Randomized Trial of Folic Acid for Prevention of Cardiovascular Events in End-Stage Renal Disease

ELIZABETH M. WRONE,* † JOHN M. HORNBERGER,‡ JAMES L. ZEHNDER,§ LINDA M. MCCANN,* NORMAN S. COPLON,* and STEPHEN P. FORTMANN, †

*Satellite Research, Redwood City, California; † Stanford Center for Research in Disease Prevention, Stanford University School of Medicine, Stanford, California; ‡ Acumen, LLC, Burlingame, California; § Department of Pathology, Stanford University School of Medicine, Stanford, California.

Abstract. High serum total homocysteine (tHcy) is gaining scrutiny as a risk factor for cardiovascular disease in the general population. The relationship between tHcy and mortality and cardiovascular events in patients with end-stage renal disease (ESRD) is unsettled. This randomized trial evaluates the efficacy of high-dose folic acid in preventing events in ESRD. A total of 510 patients on chronic dialysis were randomized to 1, 5, or 15 mg of folic acid contained in a renal multivitamin with a median follow-up of 24 mo. Mortality, cardiovascular events, and homocysteine levels were assessed. There were 189 deaths, and 121 patients experienced at least one cardiovascular event. Composite rates of mortality and cardiovascular events among the folic acid groups did not differ (at 24 mo: 43.7% in 1 mg group, 38.6% in 5 mg group, 47.1% in 15 mg group; log-rank \( P = 0.47 \)). Unexpectedly, high baseline tHcy was associated with lower event rates. From lowest to highest quartile, event rates at 24 mo were 54.5% for Q1, 41.8% for Q2, 41.2% for Q3, and 34.7% for Q4 (log-rank \( P = 0.033 \)). In contrast to some studies describing tHcy as a risk factor for mortality and cardiovascular events, this study found a reverse relationship between tHcy and events in ESRD patients. Administration of high-dose folic acid did not affect event rates.

End-stage renal disease (ESRD) afflicts nearly half a million people in the United States (1) and carries mortality rates from cardiovascular disease that are 10-fold to 100-fold higher than those of the general population (2). In ESRD, mean total homocysteine levels (tHcy) are commonly elevated, and the role of homocysteine as risk factor has been suggested in some small prospective studies (3–5). However, some studies in ESRD have observed an inverse relationship between tHcy and cardiovascular disease (6,7). Homozygosity for the common C677T mutation of methylenetetrahydrofolate reductase (MTHFR) (8), a key enzyme in homocysteine metabolism may also be associated with elevated tHcy levels and cardiovascular disease in ESRD (7,9).

Total serum homocysteine (tHcy) is readily reduced with folic acid and vitamin B12 in the general population. In ESRD, higher doses of folic acid appear to be required, and normal levels of homocysteine are not commonly achieved (10). Patients with ESRD are frequently given multivitamin supplements to compensate for dialysate losses and dietary restrictions; however, the optimal amount of folic acid supplementation in ESRD for reduction of tHcy has not been established.

To explore the relationship between folic acid, homocysteine, and clinical outcomes, we present the results of a randomized trial of folic acid for prevention of cardiovascular morbidity/mortality in patients with ESRD. The primary question addressed is “does supplementation with a multivitamin containing folic acid in 5-mg or 15-mg doses reduce a composite end point of mortality and cardiovascular events over 3 yr compared with standard therapy (1 mg of folic acid)?” Secondarily, “do these higher doses of folic acid prevent vascular access clotting?” In addition, we test the hypothesis that high levels of baseline tHcy and the TT genotype of the C677T mutation of MTHFR are associated with an increased incidence of cardiovascular events and mortality.

