Homocysteine-Lowering and Cardiovascular Disease Outcomes in Kidney Transplant Recipients

Primary Results From the Folic Acid for Vascular Outcome Reduction in Transplantation Trial

Andrew G. Bostom, MD; Myra A. Carpenter, PhD; John W. Kusek, PhD; Andrew S. Levey, MD; Lawrence Hunsicker, MD; Marc A. Pfeffer, MD, PhD; Jacob Selhub, PhD; Paul F. Jacques, ScD; Edward Cole, MD; Lisa Gravens-Mueller, MS; Andrew A. House, MD; Clifton Kew, MD; Joyce L. McKenney, MA, MPH; Alvaro Pacheco-Silva, MD, PhD; Todd Pesavento, MD; John Pirsch, MD; Stephen Smith, MD; Scott Solomon, MD; Matthew Weir, MD

Background—Kidney transplant recipients, like other patients with chronic kidney disease, experience excess risk of cardiovascular disease and elevated total homocysteine concentrations. Observational studies of patients with chronic kidney disease suggest increased homocysteine is a risk factor for cardiovascular disease. The impact of lowering total homocysteine levels in kidney transplant recipients is unknown.

Methods and Results—In a double-blind controlled trial, we randomized 4110 stable kidney transplant recipients to a multivitamin that included either a high dose (n=2056) or low dose (n=2054) of folic acid, vitamin B6, and vitamin B12 to determine whether decreasing total homocysteine concentrations reduced the rate of the primary composite arteriosclerotic cardiovascular disease outcome (myocardial infarction, stroke, cardiovascular disease death, resuscitated sudden death, coronary artery or renal artery revascularization, lower-extremity arterial disease, carotid endarterectomy or angioplasty, or abdominal aortic aneurysm repair). Mean follow-up was 4.0 years. Treatment with the high-dose multivitamin reduced homocysteine but did not reduce the rates of the primary outcome (n=547 total events; hazards ratio [95% confidence interval]=0.99 [0.84 to 1.17]), secondary outcomes of all-cause mortality (n=431 deaths; 1.04 [0.86 to 1.26]), or dialysis-dependent kidney failure (n=343 events; 1.15 [0.93 to 1.43]) compared to the low-dose multivitamin.

Conclusions—Treatment with a high-dose folic acid, B6, and B12 multivitamin in kidney transplant recipients did not reduce a composite cardiovascular disease outcome, all-cause mortality, or dialysis-dependent kidney failure despite significant reduction in homocysteine level.

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Key Words: cardiovascular disease ■ risk factors ■ mortality ■ clinical trials ■ kidney ■ kidney transplantation

Homozygous genetic disorders[1–3] resulting in marked elevations of plasma homocysteine (total homocysteine [tHcy] concentrations, 100 to 500 μmol/L), a sulfur amino acid byproduct of methionine metabolism, are clearly associated with atherothrombotic events early in life.[4] Total homocysteine–lowering treatment appears to reduce the incidence of these outcomes among such patients.[4,5] In addition, pooled data from prospective observational studies have suggested that mild to moderate hyperhomocysteinemia (tHcy levels, 12 to 99 μmol/L)[6] may also be a significant risk factor for arteriosclerotic cardiovascular disease (CVD) among the general population.[7]

Clinical Perspective on p 1770

Longitudinal investigations of persons with chronic kidney disease (CKD) without kidney failure have demonstrated a relationship between higher levels of tHcy and CVD risk. Typically, the greatest relative risk was confined to persons

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From the Rhode Island Hospital, Providence (A.G.B., J.L.M.); Department of Biostatistics, the University of North Carolina, Chapel Hill (M.A.C., L.G.-M.); National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD (J.W.K.); Tufts Medical Center, Boston, MA (A.S.L.); University of Iowa, Iowa City (L.H.); Brigham and Women's Hospital, Boston, MA (M.A.P., S. Solomon); US Department of Agriculture, Jean Mayer Human Nutrition Research Center on Aging, Boston, MA (J.S., P.F.J.); University of Toronto, Toronto, Canada (E.C.); London Health Sciences Center, London, Canada (A.A.H.); University of Alabama, Birmingham (C.K); Universidade Federal de Sao Paulo, Sao Paulo, Brazil (A.P.-S.); Ohio State University, Columbus (T.P.); University of Wisconsin, Madison (J.P.); Duke University, Durham, NC (S. Smith); University of Maryland, Baltimore (M.W.); on behalf of the FAVORIT Study Investigators.

