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Epidemiology of Dialysis Patients and Heart Failure Patients

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The epidemiology of maintenance dialysis patients and heart failure patients has striking similarities. Both groups have a high prevalence of comorbid conditions, a high hospitalization rate, a low self-reported quality of life, and an excessively high mortality risk, mostly because of cardiovascular causes. Observational studies in both dialysis and heart failure patients have indicated the lack of a significant association between the traditional cardiovascular risk factors and mortality, or the existence of a paradoxic or reverse association, in that obesity, hypercholesterolemia, and hypertension appear to confer survival advantages. The time discrepancy between the 2 sets of risk factors, that is, overnutrition (long-term killer) versus undernutrition (short-term killer) may explain the overwhelming role of malnutrition, inflammation, and cachexia in causing the reverse epidemiology, which may exist in more than 20 million Americans. We have reviewed the opposing views about the concept of reverse epidemiology in dialysis and heart failure patients, the recent Die Deutsche Diabetes Dialyze study findings, and the possible role of racial disparities. Contradictory findings on hyperhomocysteinemia in dialysis patients are reviewed in greater details as a possible example of publication bias. Additional findings related to intravenous iron and serum ferritin, calcium, and leptin levels in dialysis patients may enhance our understanding of the new paradigm. The association between obesity and increased death risk in kidney transplanted patients is reviewed as an example of the reversal of reverse epidemiology. Studying the epidemiology of dialysis patients as the archetypical population with such paradoxic associations may lead to the development of population-specific guidelines and treatment strategies beyond the current Framingham cardiovascular risk factor paradigm.
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In the United States, there currently are more than 300,000 maintenance dialysis outpatients.[1,2] This number is expected to increase to almost half a million by 2010.[1-3] Because the proportion of chronic peritoneal dialysis (CPD) patients in the United States has decreased, the maintenance hemodialysis (MHD) patients comprise more than 90% of the entire dialysis patient population.[1,3] Both CPD and MHD patients experience a low quality of life, high hospitalization rates, and a high mortality rate of currently more than 20% annually, despite many recent improvements in dialysis treatment and techniques.[1-6] Two thirds of all dialysis patients die within 5 years of initiation of dialysis treatment, a 5-year survival rate worse than that of many cancer patients.[7] The causes of death in dialysis patients are diverse; however,

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approximately half of all dialysis patients die of cardiovascular disease.[1]

Extrapolation of findings from the general population has led to decades of treating such conventional cardiovascular risk factors in dialysis patients as hypertension, obesity, and hypercholesterolemia. Moreover, hyperhomocysteinemia also is quite common in dialysis patients and has been implicated as a major role player in cardiovascular disease risk of these patients.[8] Consequently, there is no surprise that the recent National Kidney Foundation Kidney Disease Outcome Quality Initiative clinical practice guidelines for cardiovascular disease in dialysis patients has focused heavily on these conventional risk factors.[9] However, survival in dialysis patients has not improved substantially in the past 2 decades.[1] Recent randomized clinical trials have shown no survival benefit of cholesterol-decreasing interventions using atorvastatin (the Die Deutsche Diabetes Dialyze [4D] study)[10,11] or using high-dose folic acid to treat hyperhomocysteinemia[12] in dialysis patients. Additional efforts in the form of several recent multicenter clinical trials including the HEMO[13] and Adequacy of Dialysis in Mexico (ADAMEX)[14] studies have failed to show any survival advantage of increasing dialysis dose in these patients. Furthermore, observational studies have shown only a modest, if any, association between hypertension and survival in dialysis patients.[15-17] Hence, there appears to be other prevailing conditions that contribute to this substantial and persistent cardiovascular disease and mortality rate and that need to be identified and studied better.

In this article we present an evidence-based conceptual model in an attempt to explain the unique features of the epidemiology of dialysis patients as it pertains to clinical outcomes (Fig 1) and compare it with the epidemiology of patients with chronic heart failure (CHF). The contradictory findings about the role of hyperhomocysteinemia in dialysis patients will be analyzed more thoroughly. We then expand the model to include other patients with chronic kidney disease (CKD) and advance similar but mostly not yet tested hypotheses pertaining to the epidemiology of CKD patients not undergoing dialysis and those who have undergone kidney transplantation. Finally, we review clinical implications of these conceptual epidemiologic models in the current and future strategies for the management of individuals with a similar atypical epidemiology.

The Concept of Reverse Epidemiology or Risk Factor Paradox

In highly industrialized, affluent nations, undernutrition is an uncommon cause of poor outcome in the general population, instead overnutrition is associated with a greater risk for cardiovascular disease and has an immense epidemiologic impact on the burden of cardiovascular disease and on shortened survival. In contrast, in dialysis patients in the same affluent countries, undernutrition appears to be one of the most common risk factors for adverse cardiovascular events and death.[18-25] The terms *reverse epidemiology*,[7,18] *risk factor paradox*,[19,20] or *altered risk factor pattern*[25] underscore this paradoxic observation, that is, certain markers, such as decreased body mass index (BMI) and lower serum cholesterol levels, which usually predict a low likelihood of cardiovascular events and an improved survival in the general population, become strong risk factors for increased cardiovascular morbidity and death in dialysis patients, especially among those undergoing MHD. Moreover, some indicators of overnutrition such as obesity or even morbid obesity actually predict improved outcome in MHD patients, hence a so-called *obesity paradox*.

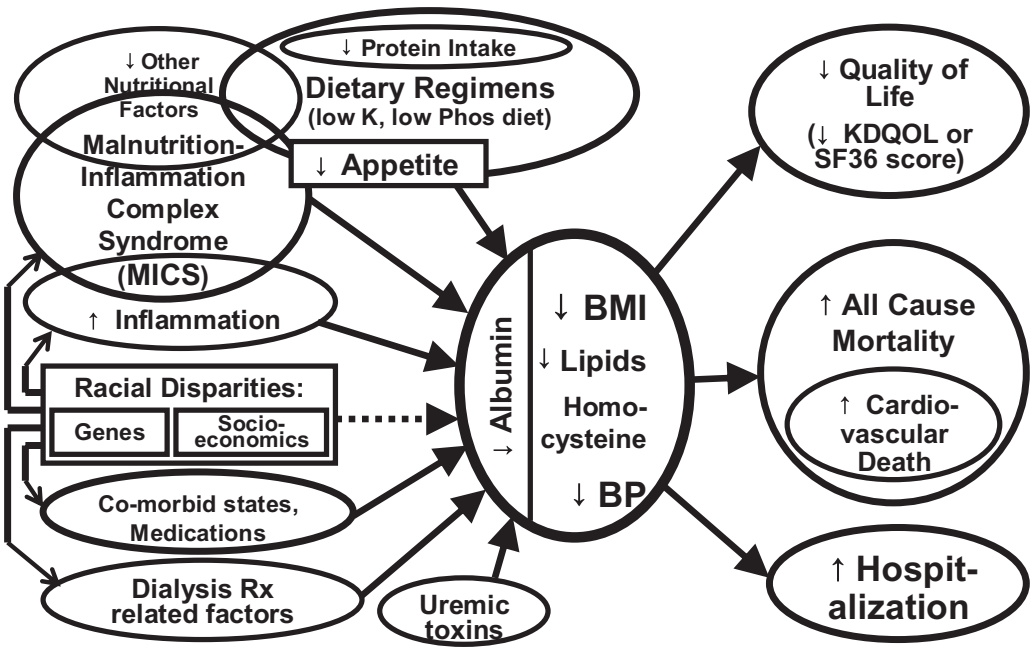

Figure 1 Potential pathophysiologic mechanisms leading to the reverse epidemiology phenomenon in maintenance dialysis patients.

Other Populations With Reverse Epidemiology

The reverse epidemiology is not unique to the dialysis population.[7] Patients with CHF,[26,27] geriatric populations,[28,29] hospitalized patients,[30] patients with malignancy,[31] those living with acquired immune deficiency syndrome,[32] and possibly other vulnerable populations such as those with chronic obstructive pulmonary disease[33] also show similar paradoxes.[18] Indeed, even chronic tobacco consumption may change the association between obesity and mortality.[34] Hence, there appears to be at least 20 million Americans (excluding healthy smokers), who are members of a population with a reverse epidemiology of cardiovascular risk factors (see Table 1). Among these distinct populations, the phenomenon of altered risk factors has been studied best among dialysis and CHF patients.[18,26] Hence, a better understanding of the reverse epidemiology phenomenon and its clinical and public health implications on survival of MHD and CHF patients may help improve poor outcome in more than 20 million Americans.

Malnutrition-Inflammation-Cachexia Syndrome

Dialysis patients not only have a high prevalence of malnutrition but also a higher occurrence rate of inflammation, as evidenced by increased biomarkers such as C-reactive protein (CRP) and proinflammatory cytokines.[35-40] Both malnutrition and inflammation are associated strongly with each other and with many nutritional measures in the same direction. As yet, the relative contributions of measures of these 2 conditions to each other and to outcomes in dialysis patients are not well defined; therefore, we have suggested the term *malnutrition-inflammation complex* (or *cachexia*) *syndrome* (MICS) to denote the important contribution of both to dialysis outcome.[35,41] The MICS may be a plausible cause of the reverse epidemiology of cardiovascular risk factors and other poor outcomes such as poor quality of life and increased hospitalization and refractory anemia in dialysis patients.[42-44] The cause of MICS in dialysis patients is not very clear, but some probable causes are depicted partially in Fig 1 and has been discussed previously.[45-53] Some of these factors such as reduced food intake owing to anorexia can be both a cause and a consequence of the MICS.[51,53]

Similarly, in CHF patients, cachexia is observed frequently and is associated with neurohormonal imbalance, inflammation, and poor outcome.[54-56] As in MHD patients, in whom anemia is associated with MICS and poor clinical outcome,[42] in CHF patients these pathophysiologic alterations also are associated with anemia,[57] which itself is an adverse prognostic factor.[58,59] Because nutritional and inflammatory conditions may be modifiable, correcting MICS in MHD patients or cachexia in CHF patients may improve outcomes and correct the reverse epidemiology.[52,53,60-62] However, before testing these hypotheses by launching expensive clinical trials, we need to know how MICS is engendered and through which mechanisms and temporal relationships it is associated with poor outcome in these patients.

Is Inflammation the Answer?