Materials and Methods

Participants

This randomized, double blind, three-arm study of homocysteine reduction was performed at 10 affiliated nonprofit outpatient dialysis facilities in Northern California. At the time of enrollment, approximately 1100 patients received treatment at these outpatient facilities. Patients were recruited by study dietitians at their dialysis units. Written consent was obtained from every patient after a full explanation of the study, which was approved by the Administrative Panel on Human Subjects in Medical Research of Stanford University. Adult patients undergoing hemodialysis or peritoneal dialysis and who were able to participate in the consent process were eligible for the study. Patients who were undergoing intradialytic parenteral nutrition, anticipating a living-related kidney transplant, receiving an anti-seizure...
terminations were performed at Satellite Laboratory Services, Inc. as
terol, albumin, blood urea nitrogen, creatinine, and pre-albumin de-
ation was performed using standard clinical diagnostic techniques by
levels higher than 45.3 nmol/L were diluted. Vitamin B12 determi-
to 45.3 nmol/L (normal range, 7.0 to 28.1 nmol/L). Specimens with
was determined using an ion capture assay, which remains linear up
Assessments
Participants were randomly assigned by computer to one of three
treatment groups using a biased-coin program. Treatment consisted of
therapeutically appearing capsules containing either (1) standard therapy
vitamin containing 1 mg of folic acid; (2) renal multivitamin containing 5 mg of folic acid; or (3) renal multivitamin
multivitamin with the study capsule once daily. Those who were not
taking a multivitamin before the study were asked to begin study
multivitamin. R&D Laboratories, Inc. (Marina del Rey, CA) donated
study capsules and participated in determining the formula of the
multivitamins. This donor did not contribute to study design, data
collection, analysis, interpretation of the data, or the decision to
approve the manuscript.

Randomization was stratified on age (18 to 54, 55 to 69, or >70
yr), gender, diabetes, and tHcy > 37 µmol/L. To maintain double-
blind status, neither the person performing the randomization nor the
person preparing study medication for distribution to clinical coordi-
nators had direct contact with participants. Patients, clinicians, and
study staff were provided with access to an information system that could identify treatment arm. Randomization codes were kept in
a separate, locked file.

Baseline clinical variables were collected at the time of enrollment.
These included age, gender, race/ethnicity, diabetes status, smoking
history, duration of renal replacement therapy, prescribed medication use
including dose and formulation of all vitamin supplements, height,
and dry weight (the prescribed, post-dialysis weight). For those on
hemodialysis, the following were collected: vascular access history,
pre and dialysis systolic and diastolic BP (averaged over nine treat-
ments), and recent dialysis adequacy parameters collected using the
K/DOQI-recommended slow flow, stop-pump procedure (11). Ade-
quacy parameters included normalized protein catabolic rate and Kt/V
(single-pool, variable volume), a unitless measure of dialysis dose.
Cardiovascular disease was defined as a history of coronary artery
intervention, myocardial infarction, stroke, transient ischemic attack,
carotid endarterectomy, or other clinical evidence of cardiovascular
disease as documented in hospital discharge summaries or history and
physical examination at admission to the dialysis unit. At baseline,
patients from four facilities were further assessed for compliance with
previous prescribed vitamins and for over-the-counter vitamin supple-
ment intake. TThcy, folate, and vitamin B12 levels were assessed at
baseline, and TThcy and folate levels at 2 mo, 6 mo, and 18 mo. All
patients had study blood samples drawn in conjunction with routine
monthly specimens, pre-dialysis for those on hemodialysis. TThcy
concentrations were determined by HPLC of serum specimens by
Quest Diagnostics (normal range, 2.8 to 13.5 µmol/L). Serum folate
determined using an ion capture assay, which remains linear up
to 45.3 nmol/L (normal range, 7.0 to 28.1 nmol/L). Specimens with
levels higher than 45.3 nmol/L were diluted. Vitamin B12 determi-
nation was performed using standard clinical diagnostic techniques by
Quest Diagnostics (normal range, 148–812 pmol/L). Total choles-
terol, albumin, blood urea nitrogen, creatinine, and pre-albumin de-
terminations were performed at Satellite Laboratory Services, Inc. as
part of the routine monthly care. Identification of the C677T translo-
cation was performed for the first 459 enrolled using HinfI digestion
and PCR amplification from specimens of peripheral blood lympho-
cytes as described by Frosst et al. (8). PCR analysis was performed in
the Molecular Diagnosis Laboratory, Department of Pathology, Stan-
ford University Medical Center.

Main outcomes of interest were cardiovascular events and mortal-
ity. Principal diagnoses and hospital discharge summaries were re-
viewed for ascertainment of coronary artery intervention, myocardial
infarction, stroke, transient ischemic attack, carotid endarterectomy,
limb amputation, or death. Secondary outcome was vascular access
thrombosis (among those with arteriovenous fistulae). Dialysis
records and discharge summaries were reviewed for ascertainment of
vascular access events. Additional information regarding renal trans-
plantation, relocation out of a participating facility, or transfer to
institutional care was collected.

