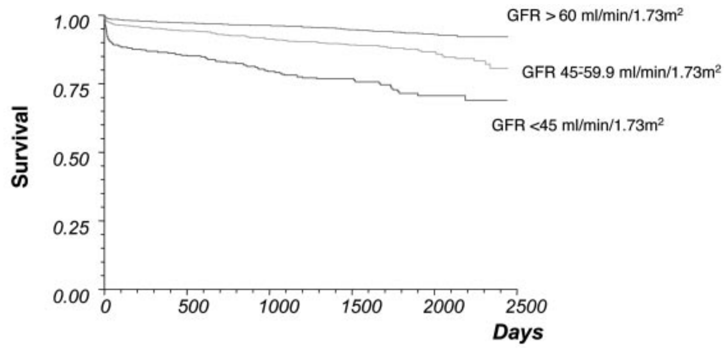
Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	*P* Value
Age	1.06	1.04	1.07	<0.0001
Male gender	0.95	0.72	1.24	0.719
Unstable angina	1.06	0.76	1.48	0.697
Previous MI	1.32	1.03	1.69	0.026
Creatinine ≥130 μmol/L	1.65	1.25	2.18	<0.001
Respiratory disease	1.51	1.10	2.06	0.009
Diabetes mellitus	1.07	0.81	1.42	0.591
Hypertension	1.06	0.84	1.34	0.637
LVEF <0.30	3.39	2.54	4.51	<0.0001
Previous stroke	1.38	0.03	2.05	0.101
Urgent surgery	1.31	0.94	1.82	0.099

MI indicates previous myocardial infarction; LVEF, left ventricular ejection fraction.

Effects of Renal Dysfunction on Survival

There has been growing interest in the relationship between mild renal dysfunction and survival. Large population-based studies have demonstrated an increase in all-cause and cardiovascular mortality in patients with mild renal dysfunction[14] with up to 20% increase in the hazards of death in patients with estimated GFR values similar to those reported in our study. Furthermore, the recent analysis of the patient population in the Valsartan in Acute Myocardial Infarction Trial, has indicated mild renal dysfunction as a major risk factor for cardiovascular complications and mortality after myocardial infarction.[1] Our study extends these findings to patients with mild renal disease undergoing CABG. The hazards for all-cause mortality increased sharply with decreasing GFR, and, when using this parameter as a continuous function, the hazard for mortality increased in patients with a GFR <60 mL/min per 1.73 m^2, a value considered the upper limit for normal renal function.[8] When using creatinine as a continuous function, the hazard of mortality increased from creatinine levels >100 μmol/L (>1.13 mg/dL). It is known that there is a group of patients in whom, despite a near-normal creatinine, the GFR is reduced and, thus, GFR may be a more accurate parameter than serum creatinine to predict long-term outcome.[1] The analysis of the creatinine continuous model, however, confirmed that the risk of death was high at levels ≥130 μmol/L or ≥1.47 mg/dL.

The mechanisms for the association between increased risk of death and mild renal disease are unknown. Mild renal dysfunction occurs in more advanced age and in patients with a number of other important cardiovascular risk factors,



No. at Risk

GFR ≥ 60 ml/min/1.73m^2	2400	1265	1141	850	437
GFR 45 to 59.9 ml/min/1.73m^2	1442	789	678	435	226
GFR < 45 ml/min/1.73m^2	561	317	262	157	61

Figure 3. Kaplan-Meier estimated survival according to preoperative estimated GFR. Cox proportional hazard probability value using GFR 60 mL/min per 1.73 m^2 as a threshold = 0.006.

including increased levels of inflammatory mediators,[15] hypercoagulability,[15] endothelial dysfunction,[16] arterial stiffness[17] or calcification,[18] and left ventricular hypertrophy.[19] The survival of patients with mild renal dysfunction undergoing CABG was lower than for patients with normal renal function, but our data do not address the question as to whether coronary revascularization affords a benefit over medical treatment in these individuals. Previous reports, mainly limited to patients with more advanced renal dysfunction, have shown a reduced post-CABG survival compared with patients with normal renal function,[20] but they have also demonstrated a consistent long-term benefit of coronary revascularization over medical treatment alone[12,20] or percutaneous revascularization with nondrug-eluting stents.[12]

The visual analysis of the survival curves after CABG in our study suggests that the highest risk of death for the renal dysfunction group can be detected in the first few weeks after surgery. This suggests a potential compounding role of the surgical insult on patients' outcome. This issue merits additional study to understand the mechanism of this enhanced risk and to improve perioperative renal protection.

Study Limitations

The follow-up data obtained via the National Institute of Statistics only provides knowledge of the survival status with no cause of death, and this does not allow differentiation between cardiovascular and other-cause mortality. Our study, however, provides data on a large unselected group of patients and, thus, provides insight into real practice. The limited number of in-hospital deaths does not allow the construction of a statistical model to ascertain a cut-off value for GFR as a predictor of in-hospital outcome. Mild renal dysfunction is generally poorly defined. In our study, the cut-off of serum creatinine ≥130 μmol/L was chosen arbitrarily on the basis of clinical observations and a smaller previous report,[6] whereas the GFR cut-off was chosen in

