

Reduced Kidney Function and Anemia as Risk Factors for Mortality in Patients With Left Ventricular Dysfunction

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OBJECTIVES	We sought to evaluate the relationship between the level of kidney function, level of hematocrit and their interaction on all-cause mortality in patients with left ventricular (LV) dysfunction.
BACKGROUND	Anemia and reduced kidney function occur frequently in patients with heart failure. The level of hematocrit and its relationship with renal function have not been evaluated as risk factors for mortality in patients with LV dysfunction.
METHODS	We retrospectively examined the Studies Of LV Dysfunction (SOLVD) database. Glomerular filtration rate (GFR) was predicted using a recently validated formula. Kaplan-Meier survival analyses were used to compare survival times between groups stratified by level of kidney function (predicted GFR) and hematocrit. Cox proportional-hazards regression was used to explore the relationship of survival time to level of kidney function, hematocrit and their interaction.
RESULTS	Lower GFR and hematocrit were associated with a higher prevalence of traditional cardiovascular risk factors. In univariate analysis, reduced kidney function and lower hematocrit, in men and in women, were risk factors for all-cause mortality ($p < 0.001$ for both). After adjustment for other factors significant in univariate analysis, a 10 ml/min/1.73 m ² lower GFR and a 1% lower hematocrit were associated with a 1.064 (95% CI: 1.033, 1.096) and 1.027 (95% CI: 1.015, 1.038) higher risk for mortality, respectively. At lower GFR and lower hematocrit, the risk was higher ($p = 0.022$ for the interaction) than that predicted by both factors independently.
CONCLUSIONS	Decreased kidney function and anemia are risk factors for all-cause mortality in patients with LV dysfunction, especially when both are present. These relationships need to be confirmed in additional studies. (J Am Coll Cardiol 2001;38:955-62) © 2001 by the American College of Cardiology

Reduced kidney function and anemia occur frequently in patients with heart failure (HF) (1-4). In fact, as many as 25% to 50% of patients with HF have creatinine clearances less than 60 ml/min to 75 ml/min (4,5), while mean hemoglobin levels range from 10 g/dl to 12 g/dl in patients with HF (1,2,6).

Although prior studies have suggested that reduced kidney function may be a risk factor for all-cause mortality (4,5), these studies did not provide a quantitative estimate of the relationship between the level of kidney function to mortality. These studies also did not consider the independent contribution of anemia, a known complication of kidney disease.

Anemia is a well-recognized risk factor for left ventricular (LV) hypertrophy, de novo and recurrent HF and all-cause

mortality in the end-stage renal disease (ESRD) population (7). Patients with ESRD are anemic secondary to erythropoietin deficiency. Anemia also occurs in patients with less severe reduction in kidney function. Treatment with erythropoietin is feasible in patients with or without ESRD. Therefore, the evaluation of anemia as a risk factor in patients with LV dysfunction is important from a mechanistic as well as a treatment standpoint.

One recent study suggested that treatment of mild-to-moderate anemia with erythropoietin may improve morbidity in patients with severe HF (8). However, no studies have evaluated the level of hematocrit as a risk factor for mortality in HF. Furthermore, no studies have evaluated patients with a wider range of LV dysfunction. We hypothesized that there may be a relationship between the level of kidney function, level of hematocrit and mortality in patients with LV dysfunction.

The Studies Of Left Ventricular Dysfunction (SOLVD) was a large randomized controlled trial that enrolled patients with ejection fraction of $\leq 35\%$. The study sample included patients with a wide range of hematocrit and level of kidney function. The current study evaluates the independent effect of hematocrit level on mortality and extends prior analyses of SOLVD by estimating kidney function primarily as a continuous variable. In so doing, we are also

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
ESRD	=	end-stage renal disease
GFR	=	glomerular filtration rate
HF	=	heart failure
LV	=	left ventricle or left ventricular
MDRD	=	Modification of Diet in Renal Disease
NYHA	=	New York Heart Association
SOLVD	=	Studies Of Left Ventricular Dysfunction

able to evaluate the relationship (interaction) between the level of hematocrit and kidney function on all-cause mortality.

