Malnutrition and Atherosclerosis in Dialysis Patients

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Abstract. Longitudinal associations of malnutrition with atherosclerotic events in uremia are unclear. In 50,732 incident Medicare dialysis patients who had normal (18.5 to 24.9 kg/m^2), low (<18.5 kg/m^2), or high (≥ 25 kg/m^2) body mass index (BMI) and initiated dialysis in the United States from January 1995 to December 1999 with reported measured creatinine clearances and acute coronary syndrome (ACS; International Classification of Diseases, Ninth Revision codes 410.x and 411.x) were examined in parametric survival models. Normal BMI was the referent group. Twenty-four-hour urinary creatinine (UCr) was used as a measure of muscle mass. There were 7213 (14.2%) hospitalized ACS events, 1528 (22%) of which were fatal (death within 30 d). One-year post-ACS mortality was 48%. Low BMI (hazard ratio [HR], 0.89; $P = 0.02$] was associated with lower hazard, and UCr was not predictive (NS) of hospitalized ACS in multivariable model. Low BMI (NS) was not associated with a composite end point of hospitalized ACS/suspected out-of-hospital ACS death, whereas lowest UCr quartile was associated with higher hazard (HR, 1.14; $P < 0.001$). Low BMI (HR, 1.24; $P < 0.001$) and decrease in UCr (highest quartile reference, second quartile HR, 1.11 [$P < 0.001$]; third quartile HR, 1.24 [$P < 0.001$]; and fourth quartile HR, 1.43 [$P < 0.001$]) were associated with increased hazard of death. Hospitalized ACS events in dialysis patients carry very high immediate and long-term mortality. Positive longitudinal associations of malnutrition with documented hospitalized ACS events could not be demonstrated. Further longitudinal studies are warranted to provide definitive evidence of malnutrition as a uremic risk factor for atherosclerosis.

Malnutrition as evidenced by low body mass index (BMI) at initiation of dialysis is a powerful predictor of mortality in dialysis patients (1–3). As cardiovascular deaths account for 50% of deaths on dialysis and atherosclerosis is the predominant cardiovascular disease in the general population, it is intuitive to infer an association between malnutrition and atherosclerosis. The malnutrition, inflammation, and atherosclerosis (MIA) hypothesis (4) proposes an association of malnutrition with atherosclerosis. To our knowledge, no studies have convincingly demonstrated the longitudinal associations of malnutrition and atherosclerotic events (not just mortality) to determine whether the excess mortality in malnourished patients is attributable to atherosclerosis. Therefore, we examined the association of malnutrition with subsequent fatal/nonfatal hospitalized acute coronary syndromes (ACS) in an incident dialysis population. In addition, we examined the effects of malnutrition on the incidence of fatal ACS events and 1 yr post-ACS survival.

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The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

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Materials and Methods

Study Population

The United States Renal Data System (USRDS) data were used to identify patients who initiated dialysis in the United States from January 1, 1996, to December 31, 1999, with measured serum creatinine and creatinine clearances reported in the Form 2728. An additional inclusion criterion was Medicare insurance at initiation of dialysis. Patients with missing data on serum albumin, height, and weight were excluded. Patients with duplicate entries, previous renal replacement therapies, and incomplete follow-up information were also excluded.

Data Assembly

Baseline data on demographics (age, gender, and race), presence of diabetes as the cause of ESRD, dialysis modality, cardiovascular disease (coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure), smoking, height and weight, serum albumin, serum creatinine, 24-h creatinine clearance, hematocrit, and pre-ESRD erythropoietin use were obtained from the Medical Evidence form.

Definition of Malnutrition

Height and weight were used to calculate BMI (kg/m^2). Malnutrition was defined as BMI <18.5 kg/m^2 (5). Total daily urinary creatinine excretion (UCr) calculated from serum creatinine and reported 24-h creatinine clearance was considered an additional measure of muscle mass and nutritional status, as lean body mass estimated from UCr was a qualitative measure of lean body mass determined by dual-energy x-ray absorptiometry in 30 predialysis patients with creatinine clearances <30 ml/min (6).

Patients were tracked until loss to follow-up, death, transplant, or the administrative censor date of December 31, 1999. Data on fol-

Table 1. Baseline patient characteristics by BMI groups[a]

	Low BMI (<18.5 kg/m^2; n = 4,052)	Normal BMI (18.5–24.9 kg/m^2; n = 23,299)	High BMI (≥25 kg/m^2; n = 23,381)
Demographics			
age (yr; mean ± SD)	72.6 ± 11.2	72.2 ± 10.8	69.5 ± 10.3
male gender (n [%])	1,789 (44)	12,514 (54)	10,099 (43)
race (n [%])			
white	2,815 (70)	17,383 (75)	16,822 (72)
black	974 (24)	4,401 (19)	5,351 (23)
other	263 (6)	1,515 (6)	1,208 (5)
Comorbid conditions			
diabetes as cause of renal failure (n [%])	1,097 (27)	8,941 (38)	12,526 (54)
coronary artery disease (n [%])	1,502 (37)	9,588 (41)	9,097 (39)
cerebrovascular disease (n [%])	605 (15)	3,361 (14)	2,845 (12)
peripheral vascular disease (n [%])	949 (23)	5,382 (23)	4,863 (21)
history of cardiac arrest (n [%])	43 (1)	294 (1)	248 (1)
heart failure (n [%])	1,860 (46)	10,742 (46)	10,974 (47)
current smoker (n [%])	374 (9)	1,334 (6)	877 (4)
hypertension (n [%])	3,031 (75)	17,686 (76)	18,379 (78)
Nutritional parameters			
body mass index (kg/m^2; mean ± SD)	17.1 ± 1.2	22.0 ± 1.8	29.9 ± 4.6
24-h urine creatinine (g/d)	0.63 ± 0.29	0.72 ± 0.31	0.81 ± 0.35
serum albumin (g/dl; mean ± SD)	3.1 ± 0.6	3.2 ± 0.6	3.2 ± 0.6
Anemia			
hematocrit (%; mean ± SD)	29.1 ± 5.2	29.4 ± 5.0	29.4 ± 4.8
predialysis erythropoietin use (n [%])	1,033 (25)	6,227 (27)	6,300 (27)

[a] BMI, body mass index.