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Correspondence to Andrew B. Bostom, MD, Rhode Island Hospital, 110 Lockwood St, Room 242, Providence, RI 02903. E-mail abostom@lifespan.org

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with tHcy concentrations in the uppermost distribution.[8,9] Whether mild to moderate, hyperhomocysteinemia is a direct cause of arteriosclerotic outcomes in these CKD populations or only a surrogate for clinical CVD remains unresolved. Although a substantial number of randomized controlled clinical trials of tHcy-lowering treatment have been undertaken to evaluate efficacy for reducing CVD events among different patient populations at high risk for atherothrombotic sequelae,[10,11] including persons with CKD,[12–16] none has revealed a significant decrease in CVD outcomes.[10–16] Kidney transplant recipients are considered to have CKD, irrespective of glomerular filtration rate (GFR) or presence or absence of markers of kidney damage.[17] Although there remains great heterogeneity among causes of CKD, many of the complications of CKD in kidney transplant recipients are similar to those experienced by persons with CKD of their native kidneys.[18] In particular, kidney transplant recipients experience a high rate of both incident and recurrent CVD and an excess prevalence of hyperhomocysteinemia despite the fortification of cereal grain flour with folic acid, a major determinant of plasma homocysteine concentrations.[8,9] Importantly, these patients are not treated routinely with supplemental folic acid, but unlike patients with kidney failure treated by dialysis, it is possible to normalize their tHcy concentrations with combined folic acid, vitamin B12, and vitamin B6 treatment.[8,9]

We conducted the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial in clinically stable kidney transplant recipients.[19] The primary objective was to determine whether decreasing tHcy levels with a multivitamin containing high doses of folic acid, vitamin B6, and vitamin B12 would reduce their risk of CVD outcomes compared to treatment with a low-dose multivitamin devoid of folic acid and with estimated average requirement amounts of vitamins B6 and B12.

Methods

Trial Design

Details of the study design are published elsewhere.[19] Briefly, the study was a multicenter, double-blind, randomized controlled clinical trial conducted to determine whether lowering homocysteine levels by vitamin therapy reduced the rate of pooled arteriosclerotic CVD outcomes. The trial received approval from the institutional review or ethics boards of all 30 clinical sites. Written informed consent was obtained from all participants.

Study Participants

Men and women aged 35 to 75 years who were at least 6 months post kidney transplantation were screened for eligibility. Key entry criteria were stable kidney function (estimated creatinine clearance[20] ≥30 mL/min through July 7, 2005, after which the cut point for women was ≥25 mL/min) and elevated homocysteine (≥11 μmol/L for women, ≥12 μmol/L for men). Race and ethnicity were determined through self report using categories as defined in the National Institutes of Health Policy on Reporting Race and Ethnicity Data.[21]

Intervention

Participants were randomized to receive either a standard multivitamin with a high dose of folic acid (5.0 mg), vitamin B6 (pyridoxine, 50 mg), and vitamin B12 (cyanocobalamin, 1.0 mg) or a multivitamin with a low dose of vitamin B6 (1.4 mg) and vitamin B12 (2.0 μg) and no folic acid. Both multivitamins were formulated to be similar in appearance and odor to facilitate blinding. Adherence was assessed by annual pill count and semiannual self report.

Baseline and Follow-Up

The trial enrolled study participants from August 2002 through January 2007. Follow-up contacts occurred every 6 months through January 31, 2010, to obtain study-related outcomes through June 24, 2009. Central laboratory methods for tHcy and creatinine determinations have been described.[22] Because of resource limitations, baseline and follow-up tHcy analyses are reported on a convenience sample of 143 participants who were among the first participants enrolled. Estimated GFR (eGFR) is produced using the Chronic Kidney Disease Epidemiology Collaboration equation.[23]

Outcomes

The primary outcome was pooled incident or recurrent CVD comprised of (1) CVD death, (2) myocardial infarction, (3) resuscitated sudden death, (4) stroke, (5) coronary artery revascularization, (6) lower extremity revascularization or amputation above the ankle for severe arterial disease, (7) carotid endarterectomy or angioplasty, (8) abdominal aortic aneurysm repair, or (9) renal artery revascularization. The first 4 components of the primary outcome noted above were centrally reviewed and adjudicated by the Clinical Endpoints Committee; the remaining outcomes were identified through medical record abstraction. The Clinical Endpoints Committee also reviewed records for unstable angina cases and urgent coronary revascularization procedures in search of myocardial infarctions that were not identified by the clinical site staff. Secondary outcomes were all-cause mortality, dialysis-dependent kidney failure, individual and meaningful combinations of components of the primary outcome, and the number of these that occur.