METHODS

Design. The SOLVD was a multicenter, randomized, double-blind, placebo-controlled trial evaluating the effect of enalapril on survival in patients with LV ejection fraction $\leq 35\%$. Patients were stratified by the presence of symptoms. Asymptomatic patients were enrolled in the SOLVD prevention trial ($n = 4,228$); symptomatic patients were enrolled in the SOLVD treatment trial ($n = 2,569$). Both groups of patients were included in the current analysis (9–11).

Exclusion criteria for the prevention trial and the treatment trial included patients with a serum creatinine >2.5 mg/dl, recent myocardial infarction, unstable angina, severe pulmonary disease, uncontrollable hypertension, major cerebrovascular disease or suspected renal artery stenosis (9–11).

This study is a retrospective analysis of the relationship of survival time to level of kidney function and hematocrit and their interaction. Baseline serum creatinine and hematocrit were measured in 6,635 and 6,563 patients, respectively. Glomerular filtration rate (GFR) was computed in 6,630 patients using a prediction formula derived from the Modification of Diet in Renal Disease (MDRD) study (12,13): $GFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female). Serum creatinine is measured in mg/dl, age in years, and GFR is expressed as ml/min/1.73 m².

Baseline characteristics included patient demographics (age, ethnicity, gender); past medical history (diabetes, hypertension, myocardial infarction, atrial fibrillation, cerebrovascular disease, abdominal aortic aneurysm and past or current smoking); measures of cardiac function (ejection fraction, New York Heart Association [NYHA] functional class, etiology of LV dysfunction, orthopnea and paroxysmal nocturnal dyspnea); previous medication use (beta-adrenergic blocking agents, diuretics, digoxin, vasodilators, nitrates, captopril, potassium replacement, anticoagulants, antiarrhythmic agents and calcium channel blockers); trial assignment (treatment vs. prevention); randomization to enalapril versus placebo; laboratory variables (serum potassium, sodium, creatinine, blood urea nitrogen and hemato-

crit) and physical examination (systolic blood pressure, diastolic blood pressure, heart rate, S₃ gallop, jugular venous pressure, rales and edema).

The end point of all-cause mortality, reached by 1,565 (23.6%) of the subjects, was chosen because prior analyses demonstrated that over 85% of deaths were due to cardiovascular disease (10,11).

Statistical analysis. Means, standard deviations and percentages were used to describe the baseline characteristics. Initially, the data were stratified into three groups by level of kidney function (GFR <60 ml/min/1.73 m², 60 ml/min/1.73 m² to 75 ml/min/1.73 m² and >75 ml/min/1.73 m²) and by level of hematocrit (<35 , 35 to 39 and ≥ 40). Chi-square tests (testing for linear trend where appropriate) and analysis of variance (ANOVA) were used to compare baseline data for each of these groupings. The cut-points for the three groups were chosen to reflect clinically meaningful values. Additionally, a Pearson correlation was used to evaluate the relationship of hematocrit to predicted GFR.

Kaplan-Meier survival analysis was used to compare survival times between the three groups stratified by level of kidney function (measured as predicted GFR) and by hematocrit. Men and women were analyzed separately for hematocrit. The log-rank statistic was used to test for differences between groups.

Cox proportional-hazards regression (stepwise, likelihood ratio, $p < 0.05$ for inclusion) was used to explore the relationship of survival time to the primary variables predicted GFR and hematocrit. A multivariable model was developed using predicted GFR and hematocrit. Regressions were run for primary variables alone and for these variables adjusted for those baseline variables that were significantly and independently related to survival time in univariate analyses ($p < 0.05$). Squares of GFR and hematocrit were calculated in order to search for nonlinear relationships. We also evaluated the product of GFR and hematocrit to search for interactions between the primary variables. The relative risk of survival for different levels of kidney function and hematocrit were estimated from the hazard ratios.

