Effect of Homocysteine Lowering on Mortality and Vascular Disease in Advanced Chronic Kidney Disease and End-stage Renal Disease
A Randomized Controlled Trial

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For the Veterans Affairs Site Investigators

I N 1969, MCCULLY[1] PROPOSED THAT high plasma total homocysteine concentration caused severe atherothrombotic disease and death in adolescents with homocystinuria. Folic acid, vitamin B_6, and vitamin B_{12} play critical roles in the metabolism of homocysteine.[2] Treatment with large doses of folic acid, pyridoxine hydrochloride (vitamin B_6), and cyanocobalamin (vitamine B_{12}) lowered the homocysteine levels and dramatically reduced mortality in these patients.[3] In the last 30 years, numerous case-control and prospective studies have extended these findings to the general population and shown that high levels of homocysteine—albeit an order of magnitude lower than those in homocystinuria—are associated with vascular disease.[4-7] On a parallel track, laboratory research has demonstrated that homocysteine causes oxidative stress, injures vascular endothelium, and stimulates formation of thrombi in vitro and in vivo.[1,8-10]

Although epidemiologic studies have confirmed the association between homocysteine and cardiovascular risk, interventional studies designed to lower homocysteine levels have not shown a consistent benefit on clinical outcomes. Several randomized controlled trials of lowering homocysteine with folic acid and B vitamins failed to find a reduction of major

See also p 1212 and Patient Page.

Context High plasma homocysteine levels are a risk factor for mortality and vascular disease in observational studies of patients with chronic kidney disease. Folic acid and B vitamins decrease homocysteine levels in this population but whether they lower mortality is unknown.

Objective To determine whether high doses of folic acid and B vitamins administered daily reduce mortality in patients with chronic kidney disease.

Design, Setting, and Participants Double-blind randomized controlled trial (2001-2006) in 36 US Department of Veterans Affairs medical centers. Median follow-up was 3.2 years for 2056 participants aged 21 years or older with advanced chronic kidney disease (estimated creatinine clearance ≤30 mL/min) (n=1305) or end-stage renal disease (n=751) and high homocysteine levels (≥15 μmol/L).

Intervention Participants received a daily capsule containing 40 mg of folic acid, 100 mg of pyridoxine hydrochloride (vitamin B_6), and 2 mg of cyanocobalamin (vitamin B_{12}) or a placebo.

Main Outcome Measures The primary outcome was all-cause mortality. Secondary outcomes included myocardial infarction (MI), stroke, amputation of all or part of a lower extremity, a composite of these 3 plus all-cause mortality, time to initiation of dialysis, and time to thrombosis of arteriovenous access in hemodialysis patients.

Results Mean baseline homocysteine level was 24.0 μmol/L in the vitamin group and 24.2 μmol/L in the placebo group. It was lowered 6.3 μmol/L (25.8%; $P<.001$) in the vitamin group and 0.4 μmol/L (1.7%; $P=.14$) in the placebo group at 3 months, but there was no significant effect on mortality (448 vitamin group deaths vs 436 placebo group deaths) (hazard ratio [HR], 1.04; 95% CI, 0.91-1.18). No significant effects were demonstrated for secondary outcomes or adverse events: there were 129 MIs in the vitamin group vs 150 for placebo (HR, 0.86; 95% CI, 0.67-1.08), 37 strokes in the vitamin group vs 41 for placebo (HR, 0.90; 95% CI, 0.58-1.40), and 60 amputations in the vitamin group vs 53 for placebo (HR, 1.14; 95% CI, 0.79-1.64). In addition, the composite of MI, stroke, and amputations plus mortality ($P=.85$), time to dialysis ($P=.38$), and time to thrombosis in hemodialysis patients ($P=.97$) did not differ between the vitamin and placebo groups.

Conclusion Treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in patients with advanced chronic kidney disease or end-stage renal disease.