Table 2. Multivariable parametric model[a] of hospitalized ACS event (N = 50,732)[b]

	Fatal/Nonfatal Hospitalized ACS			Fatal Hospitalized ACS		
	HR	(95% CI)	P Value	HR	(95% CI)	P Value
BMI groups						
normal BMI (18.5–24.9 kg/m^2)	Ref			Ref		
low BMI (<18.5 kg/m^2)	0.89	(0.81–0.98)	0.022	0.95	(0.79–1.16)	0.635
high BMI (≥25 kg/m^2)	1.03	(0.98–1.09)	0.188	0.94	(0.84–1.04)	0.216
UCr groups						
>0.92 g/d	Ref			Ref		
0.71–0.92 g/d	1.03	(0.96–1.10)	0.428	1.08	(0.94–1.25)	0.272
0.54–0.70 g/d	1.00	(0.93–1.07)	0.957	1.14	(0.98–1.32)	0.080
≤0.53 g/d	1.00	(0.94–1.07)	0.919	1.22	(1.05–1.41)	0.008
Each decade increase in age	1.08	(1.06–1.11)	<0.001	1.26	(1.19–1.34)	<0.001
White *versus* black	0.80	(0.75–0.85)	<0.001	0.69	(0.60–0.80)	<0.001
Other races *versus* white	0.95	(0.86–1.04)	0.284	0.86	(0.69–1.06)	0.152
Diabetes as cause of renal failure	1.07	(1.02–1.12)	0.007	NS	—	—
Coronary artery disease	1.93	(1.84–2.03)	<0.001	1.49	(1.34–1.66)	<0.001
Peripheral vascular disease	1.13	(1.07–1.19)	<0.001	1.28	(1.14–1.44)	<0.001
Congestive heart failure	1.13	(1.07–1.19)	<0.001	1.22	(1.10–1.35)	<0.001
Hypertension	0.92	(0.87–0.98)	0.006	0.86	(0.76–0.96)	0.010
Hematocrit, each 5% increase	1.05	(1.02–1.07)	<0.001	1.02	(1.01–1.03)	<0.001
Predialysis erythropoietin use	0.93	(0.88–0.98)	0.010	0.86	(0.76–0.96)	0.008

[a] The following covariates fell out of the model: cardiac arrest, current smoker, cerebrovascular disease, serum albumin, gender, and dialysis modality.

[b] ACS, acute coronary syndrome; HR, hazard ratio; CI, confidence interval; UCr, urinary creatinine.

low-up duration, mortality, and transplant were collected from the USRDS treatment history, claims, and patients files. Acute coronary syndromes (ACS; *International Classification of Diseases, Ninth Revision* [ICD-9] codes 410.x and 411.x) that occurred after initiation of dialysis were identified from the Medicare hospital claims data. These were considered documented hospitalized ACS events. Documented fatal ACS event was defined as death within 30 d of a documented hospitalized ACS event. Suspected out-of-hospital ischemic heart disease (IHD) death was defined as death that occurred not during a hospital admission and cause of death was coded as acute myocardial infarction or atherosclerotic heart disease in the USRDS death notification form. Cardiovascular death was defined as cause of death coded in the USRDS death notification form as myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cardiac arrest due to unknown cause, sudden death, arrhythmia, valvular heart disease, pericarditis, cerebrovascular disease, peripheral vascular disease, mesenteric infarction, hyperkalemia, pulmonary edema due to exogenous fluid, ischemic brain damage/anoxic encephalopathy, and hemorrhage from ruptured vascular aneurysm.

Statistical Analyses

The study included only Medicare patients with reported creatinine clearances, height, weight, measured serum creatinine, and serum albumin. Thus, patients with missing data for age, insurance status, BMI, serum creatinine, serum albumin, and 24-h UCr were not included in the analysis. Comorbid conditions were considered present only when they were listed as present in Medical Evidence form.

