Heart Failure

Anemia and Its Relationship to Clinical Outcome in Heart Failure

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Background—Anemia is often observed in patients with chronic heart failure (CHF), but its implications for patient outcomes are not well understood. The goal of this study was to investigate the relationship between anemia, severity of CHF, and clinical outcomes.

Methods and Results—Hemoglobin concentration (Hb) was measured in 912 subjects with CHF enrolled in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial. In a subgroup of 69 subjects, cardiac MRI was performed at randomization and 24 weeks later. Anemia (Hb ≤12.0 g/dL) was present in 12% of subjects. Cox regression analysis indicated that for every 1-g/dL-higher baseline Hb, the risk of mortality was 15.8% lower ($P=0.0009$) and the risk of mortality or hospitalization for heart failure was 14.2% lower ($P<0.0001$). Greater CHF severity was associated with significantly lower Hb concentrations. An increase in Hb over time was associated with a decrease in left ventricular mass and lower mortality, whereas a decrease in Hb over time was associated with an increase in left ventricular mass and higher mortality. In multivariate analysis, anemia remained a significant, independent predictor of death or hospitalization for heart failure, with both outcomes being significantly higher in all NYHA classes.

Conclusions—Anemia is frequently present in patients with CHF. Lower Hb is associated with greater disease severity, a greater left ventricular mass index, and higher hospitalization and mortality rates. (*Circulation*. 2004;110:149-154.)

Key Words: anemia ■ heart failure ■ morbidity ■ mortality ■ physiology

Recent studies indicate that patients with chronic heart failure (CHF) are frequently anemic and that anemia may be associated with increased mortality.\(^1\)\(^-\)\(^9\) Whether anemia is also associated with increased morbidity and whether it is an independent risk factor for adverse outcomes are less certain. Moreover, the variability in hemoglobin (Hb) concentration over time in CHF patients and the prognostic consequences of change in Hb have not been described.

The mechanisms relating the association of Hb concentration and clinical outcomes in CHF are also not clear. Anemia is associated with the development of left ventricular (LV) hypertrophy in patients with renal failure, but less is known in patients with CHF. Because LV hypertrophy has been shown to increase the risk of cardiovascular events in patients with LV dilatation and systolic dysfunction,\(^10\) the presence of such an association with anemia may have important pathophysiological consequences.

We describe here a retrospective analysis of the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial, which randomized patients with moderate to severe CHF to receive either placebo or the tumor necrosis factor-α antagonist etanercept. This analysis had 4 main objectives. The first was to confirm that anemia is common in CHF and to examine the variability in Hb concentration over time. The second was to see whether a relationship existed between severity of CHF and Hb concentration. The third objective was to examine the relationship between Hb and LV mass determined by cardiac MRI. The final objective was to determine whether low Hb is associated with increased mortality and hospitalization for worsening CHF and whether it is an independent predictor of prognosis in CHF.

Methods

Study Patients and Follow-Up

Nine hundred twelve subjects were enrolled in the multicenter, double-blind, placebo-controlled RENAISSANCE trial. The main inclusion criteria for RENAISSANCE were (1) age of 18 to 55 years; (2) NYHA class II to IV; (3) ischemic or nonischemic origin of disease; (4) LV ejection fraction (LVEF) <0.30; (5) stable doses of diuretic, ACE inhibitor (unless not tolerated), and β-blocker (if taking) for ≥3 months; and (6) 6-minute walk distance of <375 m (or <425 m if hospitalized for CHF within previous 6 months). The main exclusion criteria were (1) severe infection within 1 month,
(2) surgically correctable causes of heart failure, (3) other serious illness, and (4) recent or planned surgery/coronary revascularization. The studies received ethics approval in all participating centers, and all subjects gave written informed consent. Subjects were randomized to receive either placebo or etanercept (25 mg) 2 or 3 times per week for 24 weeks. Blood samples were obtained from all subjects at baseline and subsequently at weeks 2, 4, 12, and 24.

Patients were to continue receiving blinded study medication beyond 24 weeks until study closure. Patients discontinuing study medication continued to be followed up for vital status (death and hospitalization). This additional follow-up allowed analysis of the secondary end points of mortality and morbidity. At the time of study closure, mean duration of follow-up was 12.7 months (range, 0 to 26 months). Fewer than 1% of subjects were lost to follow-up.

