Preoperative renal function as a predictor of survival after coronary artery bypass grafting: Comparison with a matched general population

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Objective: Preoperative renal dysfunction is an established risk factor for early and late mortality after revascularization. We studied how renal function affects long-term survival of patients after coronary artery bypass grafting.

Methods: Early and late mortality were determined retrospectively among consecutive patients having isolated coronary bypass at a single Dutch institution between January 1998 and December 2007. Patients were stratified into 4 groups according to preoperative renal function. Expected survival was gauged using a general Dutch population group that was obtained from the database of the Dutch Central Bureau for Statistics; for each of our renal function groups, a general population group was assembled by matching for age, gender, and year of operation.

Results: After excluding 122 patients lost to follow-up, 10,626 patients were studied; in 10,359, preoperative creatinine clearance could be calculated. Multivariate logistic regression and Cox regression analysis identified renal dysfunction as a predictor for early and late mortality. When long-term survival of patient groups was compared with expected survival, only patients with a creatinine clearance less than 30 mL $\cdot$ min^{-1} showed a worse outcome. Patients with a creatinine clearance between 60 and 90 mL $\cdot$ min^{-1} had a long-term survival exceeding the expected survival.

Conclusions: Severity of renal dysfunction was related to poor survival. When compared with expected survival, however, patients having coronary bypass had a worse outcome only when severe preoperative renal dysfunction was present.

Severe renal dysfunction, particularly dysfunction requiring renal replacement therapy, has been identified as a risk factor for worse outcome after coronary artery bypass grafting (CABG).[1-3] Renal dysfunction not requiring dialysis also has been identified as a predictor of poor outcome.[4-8] Recently, the effect of preoperative and postoperative renal function on late survival has been described in large patient groups.[9,10] In these studies, a strong correlation was found between age and deterioration of renal function. Because advanced age has a strong influence on late survival after CABG, interpretation of long-term survival curves comparing groups of patients stratified by renal function might be difficult, despite appropriate statistical tests. Postoperative survival varies not only with age but also according to gender, year of surgery, and country. We therefore studied early and late survival of our Dutch patients who were post-CABG, stratified by preoperative creatinine clearance (CrCl), in comparison with a general Dutch population that was matched for age, gender, and year of operation.

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Received for publication Dec 24, 2008; revisions received March 24, 2009; accepted for publication May 20, 2009; available ahead of print July 6, 2009.

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J Thorac Cardiovasc Surg 2009;138:971-6
0022-5223/$36.00

doi:10.1016/j.jtcvs.2009.05.026

PATIENTS AND METHODS

Patients

We analyzed data concerning consecutive patients having isolated CABG in a single center between January 1998 and December 2007. Approval for this study was obtained from the institution's research review board. Starting in 1998, clinical data including demographic information, risk factors, and complications were collected prospectively in a database. Preoperative serum creatinine concentrations were retrieved from the hospital laboratory database. To obtain survival information for general population matched with our patient groups for age, gender, and year of operation, we used the database of the Dutch Central Bureau for Statistics, which can be downloaded online (www.CBS.nl). We considered this general population data to represent expected survival for our patient groups.

Operative Techniques

All patients received short-acting anesthetic drugs to facilitate early extubation. Extracorporeal circulation (ECC) was performed using normothermic nonpulsatile flow. Cold antegrade crystalloid cardioplegia (St Thomas' Hospital solution) or warm intermittent antegrade blood cardioplegia was used according to the surgeon's preference to induce and maintain cardioplegic arrest. All patients having CABG with use of ECC received a low dose of aprotinin

Abbreviations and Acronyms	
CABG	= coronary artery bypass grafting
CBS	= Central Bureau for Statistics
CKD	= chronic kidney disease
COPD	= chronic obstructive pulmonary disease
CrCl	= creatinine clearance
ECC	= extracorporeal circulation
EF	= ejection fraction
PVD	= peripheral vascular disease

(2 million kallikrein-inactivating units) administered in the priming solution for ECC. Patients having off-pump surgery did not receive aprotinin.

Estimation of Renal Function

Renal function was determined by calculating CrCl using the Cockcroft and Gault formula,[11] which differs between men [(140 − age) × weight/(serum creatinine × 72)] and women [(140 − age) × weight/(serum creatinine × 72) × 0.85]. The latest available preoperative serum creatinine concentration was used for calculation. Patients were grouped according to chronic kidney disease (CKD) class as defined by the National Kidney Foundation Disease Outcome Quality Initiative Advisory Board.[12] Patients with CrCl above 90 mL · min^{-1} were placed in class 1 (normal function); 60 to 90 mL · min^{-1}, class 2 (mild dysfunction); 30 to 59 mL · min^{-1}, class 3 (moderate dysfunction); and 15 to 29 mL · min^{-1}, class 4 (severe dysfunction). Patients with CrCl below 15 mL · min^{-1} and those treated with dialysis were excluded from this study.

