Hyperhomocysteinemia in Chronic Renal Disease

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Cardiovascular disease (CVD) is the major cause of death both in the general population and in patients with end-stage renal disease (ESRD). CVD is responsible for approximately 40% of all deaths in both demographic groups (1,2). Although the proportion of people dying of cardiovascular causes is similar, the risk of CVD is far greater for patients with ESRD. Even after stratification by age, gender, race, and presence of diabetes, CVD mortality in dialysis patients is 10 to 20 times higher than in the general population (3). Renal transplant recipients (RTR) experience at least twofold increases in the annual death rate from CVD, and fourfold increases in pooled nonfatal and fatal CVD incidence relative to population-based estimates (1,3–5) (Table 1). The excess risk of CVD in chronic renal disease is due in part to a higher prevalence of established arteriosclerotic risk factors, including older age, hypertension, diabetes, dyslipidemia, and physical inactivity (4,6–8). However, unique renal-related risk factors, including hemodynamic and metabolic factors characteristic of chronic renal disease, also likely contribute to this excess CVD risk (4,6–8).

Prominent among these unique renal-related risk factors are elevated levels of the putatively atherothrombotic sulfur amino acid homocysteine. Homozygous genetic disorders (i.e., the homocystinurias) result in marked hyperhomocysteinemia (to >100 µmol/L) and are clearly associated with precocious atherothrombotic events (9). However, unique renal-related risk factors, including hemodynamic and metabolic factors characteristic of chronic renal disease, also likely contribute to this excess risk (4,6–8).

Etiology of Hyperhomocysteinemia

Homocysteine Levels, and the Prevalence and Epidemiology: Determinants of Plasma/Serum Homocysteine Levels, and the Prevalence and Etiology of Hyperhomocysteinemia

General Populations

Approximately 70 to 80% of circulating plasma/serum tHcy is bound to large proteins (e.g., albumin) (22), the remainder consisting of a “free” acid-soluble fraction, i.e., reduced Hcy (<1%), homocysteine disulfide, and the predominant non-protein-bound forms, homocysteine-mixed disulfides (22). Folate, pyridoxal 5′-phosphate (PLP or “active” vitamin B6), and vitamin B12 are the main vitamin cofactors/substrates for homocysteine metabolism (Figure 1). Vitamin B12 and folate play a critical role in the remethylation of homocysteine to methionine (23). Betaine (trimethylglycine) is another substrate that participates in the remethylation of homocysteine to methionine via a B12/folate-independent reaction (24).

Vitamin B6 (as PLP), conversely, has a minor role in the remethylation pathway, but is crucial for the irreversible sulfuration of homocysteine to cystathionine, as well as the subsequent hydrolysis of cystathionine to cysteine and alphaketobutyrate (24). Consistent with this underlying biochemis-
try, population-based data indicate that intake and plasma status of folate, vitamin B6, and vitamin B12 are important determinants of tHcy levels (23). Mild, subclinical inherited defects in the key remethylation or transsulfuration pathway enzymes, alone or via interactions with B vitamin status, may also influence tHcy levels in general populations (23–25). Selhub and Miller (24) have hypothesized that two distinct forms of hyperhomocysteinemia can result when normal S-adenosylmethionine (SAM)-regulated partitioning of homocysteine between the remethylation and transsulfuration pathways is disrupted. Impairment of the remethylation pathway due primarily (on a population basis) to inadequate status of folate or vitamin B12 results in hyperhomocysteinemia under fasting conditions. Conversely, impairment of the transsulfuration pathway is associated with normal or only very mildly elevated tHcy levels under fasting conditions, but with substantial elevations after a methionine load. Both animal model findings (26,27) and clinical observations from humans (28–30) support this hypothesis. Finally, a randomized, placebo-controlled 2 × 2 factorial-designed tHcy-lowering intervention study recently demonstrated that B6 treatment independently reduced the 2-h post-methionine loading (PML) increase in tHcy levels among stable renal transplant recipients (21).