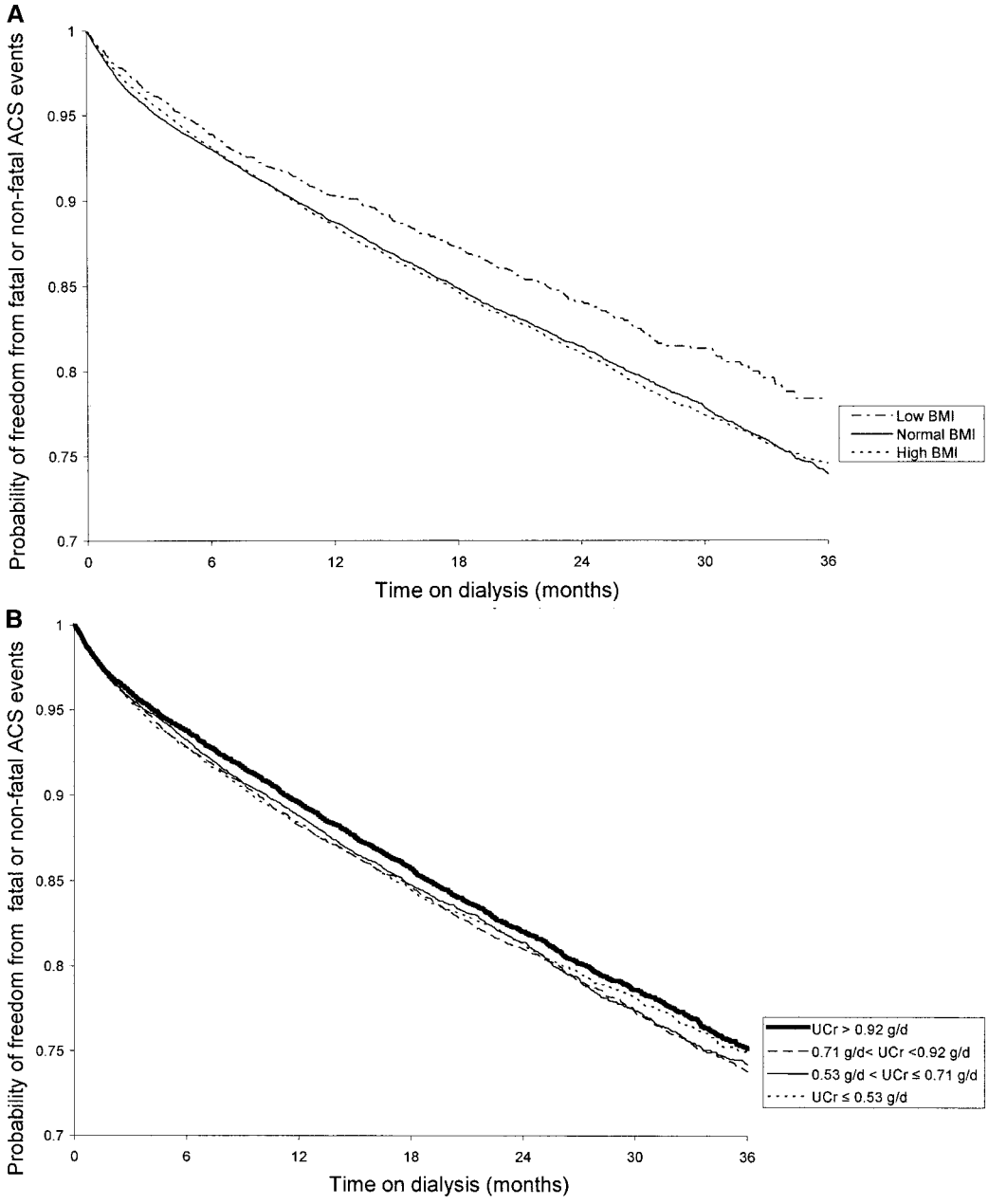

Figure 1. (A) Hospitalized fatal/nonfatal acute coronary syndrome (ACS) events by body mass index (BMI) groups. (B) Hospitalized fatal/nonfatal ACS events by urinary creatinine (UCr) groups

Table 3. Multivariable parametric model[a] of post-ACS mortality ($N = 7213$)[b]

	HR	(95% CI)	*P* Value
BMI groups			
normal BMI (18.5–24.9 kg/m^2)	Ref		
low BMI (<18.5 kg/m^2)	1.05	(0.92–1.21)	0.441
high BMI (≥25 kg/m^2)	0.93	(0.87–1.00)	0.064
UCr groups			
>0.92 g/d	Ref		
0.71–0.92 g/d	1.15	(1.04–1.27)	0.005
0.54–0.70 g/d	1.25	(1.12–1.38)	<0.001
≤0.53 g/d	1.33	(1.20–1.48)	<0.001
Dialysis type: PD *versus* HD	1.17	(1.05–1.31)	0.005
Each decade increase in age	1.25	(1.20–1.30)	<0.001
Gender: female *versus* male	1.13	(1.06–1.22)	0.001
Black *versus* white	0.90	(0.82–0.99)	0.028
Other races *versus* white	0.86	(0.75–1.00)	0.051
Cerebrovascular disease	1.10	(1.00–1.21)	0.042
Congestive heart failure	1.14	(1.07–1.22)	<0.001
Hypertension	0.91	(0.84–0.99)	0.023
Serum albumin	0.91	(0.86–0.97)	0.002

[a] The following covariates fell out of the model: current smoker, cardiac arrest, diabetes as cause of renal failure, and peripheral vascular disease. Previous history of coronary artery disease was not included in the model because all patients included had an ACS event.

[b] PD, peritoneal dialysis; HD, hemodialysis.

Because of the large sample size, baseline characteristics across BMI groups were not statistically compared. The primary end point was time to fatal/nonfatal hospitalized ACS event. As nutritional groups violated proportionality assumptions in Cox models, parametric proportional hazards survival models were used (7). The proportional hazards multivariable model with internal knots at the 33rd and 67th centiles of the distribution of the uncensored log times was the most parsimonious model with the lowest Akaike Information Criterion and was used in this analysis. In this model, patients were censored at first ACS, death, loss to follow-up, transplantation, or December 31, 1999. All baseline variables were considered in a stepwise model to identify significant independent predictors of fatal/nonfatal ACS events. However, BMI and UCr groups were retained in the model irrespective of their statistical significance. In addition, the effects of malnutrition on the incidence of hospitalized fatal ACS events and 1 yr post-ACS survival were examined. Time to death was a secondary end point. Sensitivity analysis included an analysis of time to a composite end point of hospitalized fatal/nonfatal ACS event or suspected out-of-hospital IHD death. Subgroup analyses by dialysis modality and presence or absence of diabetes were performed. Causes of death in BMI and UCr groups were examined.

Results

Of the 407,278 adult patients (over age 18) who started on dialysis from January 1, 1995, to December 31, 1999, 118,289 patients had both creatinine clearance and serum creatinine reported in the Medical Evidence form. Of these, patients with missing data on serum albumin (18,885) and weight (4,237) were excluded. Patients with duplicate records (2,258), all comorbidity information missing (3), follow-up information missing (671), probable data entry errors in baseline data (6,172), and age >90 yr (905) were also excluded. Of the remaining 85,158 patients, 50,732 had Medicare insurance at initiation of dialysis and were studied.

The mean age of the study population was 71.0 ± 10.7 yr, 48.1% were men, 72.9% were white, and 21.1% were black. Diabetes was the cause of ESRD in 44.4%, and 89.5% were on hemodialysis. The mean 24-h UCr was 0.75 ± 0.3 g/d. There were 7213 (14.2%) hospitalized fatal/nonfatal ACS events, 1588 (22%) of which were fatal (death within 30 d of ACS). One-year post-ACS survival was 52.1%. In the entire cohort, there were 26,522 (52.5%) deaths and 4,226 (8.3%) out-of-hospital suspected IHD deaths over 66,325 patient-years of follow-up.