Follow-up

Follow-up data concerning mortality were gathered using databases of health insurance companies. Initially, data for 9% of our total patient group could not be retrieved from these databases; we then contacted patients' general practitioners to obtain information about mortality and, if necessary, government authorities in the cities where patients lived at the time of the operation. Early mortality was defined as death occurring up to 30 days postoperatively for any cause, and late mortality was defined as death from any cause occurring after 30 days.

Statistical Analyses

Discrete variables were compared with the chi-square test and are presented as numbers and percentages of patients. Continuous variables were compared with *t* test and analysis of variance and are presented as the mean ± standard deviation. Univariate and multivariate logistic regression analyses were performed to investigate the impact of biomedical variables on early mortality. Univariate analyses were used to test for the potentially confounding effect of biomedical and demographic factors on outcome. Cox proportional hazard regression analyses, which are designed for analysis of time until an event, were performed to identify risk factors for late mortality. If $P < .05$, confounding variables were included in the multivariate logistic and Cox regression analyses to predict mortality. The cumulative incidence of death was depicted using the Kaplan–Meier method, comparing differences between preoperative CKD classes with log-rank statistics. ''Time zero'' was used to designate the time of CABG. Hazard ratios are reported with 95% confidence intervals. All statistical analyses were performed using SSPS version 15.0 (Chicago, Ill).

RESULTS

Between January 1998 and December 2007, 10,626 patients had isolated CABG at our hospital. In 267 patients, either preoperative CrCl or weight was lacking. After excluding patients who were lost to follow up (n = 122), 10,057 patients were evaluated. Almost all patients lost to follow-up were citizens of foreign countries or were living abroad. The minimum follow-up interval for surviving patients was 60 days. The mean follow-up period was 1696 ± 1026 days (range, 0–3708, with 0 days representing operative death). Sixty-six patients (0.6%) needed postoperative dialysis.

Baseline characteristics stratified by preoperative CKD class are shown in Table 1. Patients with impaired preoperative renal function (classes 2–4) were older; more often female; more likely to have diabetes, hypertension, chronic obstructive pulmonary disease (COPD), or peripheral vascular disease (PVD); more likely to have a left ventricular ejection fraction (EF) below 35%; and more likely to require perioperative intra-aortic balloon pump support. The number of off-pump coronary artery bypass operations was less in patients with renal impairment.

Early and late mortalities were greater in patients in higher CKD classes (Table 2). Risk factors for early mortality identified by univariate and multivariate logistic regression analyses are shown in Table 3. Univariate logistic regression analysis identified preoperative CrCl, considered as a continuous variable, as a risk factor for early mortality. Other patient-related risk factors indicated by univariate analysis included, age, female gender, COPD, diabetes, EF below 35%, PVD, previous cardiac surgery, year of operation, and emergency circumstances of CABG. Perioperative complications, such as myocardial infarction, need for intraoperative intra-aortic balloon pump support, and reexploration, also were identified as risk factors for early mortality. On the other hand, hypertension, use of extracorporeal circulation, and cold crystalloid versus warm intermittent blood cardioplegia were not identified as risk factors for early mortality.

All preoperative risk factors identified by univariate logistic regression analysis were entered in the multivariate logistic regression model. Preoperative CrCl, considered as a continuous variable, proved to be an independent risk factor for early mortality; others were age, COPD, diabetes, EF below 35%, previous cardiac surgery, and emergency CABG but not PVD or the year of operation.

Results of Cox regression analyses to identify risk factors for late mortality are shown in Table 4. Univariate analysis identified preoperative CrCl as a risk factor for late mortality. Other patient-related risk factors identified included age, year of operation COPD, diabetes, EF below 35%, PVD, female gender, hypertension, previous cardiac surgery, and emergency CABG. Perioperative complications representing risk factors for early mortality also were identified as risk factors for late mortality.

