β-Blockers improve outcomes in kidney disease patients having noncardiac vascular surgery

GMJM Welten[1], M Chonchol[2], SE Hoeks[3], O Schouten[1], JJ Bax[4], M Dunkelgrün[1], YRBM van Gestel[3], HHH Feringa[1], RT van Domburg[3] and D Poldermans[5]

[1]*Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, the Netherlands;* [2]*Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver, Colorado, USA;* [3]*Department of Cardiology, Thorax Center, Erasmus Medical Center, Rotterdam, the Netherlands;* [4]*Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands and* [5]*Department of Anaesthesiology, Erasmus Medical Center, Rotterdam, the Netherlands*

β-Blockers are known to improve postoperative outcome after major vascular surgery. We studied the effects of β-blockers in 2126 vascular surgery patients with and without kidney disease followed for 14 years. Creatinine clearance was calculated using the Cockcroft–Gault equation, and kidney function was categorized as Stage 1 for a reference group of 550 patients, Stage 2 with 808 patients, Stage 3 with 627 patients, and combined Stages 4 and 5 with 141 patients. Outcome measures were 30-day and long-term all-cause mortality with a mean follow-up of 6 years. Cox proportional hazards models were used to control cardiovascular risk factors, including propensity for β-blocker use. In all, 129 (6%) and 1190 (56%) patients died respectively. Mortality rates were three- and two-fold higher, respectively, for patients at Stages 3–5 compared to the reference group for the two outcomes. β-Blocker use was significantly associated with a lower risk of mortality after surgery. The overall adjusted hazard ratio was 0.35 and 0.62, respectively, for individuals at Stages 3–5 compared to the reference group for 30-day and long-term mortality. This study shows that kidney function is a predictor of all-cause mortality and β-blocker use is associated with a lower risk of death in kidney disease patients undergoing elective vascular surgery.

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Correspondence: *D Poldermans, Dr Molewaterplein 40, Rotterdam 3015 GA, the Netherlands. E-mail: d.poldermans@erasmusmc.nl*

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Recent estimates suggest that more than 20 million people have chronic kidney disease (CKD) in the US alone.[1] Furthermore, the CKD and dialysis populations are growing rapidly and are expected to exceed 30 million and 650 000, respectively, in the US by 2010.[2] In fact, progression of CKD exposes patients to an increased risk of development of vascular disease and cardiovascular morbidity and mortality.[3,4] In addition, it has recently been established that individuals with CKD are at moderately increased risk for developing abdominal aortic aneurysm (AAA) and peripheral arterial disease.[5,6]

Perioperative and long-term outcomes after vascular surgery are mainly dependent on the presence and extent of traditional cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, and smoking, which are commonly present in patients with CKD.[7–10] Numerous studies have shown that CKD may be associated with higher rates of morbidity and mortality when these patients undergo open infrarenal AAA repair.[11,12] In addition, even moderate CKD seems to be a risk factor for postoperative death and complications after lower extremity revascularization procedures.[13]

To improve perioperative myocardial ischemia and long-term cardiovascular complications after noncardiac surgery, guidelines recommend β-blocker therapy in all patients at high risk for coronary artery disease.[14,15] Given the proven benefit of β-blockers in patients with normal kidney function with cardiac co-morbidities, β-blockers would seem to be attractive agents to reduce cardiovascular morbidity and mortality associated with noncardiac surgery in the CKD population. Hence, the purpose of this observational study was to describe the association of β-blocker therapy on short- and long-term outcomes of patients undergoing major noncardiac vascular surgery, for different stages of kidney dysfunction.

RESULTS

Patient characteristics

The mean age of all 2126 patients was 66±11 years, 76% were male and half of patients underwent AAA surgery

(51%). The mean follow-up was 5.98 ± 3.68 years (median, 6.21 years).

A total of 757 (36%) patients received β-blockers before surgery. β-Blocker users had a higher prevalence of cardiovascular risk factors (hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypercholesterolemia, and current history of smoking; $P<0.001$ for all), a higher proportion of patients with a history of cardiovascular disease (myocardial infarction (MI), coronary revascularization, heart failure, angina, and cerebrovascular disease; $P<0.01$ for all), and additional medication use (including statins, angiotensin-converting enzyme inhibitors (ACE) inhibitors, anti-coagulants, and calcium antagonists; $P<0.001$ for all). Importantly, no difference in baseline kidney function, assessed by serum creatinine or creatinine clearance (CrCl), was observed ($P=0.3$ and 0.9, respectively). Of note, patients using β-blockers underwent more AAA surgeries and less limb arterial revascularization procedures ($P<0.001$ for all).