Table 1 depicts the baseline clinical characteristics in BMI groups. The low-BMI group had lower prevalence of diabetes and lower 24-h UCr. There were 9.5 hospitalized fatal/nonfatal ACS events per 100 patient-years (452 events in 4,760 patient years) in the low-BMI group compared with 11.1 events per 100 patient-years (3,321 events in 30,054 patient-years) in the normal and 10.9 events per 100 patient-years (3,440 events in 31,511 patient-years) in the high-BMI groups. Age, diabetes, preexistent coronary artery disease, peripheral vascular disease, congestive heart failure, and higher hematocrit at baseline were associated with increased hazard of hospitalized fatal/nonfatal ACS events, whereas black race, pre-ESRD erythropoietin use, and hypertension were associated with lower hazard of hospitalized fatal/nonfatal ACS events in multivariable model. Low BMI was associated with lower hazard (0.89; 0.81 to 0.98; Table 2, Figure 1), and UCr was not associated with hospitalized fatal/nonfatal ACS events.

The incidence of hospitalized fatal ACS events was 2.5 per 100 patient-years (118 events in 4,760 patient years) in the low-BMI group compared with 2.6 per 100 patient-years (784 events in 30,054 patient-years) in the normal and 2.2 events per 100 patient-years (6,861 events in 31,511 patient-years) in the high-BMI groups. Lowest UCr quartile had 22% ($P = 0.008$) higher hazard of hospitalized fatal ACS event in multivariable survival model (Table 2). One-year post-ACS survival was also significantly influenced by UCr quartiles (Table 3, Figure 2).

Even though low BMI was associated with lower hazard of hospitalized ACS events, there were strong associations of low BMI with death (Table 4, Figure 3). The low-BMI group compared with the normal-BMI group had 24% higher hazard of death, and the lowest compared with highest UCr quartile had 43% higher hazard of death.

There were 18.5 (880 events in 4,760 patient-years), 19.3 (5,795 events in 30,054 patient-years), and 13.9 (4,372 events in 31,511 patient-years) hospitalized fatal/nonfatal ACS events or suspected out-of-hospital IHD deaths per 100 patient-years in the low-, normal-, and high-BMI groups, respectively. In multivariable model, compared with the normal-BMI group, the low-BMI group had no increased hazard and the high-BMI group had lower hazard of hospitalized fatal/nonfatal ACS events or suspected out-of-hospital IHD deaths (Table 5, Fig-

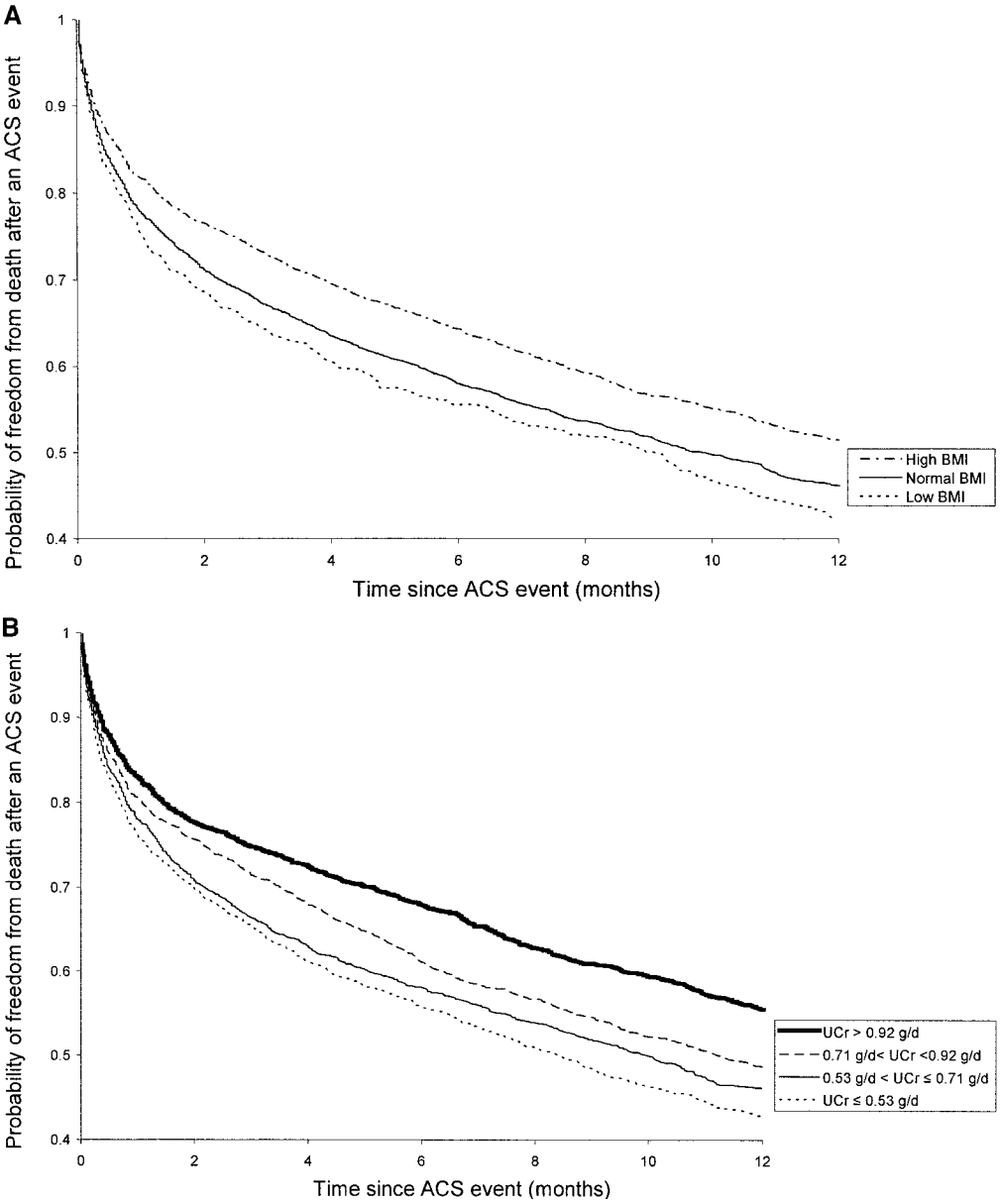

Figure 2. (A) One-year post-ACS survival by BMI groups. (B) One-year post-ACS survival by UCr groups.

