The Antioxidant Acetylcysteine Reduces Cardiovascular Events in Patients With End-Stage Renal Failure

A Randomized, Controlled Trial

Martin Tepel, MD; Markus van der Giet, MD; Mario Statz; Joachim Jankowski, PhD; Walter Zidek, MD

Background—Patients with end-stage renal failure have increased oxidative stress and show elevated cardiovascular mortality. Whether increased cardiovascular events can be prevented by the administration of antioxidants is unknown.

Methods and Results—We evaluated the effects of acetylcysteine, a thiol-containing antioxidant, on cardiovascular events in patients undergoing hemodialysis. A prospective, randomized, placebo-controlled trial was conducted between October 1, 1999, and September 30, 2001, in 134 patients (76 male and 58 female) with a mean age of 62 ± 16 years (mean ± SD) who had been undergoing maintenance hemodialysis for a minimum of 3 months 3 times weekly in an ambulatory center. Median (range) follow-up was 14.5 (1 to 24) months. Patients were randomly assigned either to receive acetylcysteine (600 mg BID) or placebo. The primary end point was a composite variable consisting of cardiac events including fatal and nonfatal myocardial infarction, cardiovascular disease death, need for coronary angioplasty or coronary bypass surgery, ischemic stroke, peripheral vascular disease with amputation, or need for angioplasty. Secondary end points included each of the component outcomes, total mortality, and cardiovascular mortality. A total of 18 (28%) of the 64 hemodialysis patients assigned to acetylcysteine group and 33 (47%) of the 70 hemodialysis patients assigned to control group had a primary end point (relative risk, 0.60 [95% CI, 0.38 to 0.95], P = 0.03). No significant differences in secondary end points or total mortality were detected.

Conclusions—In hemodialysis patients, treatment with acetylcysteine (600 mg BID) reduces composite cardiovascular end points. (Circulation. 2003;107:992-995.)

Key Words: antioxidants ■ drugs ■ mortality

The mortality rate in patients with end-stage renal failure is substantially higher than in the general population, and deaths are mainly attributable to cardiovascular diseases.1–3 Patients undergoing dialysis have poor long-term survival after acute myocardial infarction.4 Elevated oxidative stress has been observed in patients with end-stage renal failure.5,6 Elevated oxidative stress has been related with increased cardiovascular risk in patients undergoing hemodialysis.7 Oxidative stress is greater in patients undergoing hemodialysis with cardiovascular disease compared with those without.8 There is accumulating evidence that antioxidative treatment might be beneficial by reducing oxidative stress. Acetylcysteine, a thiol-containing antioxidant, has been used successfully to ameliorate the toxic effects of ischemia-reperfusion syndromes of the heart, kidney, lung, and liver. Using rat hearts, it has been shown that direct scavenging of hydroxyl radicals by acetylcysteine ameliorates the reperfusion injury.9,10 It is thought that the activity of acetylcysteine is related to its action as a free-radical scavenger or as a reactive sulfhydryl compound that increases the reducing capacity of the cell and may thereby improve coronary and peripheral vascular function.11 On the assumption that reduction of oxidative stress might reduce cardiovascular events in hemodialysis patients, we investigated the effects of acetylcysteine (600 mg BID, orally) on cardiovascular events in hemodialysis patients in a prospective, randomized, placebo-controlled study.

Methods

Patients
We prospectively studied 134 patients with end-stage renal failure in a single hemodialysis center (76 male, 58 female; mean age, 62 ± 16 years [mean ± SD]; systolic blood pressure, 145 ± 20 mm Hg; diastolic blood pressure, 79 ± 9 mm Hg) who had been undergoing maintenance hemodialysis for a minimum of 3 months. The mean duration of hemodialysis was 36 ± 52 months. The cause of end-stage renal failure was diabetic nephropathy in 42 cases, nephrosclerosis in 32 cases, chronic glomerular nephritis in 20 cases, polycystic kidney disease in 9 cases, and other/unknown in 31 cases. All of the patients were routinely dialyzed for 4 to 5 hours 3 times weekly using biocompatible membranes with no dialyzer reuse. The dialysates used were bicarbonate-based. Kt/V values (the amount of plasma
cleared of urea divided by the urea distribution volume) was measured according to the formula $\text{Kt/V} = -\ln (R - 0.03) + (4 \times \text{R})$ where $R$ is the post/preplasma urea nitrogen ratio; $\text{UF}$ is the ultrafiltrate volume (liters) removed; and $W$ is the postdialysis weight (kg). Mean $\text{Kt/V}$ values were $1.4 \pm 0.3$.