The mean serum creatinine concentration and CrCl in this population was 1.27 ± 1.1 mg dl^{-1} and 74.0 ± 34 ml min^{-1}, respectively, and 768 (36%) patients had a CrCl <60 ml min^{-1} (mean CrCl 42.7 ± 14 ml min^{-1}; Table 1). A total of 550 (26%) patients had a CrCl of $\geqslant 90$ ml min^{-1}; 38% ($n=808$) had a CrCl of 60–89 ml min^{-1}; 30% ($n=627$) had a CrCl of 30–59 ml min^{-1}; and 7% (141) had a CrCl of <30 ml min^{-1}.

Patients with lower CrCl levels had significantly higher proportions of hypertension, hypercholesterolemia, COPD, history of MI, heart failure, angina, and cerebrovascular disease and they received more diuretics, ACE inhibitors, calcium antagonists, and nitrates. Importantly, no difference in β-blocker use was found between the different kidney function groups ($P=0.1$).

Of the subjects with a CrCl <60 ml min^{-1}, 268 (35%) patients were receiving β-blockers. Baseline characteristics are summarized in Table 2. Patients with a CrCl <60 ml min^{-1} and receiving β-blockers were younger, had a higher proportion of traditional cardiovascular risk factors—including a history of hypertension, diabetes, and elevated cholesterol level—higher prevalence of cardiovascular disease, and usage of other cardioprotective medications including ACE inhibitors and statins. No differences were observed in the mean serum creatinine and CrCl.

Propensity score analysis

Within the propensity score analysis, the following baseline variables significantly predicted β-blocker therapy: hypertension (odds ratio (OR) 1.48, 95% confidence interval (CI): 1.16–1.88), history of MI (OR 1.78, 95% CI: 1.39–2.27), coronary revascularization (OR 1.65, 95% CI: 1.30–2.10), AAA surgery (OR 1.84, 95% CI: 1.49–2.29), and year of operation per 2 years of increase (OR 1.25, 95% CI: 1.61–1.34). According to medical therapy, usage of statins (OR 2.06, 95% CI: 1.56–2.72), diuretics (OR 1.39, 95% CI: 1.07–1.82), calcium antagonist (OR 1.78, 95% CI: 1.41–2.25), nitrates (OR 2.61, 95% CI: 2.00–3.41), and ACE inhibitors (OR 1.27, 95% CI: 1.01–1.62) were significant predictors of β-blocker prescription. The graphical method of examination by box plots showed a balance of the estimated propensity score between β-blocker users and β-blocker non-users within each decile of the propensity score.

Short-term outcome

In total, 129 (6.1%) patients died within 30 days after surgery. A clear relationship between the levels of kidney function and short-term mortality was observed. For patients with a baseline CrCl $\geqslant 90$, 60–89, 30–59, and <30 ml min^{-1}, the mortality within 30 days was 2.7, 4.5, 9.3, and 14.2%, respectively ($P=<0.001$; Table 3). Patients with mild impairment of kidney function, that is CrCl 60–89 ml min^{-1}, were not associated with adverse short-term outcome (OR 1.21, 95% CI: 0.62–2.36) when compared with the reference group. When CrCl was evaluated as a continuous variable, the adjusted OR for short-term mortality was 1.02 (95% CI: 1.01–1.04) per 1 ml min^{-1} decrease in CrCl ($P<0.001$). In addition, β-blocker therapy was associated with improved short-term outcome for the whole cohort (adjusted OR 0.39, 95% CI: 0.24–0.64). In addition, β-blocker use was associated with a lesser risk of all-cause mortality for patients with a CrCl $\geqslant 60$ ml min^{-1} (adjusted OR 0.39, 95% CI: 0.19–0.83) and for patients with a CrCl <60 ml min^{-1} (adjusted OR 0.35, 95% CI: 0.19–0.72; Table 4).

Long-term outcome

During 5.98 ± 3.68 years of follow-up, 1190 (56%) patients died. All-cause mortality rates according to baseline kidney function were 36.2, 53.7, 70.2, and 83.0% for patients with a baseline CrCl $\geqslant 90$, 60–89, 30–59, and <30 ml min^{-1}, respectively ($P<0.001$; Figure 1). Importantly, even patients with mild kidney dysfunction, that is CrCl 60–89 ml min^{-1}, were at significant higher risk (adjusted hazard ratio (HR) 1.20, 95% CI: 1.01–1.44; Table 3), compared to patients with normal kidney function. When CrCl was evaluated as a continuous variable, the adjusted HR for long-term mortality was 1.01 (95% CI: 1.01–1.02) per 1 ml min^{-1} decrease in CrCl ($P<0.001$). During this observation period, β-blocker use remained an independent predictor for long-term survival in all patients (adjusted HR 0.82, 95% CI: 0.71–0.93; Table 4). As shown in Figure 2, the association of β-blocker therapy was more pronounced in patients with a baseline CrCl of <60 ml min^{-1} (adjusted HR 0.62, 95% CI: 0.50–0.76), compared to patients with a CrCl of $\geqslant 60$ ml min^{-1} (adjusted HR 1.01, 95% CI: 0.84–1.22).