Statistical Analyses
We determined that we needed a sample size of 175 per treatment
arm to detect a 20% difference in the composite endpoint after 3 yr
with a power of 70% and an alpha of 0.05. With this sample size, we
estimated that we had 90% power with an alpha of 0.05 to detect a
10% difference in tHcy levels between two groups.

We used Kaplan-Meier survival estimates to analyze time to first
event by treatment arm. All analyses were performed on an intention-
to-treat basis. Additional estimates were analyzed for quartile of
tHcy and C677T genotype. Because we found that the hazard
was not proportional over time, parametric survival models were
developed for the primary and secondary endpoints to assess the
effects of the following covariates: treatment arm, age, gender, dia-
betes status, baseline tHcy, C677T genotype, smoking status, albumin,
baseline vitamin usage, body mass index, race/ethnicity, BP, dialysis
modality, and serum total cholesterol. Results are reported as mean ±
SD, except where otherwise indicated. Data analyses were performed
using SAS Systems version 6.1.2 (SAS Institute, Inc., Cary, North
Carolina).

Results
Patient Characteristics
From March 1998 to May 1999, 578 patients with ESRD
were enrolled in the protocol. Of these, 510 patients (468 on
hemodialysis; 42 on peritoneal dialysis) were randomized,
TThcy, and vitamin B12 levels were assessed at
baseline, and TThcy and folate levels at 2 mo, 6 mo, and 18 mo. All
patients had study blood samples drawn in conjunction with routine
monthly specimens, pre-dialysis for those on hemodialysis. TThcy
concentrations were determined by HPLC of serum specimens by
Quest Diagnostics (normal range, 2.8 to 13.5 µmol/L). Serum folate
determined using an ion capture assay, which remains linear up
to 45.3 nmol/L (normal range, 7.0 to 28.1 nmol/L). Specimens with
levels higher than 45.3 nmol/L were diluted. Vitamin B12 determi-
nation was performed using standard clinical diagnostic techniques by
Quest Diagnostics (normal range, 148–812 pmol/L). Total choles-
terol, albumin, blood urea nitrogen, creatinine, and pre-albumin de-
terminations were performed at Satellite Laboratory Services, Inc. as
part of the routine monthly care. Identification of the C677T translo-
cation was performed for the first 459 enrolled using Hinfl digestion
and PCR amplification from specimens of peripheral blood lympho-
cytes as described by Frosst et al. (8). PCR analysis was performed in
the Molecular Diagnosis Laboratory, Department of Pathology, Stanford University Medical Center.

Main outcomes of interest were cardiovascular events and mortal-
ity. Principal diagnoses and hospital discharge summaries were re-
viewed for ascertainment of coronary artery intervention, myocardial
infarction, stroke, transient ischemic attack, carotid endarterectomy,
limb amputation, or death. Secondary outcome was vascular access
thrombosis (among those with arteriovenous fistulae). Dialysis
records and discharge summaries were reviewed for ascertainment of
vascular access events. Additional information regarding renal trans-
plantation, relocation out of a participating facility, or transfer to
institutional care was collected.

Statistical Analyses
We determined that we needed a sample size of 175 per treatment
arm to detect a 20% difference in the composite endpoint after 3 yr
with a power of 70% and an alpha of 0.05. With this sample size, we
estimated that we had 90% power with an alpha of 0.05 to detect a
10% difference in tHcy levels between two groups.

We used Kaplan-Meier survival estimates to analyze time to first
event by treatment arm. All analyses were performed on an intention-
to-treat basis. Additional estimates were analyzed for quartile of
tHcy and C677T genotype. Because we found that the hazard
was not proportional over time, parametric survival models were
developed for the primary and secondary endpoints to assess the
effects of the following covariates: treatment arm, age, gender, dia-
betes status, baseline tHcy, C677T genotype, smoking status, albumin,
baseline vitamin usage, body mass index, race/ethnicity, BP, dialysis
modality, and serum total cholesterol. Results are reported as mean ±
SD, except where otherwise indicated. Data analyses were performed
using SAS Systems version 6.1.2 (SAS Institute, Inc., Cary, North
Carolina).