In the general population, indicators of inflammation, including increased serum CRP level, are stronger predictors of cardiovascular events than low-density lipoprotein (LDL) hypercholesterolemia.[63,64] Several studies have indicated a strong association between inflammatory markers including serum CRP level and proinflammatory cytokines such as tumor necrosis factor, interleukin-6, and interleukin-8 and prospective mortality in dialysis patients[61,65-67] and CHF patients.[68] Hence, at least by virtue of its inflammatory component, MICS may predispose dialysis patients to atherosclerotic cardiovascular disease.[69-71] However, in the general population, inflammation, similar to traditional cardiovascular risk factors, exerts its deleterious effects in a long-term basis, whereas MICS appears to result in poor outcome within a much shorter period of time. This temporal discor-

Table 1 Identified Populations With a Reverse Epidemiology Pattern

Population	Reverse Epidemiology Evidence	Estimated Census
ESRD undergoing MHD*	Obesity, HC, HTN, and more (see text)	0.3-0.4 million
Chronic heart failure†	Obesity, HC, HTN	4-5 million
Atherosclerotic coronary artery disease‡	Obesity	5-10 million
Advanced age (>75 y)§	Obesity, HC	15-20 million
Advanced malignancy§	Obesity, HC	0.4-0.8 million
AIDS§	Obesity, HC	0.1-0.3 million
Nursing home residency§	Obesity, HC	0.3-0.5 million
Advanced COPD‡	Obesity	0.1-0.3 million
Total		20-30 million

*Evidence for more than the 3 risk factors (HC, HTN, or obesity).
†Evidence for all 3 CV risk factors.
‡Evidence exists for at least 1 of the 3 traditional cardiovascular risk factors.
§Evidence for at least 2 of the 3 main CV risk factors.
Abbreviations: HC, hypercholesterolemia; HTN, hypertension; AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease.

dance is probably the key to understanding the problem (see later).

Short-Term Versus Long-Term Survival

In contrast to the conventional cardiovascular risk factors and overnutrition that require several years to decades to exert their deleterious effect, the impact of MICS and undernutrition is fast to ensue with decreased survival within a much shorter period of time. This *time discrepancy* hypothesis is a plausible explanation for the reverse epidemiology observed in vulnerable populations, in whom the undernutrition overwhelms the presence of overnutrition, leading to poor short-term survival in a number of distinct populations (see Table 1).[18,53] Hence, no matter how strongly cardiovascular risk factors such as hypertension, hypercholesterolemia, or obesity are present, MHD patients will continue to die excessively and fast as long as the short-term impact of MICS prevails. Malnourished or inflamed dialysis patients will not live long enough to die of obesity or hypertension because they die much faster of MICS (Fig 2). Similarly, CHF patients die much faster of cachexia. This hypothesis, if true, has major clinical implications in the management of MHD and CHF patients. If the main issue is indeed the high rate of short-term mortality (20% per year), it also is expected that short-term interventions that can correct MICS or cachexia will improve survival more substantially than treating traditional risk factors such as hypertension or hypercholesterolemia. Based on this core hypothesis, new dialysis population–specific ideal norms for improving short-term survival may need to be advanced to replace the Framingham guidelines.

Evidence For and Against Reverse Epidemiology

In the following sections, we review the most recent literature on the atypical epidemiology of the dialysis and CHF patient population as they pertain to the association between conventional risk factors and clinical outcomes including mortality (see Table 2).

Hypercholesterolemia

Several studies have indicated an association between low serum total cholesterol and LDL concentrations and poor survival of both dialysis[72-76] and heart failure patients.[27,77-80] In a matched study, it was shown recently that hypercholesterolemia and high LDL level are relatively uncommon conditions in MHD patients compared with other morbid populations.[81] An innovative study by Liu et al[82] showed that MICS leads to the inverse association between cholesterol and mortality in these patients. However, the conclusion by Liu et al[82] that statins would improve survival in dialysis patients was not confirmed by the 4D study[10,11] (see later). It is important to note that in the small and relatively healthy sample (n = 823) studied by Liu et al,[82] only less than a quarter of patients (n = 189) were classified as not having MICS and, hence, as having a conventional hypercholesterolemia-death association.[83] It is not clear how the risk-outcome constellation of 23% of this cohort could be generalized to the rest of the MHD patients who had MICS.[7,83]

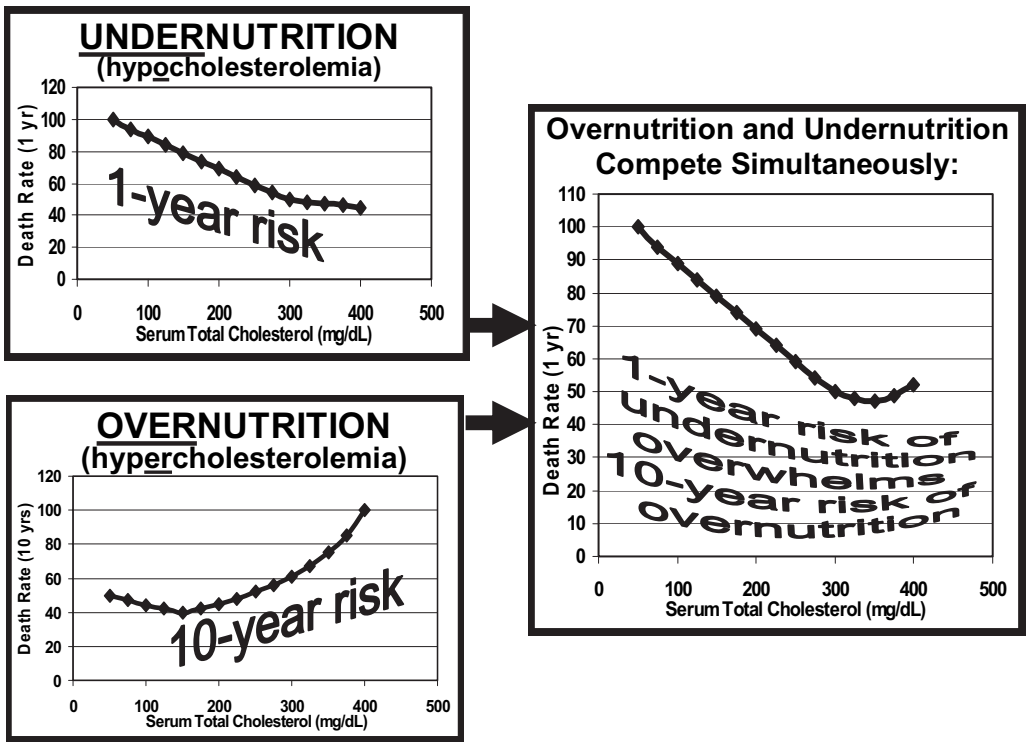

Figure 2 Competing risk factor hypothesis: short-term killer (undernutrition) versus long-term killer (overnutrition).

Table 2 Comparing Dialysis and Heart Failure Patients With the General Population Pertaining to Risk Factor–Outcome Constellations

	General Population	Maintenance Dialysis Patients	Heart Failure Patients
BMI or height-adjusted weight	Obesity is associated with increased CV events and death	Obesity confers survival advantages; weight loss over time increases death risk	Obesity confers survival advantages
TC level	Hypercholesterolemia is associated with increased CV events and death	Higher TC may be associated with greater survival	Higher TC and LDL are associated with greater survival
BP	HTN is associated with increased CV events and death	MHD patients with higher predialysis systolic BP (up to 180 mm/Hg) have greater survival	Lower BP values are associated with higher death risk
Serum homocysteine level	Hyperhomocysteinemia may be associated with increased CV events and death	Low serum homocysteine level is associated with increased death risk	No data
Calcium and vitamin D levels	Higher calcium intake may improve HTN and other CV risk factors	Hypercalcemia is associated with increased death risk; vitamin D intake is associated with better survival	No data
Iron markers and intravenous iron level	Increased serum iron and ferritin levels may be associated with increased death risk	A low serum iron level is associated with increased death risk; intravenous iron may improve survival	No data
Serum creatinine level	A high serum creatinine level is an independent risk for CV and death	High serum predialysis creatinine level is associated with better survival	No data
Serum potassium level	High dietary potassium intake may be associated with improved CV risk	High serum potassium level is associated with increased risk for CV events and death	No data
AGE	High AGE level is associated with increased CV risks	High AGE level may be associated with greater survival	No data
Acidosis (serum bicarbonate) level	Generally acidosis is associated with morbid conditions	MHD patients with lower predialysis serum bicarbonate level have better survival	No data
Serum leptin level	High serum leptin level is observed in obesity and metabolic syndrome	High serum leptin level is associated with better nutritional status	No data

Abbreviations: CV, cardiovascular; TC, total cholesterol; HTN, hypertension; AGE, advanced glycation end product.

In the 4D study[10] 1,255 diabetic dialysis patients were randomized to receive either atorvastatin 20 mg or placebo for 5 years. The results of the study were recently reported as negative[11] because only a nonsignificant 8% reduction of the primary composite end point by the cholesterol/LDL-lowering intervention was found. This was in distinct contrast to the recently published Collaborative Atorvastatin Diabetes Study[84] in type 2 diabetic patients who had not yet developed significant kidney disease. In that study, atorvastatin reduced the rate of acute coronary events by 36%, coronary revascularization by 31%, stroke by 48%, and death by 27%. The 4D study investigators concluded that their negative results might have been owing to the advanced cardiovascular diseases in the MHD patients and that the statin therapy was initiated too late.[11]

Similar to dialysis patients, the relationship between cholesterol and clinical outcome in heart failure patients is paradoxic. Vredevoe et al[77] reported that low total cholesterol, LDL, high-density lipoprotein (HDL), and triglyceride concentrations related to impaired survival in 109 heart failure patients. Rauchhaus et al[27,85] found that low total serum cholesterol levels were predictive for impaired 12-month event-free survival in patients with heart failure, independent of cause of heart disease (ischemic or nonischemic) and presence of cachexia. The largest epidemiologic study in this regard was conducted by Horwich et al[79]; cholesterol and lipoproteins were measured in 1,134 patients with advanced heart failure in a single heart transplant center. High levels of total cholesterol, LDL, HDL, and triglycerides each were associated with greater survival. Similarly, the cohort study by

Lissin et al[80] indicating "obesity paradox" in 522 heart failure patients showed that surviving patients had a higher prevalence of hyperlipidemia as compared with deceased patients. Rauchhaus et al[86] have advanced the endotoxin-lipoprotein hypothesis, which suggests that lipoproteins can bind bacterial toxins and hence have anti-inflammatory effects if bacterial toxins are indeed of relevance in the pathophysiology of CHF-associated inflammation. Recently, the same group also provided evidence from ex vivo studies that higher cholesterol levels related to lower cytokine production in whole blood exposed to endotoxin.[87]

Comparing the studies on dialysis and CHF patients, the reverse epidemiology of hyperlipidemia in heart failure appears to be supported by a higher number of independent studies, whereas the observational lipid studies on dialysis patients have larger sample sizes. Moreover, heart failure studies include all classes of lipid panels, whereas the bulk of data in dialysis patients are restricted to the reverse epidemiology to total cholesterol, although studies including LDL, HDL, and triglycerides are upcoming.[74-76,88]