Subgroup analysis was performed to evaluate whether the adjusted relative risk for mortality due to a change in hematocrit or a change in level of kidney function was different in patients treated with enalapril versus placebo. Data were entered into SPSS, Version 10, for analyses; testing was two-sided, and p values < 0.05 were considered significant.

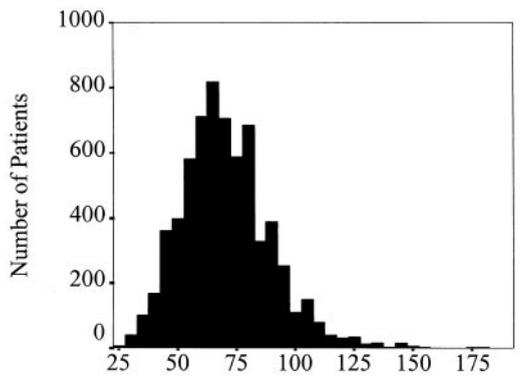
RESULTS

Baseline characteristics. The baseline characteristics of the patients are summarized in Table 1 and Figure 1A and 1B. Mean serum creatinine was 1.2 mg/dl with a range of 0.5 mg/dl to 2.4 mg/dl; mean predicted GFR was

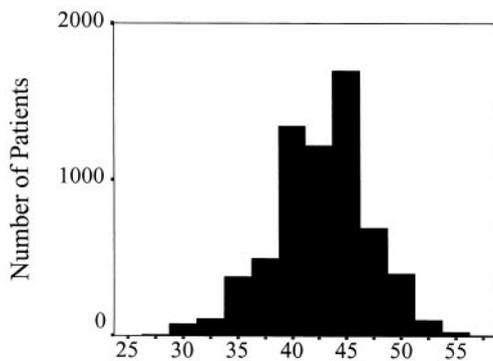
Table 1. Baseline Characteristics of the Study Population by Level of Kidney Function and Hematocrit

Characteristics	Level of Kidney Function (GFR ml/min/1.73 m ²)				Level of Hematocrit (%)			p Value
	All (n = 6,635)	<60 (n = 2,106)	60-75 (n = 2,133)	>75 (n = 2,391)	<35 (n = 290)	35-39 (n = 1,145)	≥40 (n = 5,128)	
Demographics								
Age	60 (10.3)	65 (8.1)	60 (9.7)	56 (10.7)	62 (11.1)	60 (10.0)	59 (10.2)	< 0.001
Gender (% male)	86	80	89	89	69	72	90	< 0.001
Ethnic origin (% white)	84	87	86	81	77	78	86	< 0.001
Ejection fraction	27 (6.3)	27 (6.3)	27 (6.4)	27 (6.2)	27 (6.1)	27 (6.2)	27 (6.3)	0.931
Etiology of LV dysfunction (% ischemic)	79	79	81	77	76	77	80	0.047
NYHA class								
I	46	36	49	52	37	39	48	< 0.001
II	42	46	40	40	43	43	42	
III and IV	12	18	11	8	20	19	10	
Trial assignment (% treatment)	38	49	34	31	47	45	35	< 0.001
Treatment assignment (% enalapril)	50	50	49	51	49	49	50	0.668
Previous medication use								
Beta-blockers	18	15	19	20	13	14	19	< 0.001
Diuretic	42	56	39	34	47	49	40	< 0.001
Digoxin	33	39	31	29	39	37	32	0.001
Antiarrhythmic agents	18	24	18	14	26	18	17	0.001
Past medical history								
Hypertension	39	46	37	34	43	40	38	0.134
Diabetes	19	23	17	17	27	23	18	0.003
Myocardial infarction	75	74	78	74	67	73	76	0.002
Physical exam								
Systolic blood pressure (mm Hg)	125 (17.0)	127 (18.0)	125 (16.6)	124 (16.2)	125 (18.4)	124 (17.6)	125 (16.7)	0.122
Diastolic blood pressure (mm Hg)	77 (9.9)	77 (10.2)	78 (9.7)	78 (9.7)	75 (10.2)	76 (10.0)	78 (9.7)	< 0.001
Laboratory data								
Creatinine (mg/dl)	1.18 (0.3)	1.47 (0.3)	1.17 (0.1)	0.94 (0.1)	1.23 (0.4)	1.20 (0.3)	1.17 (0.3)	< 0.001
Hematocrit	43 (4.5)	42 (4.7)	43 (4.4)	43 (4.3)				< 0.001
Blood urea nitrogen (mg/dl)	18 (6.5)	22 (7.6)	18 (5.1)	15 (4.7)	21	19	18	< 0.001
Predicted GFR (ml/min/1.73 m ²)	70 (19.3)				67 (21.6)	67 (20.6)	71 (18.6)	< 0.001

