B Vitamins and the Risk of Total Mortality and Cardiovascular Disease in End-Stage Renal Disease
Results of a Randomized Controlled Trial

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Background—In observational studies, hyperhomocysteinemia has been found to be a risk factor for total mortality and cardiovascular events in patients with end-stage renal disease. These patients have grossly elevated homocysteine levels that can be lowered by supplementation with folic acid and vitamin B12. We conducted a randomized clinical trial with B vitamins to reduce homocysteine levels and therefore cardiovascular events and total mortality.

Methods and Results—This randomized, double-blind multicenter study was conducted in 33 dialysis centers in north and east Germany between July 2002 and July 2008. We randomly assigned 650 patients with end-stage renal disease who were undergoing hemodialysis to 2 postdialysis treatments: 5 mg folic acid, 50 μg vitamin B12, and 20 mg vitamin B6 (active treatment) or 0.2 mg folic acid, 4 μg vitamin B12, and 1.0 mg vitamin B6 (placebo) given 3 times per week for an average of 2 years. The primary outcome was total mortality; the secondary outcome was fatal and nonfatal cardiovascular events. The primary outcome occurred in 102 patients (31%) receiving the active treatment and in 92 (28%) receiving placebo (hazard ratio, 1.13; 95% confidence interval, 0.85 to 1.50; P=0.51). The secondary outcome occurred in 83 patients (25%) receiving the active treatment and in 98 (30%) receiving placebo (hazard ratio, 0.80; 95% confidence interval, 0.60 to 1.07; P=0.13).

Conclusions—Increased intake of folic acid, vitamin B12, and vitamin B6 did not reduce total mortality and had no significant effect on the risk of cardiovascular events in patients with end-stage renal disease.


Key Words: B vitamins ■ cardiovascular diseases ■ hemodialysis ■ homocysteine ■ kidney ■ mortality ■ prevention

Although a number of prospective observational studies have shown that hyperhomocysteinemia is associated with cardiovascular morbidity and mortality,1–3 clinical studies aimed at lowering homocysteine levels in patients with cardiovascular disease have yielded disappointing results; overall, lowering homocysteine by vitamin intervention reduced neither cardiovascular events nor mortality.4–8

Editorial see p 1379
Clinical Perspective on p 1438

As far as cardiovascular disease and homocysteine are concerned, patients with end-stage renal disease (ESRD) are of particular interest because they experience high rates of cardiovascular disease and high rates of mortality9–11 and exhibit the highest homocysteine concentrations, except for patients with homocystinuria.12–14 On average, the homocysteine levels in patients with ESRD are ∼25 μmol/L in those who take folic acid supplementation or fortification and ∼35 μmol/L in those who do not receive additional vitamins.15 Indeed, similar to the situation in populations without renal disease, homocysteine is related to cardiovascular morbidity and mortality in patients with ESRD, as has been shown in a recent meta-analysis.15 Although the homocysteine levels are much higher in patients with ESRD than in other population groups, vitamin supplementation has been shown to be effective in lowering those levels,16,17 although so far these studies have not been summarized and no consensus has been reached on the amounts necessary or the route of administration. In addition, the clinical effect of such vitamin intervention on cardiovascular disease and mortality has not been demonstrated in randomized clinical trials in patients with ESRD without additional vitamin supplementa-
tion or fortification. We therefore conducted a randomized clinical trial to see whether homocysteine-lowering therapy with folic acid, vitamin B_{12}, and vitamin B_{6} could reduce total mortality and cardiovascular events in patients with ESRD treated with hemodialysis.

Methods

Study Design

The objective of this double-blind, placebo-controlled, randomized multicenter trial was to see whether therapy with homocysteine-lowering B vitamins could reduce total mortality and the risk of cardiovascular events in patients with ESRD. The trial design and the baseline data were reported recently.\textsuperscript{18} The study was conducted in dialysis centers in north and east Germany between July 2002 and July 2008. It was coordinated by the Institute of Clinical Chemistry at the Otto-von-Guericke University in Magdeburg, Germany, and sponsored by the School of Medicine at that university, Roche Diagnostics (Mannheim, Germany; laboratory measurements), and Fresenius Medical Care (Bad Homburg, Germany; study drug and matching placebo). The sponsors were not involved in the design, execution, analysis, or reporting of the results of this study. Safety of the intervention and scientific integrity of the study were supervised by an independent data and safety monitoring board. The study was approved by the ethics committees of the School of Medicine of Otto-von-Guericke University Magdeburg and the appropriate medical associations in the respective federal states of Germany. All patients gave informed consent.

