Cardiac Troponin T Predicts Mortality in Patients With End-Stage Renal Disease

Jutta Dierkes, PhD; Ute Domröse, MD; Sabine Westphal, MD; Andreas Ambrosch, MD; Hans-Peter Bosselmann, MD; Klaus Hinrich Neumann, MD; Claus Luley, MD

Background—Patients with end-stage renal disease have a high risk of premature death, mainly as the result of cardiovascular disease (CVD), which is not sufficiently explained by the conventional risk factors. We therefore prospectively investigated total mortality and cardiovascular events in 102 patients on hemodialysis and assessed the prognostic value of baseline disease status and laboratory variables including total homocysteine and cardiac troponin T.

Methods and Results—Patients were followed for 2 years or until their first event of CVD (for outcome variable cardiovascular events, n=33) or death (for outcome variable total mortality, n=28). Survival was computed by the Kaplan-Meier method. Cox proportional hazards model was used to determine independent predictors of CVD events or total mortality. Cardiac troponin T emerged as the most powerful predictor of mortality, resulting in an almost 7-fold risk increase at concentrations >0.10 ng/mL (hazard ratio 6.85, 95% CI 3.04 to 15.45). Total homocysteine level greater than median was also associated with mortality (hazard ratio 2.44, 95% CI 1.10 to 5.40). These hazard ratios did not change substantially after adjustment for other risk factors. Significant predictors for CVD events were baseline diabetes, cerebrovascular disease, serum glucose, and triglycerides. After adjustment, only glucose and triglycerides remained significantly related to CVD events (hazard ratio with 95% CI 1.33 [1.12 to 1.57] and 1.14 [1.04 to 1.26], respectively, for a 1-mmol/L increase in concentration).

Conclusions—We conclude that total homocysteine and particularly cardiac troponin T are important predictors of mortality in patients with end-stage renal disease, whereas other laboratory variables and baseline disease status have less prognostic value. (Circulation. 2000;102:1964-1969.)

Key Words: mortality ■ morbidity ■ cardiovascular diseases

End-stage renal disease (ESRD) occurs in ∼120 000 patients in Europe and in ∼500 000 patients worldwide. ESRD is associated with substantially reduced life expectancy,1 which has been estimated to be <50% of the life expectancy of a person of the same age but with normal renal function.2 The main causes of death in patients with ESRD are vascular disease and infections, accounting for ∼60% to 70% of deaths.3 Age and predialysis diseases such as diabetes mellitus or manifest atherosclerosis are believed to have a pronounced effect on survival time during hemodialysis therapy.3,4 Although these factors contribute to the prediction of survival, mortality rate remains high even in nondiabetic, young patients starting renal replacement therapy.5,6 It therefore remains a challenge to find markers allowing an improvement in risk assessment, diagnosis, and therapeutic outcome.

Two variables were recently suggested to be of predictive importance in these patients: total homocysteine (tHcy) and cardiac troponin T (cTNT), which are found to be elevated in 80% to 100% and 30% of the patients, respectively. Homocysteine is an amino acid of the methionine metabolism, and elevation of its plasma concentration has been shown to be predictive of cardiovascular disease (CVD) events in patients with ESRD.7,8 Troponin T is a constituent of the myocardium and is specifically released during myocardial damage and is then detectable in blood. The prognostic value of cTNT in patients with ESRD was recently investigated in small-scale studies but remained controversial.9,10 Therefore, we prospectively investigated these variables in 102 patients for 2 years. We assessed their prognostic values for total mortality and CVD events (fatal and nonfatal) in comparison to established risk factors.

Methods

Patients were included who had ESRD, treated by chronic intermittent hemodialysis at the outpatient Dialysis Center for ≥4 weeks. Only patients who were clinically stable at study entry were included into the study (no acute cardiovascular or other disease within 4 weeks before the study). Out of 112 patients treated with hemodialysis in the center at study entry, 102 (91%) were recruited. Reasons for exclusion were age >85 years (n=6) and unstable clinical status.
TABLE 1. Baseline Characteristics of Hemodialysis Patients