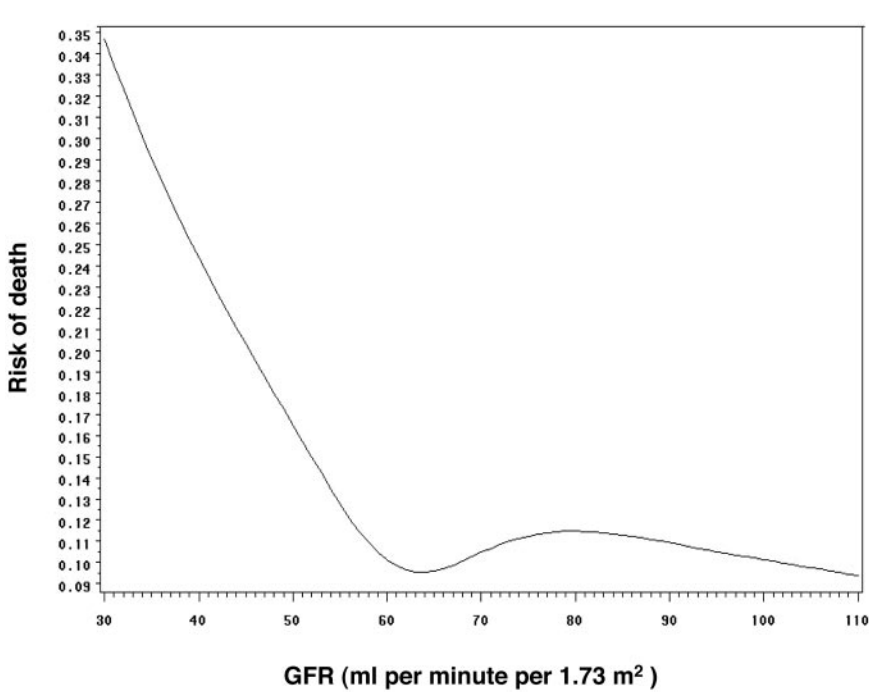


Figure 4. Cubic spline analysis for hazard of death with decreasing estimated preoperative GFR.

accordance with the U.S. National Kidney Foundation guidelines. These proved to be very strong predictors of adverse in-hospital and midterm outcome in this study. Estimated GFR proved to be more powerful then serum creatinine when predicting long-term survival post-CABG. We have no data on the underlying pathophysiology of the renal disease in the patients included in the study. All patients had no history of renal disease and had not undergone specific renal investigations other then routine serum creatinine and urea screening. The findings of our study suggest the need for additional evaluation of these patients in order to understand the pathophysiology of the renal impairment and the design of renal protection strategies.

References

1. Anevakar NS, McMurray JJV, Velasquez EJ, Solomon SD, Kober L, Rouleau J-L, White DH, Nordlander R, Maggioni A, Dickstein K, Zelonkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med.* 2004;351:1285–1295.
2. Nashef SA, Roques F, Michael P, Gauduchean E, Lemeshow S, Solamon R. European system for cardiac operation risk evaluation. (EuroSCORE). *Eur J Cardiothoracic Surg*. 1999;16:9–13.
3. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired heart disease. *Circulation*. 1989;78:I3–I12.
4. Mangano M, Diamondstone S, Ramsey J, Aggarwal A, Herskowitz A, Mangano D. Renal dysfunction after myocardial revascularisation: risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med*. 1998;128:194–203.
5. Rao V, Weisel RD, Buth KJ, Cohen G, Borger MA, Shiono N, Bhatnagar G, Fremes SE, Goldman BS, Christakis GT. Coronary artery bypass grafting in patients with non-dialysis-dependent renal insufficiency. *Circulation.* 1997;96(suppl II):II38–II45.
6. Weerasinghe A, Hornick P, Smith P, Taylor K, Ratnatunga C. Coronary artery bypass grafting in non-dialysis-depedent mild-to-moderate renal dysfunction. *J Thorac Cardiovasc Surg*. 2001;121:1083–1089.
7. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
8. Foundation NK. Kidney disease outcome quality initiative clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis.* 2002;39(suppl 1):S1–S266.
9. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C, Ozanne G, Mangano DT. Adverse cerebral outcomes after coronary bypass surgery. *N Engl J Med*. 1996;335:1857–1863.
10. McCullagh P, Nelder JA. *Generalized Linear Models.* 2nd ed. London: Chapman and Hall; 1989.
11. Harrel FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statist Med*. 1996;15:361–387.
12. Hemmelgarn BR, Southern D, Culleton BF, Mitchell BL, Knudson ML, Ghali WA. Survival after coronary artery revascularisation among patients with kidney disease. *Circulation*. 2004;110:1890–1895.
13. Luft FC. Renal disease as a risk factor for cardiovascular disease. *Basic Res Cardiol.* 2000;95:(suppl I):I72–I76.
14. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
15. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM. Elevation of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation*. 2003; 92:87–92.
16. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int*. 2003;63:1852–1860.
17. London GM, Guerin AP, Marchais SJ, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2003;18:1731–1740.
18. Raggi P, Boulay A, Chasan-Taber S, Amin A, Dillon M, Burke S, Chertow GM. Cardiac calcifications in the adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease. *J Am Coll Cardiol*. 2002;39:695–701.
19. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O. Left ventricular mass index increase in early renal disease: impact of decline in haemoglobin. *Am J Kidney Dis*. 1999;34:125–134.
20. Szczech AL, Reddan DN, Owen WF, Califf RM, Racz M, Jones RH, Hannan EL. Differential survival after coronary revascularisation procedures among patients with renal insufficiency. *Kidney Int*. 2001;60:292–299.