Data are displayed as mean (SD) or %.
 GFR = glomerular filtration rate; LV = left ventricular; NYHA = New York Heart Association.



A Glomerular Filtration Rate (ml/min/1.73m²)



B Serum Hematocrit (%)

Figure 1. (A) Distribution of glomerular filtration rate (GFR) in the Study Of Left Ventricular Dysfunction (SOLVD). Mean is 70 ml/min/1.73 m², with a standard deviation of 19.3 and n is 6,630. A total of 6.8% of patients had a GFR of <45 ml/min/1.73 m², 25% between 45 ml/min/1.73 m² to 60 ml/min/1.73 m², 32.1% between 60 to 75 ml/min/1.73 m², 21.7% between 75 to 90 ml/min/1.73 m² and 14.4% >90 ml/min/1.73 m². (B) Distribution of hematocrit in SOLVD. Mean is 43; SD is 4.49 and n is 6,563. A total of 4.3% of the patients have a hematocrit <35%, 17.5% between 35 and 39, 51.7% between 40 and 45, 23.1% between 45 and 50 and 3.3% > 50.

70.4 ml/min/1.73 m² with a range of 23 ml/min/1.73 m² to 188 ml/min/1.73 m², and mean hematocrit was 42.7% with a range of 25% to 58%. Mean ejection fraction was 27% with a range of 6% to 35%. The patients were predominantly white men, and ischemia was the cause of the LV dysfunction in approximately 80% of cases.

A total of 32% of patients had predicted GFR <60 ml/min/1.73 m², while 22% and 4.3% of the cohort had hematocrit ≤39 or <35, respectively. The cohort, therefore, included a significant percentage of patients with reduced kidney function and anemia. The correlation between hematocrit and predicted GFR was weak but statistically significant ($r = 0.084$, $p < 0.01$).

Association of reduced kidney function and anemia with other baseline factors. Reduced kidney function and anemia were significantly associated with a variety of baseline factors. Patients with lower GFR were older, had slightly lower ejection fractions and higher blood pressure and were more likely to be women, white and taking diuretics or antiarrhythmic agents, have a higher prevalence of hyper-

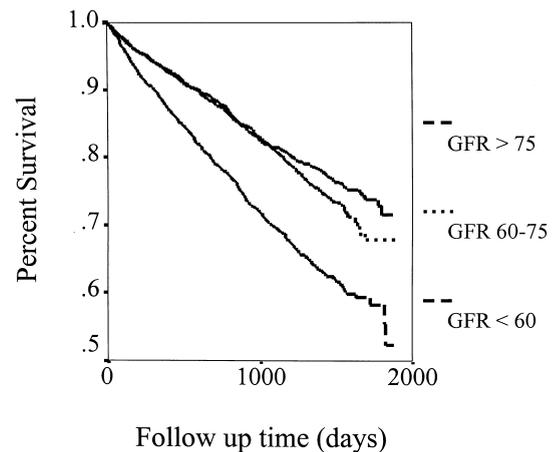


Figure 2. Kaplan-Meier survival analysis by level of glomerular filtration rate (GFR).

tension, diabetes or NYHA class III or IV, were less likely to be taking beta-blockers and less likely to be in the prevention rather than treatment trial (Table 1). Patients with lower hematocrit were more likely to be older, women, non-white, have a higher prevalence of NYHA class III or IV and diabetes, were less likely to be taking beta-blockers, more likely to be taking diuretics, digoxin and antiarrhythmic agents and more likely to be in the treatment rather than prevention trial (Table 1).

