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Angiotensin-Converting Enzyme Inhibitor as a Risk Factor for the Development of Anemia, and the Impact of Incident Anemia on Mortality in Patients With Left Ventricular Dysfunction

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OBJECTIVES We aimed to investigate the impact of angiotensin-converting enzyme inhibitors (ACEIs) on hematocrit values in those with heart failure, and the relationship between incident anemia and mortality.

BACKGROUND Prevalent anemia is an independent risk factor for morbidity and mortality in those with heart failure. Studies in patients with polycythemia have demonstrated that ACEIs are effective in lowering hematocrit values.

METHODS We used the Studies Of Left Ventricular Dysfunction (SOLVD) database to compare the odds of developing new anemia at one year in patients who were not anemic at entry and who were randomized to enalapril or placebo. Cox proportional hazards models were utilized to determine the impact of incident and prevalent anemia on subsequent mortality.

RESULTS Enalapril increased the odds of incident anemia (hematocrit ≤39% in men or ≤36% in women) at one year by 48% (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.20 to 1.82) in unadjusted and 56% (OR 1.56, 95% CI 1.26 to 1.93) in adjusted models. With multivariate analysis, prevalent anemia at randomization was associated with a 44% (hazard ratio [HR] 1.44, 95% CI 1.31 to 1.66) increase in all-cause mortality, whereas incident anemia after randomization was associated with a 108% increase (HR 2.08, 95% CI 1.82 to 2.38). After adjusting for incident and prevalent anemia, use of enalapril was associated with a survival benefit.

CONCLUSIONS Enalapril was associated with increased odds of developing anemia at one year. Those with periods of time with incident anemia had the poorest survival, followed by those with prevalent anemia, then those without anemia. Enalapril was protective of overall mortality after adjusting for incident anemia and in those with prevalent anemia. (J Am Coll Cardiol 2005;45:391–9) © 2005 by the American College of Cardiology Foundation

It is estimated that more than 4.8 million individuals have been diagnosed to have heart failure (HF) in the U.S. alone (1). In addition, there are 550,000 new cases of HF diagnosed annually (2). A recent study has demonstrated that the incidence of HF over time is unchanged in men and has improved only slightly in women (3). Improving the survival of those with HF is of significant public health importance.

An under-recognized risk factor for mortality in patients with HF has been anemia. A recent retrospective cohort study demonstrated that even a relatively mild decline in hemoglobin was associated with a reduced functional status and a higher mortality (4). An analysis of the participants in the Studies Of Left Ventricular Dysfunction (SOLVD) trial demonstrated that for each 1% lower pre-randomization hematocrit value, the risk of dying increased by 6% (5). Current guidelines on the treatment of HF make no mention of the impact of anemia on the morbidity or mortality of HF (6).

Multiple studies have documented the efficacy of angiotensin-converting enzyme inhibitors (ACEIs) in reducing the morbidity and mortality associated with HF. Consequently, the current standard for therapy in those with HF is a cocktail of medications, a key component of which is an ACEI (6). Studies in those with polycythemia have demonstrated that both ACEIs and angiotensin receptor blockers (ARBs) are effective therapeutic agents in reducing hemoglobin concentrations (7–9). The mechanism through which ACEIs cause a decline in hemoglobin concentration remains unclear; however, it is postulated that both ACEIs and ARBs inhibit growth of erythroid precursors (10). Currently, there exists very little information regarding the effect of ACEIs on hematocrit values in those with either normal hemoglobin concentrations or in those with HF.

The Studies Of Left Ventricular Dysfunction (SOLVD) trial was a large randomized trial evaluating the effect of enalapril therapy on mortality in those with asymptomatic

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker
CI = confidence interval
HF = heart failure
HR = hazard ratio
NYHA = New York Heart Association
OR = odds ratio
SOLVD = Studies Of Left Ventricular Dysfunction

left ventricular systolic dysfunction and symptomatic HF. Using the SOLVD dataset, we aimed to determine if 1) enalapril therapy was associated with an increased risk of incident anemia after randomization compared to placebo; 2) incident anemia, irrespective of etiology, was associated with an increased the risk of all-cause mortality; and 3) enalapril retained its beneficial effects in the setting of prevalent or incident anemia.