Results
Patient Characteristics
From March 1998 to May 1999, 578 patients with ESRD
were enrolled in the protocol. Of these, 510 patients (468 on
hemodialysis; 42 on peritoneal dialysis) were randomized,
received study intervention, and included in analyses (intention
to treat) (Figure 1). Baseline demographic and clinical charac-
teristics by treatment arm of the 510 randomized patients who
received study intervention are shown in Table 1. There was no
difference in any of the demographic, clinical, and laboratory
values among the treatment groups with the exception of Kt/V,
(P = 0.04). The racial/ethnic groups represented were 207
non-Hispanic white, 153 Hispanic, 76 Asian/Pacific Islander,
The findings of this randomized, double-blind clinical trial of folic acid therapy in ESRD fail to support any effect of doses above 1 mg/d on cardiovascular disease or other outcomes. The trial design provided adequate but limited power; however, there is little evidence of any benefit trend that might become significant in a larger trial. Baseline characteristics and compliance were well balanced across groups. Compliance did fall events were analyzed separately. See Table 2 for numbers of individual events at 24 mo by quartile baseline tHcy. There was no difference in event rates among the MTHFR genotypes (log-rank $P = 0.60$).

Response to Treatment

Adherence was assessed by serum folate levels. Patients in arm 1 (1 mg of folic acid) whose serum folate level dropped during follow-up were considered non-adherent. Patients in arms 2 (5 mg of folic acid) or 3 (15 mg of folic acid) were considered non-adherent if follow-up folate was not elevated by at least 45.3 nmol/L over baseline. Non-adherence rates were similar among all three arms at all three follow-up assessments (percentage non-adherent by treatment arms 1 through 3, respectively: 21, 18, 17 [$P = 0.69$] at 2 mo; 25, 26, 21 [$P = 0.69$] at 6 mo; and 23, 18, 33 [$P = 0.17$] at 18 mo).

All three treatments reduced tHcy at 2 mo, 6 mo, and 18 mo when compared with baseline tHcy in an intention-to-treat analysis. Among those remaining in the study at 18 mo, the difference in geometric mean tHcy levels from baseline to 18 mo was 3.7 $\mu$mol/L for arm 1 (1 mg of folic acid), 4.3 $\mu$mol/L for arm 2 (5 mg of folic acid), and 10.2 $\mu$mol/L for arm 3 (15 mg of folic acid). The differences between each arm were significant by Jonckheere test ($P = 0.049$ at 18 mo). At 18 mo, there was no difference in the percentage of patients with tHcy $<$15 $\mu$mol/L (7.69% arm 1, 6.85% arm 2, and 10.0% arm 3; $P = 0.81$).

Multivariate Analyses

In a parametric survival model predicting the primary outcome, mortality, and cardiovascular events, with baseline tHcy and treatment arm as predictors, only baseline tHcy remained significant. For every 1-$\mu$mol/L increase in tHcy, the RR for an event decreased by 1.4% ($P = 0.0015$). Treatment arm variables were NS. Models were developed with the following predictor variables: treatment arm, age, gender, diabetes status, baseline tHcy, C677T genotype, smoking status, albumin, baseline vitamin usage, body mass index, race/ethnicity, BP, dialysis modality, and serum total cholesterol. Age, albumin, and race/ethnicity remained the only significant predictors.

Interactions

Whereas mean albumin was lower among those with low tHcy (Table 2), there was no evidence for reversal of effects of high tHcy among those with low serum albumin on events at 24 mo (Figure 4). No interactions were detected for baseline tHcy quartile with treatment arm, MTHFR genotype, or albumin quartile.

Discussion

The side effects were equally distributed among participants, the Kaplan-Meier curve revealed no difference in event rates at 24 mo among quartiles of baseline tHcy (from lowest to highest at 24 mo: 54.5% quartile 1, 41.8% quartile 2, 41.2% quartile 3, 34.7% quartile 4; log-rank $P = 0.033$) (Figure 3). This relationship was similar when total survival and cardiovascular

Survival and Cardiovascular Events

As depicted on the Kaplan-Meier curve (Figure 2), there was no difference in the composite end point at 24 mo (43.7% in arm 1, 38.6% in arm 2, 47.1% in arm 3; log-rank $P = 0.47$) among the treatment arms. See Table 2 for numbers of individual events by treatment arm. Similarly, there was no difference among the treatment arms in total survival or cardiovascular events when analyzed separately.