Creatinine (31,32) and albumin (33) are two additional, independent determinants of tHcy levels in general populations, unrelated to B vitamin status. The generation of s-adenosylhomocysteine from s-adenosylmethionine is coupled to creatine-creatine synthesis, which likely accounts for the direct association observed between creatinine and fasting tHcy levels in people with normative renal function (31,32). As noted earlier, 70 to 80% of serum/plasma tHcy is protein-bound, most likely to albumin (22), which may account for the direct relationship between albumin and tHcy levels found in the general population (33).

Severe cases of hyperhomocysteinemia, as in homocystinuria, may be due to rare homozygous defects in genes encoding for enzymes involved in either homocysteine remethylation or transsulfuration. The classic form of such a disorder is that caused by homozygosity for a defective gene encoding for cystathionine beta synthase, a condition in which fasting plasma homocysteine concentrations can be as high as 400 to 500 μmol/L (34). Homozygous defects of other genes that lead to similar elevations in plasma homocysteine concentration include those encoding for methylenetetrahydrofolate reductase (35) or for any of the enzymes that participate in the synthesis of methylated vitamin B12 (36).

### Populations with Renal Disease

It has been convincingly demonstrated that normal urinary excretion of homocysteine is trivial (37,38), and plasma elimination of homocysteine in ESRD is grossly retarded (39). However, the ultimate etiology of the mild hyperhomocysteinemia so consistently noted in renal insufficiency and ESRD (see below) remains unexplained. Despite in vitro studies demonstrating renal tubular metabolism of homocysteine (40,41), and rat model evidence of significant in vivo renal homocysteine metabolism (42), nonsignificant mean human renal arteriovenous differences for fasting (total and non-protein-bound) homocysteine were recently reported (43). These findings (43) have rekindled a search for “uremia-induced” extrarenal (presumptively, hepatic) defects in homocysteine metabolism. It should be noted, however, that (1) it may be hazardous to extrapolate findings regarding renal homocysteine metabolism from the fasting to nonfasting state; and (2) mild decrements in GFR, determined either by direct measurement (44,45) or using a sensitive surrogate like cystatin C (46) encompassing clearly nonuremic ranges of GFR, are strongly and independently associated with (linear) increases in fasting tHcy levels. Indeed, evidence has been presented that “hyperfiltrating” diabetic subjects with supernormal GFR may have “subnormal” fasting tHcy levels (45) (Figure 2).

In an early (i.e., pre-cyclosporine/tacrolimus era) study of 27 stable RTR, Wilcken and colleagues (47) reported a significant association between creatinine and cysteine-homocysteine-mixed disulfide within a serum creatinine range of approximately 100 to 500 μmol/L. In accord with these data, we found

### Table 1. Arteriosclerotic cardiovascular disease incidence after renal transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Posttransplant Incidenceb</th>
<th>Expectedc CVD Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients without CVD</td>
<td>All Patients (%)</td>
</tr>
<tr>
<td>Pretransplant (%)</td>
<td>Posttransplant (%)</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>6.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.4</td>
<td>7.8</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>3.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Thrombotic strokes</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Coronary heart disease (1 and 2)</td>
<td>11.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Cerebrovascular disease (3 and 4)</td>
<td>6.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Total CVD (1, 2, 3, 4, and 5)</td>
<td>15.8</td>
<td>21.3</td>
</tr>
</tbody>
</table>

*From reference 7. CVD, cardiovascular disease.

*Based on a mean of 46 ± 36 mo of follow-up.

*Framingham data (94).
that renal function may be a particularly crucial determinant of tHcy levels in RTR, both under fasting conditions, and post-methionine loading (48). Although Arnadottir and colleagues (49) have contended that cyclosporine use exerts an “independent” influence on fasting tHcy levels in these patients, both multivariable regression modeling (48) and matched analyses (38) have revealed that cyclosporine use is not an independent determinant of tHcy levels in RTR after appropriate adjustment for renal function indices (in particular), age, and gender. Finally, although unadjusted correlations between fasting plasma tHcy and folate levels among RTR have been reported (38,47–49), multivariable modeling to determine the independent strength of this association (for example, relative to indices of renal function) was not performed in any of these studies.