DISCUSSION

In this cohort of men and women who underwent elective vascular surgery, the level of kidney function is an independent predictor of short- and long-term mortality. We also found that the risk of all-cause mortality increased progressively with decreasing kidney function. In particular,

Table 1 | Baseline characteristics of all patients, according to the level of baseline kidney function

	All patients N=2126 (100%)	⩾90 ml min^{-1} N=550 (26%)	60–89 ml min^{-1} N=808 (38%)	30–59 ml min^{-1} N=627 (30%)	<30 ml min^{-1} N=141 (7%)	P-value
Demographics						
Mean age (±s.d.)	66.4 (±11)	56.9 (±11)	67.6 (±9)	72.7 (±8)	67.8 (±13)	<0.001
Male (%)	76	79	78	73	63	<0.001
Abdominal aorta surgery	51	46	54	54	45	0.003
Lower limb arterial revascularization surgery	49	55	46	46	55	0.003
Cardiovascular risk factor (%)						
Hypertension	49	41	50	51	64	<0.001
Diabetes mellitus	16	15	16	17	21	0.5
Current smoker	27	27	30	26	24	0.3
Hypercholesterolemia	20	22	23	14	16	<0.001
COPD	21	18	24	23	15	0.008
Body mass index (±s.d.)	24.8 (±5)	26.2 (±4)	24.7 (±4)	24.1 (±6)	22.2 (±4)	<0.001
Serum creatinine (±s.d.)	1.27 (±1.1)	0.79 (±0.2)	0.99 (±0.2)	1.3 (±0.4)	3.61 (±2.8)	<0.001
Creatinine clearance (±s.d.)	74.0 (±34)	117.6 (±28)	74.0 (±8)	48 (±8)	18.3 (±8)	<0.001
Disease history (%)						
Myocardial infarction	29	21	30	33	36	<0.001
Coronary revascularization	26	25	28	26	22	0.5
Heart failure	7	4	6	8	14	<0.001
Angina	17	13	18	20	16	0.01
Cerebrovascular disease	7	4	7	9	15	<0.001
Medication use (%)						
β-Blockers	36	33	38	34	40	0.1
Statins	26	29	29	21	19	<0.001
Diuretics	20	13	19	27	31	<0.001
ACE inhibitors	34	27	34	38	45	<0.001
Calcium antagonists	36	29	37	37	51	<0.001
Nitrates	20	16	19	23	31	<0.001
Aspirin	32	31	32	33	29	0.7
Anti-coagulation	24	26	25	22	19	0.2

ACE inhibitors, angiotensin-converting enzyme inhibitors; COPD, chronic obstructive pulmonary disease; s.d., standard deviation.

patients with a CrCl < 60 ml min^{-1} were more likely to have a significant risk of death in the first 30 days or in the first 10 years after surgery when compared with patients without kidney impairment after controlling for demographic and clinical variables. In addition, perioperative β-blocker use was associated with a 65 and 38% reduction in the short- and long-term all-cause mortality in patients with a CrCl < 60 ml min^{-1}, respectively. To our knowledge, there are a few observational studies of the relationship between kidney dysfunction, noncardiac surgery outcomes, and β-blocker use.

Cardiovascular disease is the major cause of morbidity and mortality in the Western world.[16] Acute and long-term therapy with β-blockers has become a standard of care of patients with acute myocardial infarction and congestive heart failure.[17] In nonrenal patients, β-blocker therapy has been shown to reduce infarct size and mortality among MI patients.[16] In addition, in a recent meta-analysis, β-blockers were shown to have a large beneficial effect on hospitalizations and all-cause mortality in stable patients with New York Heart Association class II or III heart failure and normal kidney function.[18] The main proposed mechanisms underlying the efficacy of β-blockers include decreasing cardiac energy requirements and modification of arrhythmias risk by antagonizing the deleterious effects of the sympathetic nervous system.[19]

Although the increased risk of cardiovascular events among persons with kidney disease not requiring dialysis is well established, the mechanism explaining the increased risk of cardiovascular death in patients with kidney dysfunction is the focus of the ongoing investigation.[20] Multiple possible explanations have been proposed to explain the association between kidney dysfunction and increased risks of death and cardiovascular disease, including left ventricular hypertrophy,[21] endothelial dysfunction,[22] arterial stiffness,[23] and increased levels of inflammatory factors.[24]

In addition to the above factors, sympathetic nervous system activation likely plays a significant role in the increased cardiovascular risk of patients with kidney disease. Increased sympathetic activity is now recognized as an important mechanism involved in cardiovascular complications in subjects with end-stage renal disease.[25,26] A recent review by Bakris *et al.*[27] assessed an abundance of experimental and human data linking kidney disease to the activation of the sympathetic nervous system. Using different models of kidney injury, such as renal artery ligation and 5/6 nephrectomy, it has been shown that kidney damage is associated with increased afferent sympathetic activity.[28–30]