Outcomes. Mean follow-up time was 33.4 months with a range of 14.6 months to 62 months. Cardiovascular disease accounted for 89% of the 1,565 deaths. Kaplan-Meier survival analysis demonstrated that reduced kidney function (Fig. 2, $p < 0.001$ by log-rank statistics) and lower hematocrit in both men and women were risk factors for all-cause mortality (Fig. 3A and B, $p < 0.001$ by log-rank statistics).

After adjusting for variables significant in univariate analysis (Table 2), lower hematocrit and lower predicted GFR, each remained significant risk factors for all-cause mortality. A 10 ml/min/1.73 m² lower GFR was associated with a 1.064 (95% CI: 1.033, 1.096) higher risk for mortality. A 1% lower hematocrit was associated with a 1.027 (95% CI: 1.015, 1.038) higher risk for mortality. The quadratic term did not significantly improve the prediction of survival; thus, these relationships were best described by linear equations.

Subgroup analysis of patients treated with enalapril versus those treated with placebo revealed similar results in multivariable analysis. That is, in patients treated with enalapril, a 10 ml/min/1.73 m² lower GFR was associated with a 1.078 (1.031, 1.125; $p = 0.001$) higher risk for mortality, while a 1% lower hematocrit was associated with a 1.024 (1.007, 1.041; $p = 0.006$) higher risk for mortality. In patients treated with placebo, a 10 ml/min/1.73 m² lower GFR was associated with a 1.053 (1.009 to 1.099; $p = 0.017$) higher risk for mortality, while a 1% lower hemato-

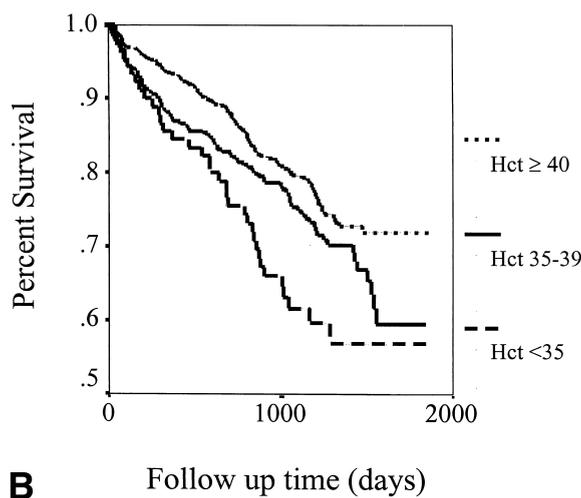
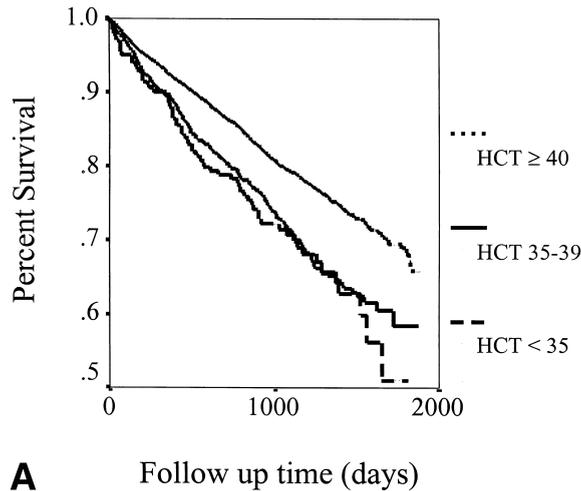


Figure 3. (A) Kaplan-Meier survival analysis by level of hematocrit (Hct) in men. (B) Kaplan Meier survival analysis by level of Hct in women.