**Study Protocol**

Recruitment began on October 1, 1999. Analysis included all end points occurring between October 1, 1999, and September 30, 2001. The study included men and women who had been undergoing maintenance hemodialysis for a minimum of 3 months. Patients known to be allergic to acetylcysteine or patients who did not give consent were excluded. None of the patients screened were excluded from the study. None of the patients consumed other antioxidants. Hemodialysis patients were randomly assigned either to receive acetylcysteine or placebo. Acetylcysteine was given orally at a dose of 600 mg twice daily. The local ethics committee approved the study, and all individuals gave written informed consent.

**Outcomes**

The primary end point was a composite variable consisting of cardiac events including fatal and nonfatal myocardial infarction, cardiovascular disease death, need for coronary angioplasty or coronary bypass surgery, ischemic stroke, peripheral vascular disease with amputation, or need for angioplasty. Nonfatal myocardial infarction was defined as the presence of at least 2 of the following criteria: chest pain of typical duration and intensity, increased cardiac enzyme concentrations (at least twice the upper limit of normal), and diagnostic electrocardiographical changes. Fatal myocardial infarction was defined as a death occurring within 24 hours of entering the hospital for myocardial infarction. Peripheral vascular disease was defined as the need for amputation attributable to ischemic disease or symptomatic peripheral vascular disease with need for angioplasty. 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 death. Deaths were classified by the treating physician and reviewed by a member of the medical monitoring committee independently of the end point analysis. Secondary outcomes included each of the individual component outcomes: fatal and nonfatal myocardial infarction, cardiovascular disease mortality (fatal myocardial infarction, fatal ischemic stroke, or sudden death), total mortality, ischemic stroke, and peripheral vascular disease.

**Baseline Data Collection**

Systolic and diastolic blood pressures were recorded, and blood samples were drawn before the patient’s usual hemodialysis session. Hemoglobin concentrations, serum creatinine concentrations, blood urea nitrogen concentrations, serum calcium concentrations, and serum phosphate concentrations were routinely analyzed. Nine months after the start of the study, we measured oxidized low-density lipoprotein in a subgroup of patients. Oxidized low-density lipoprotein was measured in plasma using nuclear magnetic resonance spectroscopy according to a recently published technique by our group.13

**Statistical Analysis**

Continuous data such as age, months of hemodialysis treatment, and biochemical data are reported as mean $\pm$ SD. Nonparametric Wilcoxon Mann-Whitney test was used to detect differences in continuous variables between the treatment groups. Frequency counts were calculated for categorical data such as treatment group, sex, specific medications, and diagnostic classifications. Differences in these categorical variables between the treatment groups were analyzed by Fisher’s exact test. Relative risk with 95% confidence intervals (95% CI) was calculated for primary and secondary end points. All analyses were based on the intention-to-treat principle. Survival curves comparing the effect of acetylcysteine treatment on primary composite end point were calculated by the Kaplan-Meier method. Analysis was repeated by Cox proportional-hazards regression with adjustment for age, baseline systolic and diastolic blood pressure, smoking, medications, and months of hemodialysis. Before starting the study, an estimate of the sample size had been made (GraphPad Instat, GraphPad Software). Assuming a control incidence rate of 0.30 over 24 months, the study had a 90% power to detect a relative risk of <0.6 in the occurrence of the primary outcome variable. At least 63 patients were needed in each group. Analyses were performed with GraphPad prism software (version 3.0, GraphPad Software) or SPSS software (release 8.0.0, SPSS). All statistical tests were two-sided.

**Results**

Recruitment began on October 1, 1999. Analysis included all end points occurring between October 1, 1999, and September 30, 2001. The study was conducted in 134 hemodialysis patients (76 male and 58 female) with a mean age of 62 $\pm$ 16 years (mean $\pm$ SD) who had been undergoing maintenance hemodialysis for a minimum of 3 months 3 times weekly. The study was designed to have 90% power to detect a 0.6 in the occurrence of the primary end point analysis with 63 patients needed in each group.