Trial Registration clinicaltrials.gov Identifier: NCT00032435

cardiovascular events or death in a variety of high-risk patients,[11-13] although a post hoc analysis in one study showed that a subgroup of stroke patients might have benefited from the intervention.[14]

Patients with chronic kidney disease or end-stage renal disease (ESRD) have higher homocysteine levels than those in the foregoing trials.[15-17] They have extensive vascular disease, with estimates of annual mortality as high as 20%.[18-20] The cerebral and cardiovascular complications of the vascular disease, and, in some studies, thrombosis of the vascular access, a common and costly complication in ESRD,[21] are correlated with high homocysteine levels.[21]

The characteristically high homocysteine levels, extensive vascular disease, and high mortality rates make this population particularly suitable to test the benefit of lowering homocysteine. We conducted a randomized controlled trial, sponsored by the Department of Veterans Affairs (VA) Cooperative Studies Program (Homocysteinemia in Kidney and End Stage Renal Disease [HOST]), to determine whether treatment with a combination of high-dose folic acid and vitamins B_6 and B_{12} can reduce mortality and cardiovascular events in patients with advanced chronic kidney disease (ACKD) and ESRD.

METHODS
Study Design
The details of the HOST study design have been described[22] and are summarized here. HOST was a multicenter, randomized, double-blind, placebo-controlled trial to determine whether treatment with folic acid plus pyridoxine and cyanocobalamin to lower plasma total homocysteine levels reduces all-cause mortality and major vascular events in a high-risk population.

Study Population
Participants aged 21 years or older, with ESRD, receiving maintenance hemodialysis or peritoneal dialysis, or with an estimated creatinine clearance of less than or equal to 30 mL/min (to convert creatinine clearance to mL/s, multiply by 0.0167) by the Cockcroft-Gault formula[23] (ACKD) were recruited from 36 participating VA

medical centers. A plasma homocysteine level of 15 µmol/L or higher was also required. Race and ethnicity were based on patient self-report by using investigator-defined options. Race and ethnicity were assessed because they have been reported to be associated with the prevalence and outcomes of individuals with chronic kidney disease.

The human rights committee at the coordinating center and the institutional review boards of all participating sites approved the study, and all study participants provided written informed consent.

Study Intervention
Participants were randomly assigned to receive a once-daily capsule containing 40 mg of folic acid, 100 mg of pyridoxine hydrochloride, and 2 mg of cyanocobalamin or an identical-appearing placebo capsule. Participants, investigators, laboratory staff, and the Endpoint Adjudication Committee were blinded to treatment assignment. The randomization scheme was stratified by site and disease strata (ESRD vs ACKD) and used a random permuted block design of varying block size. Participants in both groups were allowed to take additional vitamins containing no more than 1 mg of folate, if prescribed by their physicians as part of their general medical care.

Baseline and Follow-up Evaluations
At entry, demographic, clinical, and laboratory data, including plasma homocysteine and serum folic acid and vitamins B_6 and B_{12} levels, were obtained and participants were given a 3-month supply of study drug. Participants returned to the local sites for evaluation at 3 months. A fasting blood sample was collected for homocysteine and folic acid determination. Participants were asked about hospitalizations, medication adherence, study outcomes, and adverse events during the past 3 months and were given a new 3-month supply of study drug. All subsequent quarterly follow-up evaluations were conducted by telephone (or, if necessary, by mail or e-mail) by study coordinators located at 2 centers. The central study coordinators attempted to verify all study-related outcome events reported by the

participants by searching the VA electronic records or by requesting records for non-VA hospitalizations. The participants received a quarterly supply of study capsules by mail from the VA Cooperative Studies Program Clinical Research Pharmacy. To assess adherence, participants were asked to return the bottle with unused capsules when they received a new bottle. In a representative substudy of 358 participants from 6 participating sites, blood samples were obtained annually for homocysteine, folic acid, vitamin B_6, and vitamin B_{12} determinations. The sites were selected according to number of participants (3 smaller and 3 larger sites) and were geographically dispersed.

Trial Outcomes
The primary study outcome was time to death from any cause. Secondary outcomes included time to myocardial infarction (MI), stroke, amputation of all or part of a lower extremity, and a composite of these 3 plus all-cause mortality. In addition, we assessed time to thrombosis of arteriovenous access (fistula or graft) in hemodialysis patients and time to initiation of dialysis in ACKD patients. All participants continued to be followed up and to receive their assigned treatment after a secondary outcome event.

