

# Elevated Homocysteine Levels in Patients with End-Stage Renal Disease

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## Abstract

**Purpose:** To examine the effect of hemodialysis on plasma homocysteine levels, and the relationship of these values to clinical cardiovascular events in patients with end-stage renal disease (ESRD).

**Methods:** Adults undergoing chronic hemodialysis were studied at baseline and at six months. Their clinical histories were obtained at the baseline visit, and measurements of plasma homocysteine concentration were made immediately prior to and following routine dialysis. The occurrence of clinical cardiovascular events was assessed over six months.

**Results:** We enrolled 147 patients (85 men and 62 women, age  $58 \pm 15$  years) who required hemodialysis for  $3.4 \pm 3.4$  years (mean  $\pm$  SD). The median homocysteine level for this population (including both pre- and post-dialysis values) was 17.3 micromoles/L. Mean pre-dialysis plasma homocysteine levels of patients with clinical cardiovascular disease did not differ significantly from those without the disease ( $22.5 \pm 9.9$  vs.  $25.4 \pm 24.5$  micromoles/L, respectively), nor did post-dialysis levels differ between these populations. During six months follow-up, rates of ischemic events were not related to hyperhomocysteinemia. The difference between mean pre- and post-dialysis homocysteine levels ( $26.3 \pm 19.7$  and  $15.6 \pm 11.4$  micromoles/L, respectively) and the decline in homocysteine over the course of a single dialysis treatment session ( $10.3 \pm 10.2$  micromoles/L) were highly significant ( $p < 0.0005$ ).

**Conclusions:** Plasma homocysteine levels were elevated in 82% of 147 patients with ESRD and fell to the normal range in a majority of patients during a single dialysis treatment session. Mean pre-dialysis levels did not change significantly over six months, however, and plasma homocysteine levels did not predict cardiovascular events in this population. There was also a trend towards worse outcomes in patients with lower homocysteine levels, which correlates to findings from recent studies. Further studies are needed to clarify the association between hyperhomocysteinemia and coronary risk in patients with ESRD.

**Key Words:** Hemodialysis, homocysteine, cardiovascular disease, end-stage renal disease, hyperhomocysteinemia.

## Introduction

THE PREVALENCE OF END-STAGE renal disease (ESRD) requiring dialysis is increasing. Approximately 40% of patients with this disorder have clinical manifestations of atherosclerotic cardiovascular disease, with an annual cardiovascular

mortality rate approaching 10% (1). This mortality rate is 10- to 20-fold greater than for people with normal renal function (2–7). While traditional cardiovascular risk factors such as hypertension and dyslipidemia have been implicated (8), these alone are not sufficient to account for the increased mortality in this population. Hence nontraditional risk factors such as chronic inflammation and hyperhomocysteinemia have been investigated as potentially contributory.

Elevated plasma levels of homocysteine have been associated with adverse cardiovascular outcomes in patients with ESRD (9–17). In a study of 176 hemodialysis patients, the odds ratio for developing vascular complications was 2.9 for those with homocysteine concentrations over 27.8 micromoles/L compared to patients with low homocysteine levels, and B vitamin levels were reduced in those with complications (11). Both fatal and nonfatal coronary events occurred more frequently

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in patients with homocysteine levels greater than 27  $\mu\text{M/L}$  in a study of 73 maintenance dialysis patients (relative risk 3.0 and 4.4, respectively) (12). In other studies, the relative risk for cardiovascular events increased by 1% and mortality increased by 3% for each micromolar increase in homocysteine concentration (13, 16).

A number of variables influence plasma homocysteine concentration in patients undergoing dialysis, including the proportion of homocysteine bound to plasma proteins (80%), the dialysis membrane composition, and plasma folate and B<sub>12</sub> levels (cofactors in homocysteine metabolism) (18, 19). To examine the influence of dialysis on plasma homocysteine levels and the relationship of these values to clinical cardiovascular disease, we systematically measured plasma homocysteine prior to and immediately following dialysis in a large population of patients with ESRD at two hospitals.

## Methods

Adult patients with established ESRD undergoing maintenance hemodialysis at two hospital sites were studied at baseline and six months later. Eligibility and clinical characteristics were established by review of medical records. Inclusion criteria included ESRD requiring chronic maintenance hemodialysis, written informed consent according to a protocol approved by the institutional review board governing research involving human subjects, and the ability to give a baseline blood sample. Exclusion criteria included a history of acute coronary syndrome (including unstable angina pectoris or acute myocardial infarction) or coronary intervention within the preceding thirty days.