Obesity

In a recent critical review,[89] 11 studies with large sample sizes (>1,000 patients each) have been identified,[90-100] indicating a reverse epidemiology of obesity in MHD patients. Indeed, in a recent cohort study in 54,535 MHD patients from a large dialysis organization using time-dependent Cox models, not only was morbid obesity found to confer survival advantages, but an incremental loss of weight over time also was associated with a stepwise increase in death risk (dose-response phenomenon), whereas a weight gain over time tended to correlate with improved survival.[100] In a creative study by Beddhu et al,[101] only greater muscle mass, and not body fat, was found to improve survival in MHD patients with a high BMI. However, the investigators conclusion that the survival advantage of high BMI was restricted to high muscle mass was not consistent with the finding of the study, an error that the investigators amended in their 2 subsequent commentaries.[102,103] Additional limitations of the study by Beddhu et al[101] have been discussed by Johansen et al[99] and by Kalantar-Zadeh et al,[7,89,104] including issues related to the use of urine creatinine as a surrogate of muscle mass in patients with advanced renal failure. Indeed, in a recent study a higher total body fat and an increase in body fat over time was found to correlate with greater survival in 535 MHD patients who were followed-up for 2.5 years.[105] However, the difficulties of separating muscle versus adipose mass using measures of body size and the paucity of reliable anthropometric data in most cohort or registry studies need to be acknowledged.[106]

Increased weight is associated with an increased risk for heart failure.[107,108] However, patients with more severe heart disease tend to have lower BMI values as compared with age- and sex-matched controls from the general population.[109-111] In the Systolic Hypertension in the Elderly Program study, overweight status was associated with a lower stroke risk and a decreased total mortality compared with lean patients.[112] Horwich et al[113] studied 1,203 individuals with moderate to severe heart failure (>60% with New York Heart Association class IV). Higher BMI was associated with better 2-year survival. In the Rotterdam Study cohort,[114] a higher BMI was an independent predictor of a more favorable prognosis in a 4-year follow-up period. Both cardiac death and all-cause mortality were lower in obese heart failure patients.[114] Davos et al[115] examined the impact of BMI in 525 patients with heart failure but without cachexia and found that survival was significantly better in mildly to moderately obese patients. Lissin et al[80] and Lavie et al[116] reported similar findings in 522 veteran patients and 209 consecutive ambulatory patients with heart failure, respectively. Finally, in 2 recent analyses of data from 7,767 patients[117] and 4,700[118] patients with stable heart failure, higher BMI was associated with lower mortality risks. Weight loss—independently of BMI, heart failure etiology, and clinical disease severity—was associated strongly with higher mortality.[54,119] A cut-off for weight loss of more than 6% was validated as the best definition for cachexia in CHF patients.[54] Understanding the mechanisms and impact of the obesity paradox in patients with heart failure is necessary before recommendations are made concerning weight target and weight control in this population.

Hypertension

Despite a hypertension prevalence of 70% to 90% among dialysis patients,[3,15,120] most studies have shown only a modest, if any, association between hypertension and death in these patients. Indeed, several epidemiologic studies[15,20,121-127] have shown a paradoxic association (ie, a strong association between normal to low blood pressure [BP] and increased risk for death in MHD patients). In 2 independent critical reviews, Foley[128] and Agarwal[16] each dismissed the concept of reverse epidemiology of hypertension as flawed and misleading and maintained that analytic approaches such as cross-sectional design, inclusion of prevalent patients leading to survival bias, and unmeasured comorbidities are at fault. However, in a recent study,[15] even incident MHD patients showed a reverse epidemiology of hypertension.[17]

Increased BP may not represent the primary risk for overall survival in heart failure patients because several studies, including those based on large sample sizes, have failed to show that a high BP is an independent mortality risk factor in CHF patients.[114,129-131] Among these studies, Cowie et al[131] examined 220 patients with incident heart failure and found that higher systolic BP and lower serum creatinine concentration were predictive independently of improved cardiovascular survival. Similarly, in the Rotterdam study, a higher BP conferred a more favorable prognosis among 181 patients with heart failure.[114] In a large cohort of outpatients consecutively enrolled in the Registry of Italian Network on heart failure,[132] higher systolic BP was among one of very few independent predictors of survival in 1,033 elderly patients (age, >70 y) with heart failure. In the study by Muntwyler et al,[133] in 411 heart failure patients who were followed-up for a mean period of 1.4 years, a statistically significant death risk with lower systolic BP was reported. In a recent randomized, dou-

ble-blind trial on 3,164 patients with heart failure to evaluate the effect of different doses of lisinopril on survival over a median of 46 months (Assessment of Treatment with Lisinopril And Survival),[134] a higher systolic BP at baseline was associated independently with a statistically significant lower mortality rate.

Hyperhomocysteinemia

Hyperhomocysteinemia may be a risk for cardiovascular disease in the general population[135]; however, the association between total serum or plasma homocysteine concentration and risk for vascular disease and death is not a consistent finding in dialysis patients (see Table 3). In 11 observational studies a positive association between hyperhomocysteinemia and increased death risk in dialysis patients was reported,[136-146] whereas 4 studies did not show any association,[147-149] and 6 studies[12,150-154] showed survival advantages of hyperhomocysteinemia in dialysis patients (Table 3). The 11 positive studies had patient sample sizes of 50 to 240 patients (average sample size, 129 patients) and were published between 1993 and 2003 (ie, a median publication year of 1998). In contrast, the 10 negative or reverse studies had a sample size of 94 to 804 patients (average sample size, 297 patients), and, with the exception of 1 study,[147] the other 3 negative studies and all 6 studies with a reverse epidemiology were published in the 21st century with a median publication year of 2002.

The difference in sample size and publication year indicates a possible publication bias in the past, which may have handicapped or delayed reporting such paradoxic findings in dialysis patients because the investigators' first impression on encountering results with inversed associations may be to consider them erroneous or flawed and hence be reluctant to report them.[155] However, because more reports indicative of reverse epidemiology have been published recently, more investigators may be encouraged to report their similar findings. This also may explain why more frequent reports and publications consistent with the reverse epidemiology have emerged only recently. Nevertheless, a significant level of publication bias at the peer-review level may continue to exist against studies reporting paradoxic results on risk factors.

Other Potential Components of Reverse Epidemiology

Increased levels of serum creatinine,[73,156,157] serum iron, transferrin saturation ratio,[158,159] ferritin,[159] and advanced glycation end products[160] have been shown to be associated with better survival in MHD patients. Other possible values with a paradoxic association in MHD patients are serum bicarbonate,[161-163] calcium (see later), and leptin.[164] We briefly present the evidence and opinions pertaining to calcium, iron markers, and leptin as the 3 examples of factors that are specific to dialysis patients.

Is Calcium Good or Bad?

The recent advances in our understanding about the role of calcium in dialysis patients are an example of the changing paradigm and the sharp contrast between the general population and dialysis patients. In the general population, an increased dietary calcium intake has been shown to improve hypertension and risk for ischemic heart disease.[165-167] An 8-year follow-up study of 43,486 women found a protective effect of calcium intake against ischemic cardiovascular mortality.[168] Moreover, osteoporosis, a poor outcome predictor, is associated with a low calcium intake.[169] Consistent with these findings, until recently a high intake of calcium in dialysis patients or a high calcium concentration in dialysate bath was the recommended practice pattern for more than 2 decades.[170] However, recent data are mostly in favor of a significant association between even mild to moderate hypercalcemia (>9.5 mg/dL) and higher mortality among dialysis patients,[171,172] as also recommended by the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines.[173] Hence, in dialysis patients, these associations appear to be the opposite of what is seen in the general population and in clear contradiction to the old paradigm. Moreover, a very high vitamin D intake may increase the risk for atherosclerosis according to animal studies,[174] whereas a large dialysis database analysis recently indicated that vitamin D supplementation in dialysis patients improves survival.[175,176]

Iron and Survival in Dialysis Patients

A possible association between body iron status and the risk for coronary heart disease has been shown in some[177,178] but not all[179] studies in the general population. In dialysis patients, the *iron apprehension* is aggravated by hemochromatosis case reports from the pre-erythropoietin era[180,181] and the abundant in vitro studies indicating the association between iron and oxidative stress.[182] However, recent work had indicated a significant association between a low, rather than a high, iron saturation ratio and risk for death in dialysis patients.[158] A recent large database analysis found that MHD patients with a serum ferritin level of up to 1,200 ng/mL did not have higher mortality, compared with patients with a serum ferritin level of 100 to 200 ng/mL.[159] Indeed, after adjustment for surrogates of MICS, the survival for some groups of patients with moderately high serum ferritin levels were significantly greater than the reference group, and intravenous iron administration up to 400 mg/mo was associated with greater survival compared with receiving no intravenous iron.[159] In a recent study, intravenous iron administration to a group of dialysis patients reduced levels of circulating tumor necrosis factor.[183] Hence, the survival advantages of intravenous iron may be related to the mitigation of inflammatory processes.

Serum Leptin in Dialysis Patients: High or Low?

Although in the general population leptin is considered an appetite inhibitor, its role in dialysis patients is not clear. Serum leptin levels generally are increased in dialysis patients, but this has not been shown to be a cause of uremia-related anorexia.[184,185] Three longitudinal/observational

Table 3 Studies Examining the Association Between Total Homocysteine Levels and Death Risk in MHD Patients

Study	Patients	Design	Results
Positive studies			
Chauveau et al,[136] 1993	118 CKD and ESRD	Cross-sectional	tHcys higher in patients with history of occlusive arterial dz
Bachmann et al, [137] 1995	50 MHD	Cross-sectional	High tHcys with occlusive arterial disease
Robinson et al,[138] 1996	176 MHD/CPD	Cross-sectional	Patients with tHcys in the upper 2 quintiles had an independent OR of 2.9 of vascular complications
Junger et al,[139] 1997	93 CKD	Cross-sectional	tHcy as an independent risk factor for CVA, with an OR of 11.4
Bostum et al,[140] 1997	73 MHD/CPD	Prospective (17 mo)	tHcy in upper quartile was associated with HR for nonfatal and fatal CVD ranging from 3.0 to 4.4
Moustapha et al,[141] 1998	176 ESRD (130 MHD)	Prospective (17 mo)	Increased RR of CV events of 1% per mcmol/L increase in tHcys
Kunz et al,[142] 1999	63 MHD	Cross-sectional	OR of CV events was 12.6 comparing highest versus lowest tHcys quartile
Dierkes et al,[143] 2000	102 MHD	Prospective (24 mo)	tHcys greater than median was associated with all-cause (but not CV) mortality (HR = 2.44)
Ducloux et al,[144] 2002	240 CPD	Prospective (41 mo)	High tHcys, high CRP, and low albumin levels were associated with risk for CV events
Mallamaci et al,[145] 2002	175 MHD	Prospective (29 mo)	Risk for atherothrombotic events was 8.2 times higher in patients in the highest tHcys tertile
Kronenberg et al,[146] 2003	155 ESRD (105 MHD)	Prospective (12 mo)	tHcys was related to progression of arterial calcification
Negative studies			
Vychytil et al,[147] 1998	154 CPD	Cross-sectional	No significant difference between CPD patients with and without CVD
Bayes et al,[148] 2003	94 MHD	Prospective (24 mo)	CRP, but not tHcys, is associated with higher mortality
London et al,[149] 2004	78 MHD	Prospective (60 mo)	tHcys is not associated with all-cause mortality
Menon et al,[246] 2005	804 CKD	Retrospective (several years)	tHcys is not associated with all-cause or CV mortality in CKD patients stages 3 and 4 in the MDRD study
Paradoxic results			
Sirrs et al,[150] 1999	96 MHD 88 MHD	Cross-sectional and prospective (9 mo)	tHcys was an inverse independent predictor of vascular access failure, and patients with higher tHcys had a better survival rate
Suliman et al,[151] 2000	117 MHD 117 MHD	Cross-sectional and prospective (36 mo)	Lower tHcys correlated with history of CVD; patients with higher tHycs had better survival; tHcys was influenced by nutritional status
Wrone et al,[152] 2001	459 ESRD (430 MHD)	Cross-sectional	tHcys was an inverse independent predictor of history of CVD
Suliman et al,[153] 2002	151 CKD	Cross-sectional	Lower tHcys correlated with history of CVD; tHcys was influenced by nutritional status
Kalantar-Zadeh et al,[154] 2004	361 MHD	Prospective (12 mo)	Lower tHcys was associated with higher hospitalization and mortality (HR = 2.3)
Wrone et al,[12] 2004	510 ESRD (468 MHD)	Prospective (24 mo)	Higher tHcys was associated with fewer CV events; folic acid did not affect CV events