<table>
<thead>
<tr>
<th></th>
<th>102</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>50:52</td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>64±13</td>
</tr>
<tr>
<td>Duration of dialysis, mo</td>
<td>25 (3–86)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134±16</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77±8</td>
</tr>
<tr>
<td>No. who have ever smoked</td>
<td>45 (44%)</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>43 (42%)</td>
</tr>
<tr>
<td>Patients with baseline coronary heart disease</td>
<td>29 (28%)</td>
</tr>
<tr>
<td>Patients with baseline cerebrovascular disease</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Patients with baseline peripheral atherosclerotic disease</td>
<td>31 (30%)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.31±0.04</td>
</tr>
<tr>
<td>Erythropoietin treatment at baseline</td>
<td>77 (75%)</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.53±0.33</td>
</tr>
</tbody>
</table>

Values are mean±SD, n (%), or median (5th–9th percentiles).

Follow-Up
Patients were followed for 2 years. End points were first fatal or nonfatal CVD event or death from all causes. Outcome was recorded by the nephrologists of the dialysis center who were unaware of the results for tHcy, vitamins, cTnT, and lipoprotein(a) until the final outcome status was recorded. If a patient had changed dialysis center, information about CVD events or death was obtained from the dialysis center where the patient had been treated (9 patients). Four patients received a kidney transplant; these patients were followed until the date of transplantation and then censored. In total, 4 patients were censored for the outcome “total mortality,” all because of transplantation, and 21 patients were censored for the outcome “cardiovascular events,” including those censored because of transplantation (n=4) and patients who died of other causes without having a cardiovascular event (n=17).

Definition of Baseline Diseases
CVD at baseline was considered if the patient had had a myocardial infarction or unstable angina pectoris, if angiographically proven hemodynamically relevant stenosis (>50% of the luminal diameter) was present, or if the patient had undergone bypass surgery or angioplasty. Cerebrovascular disease was considered if the patient had a history of transient ischemic attacks, stroke verified by computer tomography, or carotid artery stenosis >70% verified by Doppler ultrasound. Peripheral vascular disease was diagnosed by intermittent claudication, combined with angiographically or sonographically proven stenosis of the major arteries of the lower limbs or ulcers caused by atherosclerotic stenosis or surgery for this disorder. Hypertension was defined either as use of antihypertensive drugs or a blood pressure >160/95 mm Hg.

Definition of Outcome Variables
Mortality
In case of death, the underlying cause and the date of death were noted. Causes of death were categorized as CVD (sudden death, myocardial infarction, heart failure, stroke, peripheral arterial disease), infections (pneumonia, sepsis, viral infections), tumors, and other causes. In 9 of 28 deaths (32%), the underlying cause of death was verified by autopsy. In all cases, the causes of death were verified by clinicians not involved in this study; however, in a few cases, the cause of death could not be established and was recorded as unknown.

Cardiovascular Events
Cardiac events were sudden death, acute myocardial infarction (AMI), newly observed unstable angina pectoris (UAP), or requirement for coronary bypass surgery or angioplasty. AMI was diagnosed if at least 2 of the following criteria were fulfilled: clinical status, elevated laboratory variables (heart enzymes, myoglobin), and ECG changes. Catheterization was performed in suspected AMI or UAP. Surgical revascularization was performed after AMI, in UAP, or after clinical signs detected by catheterization and if the patient’s general status was eligible for the procedure. Cerebrovascular events were stroke, ischemic insults, or newly diagnosed >70% stenosis of the extracranial carotid. Strokes and ischemic insults were always verified by CT. Peripheral atherosclerotic disease was diagnosed in occlusive peripheral disease stage IV according to Fontaine or by angiographically or sonographically detected >50% stenosis of the major arteries of the lower limbs.

All cardiovascular events were verified by clinicians not involved in the study.

Statistical Analysis
Values are presented as mean±SD or as median with 5th and 95th percentiles. In a first analysis, differences at baseline were investigated between those who had a new CVD event and those who remained without CVD within the follow-up period and between those who died and those who were alive after 2 years, with the Mann-Whitney U test used for skewed variables and the Student’s t test used for normally distributed variables. Discrete variables were compared by the χ² test. Observed survival was computed by the Kaplan-Meier method. Cox proportional-hazards regression analysis was used to examine the baseline variables that were predictive of total mortality and cardiovascular events. The models included those variables that showed significant differences in the univariate analyses. Adjustments were then made for baseline variables that were a priori considered to be important predictors of mortality and cardiovascular morbidity: age, time on dialysis, baseline diabetes, and cerebrovascular disease. Results are reported as relative risk (hazard ratios) with the respective 95% confidence interval. A probability value of 0.05 was considered to be significant, and all tests were 2-sided. All analyses were carried out with SPSS version 8.0.