Blood was obtained for assay of total homocysteine concentration immediately prior to routine hemodialysis (before the administration of heparin), and again immediately after dialysis at baseline and after six months. Samples were centrifuged for 15 minutes at 3,000 rpm, and supernatant plasma was shipped frozen to a commercial laboratory (Quest Diagnostics, Inc.). Samples were processed by protein decoupling, reduction with tri-*n*-butylphosphine, and thiol-specific fluorogenic separation. Total plasma homocysteine (the aggregate of all homocysteinyl moieties, whether in the sulfhydryl or disulfide form, free or protein-bound) was measured by reversed-phase liquid chromatography with fluorescence detection, and expressed as micromoles/L (normal range = 0–15 micromoles/L). Maintenance hemodialysis was carried out across Fresenius F6, F8, or F80 polysulfone membranes.

A clinical history questionnaire, including risk factors for coronary artery disease (CAD) (tobacco use, elevated cholesterol, diabetes mellitus, hypertension and family history of CAD), number of years dialysis had been required, and manifestations of overt cardiovascular disease (angina, myocardial infarction, coronary revascularization) was completed at the baseline visit. Six months later, a follow-up questionnaire was completed documenting interval cardiac events, and pre- and post-dialysis homocysteine values were measured. Serum vitamin B<sub>12</sub> (ng/L) and folate (ng/mL) levels were measured at one hospital site (normal ranges: 200–1100 ng/L for vitamin B<sub>12</sub> and >3 ng/mL for folate).

## Statistical Analysis

Associations between clinical history of cardiovascular disease and plasma homocysteine measurements were evaluated by linear regression and the Mann-Whitney U-test. The change in homocysteine levels during dialysis was analyzed using the Wilcoxon signed-rank test. To estimate the mean difference in plasma homocysteine across dialysis treatment sessions, we assumed that the differences were normally distributed, and estimated the mean of that difference by maximum likelihood estimation, censoring test values at the lower limit of detection. The relationships between folate, vitamin B<sub>12</sub> and homocysteine were analyzed using interval regression. Statistical analysis was performed using Stata version 6.0. Results are reported as the mean  $\pm$  standard deviation; statistical significance was accepted at the 0.05 level.

## Results

Of the 152 stable adult patients identified as the screening cohort, four declined to participate and one subsequently underwent kidney transplantation. Table 1 displays the characteristics of the study population, which consisted of 85 men and 62 women, mean age  $58 \pm 15.3$  years, who had required dialysis for  $3.4 \pm 3.4$  years. Forty-five (45) patients (30%) had symptomatic coronary artery disease, which manifested as angina pectoris (20%), myocardial infarction (15%) or myocardial revascularization (13%). Fifty-five (55) patients (37%) had diabetes mellitus, and 64 patients (43%) had a history of tobacco use.

In Table 2, plasma homocysteine levels are compared for patients with and without clinical cardiovascular disease. Mean pre-dialysis plasma homocysteine levels in patients with prior angina pectoris, myocardial infarction (MI) or revascular-

**TABLE 1**  
*Clinical Characteristics of the Study Population*

Characteristics	Number of Patients (n = 147)
Age (mean, min-max, years)	57.7 (21–86)
Male (percent)	58
Years on dialysis (mean, min-max)	3.4 (0.1–18)
History of myocardial infarction	22 (15%)
History of angina	30 (20%)
History of CABG or PTCA	19 (13%)
Family history of CAD	28 (19%)
Hypertension	118 (80%)
Diabetes mellitus	55 (37%)
Insulin dependent (percent of DM)	28 (51%)
Mean HbA1c (units)	7.8%
Smoking	
Within 1 month	29 (20%)
Ever	61 (43%)
Mean pack-years	19.1
Serum cholesterol (mg/dL)	167
Mean pre-dialysis systolic BP	155
Mean post-dialysis systolic BP	147
Mean pre-dialysis diastolic BP	82
Mean post-dialysis diastolic BP	78

CABG = coronary artery bypass graft

PTA = percutaneous transluminal coronary angioplasty

CAD = coronary artery disease

DM = diabetes mellitus

BP = blood pressure

ization did not differ significantly from levels in those without such history ( $22.5 \pm 9.9$  micromoles/L vs.  $25.4 \pm 24.5$  micromoles/L,  $p=NS$ ), nor did post-dialysis levels differ significantly between these populations. Homocysteine levels did not differ between patients on the basis of risk factors for coronary disease. During six-month follow-up, rates of ischemic events were not significantly associated with homocysteine values, although there was a trend towards higher event rates being associated with lower homocysteine values.