**TABLE 1. Baseline Characteristics of Patients Undergoing Hemodialysis by Treatment and Disorder**

<table>
<thead>
<tr>
<th></th>
<th>Acetylcysteine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>(n=64)</td>
<td>(n=70)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63 $\pm$ 14</td>
<td>62 $\pm$ 18</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>31 (48)</td>
<td>27 (39)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.7 $\pm$ 4.3</td>
<td>22.6 $\pm$ 4.0</td>
</tr>
<tr>
<td>Renal disease, n (%)</td>
<td>18 (28)</td>
<td>24 (34)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>16 (25)</td>
<td>16 (23)</td>
</tr>
<tr>
<td>Chronic glomerular nephritis</td>
<td>9 (14)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>5 (8)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Months of hemodialysis</td>
<td>26 $\pm$ 20</td>
<td>23 $\pm$ 15</td>
</tr>
<tr>
<td>Hemodialysis adequacy, Kt/V</td>
<td>1.5 $\pm$ 0.3</td>
<td>1.4 $\pm$ 0.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>143 $\pm$ 21</td>
<td>146 $\pm$ 18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 $\pm$ 8</td>
<td>78 $\pm$ 9</td>
</tr>
<tr>
<td>Present smoker (%)</td>
<td>8 (13)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Disease prevalence at baseline (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (28)</td>
<td>24 (34)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (41)</td>
<td>28 (40)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>10 (16)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>8 (13)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.9 $\pm$ 1.2</td>
<td>10.4 $\pm$ 1.4</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>8.0 $\pm$ 2.2</td>
<td>7.6 $\pm$ 2.9</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>71 $\pm$ 18</td>
<td>68 $\pm$ 18</td>
</tr>
<tr>
<td>Serum calcium, mmol/L</td>
<td>2.3 $\pm$ 0.3</td>
<td>2.3 $\pm$ 0.3</td>
</tr>
<tr>
<td>Serum phosphate, mmol/L</td>
<td>1.9 $\pm$ 0.7</td>
<td>1.7 $\pm$ 0.8</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>175 $\pm$ 41</td>
<td>177 $\pm$ 51</td>
</tr>
</tbody>
</table>

Continuous data are shown as mean $\pm$ SD. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. There were no significant differences between the groups ($P>0.05$ for all comparisons).
an ambulatory center. Median (range) follow-up was 14.5 (1 to 24) months. The baseline demographic, clinical, and laboratory characteristics of the hemodialysis patients are described in Table 1. There were no significant differences in baseline characteristics (age, sex, body-mass index, renal disease, months of hemodialysis, hemodialysis adequacy, systolic and diastolic blood pressure, smoking status, biochemical data, and medications) between the groups (P > 0.05 for all comparisons). Three patients (5%) in the acetylcysteine group and 5 patients (7%) in the control group had a history of coronary bypass surgery. Seven patients (11%) in the acetylcysteine group and 5 patients (7%) in the control group had a history of coronary angioplasty.

### Primary Outcomes

The effects of acetylcysteine treatment on outcome in hemodialysis patients are summarized in Table 2. The Kaplan-Meier survival curves for the primary end point are shown in the Figure. A total of 51 primary end points occurred during the follow-up, 18 in the acetylcysteine group and 33 in the control group (relative risk, 0.60 [95% CI, 0.38 to 0.95], P = 0.03). The patients in the acetylcysteine group had a risk of reaching the primary end point that was 40% lower compared with the control group.

Analysis was repeated by Cox proportional-hazards regression with adjustment for age, baseline systolic and diastolic blood pressure, smoking, medications, and months of hemodialysis. The Cox proportional-hazards regression model showed that survival to the primary end point was greater in the acetylcysteine group compared with the control group (adjusted relative risk, 0.47 [95% CI, 0.27 to 0.84], P = 0.01).

### Secondary Outcomes

A total of 28 deaths occurred during the follow-up, 14 in the acetylcysteine group and 14 in the control group (relative risk, 1.09 [95% CI, 0.57 to 2.11], P = 0.83). A total of 17 cardiovascular disease deaths (including fatal myocardial infarction, fatal ischemic stroke, and sudden death) occurred during the follow-up, 9 in the acetylcysteine group and 8 in the control group (relative risk, 1.23 [95% CI, 0.51 to 3.00], P = 0.80). A total of 10 fatal myocardial infarctions occurred during the follow-up, 4 in the acetylcysteine group and 6 in the control group (relative risk, 0.73 [95% CI, 0.22 to 2.47], P = 0.74).