METHODS

A full description of the SOLVD trial is published elsewhere (11–13). To summarize briefly, the SOLVD trial consisted of two parallel trials: a treatment trial and a prevention trial. To be included in either trial, a patient must have had a left ventricular ejection fraction <35%. Patients with symptoms of congestive HF were entered in the treatment trial, whereas asymptomatic patients were entered in the prevention trial. All patients were randomly assigned to receive either placebo or enalapril. Treatment with placebo or enalapril was initiated at 2.5 mg or 5 mg twice per day and gradually increased to 10 mg twice per day, if tolerated. After randomization, all participants were seen after two weeks, six weeks, four months, and then every four months thereafter until the end of the trial. In particular, antiplatelet drug use, creatinine, hematocrit, New York Heart Association (NYHA) functional class, and weight were measured at each visit. Hematocrit was measured at local laboratories during the trial; there were no quality control measures in place for its measurement. The current study used data from both the treatment trial (n = 2,569) and the treatment trial (n = 4,228). Because individuals were randomly assigned to receive either placebo or enalapril, we performed intent-to-treat analyses, in which all participants were included in the treatment group to which they were randomized.

The primary objective of the current study was to compare the odds of developing new anemia one year after randomization among patients without prevalent anemia in the placebo group and in the enalapril group. Consistent with the World Health Organization threshold, anemia was defined by hematocrit ≤39% in men and ≤36% in women (14). Prevalent anemia was identified by a hematocrit measurement below the threshold at randomization, whereas new anemia was identified by a hematocrit measurement below the threshold at one year. Comparisons were made with and without effects for the change in creatinine and the change in weight from randomization to one year.

Because the comparisons identified anemia at an arbitrary point in time and excluded a significant number of patients, we performed two sensitivity analyses. First, we included all patients with complete data at randomization and compared the odds of developing anemia at any time during the trial among patients in the placebo group and in the enalapril group. In this analysis, anemia included both prevalent anemia and new anemia at any point after randomization (rather than only at one year). Second, we included all patients with complete data at randomization, but excluded patients with prevalent anemia. Then, we compared odds of developing new anemia at any point during the trial.

Additionally, we performed survival analyses to determine the associations among prevalent and new anemia, enalapril therapy, and subsequent mortality. Throughout the analyses, we referred to each interval of time that began with a hematocrit measurement below the threshold and ended with another hematocrit measurement above the threshold as an anemia episode. Cox proportional hazards models were fitted to estimate the following effects of anemia episodes and hematocrit on all-cause mortality: 1) the effect of anemia episodes, regardless of whether episodes began at randomization or after randomization; 2) the differential effects of anemia episodes that began at randomization and anemia episodes that began after randomization; and 3) the effect of hematocrit, a continuous measurement, rather than anemia, a categorical definition.

In addition to anemia episodes and hematocrit, all models included time-varying covariates for antiplatelet drug use, creatinine, NYHA functional class, and weight. A time-varying covariate in a Cox proportional hazards model may change as new measurements are obtained during the course of a trial. To further account for heterogeneity, we included an estimated propensity score (15) for anemia episodes in the applicable Cox models, first as a linear effect, and second as a set of interaction effects between the tertiles of the propensity score and anemia episodes. The results did not meaningfully differ with either addition of the propensity score and are not reported.

Follow-up time for all analyses was defined as time elapsed from randomization to either the death of the participant or the end of the trial. Data were analyzed with SAS 8.0 (SAS Institute, Cary, North Carolina). All tests are presented with two sided p values; values <0.05 were considered significant. The Hennepin County Medical Center Human Subjects Research Committee approved this study.

RESULTS

The combined SOLVD trials included 6,797 patients. Of these, 361 had incomplete data at randomization and were excluded from all analyses. Incomplete data at randomiza-

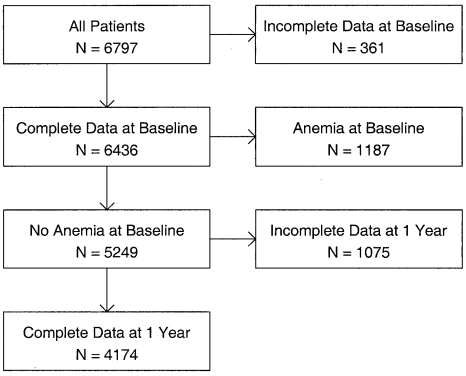

Figure 1. Patient flow diagram.

tion were typically marked by a missing value for antiplatelet drug use, creatinine, hematocrit, NYHA functional class, or weight, but more rarely by a missing value for age, gender, or race. Of those with complete data at randomization, 1,187 had prevalent anemia. These patients were excluded from analyses of only new anemia but were included in other analyses. Finally, for analyses of new anemia at one year, we required individuals to have complete data at one year; this resulted in the exclusion of 1,075 patients. Consequently, our analyses included 4,174 patients (analyses of new anemia with adjustment for data at one year), 5,249 patients (analyses of new anemia with adjustment for data at randomization), or 6,436 individuals (analyses of prevalent and new anemia and all survival analyses) (Fig. 1). The baseline characteristics of those included in our main analysis demonstrated that there were no significant differences between those assigned to the placebo group and to the enalapril group, as would be expected in a randomized trial.

