Beta-blockers for coronary heart disease in chronic kidney disease

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Abstract

Background. Limited data exist on whether the cardioprotective benefit of β-blockers is modified by the presence of chronic kidney disease (CKD).

Methods. A post hoc analysis of the data from the Bezafibrate Infarction Prevention (BIP) study was performed. CKD was defined according to the Modification of Diet in Renal Disease (MDRD) equation as an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m². The Cox proportional hazard model, including adjustment for propensity score, was used to estimate the hazard ratios (HR) for the composite endpoint combining acute myocardial infarction (AMI) or sudden cardiac death (SCD).

Results. In this cohort of 3075 coronary heart disease (CHD) patients, 568 (18.5%) had CKD and 1185 (38.5%) were treated with β-blockers. A total of 245 (43.1%) CKD patients received β-blockers at baseline. The mean (± SD) estimated GFR in the CKD and non-CKD subgroups was 55 (± 4) and 73 (± 9) mL/min/1.73 m², respectively. After a median follow-up of 6.2 years, the crude incidence rates of AMI or SCD/1000 person years (PY) were 25.6, 21.9, 34.6 and 27.5 for the β-blockers/CKD, β-blockers+/CKD, β-blockers−/CKD, β-blockers+/CKD+ and β-blockers+/CKD+ groups, respectively. Compared to patients with β-blockers−/CKD−, the adjusted HR of AMI or SCD was 0.87 (90% CI 0.71–1.06) for the β-blockers+/CKD−, 1.35 (90% CI 1.05–1.73) for the β-blockers−/CKD+, and 1.06 (90% CI 0.76–1.46) for the β-blockers+/CKD+.

Conclusions. These analyses suggest that the use of β-blockers is associated with a reduction in event risk in patients with CHD regardless of the presence or absence of CKD.

Keywords: cardiovascular mortality; chronic kidney disease; β-blockers

Introduction

Recent estimates suggest that more than 20 million people have chronic kidney disease (CKD) in the USA alone [1]. The lifespan of patients with CKD is markedly reduced and the majority of mortality is attributed to cardiovascular disease (CVD) [2]. Both traditional risk factors, including hypertension, diabetes and dyslipidaemia and non-traditional risk factors associated with kidney dysfunction, including inflammation and oxidant stress, may further increase CVD risk [3,4].

Sympathetic overactivity is commonly seen in CKD and is an important contributor to increasing the risk of cardiovascular events [5]. Beta-blockers are well known to interfere with the deleterious actions of the sympathetic nervous system on cardiac endpoints [6], and are well-established, evidence-based therapy for reducing cardiovascular risk associated with myocardial infarction (MI) and hypertension [7,8].

Although several studies [9–11] suggest definite survival benefits derived from the use of β-blockers in haemodialysis patients there is a paucity of data on the use of β-blockers in treating patients with coronary heart disease (CHD) and early stages of CKD. In light of the growing interest in β-blocker therapy in patients with kidney disease not requiring chronic dialysis, we examined the influence of β-blocker usage on the increased cardiovascular risk associated with CKD among a large cohort of male and female patients with established CHD in the Bezafibrate Infarction Prevention (BIP) study [12].