Table 2 | Baseline characteristics of patients with a creatinine clearance $<60\,ml\,min^{-1}$, according to β-blocker use

	All patients N=768 (100%)	β-Blocker use N=268 (35%)	No β-blocker use N=500 (65%)	P-value
Demographics				
Mean age (±s.d.)	71.7 (±9)	70.7 (±8)	72.4 (±10)	0.02
Male (%)	71	70	72	0.6
Abdominal aortic surgery	52	59	49	<0.001
Lower limb arterial revascularization surgery	48	41	51	<0.001
Cardiovascular risk factor (%)				
Hypertension	53	71	43	<0.001
Diabetes mellitus	17	21	15	0.041
Current smoker	26	29	24	0.1
Hypercholesterolemia	15	22	11	<0.001
COPD	21	24	19	0.1
Body mass index (±s.d.)	23.7 (±6)	23.5 (±4)	23.9 (±7)	0.5
Disease history (%)				
Myocardial infarction	33	46	27	<0.001
Coronary revascularization	25	35	20	<0.001
Heart failure	9	12	8	0.1
Angina	19	28	14	<0.001
Cerebrovascular disease	10	16	7	<0.001
Medication use (%)				
Statins	20	35	13	<0.001
Diuretics	27	36	23	<0.001
ACE inhibitors	39	52	32	<0.001
Calcium antagonists	40	58	29	<0.001
Nitrates	24	36	18	<0.001
Aspirin	32	41	28	<0.001
Anti-coagulation	22	25	20	0.06
Baseline kidney function (%)				
Serum creatinine (±s.d.)	1.90 (±1.7)	1.99 (±1.8)	1.85 (±1.7)	0.3
Creatinine clearance (±s.d.)	42.7 (±14)	42.3 (±15)	42.9 (±14)	0.6

ACE inhibitors, angiotensin-converting enzyme inhibitors; COPD, chronic obstructive pulmonary disease; s.d., standard deviation.

Table 3 | Multivariate associations of the level of baseline kidney function and short- and long-term mortality

	Short-term all-cause mortality			Long-term all-cause mortality		
	Unadjusted OR (95% CI)	Adjusted for confounders[a] OR (95% CI)	Adjusted for confounders and propensity score[b] OR (95% CI)	Unadjusted HR (95% CI)	Adjusted for confounders[a] HR (95% CI)	Adjusted for confounders and propensity score[b] HR (95% CI)
All patients (n=2126)						
CrCl $\geqslant 90\,ml\,min^{-1}$ (ref.)	1.0	1.0	1.0	1.0	1.0	1.0
CrCl 60–89 $ml\,min^{-1}$	1.66 (0.90–3.07)	1.16 (0.60–2.24)	1.21 (0.62–2.36)	1.68 (1.42–1.99)	1.19 (1.02–1.43)	1.20 (1.01–1.44)
CrCl 30–59 $ml\,min^{-1}$	3.64 (2.04–6.50)	2.29 (1.16–4.53)	2.30 (1.16–4.54)	2.64 (2.23–3.12)	1.64 (1.35–2.00)	1.63 (1.33–1.97)
CrCl $<30\,ml\,min^{-1}$	5.90 (2.93–11.85)	4.96 (2.27–10.83)	5.32 (2.42–11.69)	5.32 (4.23–6.70)	3.89 (3.02–5.01)	4.00 (3.10–5.16)

ACE inhibitors, angiotensin-converting enzyme inhibitors; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio; OR, odds ratio.

[a]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation.

[b]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulations.

Furthermore, Klein *et al.*[31] recently reported that sympathetic activity was inappropriately high in a group of 57 patients with renal parenchymal disease. The authors hypothesized that renal structural changes lead to stimulation of the sympathetic nervous system by causing local or diffuse renal ischemia, which has been reported to stimulate renal afferents in animal experiments. In addition to renal afferent sympathetic discharge, there are other plausible mechanisms connecting kidney disease to sympathetic overactivity,[32] including elevated angiotensin II,[33] and suppressed brain nitric oxide. Hence, the factors responsible for sympathetic activation in patients with CKD appear to be multifactorial.