Study Population

Men and women between 20 and 80 years of age with ESRD treated for at least 1 month by hemodialysis were enrolled, regardless of their homocysteine levels. The exclusion criteria were acute coronary events within 6 weeks before randomization, active malignant tumor, pregnancy, lactation, and addiction to drugs or alcohol. Patients who had been taking vitamins before recruitment were included after a washout phase of at least 8 weeks. The patients, who came from 33 dialysis centers in Germany, had been put on dialysis because of diabetic nephropathy (n=56), interstitial nephropathy (n=140), hemodialysis because of diabetic nephropathy (n=56), and unknown reasons (n=63), other causes (consequences of surgery, fluid overload and withdrawal from dialysis, cirrhosis of the liver, cachexia, diabetic complications, accidents, suicides, shunt complications, gastrointestinal bleeding, cerebral hemorrhage, hyperkalemia). In 15 cases, the causes of death could not be established and were recorded as unknown.

Trial Outcomes

The primary outcome was total mortality. The secondary outcome was the occurrence of the first fatal or nonfatal cardiovascular event (myocardial infarction, unstable angina pectoris, coronary vascularization procedures, sudden cardiac death, stroke, peripheral artery disease, pulmonary embolism, and thromboses). Shunt thromboses were not regarded as an end point.

Deaths were confirmed by hospital discharge summaries, autopsy reports, or the responsible physicians. Causes of death were categorized as cardiac (myocardial infarction, sudden cardiac death, pulmonary edema), vascular (stroke, pulmonary embolism, thromboses, mesenterial infarction, rupture of an aortic aneurysm), sepsis and infections, tumors, and other causes (consequences of surgery, fluid overload and withdrawal from dialysis, cirrhosis of the liver, cachexia, diabetic complications, accidents, suicides, shunt complications, gastrointestinal bleeding, cerebral hemorrhage, hyperkalemia). In 15 cases, the causes of death could not be established and were recorded as unknown.

Cardiovascular events were identified by a review of patients’ medical records and by consultation with the responsible physicians. Myocardial infarction was diagnosed if at least 2 of the following criteria had been fulfilled according to standard procedures: clinical status, elevated laboratory parameters (myocardium-specific enzymes, myoglobin), and changes in the ECG. Catheterization was performed in cases of suspected myocardial infarction or unstable angina pectoris. Surgical revascularization was carried out after myocardial infarction, in unstable angina pectoris, or when clinical signs had been detected by catheterization and the patients’ general conditions permitted surgery. Strokes and ischemic insults were verified by computed tomography. Peripheral artery disease was diagnosed according to the Fontaine stages or on the basis of >50% stenoses detected angiographically or sonographically in major arteries and lower limbs. Follow-up and the assigned treatment were continued in all participants who experienced a secondary outcome event.

Statistical Analysis

The required number of patients was calculated as 350 per treatment group on the basis of an annual mortality of 16% and a 30% mortality reduction as a result of the active treatment. A 1-year recruitment phase and a study period of 3 years were assumed, with an annual dropout rate of 10%. 2-sided type I error of 5% (adjusted for 1 interim analysis), and a type II error of 20%. Because of the
extended recruitment phase and a reduced number of participating patients (n = 650), the follow-up period was increased to 6 years. An interim analysis was carried out by the data and safety monitoring board in January 2007 after completion of a 2-year follow-up of 75% of the original number of patients, and they gave no reason to end the trial before schedule.

All analyses were performed according to the intention-to-treat principle with the exception that patients who left the study could not be followed up and were considered censored at that time. As shown in Figure 1, the proportion of these patients was similar in both treatment arms. The baseline characteristics of the patients in the 2 treatment arms are described in absolute terms and as percentages, by means with their SDs when the distribution was approximately normal, or by medians and 5th to 95th percentiles if it was not and compared between the 2 arms through the use of the \( t \) test, \( t \) test, and Mann-Whitney \( U \) test.

The effect of the study medication on the plasma levels of vitamins and homocysteine after 6 months of treatment was checked in 97 patients by nonparametric tests (Wilcoxon matched-pairs rank tests and the Mann-Whitney \( U \) test). Survival curves were estimated by the Kaplan-Meier method, and event rates were compared by the log-rank test. Proportional Cox regression analyses were used to calculate risk estimates adjusted for further risk factors.