NOTE. In the positive studies no direct associations were reported, in the negative studies no associations were found, the paradoxic association showed a low, rather than a high, tHcys level to be associated with a higher death risk.

tHcys, total homocysteine; CPD, peritoneal dialysis; OR, odds ratio; HR, hazard ratio; dz, disease; CVD, cardiovascular disease; MDRD, Modification of Diet in Renal Disease Study.

studies in MHD patients indicated that individuals with high serum leptin levels were more likely to lose weight.[186-188] However, more recent studies in dialysis patients suggested a paradoxically inverse association between higher serum leptin levels and improved markers of nutritional status.[184,185] Indeed, leptin, similar to serum albumin, has been reported to be a negative acute-phase reactant in dialysis patients.[185]

Administration of growth hormone to maintenance dialysis patients increases plasma leptin levels.[189,190] Iglesias et al[189] and Aguilera et al[191] found a strong direct correlation between serum leptin level and BMI and triceps skinfold thickness in a group of CPD patients. Healthier patients with a lower clinical atherosclerosis score had higher plasma leptin values than those with higher scores, whereas CPD patients with anorexia had lower leptin values than those with a normal appetite. In nonobese CPD patients, there were strong and positive correlations between serum leptin and markers of nutritional status, including serum albumin (r = 0.63), transferrin (r = 0.40), and cholesterol (r = 0.65).[189,191] Hence, although there currently are no data relating serum leptin to survival in dialysis patients, a reverse or paradoxic association between serum leptin and nutritional status, which is the strong marker of survival, is plausible.

Clinical Relevance of the Concept of Reverse Epidemiology

The forgoing studies have contributed to the growing confusion and have left physicians with a dilemma as to whether to treat obesity, hypercholesterolemia, and hypertension in dialysis and heart failure patients. Treatment of hyperhomocysteinemia with folic acid in dialysis patients has been questioned. It is not clear whether dietary calcium intake should be restricted or whether intravenous iron mitigates or worsens the death risk in dialysis patients. The wisdom of recommending weight loss to transplant wait-listed dialysis patients has been questioned by Johansen et al.[99] It is not clear whether muscle[101] or fat[105] confers survival advantages in dialysis patients.[102-104] Treatment of hyperhomocysteinemia with folic acid is being revisited.[192] There is even confusion about the treatment of hypertension in MHD patients.[128,193]

A number of investigators legitimately have questioned the existence and/or direction of the causality in the reverse epidemiology observations.[16,128,194-198] These are important and clinically relevant questions that require evidence-based answers. The concept of reverse epidemiology has been going beyond dialysis or heart failure populations and reaching out to non–heart-failure cardiology (patients with coronary artery disease[199-201] or undergoing cardiac surgery[202]), geriatrics,[28-30,203-205] oncology,[31,206] and acquired immune deficiency syndrome patients[32,207] (see Table 1). Studying dialysis and heart failure patients as the 2 archetypal populations with reverse epidemiology and examining their "Beyond-Framingham" risk factor constellations, as recently commented by McClellan and Chertow,[208] may offer important and clinically applicable insights leading to new recommendations and scientific evidence for population-specific guidelines for more than 20 million Americans with reverse epidemiology. Examining these paradoxes collectively instead of individually using very large but uniform and standardized databases can be a tool to that end.[209]

Racial Disparity and Reverse Epidemiology

Underlying disparities in access to health care, income, education, diet, lifestyle, and comorbid conditions have been implicated as the reason why black individuals have higher total mortality rates than whites.[210-212] In sharp contrast, black dialysis patients have a much lower annual mortality rate (18%) than whites (28%).[1] Dialysis patients of different races also have different quality-of-life scores.[213,214] Studying racial disparities in the context of reverse epidemiology may yield clinically applicable insights into how to reduce the excess risk in all dialysis patients.[215-217]

Kutner and Zhang[218] and Glanton et al[98] showed that the survival advantage of obesity in MHD patients did not apply to white women. In several studies, Asian American MHD patients are found to be the only subgroup of dialysis patients in whom obesity is associated with a worse survival,[99,100,219] a phenomenon that can be referred to as the *reversal of the reverse epidemiology* or *paradox within paradox*. In another study in large numbers of MHD patients, hypercholesterolemia and high LDL levels were associated with a lower death risk[75]; the only exception, however, were black MHD patients, in whom an LDL of more than 100 mg/dL was associated with a higher cardiovascular death risk.[88]

According to our hypothesis, nutritional factors may play a major role in causing such disparities. Indeed, according to an extreme version of our nutritional hypothesis, black dialysis patients have a greater survival rate because they tend not to follow the strict dietary restrictions (such as a low-phosphorus diet) that are imposed on all dialysis patients and that may be followed more strictly by white patients. We warn against such radical interpretation of our working hypotheses; however, such notions need to be examined, especially because excessive dietary restrictions to avoid hyperkalemia and hyperphosphatemia not only may engender protein-energy malnutrition[220] leading to secondary inflammation,[221] but also may leave atherogenic diet as the only source of food for MHD patients.[222] Moreover, a liberal food intake without dietary phosphorous and potassium restriction, although leading to hyperphosphatemia and hyperkalemia (alleged makers of the so-called noncompliant patient) may be a source of increased intake of beneficial phyto-nutrients and isoflavones found in legumes including soy products, nuts, fresh fruits and vegetables, juices, and so forth, which are restricted greatly in the typical renal diet.[223,224] Nevertheless, much work has to be performed to prove the merit of such hypotheses.

The Reversal of Reverse Epidemiology

MHD patients are the only CKD patients with consistent paradoxic associations between higher BMI and greater sur-

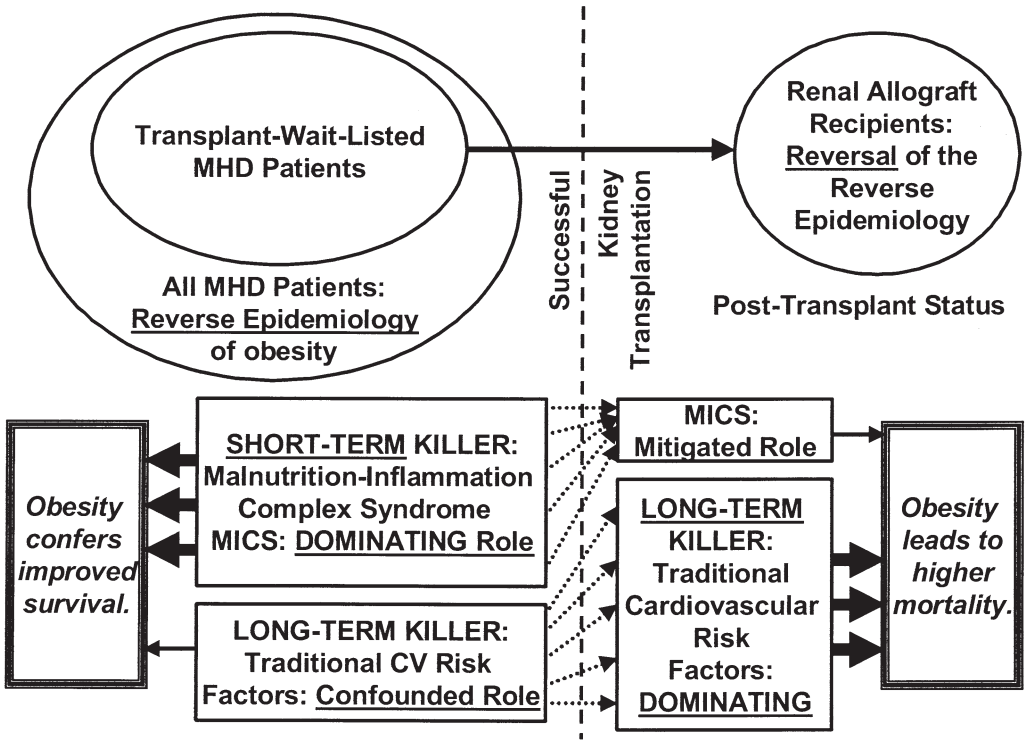

Figure 3 The reversal of reverse epidemiology or back-to-normal phenomenon after successful renal transplantation in dialysis patients.

vival. Data from CPD patients are mixed. Some,[225-230] but not all,[231-233] studies in CPD patients have reported similar inverse weight-mortality relationships. However, in patients who undergo successful kidney transplantation and maintain adequate renal function, obesity is associated with a poor long-term survival (see later). This phenomenon can be referred to as the *reversal of reverse epidemiology* or the *back-to-normal* phenomenon (see Fig 3) and is explained later.

The association between traditional cardiovascular risk factors and survival in patients with CKD not undergoing dialysis is not known. A recent secondary data analysis in 1,249 elderly individuals with CKD stages 3 to 5 showed that low HDL, increased LDL, and triglyceride levels and obesity were not associated with the mortality but systolic hypertension was.[234] In another study in 860 US Veteran male outpatients with CKD stages 3 to 5, a higher BP was associated paradoxically with greater survival in those who had a history of atherosclerotic cardiovascular disease.[235] We hypothesize that a gradual flattening and then reversal of the association between traditional risk factors and survival may exist across the advancing stages of CKD, so that in CKD stage 1, traditional relationships prevail, whereas by the time a patients has advanced to CKD stage 5, even if not yet undergoing dialysis, a reverse epidemiology will have developed.

The cardiovascular epidemiology in those dialysis patients who undergo daily hemodialysis, including home nocturnal and in-center short daily hemodialysis, is essentially unknown. We hypothesize that in these individuals, a reversal of reverse epidemiology is possible, especially if the provision of daily dialysis mitigates or corrects the effect of MICS. However, currently data virtually are nonexistent.

