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# Epidemiology of Dialysis Patients and Heart Failure Patients

Kamyar Kalantar-Zadeh, Kevin C. Abbott, Florian Kronenberg, Stefan D. Anker, Tamara B. Horwich, and Gregg C. Fonarow

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 paradoxical 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 Dialyse 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 paradoxical 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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**KEYWORDS** malnutrition-inflammation complex syndrome, dialysis, protein-energy malnutrition, cachexia, chronic heart failure, reverse epidemiology, homocysteine

In the United States, there currently are more than 300,000 maintenance dialysis outpatients.<sup>1,2</sup> This number is expected to increase to almost half a million by 2010.<sup>1-3</sup> 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.<sup>1,3</sup> Both CPD and MHD pa-

tients 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.<sup>1-6</sup> 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.<sup>7</sup> The causes of death in dialysis patients are diverse; however,

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approximately half of all dialysis patients die of cardiovascular disease.<sup>1</sup>

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.<sup>8</sup> 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.<sup>9</sup> However, survival in dialysis patients has not improved substantially in the past 2 decades.<sup>1</sup> Recent randomized clinical trials have shown no survival benefit of cholesterol-decreasing interventions using atorvastatin (the Die Deutsche Diabetes Dialyze [4D] study)<sup>10,11</sup> or using high-dose folic acid to treat hyperhomocysteinemia<sup>12</sup> in dialysis patients. Additional efforts in the form of several recent multicenter clinical trials including the HEMO<sup>13</sup> and Adequacy of Dialysis in Mexico (ADAMEX)<sup>14</sup> 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.<sup>15-17</sup> 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.

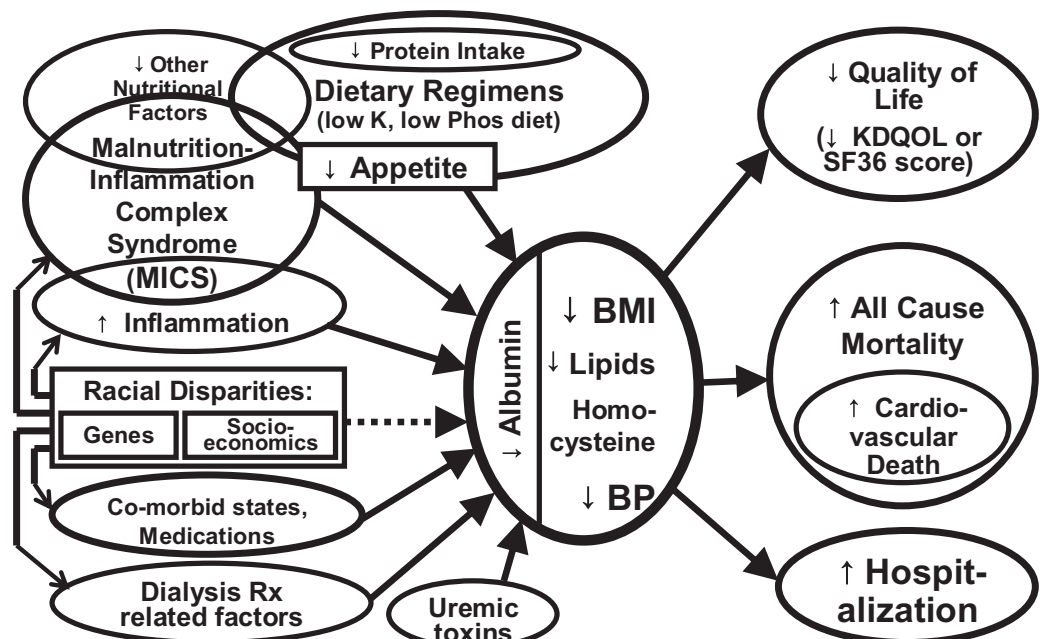
In this article we present an evidence-based conceptual model in an attempt to explain the unique features of the epidemiology of dialysis patients as it pertains to clinical outcomes (Fig 1) and compare it with the epidemiology of patients with chronic heart failure (CHF). The contradictory findings 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.<sup>18-25</sup> The terms *reverse epidemiology*,<sup>7,18</sup> *risk factor paradox*,<sup>19,20</sup> or *altered risk factor pattern*<sup>25</sup> underscore this paradoxical 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.<sup>7</sup> Patients with CHF,<sup>26,27</sup> geriatric populations,<sup>28,29</sup> hospitalized patients,<sup>30</sup> patients with malignancy,<sup>31</sup> those living with acquired immune deficiency syndrome,<sup>32</sup> and possibly other vulnerable populations such as those with chronic obstructive pulmonary disease<sup>33</sup> also show similar paradoxes.<sup>18</sup> Indeed, even chronic tobacco consumption may change the association between obesity and mortality.<sup>34</sup> 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.<sup>18,26</sup> 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.<sup>35-40</sup> 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.<sup>35,41</sup> 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.<sup>42-44</sup> 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.<sup>45-53</sup> Some of these factors such as reduced food intake owing to anorexia can be both a cause and a consequence of the MICS.<sup>51,53</sup>