A total of 23 cardiac events, including fatal and nonfatal myocardial infarction and need for coronary angioplasty or coronary bypass surgery, occurred during the follow-up, 9 in the acetylcysteine group and 14 in the control group (relative risk, 0.70 [95% CI, 0.33 to 1.51], P = 0.49). A total of 9 ischemic strokes occurred during the follow-up, 2 in the acetylcysteine group and 7 in the control group (relative risk, 0.31 [95% CI, 0.07 to 1.45], P = 0.17). A total of 19 peripheral vascular disease occurred during the follow-up, 7 in the acetylcysteine group and 12 in the control group (relative risk, 0.64 [95% CI, 0.27 to 1.52], P = 0.33). Five patients (8%) reported gastrointestinal discomfort during treatment with acetylcysteine. No major side effects were observed.

As a marker of oxidant stress we measured plasma oxidized low-density lipoprotein in a subgroup of patients from each group using nuclear magnetic resonance spectroscopy. Oxidized LDL was significantly lower in the acetylcysteine group compared with the control group (0.13 ± 0.22 arbitrary units [n = 16] versus 0.55 ± 0.14 arbitrary units [n = 10], P < 0.01). These data may indicate that the reduction of oxidative stress in the acetylcysteine group may be beneficial.

### Discussion

The main finding of the present study is that in hemodialysis patients, treatment with acetylcysteine reduces composite

![Kaplan-Meier survival curves from primary end points. Hemodialysis patients were randomly assigned either to receive acetylcysteine (ACC, 600 mg BID) or placebo (control group). The primary end point was a composite variable consisting of cardiac events including fatal and nonfatal myocardial infarction, cardiovascular disease death, need for coronary angioplasty or coronary bypass surgery, ischemic stroke, peripheral vascular disease with amputation, or need for angioplasty. Relative risk, 0.60 (95% CI, 0.38 to 0.95), P = 0.03.](Image)
cardiovascular end points. Cardiovascular diseases are the most important cause of death in all stages of renal failure. Among patients undergoing dialysis, cardiovascular deaths account for ≈50% of total mortality. Given this eminent importance of renal insufficiency as a risk factor of cardiovascular disease, many attempts have been made to shed light on the mechanisms by which renal failure affects cardiovascular survival so gravely. It became apparent that in renal failure several risk factors for cardiovascular disease coincide, which partly differ from those present in the general population, including anemia and increased oxidative stress. Among those risk factors, oxidative stress has been identified as one important cause of vascular injury in several studies. Although oxidative stress seems to be operative also in atherosclerotic disease in unselected populations, it has been documented that oxidative stress is markedly increased in renal failure. Several products of oxidative metabolism have been reported to accumulate in renal failure. Advanced glycation end products such as pentosidine or advanced oxidation protein products have been studied. A variety of mechanisms have been proposed, by which oxidation products elicit vascular injury. Oxidized low-density lipoproteins are known to accumulate in the arterial intima, inducing several initial steps of atherogenesis. By the reaction of nitric oxide with reactive oxygen species, peroxynitrite is generated, which in turn exhibits several unfavorable vascular actions, and the availability of nitric oxide is reduced. Last, the increased production of advanced glycation end products adds to the atherogenic potential of renal insufficiency.

On this background, the beneficial effects of acetylcysteine on cardiovascular events might be explained. Acetylcysteine is a sulfhydryl compound that introduces additional reductive capacity into the oxidoreductive metabolism. Recently, beneficial cardiovascular effects have been reported in hemodialysis patients treated with another antioxidant, vitamin E. There is some evidence that other medications, eg, angiotensin-converting enzyme inhibitors or lipid-lowering agents, were not significantly different between the 2 groups in the present study. In addition, Cox proportional-hazards regression with adjustment for age, baseline systolic and diastolic blood pressure, smoking, medications, and months of hemodialysis showed that survival to the primary end point was greater in the acetylcysteine group compared with the control group. In the study, although cardiac events were reduced by 30%, ischemic stroke was reduced by 69%, and peripheral vascular disease was reduced by 36% in the acetylcysteine group, neither of these secondary end point reductions was significant. The study was not designed to detect a reduction in myocardial infarction as individual end point and lacked the power to do so. Additional studies with larger sample size may be warranted to confirm the present results. One limitation of the present study is that it was not blinded. The study design, however, did allow us to make acetylcysteine-specific inferences.

Presently, the excess cardiovascular mortality in patients with end-stage renal failure continues to be an unmet challenge in cardiovascular medicine. Therefore, several approaches to reduce premature atherosclerosis in patients with end-stage renal failure will have to be tested for efficacy and practicability. In conclusion, the administration of the antioxidant, acetylcysteine, reduces composite cardiovascular end points in hemodialysis patients.

References

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