Low Plasma \(\alpha\)-Tocopherol Concentrations and Adverse Clinical Outcomes in Diabetic Hemodialysis Patients

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Summary

Background and objectives Trials with the antioxidant vitamin E have failed to show benefit in the general population. Considering the different causes of death in ESRD, this study investigated the association between plasma concentrations of \(\alpha\)-tocopherol and specific clinical outcomes in diabetic hemodialysis patients.

Design, settings, participants, & measurements In 1046 diabetic hemodialysis patients (participants of the German Diabetes and Dialysis Study), \(\alpha\)-tocopherol was measured in plasma by reversed-phase HPLC. By Cox regression analyses, hazard ratios were determined for prespecified end points according to baseline plasma \(\alpha\)-tocopherol levels: sudden death \((n=134)\), myocardial infarction \((n=172)\), stroke \((n=89)\), combined cardiovascular events \((n=398)\), fatal infection \((n=107)\), and all-cause mortality \((n=508)\).

Results Patients had a mean age of 66±8 years, and mean plasma \(\alpha\)-tocopherol level was 22.8±9.6 \(\mu\)mol/L. Levels of \(\alpha\)-tocopherol were highly correlated to triglycerides \((r=0.63, P<0.001)\). Patients in the lowest \(\alpha\)-tocopherol quartile had (in unadjusted analyses) a 79% higher risk of stroke and a 31% higher risk of all-cause mortality compared with patients in the highest quartile. The associations were attenuated after adjustment for confounders (hazard ratio\(_{stroke}=1.56\), 95% confidence interval=0.75–3.25; hazard ratio\(_{mortality}=1.22\), 95% confidence interval=0.89–1.69, respectively). There was no association between \(\alpha\)-tocopherol and myocardial infarction, sudden death, or infectious death.

Conclusions Plasma \(\alpha\)-tocopherol concentrations were not independently associated with cardiovascular outcomes, infectious deaths, or all-cause mortality in diabetic hemodialysis patients. The lack of association can partly be explained by a confounding influence of malnutrition, which should be considered in the planning of trials to reduce cardiovascular risk in dialysis patients.


Introduction

In patients undergoing maintenance dialysis, the rate of death is excessive and similar to the mortality rate of cancer (1,2). Major risk factors that affect adverse outcomes in dialysis patients include increased levels of cytokines, endothelial dysfunction, and oxidative stress causing damage to lipids, proteins, and DNA. Vitamin E derived from the diet, which is largely present as \(\alpha\)-tocopherol in human plasma and tissues, is a powerful lipid-soluble antioxidant (3). In this context, vitamin E supplementation is considered to provide benefits in the prevention of diseases, which are associated with oxidative stress by reducing the production of reactive species and membrane lipid peroxidation (4). In contrast to observational studies, large interventional trials failed so far to show a clinically relevant benefit of vitamin E supplementation on cardiovascular outcome (5,6). Similarly, the role of vitamin E in hemodialysis patients is not fully understood. One trial including 196 dialysis patients did not show a survival benefit of vitamin E supplementation during 1.5 years of follow-up, but it showed a reduction in the composite cardiovascular end point (7).

In this context, it has to be considered that the relative contribution of different causes of death to total mortality differs in advanced stages of CKD compared with the general population (8–11). Although myocardial infarction represents the most frequent cause of death in the general population, sudden cardiac death (SCD) is the major occurring event in dialysis patients (2), which as a single cause, accounts for one quarter of all deaths (2,8). Furthermore, the length of follow-up plays a major role, because short-term mortality in dialysis patients is differently affected than long-term mortality. Regarding the lack of therapeutic interventions to improve the excess mortality in dialysis patients, vitamin E remains an intriguing perspective. In addition to its antioxidant functions, vitamin E also shows additional (nonantioxidant) properties as a signaling molecule or a regulator of gene expression (3,12). Antithromboatherogenic properties of vitamin E, like the inhibition of monocyte–endothelial cell adhesion as well as platelet adhesion and aggregation,
specifically support the potential role in reducing atheroembolic events, such as ischemic stroke.