Similarly, in CHF patients, cachexia is observed frequently and is associated with neurohormonal imbalance, inflammation, and poor outcome.<sup>54-56</sup> As in MHD patients, in whom anemia is associated with MICS and poor clinical outcome,<sup>42</sup> in CHF patients these pathophysiologic alterations also are associated with anemia,<sup>57</sup> which itself is an adverse prognostic factor.<sup>58,59</sup> 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.<sup>52,53,60-62</sup> 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.<sup>63,64</sup> 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<sup>61,65-67</sup> and CHF patients.<sup>68</sup> Hence, at least by virtue of its inflammatory component, MICS may predispose dialysis patients to atherosclerotic cardiovascular disease.<sup>69-71</sup> 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).<sup>18,53</sup> 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.

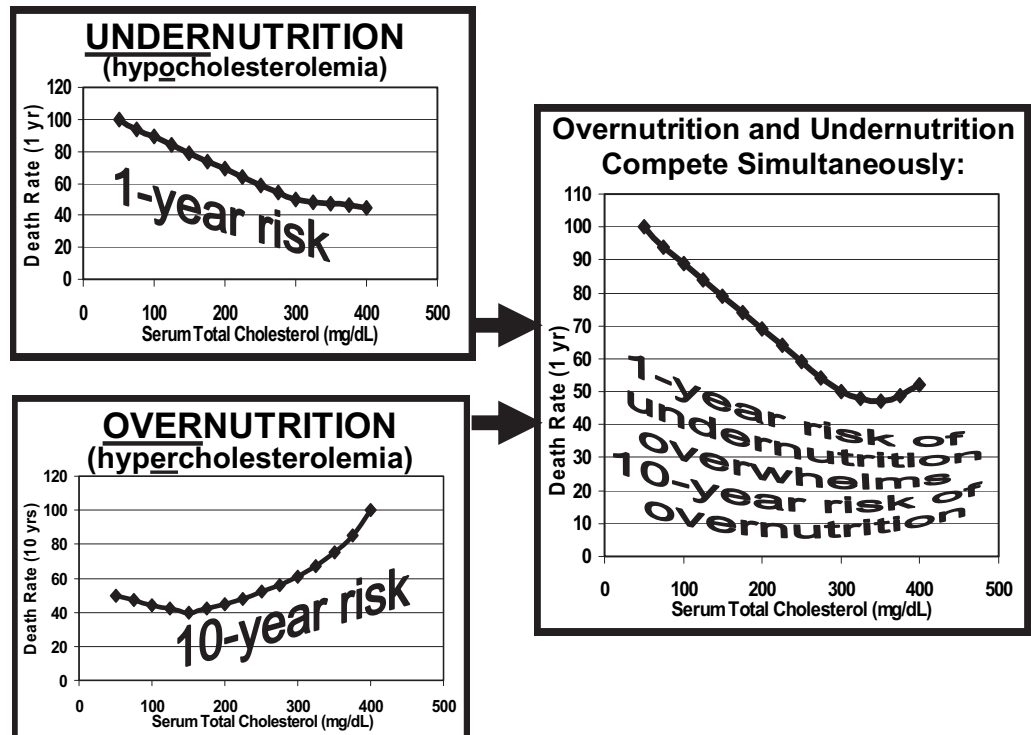
### Evidence For and Against Reverse Epidemiology