Vascular Access Clotting

Analyzing time to first vascular access clot for the hemodialysis patients, the Kaplan-Meier curve revealed no difference in event rates at 24 mo among the treatment arms (36.9% arm 1, 31.1% arm 2, 38.1% arm 3; log-rank $P = 0.82$).

Baseline tHcy and C677T Mutation of MTHFR

Using the primary outcome of cardiovascular events and mortality, there was a significant difference in event rates among quartiles of baseline tHcy (from lowest to highest at 24 mo: 54.5% quartile 1, 41.8% quartile 2, 41.2% quartile 3, 34.7% quartile 4; log-rank $P = 0.033$) (Figure 3). This relationship was similar when total survival and cardiovascular
**Table 1. Baseline characteristics of study population by folic acid group**

<table>
<thead>
<tr>
<th></th>
<th>Folic Acid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Units 1 mg 5 mg 15 mg</td>
</tr>
<tr>
<td><strong>Demographic and clinical</strong></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>168.00 176.00 166.00</td>
</tr>
<tr>
<td>age</td>
<td>61.30 ± 14.62 59.77 ± 15.42 59.51 ± 15.38</td>
</tr>
<tr>
<td>male</td>
<td>50.00 51.14 48.80</td>
</tr>
<tr>
<td>race/ethnicity = whitea</td>
<td>67.26 67.61 69.88</td>
</tr>
<tr>
<td>diabetic</td>
<td>47.62 44.32 44.58</td>
</tr>
<tr>
<td>duration of dialysis</td>
<td>3.84 3.47 3.57</td>
</tr>
<tr>
<td>BMI</td>
<td>26.81 ± 6.65 25.27 ± 5.64 26.08 ± 5.79</td>
</tr>
<tr>
<td>current smokers</td>
<td>9.52 12.50 9.04</td>
</tr>
<tr>
<td>past smokers</td>
<td>31.60 36.40 32.50</td>
</tr>
<tr>
<td>cardiovascular disease present</td>
<td>29.76 34.66 37.95</td>
</tr>
<tr>
<td>taking folate prior to study</td>
<td>77.98 78.98 81.33</td>
</tr>
<tr>
<td>peritoneal dialysis</td>
<td>8.93 9.66 6.02</td>
</tr>
<tr>
<td>systolic BPb</td>
<td>156.41 ± 19.54 155.87 ± 20.46 154.23 ± 21.49</td>
</tr>
<tr>
<td>diastolic BPb</td>
<td>78.86 ± 11.68 79.23 ± 12.66 79.41 ± 12.03</td>
</tr>
<tr>
<td><strong>Laboratory assessments</strong></td>
<td></td>
</tr>
<tr>
<td>homocysteine</td>
<td>34.71 ± 20.22 30.62 ± 14.36 33.52 ± 26.61</td>
</tr>
<tr>
<td>serum folate</td>
<td>45.91 ± 29.87 47.16 ± 34.26 49.04 ± 34.85</td>
</tr>
<tr>
<td>vitamin B12</td>
<td>503.21 ± 314.47 514.51 ± 322.93 518.16 ± 358.32</td>
</tr>
<tr>
<td>serum creatinine</td>
<td>706.93 ± 234.12 677.95 ± 218.87 664.99 ± 245.56</td>
</tr>
<tr>
<td>serum albumin</td>
<td>34.90 ± 3.5 40.00 ± 3.5 39.70 ± 3.6</td>
</tr>
<tr>
<td>pre-albumin</td>
<td>31.00 ± 7.37 33.06 ± 8.10 31.70 ± 3.93</td>
</tr>
<tr>
<td>serum cholesterol</td>
<td>4.61 ± 1.12 4.66 ± 1.09 4.52 ± 1.13</td>
</tr>
<tr>
<td>TT genotype C677T variant</td>
<td>178.10 ± 43.12 179.89 ± 42.15 174.39 ± 43.82</td>
</tr>
<tr>
<td>MTHFR%</td>
<td>12.34 13.46 12.75</td>
</tr>
<tr>
<td>CT genotype C677T variant</td>
<td></td>
</tr>
<tr>
<td>MTHFR%</td>
<td>40.26 36.54 43.62</td>
</tr>
<tr>
<td>KT/Vc</td>
<td>1.50 ± 0.38 1.59 ± 0.47 1.63 ± 0.54</td>
</tr>
<tr>
<td>NPCRd</td>
<td>0.94 0.97 0.96</td>
</tr>
</tbody>
</table>

Data expressed with the plus/minus sign are mean ± SD.
a Includes both non-Hispanic and Hispanic.
b Hemodialysis patients, predialysis, averaged over nine treatments, n = 468.
c KT/V is a unit-less measure of dialysis dose. Hemodialysis patients only, n = 466.
d NPCR, normalized protein catabolic rate. Hemodialysis patients only, n = 466.