Enalapril and anemia. Compared to placebo, enalapril therapy was associated with a decrease in hematocrit (Fig. 2). This difference in mean hematocrit was evident as early as six weeks after randomization. Figure 3 displays the cumulative hematocrit distribution for the entire SOLVD population. Enalapril use was associated with lower hematocrit at one year both among patients with prevalent anemia and without prevalent anemia. To better understand whether the magnitude of hemoglobin change in the enalapril group compared with the placebo group was driven by a small subset of patients or by the majority of patients, we categorized the percentage of individuals with differing percentage point changes in hematocrit from baseline to one year after randomization (Table 1). A test of association demonstrated that a greater percentage of individuals randomized to enalapril experienced declines in hematocrit concentration at one year compared with individuals randomized to placebo ($p < 0.0001$).

Enalapril and the odds of developing new anemia at one year. At one year after randomization, 11.3% of those randomized to enalapril had developed new anemia, compared to 7.9% of those assigned to placebo (unadjusted odds ratio [OR] 1.48, 95% confidence interval [CI] 1.20 to 1.82). In a logistic model (Table 2) with adjustment for confounders, enalapril continued to be associated with new anemia at one year (adjusted OR 1.56, 95% CI 1.26 to 1.93). A potential confounder of this analysis was that individuals randomized to enalapril had greater changes in creatinine

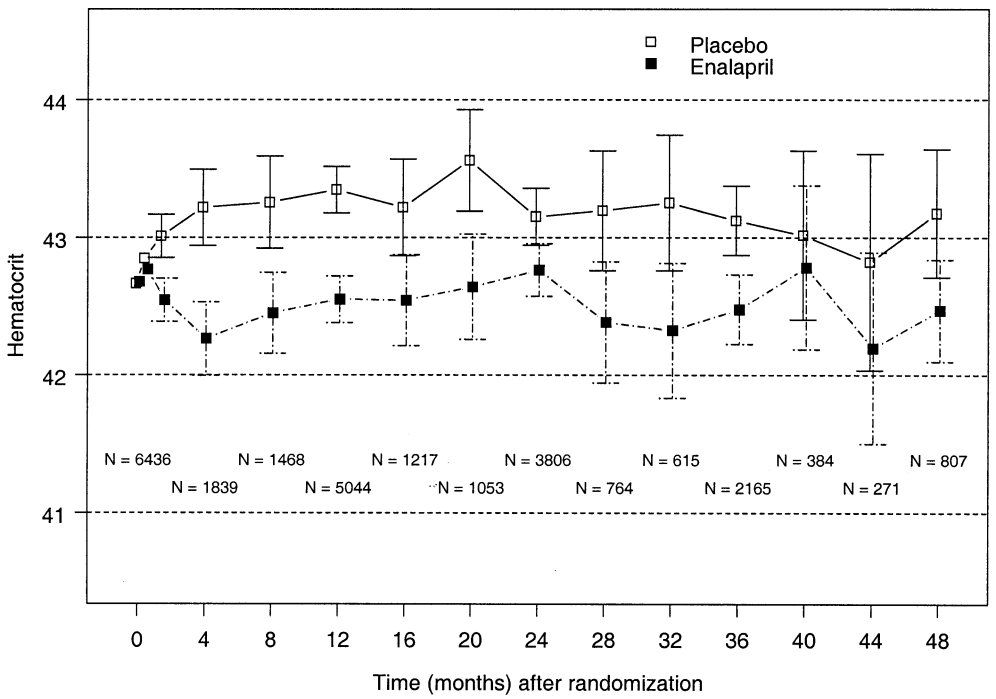

Figure 2. Mean hematocrit and 95% confidence interval around mean at each follow-up observation among those assigned either to enalapril or to placebo.