Plasma or serum levels of free, protein-bound, and tHcy are elevated in patients with varying degrees of renal impairment (19,47,49–54). Two reports (50,55) have documented the prevalence of mild-to-moderate hyperhomocysteinemia in dialysis patients relative to age-, gender-, and race-matched population-based controls free of clinical renal disease whose serum creatinine levels were ≤1.5 mg/dl (Table 2). These data indicated that hyperhomocysteinemia (fasting tHcy levels >13.9 μmol/L, the 90th percentile control value) occurred in 83% of the dialysis patients, a 105-fold increased risk (matched prevalence odds) relative to the controls. Recently, prevalence data for fasting hyperhomocysteinemia in RTR have been published (48). These analyses provide the first documentation of an apparent excess prevalence of PML hyperhomocysteinemia (matched odds ratio 6.9), and combined fasting and PML hyperhomocysteinemia (matched odds ratio 18.0) in RTR versus age and gender-matched population-based controls with normative renal function.
odds ratio (95% confidence interval) for a tHcy level ≥12 μmol, comparing the renal transplant to coronary artery disease patients, was 25.5 (range, 10.8 to 60.5), and adjustment for potential confounding by age, gender, albumin, and vitamin status did not appreciably attenuate this odds ratio: 20.3 (range, 7.9 to 52.2). In the current era of folic acid-fortified cereal grain flour, hyperhomocysteinemia is much more common in stable renal transplant versus coronary artery disease patients. As a result, RTR may be a preferable high-risk target population for controlled trials conducted in the United States evaluating the tenable hypothesis that lowering total homocysteine levels will reduce cardiovascular disease outcomes.

Homocysteine and Arteriosclerosis: Epidemiologic Evidence

General Populations

In 1969, the clinical observations of McCully first linked marked hyperhomocysteinemia (i.e., equivalent to tHcy levels of 100 to 450 μmol/L by current assays) to precocious arteriosclerotic disease in autopsied children who died from distinct metabolic forms of homocystinuria (56). Nearly 30 yr later, a burgeoning amount of observational evidence has accumulated indicating that mild-to-moderate fasting, nonfasting, or PML hyperhomocysteinemia (i.e., tHcy levels ≥12 μmol/L to ≤100 μmol/L fasting or nonfasting; or ≥50 μmol/L to ≤140 μmol/L 6-h PML) is an independent risk factor for arteriosclerotic outcomes. A recent series of meta-analyses (11–13), which has been updated through August 1998, has concluded that the best estimate for the increased risk of arteriosclerotic CVD morbidity and mortality comparing fasting and or nonfasting tHcy levels of ≥15 μmol/L to ≤10 μmol/L, after adjustment for the established CVD risk factors, was 1.4. This estimate is unaffected when only prospective studies are analyzed (seven studies, n = approximately 1400 incident events), including the recently reported Atherosclerosis Risk in Communities (57) and British United Provident Association (58) cohort studies (Dr. S. A. A. Beresford, personal communication). More recent prospective data not included in these meta-analyses from the Scottish Heart Health Study (59) indicates that tHcy levels were independently predictive of incident coronary heart disease in both Scottish women and men. Furthermore, two additional prospective studies also not included in these meta-analyses have examined the potential association between tHcy levels and CVD mortality. The first of these reports found a strong, independent link between tHcy levels and subsequent CVD death in patients with angiographically confirmed coronary artery disease (60), and the second study found a more modest, but significant independent association between tHcy levels and CVD mortality in the elderly population-based Framingham cohort (61).

Finally, a large, multicenter European case control study has confirmed that PML hyperhomocysteinemia confers a risk for prevalent CVD equal in magnitude to, and independent of, fasting hyperhomocysteinemia (62). Initial prospective follow-up (approximately 4.5 yr) of this cohort with prevalent CVD has revealed that post-load hyperhomocysteinemia may independently predict subsequent CVD death (63).
It has been proposed that clinical or even subclinical arteriosclerosis itself somehow raises tHcy levels, resulting in a spurious association between mild hyperhomocysteinemia and clinical CVD, due to reverse causality (57, 64). This hypothesis appears untenable in light of the pooled epidemiologic evidence from all published observational studies (as opposed to the highly selective citation methods used in references (57) and (64)) conducted in populations free of renal disease (re-reviewed above), the prospective data from renal disease populations (16–19) reviewed below, and the following published findings from additional human and animal studies:

1. Despite the absence of any traditional CVD risk factors, 50% of untreated children and young adults with homocystinuria due to cystathionine synthase deficiency experience a major atherothrombotic event by age 30 (9). Furthermore, strategies designed solely to reduce tHcy levels in these patients have been shown to decrease atherothrombotic event rates (9, 10).