Over time, so the intention-to-treat analysis would underestimate a true effect; however, the highest incidence of the composite end point was in the 15-mg group, so this seems an unlikely explanation for the null result. The effect of folic acid on homocysteine was less than we anticipated from preliminary data, and we cannot exclude the possibility that higher doses of folic acid would be beneficial. We conclude that folic acid supplementation in ESRD is unlikely to produce benefit at doses between 1 and 15 mg/d. Further elucidation of the role of tHcy and other risk factors in the pathogenesis of cardiovascular disease is needed before establishing guidelines concerning higher doses of folic acid in ESRD.

Unexpectedly, higher tHcy at the time of study enrollment was associated with better clinical outcomes. This finding is contrary to many prospective studies of the general population, but it is similar to findings for other cardiovascular risk factors in patients with ESRD, probably due to confounding. Although we were able to achieve a modest reduction in tHcy with the higher doses of folic acid, this reduction did not positively or negatively effect outcomes, nor did it achieve a statistically significant improvement in the fraction of patients who reached normal tHcy levels. These dose-response characteristics are in concordance with those of other studies (13-15). Homozygosity for C677T MTHFR genotype was not associated with higher clinical event rates in this prospective analysis.

The inverse association between baseline tHcy and clinical outcomes may have several explanations. First, determination of tHcy in ESRD may not represent lifetime tHcy exposure, as other factors related to renal replacement therapy, such as dialysis dose, may influence tHcy levels. Second, there may be
unmeasured nutritional and/or inflammatory factors that serve to suppress tHcy levels while simultaneously augmenting atherosclerosis (16,17). Third, these results may demonstrate “reverse epidemiology.” Reverse epidemiology has been described for other cardiovascular risk factors where a dramatically different relationship occurs for outcomes in patients with ESRD compared with the general population (6,22–24). Underlying factors are responsible for driving the apparent reversal of relationships seen in statistical analyses, rather than a reversal of basic pathophysiology. This has been demonstrated in ESRD in a hypothetical model where adjustment for malnutrition reverses the relationship between cholesterol and survival (18).

Fourth, the homocysteine hypothesis of atherosclerosis has yet to be fully confirmed. Despite two recent positive clinical trials of folic acid in those with normal renal function (19,20) not all epidemiologic studies in the general population have supported a causal relationship (21–24). Further clouding our understanding of the pathophysiology is evidence that folate may have direct beneficial effects on the vasculature, independent of homocysteine (25,26). Our study might not have been able to detect this folate effect because of the absence of a placebo arm or the much higher levels of folate and tHcy prevalent in ESRD or both.

In our study, higher doses of folic acid reduced tHcy modestly. This is not surprising given that patients with ESRD on chronic dialysis appear to be resistant to the tHcy-reducing effects of higher doses of folic acid. We found an inverse relationship between tHcy and cardiovascular events and mortality; therefore, the lack of difference in outcomes between the groups could have resulted from three hypothetical situations. One, tHcy reduction is beneficial, and this study was underpowered due to small effect size and due to strong confounding of associations. Two, tHcy reduction is harmful, and this study was too small to detect differences in outcomes. Three, tHcy is not a causative agent (or plays a very minor role) in this group of patients who tend to suffer from multiple, advanced chronic diseases. The answer will likely be discovered in populations where tHcy reduction is more readily achieved, such as in renal transplant recipients or chronic kidney disease, where clinical trials are already underway.

Our study likely represents the largest and longest prospective study of cardiovascular events, tHcy, and the MTHFR genotype in ESRD to date. Our prospective findings are similar to those of Suliman et al. (6) and differ in direction from those of Moustapha et al. (4). The most notable contrast to our findings originates from the CREED (5) study, where tHcy was found to be an independent predictor of fatal and nonfatal atherothrombotic events. Fundamental design differences in CREED, such as exclusion of those with preexisting cardiovascular disease or on folic acid supplementation, make direct comparisons difficult. The lack of association between C677T genotype of MTHFR and outcomes is consistent with findings of a meta-analysis (21) and a study in Japanese hemodialysis patients (27).