Subjects and methods

Subjects

Between February 1990 and October 1992, 15524 patients with coronary artery disease (aged 45 to 74 years) from 18 cardiology departments throughout Israel were screened for participation in a randomized placebo-controlled, secondary prevention trial, the BIP study [12]. This study evaluated the effectiveness of a lipid-modifying drug, bezafibrate, in decreasing the incidence of fatal and
nonfatal coronary events. During the first physician visit, records were obtained on medical history, conventional reported cardiovascular risk factors and medications used, and a complete physical examination was carried out. Patients with total cholesterol \( \leq 270 \) mg/dL, high-density lipoprotein cholesterol (HDL-C) \( \leq 45 \) mg/dL and serum triglycerides \( \leq 300 \) mg/dL at the time of the first visit were invited to a second visit after a 2-month diet \((n = 6993)\). For those patients, several blood levels, including serum creatinine, were measured. Patients meeting selection criteria who provided an informed consent were included in the BIP randomized clinical trial \((total 3090)\). Inclusion criteria for the trial comprised the following: age 45 to 74 years and a diagnosis of coronary artery disease which was made on the basis of a documented MI or angina pectoris \( \geq 6 \) months but \(< 5 \) years before enrolment into the study with one of the following: a positive exercise test, evidence of myocardial ischaemia in the radionuclide stress test, or at least 60% stenosis in one major coronary artery on coronary angiography. At this stage, a more restrictive lipid profile of serum total cholesterol between 180 and 250 mg/dL, low-density lipoprotein cholesterol (LDL-C) \( \leq 180 \) mg/dL or \( \leq 160 \) mg/dL for patients \(< 50 \) years, HDL-C \( \leq 45 \) mg/dL and triglycerides \( \leq 300 \) mg/dL was required. The main exclusion criteria were insulin-dependent diabetes mellitus, severe heart failure, unstable angina pectoris, disabling stroke, serum creatinine \( > 1.5 \) mg/dL and liver disease. The total number of patients included in the present analysis was 3075. In the entire cohort, 1185 were treated with \( \beta \)-blockers and 1890 did not receive \( \beta \)-blockers. The \( \beta \)-blockers prescribed included atenolol \((566 \) patients, 48%); propranolol \((451 \) patients, 38%) and metoprolol \((131 \) patients, 11%); other \( \beta \)-blockers were given to the remaining 37 patients \((3\%)\). The analysis was made according to whether or not patients were taking \( \beta \)-blockers during the screening session, and does not incorporate changes in medical treatment during the follow-up period.

Clinical endpoints

Patients included in the BIP randomized clinical trial were routinely followed up every 4 months. Mortality data \((median follow-up 6.2 \) years) were obtained through January 1999 from the Israel Population Registry, with cause of death coded according to the International Classification of Diseases (ICD-9) codes. The registry is complete for mortality. The primary composite endpoint was a combination of acute myocardial infarction (AMI) or sudden cardiac death (SCD).

Definition of chronic kidney disease

Recent published guidelines recommend estimating kidney function using a formula derived by the Modification of Diet in Renal Disease (MDRD) study group \([13]\). This equation expresses glomerular filtration rate \((GFR)\) in mL/min \(\times 1.73 \) m\(^2\) body surface area \((BSA)\) and is calculated as follows: \(186 \times (\text{serum creatinine}^{-1.154}) \times \text{(age}^{-0.203}) \times 1.21 \) (if black) \(\times 0.742 \) (if female) where serum creatinine is measured in mg/dL and age in years. We defined CKD as an estimated GFR \(<60 \text{ mL/min/1.73 m}^2\). Patients with missing data on GFR or with an estimated GFR \(<15 \text{ mL/min/1.73 m}^2\) \((15 \text{ patients})\) were excluded from the analysis.

Laboratory examinations

Laboratory measurements were all performed at a central study laboratory (the Physiologic and Hygiene Laboratory at the Wolfson Medical Center). Blood samples were taken after at least 12 h of fasting. All analyses were performed with a Boehringer-Hitachi 704 random access analyser using Boehringer diagnostic kits. Serum creatinine levels were measured employing the Jaffe method without deproteinization.

Statistical analysis

Data were analysed using the SAS\textsuperscript{®} software version 8.2 \((SAS Institute, Cary, NC, USA)\). Characteristics of patients with and without CKD are presented as frequencies or mean \(\pm\) SD and compared by the \(\chi^2\)- and \(t\)-test for normally distributed continuous variables, respectively. For the purpose of this analysis we defined four groups of patients based on CKD and \( \beta \)-blocker use: (A) normal kidney function, not treated with \( \beta \)-blockers (\( \beta \)-blockers/CKD\(-\)); (B) normal kidney function treated with \( \beta \)-blockers (\( \beta \)-blockers+/CKD\(-\)); (C) CKD, not treated with \( \beta \)-blockers (\( \beta \)-blockers/CKD\(-\)); and (D) CKD, treated with \( \beta \)-blockers (\( \beta \)-blockers+/CKD\(+\)). Combined endpoint rates/1000 person years \((PY)\) by CKD and \( \beta \)-blocker use, are presented as crude rates \((unadjusted)\) or age adjusted by a direct method using the entire group of patients as the reference group. Actuarial survival analysis was used to compute the cumulative probability of reaching a primary endpoint. Curves were compared with the log-rank test. The hazard of reaching a combined primary endpoint in study groups compared to group A \((reference)\) was estimated with the Cox proportional hazard model.

