Association of calcium channel blockers and mortality in haemodialysis patients

Martin TEPEL, Markus VAN DER GIEI, Alexander PARK and Walter ZIDEK
Univ.-Klinik Benjamin Franklin, Freie Universität Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany

ABSTRACT

Patients with end-stage renal disease show disturbances of calcium metabolism, including calcification of arterial walls. Such patients show increased mortality, in particular due to increased cardiovascular-associated deaths. The association of calcium channel blockers and mortality in patients undergoing haemodialysis was investigated. A total of 188 patients who were receiving haemodialysis as of July 1998 were followed up for 30 months. Baseline characteristics, including age, sex, laboratory and clinical data, medication and dialysis prescription, were obtained. As of December 2000, 51 of the patients (27%) had died. In the deceased group, age was significantly higher, body mass index was significantly lower, and smoking was significantly more frequent compared with the survival group (each \(P < 0.001\)). The percentage of patients taking calcium channel blockers was significantly higher in the survival group. Cox proportional hazard regression analysis showed that haemodialysis patients assigned calcium channel blocker therapy had a significantly lower risk of mortality \([\text{relative risk } 0.33 (95\% \text{ confidence interval } 0.17–0.67); P < 0.001]\). Thus, in haemodialysis patients who were at high risk of cardiovascular events, administration of calcium channel blockers was associated with lower mortality.

INTRODUCTION

Total life expectancy for adults with end-stage renal disease is still less than 10 years, similar to that for other chronic illnesses [1,2]. The annual mortality among patients with end-stage renal disease is nearly 25%. Cardiovascular disease accounts for approximately half of the deaths among adults with end-stage renal disease [3,4]. Cardiovascular disease is frequently seen in patients with end-stage renal disease, because of the high prevalence of traditional risk factors identified in the general population, including hypertension, hyperlipidaemia, diabetes mellitus and smoking. Uraemia-related risk factors, including increased oxidative stress, micro-inflammation and salt and water overload have been considered [5–10]. Malnutrition and inadequate solute clearance may be critical determinants of the mortality of patients with end-stage renal disease [11,12].

Calcification of coronary plaques, valves and myocardial tissue, as well as diffuse myocardial fibrosis, are common pathological findings in uraemic hearts [13]. Elevations of the calcium × phosphate product have been related to increased mortality in patients with end-stage renal failure [14]. Block et al. [14] showed an increased adjusted relative risk of death when the calcium × phosphate product was greater than 72 mg²/dl², leading to an increase in cardiac deaths. An increased calcium × phosphate product facilitates metastatic calcification of arterial walls, which produces high arterial tensile stress [15]. Using electron-beam computed tomography, it was shown that coronary artery calcification was much more common in patients with end-stage renal disease compared with healthy subjects [16,17].

In the general population, calcium channel blockers are effective vasodilators and antihypertensive agents [18]. These drugs (long-acting dihydropyridines, verapamil...
and diltiazem) have been given preferentially to elderly patients, or patients with systolic hypertension [19,20]. However, calcium channel blockers may be beneficial for patients with end-stage renal disease because they decrease blood pressure, uraemic calcinosis and pressure-induced calcium entry into vessel walls [21]. Calcium channel blockers inhibit macrophage proliferation [22]. These drugs have also been shown to reverse elevated cytosolic calcium concentrations and impaired proliferation in B cells from patients with end-stage renal failure [23]. Experimental data indicate that calcium channel blockers protect against calcification of arterial walls in animal models of calcification of the aorta and coronary arteries [24,25].

To evaluate prognostic factors with regard to mortality in patients with end-stage renal disease, we analysed data from a group of such patients according to their clinical and biochemical characteristics.

METHODS

A total of 188 patients (93 females, 95 males) were studied. They had been receiving haemodialysis for at least 1 month in one of three haemodialysis centres as of July 1998, the start of the study period. The causes of end-stage renal failure were diabetic nephropathy in 27%, nephrosclerosis in 22%, glomerulonephritis in 17%, tubulointerstitial diseases in 13%, polycystic nephropathy and other diseases in 13%, and unknown in 8%. By the end of the study period (December 2000), 51 patients (27%) had died. The causes of death were classified as cardiovascular, infection and cancer. Cardiovascular death was defined as fatal myocardial infarction (death occurring within 24 h of entering hospital for myocardial infarction) or death due to cardiovascular disease. Death occurring outside hospital for which no other cause was assigned was regarded as sudden death, and was included in the definition of cardiovascular-disease-related death. No patients were lost to follow-up.

All medical records were reviewed by one of us (A.P.), and the following data were obtained: date of birth, sex, laboratory and clinical data, medications, dialysis prescription, and status as of December 2000. Laboratory values were obtained before routine haemodialysis in July 1998. Laboratory and clinical data included body mass index (calculated as body weight/height$^2$; kg/m$^2$), systolic and diastolic blood pressure, total protein, serum cholesterol, serum triacylglycerols, blood urea nitrogen, serum creatinine, serum calcium, serum phosphate, serum potassium, parathyroid hormone and serum ferritin. Data on the duration of haemodialysis at inclusion (months), the duration of haemodialysis treatment per session (h), and use of a high-flux or low-flux dialysis membrane were obtained. Data on the use of angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers and erythropoietin were obtained. Patients were allocated to a special medication group only when the medication was maintained for more than half of the observation period. Patient informed consent and ethical approval were obtained for the study.