Data on the relation between vitamin E levels with stroke and other specific cardiovascular events are lacking for hemodialysis patients, and they are needed to develop potential interventional strategies. We used data from the German Diabetes and Dialysis Study (4D study), which investigated the effect of lipid-lowering treatment in 1255 diabetic hemodialysis patients. Atorvastatin (20 mg daily) during a median of 4 years follow-up did not significantly reduce the primary end point of combined cardiovascular events or mortality. Hence, we investigated the association of plasma α-tocopherol concentrations as a major part of vitamin E with stroke and other cardiovascular and fatal events in the large, well characterized 4D study population of 1255 diabetic hemodialysis patients (13).

Methods

Study Design and Participants

The 4D study methodology has previously been reported in detail (14). Briefly, the 4D study was a prospective, randomized, controlled trial investigating atorvastatin in 1255 patients with type 2 diabetes mellitus ages 18–80 years on hemodialysis for less than 2 years. Between March of 1998 and October of 2002, patients were recruited in 178 dialysis centers in Germany. At each follow-up visit until the end of the study in March of 2004, a fasting blood sample was taken, an electrocardiogram was performed, and clinical information, including adverse events, was recorded.

Definition of End Points

The primary end point of the 4D study was defined as a composite of cardiac death, nonfatal myocardial infarction (MI), and stroke, whichever occurred first (combined cardiovascular events [CVEs]). Stroke was defined as a neurologic deficit lasting longer than 24 hours. Computed tomographic or magnetic resonance imaging was available in all but 16 cases. SCD was considered as death verified by terminal rhythm disorders in an electrocardiogram; death observed within 1 hour after onset of cardiac symptoms by witnesses; death confirmed by autopsy; or unexpected death, presumably or possibly of cardiac origin and in the absence of a potassium level ≤7.5 mmol/L before the start of the three most recent hemodialysis sessions. MI was diagnosed when at least two of three criteria were met: typical symptoms; elevated levels of cardiac enzymes; and diagnostic changes in the electrocardiogram. 4D study end points were centrally adjudicated by three members of the end point committee blinded to study treatment and according to predefined criteria.

For the present analysis, stroke, SCD, MI, CVE, death caused by infection, and all-cause mortality were chosen to be separate outcome measures and based on the primary judgment of the end point committee during the 4D study. The study was approved by the responsible medical ethical committees, and all patients gave their written informed consent before inclusion.

Data Collection

Information on age, sex, and smoking status was obtained through patient interviews. Comorbidities, including the presence of coronary artery disease (CAD) and congestive heart failure as well as the duration of diabetes mellitus and dialysis treatment were reported by the patients’ nephrologists. CAD was defined by a history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention, and presence of CAD, as documented by angiography. Congestive heart failure was defined according to the classification system of the New York Heart Association.

Analytical Determination of α-Tocopherol

α-Tocopherol concentrations were measured in plasma samples taken at baseline. The plasma samples of the 4D study were immediately frozen and stored at −80°C until analysis. They were transported with dry ice to the analytical center. All blood samples were taken before the start of dialysis sessions and administration of drugs.

Plasma α-tocopherol, being stable at −80°C for at least 2.3–15 years, was determined using a modified gradient reversed-phase HPLC system (Waters, Eschborn, Germany) after organic extraction as previously described (15). Results were compared with standard reference material (968a fat-soluble vitamins in human serum; National Institute of Standards and Technology, Gaithersburg, USA). The detection limit for plasma α-tocopherol was 2.0 ng, the coefficient of variation was 4%, and the recovery rate was above 95%.