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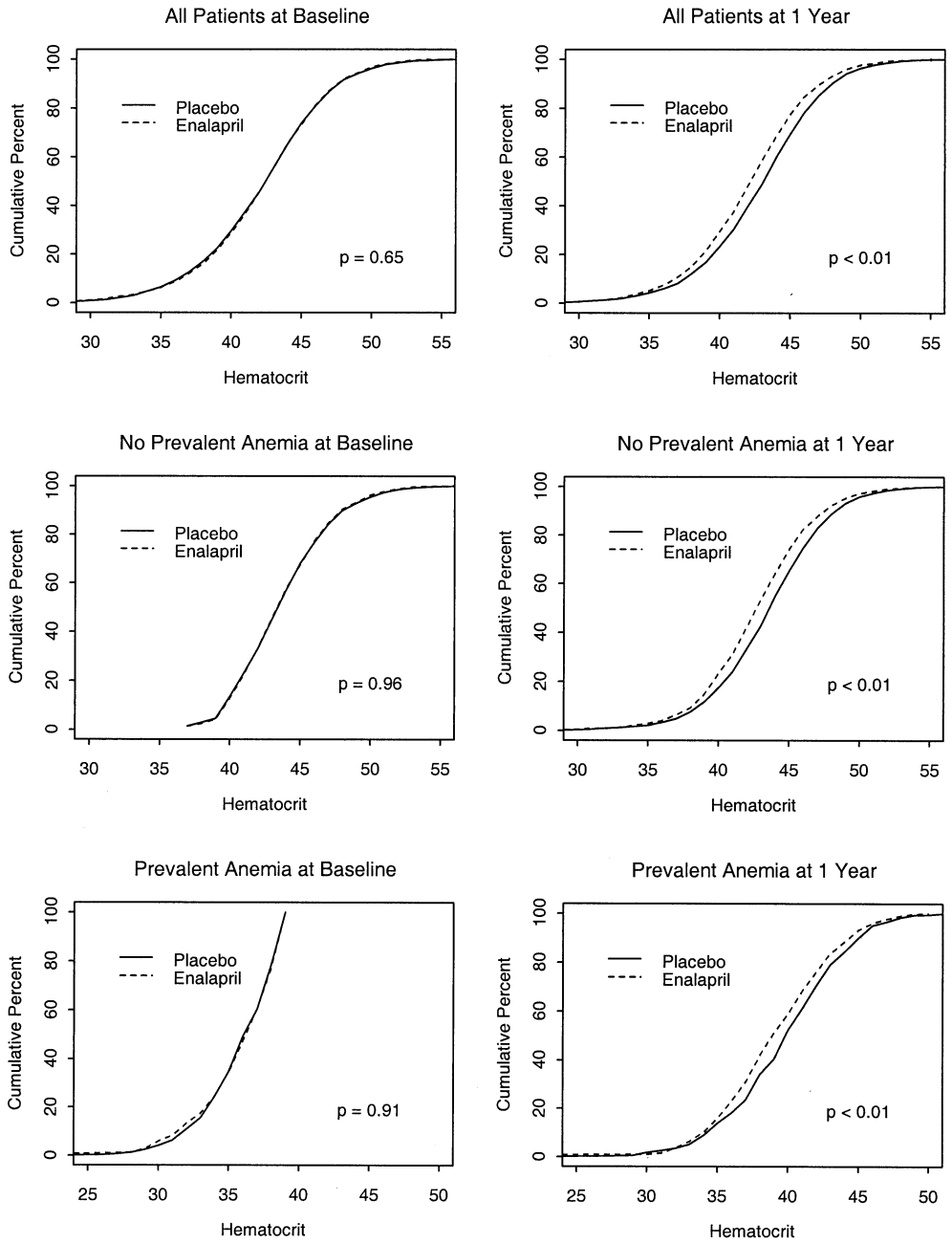

Figure 3. Cumulative distribution of hematocrit at baseline and at one year among all Studies Of Left Ventricular Dysfunction participants; among those without prevalent anemia at baseline; and among those with prevalent anemia at baseline. The p values are displayed for the Wilcoxon test of equal distributions among those assigned either to enalapril or to placebo.

and weight from randomization to one year than those randomized to placebo. These changes could have independently confounded the association between enalapril and new anemia at one year either through dilution (for volume) or through a decrease in erythropoietin production (for worsening renal function). To adjust for these potential confounders, we included in this model effects for the change in creatinine and change in weight from randomization to one year. The association between enalapril and new anemia was unchanged with the inclusion of these effects. Enalapril continued to be associated with a 52% increase in the odds of new anemia at one year (OR 1.52, 95% CI 1.22 to 1.89). Increased creatinine (OR 3.56, 95% CI 2.45 to 5.16 per 1-mg/dl increase) and decreased weight (OR 1.03, 95% CI 1.02 to 1.04 per 1-lb decrease) were associated with a significant increase in the odds of developing new anemia at one year. In both models, the type of therapy (prevention trial or treatment trial) was not associated with the odds of developing new anemia at one year.