Statistical Issues

A sample size of 4000 with an average of 5 years of follow-up was estimated to provide 83% power to detect a 19% treatment effect and 87% power to detect a 20% treatment effect. Additional details on sample size estimates and power calculations are provided elsewhere.[19]

Randomization by permuted block, stratified by clinical site, was performed through the data management system. Because the need for emergency unblinding was expected to be low, unblinding codes were stored securely at the Data Coordinating Center, accessible only to authorized staff.

In addition to having primary and secondary outcomes, we prespecified primary and secondary analysis strategies. The fundamental analysis plan included using Kaplan–Meier methods and comparing unadjusted treatment effects with proportional hazards models stratified by country, using proportional hazards models to adjust for other variables (age group, race, sex, smoking, systolic blood pressure, diabetes status, low-density lipoprotein, CKD stage based on estimated GFR,[23] and country) and performing analogous subgroup analyses by age group, sex, race, diabetes status, and baseline tHcy level.[24] Because of the limited ability of vitamins to normalize elevated tHcy levels in dialysis-dependent kidney failure patients, the primary analysis strategy invoked censoring at 3 months after return to long-term dialysis for the CVD and mortality outcomes. The secondary analysis strategy based on intention-to-treat principles was performed for all interim and final analyses. By design, the primary analysis of the secondary outcome of dialysis-dependent kidney failure is intention to treat. All computations were performed using SAS version 9.1 (SAS Institute, Cary, NC).

The Data and Safety Monitoring Board planned 2 interim efficacy analyses at accrual of 33% and 67% of the expected number of events. To provide flexibility in the number of interim analyses, a Lan-DeMets boundary[25] was used as a stopping rule. Conditional power analyses[26,27] were also planned at these time points.

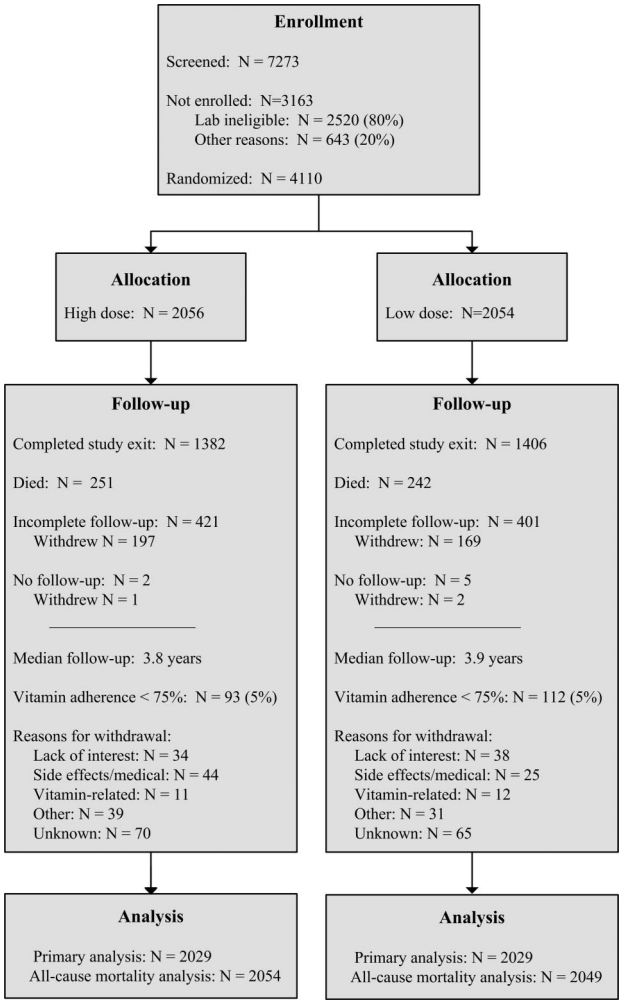

Figure 1. Enrollment, follow-up, and analysis diagram.

Results

Participant Characteristics

Participant flow is summarized in Figure 1; baseline data were presented previously.[22] Briefly, 7273 patients were screened, of whom 2056 and 2054 were randomized to high-dose and low-dose multivitamins, respectively; 34% did not meet eligibility cut points for tHcy and Ccr, and 9% were not enrolled for other reasons. Baseline characteristics (Table 1) were well balanced between treatment groups overall and within country. Based on eGFR, 78% of participants had CKD stage 3T or 4T (68% stage 3T, 10% stage 4T), and 20% reported a CVD history at baseline.