All preoperative risk factors identified by univariate analysis were entered into the multivariate Cox regression

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TABLE 1. Baseline characteristics stratified by preoperative CKD class

	Class 1 (n = 2324)	Class 2 (n = 4819)	Class 3 (n = 2798)	Class 4 (n = 116)	*P* value
Age, years (mean ± SD)	55.7 ± 8.3	64.4 ± 7.8	71.8 ± 6.4	74.8 ± 6.0	<.0001
Male	2113 (90.9)	3929 (81.5)	1660 (59.3)	51 (44.0)	<.0001
Diabetes	486 (20.9)	932 (19.3)	650 (23.2)	42 (36.2)	<.0001
Hypertension	946 (40.7)	1885 (39.1)	1279 (45.7)	73 (62.9)	<.0001
COPD	231 (9.9)	578 (12.0)	420 (15.0)	17 (14.7)	<.0001
PVD	201 (8.6)	496 (10.3)	439 (15.7)	26 (22.4)	<.0001
LVEF <35%	46 (2.0)	139 (3.0)	133 (4.9)	12 (10.6)	<.0001
Emergency CABG	97 (4.2)	165 (3.4)	98 (3.5)	8 (6.9)	<.0001
Off-pump	298 (12.4)	411 (8.5)	186 (6.6)	4 (3.4)	<.0001
Crystalloid cardioplegia	797 (33.8)	2035 (41.8)	1368 (48.5)	55 (46.6)	<.0001
Blood cardioplegia	1184 (50.2)	2212 (45.4)	1154 (40.9)	54 (45.8)	<.0001
Previous cardiac surgery	98 (4.2)	294 (6.1)	205 (7.3)	10 (8.6)	<.0001
IABP	33 (1.4)	83 (1.7)	86 (3.1)	5 (4.3)	<.0001
Reexploration	102 (4.4)	253 (5.3)	181 (6.5)	4 (3.4)	.007
Periop MI	52 (2.2)	144 (3.0)	87 (3.1)	6 (5.2)	.096

Values are expressed as number of patients (percentage) unless otherwise mentioned. *CKD*, Chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *PVD*, peripheral vascular disease; *LVEF*, left ventricular ejection fraction; *CABG*, coronary artery bypass grafting; *IABP*, intra-aortic balloon pump support; *Periop MI*, perioperative myocardial infarction.

model. Preoperative CrCl considered as a continuous variable was identified as an independent risk factor for late mortality. Other risk factors were age, COPD, year of operation diabetes, EF below 35%, PVD, male gender, and emergency operation. Hypertension and previous cardiac surgery were not identified as independent risk factors.

Figure 1 shows long-term survival stratified by preoperative CKD class. The log-rank test yielded a *P* value below .000, indicating significant differences in long-term survival between all groups. When long-term survival of patients in classes 1 and 2 was compared with the expected survival (Figure 2), survival of patients with normal function (class 1) was similar to that expected, with a *P* value of .323. Survival of patients with mild impairment (class 2) was better than expected, with a *P* value of .002. Compared with the expected survival, long-term survival of patients with moderate impairment (class 3; Figure 3) was similar, with a *P* value of .385. However, survival of patients with severe impairment (class 4; Figure 3) was worse than the expected survival ($P < .0001$; log-rank test).

Table 5 shows 1-, 5-, and 10-year survival rates corresponding to the Kaplan-Meier curves.

DISCUSSION

Preoperative renal impairment is a well-established predictor of adverse outcome in patients having CABG,[4-9] as was confirmed in this study. However, when compared with expected survival, only severe renal impairment led to worse outcome, and patients with moderate renal impairment had an outcome similar to that expected.

Renal Impairment and Early Mortality

Renal impairment is a well-established risk factor for early mortality. Currently used risk stratification algorithms use a serum creatinine concentration exceeding 200 μmol/L as a cutoff point,[13] but recent studies suggest that even mild renal dysfunction predicts poor early outcome after CABG.[4-9] This finding was confirmed in our study. How renal dysfunction is related to poor early outcome after CABG has not been well established. Possibly, renal dysfunction could be a result of myocardial dysfunction or other systemic diseases. Earlier reports[14] stated that patients with renal dysfunction have a high prevalence of traditional cardiovascular risk factors. In our study, the percentages of patients with impaired left ventricular function, PVD, and diabetes were much higher in patients in class 4 than patients in other classes. The need for postoperative dialysis in the entire study population was 0.6%. This finding is in a accordance with previous reports.[14] New risk stratification models should incorporate preoperative CrCl as a continuous but nonlinear variable.