Obesity in Kidney Allograft Recipients

The prevalence of obesity has been growing in CKD patients being evaluated for transplantation.[236] A recent study by Friedman et al[237] reported 25% of kidney transplant recipients were obese in 2000 to 2001, an increase in prevalence by 116% when compared with 1987 to 1989. Most observational studies have shown higher rates of mortality among obese renal allograft recipients.[236,238-244] Because obesity and morbid obesity confer survival advantages in MHD patients, and because morbid obesity is associated with poor survival after renal transplantation, one might conclude that morbidly obese MHD patients should not undergo transplantation. To determine if a significant survival benefit exists for obese patients after renal transplantation versus those on the waiting list, Pelletier et al[236] studied a retrospective cohort of patients identified in the Scientific Registry of Transplant Recipients database. Adjusted time-dependent Cox regression models were used to evaluate the relative risk for death after transplantation compared with waiting-list mortality for kidney transplantation.[236] These data clearly showed that mortality worsened progressively with increasing BMI group. However, it was not shown how the association between BMI and mortality reversed on renal transplantation. We hypothesize that a significant portion of this back-to-normal (or reversal of the reverse epidemiology) phenomenon is explained by the overwhelming effect of MICS in dialysis patients and is caused by the time discrepancy between the 2 competing sets of risk factors as described earlier. Successful kidney transplantation mitigates the effect of MICS on dialy-

sis survival, so that the reversal of the obesity paradox by re-emergence of the long-term effect of traditional cardiovascular risk factors is observed (Fig 3). Another possibility, however, is that the improved cardiac function after kidney transplantation leads to the observed reversal.

Future Trends and Steps

The poor clinical outcomes in dialysis patients do not seem to be amenable to interventions that target the traditional cardiovascular risk factors. If our hypothesis is true that a complex set of conditions that are related to malnutrition and inflammation, called *MICS*, is the cause of this risk factor reversal and high death rate and if the short-term death risk caused by undernutrition overwhelms the long-term effects of overnutrition, then the key to improving survival in dialysis and heart failure patients and in another 20 to 30 million Americans with a reverse epidemiology may be interventions that can correct MICS. If a decrease in weight over time is associated with poor outcome in MHD and heart failure patients and if weight gain confers improved survival,[100] nutritional interventions and anti-inflammatory strategies may be the most promising alternatives. However, because MICS is multifactorial, single therapeutic strategies are not likely to be successful. Integrated interventions that target several aspects of the MICS in the form of combined nutritional treatment strategies with novel micronutrient components that have antioxidant and anti-inflammatory properties may be a solution and need to be tested.[53] Dietary restriction in dialysis patients in the name of reducing potassium and phosphorous intake may have had unintended deleterious consequences. The optimal solution to providing the beneficial compounds in natural foods while avoiding the potassium and phosphorous intake is probably the greatest nutritional dilemma in nephrology today. Studies with large numbers of dialysis patients and their recorded food intake with the detailed information on relevant nutrients such as legumes, nuts, fruits, and vegetables are needed to examine the role of dietary restriction in clinical outcomes of dialysis patients.

The ongoing focus with treating conventional risk factors such as hypertension, hypercholesterolemia, obesity, and hyperhomocysteinemia by using treatment targets derived from community cohorts are not likely to lead to an immediate improvement of the high mortality rate in dialysis or CHF patients, as long as the short-term survival is the issue at hand. Such practices that impose ideal BMI ranges based on the general population norms or mandatory weight loss programs for kidney or heart transplant wait-listed patients may need to be re-evaluated. Dismissing the theory of reverse epidemiology as counterintuitive and potentially harmful may not be the most scientifically rigorous approach in dealing with this conundrum. The characteristics of a surviving dialysis or CHF patient stand in clear contradiction to those predicted by traditional cardiovascular risk factors. Most CKD patients die before they reach the end-stage of the disease.[245] Hence, a CKD patient who has survived CKD stages 1 through 5 and now has become a dialysis patient does not represent the epidemiology and risk factor constellations of his/her predecessors. Focusing on the management of traditional cardiovascular risk factors in dialysis patients would be similar to screening for cancer among patients who already have cancer. The MICS in MHD patients or cachexia in CHF patients is such a *disease*. For patients with CKD and MHD it may be time to go beyond the Framingham risk factors and try to explore new modalities that can correct specific risk factors in dialysis patients.

References

1. United States Renal Data System: Excerpts from the USRDS 2004 annual data report. Am J Kidney Dis 45(suppl 1):S1-S280, 2005
2. United States Renal Data System: USRDS 2001 Annual Data Report; Atlas of End Stage Renal Diseases in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2001
3. United States Renal Data System: USRDS 2003 Annual Data Report; Atlas of End Stage Renal Diseases in the United States. Bethesda, MD, National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003
4. The United States Renal Data System 2002 Annual Data Report: US Department of Public Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, 2002
5. Morbidity and mortality of dialysis. NIH Consens Statement 11:1-33, 1993
6. Symonds T, Berzon R, Marquis P, et al: Clinical Significance Consensus Meeting G. The clinical significance of quality-of-life results: Practical considerations for specific audiences. Mayo Clin Proc 77:572-583, 2002
7. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, et al: Reverse epidemiology: A spurious hypothesis or a hardcore reality? Blood Purif 23:57-63, 2005
8. Suliman ME, Stenvinkel P, Qureshi AR, et al: Hyperhomocysteinemia in relation to plasma free amino acids, biomarkers of inflammation and mortality in patients with chronic kidney disease starting dialysis therapy. Am J Kidney Dis 44:455-465, 2004
9. National Kidney Foundation I, Kidney-Dialysis Outcome Quality Initiative: K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 45, 2005 (suppl 1)
10. Wanner C, Krane V, Marz W, et al: Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): Demographic and baseline characteristics. Kidney Blood Press Res 27:259-266, 2004
11. Wanner C, Krane V, Marz W, et al: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 353:238-248, 2005
12. Wrone EM, Hornberger JM, Zehnder JL, et al: Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. J Am Soc Nephrol 15:420-426, 2004
13. Eknoyan G, Beck GJ, Cheung AK, et al: Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 347: 2010-2019, 2002
14. Paniagua R, Amato D, Vonesh E, et al: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 13:1307-1320, 2002
15. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, et al: Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: The 58th annual fall conference and scientific sessions. Hypertension 45:811-817, 2005
16. Agarwal R: Hypertension and survival in chronic hemodialysis patients—past lessons and future opportunities. Kidney Int 67:1-13, 2005
17. Kalantar-Zadeh K, Kilpatrick RD, Kopple JD: Reverse epidemiology of blood pressure in dialysis patients. Kidney Int 67:2067-2068, 2005
18. Kalantar-Zadeh K, Block G, Humphreys MH, et al: Reverse epidemi-

ology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int 63:793-808, 2003
19. Nishizawa Y, Shoji T, Ishimura E, et al: Paradox of risk factors for cardiovascular mortality in uremia: Is a higher cholesterol level better for atherosclerosis in uremia? Am J Kidney Dis 38:S4-S7, 2001
20. Fleischmann EH, Bower JD, Salahudeen AK: Risk factor paradox in hemodialysis: Better nutrition as a partial explanation. ASAIO J 47: 74-81, 2001
21. Salahudeen AK: Obesity and survival on dialysis. Am J Kidney Dis 41:925-932, 2003
22. Kalantar-Zadeh K, Kopple J: Malnutrition as a cause of morbidity and mortality in dialysis patients, in Kopple J, Massry S (eds): Nutritional Management of Renal Disease (ed 2). Philadelphia, Lippincott, Williams & Wilkins, 2004
23. Kopple JD: Nutritional status as a predictor of morbidity and mortality in maintenance dialysis patients. ASAIO J 43:246-250, 1997
24. Fung F, Sherrard DJ, Gillen DL, et al: Increased risk for cardiovascular mortality among malnourished end-stage renal disease patients. Am J Kidney Dis 40:307-314, 2002
25. Kopple JD: The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. Am J Clin Nutr 81:1257-1266, 2005
26. Kalantar-Zadeh K, Block G, Horwich T, et al: Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 43:1439-1444, 2004
27. Rauchhaus M, Clark AL, Doehner W, et al: The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 42:1933-1940, 2003
28. Stevens J, Cai J, Pamuk ER, et al: The effect of age on the association between body-mass index and mortality. N Engl J Med 338:1-7, 1998
29. Yeh S, Wu SY, Levine DM, et al: Quality of life and stimulation of weight gain after treatment with megestrol acetate: Correlation between cytokine levels and nutritional status, appetite in geriatric patients with wasting syndrome. J Nutr Health Aging 4:246-251, 2000
30. Landi F, Onder G, Gambassi G, et al: Body mass index and mortality among hospitalized patients. Arch Intern Med 160:2641-2644, 2000
31. Chao FC, Efron B, Wolf P: The possible prognostic usefulness of assessing serum proteins and cholesterol in malignancy. Cancer 35: 1223-1229, 1975
32. Roubenoff R: Acquired immunodeficiency syndrome wasting, functional performance, and quality of life. Am J Manag Care 6:1003-1016, 2000
33. Wilson DO, Rogers RM, Wright EC, et al: Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis 139: 1435-1438, 1989
34. Calle EE, Thun MJ, Petrelli JM, et al: Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 341:1097-1105, 1999
35. Kalantar-Zadeh K, Ikizler TA, Block G, et al: Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. Am J Kidney Dis 42:864-881, 2003
36. Kalantar-Zadeh K, Kopple JD: Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis 38:1343-1350, 2001
37. Bergstrom J: Inflammation, malnutrition, cardiovascular disease and mortality in end-stage renal disease. Pol Arch Med Wewn 104:641-643, 2000
38. Qureshi AR, Alvestrand A, Divino-Filho JC, et al: Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol 13(suppl 1):S28-S36, 2002
39. Stenvinkel P: Malnutrition and chronic inflammation as risk factors for cardiovascular disease in chronic renal failure. Blood Purif 19:143-151, 2001
40. Stenvinkel P, Chung SH, Heimburger O, et al: Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. Perit Dial Int 21(suppl 3):S157-S162, 2001
41. Ifudu O, Uribarri J, Rajwani I, et al: Low hematocrit may connote a malnutrition-inflammation syndrome in hemodialysis patients. Dial Transplant 31:845-878, 2002
42. Kalantar-Zadeh K, McAllister CJ, Lehn RS, et al: Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. Am J Kidney Dis 42:761-773, 2003
43. Kalantar-Zadeh K, Regidor DL, Nissenson AR, et al: Association between changes in hemoglobin over time and survival in hemodialysis patients. J Am Soc Nephrol 16:489A, 2005 (abstract)
44. Kalantar-Zadeh K, Regidor DL, Nissenson AR, et al: Association between changes in hemoglobin over time and survival in hemodialysis patients. J Am Soc Neph 16 abstract issue:489A, 2005 (abstract)
45. Kopple JD: McCollum Award Lecture, 1996: Protein-energy malnutrition in maintenance dialysis patients. Am J Clin Nutr 65:1544-1557, 1997
46. Kopple JD: Pathophysiology of protein-energy wasting in chronic renal failure. J Nutr 129:247S-251S, 1999
47. Mehrotra R, Kopple J: Causes of protein-energy malnutrition in chronic renal failure, in Kopple J, Massry S (eds): Nutritional Management of Renal Disease (ed 2). Philadelphia, Lippincott, Williams & Wilkins, 2003
48. Qureshi AR, Alvestrand A, Danielsson A, et al: Factors predicting malnutrition in hemodialysis patients: A cross-sectional study. Kidney Int 53:773-782, 1998
49. Bergstrom J: Why are dialysis patients malnourished? Am J Kidney Dis 26:229-241, 1995
50. Kalantar-Zadeh K, Kopple J: Inflammation in renal failure, in Rose B (ed): UpToDate (since Oct 2002). Wellesley, MA, UpToDate, Inc, 2003
51. Kalantar-Zadeh K, Block G, McAllister CJ, et al: Appetite and inflammation, nutrition, anemia and clinical outcome in hemodialysis patients. Am J Clin Nutr 80:299-307, 2004
52. Kalantar-Zadeh K: Recent advances in understanding the malnutrition-inflammation complex syndrome in CKD patients: What is next? Semin Dial 18:365-369, 2005 (in press)
53. Kalantar-Zadeh K, Stenvinkel P, Bross R, et al: Kidney insufficiency and nutrient-based modulation of inflammation. Curr Opin Clin Nutr Metab Care 8:388-396, 2005
54. Anker SD, Negassa A, Coats AJ, et al: Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: An observational study. Lancet 361:1077-1083, 2003
55. Anker SD, Chua TP, Ponikowski P, et al: Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 96:526-534, 1997
56. Anker SD, Steinborn W, Strassburg S: Cardiac cachexia. Ann Med 36:518-529, 2004
57. Okonko DO, Crosato M, Kalra PR, et al: Association of deranged adrenal steroid metabolism with anemia in chronic heart failure. Am J Cardiol 96:101-103, 2005
58. Horwich TB, Fonarow GC, Hamilton MA, et al: Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 39:1780-1786, 2002
59. Sharma R, Francis DP, Pitt B, et al: Haemoglobin predicts survival in patients with chronic heart failure: A substudy of the ELITE II trial. Eur Heart J 25:1021-1028, 2004
60. Kalantar-Zadeh K, Braglia A, Chow J, et al: An anti-inflammatory and anti-oxidant nutritional supplement for hypoalbuminemic dialysis patients: A pilot/feasibility study. J Ren Nutr 15:318-331, 2005
61. Kalantar-Zadeh K: The latest addition to the inflammatory homeboys in chronic kidney disease: Interleukin-8. Nephron Clin Pract 102: c59-c60, 2005
62. Rammohan M, Kalantar-Zadeh K, Liang A, et al: Megestrol acetate in moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. J Ren Nutr 15:345-355, 2005
63. Ridker PM, Rifai N, Rose L, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 347:1557-1565, 2002