Follow-Up and Early Termination

Follow-up ranged from 0 to 82 months, yielding a mean of 4.0±1.5 years. Complete follow-up through June 24, 2009, was available for 2788 participants, 493 participants were deceased, 822 had incomplete follow-up, and 7 participants had no follow-up. Slightly more participants in the high-dose group withdrew consent during the study (198 high dose, 171 low dose; $P=0.16$). Lack of interest in continuing participation and health issues or side effects were the most frequently cited reasons for withdrawal.

Table 1. Baseline Characteristics of Study Participants

Characteristics	Overall (n=4110)	High Dose (n=2056)	Low Dose (n=2054)
Age, y	52±9.4	52±9.4	52±9.5
Female sex, n (%)	1528 (37.2)	767 (37.3)	761 (37.0)
Nonwhite race, n (%)	945 (23.5)	477 (23.7)	468 (23.3)
Location, n (%)			
Brazil	612 (14.9)	307 (14.9)	305 (14.8)
Canada	498 (12.1)	249 (12.1)	249 (12.1)
United States	3000 (73.0)	1500 (73.0)	1500 (73.0)
Graft vintage, y	5±5.0	6±5.1	5±5.0
History of CVD, n (%)	820 (20.0)	406 (19.8)	414 (20.3)
History of diabetes mellitus, n (%)	1663 (40.5)	813 (39.6)	850 (41.5)
Prevalent hypertension, n (%)	3778 (92.0)	1879 (91.5)	1899 (92.5)
Body mass index, kg/m^2	29±6.2	29±6.2	29±6.3
Current smoker, n (%)	451 (11.1)	230 (11.3)	221 (10.9)
Total cholesterol, mmol/L	4.8±1.1	4.8±1.2	4.8±1.1
High-density lipoprotein cholesterol, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4
Calculated or direct low-density lipoprotein cholesterol, mmol/L	2.6±0.9	2.6±0.9	2.6±0.9
Triglycerides levels, mmol/L	2.2±2.1	2.3±2.5	2.2±1.6
Screening homocysteine, μmol/L	16.4±1.3	16.4±1.3	16.4±1.3
Female	16.8±1.3	17.0±1.3	16.7±1.3
Male	15.6±1.3	15.3±1.3	15.8±1.3
Screening creatinine, μmol/L	144.3±42.1	145.0±42.5	143.6±41.6
Screening (eGFR, mL/min per 1.73 m^2)*	48.8±16.2	48.5±15.9	49.0±16.5
CKD Stage, n (%)*			
Stage 1T (eGFR 90+ mL/min per 1.73 m^2)	69 (1.7)	28 (1.4)	41 (2.0)
Stage 2T (eGFR 60–89 mL/min per 1.73 m^2)	819 (20.4)	405 (20.1)	414 (20.6)
Stage 3T (eGFR 30–59 mL/min per 1.73 m^2)	2738 (68.1)	1380 (68.7)	1358 (67.5)
Stage 4T (eGFR 15–29 mL/min per 1.73 m^2)	394 (9.8)	197 (9.8)	197 (9.8)
Stage 5T (eGFR <15 mL/min per 1.73 m^2)	1 (0.0)	0 (0.0)	1 (0.0)

*Based on CKD-EPI eGFR formula.[23]

Data presented as mean±standard deviation where appropriate.

CVD indicates cardiovascular disease; eGFR, estimated glomerular filtration rate; and CKD, chronic kidney disease.

Interim analyses were performed at 4 points (proportion of total expected events): May 2007 (0.31), April 2008 (0.43, conditional power only), May 2009 (0.60), and June 2009 (0.60). The Data Safety and Monitoring Board considered the fourth interim analysis on June 24, 2009, and recommended an early and orderly closeout of the study because it had "conclusively answered its original hypothesis." Conditional power[27] at information time 0.60 was 0.19 (80% confidence interval [CI], 0.03 to 0.56) assuming the study design effect for the remainder of the trial and 0.004 (80% CI, 0.000 to 0.052) assuming that the trend observed to date continued for the duration of the study. The sponsor accepted this recommendation and closeout preparations commenced immedi-