Enalapril and the odds of developing anemia at any time after randomization. To assess both the impact of the identification of anemia at the arbitrary time of one year

Table 1. Percentage of Individuals With Differing Changes in Hematocrit Concentration From Baseline to One Year Stratified by Treatment Type (n = 4,174)

Change in Hematocrit	Placebo (n = 2,086)	Enalapril (n = 2,088)	p Value*
Decrease >6 (%)	4.1	5.2	<0.0001
Decrease between 4 and 6 (%)	5.4	8.8	
Decrease between 2 and 4 (%)	13.8	16.7	
Decrease between 0 and 2 (%)	20.9	24.9	
No change (%)	13.5	12.8	
Increase between 0 and 2 (%)	22.9	17.9	
Increase between 2 and 4 (%)	11.8	9.6	
Increase between 4 and 6 (%)	4.5	2.7	
Increase >6 (%)	3.1	1.4	

*Chi-square test.

after randomization and the impact of the exclusion of patients because of prevalent anemia and incomplete data at one year, we performed two sensitivity analyses. For the first analysis, we included all patients with complete data at randomization (n = 6,436). Anemia during follow-up included both prevalent anemia and new anemia at any time after randomization (rather than only at one year). Approximately one-half (n = 1,187) of the patients with at least one anemia episode during follow-up (n = 2,466) were identified as a result of prevalent anemia. Patients with at least one anemia episode were more likely to have been randomized to enalapril and included in the treatment arm of the SOLVD trial; to have been older and African American; and to have had diabetes, a worse NYHA functional class score, and a lower weight at randomization (Table 3). Logistic regression (Table 4) demonstrated that enalapril continued to be significantly associated with developing anemia, but the association was attenuated (OR 1.20, 95% CI 1.09 to 1.34). This attenuation was partly driven by the inclusion of patients with prevalent anemia. For the second analysis, we included all patients with complete data at randomization but excluded patients with prevalent anemia (n = 5,249). Anemia during follow-up included new anemia at any time after randomization. The odds ratio of developing new anemia at any time after randomization increased to 1.36 (95% CI 1.20 to 1.55).

Table 2. Logistic Regression in Those Without Prevalent Anemia at Randomization and With Complete Data at One Year (n = 4,174), Demonstrating the Effect of Enalapril on the Development of New Anemia at One Year, With Adjustment for Confounders

Parameter	Odds Ratio	95% CI	p Value
Enalapril	1.561	(1.261, 1.932)	<0.001
Trial (reference = prevention)			
Treatment	1.167	(0.915, 1.488)	0.213
Age	1.027	(1.015, 1.039)	<0.001
Gender (reference = female)			
Male	1.635	(1.154, 2.317)	0.006
Race (reference = Caucasian)			
Black	1.753	(1.263, 2.433)	<0.001
Hispanic	1.924	(1.075, 3.443)	0.027
Other (including Native American)	0.637	(0.227, 1.785)	0.391
Creatinine (mg/dl) at randomization	1.743	(1.168, 2.601)	0.007
Diabetes	1.433	(1.100, 1.867)	0.008
Ejection fraction (%) at randomization	1.014	(0.997, 1.032)	0.113
NYHA functional class at 1 yr (reference = class I or II)			
III or IV	1.959	(1.435, 2.674)	<0.001
Weight (lbs) at randomization	0.991	(0.988, 0.995)	<0.001

CI = confidence interval; NYHA = New York Heart Association.

Table 3. Baseline Characteristics of Individuals With No Periods of Anemia Compared to Individuals With at Least One Anemia Episode During the SOLVD Trial

Parameter	No Anemia Episode During Trial (n = 3,970)	At Least One Anemia Episode During Trial (n = 2,466)
Enalapril (% of n)	48.2	52.5
Trial (% of n)		
Prevention	66.7	56.0
Treatment	33.3	44.0
Age (yrs)		
Mean (standard deviation)	58.8 (10.2)	61.6 (10.0)
Gender (% of n)		
Female	13.6	15.2
Male	86.4	84.8
Race (% of n)		
Caucasian	87.7	79.4
Black	8.4	16.4
Hispanic	2.2	3.0
Native American	0.4	0.3
Other	0.9	0.6
Creatinine (mg/dl) at randomization		
Mean (standard deviation)	1.2 (0.3)	1.2 (0.3)
Diabetes (% of n)	16.6	22.9
Ejection fraction (%) at randomization		
Mean (standard deviation)	27.1 (6.3)	26.9 (6.4)
NYHA functional class (% of n) at randomization		
I	49.1	40.6
II	41.1	43.6
III	9.3	15.0
IV	0.5	0.9
Weight (lbs) at randomization		
Mean (standard deviation)	181.6 (33.6)	171.7 (33.4)

NYHA = New York Heart Association; SOLVD = Studies Of Left Ventricular Dysfunction.