Deaths were confirmed by hospital discharge summary, autopsy report, Medicare End Stage Renal Disease Death Notification, or death certificate. Deaths were also tracked with the Beneficiary Identification and Records Locator Subsystem, a VA data file used to record death benefits and dates.[24] Fatal and nonfatal events were ascertained through self-reporting by participants in response to specific queries during quarterly follow-up contacts and by review of the patient's VA medical record. Myocardial infarction was diagnosed when 2 of the following 3 criteria were met: typical symptoms, increased cardiac enzyme levels, and diagnostic electrocardiographic changes.[25] Stroke was defined as rapid onset of a persistent neurologic deficit attributed to an obstruction in the arterial system of the brain, providing the deficit was not known to be a result of cerebral hemorrhage, trauma, tumor, infection, or other nonthrombotic

causes.[26] Thrombosis events were collected only for vascular accesses that were actually being used for dialysis and did not include events that occurred before dialysis initiation or that resulted in failure of access maturation.

An independent review committee, blinded to treatment assignment, adjudicated all secondary outcome events: MIs, strokes, and thromboses of the vascular access. Discharge summaries, neurologic examinations, imaging results, cardiac enzyme reports, and electrocardiograms were obtained to verify hospitalization, diagnosis, and outcomes. Only definite or probable events were included in the analysis. An independent data and safety monitoring board monitored the study for safety and scientific integrity.

Laboratory Analyses

Plasma homocysteine level was determined with the Fluorescence Polarization Immunoassay/Abbott Axsym in kits provided by Abbott Laboratories (Abbott Park, Illinois).[27] The determination of serum concentrations of folic acid and vitamin B_{12} (Bayer Direct Chemiluminescence Method [immunoassay]; Bayer Advia Centaur/Bayer Diagnostics, Tarrytown, New York) and vitamin B_6 (Alpco REA; RKVB$_6$, Salem, New Hampshire) was performed in a central chemistry laboratory.

Statistical Analysis

The study was designed to enroll 2006 patients, with a median follow-up of 5 years to detect a relative risk reduction in time to event for the primary outcome of 17%, with 80% power, given a loss rate of approximately 1% per year, an annual event rate of 10.3% in the placebo group, and a 2-sided type I error of .05. The target number of events was 820.

All analyses were performed according to intention to treat. Participants who withdrew consent from all follow-up contacts and medical record reviews were included in the primary end point analysis but were censored from secondary outcome analyses at withdrawal. Survival curves for the 2 groups were estimated according to the Kaplan-Meier procedure and compared with the log-rank statistic.
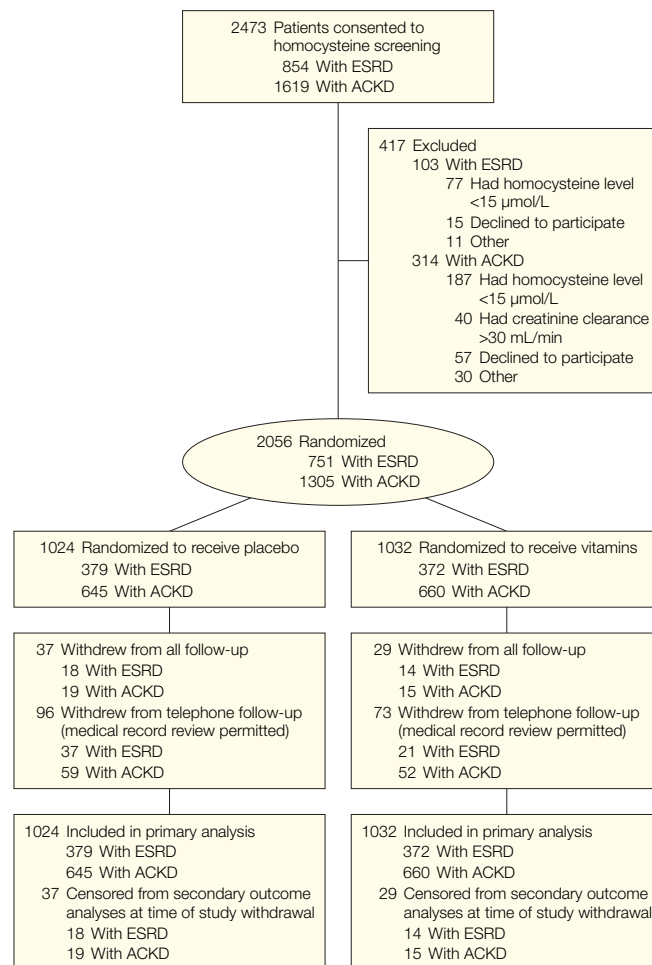
The hazard ratios (vitamins relative to placebo) for all primary and secondary outcomes were calculated with the Cox proportional hazards regression model, adjusted for strata (ACKD vs ESRD). Cox models were also used to evaluate the treatment effect on the primary outcome in the prespecified subgroups of age, race, diabetes history, cardiac disease history, renal disease strata, and baseline homocysteine levels. Treatment $\times$ subgroup interactions were performed to test for homogeneity. Additional sensitivity analyses of the treatment effect adjusted for baseline covariates were conducted to evaluate the stability of the study conclusions. All reported P values are 2-sided and

