Homocysteine: “Expensive Creatinine” or Important, Modifiable Risk Factor for Arteriosclerotic Outcomes in Renal Transplant Recipients?

ANDREW G. BOSTOM
Division of General Internal Medicine, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island.

Arteriosclerotic cardiovascular disease (CVD) is the most common cause of death after renal transplantation (1–3), as well as a major source of morbidity (2,3). Renal transplant recipients (RTR) experience at least twofold increases in arteriosclerotic CVD mortality (1–3), and fourfold increases in pooled nonfatal and fatal CVD incidence (2,3), relative to population-based estimates. Established arteriosclerotic risk factors such as age, gender, cigarette smoking, diabetes mellitus, hypertension, and dyslipidemia do not account adequately for this excess risk (2,3). Furthermore, management of dyslipidemia and hypertension in this patient population may be complicated by immunosuppressive medication interactions and residual renal insufficiency, or renal vascular disease (4). Accordingly, there is a compelling need to identify and safely manage other putative CVD risk factors contributing to the excess occurrence of CVD among RTR. Given these considerations, mild hyperhomocysteinemia (i.e., elevated levels of the putatively atherothrombotic sulfur amino acid homocysteine) (3,5,6), is an excellent candidate risk factor because total homocysteine (tHcy) lowering can be achieved safely, relatively rapidly, and inexpensively with B-vitamin intervention (7–9).

Survivorship (1–3), and the failure to establish whether arteriosclerotic outcomes antedated the development of end-stage renal disease (ESRD), renders hazardous any inference about tHcy-CVD associations suggested by cross-sectional studies of patients on maintenance dialysis, or postrenal transplantation (10). The potential relationship between hyperhomocysteinemia and arteriosclerotic outcomes in chronic renal disease populations requires more rigorous validation via prospective observational studies, and, ultimately, clinical tHcy-lowering intervention trials. Three recent prospective studies of ESRD patients (11–13) have each revealed an independent, continuous relationship between fasting tHcy levels and CVD occurrence. Dr. Robert Clarke and colleagues from the Homocysteine Trialists Collaborative Group (Radcliffe Infirmary, Oxford, United Kingdom) pooled the data from these three investigations (personal communication). The pooled relative risk estimate for incident (de novo) or recurrent CVD (95 total events) conferred by mild-to-moderate hyperhomocysteinemia (i.e., comparing the upper to the lowest tertile of fasting tHcy) in these three prospective studies (11–13) was 2.8 (95% confidence interval [CI], 1.6 to 5.0). Earlier, Massy et al. (14) reported the potential association between fasting tHcy levels and CVD occurrence in a preliminary, nested case-control study of 42 renal transplant recipients. These pilot prospective data suggested that mildly elevated fasting tHcy levels (>14 μmol/L) were associated with the development of arteriosclerotic outcomes. Ducloux and colleagues recently reported cross-sectional data on tHcy levels in 227 RTR (15). Limiting their analyses to those 207 RTR (48 ± 14 yr old) operationally defined as “chronic and stable” (i.e., transplant duration >6 mo; no evidence of acute rejection; serum creatinine concentration <4.5 mg/dl), Ducloux et al. now report follow-up data from this RTR study group in the current issue of the Journal of the American Society of Nephrology (16). The authors carefully evaluated the potential association between baseline tHcy levels in this RTR population, and the subsequent development of CVD outcomes (i.e., pooled coronary heart disease, cerebrovascular disease, or lower extremity arterial disease events). After a mean follow-up of 19.7 ± 4.4 mo, there was a total of 30 new CVD events (cumulative incidence 14.5%). Using multivariable-adjusted (i.e., for age, gender, prior CVD, creatinine, cyclosporine use, smoking, hypertension, diabetes, dyslipidemia, and tHcy) proportional hazards modeling, only age, serum creatinine, and fasting tHcy levels were independently predictive of CVD events during follow-up. Specifically, each 1 μmol/L increase in tHcy was associated with a 6% increase in the risk for developing CVD (i.e., multivariable-adjusted hazards ratio 1.06; 95% CI, 1.04 to 1.09; P < 0.001). Creatinine levels were independently related to CVD outcomes (16), and predictably (9,17) were also the major determinant of tHcy levels (16). These latter findings highlight a particularly critical limitation inherent in any observational study of the potential relationship between tHcy levels and CVD outcomes among RTR, or patients with chronic renal insufficiency in general. Certainly, additional prospective data such as those reported by Ducloux et al. (16) might clarify the external validity of the current report. However, no observational study will ever adequately resolve whether an elevated
The tHcy level is merely a benign epiphenomenon of renal dysfunction in patients with renal insufficiency, i.e., an “expensive creatinine,” or a true risk factor for CVD. Randomized, placebo-controlled clinical trials of the effect of tHcy lowering on CVD event rates in RTR will be required to help resolve this vexing issue.