In addition to the analysis of first cardiovascular events, we carried out an analysis of all cardiovascular events that occurred in the course of the study. Cardiovascular events that occurred after the first event were counted for this purpose. For this analysis, the method suggested by Andersen and Gill\(^{23}\) was used.

All reported \( P \) values are 2 sided. After adjustment for 1 interim analysis according to the O’Brien-Fleming method at an information rate of 75%, in the final analysis, values of \( P \leq 0.044 \) were taken as significant for the primary and secondary end points. All statistical analyses were done with SPSS version 15.0.1.1 for Windows (SPSS Inc, Chicago, Ill) and SAS version 9.2 for Windows (SAS Institute, Inc, Cary, NC; PHREG procedure).

### Results

#### Compliance, Follow-Up, and Adverse Events

Between July 2002 and November 2006, a total of 650 patients were included in the trial from 33 dialysis centers in Germany and were assigned at random to the 2 treatment arms. The median duration of follow-up was 2.1 years (5th to 95th percentiles, 0.2 to 5.2 years). Of the 650 patients, 107 received a transplant, 75 withdrew from participation during the trial, and 18 discontinued treatment because of a change in dialysis center (Figure 1).\(^{23}\)

No serious adverse events relating to the study intervention were reported. Fifteen patients discontinued the treatment because of intolerance of the vitamins. The disorders reported included gastrointestinal discomfort, skin rashes, and headaches. Patients who did not continue the therapy until the end of the study for the reasons mentioned above were included in the final analysis with data censored at the time of the last follow-up visit.

#### Baseline Characteristics

The clinical and demographic characteristics of the patients are presented in Table 1. The baseline characteristics in the placebo and active treatment groups were generally well balanced. Significant differences were found only in the percentage of patients with hypertension, including patients receiving antihypertensive therapy. There were no differences in the total blood pressure values between the treatment groups. With respect to age, sex, distribution, and prevalence of diabetes mellitus, the randomized patients were comparable to the entire dialysis population in Germany.\(^{24}\)

#### Effect of Vitamin Supplementation on Plasma Homocysteine and B Vitamin Levels

The effects of vitamin supplementation on plasma concentrations of homocysteine, folate, cobalamin, and PLP are presented in Table 2. These measurements had been carried out for efficacy control on biochemical parameters after 6 months in a subset of patients (n = 97). In the active treatment group, the median change in homocysteine was \(-10.4 \mu \text{mol/L} (P<0.001)\), which corresponds to a 35% decrease in the baseline level. The median values of folate, cobalamin, and PLP all increased in the active treatment group: folate, 5-fold; PLP, 2-fold; and cobalamin, \( \approx 30\% \) (all \( P<0.001 \)). The placebo group had been receiving a low-dose preparation of the same vitamins, and this was associated with an insignificant increase in PLP (\(<5\%\) and in both folate and cobalamin by \( \approx 30\% \) (all \( P=0.05 \) for folate and \( P<0.001 \) for cobalamin). The median homocysteine concentration in the placebo arm was lowered by 1.8 \( \mu \text{mol/L} \) compared with baseline (\( P=0.07 \)).

#### Primary Outcome: Total Mortality

Of the 650 randomized patients, 194 died during the study period as a result of all causes, 102 (31%) in the active treatment group, and 92 (28%) in the placebo group (Table 3 and Figure 2A). The treatment therefore had no effect on total mortality (hazard ratio [HR], 1.13; 95% confidence interval [CI], 0.85 to 1.50; \( P=0.51 \)). Adjustment for prespecified baseline covariates did not lead to any substantial change in results. An analysis for
specific causes of mortality did not bring to light any significant effects for particular causes (Table 3).

**Secondary Outcome: First Fatal and Nonfatal Cardiovascular Events**

The secondary outcome occurred in 83 patients (25%) in the active treatment and in 98 (30%) in the placebo group. The treatment had no significant effect on fatal and nonfatal cardiovascular events (HR, 0.80; 95% CI, 0.60 to 1.07; \(P=0.13\)). After adjustment for the baseline covariates, the results remained unaltered (Table 3 and Figure 2B). The numbers of events and HRs specified for individual events are listed in Table 3. Only symptoms of unstable angina pectoris were significantly reduced by the active treatment.