To minimize selection bias, we also adjusted for propensity score of \( \beta \)-blocker use. For each patient, a propensity score indicating the likelihood of being prescribed a \( \beta \)-blocker was calculated by a saturated logistic regression model in addition to gender, diabetes, hypertension, history of MI, peripheral vascular disease, functional limitation \([defined as New York Heart Association Function (NYHA) class <3]\), smoking status, chronic obstructive pulmonary disease, concomitant treatment, CKD \([defined as an estimated GFR <60 \text{ mL/min/1.73 m}^2\] and baseline levels of alkaline phosphatase, glucose, HDL-C, triglycerides \(\log\) transformed), blood pressure and heart rate. C-statistic of 0.74 indicates a good fit of the model. Propensity score was included as a covariate in the age and fully adjusted model in addition to gender, diabetes, hypertension, history of MI, peripheral vascular disease, smoking and usage of angiotensin-converting enzyme inhibitors (ACEI). Furthermore, the validity of the proportional hazard assumption was tested by running a model including the study group and a time-dependent explanatory variable.
Among the 3075 study patients, 568 (18.5%) had an estimated GFR <60 mL/min/1.73 m² at baseline (range: 59.9–37.4 mL/min/1.73 m²). The mean estimated GFR among subjects with CKD was 55 ± 4 mL/min/1.73 m². Patients with CKD were older, more likely to be female, less likely to be smokers and had a higher proportion of traditional cardiovascular risk factors, including a history of hypertension, higher mean of blood total cholesterol levels and of systolic and diastolic blood pressure. Medical therapy with ACEI, diuretics, antiarrhythmics and digoxin was administered to a significantly higher proportion of patients with CKD as compared to those without kidney disease (Table 1).

Table 2 presents systolic and diastolic blood pressure and heart rate at baseline and at the end of the study in relation to CKD status and β-blocker usage at baseline. At both time points, patients who presented to the study with CKD and were receiving β-blockers were more likely to have higher levels of systolic blood pressure than patients presenting without kidney dysfunction and using β-blockers. No differences were observed regarding diastolic blood pressure control between all groups. Furthermore, patients using β-blockers at baseline were more likely to have lower heart rates than patients not using β-blockers independent of kidney function. The effects of β-blockers on heart rate appeared to remain unchanged until the end of the observation period.

### Results

#### Patient characteristics

Among the 3075 study patients, 568 (18.5%) had an estimated GFR <60 mL/min/1.73 m² at baseline (range: 59.9–37.4 mL/min/1.73 m²). The mean estimated GFR among subjects with CKD was 55 ± 4 mL/min/1.73 m². Patients with CKD were older, more likely to be female, less likely to be smokers and had a higher proportion of traditional cardiovascular risk factors, including a history of hypertension, higher mean of blood total cholesterol levels and of systolic and diastolic blood pressure. Medical therapy with ACEI, diuretics, antiarrhythmics and digoxin was administered to a significantly higher proportion of patients with CKD as compared to those without kidney disease (Table 1).

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### Primary endpoint

After 6.2 years of follow-up, on average, 345 (13.8%) among the 2507 patients without kidney disease and 96 (16.9%) among the 568 patients with CKD achieved the combined primary endpoint of AMI or SCD. In the entire cohort, 1185 were treated with β-blockers and 1890 did not receive β-blockers. Of the subjects with CKD, 245 (43.1%) patients were receiving β-blockers at baseline. The crude incidence rates/1000 PY were 25.6, 21.9, 34.6 and 27.5 for the β-blockers−/CKD−, β-blockers+/CKD−, β-blockers−/CKD+ and β-blockers+/CKD+ groups, respectively. To eliminate a possible confounding effect associated with age, we examined age-adjusted primary endpoint rates in patients with and without CKD treated with and without β-blockers (Table 3). Treatment with β-blockers was associated with a lower event rate in patients with CKD irrespective of age. The Kaplan–Meier survival curves of patients according to CKD status and β-blocker therapy are presented in Figure 1. Of note, for all comparisons the β-blockers−/CKD− group was used as a reference group.