Table 4. Multivariable parametric model[a] of death ($N = 50{,}732$)

Covariates	HR	CI	*P* Value
BMI groups			
normal BMI (18.5–24.9 kg/m^2)	Ref		
low BMI (<18.5 kg/m^2)	1.24	(1.19–1.29)	<0.001
high BMI (≥25 kg/m^2)	0.89	(0.87–0.92)	<0.001
UCr quartiles			
>0.92 g/d	Ref		
0.71–0.92 g/d	1.11	(1.07–1.15)	<0.001
0.54–0.70 g/d	1.24	(1.19–1.29)	<0.001
≤0.53 g/d	1.43	(1.38–1.48)	<0.001

[a] Model adjusted for dialysis modality, age, gender, race, diabetes as cause of renal failure, coronary artery disease, history of cardiac arrest, cerebrovascular disease, peripheral vascular disease, heart failure, hypertension, current smoker, serum albumin, hematocrit, and predialysis erythropoietin use.

ure 4). The incidence of hospitalized fatal/nonfatal ACS events or suspected out-of-hospital IHD deaths per 100 patient-years in the highest to lowest UCr quartiles were 14.5 (3,264 events in 22,455 patient-years), 16.5 (2,734 events in 16,601 patient-years), 17.8 (2,565 events in 14,430 patient-years), and 19.3 (2,484 events in 12,836 patient-years), respectively. The lowest compared with the highest UCr quartile had 14% higher hazard of hospitalized fatal/nonfatal ACS events or suspected out-of-hospital IHD deaths in multivariable model (Table 5).

Causes of death in BMI and UCr groups are presented in Table 6. Whereas more malnourished patients died, the distribution of causes of death within BMI and UCr groups were remarkably similar, suggesting that both malnourished and well-nourished patients died of the same disease processes but malnourished patients were more susceptible to those disease processes. Subgroup analyses by dialysis modality and presence or absence of diabetes showed similar

associations of malnutrition with ACS, death, and ACS/death (data not shown).

Discussion

In contrast to the general population, high BMI in dialysis patients is associated with better outcomes (1, 2, 8–13). As a logical corollary, an association of malnutrition, inflammation, and atherosclerosis (MIA hypothesis) in uremia has been suggested (4). Furthermore, as malnutrition is a powerful predictor of death in chronic kidney disease but still malnutrition is rarely listed as the cause of death, it has been suggested that malnutrition and atherosclerosis must be associated (14). Thus, the current paradigm is that malnutrition is a uremic risk factor for cardiovascular disease (15), which results in increased cardiovascular mortality in malnourished patients. However, to our knowledge, no studies in uremia have convincingly demonstrated in multivariable models longitudinal associations of malnutrition with incidence of atherosclerotic events or progression of atherosclerosis. The MIA syndrome was proposed on the basis of observations in a cross-sectional study of 109 predialysis patients. It is of extreme relevance that in that study, only unadjusted analyses showed that malnourished patients compared with well-nourished patients had greater ultrasound evidence of carotid intima-media thickening (4). Furthermore, even these unadjusted associations of malnutrition with atherosclerosis were present only when subjective global assessment (SGA) was used to define malnutrition. Lean body mass measured by dual-energy x-ray absorptiometry scans and BMI were not associated with atherosclerosis. Unadjusted associations of malnutrition and atherosclerosis were described in other studies (16, 17). Cross-sectional associations of serum albumin with cardiovascular disease have