Table 3 shows pre- and post-dialysis homocysteine levels, categorized as normal (0–15 micromoles/L), mildly elevated (15–30 micromoles/L), intermediately elevated (30–100 micromoles/L), and markedly elevated (> 100 micromoles/L). The median homocysteine level for this population (including both pre- and post-dialysis values) was 17.3 micromoles/L. Of the 147 patients, 121 (82%) had elevated (>15 micromoles/L) homocysteine levels prior to dialysis. In contrast, homocysteine levels immediately after dialysis were elevated in only 58 patients (40%). Of the 106 patients with pre-dialysis levels above the median, 67 (63%) fell below the median after dialysis, while all but one (98%) of 41 patients with low pre-dialysis homocysteine levels

**TABLE 2**  
*Homocysteine Levels in Patients in Relation to Clinical Cardiovascular Disease*

	Number	Mean pre-HD homocysteine levels	Number	Mean post-HD homocysteine levels
Angina, MI, CABG, PTCA (history of at baseline)	No (101)	$25.4 \pm 24.5$	No (101)	$14.6 \pm 16.8$
	Yes (45)	$22.5 \pm 9.9$ ( $p=0.11$ )	Yes (45)	$13.3 \pm 5.3$ ( $p=0.30$ )
Angina, MI, CVA, PTCA, CABG, PVD procedure (at six months)	No (134)	$25.4 \pm 19.4$	No (134)	$15.0 \pm 11.2$
	Yes (16)	$19.1 \pm 8.5$ ( $p=0.04$ )	Yes (16)	$11.6 \pm 6.0$ ( $p=0.14$ )
DM	No (91)	$26.7 \pm 22.0$	No (91)	$14.1 \pm 17.4$
	Yes (55)	$20.9 \pm 19.1$ ( $p=0.25$ )	Yes (55)	$14.5 \pm 6.7$ ( $p=0.66$ )
HTN	No (29)	$20.1 \pm 25.2$	No (29)	$13.5 \pm 7.7$
	Yes (117)	$25.7 \pm 19.3$ ( $p=0.65$ )	Yes (117)	$14.4 \pm 15.5$ ( $p=0.28$ )
Cholesterol >240	No (137)	$25.3 \pm 18.7$	No (136)	$15.0 \pm 11.0$
	Yes (8)	$26.1 \pm 14.8$ ( $p=0.96$ )	Yes (8)	$15.3 \pm 6.4$ ( $p=0.71$ )
Smoking within one month	No (118)	$25.7 \pm 20.3$	No (117)	$15.2 \pm 11.5$
	Yes (29)	$23.3 \pm 7.8$ ( $p=0.83$ )	Yes (29)	$13.7 \pm 7.4$ ( $p=0.32$ )

MI =myocardial infarction

CABG = coronary artery bypass graft

PTCA = percutaneous transluminal coronary angioplasty

CVA = cerebral vascular accident

PVD = peripheral vascular disease

DM = diabetes mellitus

HTN = hypertension

remained below the median value after dialysis. The difference between mean homocysteine levels before and after dialysis ( $26.3 \pm 19.7$  and  $15.6 \pm 11.4$  micromoles/L, respectively) and the mean decline in homocysteine over the course of a single dialysis treatment session,  $10.3 \pm 10.2$  micromoles/L, was highly significant ( $p < 0.0005$ ).

Baseline and six-month pre-dialysis homocysteine values are compared in Table 4. Pre-dialysis homocysteine values did not decrease over this period. Table 5 shows pre-dialysis serum vitamin B<sub>12</sub> and folate values in a subgroup of 62 patients at six months. Fifty-five (55) of these 62 patients (89%) had normal vitamin B<sub>12</sub> levels, while 3 (5%) had values below normal and 4 (6%) had values above normal. All 62 patients had normal serum folate values. According to interval regression analysis, there was a significant inverse relationship between folate and homocysteine levels, but no relationship between vitamin B<sub>12</sub> and homocysteine levels.