64. Ridker PM, Cannon CP, Morrow D, et al: C-reactive protein levels and outcomes after statin therapy. N Engl J Med 352:20-28, 2005
65. Stenvinkel P, Ketteler M, Johnson RJ, et al: IL-10, IL-6, and TNF-alpha: Central factors in the altered cytokine network of uremia—the good, the bad, and the ugly. Kidney Int 67:1216-1233, 2005
66. Kalantar-Zadeh K, Kopple JD, Humphreys MH, et al: Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. Nephrol Dial Transplant 19:1507-1519, 2004
67. Panichi V, Taccola D, Manca Rizza J, et al: Interleukin 8 is a powerful prognostic predictor of all cause and cardiovascular mortality in dialytic patients. Nephron Clin Pract 102:c51-c58, 2005
68. Rauchhaus M, Doehner W, Francis DP, et al: Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 102:3060-3067, 2000
69. Stenvinkel P, Barany P, Heimburger O, et al: Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? Kidney Int 103-108, 2002 (suppl 1)
70. Zimmermann J, Herrlinger S, Pruy A, et al: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 55:648-658, 1999
71. Bologa RM, Levine DM, Parker TS, et al: Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis 32:107-114, 1998
72. Iseki K, Yamazato M, Tozawa M, et al: Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. Kidney Int 61:1887-1893, 2002
73. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 15:458-482, 1990
74. Habib AN, Baird BC, Leypoldt JK, et al: The association of lipid levels with mortality in patients on chronic peritoneal dialysis. Am J Kidney Dis 45:A28, 2005 (abstr)
75. Kilpatrick RD, McAllister CJ, Kalantar-Zadeh K: Comparing mortality-predictability of serum total cholesterol and low density lipoprotein (LDL) cholesterol in hemodialysis patients. J Am Soc Nephrol 16:728A, 2005 (abstract)
76. Kalantar-Zadeh K, Horwich TB, Fonarow GC, et al: A low, rather than a high, serum LDL cholesterol is associated with increased mortality in hemodialysis patients even after controlling for inflammation. 37th annual conference of the American Society of Nephrology. J Am Soc Nephrol 15:173A, 2004 (abstr, suppl)
77. Vredevoe DL, Woo MA, Doering LV, et al: Skin test anergy in advanced heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 82:323-328, 1998
78. Richartz BM, Radovancevic B, Frazier OH, et al: Low serum cholesterol levels predict high perioperative mortality in patients supported by a left-ventricular assist system. Cardiology 89:184-188, 1998
79. Horwich TB, Hamilton MA, Maclellan WR, et al: Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 8:216-224, 2002
80. Lissin LW, Gauri AJ, Froelicher VF, et al: The prognostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. J Card Fail 8:206-215, 2002
81. Kalantar-Zadeh K, Kilpatrick RD, Kopple JD, et al: A matched comparison of serum lipids between hemodialysis patients and nondialysis morbid controls. Hemodialysis Int 9:314-324, 2005
82. Liu Y, Coresh J, Eustace JA, et al: Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. JAMA 291:451-459, 2004
83. Kalantar-Zadeh K, Anker SD: Inflammation, cholesterol levels, and risk of mortality among patients receiving dialysis. JAMA 291:1834-1835, 2004
84. Colhoun HM, Betteridge DJ, Durrington PN, et al: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 364:685-696, 2004
85. Rauchhaus M, Koloczek V, Volk H, et al: Inflammatory cytokines and the possible immunological role for lipoproteins in chronic heart failure. Int J Cardiol 76:125-133, 2000
86. Rauchhaus M, Coats AJ, Anker SD: The endotoxin-lipoprotein hypothesis. Lancet 356:930-933, 2000
87. Sharma R, von Haehling S, Rauchhaus M, et al: Whole blood endotoxin responsiveness in patients with chronic heart failure: The importance of serum lipoproteins. Eur J Heart Fail 7:479-484, 2005
88. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ: Black race modifies the reverse association between low density lipoprotein (LDL) and death risk in hemodialysis patients. J Am Soc Nephrol 16:295A, 2005 (abstr)
89. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, et al: Survival advantages of obesity in dialysis patients. Am J Clin Nutr 81:543-554, 2005
90. Degoulet P, Legrain M, Reach I, et al: Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study. Nephron 31:103-110, 1982
91. Leavey SF, Strawderman RL, Jones CA, et al: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 31:997-1006, 1998
92. Fleischmann E, Teal N, Dudley J, et al: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. Kidney Int 55:1560-1567, 1999
93. Kopple JD, Zhu X, Lew NL, et al: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. Kidney Int 56:1136-1148, 1999
94. Wolfe RA, Ashby VB, Daugirdas JT, et al: Body size, dose of hemodialysis, and mortality. Am J Kidney Dis 35:80-88, 2000
95. Leavey SF, McCullough K, Hecking E, et al: Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 16:2386-2394, 2001
96. Port FK, Ashby VB, Dhingra RK, et al: Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol 13:1061-1066, 2002
97. Lowrie EG, Li Z, Ofsthun N, et al: Body size, dialysis dose and death risk relationships among hemodialysis patients. Kidney Int 62:1891-1897, 2002
98. Glanton CW, Hypolite IO, Hshieh PB, et al: Factors associated with improved short term survival in obese end stage renal disease patients. Ann Epidemiol 13:136-143, 2003
99. Johansen KL, Young B, Kaysen GA, et al: Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr 80:324-332, 2004
100. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al: Association of morbid obesity and weight change on cardiovascular survival in hemodialysis population. Am J Kidney Dis 46:489-500, 2005
101. Beddhu S, Pappas LM, Ramkumar N, et al: Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol 14:2366-2372, 2003
102. Beddhu S, Pappas LM, Ramkumar N, et al: Body mass index and survival in incident dialysis patients: The answer depends on the question. Am J Clin Nutr 81:534-536, 2005
103. Beddhu S, Ramkumar N, Samore MH: The paradox of the BMI paradox in dialysis patients: Associations of adiposity with inflammation. Am J Clin Nutrition 82:909-910, 2005
104. Kalantar-Zadeh K, Abbott KC, Salahudeen AK: Reverse epidemiology of obesity in dialysis patients: Fat or muscle (letter)? Am J Clin Nutr 2005 (in press)
105. Kalantar-Zadeh K, Kuwae K, Wu DY, et al: Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutrition, 2006 (in press)
106. Kimmel PL, Chawla LS, Amarasinghe A, et al: Anthropometric measures, cytokines and survival in haemodialysis patients. Nephrol Dial Transplant 18:326-332, 2003
107. Contaldo F, Pasanisi F, Finelli C, et al: Obesity, heart failure and sudden death. Nutr Metab Cardiovasc Dis 12:190-197, 2002
108. Kenchaiah S, Evans JC, Levy D, et al: Obesity and the risk of heart failure. N Engl J Med 347:305-313, 2002
109. Pasini E, Aquilani R, Gheorghiade M, et al: Malnutrition, muscle wast-