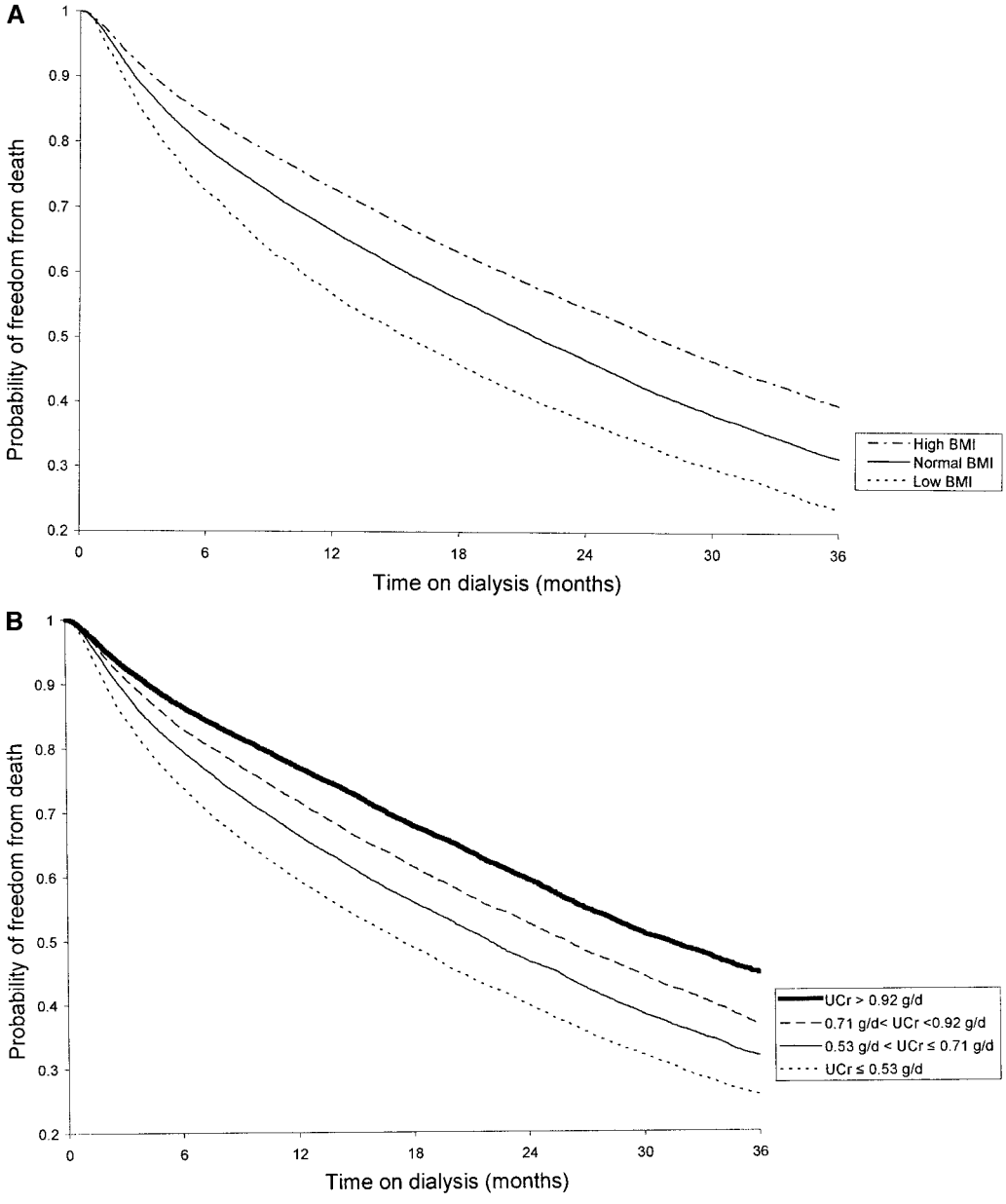

Figure 3. (A) Survival by BMI groups. (B) Survival by UCr groups.

Table 5. Multivariable parametric model[a] of hospitalized fatal/nonfatal ACS or suspected out-of-hospital IHD death ($N = 50{,}732$)[b]

Covariates	HR	CI	*P* Value
BMI groups			
normal BMI (18.5–24.9 kg/m^2)	Ref		
low BMI (<18.5 kg/m^2)	0.98	(0.91–1.05)	0.555
high BMI (≥25 kg/m^2)	0.78	(0.75–0.81)	<0.001
UCr quartiles			
>0.92 g/d	Ref		
0.71–0.92 g/d	1.05	(0.99–1.11)	0.079
0.54–0.70 g/d	1.07	(1.01–1.13)	0.024
≤0.53 g/d	1.14	(1.08–1.21)	<0.001

[a] Model adjusted for dialysis modality, age, gender, race, diabetes as cause of renal failure, coronary artery disease, history of cardiac arrest, cerebrovascular disease, peripheral vascular disease, heart failure, hypertension, current smoker, serum albumin, hematocrit, and predialysis erythropoietin use.
[b] IHD, ischemic heart disease.

been described (18–20), but as serum albumin is also a measure of inflammation, it is unclear whether these associations describe the malnutrition, inflammation, and cardiovascular disease triad. In a recent study of the USRDS Dialysis Morbidity Mortality Wave data, a longitudinal association of clinical diagnosis of malnutrition and body weight with incident stroke was described (20). Even though preexistent peripheral vascular disease is known to have strong association with subsequent atherosclerotic events, peripheral vascular disease was not considered in that study. Racial groups were stratified by the presence or absence of cardiovascular disease in the multivariable model of predictors of subsequent stroke. However, it is unclear whether preexistent coronary artery disease and congestive heart failure were included as independent covariables in the multivariable model to adjust adequately for the associations of malnutrition with stroke. Furthermore, false-positive significant associations could be identified in studies with a large sample size. Given that the sample size in the multivariable model was 6862 patients, $P = 0.06$ (with 1.00 as the lower bound of confidence interval) for a small 9% increment in the risk of stroke with 25% relative decrease in height-adjusted weight may be nonsignificant. It is also unclear whether a similar association with incident stroke was observed when malnutrition was defined by BMI.

In this analysis, even though malnutrition was a strong predictor of all-cause death, it was associated with lower baseline prevalence of diabetes and coronary artery disease and lower subsequent incidence of hospitalized fatal/nonfatal ACS events. Because we examined the association of malnutrition and atherosclerosis in a very large sample of a population at very high risk for ACS events, *a priori* we expected a strikingly higher incidence of ACS in malnourished patients on the basis of the MIA hypothesis but did not find evidence to support it. The results of this study are also supported by two cross-sectional studies that found an association of coronary calcification in dialysis patients with high and not low BMI (21, 22).

There are several possible explanations for this observation. First, identification of ACS by ICD-9 codes may be inaccurate. However, Jollis *et al.* (23) found an 88% rate of agreement between claims data and clinical data with respect to the ICD-9 code for acute myocardial infarction, with a specificity of 95%. In addition, in the current study, age, diabetes, preexistent coronary artery disease, peripheral vascular disease, and congestive heart failure were associated with increased hazard of hospitalized fatal/nonfatal ACS events. It is unlikely that these biologically plausible associations will be identified if the ICD-9 codes were incorrect. More important, 22% of patients with a diagnosis of ACS died within 1 mo and 48% died within 1 yr. This very poor post-ACS 1-yr survival is similar to the post-myocardial infarction 1-yr survival reported by Herzog *et al.* (24) in Medicare dialysis patients. Thus, these data indicate that a life-threatening acute disease process with lasting impact and associated with old age, diabetes, preexistent coronary artery disease, peripheral vascular disease, and congestive heart failure did occur in those patients identified by ICD 9 codes 410.x and 411.x.