Statistical Analyses

Patient characteristics are presented according to quartiles (Qs) of plasma α-tocopherol levels (Q1: <18.3, Q2: 18.3–22.8, Q3: 22.8–29.1, Q4: ≥29.1 μmol/L). We performed correlation analyses of α-tocopherol with clinical and nutritional parameters. Then, we determined associations of α-tocopherol concentrations with the clinical outcomes stroke, sudden death, MI, combined cardiovascular events, and infectious and all-cause deaths. These associations were assessed with α-tocopherol as a continuous variable (per SD) and in the categorical approach using Qs. Kaplan–Meier estimates were calculated, and relative risks were derived from Cox regression analyses (i.e., hazard ratios [HRs] and corresponding 95% confidence intervals). The Cox regression analyses were adjusted for confounders. The adjusted model 1 included age and sex, model 2 additionally included body mass index (BMI), levels of phosphate, glycated hemoglobin, albumin, and LDL cholesterol, and model 3 also included triglycerides (main model). Adjustments for confounders were performed in line with epidemiologic and statistical recommendations; in case of linearity, such as for triglycerides and total cholesterol, sensitivity analyses investigated adjustment for total cholesterol in separate models. We performed additional Cox regression analyses with inclusion of potential intermediate variables, including arrhythmia and C-reactive protein (CRP). Finally, analyses were performed investigating potential interaction of plasma α-tocopherol status with atorvastatin in the association with outcomes. Regarding stroke, subtypes of ischemic and hemorrhagic stroke were investigated as well as potential interaction by previous history of cerebrovascular events.

All P values are reported as two-sided. Analyses were performed using SPSS version 16.0.
Results

Patient Characteristics

Between March of 1998 and October of 2002, 1255 patients were included in the 4D study. The mean follow-up period was 4.0 years (median=4.0 years) on atorvastatin and 3.9 years (median=4.08 years) on placebo. A total of 1046 patients had an α-tocopherol measurement at baseline. Of those patients, 508 patients died during follow-up: 134 patients died of SCD, and 107 patients died because of infection. A total of 398 patients had CVEs, with MI and stroke occurring in 172 and 89 patients, respectively. Of all strokes, 70 strokes were of ischemic origin, and 8 strokes were hemorrhagic. A total of 843 patients had no history of cerebrovascular events, and 201 patients did have a history of cerebrovascular events in the past.

Mean age of the patients was 66±8 years, and mean α-tocopherol at baseline was 22.8±9.6 μmol/L. Patients' baseline characteristics are shown in Table 1. In correlation analyses, plasma concentrations of α-tocopherol were strongly related to concentrations of triglycerides (Spearman correlation coefficient r=0.63, P<0.001), cholesterol (r=0.61, P<0.001), LDL cholesterol (r=0.29, P<0.001), HDL cholesterol (r=−0.26, P<0.001), and BMI (r=0.15, P<0.001). Coefficients for the correlation of α-tocopherol with additional...
parameters were phosphate ($r=0.08, P=0.006$), HbA1c ($r=0.09, P=0.004$), CRP ($r=0.08, P=0.01$), albumin ($r=0.06, P=0.06$), and asymmetric dimethylarginine (ADMA; $r=-0.13, P<0.001$).

**α-Tocopherol Status and Risk of Cerebrovascular Events**

Patients of the lowest α-tocopherol quartile had, in unadjusted analyses, a 79% higher risk of stroke compared with patients of the highest quartile (HR=1.79, 95% confidence interval [CI]=1.02–3.13) (Table 2). Adjustments for the confounders age, sex, BMI, levels of phosphate, glycated hemoglobin, albumin, and LDL cholesterol revealed an HR for the first versus fourth quartile of 2.38 (95% CI=1.30–4.36) and additional adjustment for triglycerides attenuated the association (HR=1.56, 95% CI=0.75–3.25; main model).