Table 2. Primary and Secondary Outcomes

	Censored at 3 Months After Return to Dialysis				Intention-to-Treat			
	High Dose, n	Low Dose, n	Hazard Ratio (95% CI)	P*	High Dose, n	Low Dose, n	Hazard Ratio (95% CI)	P*
Any primary CVD outcome	269	278	0.99 (0.84 to 1.17)	0.93	290	294	1.01 (0.86 to 1.19)	0.91
Component event								
Fatal/Nonfatal MI	90	86	1.08 (0.80 to 1.45)	0.61	96	94	1.05 (0.79 to 1.40)	0.73
Fatal/Nonfatal Stroke	35	32	1.12 (0.69 to 1.81)	0.64	38	35	1.11 (0.70 to 1.75)	0.67
RSD	7	9	0.80 (0.30 to 2.15)	0.66	8	10	0.82 (0.32 to 2.08)	0.67
CVD death	75	91	0.84 (0.62 to 1.15)	0.28	91	100	0.93 (0.70 to 1.24)	0.63
Coronary artery revascularization	111	120	0.95 (0.73 to 1.23)	0.70	116	124	0.96 (0.74 to 1.24)	0.75
Lower extremity PAD†	59	53	1.14 (0.79 to 1.65)	0.49	63	54	1.19 (0.83 to 1.72)	0.34
Carotid endarterectomy or angioplasty	10	9	1.14 (0.46 to 2.80)	0.78	10	9	1.14 (0.46 to 2.79)	0.78
Abdominal aortic aneurysm repair	3	5	0.61 (0.15 to 2.57)	0.50	3	5	0.61 (0.15 to 2.57)	0.50
Renal artery revascularization	9	7	1.30 (0.48 to 3.50)	0.60	9	7	1.30 (0.48 to 3.49)	0.60
All-cause mortality	217	214	1.04 (0.86 to 1.26)	0.67	251	242	1.06 (0.89 to 1.27)	0.50
Dialysis-dependent kidney failure	NA	NA	NA	NA	181	162	1.15 (0.93 to 1.43)	0.19

*P was calculated with stratified proportional hazards models stratified by country.

†Lower extremity PAD includes lower extremity revascularization or amputation above the ankle for severe arterial disease.

CI indicates confidence interval; CVD, cardiovascular disease; RSD, resuscitated sudden death; and PAD, peripheral arterial disease.

ately. Final telephone contacts or clinic visits were conducted from June 25, 2009, through January 31, 2010.

Adherence, Hyperhomocysteinemia Lowering, and Blinding

On the basis of pill count, 84% of participants took at least 75% of the expected number of study multivitamins, 5% took <75% of the expected vitamins, and adherence could not be assessed for 11%. Adherence based on pill count was balanced between the treatment groups and consistent with self-reported adherence**.** The high-dose multivitamin was effective in lowering tHcy. On the basis of a sample of 143 participants, the mean 4-year change from baseline tHcy was −4.6 μmol/L (SD=4.5, n=72) in the high-dose group compared with −0.2 (SD=5.1, n=71; $P<0.0001$) in the low-dose group, resulting in 4-year mean tHcy levels (μmol/L) of 11.8 (SD=3.8) and 15.9 (SD=5.5), respectively. Blinding was successful; 49% of participants and 49% of study coordinators provided incorrect guesses for treatment assignment.

Cardiovascular Disease, Mortality, and Kidney Failure Outcomes

A total of 547 pooled CVD events are included in the primary (censored) analysis. Treatment groups did not differ significantly in occurrence of postrandomization CVD (269 high dose, 278 low dose; $P=0.93$), all-cause mortality (217 high dose, 214 low dose; $P=0.67$), or dialysis-dependent kidney failure (181 high dose, 162 low dose; $P=0.19$) outcomes. (Table 2) As shown in Figure 2, no trends in event rates over 6 years were suggested for either the primary CVD outcome or all-cause mortality. A trend for more frequent return to dialysis-dependent kidney failure in the high-dose group was not statistically significant ($P=0.20$). Adjustment for country, age group, race, sex, smoking, systolic blood pressure, diabetes mellitus status, low-density lipoprotein, and CKD stage had little impact on the estimated effects. The hazard ratios (95% CIs) were: CVD primary outcome 1.02 (0.85 to 1.22), all-cause mortality 0.99 (0.81 to 1.22), and dialysis-dependent kidney failure 0.90 (0.71 to 1.14).

Analyses of the primary and secondary outcomes by subgroups also failed to demonstrate a statistically significant treatment effect (Figure 3).

In the primary analyses, 37 CVD outcomes and 62 deaths were censored for occurring >3 months after dialysis-dependent kidney failure. Importantly, all intention-to-treat analyses yielded results very similar to the primary analyses, with censoring at 3 months after return to long-term dialysis. The intention-to-treat analysis for the pooled primary CVD outcome (290 high dose, 294 low dose; $P=0.91$) was not statistically significant. For all-cause mortality, the intention-to-treat analysis included an additional 34 deaths in the high-dose group and 28 deaths in the low-dose group and did not appreciably modify the survival curves ($P=0.50$).