Table 3. Standardized* RR for All-Cause Mortality Predicted by Level of GFR and Hematocrit (Including the Interaction Term)

GFR (ml/min/1.73 m ²)	Hematocrit (%)			
	35	40	45	50
30	2.1	1.7	1.3	1.0
45	1.8	1.5	1.2	1.0
60	1.5	1.3	1.1	1.0
75	1.3	1.2	1.1	1.0
90	1.1	1.1	1.0	1.0

*Values are standardized to reference levels of hematocrit of 45 and GFR of 90 ml/min/1.73 m².
 GFR = predicted glomerular filtration rate; RR = relative risk.

crit was associated with a 1.031 (1.014 to 1.047; $p < 0.001$) higher risk for mortality.

There was a statistically significant interaction ($p = 0.022$) between hematocrit and predicted GFR on all-cause mortality (Table 2). Thus, a lower level of both hematocrit and GFR was associated with higher all-cause mortality than expected from the sum of the individual effects. This is illustrated in Table 3. At high levels of hematocrit, the effect of lower GFR is not as large as it is at low levels of hematocrit. Conversely, at high levels of GFR, the effect of a decline in hematocrit is not as large as it is at low levels of GFR. However, at low levels of both GFR and hematocrit, the combined effect is larger than the sum of the individual effects. For example, at a GFR of 45 ml/min/1.73 m² and a hematocrit of 50%, the standardized relative risk is 1.0, while at a GFR of 90 ml/min/1.73 m² and a hematocrit of 35%, the standardized relative risk for mortality is 1.1. However, at a GFR of 45 ml/min/1.73 m² and a hematocrit of 35%, the relative risk is 1.8.

Table 2. Results of Unadjusted and Adjusted Cox Regression of All-Cause Mortality by Predicted GFR and Hematocrit

Model	Factor	Unadjusted			Adjusted*		
		RR	CI	p Value	RR	CI	p Value
Model† without interaction	Predicted GFR for each 10 ml/min/1.73 m ² ↓	1.157	1.125, 1.192	< 0.001	1.067	1.035, 1.100	< 0.001
	Hematocrit for each 1% ↓	1.038	1.027, 1.049	< 0.001	1.028	1.016, 1.040	< 0.001
Model‡ with interaction¶	Predicted GFR for each 10 ml/min/1.73 m ² ↓		As above		1.064	1.033, 1.096	< 0.001
	Hematocrit for each 1% ↓		As above		1.027	1.015, 1.038	< 0.001
	Predicted GFR for each 10 ml/min/1.73 m ² ↓		—		1.416§	1.106, 1.815	0.006
	Hematocrit for each 1% ↓		—		1.074	1.032, 1.119	< 0.001
	Interaction term (product hematocrit × predicted GFR as above)		—		1.007	1.001, 1.013	0.022

*Adjustment is for baseline variables that were univariate predictors of mortality (gender, treatment assignment, trial assignment, NYHA functional class, ejection fraction, presence of hypertension, cause of left ventricular dysfunction, history of myocardial infarction, presence of diabetes, beta-blocker, digoxin and diuretic use; †Model adjusts for predicted GFR and hematocrit in addition to baseline variables; ‡Model including the interaction term hematocrit multiplied by predicted GFR; §RR for GFR when hematocrit = 0%; ||RR for hematocrit when GFR = 0 ml/min/1.73 m²; ¶RR (CI) for other baseline variables that were significant in multivariable analysis including the interaction term: age (per one year increase), 1.015 (1.010, 1.021); gender (reference = female), 0.784 (0.678, 0.908); treatment assignment (reference = control), 0.897 (0.811, 0.991); NYHA functional class (per unit class increase), 1.355 (1.255, 1.464); ejection fraction (per 1% increase), 0.963 (0.955, 0.970); presence of diabetes (reference = no), 1.246 (1.106, 1.403); use of beta-blockers (reference = no), 0.829 (0.701, 0.979); use of digoxin (reference = no), 1.409 (1.257, 1.580) and use of diuretics (reference = no), 1.385 (1.221, 1.570).