Of note, concerning the strong correlation between α-tocopherol and triglycerides as well as between α-tocopherol and total cholesterol as mentioned above, separate sensitivity analyses were performed. They revealed that adjustment for total cholesterol likewise attenuated the association similar to triglycerides. Additional adjustment for CRP and arrhythmia did not meaningfully change the results. The results of the analyses using α-tocopherol as a continuous variable are shown in Table 2, and they revealed no association between α-tocopherol and stroke after full adjustment and inclusion of triglycerides (model 3). We also performed stratified analyses according to stroke subtype and previous history of CVEs. Because of the limited number of events in the subgroup analyses, we restricted the adjustments to age and sex (Table 2). To test the robustness of our results, all analyses were repeatedly stratified by atorvastatin treatment. These analyses revealed similar results, indicating no interaction between α-tocopherol and stroke outcomes.

**α-Tocopherol Status, Total Mortality, and Additional Adverse Clinical Outcomes**

Patients of the lowest α-tocopherol quartile had, in unadjusted analyses, a 31% higher risk of all-cause mortality compared with patients of the highest quartile (HR=1.31, 95% CI=1.03–1.69). The associations were attenuated after full adjustment for confounders (HR=1.22, 95% CI=0.89–1.69). In analyses using α-tocopherol as a continuous variable, the risk of mortality was lower by 9% per 1 SD increase in α-tocopherol plasma concentration (HR=0.91, 95% CI=0.83–0.99) (Table 3). Similarly, the associations were neutralized after controlling for confounders. There were no significant associations with sudden death, MI, or combined cardiovascular events. Investigating the specific noncardiovascular outcome of deaths caused by infection, no significant associations were found. In addition, we investigated potential influence by study treatment but did not find any significant interaction.

**Discussion**

We analyzed data from 1046 hemodialysis patients with type 2 diabetes mellitus who took part in the 4D study and experienced a high incidence of prespecified and centrally adjudicated end points. In the present analysis, baseline plasma α-tocopherol concentrations were not independently associated with stroke, additional specific cardiovascular outcomes, infectious deaths, or all-cause mortality. α-Tocopherol was highly correlated to triglycerides. Adjustment for triglycerides in addition to common confounders mainly explained the lack of an association between α-tocopherol and stroke.

Stroke is a major cause of cognitive and functional impairment, and it considerably contributes to a reduced quality of life and death in dialysis patients. A recent study in dialysis patients in the United States showed that the age-adjusted risks for clinical stroke were 6.1- and 9.7-fold higher in white men and women on dialysis, respectively, than men and women from the general population (16).

The Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease trial investigated the effect of vitamin E supplementation in secondary prevention (7) in 196 dialysis patients with prevalent cardiovascular or cerebrovascular disease. The investigators found no significant effect of vitamin E supplementation on newly occurring strokes. In our study, patients had a significant burden of cardiovascular disease (about one third of these patients had CAD at baseline). Similarly, we found no significant association between α-tocopherol and stroke. This finding is also in line with the findings of most large interventional trials that failed, so far, to show a clinically relevant benefit of vitamin E supplementation on cardiovascular outcome in non-ESRD patients (5,6). The meta-analysis in the work by Bin et al. (17), including 13 randomized trials, could not show a statistically significant benefit of vitamin E supplementation in the prevention of stroke.

Importantly, plasma α-tocopherol was highly correlated to triglycerides. Because of its hydrophobic character, α-tocopherol cannot distribute as a free monomer in the blood, and it depends, therefore, on the association with lipoproteins. Consequently, the α-tocopherol metabolism shares similar features with lipoprotein metabolism and cholesterol transport. LDL enables the transport of lipophilic compounds, such as α-tocopherol, to the peripheral tissues. The lipid content of LDL is around 80%, with a high amount of triglycerides. Therefore, a close association between α-tocopherol and triglycerides is reasonable (18).

Of interest, adjustment for triglycerides was the main mechanism by which the associations of plasma α-tocopherol with stroke outcomes were attenuated. In this context, protein malnutrition may be of major importance. This finding is supported by the fact that adjustment for total cholesterol similarly attenuated the associations in the sensitivity analyses. Variations in dietary intake of micronutrients rarely occur in isolation. Low protein and energy intake is especially common in dialysis patients, and it may be accompanied by inadequate ingestion of antioxidant vitamins (19).