Table 4 | Multivariate associations of the level of baseline kidney function, β-blocker therapy, and short- and long-term mortality

	Short-term all-cause mortality			Long-term all-cause mortality		
	Unadjusted OR (95% CI)	Adjusted for confounders[a] OR (95% CI)	Adjusted for confounders and propensity score[b] OR (95% CI)	Unadjusted HR (95% CI)	Adjusted for confounders[a] HR (95% CI)	Adjusted for confounders and propensity score[b] HR (95% CI)
All patients (n=2126)						
β-Blocker therapy	0.48 (0.31–0.74)	0.34 (0.21–0.55)	0.39 (0.24–0.64)	0.91 (0.81–1.03)	0.79 (0.69–0.90)	0.82 (0.71–0.93)
Patients with CrCl ⩾ 60 ml min^{-1} (n=1358)						
β-Blocker therapy	0.54 (0.28–1.03)	0.36 (0.17–0.74)	0.39 (0.19–0.83)	1.06 (0.90–1.24)	0.92 (0.77–1.11)	1.01 (0.84–1.22)
Patients with CrCl < 60 ml min^{-1} (n=768)						
β-Blocker therapy	0.45 (0.25–0.79)	0.32 (0.17–0.61)	0.35 (0.19–0.72)	0.74 (0.61–0.88)	0.62 (0.51–0.76)	0.62 (0.50–0.76)

ACE inhibitors, angiotensin-converting enzyme inhibitors; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio; OR, odds ratio.
[a]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation.
[b]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulations.

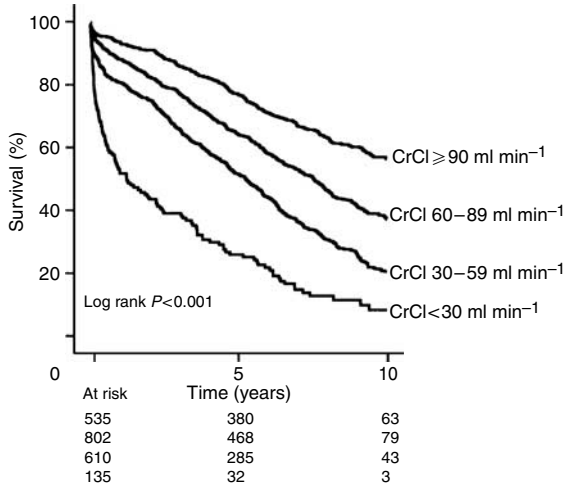

Figure 1 | Kaplan–Meier estimate of overall survival by level of kidney function (CrCl) during 5.98 ± 3.68 years of follow-up.

The sympathetic nervous system, by acting through β_1 and β_2 receptors, in addition to its effect on myocardial repolarization, can increase heart rate, which not only adversely affects the relation between myocardial demand and supply, but can also alter the structure and function of the heart, in particular by causing hypertrophy and fibrosis.[19] Therefore, the use of adrenergic inhibitors is a logical strategy to examine whether interference with the sympathetic system reduces the high cardiovascular morbidity and mortality of patients with kidney dysfunction. Although several observational studies and a small randomized trial[34–36] suggest definite survival benefits derived from the use of β-blockers in hemodialysis patients, there are a few data on the use of β-blockers in treating patients with different stages of kidney dysfunction and its relationship with short- and long-term outcomes after major noncardiac surgery. Of note, β-blockers have been associated with a reduction in mortality in 419 patients with renal insufficiency and heart failure in a Canadian prospective study.[37]

Estimates of β-blocker use in patients with kidney disease vary, but all studies show that β-blockers are used by only a minority of patients. The US Renal Data System Waves 3 and 4 studies observe that only 8.5% of the chronic dialysis patient population was using a β-blocker.[34] In addition, available data indicate that the actual use of β-blockers in patients with kidney dysfunction actually decreases as the kidney function declines.[38] McAlister *et al.*[37] and Gibney *et al.*[39] have reported that only 18 and 32% of CKD patients with heart failure and post-coronary artery bypass graft were receiving β-blockers, respectively. These observations are consistent with our findings as only 35% of patients of our cohort with a CrCl < 60 ml min^{-1} were receiving some type of β-blocker. The juxtaposition of these results suggests that the underutilization of β-blockers appears to be present in all stages of kidney disease including in the chronic dialysis patients. The four major reasons cited for this low utilization are as follows: (1) therapeutic nihilism for these chronically ill patients; (2) the unconventional epidemiology of CVD in this population; (3) the paucity of efficacy data in patients with serum creatinine > 2.0 mg dl^{-1}; and (4) the potential for higher rates of adverse effects, including hypotension, hyperkalemia, and glycemic abnormalities.[40]

Limitations of this study should be noted. First, the analysis of cardioprotective medication, like β-blockers, in a retrospective cohort analysis is prone to potential bias, as the use of β-blockers was not randomized. Despite using propensity to adjust as much as possible for the bias inherent in the decision about β-blocker therapy,[41] we cannot exclude the possibility of residual confounding. Second, the analysis was performed on the basis that if patients were or not receiving β-blocker therapy on the day of hospital admission, we could not assess changes in the type or dosage of β-blockers after the initiation of the study. Third, the study