Renal Impairment and Late Mortality

In agreement with others,[9] we noted that patients in a higher preoperative CKD class had poorer late survival. Renal impairment has been described as a strong risk factor

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TABLE 2. Early and late mortality stratified by preoperative CKD class

	Class 1 (n = 2324)	Class 2 (n = 4819)	Class 3 (n = 2798)	Class 4 (n = 116)	*P* value
Early mortality	14 (0.6%)	86 (1.8%)	112 (4.0%)	13 (11.2%)	<.0001
Late mortality	85 (3.7%)	438 (9.1%)	535 (19.1%)	52 (44.8%)	<.0001

CKD, Chronic kidney disease.

TABLE 3. Predictors of early mortality (≤30 days after CABG) by univariate and multivariate logistic regression analyses

	Univariate analysis		Multivariate analysis	
Risk factor	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Preop CrCl*	0.965 (0.958–0.972)	<.0001	0.980 (0.971–0.990)	<.0001
Year of operation	0.944 (0.901–0.989	.015	0.965 (0.917–1.016)	.175
Age*	1.083 (1.065–1.102)	<.0001	1.055 (1.031–1.079)	<.0001
COPD	2.06 (1.49–2.84)	<.0001	1.78 (1.26–2.50)	.001
Diabetes	1.51 (1.12–2.02)	.006	1.49 (1,08–2.04)	.013
LVEF <35%	6.15 (4.18–0.04)	<.0001	4.19 (2.76–6.36)	<.0001
PVD	1.62 (1.14–2.30)	.007	1.30 (0.89–1.90)	.171
Previous cardiac surgery	4.26 (3. 11–5.83)	<.0001	2.49 (1.66–3.74)	<.0001
Emergency	6.56 (4.21–8.70)	<.0001	3.73 (2.30–6.04)	<.0001
Periop MI	6.42 (4.35–9.49)	<.0001		
Reexploration	5.29 (3.81–7.36)	<.0001		
IABP	14.41 (10.01–20.74)	<.0001		
Male gender	0.74 (0.55–0.99)	.047	1.15 (0.83–1.61)	.385
Hypertension	0.97 (0.74–1.27)	.745		
Crystalloid cardioplegia	1.18 (0.89–1.57)	.242		
Off-pump	0.67 (0.39–1.17)	.163		

CABG, Coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *HR,* hazard ratio; *CI,* confidence interval; *IABP,* intra-aortic balloon pump support; *LVEF,* left ventricular ejection fraction; *Periop MI,* perioperative myocardial infarction; *Preop CrCl,* preoperative creatinine clearance; *PVD,* peripheral vascular disease. *Entered as a continuous variable.

for development of cardiovascular disease.[15,16] It occurs more often in advanced age and in patients with a number of other important cardiovascular risk factors including hypercoagulability,[17] endothelial dysfunction,[18] arteriosclerosis,[19] and left ventricular hypertrophy.[20] This means increased incidence of new cardiovascular events for those who survive the postoperative period. Holzmann and colleagues[21] showed an 8% incidence of myocardial infarction in patients with renal dysfunction within 5 years after CABG. In 35% of the cases, death was the outcome within 1 month. It is also possible that in the presence of renal dysfunction, traditional risk factors such as smoking, hyperlipidemia, hypertension, and diabetes will have a different qualitative relationship with cardiovascular events.[22] Our data show that higher CKD class is associated with greater mean age.

In our study, we found that no patients in the class 4 group survived 10 years, and less than 50% survived 5 years, although the same operative and perioperative techniques were adopted in all groups. These results must be weighed

TABLE 4. Predictors of late mortality (>30 days after CABG) by univariate and multivariate Cox regression analyses

	Univariate analysis		Multivariate analysis	
Risk factor	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Preop CrCl*	0.966 (0.964–0.969)	<.0001	0.984 (0.980–0.988)	<.0001
Year of operation	0.954 (0.931–0.978)	<.0001	0.952 (0.928–0.977)	<0.0001
Age*	1.092 (1.084–1.099)	<.0001	1.067 (1.057–1.077)	<.0001
COPD	1.95 (1.71–2.23)	<.0001	1.66 (1.45–1.90)	<.0001
Diabetes	1.68 (1.49–1.89)	<.0001	1.52 (1.34–1.72)	<.0001
LVEF < 35%	3.15 (2.59–3.83)	<.0001	2.58 (2.12–3.15)	<.0001
PVD	2.12 (1.85–2.43)	<.0001	1.61 (1.40–1.86)	<.0001
Male gender	0.84 (0.75–0.95)	.008	1.39 (1.22–1.59)	<.0001
Hypertension	1.17 (1.04–1.30)	.005	1.07 (0.96–1.20)	.201
Previous cardiac surgery	1.95 (1.66–2.31)	<.0001	1.47 (1.23–1.20)	<.0001
Emergency CABG	1.95 (1.58–2.41)	<.0001	1.92 (0.50–2.47)	<.0001
Off-pump	0.69 (0.54–0.88)	.003		
Periop MI	2.61 (2.09–3.27)	<.0001		
Reexploration	1.96 (1.64–2.35)	<.0001		
Crystalloid cardioplegia	1.10 (0.98–1.23)	.097		
IABP	3.69 (2.96–4.61)	<.0001		