The possibility that a higher proportion of malnourished patients with ACS died before they reached the hospital, resulting in lower hospitalized ACS events, should be considered. This theory is supported by the observation that the lowest UCr quartile compared with the highest UCr quartile had 14% higher hazard of a composite end point of hospitalized fatal/nonfatal ACS or suspected out-of-hospital IHD death. However, we believe that these data should be interpreted with caution for several reasons. The association of UCr quartiles with hospitalized fatal/nonfatal ACS events or suspected out-of-hospital IHD deaths was entirely driven by out-of-hospital suspected but not proven IHD deaths. The sensitivity of USRDS death notification form classification compared with the HEMO outcomes committee classification of IHD death was only 36% (25). Even the HEMO Study did not use predefined criteria for definition of IHD death. It is unclear how many of the IHD deaths classified by the HEMO Study outcomes committee were associated with documented ACS and how many were suspected IHD deaths. A dialysis patient who has a history of coronary disease and is found dead at home could be suspected to have died of ACS, but it is also possible that sudden death in dialysis patients might be related to electrolyte disturbances, drugs such as digitalis, and underlying cardiomyopathy as a result of conditions such as anemia. Therefore, the association of malnutrition with atherosclerosis described in an unadjusted cross-sectional analysis of 109 predialysis patients (4) could not be demonstrated conclusively in this large longitudinal study of 50,732 dialysis patients with 7,213 ACS events. Hence, the results of the current study do not prove definitively an association of malnutrition with atherosclerosis in uremia. Further longitudinal studies of the association of malnutrition with clinical atherosclerotic events or progression of atherosclerosis are warranted to

demonstrate conclusively an association of malnutrition with atherosclerosis.

It is also possible that even if malnourished patients might be at higher risk of atherosclerosis, they may be at even higher risk of death from other causes that they die before they develop ACS (competing risks and informative censoring). This explanation is plausible but problematic because it could be theorized that malnourished patients are at higher risk for incidence of any disease process (*e.g.*, malignancy), but they die before the given process develops. Because this argument can be neither proved nor disproved, other evidence for the association of that disease process with malnutrition should be sought.

The definitions of malnutrition used in these studies might have influenced the associations of malnutrition and atherosclerosis. We defined malnutrition as low BMI (reflecting protein-energy malnutrition) or low UCr (reflecting protein malnutrition), and previous studies used SGA. Even though SGA has been shown to be a predictor of death (26), it is unclear whether SGA is a measure of nutrition. In fact, in the study in which the MIA hypothesis was proposed, the unadjusted associations of malnutrition with atherosclerosis were present only when SGA scores were used to define malnutrition (4). Furthermore, SGA in dialysis patients performed poorly when compared against total body nitrogen content, the gold standard for determination of nutritional status (27).

Finally, as explained in Figure 5, despite higher cardiovascular and all-cause deaths in malnourished patients, the positive association of malnutrition with atherosclerosis might not exist. As low UCr level did not influence the total incidence of ACS but increased the incidence of fatal ACS and 1-yr post-

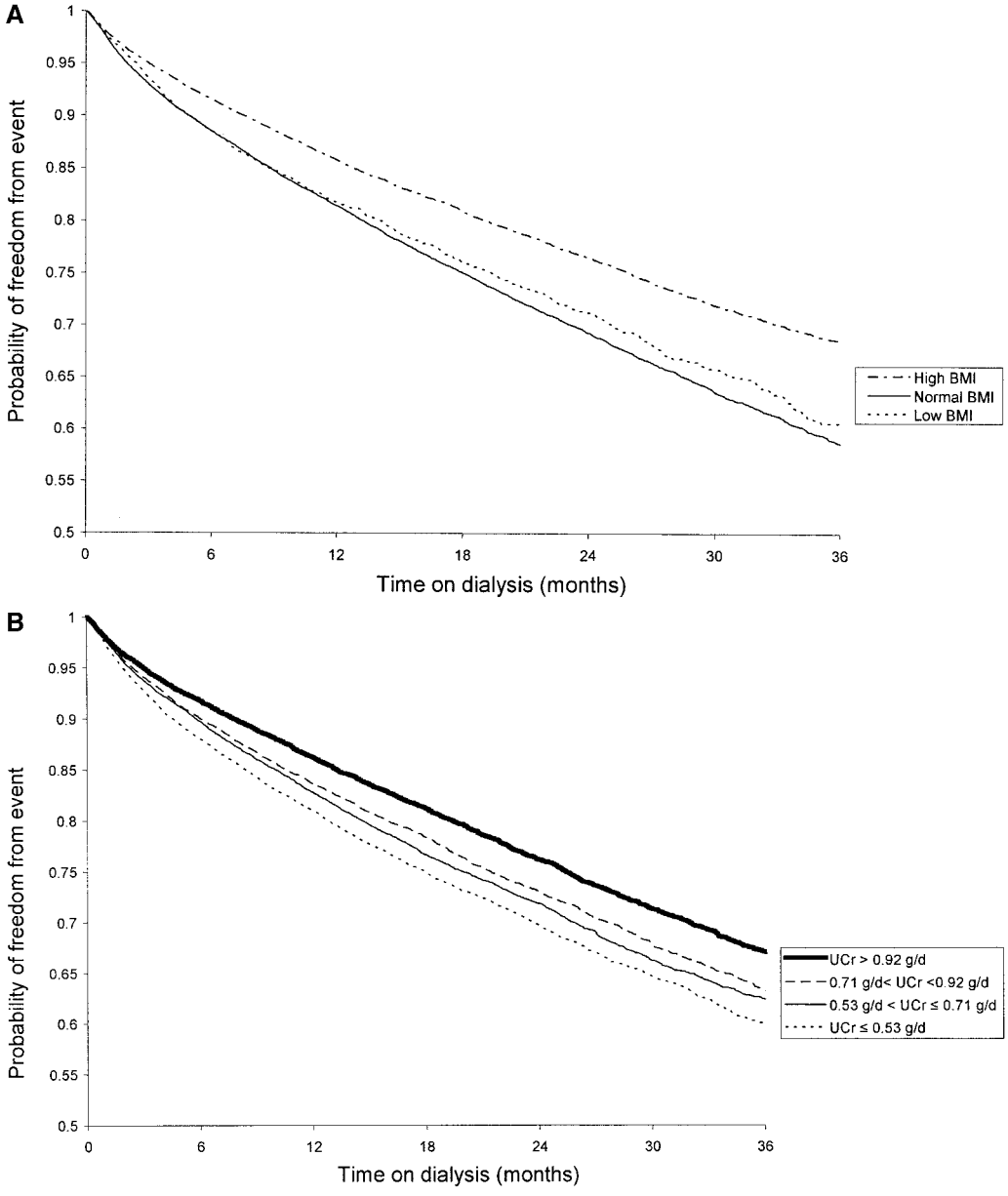

Figure 4. (A) Hospitalized fatal/nonfatal ACS or suspected out-of-hospital ischemic heart disease (IHD) deaths by BMI groups. (B) Hospitalized fatal/nonfatal ACS or suspected out-of-hospital IHD deaths by UCr groups