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<sup>72-76</sup> and heart failure patients.<sup>27,77-80</sup> 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.<sup>81</sup> An innovative study by Liu et al<sup>82</sup> showed that MICS leads to the inverse association between cholesterol and mortality in these patients. However, the conclusion by Liu et al<sup>82</sup> that statins would improve survival in dialysis patients was not confirmed by the 4D study<sup>10,11</sup> (see later). It is important to note that in the small and relatively healthy sample (n = 823) studied by Liu et al,<sup>82</sup> only less than a quarter of patients (n = 189) were classified as not having MICS and, hence, as having a conventional hypercholesterolemia-death association.<sup>83</sup> 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.<sup>7,83</sup>

**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

	<b>General Population</b>	<b>Maintenance Dialysis Patients</b>	<b>Heart Failure Patients</b>
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<sup>10</sup> 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<sup>11</sup> 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<sup>84</sup> 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.<sup>11</sup>

Similar to dialysis patients, the relationship between cholesterol and clinical outcome in heart failure patients is paradoxical. Vredevoe et al<sup>77</sup> 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<sup>27,85</sup> 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<sup>79</sup>; 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<sup>80</sup> 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<sup>86</sup> 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.<sup>87</sup>

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.<sup>74-76,88</sup>

## Obesity

In a recent critical review,<sup>89</sup> 11 studies with large sample sizes (>1,000 patients each) have been identified,<sup>90-100</sup> 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.<sup>100</sup> In a creative study by Beddhu et al,<sup>101</sup> 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.<sup>102,103</sup> Additional limitations of the study by Beddhu et al<sup>101</sup> have been discussed by Johansen et al<sup>99</sup> and by Kalantar-Zadeh et al,<sup>7,89,104</sup> 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.<sup>105</sup> 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.<sup>106</sup>

Increased weight is associated with an increased risk for heart failure.<sup>107,108</sup> 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.<sup>109-111</sup> 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.<sup>112</sup> Horwich et al<sup>113</sup> 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,<sup>114</sup> 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.<sup>114</sup> Davos et al<sup>115</sup> 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<sup>80</sup> and Lavie et al<sup>116</sup> 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<sup>117</sup> and 4,700<sup>118</sup> 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.<sup>54,119</sup> A cut-off for weight loss of more than 6% was validated as the best definition for cachexia in CHF patients.<sup>54</sup> 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,<sup>3,15,120</sup> most studies have shown only a modest, if any, association between hypertension and death in these patients. Indeed, several epidemiologic studies<sup>15,20,121-127</sup> have shown a paradoxical 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<sup>128</sup> and Agarwal<sup>16</sup> 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,<sup>15</sup> even incident MHD patients showed a reverse epidemiology of hypertension.<sup>17</sup>

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.<sup>114,129-131</sup> Among these studies, Cowie et al<sup>131</sup> 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.<sup>114</sup> In a large cohort of outpatients consecutively enrolled in the Registry of Italian Network on heart failure,<sup>132</sup> 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,<sup>133</sup> 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),<sup>134</sup> 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<sup>135</sup>; 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,<sup>136-146</sup> whereas 4 studies did not show any association,<sup>147-149</sup> and 6 studies<sup>12,150-154</sup> 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,<sup>147</sup> 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 paradoxical 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.<sup>155</sup> 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 paradoxical results on risk factors.

## Other Potential

### Components of Reverse Epidemiology

Increased levels of serum creatinine,<sup>73,156,157</sup> serum iron, transferrin saturation ratio,<sup>158,159</sup> ferritin,<sup>159</sup> and advanced glycation end products<sup>160</sup> have been shown to be associated with better survival in MHD patients. Other possible values with a paradoxical association in MHD patients are serum bicarbonate,<sup>161-163</sup> calcium (see later), and leptin.<sup>164</sup> 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.<sup>165-167</sup> An 8-year follow-up study of 43,486 women found a protective effect of calcium intake against ischemic cardiovascular mortality.<sup>168</sup> Moreover, osteoporosis, a poor outcome predictor, is associated with a low calcium intake.<sup>169</sup> 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.<sup>170</sup> 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,<sup>171,172</sup> as also recommended by the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines.<sup>173</sup> 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,<sup>174</sup> whereas a large dialysis database analysis recently indicated that vitamin D supplementation in dialysis patients improves survival.<sup>175,176</sup>