CABG, Coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *HR,* hazard ratio; *CI,* confidence interval; *IABP,* intra-aortic balloon pump support; *LVEF,* left ventricular ejection fraction; *Periop MI,* perioperative myocardial infarction; *Preop CrCl,* preoperative creatinine clearance; *PVD,* peripheral vascular disease. *Entered as a continuous variable.

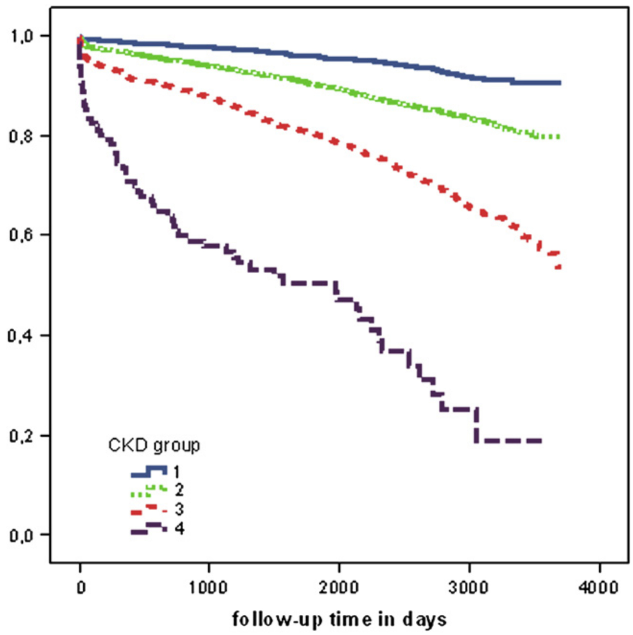

FIGURE 1. Kaplan–Meier survival curves stratified by preoperative chronic kidney disease *(CKD)* class.

against alternative procedures, namely percutaneous coronary intervention (PCI). Prior PCI studies have found that although procedural success rates tend to be high in patients with renal dysfunction, these patients face higher risks for mortality, morbidity, and restenosis.[23,24] The risk of revas-

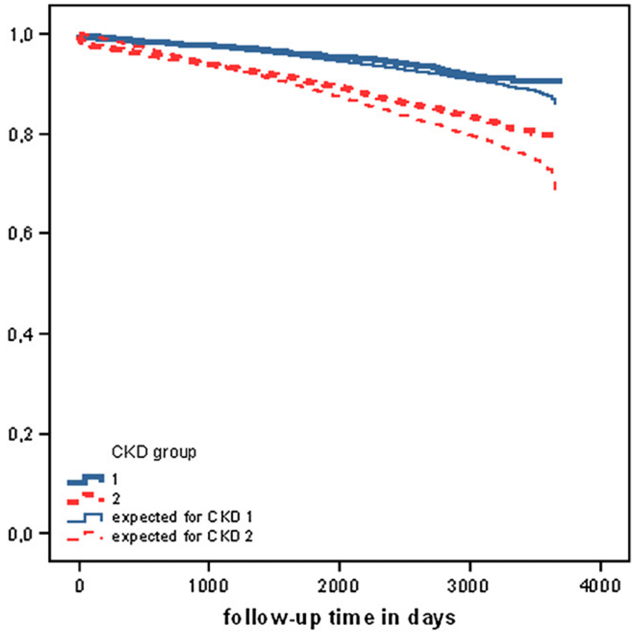

FIGURE 2. Kaplan–Meier curves for patients with chronic kidney disease *(CKD)* class 1 and 2 compared with matched general population groups. *Expected for patients in CKD class 1; **expected for patients in CKD class 2.