This result is supported by our finding that α-tocopherol was also significantly correlated to BMI and—to a lesser extent—phosphate as nutritional parameters. It is, therefore, difficult to dissect potential confounding by a low dietary intake of micronutrients in the association with stroke from effects attributable to α-tocopherol.

Furthermore, we found no association between α-tocopherol and MI, sudden or infectious death, and all-cause mortality. This finding is in contrast to our expectation based on previous studies, which suggested beneficial effects of α-tocopherol, particularly with regard to inflammation.
Table 2. Risk (hazard ratio and 95% confidence interval) of stroke and subtypes of stroke by quartiles of baseline α-tocopherol (study population \( n = 1046 \))

<table>
<thead>
<tr>
<th></th>
<th>Stroke(^a)</th>
<th>Stroke in Patients without History of Cerebrovascular Events(^b)</th>
<th>Stroke in Patients with History of Cerebrovascular Events(^c)</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
</tr>
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<tbody>
<tr>
<td><strong>Number of events</strong></td>
<td>89</td>
<td>63</td>
<td>26</td>
<td>70</td>
<td>8</td>
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<tr>
<td><strong>Number of study subjects</strong></td>
<td>1046</td>
<td>845</td>
<td>201</td>
<td>1046</td>
<td>1046</td>
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<tr>
<td><strong>α-Tocopherol</strong></td>
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<tr>
<td><strong>Crude</strong></td>
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<tr>
<td>Q1</td>
<td>1.79 (1.02–3.13)</td>
<td>2.66 (1.30–5.47)</td>
<td>0.59 (0.23–1.51)</td>
<td>2.50 (1.27–4.94)</td>
<td>0.79 (0.13–4.79)</td>
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<td>Q2</td>
<td>1.01 (0.54–1.88)</td>
<td>1.78 (0.83–3.80)</td>
<td>0.17 (0.04–0.64)</td>
<td>1.26 (0.59–2.70)</td>
<td>0.66 (0.11–3.95)</td>
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<tr>
<td>Q3</td>
<td>0.89 (0.47–1.71)</td>
<td>1.29 (0.57–2.92)</td>
<td>0.33 (0.11–1.00)</td>
<td>1.40 (0.66–2.95)</td>
<td>0.37 (0.04–3.59)</td>
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<tr>
<td>Q4</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td><strong>Adjusted 1</strong></td>
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<tr>
<td>Q1</td>
<td>2.04 (1.15–3.64)</td>
<td>2.91 (1.41–6.01)</td>
<td>0.62 (0.24–1.60)</td>
<td>2.70 (1.36–5.35)</td>
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<tr>
<td>Q2</td>
<td>1.14 (0.61–2.15)</td>
<td>1.94 (0.91–4.17)</td>
<td>0.17 (0.05–0.66)</td>
<td>1.33 (0.62–2.84)</td>
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<tr>
<td>Q3</td>
<td>0.88 (0.45–1.71)</td>
<td>1.28 (0.56–2.90)</td>
<td>0.34 (0.11–1.01)</td>
<td>1.38 (0.65–2.92)</td>
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<td>Q4</td>
<td>Reference</td>
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<td><strong>Adjusted 2</strong></td>
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<tr>
<td>Q1</td>
<td>2.38 (1.30–4.36)</td>
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<tr>
<td>Q2</td>
<td>1.23 (0.65–2.34)</td>
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<tr>
<td>Q3</td>
<td>0.90 (0.46–1.75)</td>
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<td>Q4</td>
<td>Reference</td>
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<tr>
<td><strong>Adjusted 3</strong></td>
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<tr>
<td>Q1</td>
<td>1.56 (0.75–3.25)</td>
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<tr>
<td>Q2</td>
<td>0.87 (0.43–1.79)</td>
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<td>Q3</td>
<td>0.72 (0.36–1.45)</td>
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<td>Q4</td>
<td>Reference</td>
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<tr>
<td><strong>α-Tocopherol as continuous variable (per SD)</strong></td>
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<tr>
<td><strong>Crude</strong></td>
<td>0.79 (0.62–1.00)</td>
<td>0.66 (0.49–0.90)</td>
<td>1.19 (0.85–1.65)</td>
<td>0.71 (0.53–0.94)</td>
<td>1.05 (0.54–2.04)</td>
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<tr>
<td><strong>P value</strong></td>
<td>0.05</td>
<td>0.008</td>
<td>0.31</td>
<td>0.02</td>
<td>0.88</td>
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<tr>
<td><strong>Adjusted 1</strong></td>
<td>0.75 (0.58–0.96)</td>
<td>0.64 (0.47–0.86)</td>
<td>1.17 (0.83–1.63)</td>
<td>0.68 (0.51–0.91)</td>
<td>1.01 (0.52–1.99)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.02</td>
<td>0.004</td>
<td>0.37</td>
<td>0.01</td>
<td>0.97</td>
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<tr>
<td><strong>Adjusted 2</strong></td>
<td>0.72 (0.56–0.94)</td>
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<tr>
<td><strong>P value</strong></td>
<td>0.01</td>
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<tr>
<td><strong>Adjusted 3</strong></td>
<td>0.87 (0.63–1.21)</td>
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<tr>
<td><strong>P value</strong></td>
<td>0.42</td>
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</table>