**Additional Analysis: Multiple Cardiovascular Events**

The total number of cardiovascular events was 234 (181 first events and 53 subsequent events). The rate per 100 patient-years was 13.7 in the active treatment group and 17.1 in the placebo group. The HR adjusted for multiple covariates was 0.79 (95% CI, 0.59 to 1.05; \(P=0.10\); data not shown).

**Discussion**

The association of high homocysteine levels with the risk of mortality and cardiovascular disease is an attractive explanation for the elevated risk in hemodialysis patients because almost every patient exhibits elevated homocysteine levels. Patients with ESRD show the highest homocysteine concen-
trations compared with any other patient group except those with homocystinuria. Numerous studies have shown that in these patients there is an association between homocysteine on the one hand and cardiovascular events and mortality on the other hand (see the summary by Heinz et al), and that homocysteine can be lowered by supplementation with folic acid, vitamin $B_{12}$, and vitamin $B_6$. It was therefore reasonable to embark on a randomized controlled trial with the aim of reducing homocysteine by vitamin supplementation and thus also reducing cardiovascular risk and mortality.

### Table 2. Plasma Levels of Total Homocysteine, Serum Levels of Folate, Serum Levels of Cobalamin, and Plasma Levels of PLP at Baseline and After 6 Months in a Subgroup of 97 Patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At 6 mo</th>
<th>$P$, Baseline vs 6 mo*</th>
<th>Changes During 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total homocysteine, $\mu$mol/L</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Placebo (n=37)</td>
<td>28.8 (14.1–68.2)</td>
<td>22.3 (9.8–54.1)</td>
<td>0.07</td>
<td>−1.8 (−42.3–15.05)</td>
</tr>
<tr>
<td>Active treatment (n=59)</td>
<td>28.7 (16.5–69.4)</td>
<td>18.8 (7.2–33.6)</td>
<td>&lt;0.001</td>
<td>−10.4 (−35.8–2.5)</td>
</tr>
<tr>
<td>$P$ (placebo vs treatment)$†$</td>
<td>0.49</td>
<td>0.03</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Folate, nmol/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=37)</td>
<td>11.8 (5.7–61.4)</td>
<td>15.0 (8.2–83.6)</td>
<td>0.05</td>
<td>3.0 (−22.9–16.4)</td>
</tr>
<tr>
<td>Active treatment (n=54)</td>
<td>12.7 (5.7–118.5)</td>
<td>81.8 (34.0–117.4)</td>
<td>&lt;0.001</td>
<td>66.4 (−2.0–105.8)</td>
</tr>
<tr>
<td>$P$ (placebo vs treatment)$†$</td>
<td>0.35</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cobalamin, pmol/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo (n=38)</td>
<td>288 (140–690)</td>
<td>399 (227–731)</td>
<td>&lt;0.001</td>
<td>125 (−158–372)</td>
</tr>
<tr>
<td>Active treatment (n=58)</td>
<td>279 (72–999)</td>
<td>407 (163–1058)</td>
<td>&lt;0.001</td>
<td>100 (−225–459)</td>
</tr>
<tr>
<td>$P$ (placebo vs treatment)$†$</td>
<td>0.45</td>
<td>0.87</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td><strong>PLP, nmol/L</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Placebo (n=38)</td>
<td>20.6 (9.9–135.5)</td>
<td>22.1 (8.0–284.0)</td>
<td>0.53</td>
<td>0.4 (−58.0–218.7)</td>
</tr>
<tr>
<td>Active treatment (n=57)</td>
<td>26.0 (8.8–333.6)</td>
<td>80.5 (14.1–305.7)</td>
<td>&lt;0.001</td>
<td>58.4 (−238.9–259.3)</td>
</tr>
<tr>
<td>$P$ (placebo vs treatment)$†$</td>
<td>0.35</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are given as medians (5th to 95th percentiles).
*Wilcoxon matched-pairs rank test for repeated measurements.
†Mann-Whitney $U$ test.