Analytical Methods
Routine clinical-chemical variables were measured by standardized methods on autoanalyzers (Hitachi 747, Roche Diagnostics) at the start of the study.

Plasma tHcy was determined in EDTA-plasma at study entry with a high-performance liquid chromatography method with fluorescence detection. Test tubes were immediately cooled and centrifuged, and the plasma was separated from the blood cells within 30 minutes. The upper reference limit of tHcy is 15 μmol/L, based on the mean±2 SD in a healthy population. Vitamin B₁₂ and serum
Total Mortality

After a follow-up period of 2 years (104 weeks), 28 patients (14 men and 14 women) had died. CVD was the main cause of death (n=11, 39%), followed by infections (n=9, 32%). Other causes of death were tumors (n=2), unknown (n=3), and other causes (lung embolism, n=1; acute pancreatitis, n=1; and discontinuation of dialysis, n=1). CVD cases died of acute myocardial infarction (n=4), heart failure (n=5), stroke (n=1), and peripheral vascular disease (n=1).

In a crude analysis performed with the Mann-Whitney U test, there was no significant difference in age, time on dialysis, blood pressure, or any of the lipids or lipoproteins measured between patients who died and patients who survived. Significant lower concentrations of creatinine and albumin but higher concentrations of glucose, tHcy, and cTNT were measured in those who died compared with patients who survived (Table 2). Furthermore, significantly more patients with preexisting cerebrovascular disease and patients with diabetes mellitus (type 1 or 2) died during follow-up.

We calculated hazard ratios for total mortality by Cox regression modeling. In the univariate Cox regression model, creatinine, albumin, glucose, tHcy greater than the median (33.6 μmol/L), baseline diabetes and cerebrovascular disease, and cTNT were significantly associated with total mortality. After adjustment for age, time on dialysis, baseline diabetes and cerebrovascular disease, albumin, tHcy and cTNT were significantly associated with mortality (Table 2). Quartiles of tHcy were significantly associated with mortality (Table 4). The Figure shows the association of cTNT with survival.

Sensitivity and Specificity of cTNT

Cardiac troponin T concentrations >0.10 ng/mL were measured in 12 patients. Of these 12 patients, 10 died during the follow-up period. Out of 40 patients showing cTNT concentrations >0.04 ng/mL, 18 patients died. Thus, the sensitivity of elevated cTNT for predicting all-cause mortality was 83% at concentrations >0.10 ng/mL and 45% at concentrations >0.04 ng/mL. Out of those with nondetectable cTNT concentrations (n=17), all patients were alive after 2 years, leading to a specificity of 100%.
New Events of CVD
During the follow-up period of 104 weeks, 33 patients had ≥1 new fatal or nonfatal event of CVD (n = 14 coronary, n = 8 cerebrovascular, and n = 13 peripheral vascular events). Two patients had >1 event of CVD. In total, 18 of the 33 patients with CVD events died (n = 11 of CVD causes [n = 9 related to coronary heart disease], n = 5 of infections, n = 1 of a tumor, and n = 1 of an unknown cause).

There was no significant difference (by comparing the baseline data with the Mann-Whitney U test) between those with an event and those without an event with regard to age, time on dialysis, baseline coronary heart disease, tHcy and related variables, or cTNT. Significant differences were observed in triglyceride, glucose, and HDL-cholesterol levels. Higher HDL-cholesterol appeared to be protective. Patients with CVD event during follow-up had significantly more frequent baseline cerebrovascular disease and diabetes mellitus (type 1 or 2).

In the univariate Cox regression analysis, baseline diabetes, cerebrovascular disease, glucose, and triglycerides were associated with event-free follow-up. In the adjusted model, only glucose and triglycerides were significantly associated with event-free follow-up (Table 3).