### Discussion

A sulfur-containing amino acid derived from dietary methionine, homocysteine is metabolized

along two pathways. Remethylation to methionine is catalyzed by methionine synthase, which requires vitamin B<sub>12</sub> as a co-factor. Folate, converted to 5-methyltetrahydrofolate, serves as the methyl donor in this reaction. In the presence of excess methionine, the trans-sulfuration pathway converts homocysteine to cysteine via a vitamin B<sub>6</sub>-dependent enzyme (20). Normal levels of plasma homocysteine fall between 5 and 15 micromoles/L. Elevations can result from genetic defects in the enzymes involved in homocysteine metabolism, deficiencies in the vitamins that serve as metabolic cofactors, or a number of disease states. Deficiency of cystathionine  $\beta$ -synthase results in homocysteinuria, in which plasma homocysteine levels rise to 100–400 micromoles/L. Though homocysteinuria occurs in only 1 of 100,000 births, about half the patients with this disease develop atherothrombotic complications by age 30.

A much more common genetic cause of hyperhomocysteinemia is a point mutation in the gene for methylene tetrahydrofolate reductase (MTHFR), an enzyme critical to the remethylation cycle (21). This mutation, also referred to as the TT polymorphism or the thermolabile variant, re-

**TABLE 3**  
*Homocysteine Levels before and after Hemodialysis (micromoles/L)*

	Pre-dialysis	Post-dialysis			
		<15	15–30	30–100	>100
Normal (<15)	26	25	1	0	0
Moderate elevation (15–30)	85	58	26	1	0
Intermediate elevation (30–100)	35	6	28	1	0
Severe elevation (>100)	1	0	0	0	1

**TABLE 4**  
*Homocysteine Levels over Six Months (n=123)*

	Pre-HD homocysteine	Post-HD homocysteine	Min-max
Month 0	$26.3 \pm 19.7$	$15.6 \pm 11.4$	0–211
Month 6	$26.2 \pm 9.4$	N/A	10.1–56.3

HD = hemodialysis

**TABLE 5**  
*Baseline Pre-dialysis Serum Vitamin B<sub>12</sub> and Folate Levels (n = 62)*

B12 (ng/L)	Low (<200)	Normal (200–1100)	High (>1100)
Number of patients	3	55	4
Folate (ng/mL)	Low (0–2.1)	Borderline (2.2–3)	Normal (>3)
Number of patients	0	0	62

sults from a C-to-T substitution in base 677, which causes an amino acid change of alanine to valine. The homozygous state of this mutation occurs in 10–15% of the Caucasian population and is associated with a 25–50% increase in plasma homocysteine levels, amplified by folate deficiency (21–24). Heterozygotes do not appear to share the incremental risk for developing hyperhomocysteinemia. A meta-analysis of 40 European studies encompassing 11,162 patients homozygous for the TT polymorphism and 12,758 matched controls found a 16% increase in risk of clinical CAD among individuals with the defect (23). The observation was not sustained in North American studies conducted after fortification of the dietary sources with B vitamins and folic acid became commonplace.

Hyperhomocysteinemia also results from deficiencies in folic acid, vitamin B<sub>12</sub> and, to a lesser extent, pyridoxine (vitamin B<sub>6</sub>); two thirds of patients with elevated homocysteine levels have low plasma levels of these vitamins or related co-enzymes (25). In patients with normal renal function, a single 400–600 µg dose of folic acid produces a 20–30% decrease in plasma homocysteine levels (26).

Up to 7% of the general population and almost 50% of patients with clinical atherosclerosis have moderate plasma homocysteine elevations (27). And hyperhomocysteinemia has been identified in 85% of patients undergoing maintenance dialysis in previous studies (28). In addition to atherosclerosis and renal dysfunction, hyperhomocysteinemia has been associated with certain malignancies and with cigarette smoking in patients treated with drugs that interfere with folate metabolism.

In 1996 the U.S. Food and Drug Administration, motivated by evidence that folic acid supplementation reduced the incidence of congenital neural tube defects, issued a regulation requiring enriched grain products to be fortified with folic acid at a concentration sufficient to increase the average daily intake by 100 µg per individual. By January 1998 the regulation had been fully implemented. Based on one trial, the proportion of the population with homocysteine levels greater than 13 micromoles/L decreased during this period from 18.7 to 9.8% (29).