Quartiles (Q) of α-tocopherol: Q1: <18.3 (\( n = 261 \)), Q2: ≥18.3 and <22.8 (\( n = 263 \)), Q3: ≥22.8 and <29.1 (\( n = 261 \)), Q4: ≥29.1 (\( n = 261 \)) μmol/L. Adjusted 1, analyses were adjusted for age and sex; adjusted 2, analyses were additionally adjusted for body mass index, albumin, phosphate, HbA1c, and LDL cholesterol; adjusted 3, in addition to all the parameters mentioned above, analyses were also adjusted for triglycerides.

\(^a\)Stroke (\( n = 89 \)) consisted of the following subtypes: ischemic (\( n = 70 \)), hemorrhagic (\( n = 8 \)), and unknown type (\( n = 11 \)).

\(^b\)The numbers of study subjects in the respective quartiles of this subanalysis were Q1, 209; Q2, 207; Q3, 209; and Q4, 220.

\(^c\)The numbers of study subjects in the respective quartiles of this subanalysis were Q1, 52; Q2, 56; Q3, 52; and Q4, 41.
In fact, we also found an inverse signifi-
cant nitric oxide (NO) availability by vitamin E in renal pa-
tients. Lower ADMA levels in CKD patients, implying in-
creased CEHC in both hemodialysis patients and healthy sub-
cjects. Supplementation of tocopherols leads to an increase of serum
carboxyethyl-hydroxychroman (CEHC) levels (20).