CI = 95% confidence intervals for the relative risk (RR); GFR = predicted glomerular filtration rate; NYHA = New York Heart Association.

DISCUSSION

Heart failure is a major public health problem in the U.S. There are approximately 400,000 incident cases per year (14), and deaths likely exceed 200,000 per year (15). Novel approaches to the treatment of HF and its most common cause, LV dysfunction, are, therefore, warranted.

Treatment modalities that have resulted in decreased mortality in patients with HF include angiotensin-converting enzyme (ACE) inhibitors (10), hydralazine in combination with nitrates (16), beta-blockers (17) and, more recently, spirinolactone (18). Although there has been some improvement in survival in patients with HF, primarily due to the introduction of ACE inhibitors, mortality remains high.

Level of kidney function. A few (4,5), but not all (19,20), studies have suggested that reduced kidney function may be an important risk factor for mortality in patients with HF. In one study (4), patients in the lowest quartile of creatinine clearance had almost three times the risk of mortality of patients in the highest quartile.

The level of GFR is usually regarded as the best overall index of the level of kidney function. Serum creatinine is determined by a number of factors, other than GFR, such as gender, age, muscle mass and ethnicity and, therefore, provides only a rough estimate of level of kidney function (21). To provide a more accurate measure of kidney function, we estimated GFR using a recently validated formula from the MDRD study (12,13). In patients with reduced kidney function, this formula has been shown to be a more accurate measure of kidney function than serum creatinine or creatinine clearance estimated using either the Cockcroft Gault equation or measured creatinine clearance using 24-h urine collections (12).

Table 1 demonstrates that there is a high prevalence of reduced kidney function in patients with LV dysfunction. Only 36% of the cohort had a predicted GFR >75 ml/min/1.73². Reduced kidney function is associated with a higher prevalence of risk factors for mortality, for example lower ejection fraction and higher NYHA functional class. This is consistent with previous studies that suggest a higher prevalence of cardiac risk factors in patients with greater reduction in kidney function (22,23).

Survival analysis demonstrates that level of kidney function is a significant risk factor for mortality in patients with LV dysfunction. This is consistent with prior studies including those of the SOLVD cohort (4,5). Multivariable analysis confirms that reduced kidney function is an independent risk factor for mortality in the entire study population as well as in subgroups of patients treated with enalapril versus placebo. Our analyses suggest that there is a continuous relationship between the level of kidney function and mortality, rather than a threshold value below which reduced kidney function is a risk factor. That is, quadratic terms did not significantly improve the prediction of survival.

We hypothesize three potential explanations why level of kidney function may be a risk factor for all-cause mortality in patients with HF. First, the level of kidney function may be an additional marker of the level of cardiac function over and above measures such as ejection fraction and NYHA functional class. Second, reduced kidney function may be associated with other risk factors for mortality that were not measured in this study, such as hyperhomocysteinemia, hyperfibrinogenemia and elevated C-reactive protein levels (4,24-26). Third, reduced kidney function itself may be a risk factor for progression of ventricular remodeling and cardiac dysfunction. That is, kidney disease may worsen sodium and fluid retention and result in progressive ventricular dilation. Unfortunately, our retrospective analysis cannot distinguish among these possibilities.

Level of hematocrit. The prevalence of anemia is high in patients with HF (1,2,6). These mild levels of anemia have not been evaluated as risk factors for mortality, although a recent study demonstrated improved cardiac morbidity in patients with severe HF treated with erythropoietin (8). In contrast with the limited data in patients without kidney disease, it is well recognized that anemia is an independent risk factor for the development of LV hypertrophy, de novo and recurrent HF and all-cause mortality in patients with ESRD (7). Furthermore, treatment of anemia with erythropoietin has improved many of the cardiac abnormalities associated with HF in the ESRD population (27,28). The prevalence of patients with both HF and anemia in the U.S. exceeds the prevalence of ESRD; therefore, evaluation of anemia as a potential independent risk factor in patients with HF is clinically important.