If only fatal CVD events (n = 11) were included in the analysis, cTNT and glucose were strongly related to CVD mortality in the adjusted Cox regression model (hazard ratio [HR] 7.31 [1.85 to 28.83] for cTNT >0.05 ng/mL, HR 1.42 [1.08 to 1.87] for a 1-mmol/L increase of glucose, respectively), whereas albumin and tHcy greater than median were weakly related to CVD mortality (HR 0.77 [0.58 to 1.03] for a 2-g/L increase of albumin, HR 3.51 [0.89 to 14.02] for tHcy greater than median, respectively).

Discussion
This prospective study investigated predictors for CVD and total mortality in patients with ESRD. The analysis revealed that established risk factors for CVD, unlike in populations with normal renal function, were only weakly related to CVD.
events and total mortality. In contrast, tHcy and particularly cTNT were closely related to total mortality.

Total homocysteine has been shown to be related to CVD events in populations with normal renal function, to mortality in patients with coronary heart disease, and to CVD events in patients with non–insulin-dependent diabetes mellitus. Three prospective studies have shown that tHcy is associated with CVD events in dialysis or predialysis patients. In the present study, we did not observe an association between CVD events and tHcy but a strong and independent association with total mortality. The lack of association between tHcy and CVD in patients with ESRD is difficult to explain but may be due to a dominant interference of renal failure as the primary determinant of tHcy concentrations, thus superimposing potential atherogenic processes that link tHcy with CVD. On the other hand, tHcy elevations were associated with total mortality. Potential underlying mechanisms might be an association of tHcy with inadequate nutrition and consequent vitamin deficiencies, wasting, or infections, all of which can increase all-cause morbidity and mortality. A biological explanation may be the concomitant increase seen if cTNT exceeded 0.1 ng/mL.

A biological explanation may be the concomitant increase seen if cTNT exceeded 0.1 ng/mL. This association was independent of baseline heart disease. In fact, among 12 patients with cTNT levels >0.10 ng/mL, 10 had died within 2 years (sensitivity 83%), whereas all 17 patients with undetectable cTNT concentrations were still alive (specificity 100% at this cutoff).

The cTNTs were only recently introduced into routine diagnostic strategies, and their prognostic value is still under investigation. For patients with ESRD, 2 recent studies with limited sample sizes and observation periods indicate that elevated cardiac troponin levels predict mortality. This finding, however, could not be reproduced in a recent study by Möckel et al. Our data are obtained from a larger patient group and a longer observation period and confirms the association between elevated cTNT and mortality. Furthermore, it shows that the prognostic power grows considerably as the follow-up period is extended.

The specificity of cTNT in patients with ESRD has been questioned, arguing that elevated levels might be due to cross-reactivity with skeletal muscle troponin T. However, the expression of cTNT isoforms in skeletal muscle of patients with ESRD has also been discussed. Furthermore, the second-generation troponin T assay used in the present study does not show cross-reactivity with skeletal muscle troponin. The data therefore suggest that the cTNT elevations in 40% of the patients truly reflect minor myocardial damage regardless of whether heart disease has been diagnosed at baseline. Patients with minor myocardial damage may consequently be more susceptible to infections and other causes of death. The lack of association between cTNT and CVD events, on the other hand, is explained by the fact that only 42% of all CVD events were cardiac events and that the remaining 58% (peripheral or cerebral events) are unlikely to affect cTNT concentrations.

It should be noted that other established risk parameters were less useful in prediction of mortality or CVD events. These were the conventional lipid parameters, including lipoprotein(a), which had been proposed to be of prognostic value. Only CVD events were modestly associated with baseline glucose and triglycerides. However, this risk increase was substantially lower than the ~7-fold mortality risk increase seen if cTNT exceeded 0.1 ng/mL.

In conclusion, we observed a strong association of tHcy and, particularly, cTNT with all-cause mortality in patients with ESRD. Both deviations may be important for subsequent therapeutic strategies. tHcy can be reduced by vitamin supplementation. Nonetheless, even if tHcy concentrations cannot be normalized in patients with ESRD, vitamin supplementation may reduce mortality and morbidity. Concerning cTNT, preventive inhibition of platelet aggregation may be beneficial in analogy to patients with UAP. The clinical benefit of such approaches, however, remains to be proven.

References


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