2. In adults \((n = 38; \text{mean age, } 58 \pm 12 \text{ yr})\) with mild hyperhomocysteinemia, tHcy-lowering treatment reduces the rate of progression of ultrasound-determined extracranial carotid artery plaque area (65).

3. Young, healthy subjects, free of clinical arteriosclerosis or CVD risk factors, who have normal baseline flow-mediated brachial artery reactivity, experience a dramatic “dose–response” reduction in their flow-mediated brachial artery reactivity following acute hyperhomocysteinemia produced by an oral L-methionine load (66).

4. Randomized, controlled studies have revealed that mild, dietary-induced, hyperhomocysteinemia resulted in abnormal vascular reactivity among nonhuman primates (67), as well as increased arterial stiffness and frank atherothrombotic sequelae in minipigs (68).

Indeed, a plausible alternative to the reverse causality hypothesis is quite possible. There is a well established association between subclinical coronary artery disease or generalized arteriosclerosis and nephrosclerosis (69, 70). Bearing these data in mind, a strong, independent association \((r = 0.379; \text{P } < 0.001)\) has been demonstrated between the serum levels of cystatin C, a more sensitive marker of mildly impaired GFR than serum creatinine, and plasma tHcy levels, in 164 consecutively examined coronary artery disease patients whose serum creatinine was \<=1.4 mg/dl (71). Accordingly, subclinical renal impairment (secondary to nephrosclerosis) and resultant mild hyperhomocysteinemia may antedate, and hence contribute to, the development of clinical arteriosclerosis, including coronary artery disease.

Finally, although we do not believe the reverse causality hypothesis is tenable, we certainly agree that the simultaneous pursuit of two related areas of investigation will be required to confirm a causal relationship between hyperhomocysteinemia and CVD: (1) randomized, placebo-controlled trials of the effect of tHcy-lowering on recurrent and de novo CVD outcomes; and (2) elucidation of the basic biologic mechanism linking hyperhomocysteinemia to arteriosclerosis.

### Populations with Renal Disease

Intractable survivorship effects resulting from the excess yearly mortality in dialysis-dependent ESRD, and the failure to establish whether arteriosclerotic outcomes antedated the development of clinical arteriosclerosis, including coronary artery disease.

#### Table 2. Comparison of fasting plasma total homocysteine levels in population-based controls free of renal disease who were age-, gender-, and race-matched (one to one) to ESRD patients on maintenance dialysis, and children and young adults with homocystinuria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>ESRD Patients</th>
<th>Homocystinuric Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>10th to 90th percentile range of tHcy ((\mu\text{mol/L}))</td>
<td>7 to 14</td>
<td>12 to 39</td>
<td>50 to 300</td>
</tr>
</tbody>
</table>

*Data from references 9, 10, 22, 34–36, 55, and 81. ESRD, end-stage renal disease; tHcy, total homocysteine.*

#### Table 3. Comparison of plasma folate status and prevalence of fasting tHcy levels \(\geq 12 \mu\text{mol/L}\) among Rhode Island renal transplant recipients and coronary artery disease patients examined in the postfortification period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Renal Transplant Recipients</th>
<th>Coronary Artery Disease Patients</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>86</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Age (yr; mean (\pm) SD)</td>
<td>46 (\pm) 12</td>
<td>61 (\pm) 9</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Gender (no./% men)</td>
<td>53 (61.6%)</td>
<td>140 (80.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>tHcy ((\mu\text{mol/L}))</td>
<td>15.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.3</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>tHcy (\geq 12 \mu\text{mol/L}) (%)</td>
<td>69.8</td>
<td>10.9</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Folate &lt;3 ng/mL (%)</td>
<td>3.5</td>
<td>1.1</td>
<td>0.194</td>
</tr>
</tbody>
</table>

<sup>a</sup> From reference 20.