## 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<sup>177,178</sup> but not all<sup>179</sup> studies in the general population. In dialysis patients, the *iron apprehension* is aggravated by hemochromatosis case reports from the pre-erythropoietin era<sup>180,181</sup> and the abundant in vitro studies indicating the association between iron and oxidative stress.<sup>182</sup> 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.<sup>158</sup> 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.<sup>159</sup> 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.<sup>159</sup> In a recent study, intravenous iron administration to a group of dialysis patients reduced levels of circulating tumor necrosis factor.<sup>183</sup> 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.<sup>184,185</sup> Three longitudinal/observational



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

Study	Patients	Design	Results
<b>Positive studies</b>			
Chauveau et al, <sup>136</sup> 1993	118 CKD and ESRD	Cross-sectional	tHcys higher in patients with history of occlusive arterial dz
Bachmann et al, <sup>137</sup> 1995	50 MHD	Cross-sectional	High tHcys with occlusive arterial disease
Robinson et al, <sup>138</sup> 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, <sup>139</sup> 1997	93 CKD	Cross-sectional	tHcy as an independent risk factor for CVA, with an OR of 11.4
Bostum et al, <sup>140</sup> 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, <sup>141</sup> 1998	176 ESRD (130 MHD)	Prospective (17 mo)	Increased RR of CV events of 1% per $\mu\text{mol/L}$ increase in tHcys
Kunz et al, <sup>142</sup> 1999	63 MHD	Cross-sectional	OR of CV events was 12.6 comparing highest versus lowest tHcys quartile
Dierkes et al, <sup>143</sup> 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, <sup>144</sup> 2002	240 CPD	Prospective (41 mo)	High tHcys, high CRP, and low albumin levels were associated with risk for CV events
Mallamaci et al, <sup>145</sup> 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, <sup>146</sup> 2003	155 ESRD (105 MHD)	Prospective (12 mo)	tHcys was related to progression of arterial calcification
<b>Negative studies</b>			
Vychytil et al, <sup>147</sup> 1998	154 CPD	Cross-sectional	No significant difference between CPD patients with and without CVD
Bayes et al, <sup>148</sup> 2003	94 MHD	Prospective (24 mo)	CRP, but not tHcys, is associated with higher mortality
London et al, <sup>149</sup> 2004	78 MHD	Prospective (60 mo)	tHcys is not associated with all-cause mortality
Menon et al, <sup>246</sup> 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
<b>Paradoxical results</b>			
Sirrs et al, <sup>150</sup> 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, <sup>151</sup> 2000	117 MHD 117 MHD	Cross-sectional and prospective (36 mo)	Lower tHcys correlated with history of CVD; patients with higher tHcys had better survival; tHcys was influenced by nutritional status
Wrone et al, <sup>152</sup> 2001	459 ESRD (430 MHD)	Cross-sectional	tHcys was an inverse independent predictor of history of CVD
Suliman et al, <sup>153</sup> 2002	151 CKD	Cross-sectional	Lower tHcys correlated with history of CVD; tHcys was influenced by nutritional status
Kalantar-Zadeh et al, <sup>154</sup> 2004	361 MHD	Prospective (12 mo)	Lower tHcys was associated with higher hospitalization and mortality (HR = 2.3)
Wrone et al, <sup>12</sup> 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 paradoxical 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.<sup>186-188</sup> However, more recent studies in dialysis patients suggested a paradoxically inverse association between higher serum leptin levels and improved markers of nutritional status.<sup>184,185</sup> Indeed, leptin, similar to serum albumin, has been reported to be a negative acute-phase reactant in dialysis patients.<sup>185</sup>

Administration of growth hormone to maintenance dialysis patients increases plasma leptin levels.<sup>189,190</sup> Iglesias et al<sup>189</sup> and Aguilera et al<sup>191</sup> 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 ( $r = 0.65$ ).<sup>189,191</sup> Hence, although there currently are no data relating serum leptin to survival in dialysis patients, a reverse or paradoxical 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.<sup>99</sup> It is not clear whether muscle<sup>101</sup> or fat<sup>105</sup> confers survival advantages in dialysis patients.<sup>102-104</sup> Treatment of hyperhomocysteinemia with folic acid is being revisited.<sup>192</sup> There is even confusion about the treatment of hypertension in MHD patients.<sup>128,193</sup>

