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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-