I believe the findings of Ducoux et al. (16) underscore why RTR are uniquely suited for such clinical trials, given, in addition:

- The high rate of de novo and recurrent cardiovascular disease outcomes in these patients (1–3);
- Their excess prevalence of hyperhomocysteinemia in the era of folic acid-fortified cereal grain flour, which contrasts with other potential target populations with normal renal function (18);
- The ability to safely and successfully “normalize” their tHcy levels with combined folic acid, vitamin B12, and vitamin B6 treatment (8,9), which is not true of dialysis-dependent ESRD patients (10,19);
- That RTR are a highly motivated group of patients (20) treated almost exclusively in large medical centers, which is conducive to overall recruitment into clinical trials, while minimizing sampling bias, and greatly enhancing follow-up for endpoint ascertainment; and

Overall “conditions” in the RTR population (e.g., renal impairment, mild-to-moderate hyperhomocysteinemia that can be normalized by B-vitamin supplements, and excess CVD outcomes) that are representative of the larger population of patients with chronic renal disease who have not yet reached ESRD (3).

Several of these points merit elaboration. It is very plausible that the dramatic (nutritional) biochemical effects of the recently implemented U.S. policy to fortify cereal grain flour products with folic acid (21) could render planned or ongoing clinical trials of the effect of tHcy lowering on CVD that the dramatic (nutritional) biochemical effects of the re-

Interpretation of results from similar trials conducted outside the United States for both primary and secondary CVD prevention (25) may be even more difficult. In Europe and Australia, for example, fortification may occur literally in the midst of the treatment phases of these trials (25), as opposed to having largely been in place already during screening and recruitment.

Beyond the practical issue of centralized care, why do I consider the RTR population a particularly suitable target population for a tHcy-lowering trial, within the overall chronic renal disease population? There are major overriding similarities between the total RTR and chronic renal insufficiency (CRI) populations in European and North American countries, including: the same predominant causes of renal disease, namely diabetes and hypertension (1); an equivalent plethora of CVD risk factors (2,3); an equivalent, fairly wide range of renal function, i.e., GFR (3); and, a very similar demography (1–3). With respect to the potential tHcy risk factor, the major, independent determinant of tHcy levels in both RTR and CRI patients is GFR, regardless of the etiology or treatment of the underlying renal disease (10,15,17), and high-dose folic acid-based B-vitamin supplementation can effectively normalize fasting tHcy levels in the preponderance of RTR and CRI patients (8–10), which is not true of patients with dialysis-dependent ESRD (10,19). We have just reported data that help clarify this latter point. In a block-randomized, controlled study, we demonstrated that a supraphysiologic dose of folic acid (2.4 mg/d) is superior to standard multivitamin dosing (0.4 mg/d) for the reduction of fasting tHcy levels in chronic RTR (9). These data argue strongly that in the context of a controlled clinical outcomes trial, the RTR population, relative to any U.S. target population with normal renal function, would be much less responsive to “drop-in” effects of over-the-counter multivitamin usage. However, RTR would be very responsive to supraphysiologic dose folic acid-based supplementation, particularly when assessed by the overall percentage achieving normal fasting tHcy levels. Finally, the ability to normalize fasting tHcy levels with supraphysiologic dose (2.4 mg/d) folic acid-based supplementation among the preponderance of RTR, i.e., 13/20 = 65% with final on treatment tHcy levels <12 µmol/L (9), distinguishes this patient population from the ESRD population who are largely refractory to doses of folic acid up to six times greater (16 mg/d), i.e., only 1/15 = 6.7% with final on treatment tHcy levels <12 µmol/L (19). Regarding concerns over the use of immunosuppressive regimens in RTR, there are no appropriately controlled data indicating that any of the major agents used, i.e., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, or prednisone, exert a significant effect on tHcy levels among chronic, stable RTR, independent of renal function (10,15,17,26); standard triple agent immunosuppression, independent of effects on renal function, has no clinically relevant impact on tHcy-lowering treatment responsiveness to typical high-dose folic acid-based B-vitamin treatment regimens (8,9); and, finally, data from the best-characterized RTR cohort in the United States with re-
pect to prospective ascertainment of CVD outcomes (i.e., the Hennepin County Medical Center Cohort (2) have revealed that cyclosporin A use was not associated with subsequent CVD events ($n = 243$ CVD events, occurring in a cohort of 1500 patients) in either unadjusted ($P = 0.406$) or multivariable-adjusted (hazards ratio 1.04; 95% CI, 0.63 to 1.73; $P = 0.876$) proportional hazards analyses (Dr. B. Kasiske, personal communication).

My conclusion is that the data of Ducloux et al. (16) compel us to move ahead promptly with a formal clinical trial that will clarify whether the identification and treatment of hyperhomocysteinemia are warranted in RTR specifically, and people with CRI in general. Such a trial could help resolve this critical question: Is homocysteine merely an “expensive creatinine,” or an important, modifiable risk factor for arteriosclerotic outcomes in CVD?

References