Table 6. Causes of death by BMI and UCr groups

	Deaths:Total No. of Patients (%)	Cardiovascular Causes of Death				Non-CV Causes of Death		
		MI/IHD (*n* [%])[a]	CHF (*n* [%])[a]	Sudden Death/ Arrhythmia (*n* [%])[a]	Other CV (*n* [%])[a]	Infection (*n* [%])[a]	Unknown (*n* [%])[a]	Other Non-CV (*n* [%])[a]
BMI groups								
<18.5 kg/m^2	2,637: 4,052 (65)	292 (11)	124 (5)	669 (25)	290 (11)	315 (12)	209 (8)	738 (28)
18.5–24.9 kg/m^2	13,036:23,299 (56)	1710 (13)	746 (6)	3436 (26)	1586 (12)	1379 (11)	843 (6)	3336 (26)
≥25 BMI kg/m^2	10,849:23,381 (46)	1451 (13)	610 (6)	2965 (27)	1397 (13)	1219 (11)	694 (6)	2513 (23)
UCr groups								
>0.92 g/d	5,412:12,626 (43)	746 (14)	275 (5)	1442 (27)	679 (13)	586 (11)	350 (6)	1334 (25)
0.71–0.92 g/d	6,236:12,535 (50)	834 (13)	351 (6)	1653 (27)	762 (12)	682 (11)	379 (6)	1575 (25)
0.54–0.70 g/d	6,937:12,564 (55)	888 (13)	373 (5)	1834 (26)	883 (13)	747 (11)	508 (7)	1704 (25)
≤0.53 g/d	7,937:13,007 (61)	985 (12)	481 (6)	2141 (27)	949 (12)	898 (11)	509 (6)	1974 (25)

[a] Row percentage; denominator, number of patients died within each BMI or UCr group.

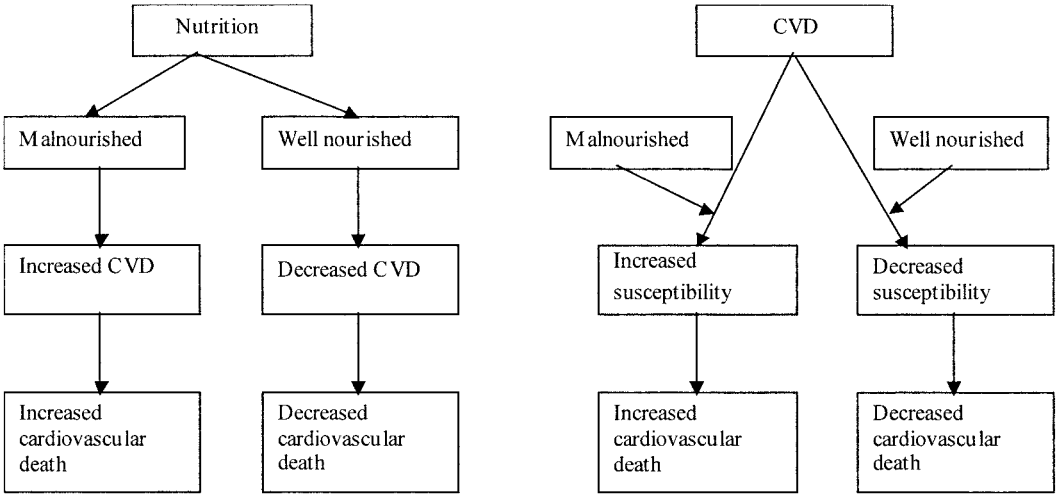

Figure 5. Two alternative hypotheses to explain higher cardiovascular deaths in malnourished patients. CVD, cardiovascular disease.

ACS mortality (Figure 2B, Tables 2 and 3), it is conceivable that malnutrition is not a risk factor for cardiovascular disease, but cardiovascular disease is more fatal in malnourished than in well-nourished patients. Thus, malnutrition could be associated with increased cardiovascular mortality without an association with atherosclerosis. Therefore, on the basis of higher cardiovascular and all-cause deaths in malnourished patients, one cannot necessarily infer that the incidence and prevalence of atherosclerosis should be higher in malnourished patients. Thus, malnutrition might rarely be a sufficient primary cause of death but a powerful contributor to death in the presence of concomitant diseases, and this might explain why malnutrition might not be listed as the direct cause of death in the USRDS death notification form but still a powerful predictor of death in epidemiologic analyses of the USRDS data.

There are several limitations to our study. First, this retrospective analysis of an existing database did not examine markers of inflammation. However, to examine the hypothesis that malnutrition is associated with increased baseline prevalence of atherosclerosis and subsequent atherosclerotic events, examination of markers of inflammation is not essential. Second, our study population included only elderly Medicare patients with reported creatinine clearances. Thus, there is a selection bias. As noted in our earlier study, patients with reported creatinine clearances compared with those without were older, were more malnourished, and had a higher baseline prevalence of coronary disease (28). Therefore, we selected a population with higher prevalence of malnutrition and atherosclerosis to increase the likelihood that the association of malnutrition with atherosclerosis, if any, would be manifest. It is remarkable that even in this population, we could not demonstrate an association of malnutrition with atherosclerosis. Finally, the limitations of this study include that of all observational studies that rely on existent databases.

In summary, we conclude that our study did not demonstrate conclusively an increased incidence of atherosclerotic events in malnourished dialysis patients. Earlier studies did not demon-

strate an unequivocal positive association of malnutrition with atherosclerosis. Further studies are warranted to provide definitive evidence of malnutrition as a uremic risk factor for cardiovascular disease.

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