Impact of anemia on mortality. To determine the impact of anemia on survival, we constructed a Cox proportional hazards model with anemia as a time-varying covariate (Table 5). In this model, an anemia episode was associated with a 47% increase in the hazard of mortality (hazard ratio [HR] 95%, CI 1.31 to 1.66). To eliminate potential confounding between the effects of enalapril and anemia, we fit the same model within each of the two treatment subgroups. Among patients receiving placebo, an anemia episode was associated with a 56% increase in the hazard of mortality (HR 95%, CI 1.32 to 1.84), whereas among

Table 4. Logistic Regression in all SOLVD Participants With Complete Data at Randomization (n = 6,436), Demonstrating the Effect of Enalapril on the Development of Anemia at Any Time During the Trial, With Adjustment for Confounders

Parameter	Odds Ratio	95% CI	p Value
Enalapril	1.204	(1.085, 1.337)	<0.001
Trial (reference = prevention)			
Treatment	1.274	(1.124, 1.446)	<0.001
Age	1.019	(1.013, 1.025)	<0.001
Gender (reference = female)			
Male	1.243	(1.057, 1.462)	0.009
Race (reference = Caucasian)			
Black	2.156	(1.824, 2.548)	<0.001
Hispanic	1.318	(0.951, 1.828)	0.097
Other (including Native American)	0.718	(0.455, 1.132)	0.154
Creatinine (mg/dl) at randomization	1.906	(1.569, 2.314)	<0.001
Diabetes	1.400	(1.223, 1.604)	<0.001
Ejection fraction (%) at randomization	1.011	(1.002, 1.020)	0.015
NYHA functional class at randomization (reference = class I or II)			
III or IV	1.301	(1.088, 1.556)	0.004
Weight (lbs) at randomization	0.990	(0.989, 0.992)	<0.001

Abbreviations as in Table 3.

patients receiving enalapril, an anemia episode was associated with a 38% increase (HR 95%, CI 1.16 to 1.63). To assess further whether this hazard differed between those with prevalent anemia and those with incident anemia, we constructed a Cox model that included separate effects for prevalent anemia (i.e., anemia episodes that began at randomization) and for new anemia (i.e., anemia episodes that began after randomization). Prevalent anemia was associated with a 44% increase in the hazard of mortality (HR 95%, CI 1.27 to 1.64), compared to a 108% increase in the hazard of mortality associated with new anemia (HR 95%, CI 1.82 to 2.38). In both of the models that included all patients with complete data at randomization, enalapril therapy was associated with a decreased risk of mortality compared to placebo, with a magnitude of benefit similar to that found in the original SOLVD study. In particular, all interaction effects between enalapril and anemia (including anemia episodes, prevalent anemia, and incident anemia) failed to achieve significance and were not included in the reported models.

Impact of time-varying hematocrit on mortality. Because the World Health Organization threshold for the definition of anemia is arbitrary, and because the effect of hematocrit on mortality is likely linear, we constructed a Cox model with hematocrit, rather than anemia, as a time-varying covariate (Table 6). After adjustment for the effects of

Table 5. Results of Adjusted Cox Regression of All-Cause Mortality by Anemia Episode During the Trial

	All Patients (n = 6,436)		Placebo (n = 3,228)		Enalapril (n = 3,208)	
Parameter	HR	95% CI	HR	95% CI	HR	95% CI
Anemia episode	1.472	(1.309, 1.657)	1.562	(1.324, 1.843)	1.376	(1.162, 1.629)
Enalapril	0.885	(0.799, 0.979)	NA		NA	
Trial (reference = prevention)						
Treatment	1.335	(1.182, 1.508)	1.398	(1.183, 1.653)	1.291	(1.080, 1.543)
Age (yrs)	1.008	(1.003, 1.014)	1.006	(0.999, 1.013)	1.012	(1.003, 1.020)
Gender (reference = female)						
Male	1.292	(1.111, 1.501)	1.188	(0.967, 1.459)	1.453	(1.164, 1.815)
Race (reference = Caucasian)						
Black	1.088	(0.942, 1.257)	1.079	(0.884, 1.318)	1.102	(0.893, 1.361)
Hispanic	0.751	(0.527, 1.069)	0.965	(0.602, 1.547)	0.580	(0.340, 0.989)
Other (including Native American)	1.073	(0.721, 1.597)	1.352	(0.822, 2.224)	0.776	(0.401, 1.502)
Antiplatelet drug use	0.719	(0.646, 0.800)	0.692	(0.596, 0.802)	0.741	(0.635, 0.865)
Creatinine (mg/dl)	1.501	(1.359, 1.658)	1.533	(1.327, 1.771)	1.461	(1.274, 1.675)
Diabetes	1.277	(1.131, 1.442)	1.238	(1.049, 1.461)	1.340	(1.119, 1.605)
Ejection fraction (%) at randomization	0.964	(0.957, 0.972)	0.958	(0.948, 0.968)	0.972	(0.960, 0.983)
NYHA class (reference = class I)						
II	1.555	(1.354, 1.787)	1.665	(1.369, 2.026)	1.447	(1.189, 1.761)
III	2.876	(2.429, 3.405)	2.695	(2.126, 3.417)	3.121	(2.453, 3.971)
IV	8.922	(7.035, 11.32)	8.412	(6.019, 11.76)	9.369	(6.678, 13.15)
Weight (lbs)	0.995	(0.994, 0.997)	0.998	(0.995, 1.000)	0.993	(0.990, 0.995)

CI = confidence interval; HR = hazard ratio; NA = not applicable.