Survival analysis also demonstrates that lower hematocrit is a significant risk factor for mortality in both men and women, and multivariable analysis confirms that reduced hematocrit is an independent risk factor for mortality in the entire study population, as well as in subgroups of patients treated with enalapril versus placebo.

We hypothesize four potential explanations for this finding. First, the level of hematocrit may be an additional marker of cardiac function over and above measures such as ejection fraction and NYHA functional class. That is, severe HF, through as yet undefined mechanisms, may cause anemia. Second, reduced hematocrit may be associated with other risk factors for mortality that were not measured in this study, such as elevated inhibitory cytokine levels or malnutrition. The first two explanations are likely not mutually exclusive. Third, reduced hematocrit may be a risk factor for ischemia, a fact supported by animal studies that have suggested that a small decrease in hematocrit can result in worsening of ischemia, especially in those animals with pre-existing heart disease (29). Fourth, reduced hematocrit may result in ventricular remodeling and cardiac dysfunction. Chronic anemia is known to result in increased venous return and increased cardiac work (30), which may lead to LV hypertrophy and subsequent cardiac enlargement. The latter is well appreciated in patients with ESRD who are

anemic secondary to their kidney disease (7,31) but likely also plays a role in patients with other causes of anemia. As mentioned previously, our retrospective analysis cannot distinguish among these four possibilities.

Although anemia was inversely correlated with the level of kidney function in the SOLVD cohort, the correlation was weak. The reason for the low correlation in this cohort is likely due to a combination of lesser degrees of erythropoietin deficiency with less severe reduction in GFR and the exclusion of patients with more severe reduction in GFR. The level of kidney function, therefore, does not appear to be the primary determinant of hematocrit in this cohort.

Relationship between level of kidney function and level of hematocrit on all-cause mortality. Evaluation of the interaction between the level of hematocrit and the level of GFR on all-cause mortality suggests that anemia and reduction in kidney function are more than additive as risk factors. One could extrapolate this further and propose that patients with kidney function low enough to cause erythropoietin deficiency may have two synergistic risk factors for mortality, namely reduction in GFR as well as anemia.

Implications. From a treatment standpoint, our results lead to two questions. First, is it feasible to correct anemia with erythropoietin in HF patients? The study conducted by Silverberg et al. (8) would suggest that partial correction of anemia to a hemoglobin level of 12 g/dl is feasible and safe in patients with severe HF. Other studies, however, have documented that erythropoietin levels may already be elevated in patients with severe HF (3) and raise the question whether additional erythropoietin would be helpful. Evaluating the causes of anemia in patients with HF will be important in answering this question. Second, assuming that anemia can be corrected in patients with HF, will partial or complete correction lower morbidity and mortality in randomized trials?

Study limitations. There are three potential limitations of our retrospective analyses. First, the MDRD study prediction equation for GFR has not been validated in patients with LV dysfunction. Second, the range of hematocrit and GFR was limited by exclusion criteria, and only a few patients had severe anemia or severe kidney dysfunction. Therefore, one needs to be cautious when extrapolating the results to the extremes. Third, although SOLVD was a randomized trial, the relationships that we have evaluated were not the subject of the treatment comparison, and, therefore, like any observational study, our findings may be limited by confounding from variables we did not take into account.

Conclusions. We conclude that a lower level of kidney function and hematocrit appear to be independent risk factors for mortality in patients with LV dysfunction. Furthermore, there appears to be a synergistic relationship between these risk factors in the lower range of GFR and hematocrit. Documentation that kidney function is a risk

factor for mortality in patients with LV dysfunction confirms previous analyses of SOLVD as well as other HF studies. The findings that anemia is a risk factor for mortality and that anemia and reduced kidney function appear to have a synergistic effect on mortality when both are compromised need to be confirmed in additional studies. If these findings are reproduced, then further studies need to be performed, first to evaluate the causes of anemia in patients with LV dysfunction and, ultimately, to prospectively evaluate the potential benefit of the correction of anemia with erythropoietin.

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