unadjusted for multiple comparisons. $P \leq .05$ was considered significant. SAS version 8.2 was used for all analyses (SAS Institute Inc, Cary, North Carolina).

RESULTS

Between September 2001 and October 2003, of the 2473 patients who consented for screening laboratory tests, 2056 participants—751 with ESRD and 1305 with ACKD—were randomized to the vitamin treatment (1032) or placebo groups (1024) (**FIGURE 1**). In May 2006, the data and safety monitoring board recommended that the study be stopped because the required number of primary end points had been reached. Patient

Figure 1. Flow of Participants in the Study

To convert creatinine clearance to mL/s, multiply values by 0.0167. ESRD indicates end-stage renal disease; ACKD, advanced chronic kidney disease.

Table 1. Baseline Characteristics

Characteristic	Placebo (n = 1024)	Vitamins (n = 1032)
Age, mean (SD), y	66.2 (11.5)	65.4 (12.0)
Male sex, No. (%)	1009 (98)	1014 (98)
Racial/ethnic group, No. (%)		
White, non-Hispanic	519 (51)	502 (49)
Black, non-Hispanic	357 (35)	384 (37)
Hispanic	130 (13)	121 (12)
Other or missing information	18 (2)	25 (2)
Smoking status, No. (%)		
Never	265 (26)	249 (24)
Former	567 (55)	565 (55)
Current	190 (19)	214 (21)
Body mass index, mean (SD)[a]	27.5 (5.2)	27.90 (5.0)
Systolic blood pressure, mean (SD), mm Hg	142 (24)	143 (23)
Diastolic blood pressure, mean (SD), mm Hg	74 (13)	75 (14)
Medical history, No. (%)		
Myocardial infarction	257 (25)	254 (25)
Congestive heart failure	257 (25)	229 (22)
Hypertension	987 (96)	977 (95)
Angina	263 (26)	253 (24)
Percutaneous coronary angioplasty or stenting	145 (14)	132 (13)
Coronary artery bypass graft surgery	180 (18)	172 (17)
Stroke	173 (17)	138 (13)
Diabetes mellitus	561 (55)	568 (55)
Concomitant medication use, No. (%)		
β-Blockers	605 (59)	589 (57)
Calcium channel blockers	592 (58)	603 (58)
Lipid-lowering agents	513 (50)	501 (48)
Aspirin or antiplatelet agents	458 (45)	415 (40)
ACE inhibitors	429 (42)	402 (39)
Angiotensin II receptor blockers	118 (12)	117 (11)
Laboratory values, mean (SD)		
Hemoglobin, g/dL	11.8 (1.7)	12.0 (1.7)
Albumin, g/dL	4.0 (0.5)	4.0 (0.5)
Total cholesterol, mg/dL	167.0 (44.1)	166.3 (43.7)
HDL cholesterol, mg/dL	42.2 (15.2)	41.8 (13.5)
LDL cholesterol, mg/dL	90.2 (33.3)	91.2 (36.3)
Triglycerides, mg/dL	175.0 (120.0)	174.6 (130.1)

Abbreviations: ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: To convert values for hemoglobin and albumin to g/L, multiply by 10; to convert values for cholesterol to mmol/L, multiply by 0.0259; to convert values for triglycerides to mmol/L, multiply by 0.0113.
[a]Body mass index was calculated as weight in kilograms divided by height in meters squared.