<sup>b</sup> Based on unpaired t test, analysis of covariance, or \(\chi^2\) test.

<sup>c</sup> Geometric means.
development of ESRD, renders hazardous any inference about tHcy-CVD associations suggested by cross-sectional studies. The potential relationship between hyperhomocysteinemia and arteriosclerotic outcomes in ESRD requires more rigorous validation via prospective observational studies, and ultimately, clinical tHcy-lowering intervention trials.

Recently, the results from a prospective study of the relationship between baseline fasting tHcy levels and subsequent CVD occurrence in 73 dialysis-dependent ESRD patients were reported (17). After a median follow-up of 17 mo, 16 individuals experienced nonfatal and/or fatal CVD events. After adjusting for prevalent CVD, traditional arteriosclerotic risk factors, serum creatinine, serum albumin, and dialysis adequacy, fasting hyperhomocysteinemia (i.e., comparing the upper [tHcy ≥27 μmol/L] to lower three quartiles [tHcy <27 μmol/L]) conferred an increased risk for CVD of approximately sevenfold for fatal events, and approximately 3.5-fold for pooled nonfatal and fatal events. The risk conferred by hyperhomocysteinemia was similar in women and men. Two subsequent longitudinal studies (16,18), one conducted in predialysis ESRD patients (18) and another in maintenance dialysis patients (16), yielded similar results. Dr. Robert Clarke and colleagues from the Homocysteine Trialists Collaborative Group pooled the data from these three investigations (personal communication). The pooled relative risk estimate for incident (de novo) or recurrent CVD (n = 95 total events) conferred by mild-to-moderate hyperhomocysteinemia (i.e., comparing the lowest to the upper tertile of fasting tHcy) in these three prospective studies was 2.8 (95% confidence interval, 1.6 to 5.0).

More recently, using a prospective design (72), the potential relationship between baseline nonfasting, predialysis plasma tHcy levels and vascular access-related morbidity was examined in a cohort of 84 hemodialysis patients with a fistula or prosthetic graft as their primary hemodialysis access. Vascular access thrombotic episodes were recorded over an 18-mo follow-up period. Forty-seven patients (56% of the total) had at least one access thrombosis during follow-up (median follow-up 13 mo; rate = 0.6 events per patient-year of follow-up). Proportional hazards modeling revealed that each 1 μmol/L increase in the tHcy level was associated with a 4.0% increase in the risk of access thrombosis (95% confidence interval: 1.0 to 6.0%, P = 0.008). This association persisted after adjustment for type of access (fistula versus graft), age, gender, time on dialysis, diabetes, smoking, hypertension, nutritional status, urea reduction ratio, dyslipidemia, and the presence of previous vascular disease.

The association between fasting tHcy levels and incident CVD has also been examined in a preliminary, nested case-control study of 42 renal transplant recipients (19). These pilot data indicated that mildly elevated fasting tHcy levels (>14 μmol/L) at a baseline examination were associated with the subsequent development of CVD outcomes.