ing and cachexia in chronic heart failure: The nutritional approach. Ital Heart J 4:232-235, 2003
110. Conraads VM, Bosmans JM, Vrints CJ: Chronic heart failure: An example of a systemic chronic inflammatory disease resulting in cachexia. Int J Cardiol 85:33-49, 2002
111. Ajayi AA, Adigun AQ, Ojofeitimi EO, et al: Anthropometric evaluation of cachexia in chronic congestive heart failure: The role of tricuspid regurgitation. Int J Cardiol 71:79-84, 1999
112. Wassertheil-Smoller S, Fann C, Allman RM, et al: Relation of low body mass to death and stroke in the systolic hypertension in the elderly program. The SHEP Cooperative Research Group. Arch Intern Med 160:494-500, 2000
113. Horwich TB, Fonarow GC, Hamilton MA, et al: The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 38:789-795, 2001
114. Mosterd A, Cost B, Hoes AW, et al: The prognosis of heart failure in the general population: The Rotterdam Study. Eur Heart J 22:1318-1327, 2001
115. Davos CH, Doehner W, Rauchhaus M, et al: Body mass and survival in patients with chronic heart failure without cachexia: The importance of obesity. J Card Fail 9:29-35, 2003
116. Lavie CJ, Osman AF, Milani RV, et al: Body composition and prognosis in chronic systolic heart failure: The obesity paradox. Am J Cardiol 91:891-894, 2003
117. Curtis JP, Selter JG, Wang Y, et al: The obesity paradox: Body mass index and outcomes in patients with heart failure. Arch Intern Med 165:55-61, 2005
118. Gustafsson F, Kragelund CB, Torp-Pedersen C, et al: Effect of obesity and being overweight on long-term mortality in congestive heart failure: Influence of left ventricular systolic function. Eur Heart J 26:58-64, 2005
119. Anker SD, Ponikowski P, Varney S, et al: Wasting as independent risk factor for mortality in chronic heart failure. Lancet 349:1050-1053, 1997
120. Salem M: Hypertension in the hemodialysis population? High time for answers. Am J Kidney Dis 33:592-594, 1999
121. Iseki K, Miyasato F, Tokuyama K, et al: Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. Kidney Int 51:1212-1217, 1997
122. Zager PG, Nikolic J, Brown RH, et al: "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. Kidney Int 54:561-569, 1998
123. Port FK, Hulbert-Shearon TE, Wolfe RA, et al: Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis 33:507-517, 1999
124. Klassen PS, Lowrie EG, Reddan DN, et al: Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. JAMA 287:1548-1555, 2002
125. Lowrie EG, Huang WH, Lew NL, et al: The relative contribution of measured variables to death risk among hemodialysis patients, in E G (ed): Death on Hemodialysis. Amsterdam, Kluwer Academic Publishers, 1994, p 121
126. Duranti E, Imperiali P, Sasdelli M: Is hypertension a mortality risk factor in dialysis? Kidney Int Suppl 55:S173-S174, 1996
127. Salem MM, Bower J: Hypertension in the hemodialysis population: Any relation to one-year survival? Am J Kidney Dis 28:737-740, 1996
128. Foley RN: Cardiac disease in chronic uremia: Can it explain the reverse epidemiology of hypertension and survival in dialysis patients? Semin Dial 17:275-278, 2004
129. Ghali JK, Kadakia S, Bhatt A, et al: Survival of heart failure patients with preserved versus impaired systolic function: The prognostic implication of blood pressure. Am Heart J 123:993-997, 1992
130. Rihal CS, Nishimura RA, Hatle LK, et al: Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. Relation to symptoms and prognosis. Circulation 90:2772-2779, 1994
131. Cowie MR, Wood DA, Coats AJ, et al: Survival of patients with a new diagnosis of heart failure: A population based study. Heart 83:505-510, 2000
132. Pulignano G, Del Sindaco D, Tavazzi L, et al: Clinical features and outcomes of elderly outpatients with heart failure followed up in hospital cardiology units: Data from a large nationwide cardiology database (IN-CHF Registry). Am Heart J 143:45-55, 2002
133. Muntwyler J, Abetel G, Gruner C, et al: One-year mortality among unselected outpatients with heart failure. Eur Heart J 23:1861-1866, 2002
134. Poole-Wilson PA, Uretsky BF, Thygesen K, et al: Mode of death in heart failure: Findings from the ATLAS trial. Heart 89:42-48, 2003
135. Nygard O, Nordrehaug JE, Refsum H, et al: Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med 337:230-236, 1997
136. Chauveau P, Chadefaux B, Coude M, et al: Hyperhomocysteinemia, a risk factor for atherosclerosis in chronic uremic patients. Kidney Int Suppl 41:S72-S77, 1993
137. Bachmann J, Tepel M, Raidt H, et al: Hyperhomocysteinemia and the risk for vascular disease in hemodialysis patients. J Am Soc Nephrol 6:121-125, 1995
138. Robinson K, Gupta A, Dennis V, et al: Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. Circulation 94:2743-2748, 1996
139. Jungers P, Chauveau P, Bandin O, et al: Hyperhomocysteinemia is associated with atherosclerotic occlusive arterial accidents in predialysis chronic renal failure patients. Miner Electrolyte Metab 23:170-173, 1997
140. Bostom AG, Shemin D, Verhoef P, et al: Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients. A prospective study. Arterioscler Thromb Vasc Biol 17:2554-2558, 1997
141. Moustapha A, Naso A, Nahlawi M, et al: Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end-stage renal disease. Circulation 97:138-141, 1998
142. Kunz K, Petitjean P, Lisri M, et al: Cardiovascular morbidity and endothelial dysfunction in chronic haemodialysis patients: Is homocyst(e)ine the missing link? Nephrol Dial Transplant 14:1934-1942, 1999
143. Dierkes J, Domrose U, Westphal S, et al: Cardiac troponin T predicts mortality in patients with end-stage renal disease. Circulation 102: 1964-1969, 2000
144. Ducloux D, Bresson-Vautrin C, Kribs M, et al: C-reactive protein and cardiovascular disease in peritoneal dialysis patients. Kidney Int 62: 1417-1422, 2002
145. Mallamaci F, Zoccali C, Tripepi G, et al: Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. Kidney Int 61:609-614, 2002
146. Kronenberg F, Mundle M, Langle M, et al: Prevalence and progression of peripheral arterial calcifications in patients with ESRD. Am J Kidney Dis 41:140-148, 2003
147. Vychytil A, Fodinger M, Wolfl G, et al: Major determinants of hyperhomocysteinemia in peritoneal dialysis patients. Kidney Int 53:1775-1782, 1998
148. Bayes B, Pastor MC, Bonal J, et al: Homocysteine, C-reactive protein, lipid peroxidation and mortality in haemodialysis patients. Nephrol Dial Transplant 18:106-112, 2003
149. London GM, Pannier B, Agharazii M, et al: Forearm reactive hyperemia and mortality in end-stage renal disease. Kidney Int 65:700-704, 2004
150. Sirrs S, Duncan L, Djurdjev O, et al: Homocyst(e)ine and vascular access complications in haemodialysis patients: Insights into a complex metabolic relationship. Nephrol Dial Transplant 14:738-743, 1999
151. Suliman ME, Qureshi AR, Barany P, et al: Hyperhomocysteinemia, nutritional status, and cardiovascular disease in hemodialysis patients. Kidney Int 57:1727-1735, 2000
152. Wrone EM, Zehnder JL, Hornberger JM, et al: An MTHFR variant, homocysteine, and cardiovascular comorbidity in renal disease. Kidney Int 60:1106-1113, 2001
153. Suliman ME, Stenvinkel P, Heimburger O, et al: Plasma sulfur amino

acids in relation to cardiovascular disease, nutritional status, and diabetes mellitus in patients with chronic renal failure at start of dialysis therapy. Am J Kidney Dis 40:480-488, 2002
154. Kalantar-Zadeh K, Block G, Humphreys MH, et al: A low, rather than a high, total plasma homocysteine is an indicator of poor outcome in hemodialysis patients. J Am Soc Nephrol 15:442-453, 2004
155. Montori VM, Smieja M, Guyatt GH: Publication bias: A brief review for clinicians. Mayo Clin Proc 75:1284-1288, 2000
156. Hatamizadeh P, Regidor DL, Kopple JD, et al: Association between baseline serum creatinine and all-cause and cardiovascular mortality in maintenance hemodialysis patients. J Am Soc Nephrol 2005 (abstr) (in press)
157. Combe C, McCullough KP, Asano Y, et al: Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): Nutrition guidelines, indicators, and practices. Am J Kidney Dis 44:39-46, 2004
158. Kalantar-Zadeh K, McAllister CJ, Lehn RS, et al: A low serum iron level is a predictor of poor outcome in hemodialysis patients. Am J Kidney Dis 43:671-684, 2004
159. Kalantar-Zadeh K, Regidor DL, McAllister CJ, et al: Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 16:3070-3080, 2005
160. Schwedler SB, Metzger T, Schinzel R, et al: Advanced glycation end products and mortality in hemodialysis patients. Kidney Int 62:301-310, 2002
161. Wu DY, Kilpatrick RD, Dadres S, et al: Association between serum bicarbonate and death in hemodialysis patients: Is it better to be acidotic or alkalotic? Hemodialysis Int 9:110, 2005 (abstr)
162. Kalantar-Zadeh K, Kilpatrick RD, Wu DY, et al: Association between serum bicarbonate and cardiovascular death in hemodialysis patients. J Am Soc Neph 16:717A-718A, 2005 (abstr)
163. Wu DY, McAllister CJ, Kilpatrick RD, et al: Association between serum bicarbonate and death in hemodialysis patients: Is it better to be acidotic or alkalotic? Clin J Am Soc Neph 1, 2006 Jan (in press)
164. Kalantar-Zadeh K, Mehrotra R, Fouque D, et al: Metabolic acidosis and malnutrition-inflammation complex syndrome in chronic renal failure. Semin Dial 17:445-465, 2004
165. Ascherio A, Rimm EB, Giovannucci EL, et al: A prospective study of nutritional factors and hypertension among US men. Circulation 86: 1475-1484, 1992
166. Allender PS, Cutler JA, Follmann D, et al: Dietary calcium and blood pressure: A meta-analysis of randomized clinical trials. Ann Intern Med 124:825-831, 1996
167. Bucher HC, Cook RJ, Guyatt GH, et al: Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. JAMA 275:1016-1022, 1996
168. Bostick RM, Kushi LH, Wu Y, et al: Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 149:151-161, 1999
169. Tussing L, Chapman-Novakofski K: Osteoporosis prevention education: Behavior theories and calcium intake. J Am Diet Assoc 105:92-97, 2005
170. Crooks PW, Coburn JW: Management of bone disease in the dialysis patient. Blood Purif 3:27-41, 1985
171. Block GA, Klassen PS, Lazarus JM, et al: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15:2208-2218, 2004
172. Slinin Y, Foley RN, Collins AJ: Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS waves 1, 3, and 4 study. J Am Soc Nephrol 16:1788-1793, 2005
173. National Kidney Foundation I, Kidney Disease-Dialysis Outcome Quality Initiative: K/DOQI Clinical Practice Guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42:S1-S202, 2003
174. Hines TG, Jacobson NL, Beitz DC, et al: Dietary calcium and vitamin D. Risk factors in the development of atherosclerosis in young goats. J Nutr 115:167-178, 1985
175. Teng M, Wolf M, Ofsthun MN, et al: Activated injectable vitamin D and hemodialysis survival: A historical cohort study. J Am Soc Nephrol 16:1115-1125, 2005
176. Kalantar-Zadeh K, Regidor DL, McAllister CJ: Time-varying association between paracalcitol and survival in hemodialysis patients. J Am Soc Nephrol 16:278A-279A, 2005 (abstr)
177. Salonen JT, Nyyssonen K, Korpela H, et al: High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation 86:803-811, 1992
178. Sullivan JL: The iron paradigm of ischemic heart disease. Am Heart J 117:1177-1188, 1989
179. Sempos CT, Looker AC, Gillum RF, et al: Body iron stores and the risk of coronary heart disease. N Engl J Med 330:1119-1124, 1994
180. Taccone-Gallucci M, Di Nucci G, Meloni C, et al: Risk of iron overload and 'hemochromatosis allele(s)' in patients on maintenance hemodialysis. Am J Nephrol 7:28-32, 1987
181. Kalantar-Zadeh K, Luft FC: Diagnosis of hemochromatosis. Ann Intern Med 131:311, 1999
182. Zager RA, Johnson AC, Hanson SY, et al: Parenteral iron formulations: A comparative toxicologic analysis and mechanisms of cell injury. Am J Kidney Dis 40:90-103, 2002
183. Weiss G, Meusburger E, Radacher G, et al: Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoietin. Kidney Int 64:572-578, 2003
184. Pecoits-Filho R, Lindholm B, Stenvinkel P: End-stage renal disease: A state of chronic inflammation and hyperleptinemia. Eur J Clin Invest 33:527-528, 2003
185. Don BR, Rosales LM, Levine NW, et al: Leptin is a negative acute phase protein in chronic hemodialysis patients. Kidney Int 59:1114-1120, 2001
186. Stenvinkel P, Lindholm B, Lonnqvist F, et al: Increases in serum leptin levels during peritoneal dialysis are associated with inflammation and a decrease in lean body mass. J Am Soc Nephrol 11:1303-1309, 2000
187. Odamaki M, Furuya R, Yoneyama T, et al: Association of the serum leptin concentration with weight loss in chronic hemodialysis patients. Am J Kidney Dis 33:361-368, 1999
188. Heimburger O, Lonnqvist F, Danielsson A, et al: Serum immunoreactive leptin concentration and its relation to the body fat content in chronic renal failure. J Am Soc Nephrol 8:1423-1430, 1997
189. Iglesias P, Diez JJ, Fernandez-Reyes MJ, et al: Effects of short-term recombinant human growth hormone therapy on plasma leptin concentrations in dialysis patients. Nephrol Dial Transplant 17:260-264, 2002
190. Fouque D, Juillard L, Lasne Y, et al: Acute leptin regulation in end-stage renal failure: The role of growth hormone and IGF-1. Kidney Int 54:932-937, 1998
191. Aguilera A, Bajo MA, Rebollo F, et al: Leptin as a marker of nutrition and cardiovascular risk in peritoneal dialysis patients. Adv Perit Dial 18:212-217, 2002
192. Suliman ME, Barany P, Kalantar-Zadeh K, et al: Homocysteine in uraemia—a puzzling and conflicting story. Nephrol Dial Transplant 20:16-21, 2005
193. Lynn KL: Hypertension and survival in hemodialysis patients. Semin Dial 17:270-274, 2004
194. Agarwal R: Exploring the paradoxical relationship of hypertension with mortality in chronic hemodialysis. Hemodial Int 8:207-213, 2004
195. Lavie CJ, Mehra MR, Milani RV: Obesity and heart failure prognosis: Paradox or reverse epidemiology? Eur Heart J 26:5-7, 2005
196. Charra B, Chazot C, Jean G, et al: Reverse epidemiology and hemodialysis blood pressure. Kidney Int 64:2323-2324, 2003
197. Abbott KC: Reverse epidemiology and obesity in maintenance dialysis patients. Kidney Int 64:1138, 2003
198. Perna AF, Acanfora F, Satta E, et al: Hyperhomocysteinemia and cardiovascular disease in uremia: The newest evidence in epidemiology and mechanisms of action. Semin Nephrol 24:426-430, 2004
199. Gruberg L, Weissman NJ, Waksman R, et al: The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: The obesity paradox? J Am Coll Cardiol 39:578-584, 2002