Table 2. Plasma Levels of Total Homocysteine and Folate at Baseline and 3 Months

	Baseline	3 Months
Total homocysteine, µmol/L		
Placebo group, No.	1022	922
Median (IQR)	22.3 (18.7-26.9)	21.6 (18.1-26.9)
Vitamin group, No.	1030	926
Median (IQR)	22.5 (18.9-27.3)	16.5 (13.8-20.1)
Folate, ng/mL		
Placebo group, No.	987[a]	922
Median (IQR)	15.5 (9.6-25.0)	16.5 (8.6-37.0)
Vitamin group, No.	983[a]	927
Median (IQR)	15.7 (9.6-25.0)	2019 (501-4067)

Abbreviation: IQR, interquartile range (first to third quartiles).
SI conversion factors: To convert folate to nmol/L, multiply by 2.266.
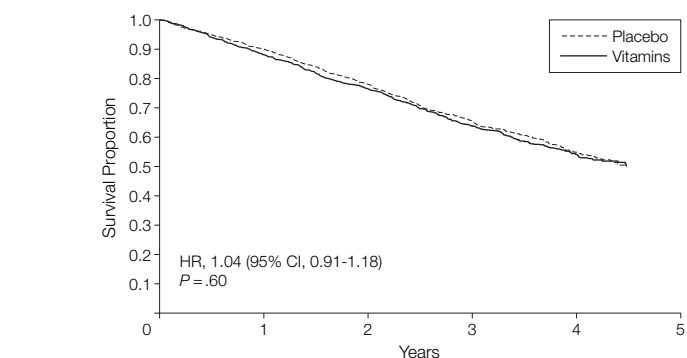[a]Four hundred twenty-five patients (201 in the placebo group and 224 in the vitamin group) with tests results reported as >25 ng/mL at baseline were analyzed as 25.

contacts were completed August 31, 2006. The median length of follow-up was 3.2 years. Of the 2056 randomized participants, 169 (8.2%) withdrew from regular telephone follow-up but continued to allow medical record review, and 66 (3.2%) withdrew consent from follow-up contacts and medical record review.

Baseline Characteristics

The treatment and control groups were well balanced in baseline characteristics (**TABLE 1**). The mean (SD) estimated creatinine clearance of participants with ACKD was 21.6 (6.9) mL/min by the Cockcroft-Gault method, and the estimated glomerular filtration rate was 18.3 (6.3) mL/min per 1.73 m^2 by the Modification of Diet in Renal Disease abbreviated equation.[28]

Effect of Intervention on Plasma Homocysteine and B Vitamin Levels

The median plasma homocysteine and folate levels at baseline and 3 months are presented in **TABLE 2**. The mean (SD) plasma homocysteine levels at baseline were 24.0 (7.7) and 24.2 (9.8) µmol/L for treatment and placebo groups, respectively. The mean homocysteine level was reduced by 6.2 µmol/L (25.8%) in the treatment group at 3 months ($P<.001$); values for 36% (332) of the patients in the treatment group decreased into the normal range (<15 µmol/L). The mean decrease in homocysteine level of 0.4 µmol/L (1.7%) in the placebo group at 3 months was not significant ($P=.14$). There was a dramatic increase in the level of serum folic acid between baseline and 3 months in the treatment group but little change at 3 months in the placebo group (Table 2). In the cohort of 358 patients who had annual determinations of serum folic acid and plasma homocysteine levels, the effect of active treatment on homocysteine and folic acid at 3 months was maintained throughout the first 3 years of the study (the median follow-up time) (**TABLE 3**).