### Table 3. Primary and Secondary Outcomes in the Treatment Groups, Respective Causes of Mortality, Individual Cardiovascular End Points, and the Corresponding HRs With 95% CIs

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment (n=327), n (%)</th>
<th>Placebo (n=323), n (%)</th>
<th>Crude HR (95% CI)</th>
<th>P</th>
<th>Adjusted* HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total mortality</td>
<td>102 (31)</td>
<td>92 (28)</td>
<td>1.13 (0.85–1.50)</td>
<td>0.51</td>
<td>1.14 (0.85–1.52)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
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<tr>
<td>Cardiovascular events</td>
<td></td>
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</tr>
<tr>
<td>Cardiac causes</td>
<td>37 (11)</td>
<td>32 (10)</td>
<td>1.18 (0.73–1.89)</td>
<td>0.50</td>
<td>1.26 (0.77–2.06)</td>
<td>0.36</td>
</tr>
<tr>
<td>Vascular causes</td>
<td>6 (2)</td>
<td>10 (3)</td>
<td>0.61 (0.22–1.68)</td>
<td>0.34</td>
<td>0.51 (0.18–1.42)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sepsis and infections</td>
<td></td>
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</tr>
<tr>
<td>Tumors</td>
<td>8 (2)</td>
<td>7 (2)</td>
<td>1.17 (0.43–3.23)</td>
<td>0.76</td>
<td>1.44 (0.50–4.17)</td>
<td>0.50</td>
</tr>
<tr>
<td>Other causes</td>
<td>14 (4)</td>
<td>15 (5)</td>
<td>0.95 (0.46–1.97)</td>
<td>0.89</td>
<td>1.00 (0.48–2.11)</td>
<td>0.99</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (3)</td>
<td>6 (2)</td>
<td>1.56 (0.56–4.39)</td>
<td>0.40</td>
<td>1.74 (0.61–4.98)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Category of causes of mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Individual cardiovascular events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (nonfatal and fatal)</td>
<td>20 (6)</td>
<td>19 (6)</td>
<td>1.06 (0.57–1.99)</td>
<td>0.86</td>
<td>1.00 (0.53–1.88)</td>
<td>0.99</td>
</tr>
<tr>
<td>Coronary vascularization procedures</td>
<td>8 (2)</td>
<td>18 (6)</td>
<td>0.44 (0.19–1.02)</td>
<td>0.06</td>
<td>0.44 (0.19–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>5 (2)</td>
<td>15 (5)</td>
<td>0.32 (0.12–0.89)</td>
<td>0.03</td>
<td>0.32 (0.12–0.89)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>22 (7)</td>
<td>24 (7)</td>
<td>0.93 (0.52–1.66)</td>
<td>0.81</td>
<td>1.04 (0.57–1.91)</td>
<td>0.89</td>
</tr>
<tr>
<td>Stroke (nonfatal and fatal)</td>
<td>11 (3)</td>
<td>15 (5)</td>
<td>0.74 (0.34–1.62)</td>
<td>0.45</td>
<td>0.73 (0.33–1.60)</td>
<td>0.43</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>26 (8)</td>
<td>34 (11)</td>
<td>0.74 (0.45–1.24)</td>
<td>0.26</td>
<td>0.77 (0.46–1.31)</td>
<td>0.34</td>
</tr>
<tr>
<td>Pulmonary embolism and thromboses</td>
<td>7 (2)</td>
<td>6 (2)</td>
<td>1.16 (0.39–3.44)</td>
<td>0.79</td>
<td>1.14 (0.37–3.48)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Cox regression analysis adjusted for age, sex, diabetes mellitus, hypertension, time on dialysis, C-reactive protein, and albumin.
The results of our study, however, do not support the idea that vitamin supplementation with folic acid, vitamin B12, and vitamin B6 can generally reduce cardiovascular events and mortality in patients with ESRD. Although this result is rather disappointing at first glance, some important points must be noted. First, the patients in the placebo group received a low-dose vitamin supplement with the aim of avoiding vitamin deficiencies in this group, which would then have been treated by the physicians in charge. Preliminary studies had suggested that this low-dose supplement would not have any influence on the homocysteine levels and vitamin levels. However, we did not observe a significant difference in the cobalamin levels between the treatment groups.

Second, we could have expected this result if we had known the results from other trials that have been published since the beginning of our study in 2002. Although this result is rather disappointing at first glance, some important points must be noted. First, the patients in the placebo group received a low-dose vitamin supplement with the aim of avoiding vitamin deficiencies in this group, which would then have been treated by the physicians in charge. Preliminary studies had suggested that this low-dose supplement would not have any influence on the homocysteine levels and vitamin levels. However, we did not observe a significant difference in the cobalamin levels between the treatment groups.