Adverse Events

During follow-up, 62% of the participants were hospitalized at least once (1272 high dose, 1294 low dose; $P=0.46$) and accrued a total of 7996 hospitalizations (3933 high dose, 4063 low dose). There were no statistically significant differences in discharge diagnosis (on the basis of major *International Classification of Diseases*, 9th edition, Clinical Modification groupings) by treatment group. Disease of the circulatory system was the most prevalent discharge diagnosis grouping (1934 high dose, 1958 low dose) reported across all hospitalizations. Participant-reported multivitamin side effects also did not differ by treatment group. Among the high-dose group, 269 participants reported side effects compared with 263 participants receiving the low-dose multivitamin ($P=0.32$). Gastrointestinal disturbance was the side effect most often reported (121 high dose, 114 low dose; $P=0.69$).

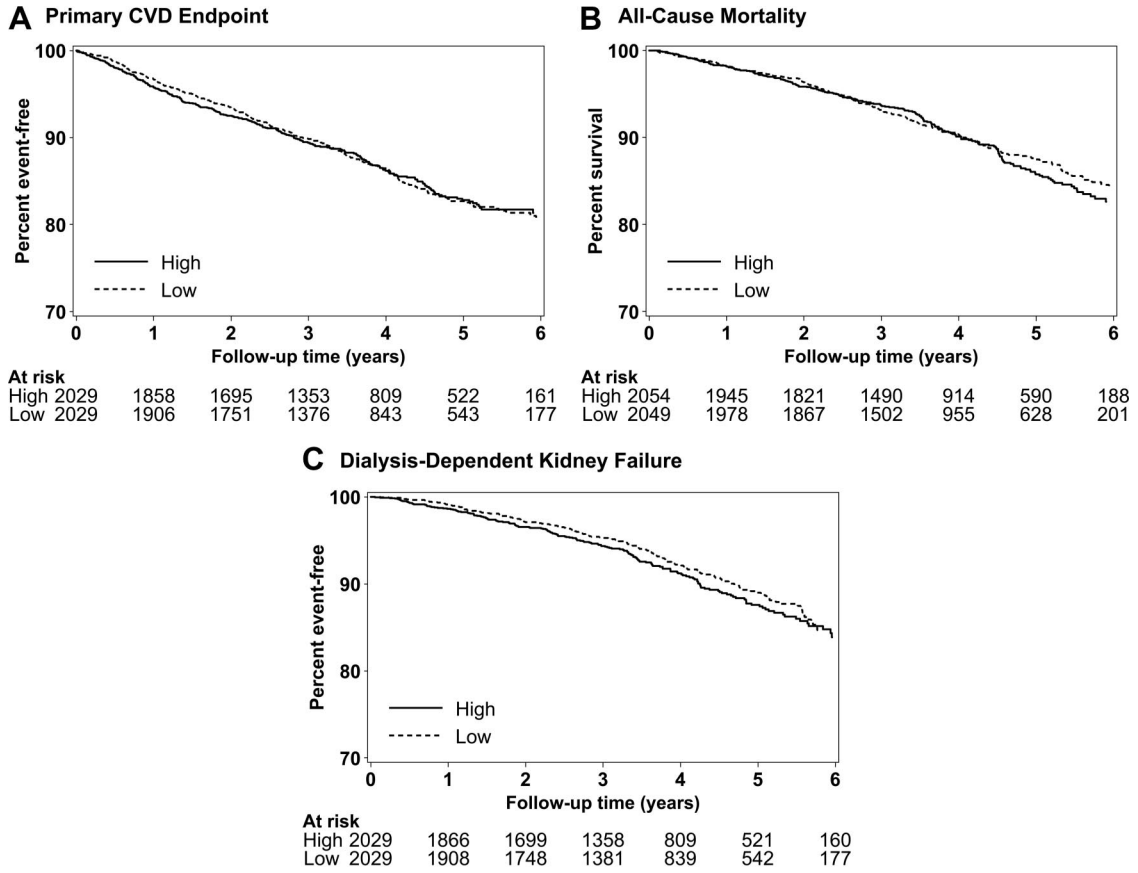

Figure 2. Kaplan–Meier analyses for (**A**) Primary CVD, (**B**) all-cause mortality, and (**C**) dialysis-dependent kidney failure outcomes. CVD indicates cardiovascular disease.

Discussion

Among stable kidney transplant recipients with increased levels of homocysteine and reduced kidney function, treatment with a multivitamin containing high doses of vitamin B6, vitamin B12, and folic acid did not reduce cardiovascular disease compared to a multivitamin with low doses of these ingredients. The high-dose multivitamin also did not reduce all-cause mortality or onset of dialysis-dependent kidney failure. The lack of a beneficial effect on these outcomes was observed despite a significant reduction in tHcy in a sample of the high-dose group. The frequency of adverse events did not differ by treatment group assignment.