There are several limitations of this study. First, it was an effectiveness study, performed in a clinical environment. There were no washout or run-in periods to establish patterns of compliance or to examine the effect of the study medication after creating a uniform, supplement-free environment. Previous supplement use, however, did not influence homocysteine reduction in this study. Conceivably, with a vitamin-free run-in period, there would have been patients with higher baseline tHcy and correspondingly larger reductions in response to treatment. Despite the fact that more than three quarters of the participants were taking a folate-containing multivitamin before enrollment, there was a dose response at 2 and 18 mo. The fortification of the national grain supply started during this period, there would have been patients with higher baseline tHcy and correspondingly larger reductions in response to treatment. Despite the fact that more than three quarters of the participants were taking a folate-containing multivitamin before enrollment, there was a dose response at 2 and 18 mo. The fortification of the national grain supply started during this period, an amount that we would not anticipate to influence a study using 1 to 15 mg/d folic acid. All three treatment arms achieved a significant reduction in tHcy. We could have conceivably missed an effect of folic acid if there was one between a placebo and 1 mg. Finally, survivor bias can exert a strong influence when patients are enrolled with varying degrees of dialysis duration. Ideally, clinical studies include patients from the same duration cohort and attempt to control for differences in residual renal function.

In conclusion, for patients with ESRD treated with dialysis, these results do not support administration of doses of folic acid beyond the generally recommended 1 mg/d. There are several large clinical trials in the general population that over the next few years will shed light on the role of folic acid and other B-vitamins in preventing cardiovascular disease, as well as a large trial in ESRD and renal insufficiency patients that is using higher doses of folic acid.

Acknowledgments

Dr. Wrone was supported by a National Institutes of Health Training Grant DK 07357–16A to the Division of Nephrology, Department of Medicine, Stanford University School of Medicine from July 1997 through June 1999. Study multivitamins were provided by R&D Laboratories, Inc., Marina del Rey, CA.

Figure 2. Event-free survival by folic acid group.
Table 2. Number of events at 24 mo by folic acid group and baseline total homocysteine quartile (low to high)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>1 mg (n = 168)</th>
<th>5 mg (n = 176)</th>
<th>15 mg (n = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>8</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Revascularization procedurea</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>56</td>
<td>44</td>
<td>61</td>
</tr>
<tr>
<td>Vascular access eventb</td>
<td>70</td>
<td>68</td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Homocysteine Quartile</th>
<th>Q1 (n = 128)</th>
<th>Q2 (n = 130)</th>
<th>Q3 (n = 125)</th>
<th>Q4 (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>9</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Revascularization procedurea</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>51</td>
<td>39</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Vascular access eventb</td>
<td>49</td>
<td>53</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>Serum albumin, mean, g/L</td>
<td>38.4</td>
<td>39.4</td>
<td>40.4</td>
<td>40.8</td>
</tr>
</tbody>
</table>

a Includes cardiac surgery, percutaneous coronary intervention, and carotid endarterectomy.
b Includes vascular access thrombosis and new permanent vascular access.

Figure 3. Event-free survival by quartile of baseline total homocysteine (quartile 1 lowest).

Figure 4. Composite events at 24 mo by high and low (split at median) tHcy and albumin.

References


The Consequences and Costs of Chronic Kidney Disease Before ESRD

Lawrence G. Hunsicker

See related article by Smith et al. (pp. 1300–1306).

ANNOUNCEMENTS

Cover picture: Strategy for therapeutic cloning and tissue engineering. For detailed information, see Koh and Atala on pages 1113–1125.

For all articles highlighted in green, access to UpToDate online is available for additional clinical information.

Blue stars indicate articles that are featured in This Month’s Highlights.

ERRATA


In the legends to Figures 2, 3, 4, 5, and 6, all values reported in milligrams (mg) should have been reported in micrograms (µg). JASN regrets the error.


The legend to Figure 3 should read as follows: “Event-free survival by quartile of baseline total homocysteine (quartile 1 highest).” JASN regrets the error.