Concerning mortality, the results of our study are comparable to the results of HOST. We did not observe any effect on specific causes of death. Regarding cardiovascular events, analysis of specific events showed a significant reduction in unstable angina pectoris and fewer vascularization procedures (Table 3). Because this is a post hoc analysis, the results must be considered carefully.

The results of the present study and of other controlled randomized trials in patients with (end-stage) renal disease suggest that B vitamins do not have an effect on total mortality in this population. However, there is a consistent between-trial reduction in relative risk of cardiovascular disease, on the order of 10%. The trials conducted so far, including ours, have been too small to establish a significant effect of this magnitude. Doing so would require a trial with >2700 patients in each treatment group. It is not likely that an investigation on this scale will ever be conducted to prove this statement. The traditional approaches that have been successful in cardiovascular disease risk reduction in patients without renal disease are, however, ineffective in patients with ESRD.

A major criticism of vitamin supplementation trials in patients without renal disease is that homocysteine is normal or nearly normal in these patients. The median baseline homocysteine level in our study was 28 μmol/L, about twice the value of the homocysteine levels in these trials. Whether a similar effect would be observed in patients without renal disease but with homocysteine levels of this magnitude remains unknown.

Conclusions
Active treatment with folic acid, vitamin B12, and vitamin B6 did not significantly reduce total mortality and cardiovascular risk in patients with ESRD. Our findings do not support the administration of high-dose vitamin supplements in this total population. However, in accordance with other studies with B vitamins in patients with chronic kidney failure, a smaller protective effect of the vitamins on cardiovascular events is possible.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

We studied the effect of homocysteine-lowering treatment with B vitamins in patients with end-stage renal disease in a randomized controlled trial. After each dialysis session, patients received either a high-dose vitamin supplement (active treatment: 5 mg folic acid, 50 μg vitamin B12, and 20 mg vitamin B6) or a low-dose vitamin supplement to avoid vitamin deficiencies (control: 0.2 mg folic acid, 4 μg vitamin B12, and 1 mg vitamin B6). Homocysteine concentrations were significantly lowered in the group receiving high amounts of vitamins. Patients were followed up for a median period of 25 months. The vitamin treatment did not affect total mortality (hazard ratio, 1.13; 95% confidence interval, 0.85 to 1.50; P=0.51) or cardiovascular morbidity (hazard ratio, 0.80; 95% confidence interval, 0.60 to 1.07; P=0.13). Adjustment for other risk factors did not change these results substantially. In this randomized clinical trial, a significant clinical benefit of additional amounts of B vitamins for lowering of homocysteine concentrations was not shown. The results are in accordance with other trials that used B vitamins in patients with renal disease.
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Antécédents parentaux d’accident vasculaire cérébral et risque d’AVC encouru par les enfants

L’Etude de Framingham

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Contexte—Les données sur le lien existant entre les antécédents parentaux d’accident vasculaire cérébral (AVC) et le risque de survenue d’un tel événement chez les enfants sont étonnamment divergentes, cela tenant en grande partie à l’hétérogénéité des protocoles d’études et à l’absence d’informations validées, contrairement au statut des ascendants en matière d’AVC pour lequel on dispose de données historiques.

Méthodes et résultats—Nous avons mené une étude en milieu communautaire pour savoir si la survenue d’un A VC chez un parent (documentée sur un mode prospectif) avait eu ou non pour effet d’accroître le risque encouru par ses enfants de présenter un tel accident ; pour ce faire, parmi les participants, victimes d’un accident du mésencéphale ou chez un ascendant, d’un antécédent d’AVC (53 % de femmes ; âge moyen : 48 ± 14 ans) mais dont un parent avait été victime d’un tel événement (avant l’âge de 65 ans) et qui s’étaient prétés aux premier, troisième, cinquième et/ou septième examens prévus, ces sujets ayant été suivis pendant 8 ans après le bilan initial. Sur plus de 11 029 périodes d’observation individuées (soit 77 534 années-patients), nous avons recensé 106 A VC parentaux survenus avant l’âge de 65 ans et 128 ayant frappé la descendance (respectivement 74 et 106 de ces accidents ayant été de type ischémique). Par l’emploi de modèles de Cox multivariés ajustés pour l’âge, le sexe, la place dans la fratrie et les facteurs de risque d’AVC initialement présents, nous avons établi que la survenue, chez un ascendant, d’un quelconque type d’AVC et, notamment, d’un accident d’origine ischémique avait concouru à augmenter le risque de survenue du même type d’AVC chez les enfants (rapport de risques : 2,79 ; intervalle de confiance [IC] à 95 % : 1,68 à 4,66 ; p <0,001 pour l’analyse portant sur les A VC de tous types ; rapport de risques : 3,15 ; IC à 95 % : 1,69 à 5,88 ; p <0,001 pour l’analyse portant sur les A VC de type ischémique). La corrélation s’est montrée valide, que l’antécédent d’A VC ait été enregistré chez la mère ou chez le père.