Primary End Point

Treatment had no effect on all-cause mortality (hazard ratio, 1.04; 95% confidence interval [CI], 0.91-1.18) (**FIGURE 2**; **TABLE 4**). There were 884 deaths: 448

Table 3. Plasma Total Homocysteine and Folate at Baseline and Annually in Substudy Population

	Baseline	Year		
		1	2	3
Total homocysteine, µmol/L				
Placebo group, No.	181	114	86	53
Median (IQR)	21.4 (18.6-25.0)	23.4 (18.5-27.3)	21.1 (18.2-26.3)	20.6 (16.9-24.4)
Vitamin group, No.	177	123	92	60
Median (IQR)	21.5 (19.0-26.6)	16.9 (13.6-21.5)	16.3 (13.7-19.4)	15.3 (13.6-21.1)
Folate, ng/mL				
Placebo group, No.	180[a]	114	86	53
Median (IQR)	14.6 (9.8-25.0)	15.0 (8.7-33.7)	15.6 (7.8-32.8)	14.0 (7.2-26.8)
Vitamin group, No.	174[a]	124	92	60
Median (IQR)	19.0 (10.5-25.0)	2644 (94-5410)	2350 (29-4453)	2008 (20-4262)

Abbreviation: IQR, interquartile range (first to third quartiles).
SI conversion factors: To convert folate to nmol/L, multiply by 2.266.
[a]Sixty-two patients (29 in the placebo group and 33 in the vitamin group) with tests results reported as >25 ng/mL at baseline were analyzed as 25.

(43.4%) in the treatment group and 436 (42.6%) in the placebo group. The cumulative 3-year mortality rate was 36.3% in the treatment group and 34.6% in the placebo group, with a mortality rate at 1 year of 11.8% vs 10.0%, respectively. After adjusting for the prespecified baseline covariates of age, race, smoking status, history of diabetes or cardiovascular disease, homocysteine, low-density lipoprotein cholesterol, and albumin, the effect of treatment was virtually unchanged (hazard ratio, 1.06; 95% CI, 0.92-1.22).

Secondary End Points, Subgroups, and Adverse Events

Treatment had no effect on any of the major vascular events that comprise the secondary end points, the composite end point, the need to start maintenance dialysis, or thrombosis of the vascular access (Table 4). Vascular access thrombosis occurred in 73 of the 336 patients (22%) with fistulae and 101 of the 221 patients (46%) with grafts at baseline. All-cause mortality did not differ significantly between the treatment and placebo groups in any of the subgroups examined (**FIGURE 3**). The hazard ratio of treatment vs placebo for ACKD participants was 1.04 (95% CI, 0.88-1.23) and for ESRD participants, 1.04 (95% CI, 0.83-1.28) (*P*=.93). The mortality rates for the ACKD participants were 43.1% (placebo) vs 43.8% (treatment); for ESRD participants, 41.7% vs 42.7%, respectively.

Figure 2. Kaplan-Meier Estimates of Survival

HR, 1.04 (95% CI, 0.91-1.18)
P = .60

Placebo, No.						
At risk	1024	922	800	672	603	588
Deaths	0	102	224	352	421	436
Vitamins, No.						
At risk	1032	910	790	660	596	584
Deaths	0	122	242	372	436	448

There were at total of 884 deaths.

There was no significant difference in the number and types of adverse events, including serious adverse events, between the treatment and control groups. There were no statistically significant differences between the treatment groups for any of the potential adverse effects of the vitamins that were specifically queried, including gastrointestinal and dermatological events, headache, paresthesia, and fatigue, or for any self-reported adverse events, or hospital admissions.

Adherence

Among patients assigned to the vitamin treatment group, 90.3% reported taking study medication at 1 year,

87.6% at 2 years, and 85.3% at 3 years. In the placebo group, the figures were similar: 90.7% at 1 year, 87.2% at 2 years, and 86.5% at 3 years. A total of 73% in the treatment group and 74% in the placebo group reported never stopping their study medication. Counts of capsules in the returned bottles (77% of those dispensed) revealed that 90% of study capsules were taken by patients in both treatment and placebo groups.