In addition to coronary artery disease, hyperhomocysteinemia has been linked with peripheral vascular and cerebrovascular disease, venous thrombosis, osteoporotic fractures and Alzheimer's disease. Proposed mechanisms for the role of homocysteine in the development or progression of vascular disease include endothelial dysfunction related to oxidative damage, oxidation of low-density lipoprotein (LDL)-cholesterol,

smooth muscle cell proliferation and abnormalities of coagulation (30–38). Homocysteine is auto-oxidized in plasma to mixed disulfides, thiolactone and the reactive oxygen species, superoxide and hydrogen peroxide (30), which have been directly linked to endothelial injury (31). The thiolactone metabolite enhances uptake of LDL-cholesterol by macrophages critical to the instability of the atherosclerotic plaque (30, 34, 35).

Exposure of endothelial cells to homocysteine for prolonged periods inhibits the function of nitric oxide synthase, impairing the vasodilatory and antithrombotic effects of nitric oxide (36). And several studies have shown improvement in arterial endothelial function following homocysteine-lowering therapy (39–41). Homocysteine has been shown to upregulate monocyte chemoattractant protein-1 and interleukin-8 and to stimulate smooth muscle cell proliferation leading to atheroma formation (42–44).

Finally, homocysteine has several prothrombotic effects, including activation of factors VIIa and V, and inhibition of protein C, thrombomodulin and endogenous heparin sulfate (45–48). Homocysteine induces tissue factor expression and reduces the binding of tissue plasminogen activator to its receptor on the endothelial cell (30). All of these effects lead to the generation of thrombin and have been invoked to explain the association of hyperhomocysteinemia with venous thrombosis.

Of the patients with ESRD we studied, 82% had elevated plasma homocysteine levels ( $\geq 15$  micromoles/L) at baseline. In 63% of those with homocysteine levels above the median (17.3 micromoles/L), levels fell to below the median after a single hemodialysis session, such that only 39% had persistent elevations. The fall in homocysteine levels after a single dialysis treatment is consistent with other studies and consistent with the additional observation that initial homocysteine levels were not significantly different from those measured after six months of dialysis. Since these patients were undergoing dialysis regularly before enrollment, any change in homocysteine levels may already have occurred and may not have been detected over the course of the study.

We were unable to demonstrate a relationship between plasma homocysteine and either a history of CAD or its development over a six-month period of observation. On the contrary, there was a slightly higher prevalence of CAD among those with lower homocysteine levels. The mean homocysteine level of those suffering ischemic events during follow-up was  $19.1 \pm 8.5$  micromoles/L, compared with  $25 \pm 19.4$  micromoles/L among

those who remained event free ( $p=0.04$ ). There was no correlation between homocysteine levels and cardiovascular events in our patient population; in fact, a slight inverse correlation between homocysteine levels and outcome was suggested.

Plasma homocysteine levels rise with increasing renal dysfunction (18, 19, 49). Furthermore, dialysis transiently reduces homocysteine levels for roughly eight hours, after which they rise again (50). It has also been shown that plasma homocysteine levels rise in living kidney donors immediately after uninephrectomy and progressively decline as renal function improves (51). The mechanism of these elevated homocysteine levels is not clear, however, since renal homocysteine excretion accounts for less than 1% of its elimination. The amount of homocysteine removed by dialysis did not contribute significantly to the fall in homocysteine levels in animals, and although folate-dependent transmethylation and remethylation pathways seem diminished in patients undergoing dialysis compared to normal controls (52), defects in transsulfuration pathways may contribute to homocysteinemia in patients with ESRD (53).

Multiple, retrospective, observational studies of adult populations have suggested that even mild elevations in homocysteine levels may confer an increased risk for cardiovascular disease and that hyperhomocysteinemia is associated with more recurrent events and greater mortality for those with already-established vascular disease (54–59). However, the results of large, prospective studies have been inconsistent. In a cohort of 14,000 male physicians without known atherosclerosis enrolled in the Physicians' Health Study, elevated homocysteine levels at entry were associated with a threefold increased risk of MI after five years, but the finding was no longer statistically significant at 7.5 years. Similar prospective, observational data from the MRFIT study showed no relationship between baseline homocysteine level and subsequent risk of MI or cardiac mortality (60).