Statistical analyses were done with SPSS for Windows, release 8.0.0 (SPSS Inc.) and GraphPad Prism 3.0 (GraphPad Software). Dichotomous baseline characteristics were compared between groups by use of Fisher’s exact test, and continuous baseline characteristics by use of the Wilcoxon rank-sum test. A P value of < 0.01 was taken to indicate significance. All statistical tests were two sided. Cox proportional hazards regression analysis was used to look for interactions between groups and the co-variates age, sex, diabetes mellitus, smoking, body mass index, systolic and diastolic blood pressure, duration of haemodialysis at inclusion, use of high-flux dialyser, haemoglobin, leucocyte count, platelet count, total protein, serum cholesterol, triacylglycerols, blood urea nitrogen, serum creatinine, serum potassium, calcium × phosphate product, parathyroid hormone, serum ferritin, and use of angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers and erythropoietin. In a stepwise forward regression analysis, variables with a P value of 0.05 or more were removed from the analysis, and variables with a P value of 0.01 or less were retained. Adjusted hazard rate ratios (RR) were calculated as the antilogarithm of the β coefficient of the Cox proportional hazards regression analysis. The 95% confidence interval for the adjusted rate ratio estimates were obtained using the antilogarithm ($β \pm 1.96 \times$ standard error of $β$). Data are expressed as means ± S.D.

RESULTS

The clinical and biochemical characteristics of the patients that died and those that survived are shown in Table 1. In the 51 patients who died, the cause of death was cardiovascular in 72%, infection in 24% and cancer in 4%. In the deceased group, age was significantly higher and body mass index was significantly lower compared with the survival group. The percentage of smokers was significantly higher in the deceased group. The percentage of patients taking calcium channel blockers was significantly higher in the survival group (Fisher’s exact test; $P < 0.001$).

There were no significant differences between the groups with regard to systolic and diastolic blood pressure, duration of haemodialysis at inclusion, duration of haemodialysis treatment per session, use of high-flux dialysers, haemoglobin, leucocyte count, platelet count, total protein, serum cholesterol, triacylglycerols, blood urea nitrogen, serum creatinine, serum potassium, calcium × phosphate product, parathyroid hormone or...
Table 1  Clinical and biochemical characteristics at the start of the study of patients with end-stage renal failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Died (n = 51)</th>
<th>Survived (n = 137)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 11</td>
<td>62 ± 15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>27/24</td>
<td>69/68</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>55</td>
<td>38</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>43</td>
<td>18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22 ± 3</td>
<td>24 ± 4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138 ± 16</td>
<td>140 ± 17</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 8</td>
<td>78 ± 8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of haemodialysis at inclusion (h)</td>
<td>42 ± 61</td>
<td>47 ± 53</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of haemodialysis treatment (h)</td>
<td>4.2 ± 0.5</td>
<td>4.4 ± 0.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>High-flux dialyser (%)</td>
<td>69</td>
<td>82</td>
<td>n.s.</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.2 ± 1.2</td>
<td>11.0 ± 1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Leucocytes (g/l)</td>
<td>8.8 ± 3.2</td>
<td>7.8 ± 2.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Platelets (g/l)</td>
<td>232 ± 99</td>
<td>218 ± 74</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.6 ± 0.6</td>
<td>6.7 ± 0.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>191 ± 55</td>
<td>203 ± 47</td>
<td>n.s.</td>
</tr>
<tr>
<td>Triacylglycerol (mg/dl)</td>
<td>203 ± 131</td>
<td>218 ± 146</td>
<td>n.s.</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>66 ± 16</td>
<td>65 ± 17</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>8.2 ± 2.4</td>
<td>8.6 ± 2.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>5.5 ± 0.8</td>
<td>5.4 ± 0.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Calcium × phosphate product (mg²/dl²)</td>
<td>56 ± 19</td>
<td>54 ± 19</td>
<td>n.s.</td>
</tr>
<tr>
<td>Parathyroid hormone (pmol/l)</td>
<td>13 ± 7</td>
<td>17 ± 11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum ferritin (ng/ml)</td>
<td>585 ± 708</td>
<td>547 ± 449</td>
<td>n.s.</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors (%)</td>
<td>31</td>
<td>40</td>
<td>n.s.</td>
</tr>
<tr>
<td>β-Blockers (%)</td>
<td>25</td>
<td>29</td>
<td>n.s.</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>20</td>
<td>47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Erythropoietin therapy (%)</td>
<td>78</td>
<td>84</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

serum ferritin. The percentages of patients taking angiotensin-converting enzyme inhibitor (Fisher’s exact test; \( P = 0.31 \)), β-blocker \( P = 0.72 \) or erythropoietin therapy \( P = 0.39 \) were not significantly different between the groups.