Mots clés : épidémiologie ■ hérédité ■ ischémie ■ accident vasculaire cérébral

Influence de la supplémentation en vitamines B sur la mortalité globale et le risque d’événements cardiovasculaires dans l’insuffisance rénale terminale

Résultats d’un essai randomisé et contrôlé

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Contexte—Des études observationnelles ont montré que l’hyperhomocystéinémie contribue à augmenter la mortalité globale et le risque d’événements cardiovasculaires chez les patients atteints d’insuffisance rénale terminale. Ces individus présentent des taux d’homocystéine extrêmement élevés, qu’il est possible de réduire par une supplémentation en acide folique et en vitamine B12. Nous avons donc entrepris un essai clinique randomisé visant à abaisser l’homocystéinémie par l’apport de vitamines B afin de vérifier si cela avait pour effet de diminuer l’incidence des événements cardiovasculaires et la mortalité globale.

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Incidence, facteurs prédictifs et implications pronostiques de l’hospitalisation pour saignement différé après intervention coronaire percutanée chez les patients âgés de plus de 65 ans

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Contexte—Les données recueillies sur les complications hémorragiques des interventions coronaires percutanées (ICP) émanent essentiellement d’essais randomisés qui étaient axés sur les saignements survenus pendant l’hospitalisation. De ce fait, on ne connaît pas avec précision l’incidence des hémorragies postopératoires différées, les facteurs indépendants qui les favorisent ni leur importance pronostique en pratique clinique.

Méthodes et résultats—Notre étude a porté sur 22 798 patients âgés de plus de 65 ans qui avaient fait l’objet d’une ICP entre le 1er décembre 2003 et le 31 mars 2007 en Ontario (Canada). Nous avons eu recours à des modèles de risques proportionnels de Cox pour établir les facteurs corrélés avec la survenue d’un saignement différé (défini comme ayant motivé l’hospitalisation du patient postérieurement à celle au cours de laquelle l’ICP avait été pratiquée) et estimer le risque de décès ou d’infarctus du myocarde associé à un tel saignement. Nous avons observé que 2,5 % des patients avaient été hospitalisés pour un événement hémorragique dans l’année ayant suivi l’ICP, 56 % des épisodes ayant eu pour siège la sphère digestive. Le facteur ayant le plus significativement majoré le risque de saignement différé a été l’administration postopératoire de warfarine (rapport de risques [RR] : 3,12). Les autres facteurs de risque significatifs ont été l’âge (RR : 1,41 par tranche de 10 ans), le sexe masculin (RR : 1,24), le cancer (RR : 1,80), les antécédents hémorragiques (RR : 2,42), l’insuffisance rénale chronique (RR : 1,93) et la prise d’anti-inflammatoires non stéroïdiens (RR : 1,73). Après ajustement en fonction des covariables initiales, il est apparu que l’hospitalisation pour épisode hémorragique avait concouru à augmenter significativement le risque de décès ou d’infarctus du myocarde à un an (RR : 2,39 ; IC à 95 % : 1,93 à 2,97) ainsi que la mortalité globale (RR : 3,38 ; IC à 95 % : 2,60 à 4,40).

Conclusions—L’hospitalisation motivée par la survenue d’un saignement différé après ICP contribue à accroître fortement le risque de décès ou d’infarctus du myocarde. C’est la prescription d’une trithérapie anticoagulante (aspirine, thiéнопyriderine et warfarine) qui est à l’origine du risque d’événement hémorragique différé le plus élevé. (Traduit de l’anglais : Incidence, Predictors, and Prognostic Implications of Hospitalization for Late Bleeding After Percutaneous Coronary Intervention for Patients Older Than 65 Years. Circ Cardiovasc Inter. 2010;3:140–147.)

Mots clés : saignement ■ intervention coronaire percutanée ■ mortalité ■ anticoagulants oraux