COMMENT

Patients with chronic kidney disease have a high risk for complications of atherosclerosis, including increased mor-

tality. Although traditional risk factors such as hypertension are more prevalent in this population, there has been increasing emphasis on the role of nontraditional risk factors such as anemia, hyperparathyroidism, and hyperhomocysteinemia.[29] The association of elevated homocysteine levels with risk of cardiovascular disease has drawn attention because of the nearly universal elevation of homocysteine in patients with chronic kidney disease to levels higher than that of any other patient popula-

tion except those with homocystinuria, the epidemiologic correlation between homocysteine and cardiovascular risk in the chronic kidney disease population,[15-17] and the finding that ingestion of folic acid plus pyridoxine and cyanocobalamin lowers homocysteine levels in these patients.[16,30]

The results of our trial, however, indicate that although administration of large daily doses of folic acid plus pyridoxine and cyanocobalamin to patients with ACKD or ESRD lowered plasma ho-

mocysteine levels, it did not improve survival during a median of 3.2 years of follow-up. Furthermore, there was no significant decrease in the incidence of cardiovascular events or, in hemodialysis patients, the rate of thrombosis of the vascular access, a common event requiring hospitalization in these patients.[21]

Recent reports of several large randomized trials in lower-risk patients without kidney disease, in whom smaller doses of vitamins were used and smaller reductions in homocysteine levels were observed,

Table 4. Primary and Secondary Outcomes

	No. (%) of Patients With an Event			
End Point	Vitamin Group (n = 1032)	Placebo Group (n = 1024)	Hazard Ratio (95% CI)[a]	P Value[b]
Primary outcome				
All-cause mortality	448 (43)	436 (43)	1.04 (0.91-1.18)	.60
Secondary outcomes				
MI (fatal and nonfatal)	129 (13)	150 (15)	0.86 (0.67-1.08)	.18
Stroke (fatal and nonfatal)	37 (4)	41 (4)	0.90 (0.58-1.40)	.64
Amputation	60 (6)	53 (5)	1.14 (0.79-1.64)	.50
Composite of all-cause mortality, MI, stroke, or amputation	523 (51)	525 (51)	0.99 (0.88-1.12)	.85
Dialysis in advanced chronic kidney disease patients only (n = 1305)	365 (55)	340 (53)	1.07 (0.92-1.24)	.38
Thrombosis in hemodialysis patients (n = 1397)	166 (24)	163 (23)	1.01 (0.81-1.25)	.97

Abbreviation: CI, confidence interval; MI, myocardial infarction.
[a] Hazard ratios were adjusted for kidney disease strata.
[b] P values were based on the unadjusted log-rank test.

Figure 3. Hazard Ratios for All-Cause Mortality by Subgroups

	Mortality, No./Total (%)		Hazard Ratio (95% CI)		P Value for Interaction
Subgroup	Vitamins	Placebo			
Disease strata					
ESRD	159/372 (42.7)	158/379 (41.7)	1.04 (0.83-1.28)		.93
ACKD	289/660 (43.8)	278/645 (43.1)	1.04 (0.88-1.23)		
Age, y					
≤65	164/490 (33.5)	141/453 (31.1)	1.12 (0.89-1.40)		.30
>65	284/539 (52.7)	295/569 (51.8)	1.03 (0.88-1.21)		
Race					
Black	135/384 (35.2)	129/357 (36.1)	0.97 (0.76-1.23)		.46
Other	312/644 (48.4)	307/665 (46.2)	1.08 (0.93-1.27)		
Homocysteine level at baseline					
Lower third (15-19.8 µmol/L)	150/337 (44.5)	149/348 (42.8)	1.06 (0.84-1.33)		
Middle third (>19.8-25.2 µmol/L)	141/341 (41.3)	154/346 (44.5)	0.92 (0.73-1.15)		.54
Upper third (>25.2-133 µmol/L)	157/352 (44.6)	131/328 (39.9)	1.17 (0.93-1.48)		
Cardiovascular disease history					
No	180/549 (32.8)	176/507 (34.7)	0.94 (0.77-1.16)		.15
Yes	268/483 (55.5)	260/517 (50.3)	1.16 (0.98-1.38)		
Diabetes history					
No	163/460 (35.4)	174/461 (37.7)	0.93 (0.75-1.15)		.18
Yes	285/568 (50.2)	262/561 (46.7)	1.12 (0.95-1.33)		