### Multivariate analysis

After adjusting for age, gender, diabetes, hypertension, history of MI, peripheral vascular disease, smoking and...
propensity scores for β-blocker use, treatment with β-blockers had a similar association with clinical events regardless of CKD status when compared to the group with normal kidney function not treated with β-blockers (Table 3). Of note, no significant interaction was observed between β-blocker usage and CKD ($P = 0.7$). After adding ACEI as a concomitant medical therapy to the model, the risk for the primary endpoint in each of the groups when compared to the referent group did not change significantly (data not shown). No deviation from the proportional hazard assumption was detected ($P$ for time-dependent trend in proportional hazard $= 0.66$).

**Discussion**

This analysis shows that β-blockers are associated with a reduced risk of AMI or SCD in patients with CHD irrespective of kidney function when compared to CHD patients without kidney impairment and not receiving β-blockers. The relative reduction in the incidence of the primary endpoint by β-blockers was somewhat better for patients with relatively preserved kidney function. Furthermore, the observed relationship remained significant after multivariate analysis.

While it is well established that patients on dialysis are at high risk of cardiovascular death [14], patients in the early stages of kidney disease also experience a high rate of fatal and nonfatal cardiovascular events [15]. Observational studies suggest that β-blocker use has survival benefits in patients with advance kidney disease requiring haemodialysis [9,10]. Furthermore, a small prospective, randomized trial showed a significant survival benefit with the use of carvedilol in chronic dialysis patients with severe cardiomyopathy [11]. Although the use of β-blockers appears to be beneficial in patients requiring renal replacement therapy there is a complete lack of data about the use of β-blockers in patients with CHD and CKD not requiring dialysis. Our study appears to be the first to report lower crude incidence rates of AMI or SCD in patients with CKD and β-blocker use (27.5 events per 1000 PY) over the CKD patients not receiving β-blockers (34.6 events per 1000 PY) when compared to the reference group (i.e. β-blockers−/CKD−).

Scientific evidence supports sympathetic overactivity as an important contributor of CHD in patients with kidney disease.
disease. Furthermore, in animal models of kidney damage an increase in norepinephrine release upon stimulation of renal nerves has been documented [17]. The increased risk of sudden death [18,19] in patients with CKD and the potential benefit obtained from β-blocker [11] usage might be explained, at least in part, by these observations.

The high prevalence and case fatality rate of CVD in CKD patients would seem to argue for the use of cardioprotective medications, specifically β-blockers, in these patients. Yet, available data indicate that the actual use of these interventions in this population actually decreases as the GFR declines [20,21]. Four major reasons cited for this low utilization are (1) the potential for higher rates of adverse effects; (2) the paucity of efficacy data in patients with serum creatinine >2.0 mg/dL; (3) therapeutic nihilism for these chronically ill patients and (4) that β-blockers are withheld from CKD patients perceived to be at the highest risk of heart failure or death.

The strengths of this study are the large number of patients, the complete nature of the dataset and the ability to link demographic and clinical factors with cardiovascular outcomes. Other strengths include the ability to adjust for multiple factors that may affect cardiovascular mortality. Despite the comprehensive nature of the dataset, this study also has several limitations. First, in the BIP study β-blocker therapy was not randomly allocated; as a consequence significant differences regarding concomitant therapy were observed in patients receiving and not receiving β-blocker therapy. To address this issue, we used statistical techniques to minimize selection bias. Though propensity analysis cannot adjust for unmeasured covariates that could have influenced both prescription of β-blockers and survival, the heart rate in patients receiving β-blockers was lower when compared to patients not receiving β-blockers. Still, we cannot exclude the possibility of residual confounding. Second, BIP consisted of predominantly white Caucasians and excluded patients with advanced kidney disease, which limits generalizability. Third, the definition of CKD was based on estimated GFR rather than more precise measures of kidney function, like iothalamate clearance. Fourth, we were unable to determine the cause and duration of kidney dysfunction and we did not have information regarding microalbuminuria or overt proteinuria. Finally, our findings are based on a group of patients with pre-existing blood lipid boundaries and caution should be used in the generalization of these findings.

In conclusion, β-blockers significantly reduced the incidence of cardiovascular endpoints in high-risk patients with CHD irrespective of kidney function. Our results are of clinical interest because they are based on long-term mortality data in a large group of patients with CKD, in whom treatment with β-blockers is not yet clearly established. This finding has important public health implications, as kidney disease has been shown to be associated with decreased utilization of β-blockers, despite the presence of severe cardiac disease.

Conflict of interest statement. None declared.

References

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