Table 6. Results of Adjusted Cox Regression of All-Cause Mortality by Time-Varying Hematocrit During the Trial

	All Patients (n = 6,436)		Placebo (n = 3,228)		Enalapril (n = 3,208)	
Parameter	HR	95% CI	HR	95% CI	HR	95% CI
Hematocrit	0.973	(0.963, 0.984)	0.968	(0.954, 0.983)	0.980	(0.964, 0.996)
Enalapril	0.885	(0.799, 0.979)	NA		NA	
Trial (reference = prevention)						
Treatment	1.342	(1.188, 1.516)	1.406	(1.190, 1.662)	1.296	(1.084, 1.550)
Age (yrs)	1.009	(1.003, 1.014)	1.006	(0.999, 1.014)	1.012	(1.004, 1.020)
Gender (reference = female)						
Male	1.419	(1.218, 1.652)	1.320	(1.072, 1.626)	1.566	(1.250, 1.961)
Race (reference = Caucasian)						
Black	1.090	(0.943, 1.260)	1.083	(0.886, 1.323)	1.106	(0.895, 1.367)
Hispanic	0.761	(0.534, 1.083)	0.967	(0.603, 1.550)	0.592	(0.347, 1.008)
Other (including Native American)	1.053	(0.708, 1.567)	1.328	(0.808, 2.185)	0.763	(0.394, 1.477)
Antiplatelet drug use	0.716	(0.644, 0.797)	0.692	(0.597, 0.802)	0.735	(0.629, 0.858)
Creatinine (mg/dl)	1.508	(1.366, 1.664)	1.549	(1.338, 1.792)	1.466	(1.280, 1.678)
Diabetes	1.288	(1.140, 1.454)	1.249	(1.059, 1.474)	1.351	(1.128, 1.618)
Ejection fraction (%) at randomization	0.965	(0.957, 0.972)	0.959	(0.949, 0.969)	0.972	(0.961, 0.983)
NYHA class (reference = class I)						
II	1.556	(1.355, 1.787)	1.662	(1.366, 2.023)	1.450	(1.191, 1.764)
III	2.899	(2.449, 3.433)	2.701	(2.130, 3.424)	3.161	(2.484, 4.022)
IV	9.103	(7.177, 11.55)	8.599	(6.156, 12.01)	9.511	(6.772, 13.36)
Weight (lbs)	0.995	(0.994, 0.997)	0.998	(0.995, 1.000)	0.992	(0.990, 0.995)

Abbreviations as in Tables 3 and 5.

confounders, each percentage point increase in hematocrit was associated with a 3% reduction in mortality (HR 0.97, 95% CI 0.96 to 0.98). Again, we fit the same model within each of the two treatment subgroups. Among patients receiving placebo, each percentage point increase in hematocrit was associated with a 3% reduction in mortality (HR 0.97, 95% CI 0.95 to 0.98), whereas among patients receiving enalapril, each percentage point increase in hematocrit was associated with a 2% reduction (HR 0.98, 95% CI 0.96 to 1.00). Enalapril continued to be associated with a survival benefit (HR 0.89, 95% CI 0.80 to 0.98). Similar to previously described models, the interaction effect between enalapril and hematocrit failed to achieve significance, and was not included in the reported model.

DISCUSSION

Utilizing data from both the SOLVD prevention trial and treatment trial, we have demonstrated that prevalent anemia is common in the HF population. Anemia was present in 18.4% of the SOLVD trial participants at randomization. In addition, after excluding prevalent cases, incident cases of anemia at one year occurred in 9.6% of the population. In an intent-to-treat model, use of enalapril increased the odds of new anemia at one year by 56%. This association persisted when the change in creatinine and weight were included as effects. However, this association was attenuated when individuals with prevalent anemia were included in the analysis. An anemia episode was significantly associated with an increased risk of mortality (HR 1.47). This risk appeared to differ depending on whether the anemia was present at randomization (HR 1.44) versus whether the anemia was incident after randomization (HR 2.08). Despite the increase in anemia, enalapril use overall continued to be associated with a survival benefit, even among those with prevalent anemia at baseline. We did not evaluate whether there existed a dose response between the incidence of anemia and the dose of enalapril utilized, as the enalapril dose was determined by clinical factors and individualized to each participant. Any attempt at delineating a dose response would have been confounded by the individual's clinical circumstance.