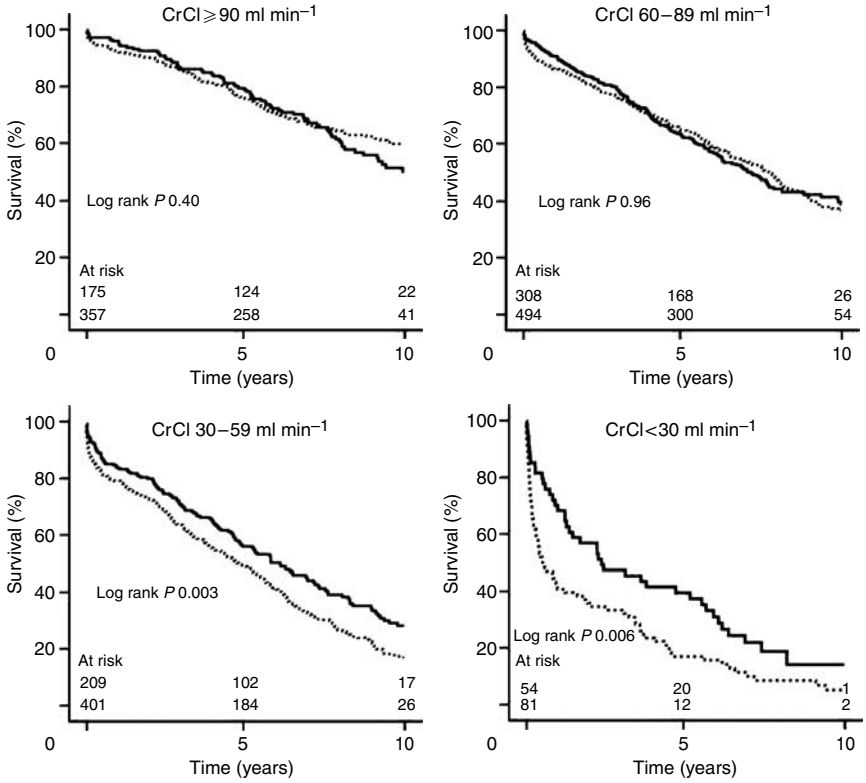

Figure 2 | Kaplan–Meier estimate of overall survival by level of kidney function (CrCl) and β-blocker therapy during 5.98 ± 3.68 years of follow-up. —β-Blocker use; ..... No β-blocker use.

population included in this analysis is almost entirely Caucasian, making these results not generalizable to other populations or places. Finally, our definition of kidney function was based on a CrCl derived from a single serum creatinine on the day of the procedure, rather than on a direct measurement of kidney function like iothalamate clearance. Additionally, the creatinine value we did use could have been influenced by cardioprotective medications or clinical status. It is possible that within-person variation in serum creatinine resulted in misclassification of kidney function. Furthermore, we did not collect data regarding the duration or cause of kidney dysfunction or other signs of kidney disease such as microalbuminuria or overt proteinuria, which is a well-established risk factor for cardiovascular mortality.[42]

In this large observational study, the perioperative administration of β-blockers was associated with clear and clinically significant reductions in short- and long-term mortality in patients with moderate and advanced kidney dysfunction who underwent high-risk elective vascular surgery. This study also demonstrates an underuse of β-blocker therapy in patients with kidney dysfunction undergoing major vascular surgery, which is comparable to other epidemiologic studies. Although the data reported in this cohort suggest a beneficial association of β-blockers with survival in a high-risk patient population, large long-term clinical trials are desperately needed to evaluate the safety and efficacy of β-blockers in patients with kidney disease not requiring dialysis.

MATERIALS AND METHODS

Study design and patient selection

Between January 1993 and June 2006, a cohort of 2126 patients older than 18 years of age underwent open noncardiac vascular surgery at Erasmus MC, Rotterdam, the Netherlands, and were entered into a computerized database. All patients had undergone elective open infrarenal AAA or lower limb arterial revascularization procedures. Patients scheduled for lower extremity amputations were excluded. The analysis was made according to whether or not patients were taking β-blockers on the day of hospital admission, and does not incorporate changes in medical treatment during the follow-up period. All patients agreed on participation in the study, and the study was conducted according to the Declaration of the Helsinki Principle.

Baseline characteristics

On all patients the information on cardiovascular risk factors was recorded and included age, gender, hypertension (defined as systolic blood pressure $\geqslant$140 mm Hg, diastolic blood pressure $\geqslant$90 mm Hg, or use of anti-hypertensive medication), diabetes mellitus (the presence of a fasting blood glucose $\geqslant 140\,mg\,dl^{-1}$ ($\geqslant 7.8\,mmol\,l^{-1}$) or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia (total cholesterol of $>200\,mg\,dl^{-1}$ ($>5.2\,mmol\,l^{-1}$)), COPD according to symptoms and pulmonary function tests (i.e. forced expiratory volume in 1 s <70% of maximal age and gender predictive value), body mass index, serum

creatinine, the presence of ischemic heart disease (prior MI, prior coronary revascularization and angina pectoris), heart failure (defined according to the New York Heart Association classification), cerebrovascular disease (history of cerebrovascular accident or transient ischemic attack), and preoperative medication use (β-blockers, statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulants). All prescription and over-the-counter medications were noted on the day of admission and were ascertained if medication was documented at least 1–3 months before hospital admission for surgery.