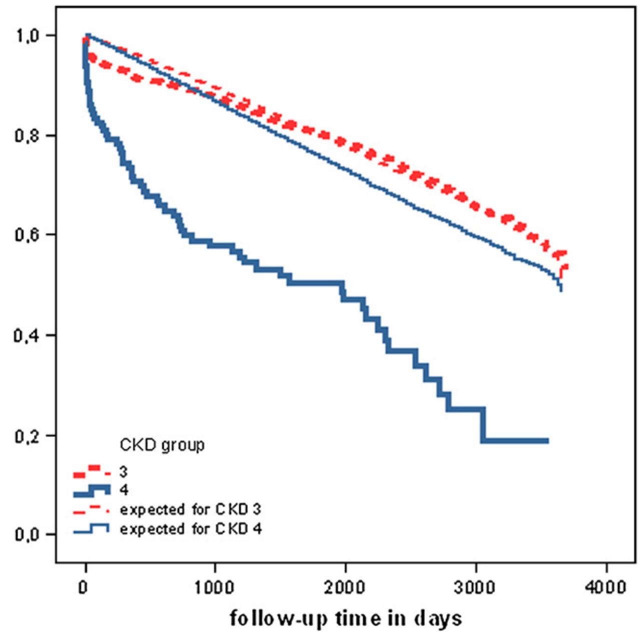

FIGURE 3. Kaplan–Meier curves for patients with chronic kidney disease *(CKD)* class 3 and 4 compared with matched general population groups. *Expected for patients in CKD class 3; **expected for patients in CKD class 4.

cularization has also to be weighed against the long-term hazards of conservative treatment in patients with coronary artery disease. In this regard, Hemmelgarn and colleagues[25] reported worse 8-year adjusted survival rates for patients with kidney disease who were not on dialysis but were medically managed after catheterization compared with those who had revascularization (54.9% for CABG and 32.7% for PCI versus 29.7% for no revascularization).

Although appropriate statistical tests can be used to distinguish between effects caused by age and by renal function, interpretation of survival curves remains difficult. Life expectancy also may vary with age, gender, and race. Changing life expectancy over the years has been well documented in the Netherlands by the Central Bureau for Statistics (CBS), which keeps track of mortality rates for the entire Dutch population. We used the CBS database, which can be downloaded online (www.CBS.nl), to calculate survival in the general population groups. We compared late survival of patients stratified by CKD class with general population

TABLE 5. Survival rates (%) for 1, 5, and 10 years, stratified by CKD class

	1 y	5 y	10 y
Class 1	98.1 ± 0.3	94.9 ± 0.6	90.1 ± 1.4
Class 2	95.0 ± 0.3	86.0 ± 0.2	79.4 ± 1.2
Class 3	89.5 ± 0.6	76.7 ± 1.0	53.2 ± 3.8
Class 4	62.4 ± 4.3	44.3 ± 5.4	*

CKD, Chronic kidney disease. *No patient in CKD class 4 survived for 10 years.

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groups matched for age, gender, and year of operation. Patients in CKD class 1 were relatively young, and survival was similar to that in a matched general population (expected survival). Kaplan–Meier curves and log-rank tests suggested that patients in class 2 had better than expected survival. Patients in class 3 were older than patients in class 2 and showed worse survival, but one that still was similar to the expected survival (Kaplan-Meyer curves and log-rank test). For patients in class 4, survival was far worse than the expected survival.

Caution to interpret these results is needed, because the CBS database contains data of the total Dutch population including patients described in this study as well as patients who were treated in other Dutch cardiac surgery centers. If differences between groups are found, the results of the general population group shift toward the average of the patient group, making the differences smaller than what our study shows. In comparing late survival of our patients with outcome in a matched group from the general population, we should take into account that a certain but unknown percentage of the general population suffers from renal impairment and coronary disease. One also may assume that our patients were adequately treated for their coronary problem and postoperatively were treated with aspirin, hypocholesterolemic drugs, and medications for underlying diseases such as hypertension. This treatment, as well as protection by revascularization, may contribute to improved survival and explain why patients in CKD classes 1, 2, and 3 had a similar or even better survival than matched general population groups. Further, before having CABG, patients are screened for severe underlying disease. If severe underlying disease is present, treatment alternatives to CABG are considered, thus biasing the CABG group.

Renal impairment was confirmed to be a risk factor for early mortality after CABG. Concerning late outcome, low CrCl was associated with a poor survival. When compared with groups from the general population matched for age, gender, and year of CABG, only patients with a CrCl of 15 to 30 $mL \cdot min^{-1}$ had a worse long-term survival, and patients with a CrCl of over 30 $mL \cdot min^{-1}$ had a similar or better outcome than expected.

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Study Limitations

This study had a retrospective design. Some patients were lost to follow-up and some data were unobtainable, making results less accurate.

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