Our findings may have applicability to the broader population of persons with CKD. Over three fourths of our study participants had an eGFR $<$60 mL/min per 1.73 m^2 (CKD stage 3T or 4T). As is the case for people with CKD of their native kidneys, the risk of CVD in kidney transplant recipients is increased compared to the general population. Levels of tHcy in the patients with CKD vary according to the level of GFR, ranging from $>$25 μmol/L in kidney failure treated by dialysis to 10 to 25 μmol/L for earlier stages of CKD, and higher doses of B vitamins than those provided in cereal grain fortification are required to lower homocysteine levels to the range observed in the upper quartile of the general population. Our findings in kidney transplant recipients are in accord with 2 clinical trials of patients with CKD stage 5 (eGFR $<$15 mL/min per 1.73 m^2 or dialysis),[12] or CKD stages 4 and 5 (eGFR of $<$30 mL/min per 1.73 m^2 or dialysis),[13] and a secondary analysis of the Heart Outcomes Prevention Evaluation (HOPE) 2 study participants with (primarily) CKD stage 3 (eGFR of 30 to 59 mL/min per 1.73 m^2).[14] Despite sustained $\approx$4.0 to 8.5 mmol reductions in tHcy achieved by these trials comparing active to placebo treatment, no decrease in CVD event or mortality rates was observed.[12–14]

The lack of a beneficial effect of homocysteine lowering that we observed in kidney transplant recipients can be added to the largely negative findings of a substantial number of clinical trials in a wide range of patient populations.[28–35] Those studies effectively rule out the possibility of large effects on risk of coronary heart disease, stroke, and all-cause mortality, given that the pooled risk ratio for major cardiovascular disease events in those studies was 1.02 (95% CI, 0.98 to 1.06).[10] However, our trial shares a few limitations with these studies. Although the high-dose multivitamin significantly reduced tHcy levels, mean values remained somewhat elevated. Importantly, the B-vitamin pathway for reducing tHcy may not be the optimal one for reducing CVD risk. Also, the duration of follow-up may not have been sufficient to identify a lagged impact on modification of CVD risk.

The lack of deleterious effects of homocysteine-lowering treatment on any of the major primary or secondary outcomes studied in FAVORIT is also concordant with results from trials of CKD and non-CKD populations.[10–14] In particular,