Kidney function assessment

Fasting serum creatinine was measured preoperatively in all patients, either at the outpatient preoperative screening visit or on the day of hospital admission. Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method.[43] Because a number of factors such as age and gender can influence serum creatinine concentrations,[44,45] the level of kidney function was defined by CrCl using the Cockcroft and Gault formula, which includes measures of age, weight, and sex:

CrCl $(\mathrm{ml\,min^{-1}}) = (140 - \mathrm{age}) \star (\mathrm{body\ weight})/72 \star \mathrm{serum\ creatinine}$ (multiplied by 0.85 in women),[46] where serum creatinine is in $\mathrm{mg\,dl^{-1}}$, age is in years, and weight is in kilograms.

Classification of kidney function

Patients were divided into four categories, based on the baseline CrCl value: $\geqslant 90$, (reference); 60–89; 30–59, and $< 30\,\mathrm{ml\,min^{-1}}$. These cutoffs were chosen on the basis of the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines as they correspond to the different stages of CKD.[47,48]

Clinical follow-up and end points

Postoperative clinical information was retrieved from an electronic database of patients maintained in our hospital. From the municipal civil registries, we obtained the survival status. Follow-up was complete in 97.9%. The primary end point of this analysis was the composite of short- and long-term all-cause mortality. Short-term mortality was defined as all deaths occurring during postoperative in-hospital stay or after hospital discharge but within the first 30 days after surgery. Long-term mortality was defined as death occurring in the first 10 years after surgery. For both the short- and long-term mortality survival time was calculated from the date of surgery to the date of censoring for the occurrence of death.

Data analysis

Continuous data are described as mean values and their standard deviations (SDs), and dichotomous data are described as percentage frequencies. The χ^2-test was used for categorical variables, and the analysis of variances test was used for continuous variable to evaluate differences in baseline characteristics between β-blocker users and between the four kidney function categories.

We developed a propensity score for the likelihood of receiving β-blocker therapy, and applied a multivariable logistic regression analysis to calculate the propensity score. The variables included in the model were age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of MI and coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, and use of statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulation.

Kaplan–Meier survival analysis was used to describe the incidence of death over time. The log-rank test was applied to study differences in survival between the four categories of kidney function ($\geqslant 90$, 60–89, 30–59, and $< 30\,\mathrm{ml\,min^{-1}}$) and the association with β-blocker use within different categories of kidney function. For further evaluation, the multivariate logistic regression analysis and the Cox proportional hazard regression analysis, with adjustment for confounders and propensity, were performed for the short- and long-term analysis, respectively. All potential confounders (age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation) were entered in the multivariable model to ensure an unbiased estimate for the relation between β-blocker use and short- and long-term all-cause mortality for all patients and for the different stages of kidney dysfunction.

Unadjusted and adjusted ORs and HRs were reported with corresponding 95% CIs. $P < 0.05$ was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, IL, USA), running under Windows 2000 Professional.

CONFLICT OF INTEREST

There are no conflicts of interest, including specific financial interest and relationships and affiliations relevant to the subject matter or materials discussed in this study.

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REFERENCES

1. Coresh J, Wei GL, McQuillan G *et al.* Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 2001; **161**: 1207–1216.
2. Xue JL, Ma JZ, Louis TA *et al.* Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. *J Am Soc Nephrol* 2001; **12**: 2753–2758.
3. Manjunath G, Tighiouart H, Ibrahim H *et al.* Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003; **41**: 47–55.
4. Keith DS, Nichols GA, Gullion CM *et al.* Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; **164**: 659–663.
5. Hua HT, Cambria RP, Chuang SK *et al.* Early outcomes of endovascular versus open abdominal aortic aneurysm repair in the National Surgical Quality Improvement Program-Private Sector (NSQIP-PS). *J Vasc Surg* 2005; **41**: 382–389.
6. Wattanakit K, Folsom AR, Selvin E *et al.* Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol* 2007; **18**: 629–636.
7. Yasuhara H, Ishiguro T, Muto T. Factors affecting late survival after elective abdominal aortic aneurysm repair. *Br J Surg* 1999; **86**: 1047–1052.
8. Back MR, Leo F, Cuthbertson D *et al.* Long-term survival after vascular surgery: specific influence of cardiac factors and implications for preoperative evaluation. *J Vasc Surg* 2004; **40**: 752–760.
9. Criqui MH, Langer RD, Fronek A *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; **326**: 381–386.