200. Gurm HS, Brennan DM, Booth J, et al: Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). Am J Cardiol 90:42-45, 2002
201. Lavie CJ, Milani RV: Obesity and cardiovascular disease: The Hippocrates paradox? J Am Coll Cardiol 42:677-679, 2003
202. Potapov EV, Loebe M, Anker S, et al: Impact of body mass index on outcome in patients after coronary artery bypass grafting with and without valve surgery. Eur Heart J 24:1933-1941, 2003
203. Lew SQ, Cohn F, Cohen LM, et al: Ethical issues in aging and renal disease. Adv Ren Replace Ther 7:63-69, 2000
204. Gruberg L, Mercado N, Milo S, et al: Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? Am J Cardiol 95:439-444, 2005
205. Grabowski DC, Ellis JE: High body mass index does not predict mortality in older people: Analysis of the Longitudinal Study of Aging. J Am Geriatr Soc 49:968-979, 2001
206. Halabi S, Small EJ, Vogelzang NJ: Elevated body mass index predicts for longer overall survival duration in men with metastatic hormone-refractory prostate cancer. J Clin Oncol 23:2434-2435, 2005
207. Chlebowski RT, Grosvenor M, Lillington L, et al: Dietary intake and counseling, weight maintenance, and the course of HIV infection. J Am Diet Assoc 95:428-435, 1995
208. McClellan WM, Chertow GM: Beyond Framingham: Cardiovascular risk profiling in ESRD. J Am Soc Nephrol 16:1539-1541, 2005
209. Kalantar-Zadeh K, Anker SD, Coats AJ, et al: Obesity paradox as a component of reverse epidemiology in heart failure (letter). Arch Intern Med 165:1797, 2005
210. Mortality patterns—United States, 1997. MMWR Morb Mortal Wkly Rep 48:664-668, 1999
211. Asher CR, Topol EJ, Moliterno DJ: Insights into the pathophysiology of atherosclerosis and prognosis of black Americans with acute coronary syndromes. Am Heart J 138:1073-1081, 1999
212. Davey Smith G, Neaton JD, Wentworth D, et al: Mortality differences between black and white men in the USA: Contribution of income and other risk factors among men screened for the MRFIT. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Lancet 351: 934-939, 1998
213. Unruh M, Miskulin D, Yan G, et al: Racial differences in health-related quality of life among hemodialysis patients. Kidney Int 65:1482-1491, 2004
214. Kutner NG, Zhang R, Brogan D: Race, gender, and incident dialysis patients' reported health status and quality of life. J Am Soc Nephrol 16:1440-1448, 2005
215. Reddan DN, Szczech LA, Klassen PS, et al: Racial inequity in America's ESRD program. Semin Dial 13:399-403, 2000
216. Sehgal AR: Impact of quality improvement efforts on race and sex disparities in hemodialysis. JAMA 289:996-1000, 2003
217. Alexander GC, Sehgal AR: Barriers to cadaveric renal transplantation among blacks, women, and the poor. JAMA 280:1148-1152, 1998
218. Kutner NG, Zhang R: Body mass index as a predictor of continued survival in older chronic dialysis patients. Int Urol Nephrol 32:441-448, 2001
219. Wong JS, Port FK, Hulbert-Shearon TE, et al: Survival advantage in Asian American end-stage renal disease patients. Kidney Int 55:2515-2523, 1999
220. Zimmerer JL, Leon JB, Covinsky KE, et al: Diet monotony as a correlate of poor nutritional intake among hemodialysis patients. J Ren Nutr 13:72-77, 2003
221. Ling PR, Smith RJ, Kie S, et al: Effects of protein malnutrition on IL-6-mediated signaling in the liver and the systemic acute-phase response in rats. Am J Physiol 287:R801-R808, 2004
222. Kalantar-Zadeh K, Kopple JD, Deepak S, et al: Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. J Ren Nutr 12:17-31, 2002
223. Fanti P, Stephenson TJ, Kaariainen IM, et al: Serum isoflavones and soya food intake in Japanese, Thai and American end-stage renal disease patients on chronic haemodialysis. Nephrol Dial Transplant 18:1862-1868, 2003
224. Fanti P, Sawaya BP, Custer LJ, et al: Serum levels and metabolic clearance of the isoflavones genistein and daidzein in hemodialysis patients. J Am Soc Nephrol 10:864-871, 1999
225. Canada-USA Peritoneal Dialysis Study Group: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. J Am Soc Nephrol 7:198-207, 1996
226. Hakim RM, Lowrie E: Obesity and mortality in ESRD: Is it good to be fat? Kidney Int 55:1580-1581, 1999
227. McCusker FX, Teehan BP, Thorpe KE, et al: for the Canada-USA (CANUSA) Peritoneal Dialysis Study Group: How much peritoneal dialysis is necessary for maintaining a good nutritional status? Kidney Int Suppl 56:S56-S61, 1996
228. Johnson DW, Herzig KA, Purdie DM, et al: Is obesity a favorable prognostic factor in peritoneal dialysis patients? Perit Dial Int 20:715-721, 2000
229. Chung SH, Lindholm B, Lee HB: Influence of initial nutritional status on continuous ambulatory peritoneal dialysis patient survival. Perit Dial Int 20:19-26, 2000
230. Snyder JJ, Foley RN, Gilbertson DT, et al: Body size and outcomes on peritoneal dialysis in the United States. Kidney Int 64:1838-1844, 2003
231. McDonald SP, Collins JF, Johnson DW: Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. J Am Soc Nephrol 14:2894-2901, 2003
232. Abbott KC, Glanton CW, Trespalacios FC, et al: Body mass index, dialysis modality, and survival: Analysis of the United States Renal Data System Dialysis Morbidity and Mortality Wave II Study. Kidney Int 65:597-605, 2004
233. Aslam N, Bernardini J, Fried L, et al: Large body mass index does not predict short-term survival in peritoneal dialysis patients. Perit Dial Int 22:191-196, 2002
234. Shlipak MG, Fried LF, Cushman M, et al: Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 293:1737-1745, 2005
235. Kovesdy CP, Trivedi BK, Anderson JE, et al: Atherosclerotic cardiovascular disease explains the inverse association between blood pressure and mortality in patients with chronic kidney disease not yet on dialysis. J Am Soc Nephrol 16:335A, 2005 (abstr)
236. Pelletier SJ, Maraschio MA, Schaubel DE, et al: Survival benefit of kidney and liver transplantation for obese patients on the waiting list. Clin Transpl 1:77-88, 2003
237. Friedman AN, Miskulin DC, Rosenberg IH, et al: Demographics and trends in overweight and obesity in patients at time of kidney transplantation. Am J Kidney Dis 41:480-487, 2003
238. Meier-Kriesche HU, Vaghela M, Thambuganipalle R, et al: The effect of body mass index on long-term renal allograft survival. Transplantation 68:1294-1297, 1999
239. Meier-Kriesche HU, Arndorfer JA, Kaplan B: The impact of body mass index on renal transplant outcomes: A significant independent risk factor for graft failure and patient death. Transplantation 73:70-74, 2002
240. Halme L, Eklund B, Kyllonen L, et al: Is obesity still a risk factor in renal transplantation? Transpl Int 10:284-288, 1997
241. Feldman HI, Fazio I, Roth D, et al: Recipient body size and cadaveric renal allograft survival. J Am Soc Nephrol 7:151-157, 1996
242. Pischon T, Sharma AM: Obesity as a risk factor in renal transplant patients. Nephrol Dial Transplant 16:14-17, 2001
243. Drafts HH, Anjum MR, Wynn JJ, et al: The impact of pre-transplant obesity on renal transplant outcomes. Clin Transplant 11:493-496, 1997
244. Modlin CS, Flechner SM, Goormastic M, et al: Should obese patients lose weight before receiving a kidney transplant? Transplantation 64: 599-604, 1997
245. Keith DS, Nichols GA, Gullion CM, et al: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164:659-663, 2004
246. Menon V, Sarnak M, Greene T, et al: Homocysteine as a predictor of all-cause and cardiovascular mortality in chronic kidney disease. J Am Soc Nephrol 2005 (abstr) (in press)