CI indicates confidence interval; ESRD, end-stage renal disease; ACKD, advanced chronic kidney disease. The sizes of the data markers relate to subgroup sample size.

have failed to show a benefit of vitamin supplementation: the Vitamin Intervention for Stroke Prevention,[13] the Heart Outcomes Prevention Evaluation (HOPE-2) study,[12] and the Norwegian Vitamin (NORVIT) trial.[11] Patients with kidney disease have higher plasma homocysteine levels and a higher risk for cardiovascular events than patients included in the previously cited trials. There have been a limited number of trials of homocysteine lowering in dialysis patients, but these trials were small and therefore underpowered to detect a clinically significant effect on mortality.[31-33] In our trial, however, which used large doses of vitamins, resulting in a change in homocysteine levels twice that reported in previous trials,[11-13] and was adequately powered to detect a relative risk reduction in mortality of 17%, we failed to find a benefit of vitamin supplementation. In contrast to the NORVIT study, we did not observe an increased risk of vascular events in the treatment group.[11]

What might account for the failure of the treatment in our study? Possibly the underlying burden of disease was too great for a measurable benefit from lowering homocysteine. A trial of statins in diabetic dialysis patients failed to show a mortality benefit despite lowering low-density lipoprotein cholesterol,[34] suggesting that even the reduction of some traditional risk factors may not be beneficial in this high-risk population. It may be that although homocysteine levels were substantially reduced, amelioration of the consequences of hyperhomocysteinemia requires lowering to normal levels, an effect that was achieved in only one-third of our participants, despite administration of the highest vitamin doses among homocysteine-lowering studies reported to date.[35] Loscalzo,[10] commenting on the results of the NORVIT and HOPE-2 trials, has suggested that vitamin therapy may have had adverse effects that offset its homocysteine-lowering benefit.

The disparity between our findings and the epidemiologic literature showing an association between moderate increases in homocysteine and atherothrombotic disease could reflect an unrecognized adverse effect of the folic acid or vitamins but in all probability reflects the inherent limitations of observational studies. It has been suggested that homocysteine marks the existence of vascular disease rather than causes it[6,10-13,32]; yet in homocystinuria, vitamin therapy has an impressive benefit on mortality and cardiovascular events.[3] It may be that the relationship between homocysteine and vascular injury is nonlinear or that the potential for amelioration of the vascular injury is too slight in patients without homocystinuria to be detectable, particularly in patients with many other risk factors.

There are several limitations of this study. First, the population was nearly all male. The relationship between homocysteine and vascular disease and the response to vitamin therapy is similar in men and women.[2,5,36] The homocysteine levels and extent of vascular disease in the veterans in this trial are similar to those reported in nonveteran men and women with ACKD or ESRD[16,18,32,33]; we would therefore not expect that the enrollment of a predominantly male population accounts for our null results. Second, to achieve adequate power we enrolled both ACKD and ESRD patients. Jungers et al[16] reported an association of homocysteine and cardiovascular disease in chronic kidney disease similar to that in ESRD. In our study, homocysteine levels and prevalence of cardiovascular disease in the ACKD and ESRD strata were remarkably similar, as was the homocysteine-lowering effect of the vitamins. The proportion of participants who died during the study in the 2 groups was nearly identical. Although our study was not powered to examine these 2 strata separately, subgroup analyses did not show any difference in the treatment effect across strata. Third, follow-up contacts after the return visit at 3 months were not in person; thus, adherence and ascertainment of outcomes might have been incomplete. Previous studies have shown, however, that death can be reliably ascertained from death registries and patients' electronic records within the VA health care system.[24] Secondary outcomes of cardiovascular events may be less complete, but there is no a priori rea-

son to expect differential ascertainment in the randomized groups.

In conclusion, treatment with high doses of folic acid and B vitamins did not reduce mortality or the incidence of cardiovascular events. Our findings do not support the administration of folic acid and B vitamin supplements to prevent vascular injury or improve survival in patients with ACKD or ESRD.

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