10. Manjunath G, Tighiouart H, Ibrahim H *et al.* Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003; **41**: 47–55.
11. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. *J Vasc Surg* 1989; **9**: 437–447.
12. Hertzer NR, Mascha EJ, Karafa MT *et al.* Open infrarenal abdominal aortic aneurysm repair: the Cleveland Clinic experience from 1989–1998. *J Vasc Surg* 2002; **35**: 1145–1154.
13. O'Hare AM. Management of peripheral arterial disease in chronic kidney disease. *Cardiol Clin* 2005; **23**: 225–236.
14. Mangano DT, Layug EL, Wallace A *et al.* Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; **335**: 1713–1720.
15. Poldermans D, Boersma E, Bax JJ *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999; **341**: 1789–1794.
16. Lanfear DE, Jones PG, Marsh S *et al.* Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. *JAMA* 2005; **294**: 1526–1533.
17. Hennekens CH, Braunwald E. *Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease*. Philadelphia, PA: WB Saunders, 1999.
18. Brophy JM, Joseph L, Rouleau JL. β-Blockers in congestive heart failure. *Ann Inter Med* 2002; **134**: 550–560.
19. Packer M. Current role of beta-adrenergic blockers in the management of chronic heart failure. *Am J Med* 2001; **110**(Suppl 7A): 81S–94S.
20. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
21. Levin A, Thompson CR, Ethier J *et al.* Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; **34**: 125–134.
22. Blacher J, Safar ME, Guerin AP *et al.* Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003; **63**: 1852–1860.
23. London GM, Guerin AP, Marchais SJ *et al.* Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; **18**: 1731–1740.
24. Muntner P, Hamm LL, Kusek JW *et al.* The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med* 2004; **140**: 9–17.
25. Zoccali C, Mallamaci F, Parlongo S *et al.* Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; **105**: 1354–1359.
26. Zoccali C, Mallamaci F, Tripepi G *et al.* Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. *Hypertension* 2002; **40**: 41–46.
27. Bakris GL, Hart P, Ritz E. Beta blockers in the management of chronic kidney disease. *Kidney Int* 2006; **70**: 1905–1913.
28. Faber JE, Brody MJ. Neural contribution to renal hypertension following acute renal artery stenosis in conscious rats. *Hypertension* 1983; **5**: 155–164.
29. Ye S, Ozgur B, Campese VM. Renal afferent impulses, the posterior hypothalamus, and hypertension in rats with chronic renal failure. *Kidney Int* 1997; **51**: 722–727.
30. Neumann J, Ligtenberg G, Klein II *et al.* Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 2004; **65**: 1568–1576.
31. Klein IH, Ligtenberg G, Neumann J *et al.* Sympathetic nerve activity is inappropriately increased in chronic renal disease. *J Am Soc Nephrol* 2003; **14**: 3239–3244.
32. Koomans HA, Blankestijn PJ, Joles JA. Sympathetic hyperactivity in chronic renal failure: a wake-up call. *J Am Soc Nephrol* 2004; **15**: 524–537.
33. Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease. *Nephrol Dial Transplant* 2004; **19**: 1354–1357.
34. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS waves 3 and 4 study. *Kidney Int* 2002; **62**: 1784–1790.
35. Horl MP, Horl WH. Drug therapy for hypertension in hemodialysis patients. *Semin Dial* 2004; **17**: 288–294.
36. Cice G, Ferrara L, D'Andrea A *et al.* Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003; **41**: 1438–1444.
37. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109**: 1004–1009.
38. Ishani A, Herzog CA, Collins AJ *et al.* Cardiac medications and their association with cardiovascular events in incident dialysis patients: cause or effect? *Kidney Int* 2004; **65**: 1017–1025.
39. Gibney EM, Casebeer AW, Schooley LM *et al.* Cardiovascular medication use after coronary bypass surgery in patients with renal dysfunction: a national Veterans Administration study. *Kidney Int* 2005; **68**: 826–832.
40. McCullough PA. Why is chronic kidney disease the 'spoiler' for cardiovascular outcomes? *J Am Coll Cardiol* 2003; **41**: 725–728.
41. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**: 2265–2281.
42. Gerstein HC, Mann JF, Yi Q *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**: 421–426.
43. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; **38**: 1933–1953.
44. Huynh TT, van Eps RG, Miller III CC *et al.* Glomerular filtration rate is superior to serum creatinine for prediction of mortality after thoracoabdominal aortic surgery. *J Vasc Surg* 2005; **42**: 206–212.
45. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 2002; **13**: 2140–2144.
46. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
47. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am J Kidney Dis* 2000; **35**(Suppl 2): S1–S140.
48. Levey AS, Coresh J, Balk E *et al.* National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137–147.