Homocysteine and Arteriosclerosis:
Experimental Evidence

The pathologic mechanisms by which homocysteine promotes arteriosclerosis remain unclear. Experimental data support a range of possibilities, including endothelial cell injury (73,74), enhanced LDL oxidation (75), increased thromboxane-mediated platelet aggregation (76), inhibition of cell surface thrombomodulin expression and protein C activation (77), enhancement of lipoprotein(a)-fibrin binding (78), and promotion of smooth muscle cell proliferation (79). The in vivo relevance of findings from such experimental studies, however, has been seriously questioned (80) due to their lack of specificity to Hcy versus other much more abundant plasma thiols, including cysteine, and the use of grossly supraphysiologic concentrations or nonphysiologic forms (i.e., D,L as opposed to L) of reduced Hcy. The data of Mansoor and colleagues (81) provide the background needed for adequate understanding of the specific criticism regarding grossly supraphysiologic concentrations. These investigators assessed concentrations of reduced Hcy across the widest possible spectrum of tHcy concentrations. Their data revealed that at tHcy concentrations of up to 100 μmol/L, levels of reduced Hcy accounted for only 1% or less (i.e., <1 μmol/L) of plasma tHcy. When tHcy exceeded 100 μmol/L, reduced Hcy began to rise exponentially, likely due to saturation of plasma protein-binding sites (81). However, the highest reduced Hcy value these authors documented was in a subject with homozgyous homocystinuria who had a tHcy >350 μmol/L, but a reduced Hcy of <100 μmol/L (81). When juxtaposed to the concentrations of reduced Hcy used in experimental studies (73–79), i.e., 1000 to 10,000 μmol/L, the findings of Mansoor and colleagues (81) illustrate the very dubious clinical relevance of these published data. In contrast, physiologic models of mild, dietary-induced hyperhomocysteinemia (i.e., tHcy ≤15 μmol/L) causing subclinical or frank atherothrombotic sequelae have recently been described in animal models (67,68). Follow-up investigations using these models may elucidate the in vivo relevance of the putative pathologic mechanisms cited above (73–79).

Hyperhomocysteinemia: Screening and Treatment in Chronic Renal Disease

With a single exception (82), all of the published Hcy-lowering intervention studies conducted in predialysis or maintenance dialysis ESRD patients were uncontrolled, open-label investigations (47,50,83–90). Bearing this important caveat in mind, the following conclusions may be drawn from these studies:

1. Folic acid-based B vitamin regimens, including folic acid at doses of 5 to 10 mg/d, appear to lower fasting tHcy levels by approximately 30 to 50%.

2. The addition of folic acid at 15 mg/d (versus additional placebo) to a baseline regimen including 1 mg/d of folic acid, reduces fasting tHcy levels by approximately 25 to 30%.

3. Even when given a total dose of 16 mg/d of folic acid, two-thirds of maintenance dialysis patients whose baseline fasting or nonfasting tHcy levels are >15 to 16 μmol/L, will continue to maintain tHcy levels at or above this value.

4. There are no data available on the independent effect of vitamin B12 on fasting tHcy levels.
5. In accord with findings from general populations, vitamin B6 at up to 300 mg/d has no apparent effect on fasting tHcy levels. There are no data on the independent effect of vitamin B6 on PML tHcy levels.

6. Neither serine at 3 to 4 g/d, nor betaine at 6 g/d, appears to have any effect on fasting tHcy levels.

7. Oral N-acetylcysteine at 1.2 g/d subacutely lowers nonfasting prehemodialysis tHcy levels by approximately 16%.

8. Oral 5-methyltetrahydrofolate treatment may afford greater tHcy-lowering efficacy relative to folic acid, although no controlled, direct comparative data are currently available.

Finally, given that ESRD patients are at high risk for morbidity and mortality related to protein-calorie malnutrition (91), methionine restriction to lower tHcy levels in these patients, as suggested elsewhere (51), seems unwarranted.

Open-label findings from RTR with much milder decrements in renal function (47,92) have suggested that these patients are also refractory to low-dose folic acid-based tHcy-lowering supplementation. Finally, a recent block-randomized, placebo-controlled, two-by-two factorial study of 29 clinically stable RTR demonstrated that, in contrast to what was observed in their maintenance dialysis counterparts (82), the mild hyperhomocysteinemia in RTR is very amenable to high-dose combination B vitamin therapy (folic acid 5.0 mg/d, vitamin B6 50 mg/d, and vitamin B12 0.4 mg/d). Treated patients experienced mean reductions of fasting and PML tHcy levels of at least 25% after only 6 wk, with 75% achieving “normalization” of their tHcy levels (21).

In the absence of any data from randomized, controlled trials demonstrating a reduction in CVD outcomes with successful treatment of hyperhomocysteinemia in patients with chronic renal disease, we do not believe that screening and treatment recommendations for mild hyperhomocysteinemia in this patient population can or should be provided. This suggested “policy” is concordant with the recently published American Heart Association Position Paper on Homocysteine (93), which emphasized that screening and treatment recommendations for hyperhomocysteinemia in the general population were premature, and must await the results of clinical trials of tHcy lowering for secondary or primary CVD outcome prevention.

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