A number of investigators legitimately have questioned the existence and/or direction of the causality in the reverse epidemiology observations.<sup>16,128,194-198</sup> 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<sup>199-201</sup> or undergoing cardiac surgery<sup>202</sup>), geriatrics,<sup>28-30,203-205</sup> oncology,<sup>31,206</sup> and acquired immune deficiency syndrome patients<sup>32,207</sup> (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,<sup>208</sup> may offer important and clinically applicable insights leading to new recom-

mendations 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.<sup>209</sup>

## Racial Disparity and Reverse Epidemiology

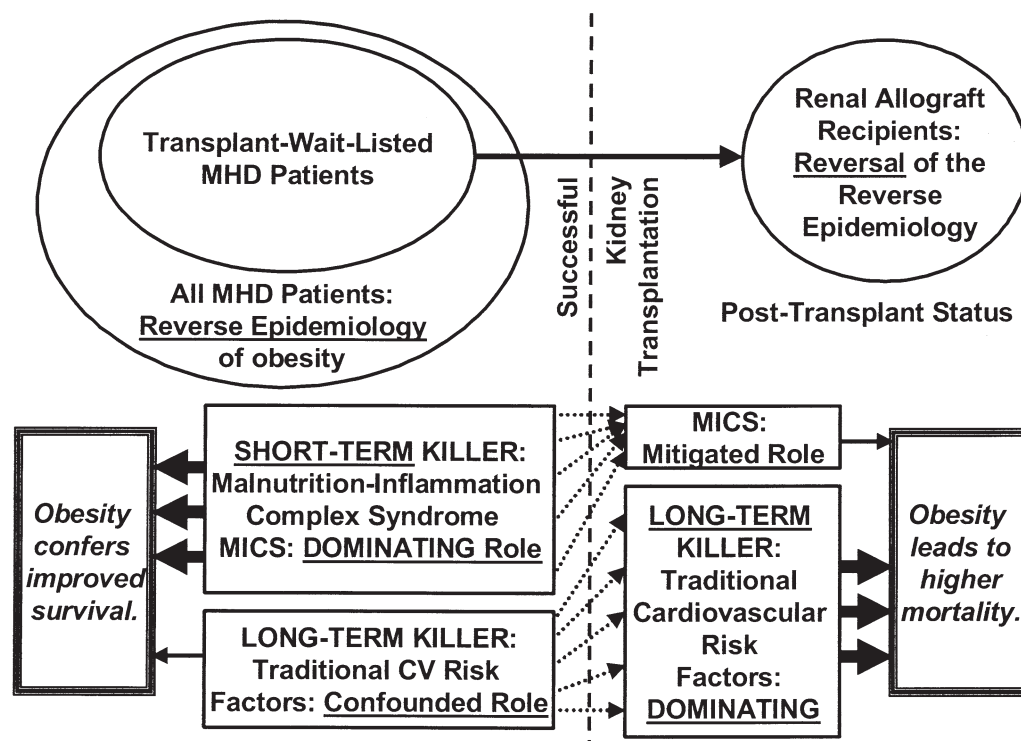
Underlying disparities in access to health care, income, education, diet, lifestyle, and comorbid conditions have been implicated as the reason why black individuals have higher total mortality rates than whites.<sup>210-212</sup> In sharp contrast, black dialysis patients have a much lower annual mortality rate (18%) than whites (28%).<sup>1</sup> Dialysis patients of different races also have different quality-of-life scores.<sup>213,214</sup> 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.<sup>215-217</sup>

Kutner and Zhang<sup>218</sup> and Glanton et al<sup>98</sup> 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,<sup>99,100,219</sup> 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<sup>75</sup>; 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.<sup>88</sup>

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<sup>220</sup> leading to secondary inflammation,<sup>221</sup> but also may leave atherogenic diet as the only source of food for MHD patients.<sup>222</sup> 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.<sup>223,224</sup> 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 paradoxical 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,<sup>225-230</sup> but not all,<sup>231-233</sup> 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.<sup>234</sup> 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.<sup>235</sup> 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 patient 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.<sup>236</sup> A recent study by Friedman et al<sup>237</sup> 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.<sup>236,238-244</sup> 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<sup>236</sup> 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.<sup>236</sup> 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,<sup>100</sup> 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.<sup>53</sup> 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.<sup>245</sup> 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.

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