The effect of calcium channel blockers on patient survival is shown in Figure 1. In haemodialysis patients the administration of calcium channel blockers was associated with significantly prolonged patient survival. Cox proportional hazard regression analysis showed that age and smoking were significantly related to mortality in patients with end-stage renal failure. The relative risk of death was significantly lower in patients with a higher body mass index. Among patients with end-stage renal failure assigned to calcium channel blocker therapy, there was a significant reduction in mortality of 67% (Figure 2). A total of 74 haemodialysis patients received calcium channel blockers. Long-lasting dihydropyridine-type calcium channel blockers were taken by 82%, verapamil-type by 16%, and diltiazem-type by 2%.

**DISCUSSION**

The main finding of the present study is that increased age, a lower body mass index and smoking are independent risk factors for death in haemodialysis patients, whereas the use of calcium channel blockers was associated with a significant reduction in mortality of 67%.

According to previous studies, increased age is an important predictor of mortality in patients with end-stage renal failure [5,12]. As confirmed in our present study, a low baseline body mass index has already been established as an independent risk factor for mortality in patients with end-stage renal failure [26].

Studies on the effects of calcium channel blockers on patient survival demonstrated a survival benefit among patients treated with calcium channel blockers [3]. A total of 74 haemodialysis patients received calcium channel blockers. Long-lasting dihydropyridine-type calcium channel blockers were taken by 82%, verapamil-type by 16%, and diltiazem-type by 2%.

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mortality in patients with end-stage renal disease are sparse in the literature. However, beneficial effects of calcium channel blocker administration have been reported in the general population. The SYST-EUR trial [27], comparing nitrendipine with placebo in a prospective randomized trial, showed reductions in stroke and major cardiovascular events in the nitrendipine group. The PREVENT study [28], which was carried out in patients with coronary heart disease, looked at amlodipine versus placebo. An overview of placebo-controlled trials of calcium channel blockers in the general population [18], including the SYST-EUR trial and the PREVENT study, showed that, among patients assigned calcium channel blocker-based therapy, there were significant decreases in stroke, major cardiovascular events and cardiovascular death. However, there were no significant reductions in coronary heart disease, heart failure or total mortality, but the 95% confidence intervals did not exclude moderate advantages for patients assigned calcium channel blocker therapy [18]. In hypertensive patients, long-acting calcium channel blockers and diuretics have been reported to be equally effective in preventing overall cardiovascular complications [29,30]. That was found for both dihydropyridine (nifedipine) or non-dihydropyridine (diltiazem) calcium channel blockers. Recently, Motro and Shemesh [31] reported that the calcium channel blocker nifedipine slows the progression of coronary calcification in hypertensive patients when compared with the effect of diuretics.

Concern has been aroused about short-acting dihydropyridine derivatives, since they may increase the risk of cardiovascular events in patients with coronary heart disease or Type II (non-insulin-dependent) diabetes mellitus and hypertension [32,33]. A recent meta-analysis of randomized controlled trials in the general population suggested that, compared with other types of antihypertensive drugs, patients assigned calcium channel blocker therapy had a significantly higher risk of acute myocardial infarction, congestive heart failure and major cardiovascular events. However, no significant difference could be observed for all-cause mortality [34].

Disturbances of calcium metabolism are more frequent in patients with end-stage renal disease than in the general population. Morbidity resulting from atherosclerotic lesions, ischemic heart disease and cardiomyopathy is high. There are several lines of evidence that abnormalities of serum calcium, or calcium × phosphate product, contribute to the risk of cardiovascular death in patients with end-stage renal disease [14,15,17]. Compared with the general population, the administration of calcium channel blockers may be more beneficial in patients with end-stage renal disease, because these drugs interfere directly with disturbed calcium metabolism.

There are some limitations concerning the present study. Retrospective studies might be influenced by treatment selection bias and problems with different comorbidities. Therefore retrospective analysis of data can generate hypotheses that should be tested in prospective studies. In our analysis we controlled for many known factors that may influence mortality in haemodialysis patients. We showed that calcium channel blockers significantly reduced mortality in patients with end-stage renal failure. Calcium channel blockers are commonly prescribed for hypertension, a condition that increases cardiovascular mortality. One would therefore imagine that prescription of calcium channel blockers indicates patients with increased risk. It should be noted that our analysis did not show similar results for other antihypertensive drugs, e.g. angiotensin-converting enzyme antagonists or β-blockers. In our present study, after controlling for known risk factors and potential confounders, calcium antagonists were found to reduce mortality in patients with end-stage renal failure. Further prospective studies are needed to confirm these results and to allow the formulation of therapeutic recommendations.

In a very recently published study [35], data from United States Renal Data System Dialysis Morbidity and Mortality Wave II were also analysed according to use of calcium channel blockers. The analysis showed that the use of a calcium channel blocker was associated with a 21% lower risk of total mortality in dialysis patients, confirming the results of our present study.

In conclusion, we have shown that increased age, a lower body mass index and smoking are significant predictors of death in patients with end-stage renal disease, whereas the use of calcium channel blockers was associated with a significant reduction of mortality.

REFERENCES