The occurrence of a decline in hematocrit demonstrated in our study is consistent with the decline in hemoglobin established in other studies. These studies have shown that ACEIs reduce hemoglobin concentrations in healthy individuals (16), those receiving dialysis (17), those with post-transplant erythrocytosis (7,8,10,18–21), and in those with high-altitude polycythemia (9). Although these studies have demonstrated an association between ACEI use and a decline in hemoglobin concentration, the majority have been either case series or small crossover studies of short duration. We have demonstrated for the first time, in the setting of a large randomized controlled trial, that administration of enalapril to individuals with HF and normal hematocrit values was associated with an increased incidence of anemia at one year. As shown in Figure 2, this reduction in hematocrit is seen as early as six weeks after initiating therapy and is sustained for the duration of the trial. The effect of enalapril on hemoglobin is modest and appears to affect only a selected population.

The mechanism by which ACEIs cause anemia remains unclear. There have been numerous attempts to delineate the pathophysiology in patients with post kidney transplant polycythemia. In vitro studies have demonstrated that angiotensin II stimulates erythroid precursors through activation of an AT1 receptor on blast-forming units—erythroid

(22,23). Use of ACEIs decreases circulating angiotensin II levels with subsequent inhibition of erythroid precursors. In addition, other studies have demonstrated that ACEIs lower insulin growth factor levels (8,24), which have been associated with erythroid stimulation. Finally, ACEIs inhibit catabolism of N-acetyl-seryl-aspartyl-proline, a natural peptide that decreases proliferation of red cell precursors (25).

Anemia is associated with a significantly increased risk of death in those with either asymptomatic left ventricular systolic dysfunction or symptomatic HF. Prevalent anemia at the initiation of the SOLVD study has previously been demonstrated to be an independent risk factor for cardiovascular and all-cause mortality (5). Additionally, four large epidemiologic studies have demonstrated that anemia is a risk factor for hospitalization as well as mortality (4,26–28). Moreover, anemia is an independent predictor of death in severely ill HF patients awaiting heart transplantation (29), in those admitted to the hospital with myocardial infarctions (30), and in dialysis patients (31). Prior studies have been limited in that all assessed the impact of prevalent anemia on outcome. We have demonstrated that a relatively short duration of incident anemia is associated with an increased risk of mortality.

There are several limitations to our study results. For the first part of the study, participants were analyzed using an intent-to-treat rule, and more than 1,200 individuals were excluded because of prevalent anemia, potentially biasing the results obtained. However, because exclusion was performed before any analysis and participants were excluded on the basis of a pre-randomization variable, and our sensitivity analysis was consistent with our primary results, we feel that these exclusions had minimal impact on our results. Additionally, the World Health Organization definition for anemia is based on measured hemoglobin, whereas our results are based on hematocrit, though we are unaware of any systematic bias between the two. For the survival analysis, participants were not analyzed on the basis of the group to which they were randomized. Results from this section should be interpreted as if they had been derived from a cohort study. Many pre-one-year visit factors differed significantly between those who developed anemia and those who did not, as demonstrated in Table 3. We have attempted to adjust for possible confounders; however, there may exist other factors that were not measured and could be influencing our study results (such as blood transfusions). It may simply be that anemia is an early marker of those that are likely to die from their HF and bears no etiologic role in the morbidity and mortality of HF. Because of power limitations we were unable to determine if individuals who developed anemia attributable to enalapril had a poorer survival than those who did not develop anemia on enalapril. Also, because of the design of our study we are not able to address whether individuals that develop incident anemia as a results of ACEI therapy should have their ACEIs withheld. However, we did demonstrate that in those with prevalent anemia at baseline, use of enalapril was associated with a significant survival advantage similar to the magnitude originally described (12,13). Finally, hematocrit was not centrally measured and there were no quality control measures in place to determine the accuracy of reported hematocrit values.

Small randomized controlled trials have demonstrated that correction of mild anemia in patients with HF resulted in improved cardiac and patient function (31,33), as well as reduced overall hospitalizations. Anemia appears to be an under-recognized risk factor for both morbidity and mortality in those with established HF. Given the current evidence, there ought to be a large, randomized placebo-controlled trial to determine if anemia correction and/or prevention in those with HF can reduce the associated morbidity or mortality.

Conclusions. Incident anemia at one year is common in those with reduced left ventricular function. Treatment with enalapril increases the odds of anemia at one year. Participants with anemia had an increased mortality risk compared with those that never develop anemia. This risk is magnified in those with incident anemia as compared to those with prevalent anemia. Enalapril was protective of overall mortality after adjusting for incident anemia and in those with prevalent anemia.

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