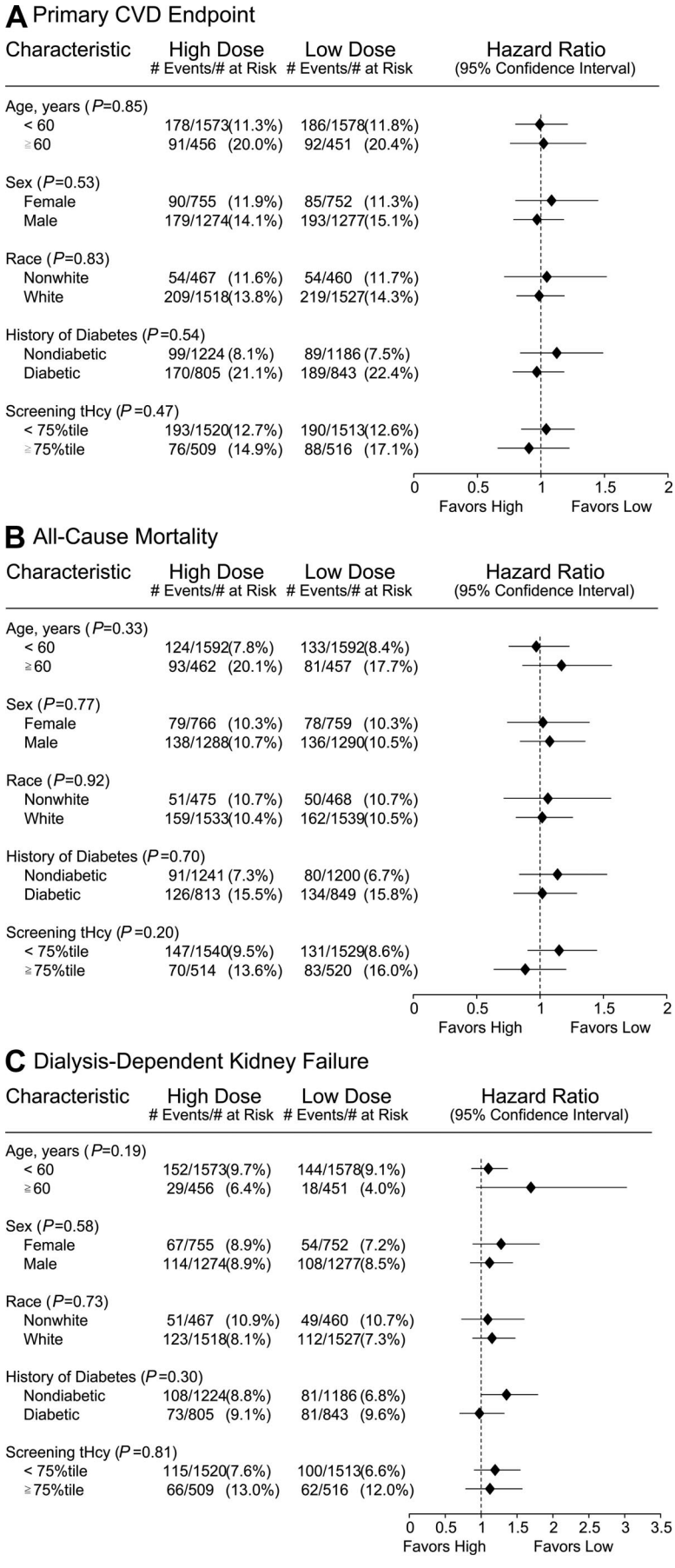

Figure 3. Hazard ratios for treatment group comparisons from primary and secondary outcome subgroup analyses. CVD indicates cardiovascular disease.

previously reported trials of CKD patients[12] found no evidence of increased overall mortality, fatal or nonfatal cancer incidence, or progression to dialysis-dependent kidney failure associated with any of the high-dose folic acid–based homocysteine-lowering regimens studied, relative to placebo treatment. Moreover, the absence of an increased hazard ratio for dialysis-dependent kidney failure in the high-dose group, despite 343 total events, is important given limited findings of a higher rate of decline in renal function observed among participants on B-vitamin therapy in the much smaller Diabetic Intervention with Vitamins to Improve Nephropathy trial.[36]

Why have clinical trials of homocysteine lowering uniformly failed to show a beneficial effect on CVD despite strong evidence for a beneficial effect seen in patients with marked hyperhomocysteinemia due to cystathionine β synthetase deficiency, whose risk for CVD is reduced by 90% with treatment,[4–5] and in view of the association of elevated tHcy levels with CVD seen in epidemiological studies?[37–42] It is likely that this is related to the marked difference in tHcy levels seen in patients with cystathionine β synthetase deficiency, whose levels even after treatment remain above 100 μmol/L,[5] compared with the levels more typically in the ranges of 12 to 25 μmol/L seen among patients in the observational studies. At these lower levels, it appears that the tHcy levels are a surrogate for other factors associated with increased CVD risk rather than a directly causative factor.

In conclusion, treatment of stable kidney transplant recipients with a multivitamin containing high-dose folic acid, B6, and B12 lowers tHcy levels relative to standard multivitamin supplementation and in many cases to normal levels but does not reduce CVD outcomes or total mortality in this patient population. Our findings add to the growing body of evidence from clinical trials of the failure of homocysteine lowering to reduce CVD, stroke, and all-cause mortality in a wide range of patient populations.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Kidney transplant recipients experience an excess risk of cardiovascular disease and elevated total homocysteine concentrations. Although observational studies of patients with chronic kidney disease suggest that increased homocysteine is a risk factor for cardiovascular disease, the clinical benefit of lowering total homocysteine levels in kidney transplant recipients is unknown. We randomized 4110 stable kidney transplant recipients to a multivitamin that included either a high dose (n=2056) or low dose (n=2054) of folic acid, vitamin B6, and vitamin B12 to determine whether decreasing total homocysteine concentrations reduced the rate of arteriosclerotic cardiovascular disease outcomes. After a follow-up of 4.0 years, the high-dose multivitamin reduced homocysteine levels but not the rates of the pooled arteriosclerotic outcome (n=547 total events; hazards ratio [95% confidence interval]=0.99 [0.84 to 1.17]), secondary outcomes of all-cause mortality (n=431 deaths; 1.04 [0.86 to 1.26]), or dialysis-dependent kidney failure (n=343 events; 1.15 [0.93 to 1.43]) compared to the low-dose multivitamin. We concluded that treatment with a high-dose folic acid, B6, and B12 multivitamin in kidney transplant recipients does not reduce cardiovascular disease outcome, all-cause mortality, or dialysis-dependent kidney failure despite significant reduction in homocysteine level.