In the absence of randomized trials examining homocysteine-lowering strategies for primary and secondary prevention, it remains uncertain whether the relationship between hyperhomocysteinemia and coronary disease is causal. In a randomized trial of folic acid (5 mg/day) in 593 patients with stable CAD on statin therapy, plasma homocysteine levels declined by 18% yet, at four-year follow-up, there was no difference in vascular events or all-cause mortality (61). In the Vitamin Intervention for Stroke Prevention (VISP) trial, 3,680 patients with a history of stroke were randomized to low-dose (20  $\mu$ g) folic acid, with 200  $\mu$ g vitamin B<sub>6</sub> and 6  $\mu$ g vitamin B<sub>12</sub> daily or high-

dose (2.5 mg) folic acid, 25 mg vitamin B<sub>6</sub> and 0.4 mg vitamin B<sub>12</sub>) (62). Although there was a correlation between baseline homocysteine levels and recurrent stroke, coronary events and death at two years, there was no difference between the two homocysteine-lowering regimens on those endpoints. In the Swiss Heart Study, 553 patients undergoing percutaneous coronary intervention (PCI) were randomized to 6 months of homocysteine-lowering therapy (folic acid, vitamin B<sub>12</sub> and vitamin B<sub>6</sub>) or placebo (63). At one year of follow-up, there was a 68% relative risk reduction in the composite endpoint of death, MI and tricuspid valve replacement (TVR) with homocysteine-lowering therapy. Subsequently, however, the Dutch FACIT study found that coronary restenosis at six months occurred significantly more frequently among 636 patients receiving intravenous and then oral homocysteine-lowering therapy following elective coronary stenting compared to those given placebo (64), despite reduction of homocysteine levels from 12.2 micromoles/L to 9.0 micromoles/L in the therapy group and no change in the placebo group. Other studies addressing this issue are currently in progress.

In the ESRD population, deficiencies of vitamins B<sub>6</sub>, B<sub>12</sub> and folic acid are rare, even when plasma homocysteine levels are elevated (11), suggesting a defect in metabolism. Although the patients in our study had normal serum folate levels ( $>3$  ng/mL), elevated homocysteine levels were still associated with lower folate values, consistent with findings in other studies that elevated folate levels are an independent predictor of plasma homocysteine levels in patients undergoing dialysis (64). These observations suggest that patients with ESRD may require greater folic acid supplementation than conventionally prescribed, or that supplemental administration of vitamin B<sub>12</sub> and B<sub>6</sub> might lower homocysteine levels in this setting (65–68).

The results of our study are similar to others that have shown a paradoxically inverse correlation of plasma homocysteine levels and cardiovascular mortality in patients undergoing dialysis. Suliman et al., found lower homocysteine levels in patients with established coronary disease associated with worse survival rates (69). In another study of 367 patients on maintenance hemodialysis, those with homocysteine levels in the lowest quartile had higher mortality rates than those with higher homocysteine levels. Several studies have demonstrated that homocysteine levels are related to serum albumin concentration, suggesting that homocysteine may be a marker of nutritional status and that impaired nutrition may be related to adverse coronary outcomes in patients

with ESRD (49). The “malnutrition, inflammation and atherosclerosis complex syndrome” may thus describe the process of inflammation in patients with chronic renal insufficiency who are wasted and succumb to cardiovascular events (70). In this scenario, malnutrition and chronic inflammation may confound the association of homocysteine with cardiovascular events, a “reverse epidemiology” of risk factors that complicates assessment of homocysteine levels and other indicators of cardiovascular risk, as occurs in patients with advanced congestive heart failure (71–75). Thus, while homocysteine may be a marker of atherosclerosis in patients without renal dysfunction, levels in patients maintained on dialysis cannot be fully interpreted without recognition of their nutritional status and concurrent inflammatory processes that may be related to overall mortality.

### Summary

Despite previous studies showing that homocysteine is a predictor of coronary outcomes in dialysis patients, our findings fail to support such a correlation. Hyperhomocysteinemia was not predictive of adverse cardiac outcome in the population we studied, and there was a trend towards worse outcomes with lower homocysteine levels. While homocysteine levels may partially account for thrombotic disease in dialysis patients, the correlation is confounded by malnutrition and inflammation. This study involved a relatively short period of follow-up, and additional studies involving a larger sample size and longer follow-up are needed to assess the impact of homocysteine in patients with ESRD. Such studies should take into account markers of inflammation and malnutrition that may contribute to increased cardiovascular morbidity.

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