Investigations have shown a changed vitamin E metab-
olism in hemodialysis patients indicated by accumulating
carboxyethyl-hydroxychroman (CEHC) levels (20–22). Sup-
plementation of tocopherols leads to an increase of serum
CEHC in both hemodialysis patients and healthy subjects
and decreased CRP concentrations in hemodialysis patients
(22,23). Thus, the accumulation of CEHC in hemodialysis
patients may reflect anti-inflammatory functions contribut-
ing to the protective effects, which were shown in previous
investigations dealing with vitamin E in hemodialysis pa-
tients (7,24–26). Furthermore, one study by Saran et al. (27)
showed that antioxidant therapy with vitamin E resulted in
lower ADMA levels in CKD patients, implying increased
nitric oxide (NO) availability by vitamin E in renal patients.
In fact, we also found an inverse significant association be-
tween α-tocopherol and ADMA, suggesting a putative role
of this mechanism. Apart from this finding, it was shown that supplementation of vitamin E decreased the release of
superoxide anion, proinflammatory IL-1β secretion, lipid
oxidation, and monocyte–endothelial cell adhesion in mono-
cytes of healthy individuals (28,29). Vitamin E supplemen-
tation was found to be associated with the inhibition of proatherogenic events and stabilization of atherosclerotic
plaque (30). However, we acknowledge that experimental
results or findings from clinical observations in other pa-
tient populations cannot be extrapolated, particularly when surrogate end points had been investigated. Our cohort
represented a large population of diabetic patients under-
going hemodialysis with assessment of hard outcomes. Di-
abletic patients on hemodialysis have a higher comorbidity
and poorer outcome compared with nondiabetic patients on
dialysis (2), which is reflected by a 5-year survival of only
35% (31). Malnutrition as a key problem in these patients is
part of the wasting syndrome, characterized by loss of body
weight, low protein-energy stores, muscle loss, and low
concentrations of albumin and other proteins (32). In a pa-
tient group such as our cohort, the wasting situation may
even be aggravated, because diabetes mellitus is known to
independently promote muscle protein breakdown (33,34).

Thus, malnutrition with accompanied low intake of vita-
mins may be a major aspect of the unanticipated missing
association between α-tocopherol and cardiovascular out-
comes in the present study. In contrast to the promising
mechanistic suggestions from the previous studies on sur-
rogate end points, there was also no independent associa-
tion of α-tocopherol with hard outcome in one recent study
of 261 hemodialysis patients (35). That study showed that
α-tocopherol levels were not significantly associated with
cardiovascular or all-cause mortality, which is in line with
the findings of our study. The present study, therefore, con-
tributes important information by evaluating the role of a
candidate marker in a large population under daily com-
mon conditions and considering specific hard end points,
which are relevant for clinical practice.

Potential limitations of the study need to be acknowledged.
It was a posthoc analysis within a selected cohort of Ger-
man patients with type 2 diabetes mellitus on hemodialy-
sis. Therefore, the relationship between low vitamin E and
adverse outcome may not be generalizable to other patient
populations. Because of the observational character of this
investigation, we have no information about nutritional ha-
bits and dietary intake of vitamin E. The main strengths of
this study were the specific and centrally adjudicated out-
comes, including stroke, that were analyzed.

In conclusion, low plasma α-tocopherol concentrations
were not independently associated with stroke or all-cause
mortality in hemodialysis patients with type 2 diabetes mel-
litus. Furthermore, there was no association with sudden
death, MI, or cardiovascular events combined. In addition,
α-tocopherol did not associate with infectious deaths. The
lack of an association can partly be explained by a confound-
ing influence of malnutrition, which should be considered in
the planning of trials to reduce cardiovascular risk in dialy-
sis patients.

Acknowledgments
We thank all patients, investigators, and study nurses who par-
ticipated in the 4D study.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% Confidence Interval) According to Baseline α-Tocopherol Levels (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>0.94 (0.85–1.05)</td>
</tr>
<tr>
<td>P value</td>
<td>0.27</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0.92 (0.77–1.10)</td>
</tr>
<tr>
<td>P value</td>
<td>0.35</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.05 (0.90–1.21)</td>
</tr>
<tr>
<td>P value</td>
<td>0.56</td>
</tr>
<tr>
<td>Death caused by infection</td>
<td>0.89 (0.73–1.10)</td>
</tr>
<tr>
<td>P value</td>
<td>0.28</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.91 (0.83–0.99)</td>
</tr>
<tr>
<td>P value</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjusted 1, analyses were adjusted for age and sex; adjusted 2, analyses were additionally adjusted for body mass index, albumin, phosphate, HbA1c, and LDL cholesterol; adjusted 3, in addition to all the parameters mentioned above, analyses were also adjusted for triglycerides.
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Disclosures
None.

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