Cardiac MRI
A subgroup of 69 randomly selected eligible subjects underwent cardiac MRI at trial entry and after 24 weeks. ECG-gated, gradient-echo imaging with segmented acquisition and complete coverage of the heart from base to apex was applied with 6- to 8-mm-thick slices during breathhold with an 8- to 10-mm interslice gap. To obtain good temporal resolution, 15 to 20 cardiac phases were acquired for each slice during the R-R interval. Images were analyzed with the MRI-MASS MR Analytical Software System (MEDIS Medical Imaging Systems BV). Twenty-nine subjects received placebo; 40 subjects received etanercept (2 times per week, n = 14; 3 times per week, n = 26). Three subjects failed to have Hb measured at week 24 and were excluded from analysis. Cardiac MRI has been shown to have excellent reproducibility, with a coefficient of variation of <5% for the determination of ventricular mass.11

Statistical Analysis
Baseline Hb concentrations were compared among and between NYHA functional classifications with the Kruskal-Wallis and Wilcoxon rank tests. A last-observation-carried-forward approach was used to handle missing Hb concentrations and MRI evaluations at postbaseline visits. The Wilcoxon signed-rank test was used to assess whether changes from the baseline were different from 0; changes from baseline were compared among groups by use of the Wilcoxon rank-sum test. Analyses of time to event data (death; death or CHF hospitalization) were conducted with the log-rank test. The Cox proportional-hazards regression model was used to explore continuous predictor variables. A value of P < 0.05 was considered statistically significant.

Results
Characteristics of Study Population
Baseline characteristics of the subjects enrolled in the RENAISSANCE trial are given in Table 1. Mean age, LVEF, gender, and NYHA class distributions were similar in all groups. Subjects undergoing cardiac MRI analysis did not show any significant differences compared with other groups.

Distribution of Hb Concentrations Across NYHA Heart Classes
The mean ± SD Hb concentration for all 912 subjects was 13.8 ± 1.6 g/dL. Twelve percent of subjects were anemic as defined by an Hb ≤ 12.0 g/dL, and 20% of subjects had an Hb concentration ≤ 12.5 g/dL. As shown in Figure 1, lower mean baseline Hb concentrations correlated significantly with greater CHF severity as assessed by NYHA classification (P = 0.0017, difference among the 3 NYHA classes in baseline Hb). The mean ± SD Hb concentrations for subjects with NYHA class II, IIIa, and IIIb/IV CHF were 14.1 ± 1.6, 13.8 ± 1.6, and 13.6 ± 1.5 g/dL, respectively. We found that 10%, 13%, and 17% of subjects in NYHA class II, IIIa, and IIIb/IV, respectively, had an Hb ≤ 12.0 g/dL.

Variability in Hb Concentration Over Time
Changes in mean ± SD Hb concentrations over the study period for all 912 subjects were small and statistically significantly different from 0 only at 4 weeks (P = 0.0045). At 2, 4, 12, and 24 weeks after randomization, Hb concentrations had changed compared with the value at baseline by −0.03 ± 0.79, −0.07 ± 0.92, 0.02 ± 1.03, and −0.02 ± 1.16 g/dL (mean ± SD), respectively. No difference in changes in Hb concentration was seen between subjects receiving placebo and those on etanercept at any time point (P > 0.05).

Correlation Between Changes in Hb Concentrations and LV Mass
In the 66 subjects who had both cardiac MRI and Hb concentration measured, the mean ± SD Hb concentrations at baseline were 13.6 ± 1.4 and 13.8 ± 1.4 g/dL after 24 weeks.

### TABLE 1. Characteristics of RENAISSANCE Trial Study Population

<table>
<thead>
<tr>
<th></th>
<th>All Study Subjects (n=912)</th>
<th>Subjects Not Undergoing MRI (n=843)</th>
<th>Subjects Undergoing MRI (n=69)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, y</td>
<td>62 (12)</td>
<td>63 (12)</td>
<td>59 (12)*</td>
</tr>
<tr>
<td>Male subjects, %</td>
<td>78</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>IIIa</td>
<td>47</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>IIIb/IV</td>
<td>30</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Mean (SD) LVEF</td>
<td>0.22 (0.06)</td>
<td>0.22 (0.06)</td>
<td>0.23 (0.05)</td>
</tr>
</tbody>
</table>

*Week 24 Hb measurements were unavailable for 3 subjects.

### Figure 1. Greater severity of CHF is associated with lower Hb concentrations ([Hb]). Mean ± SE baseline Hb concentration from subjects with NYHA class II (n = 210), IIIa (n = 428), and IIIb/IV (n = 274) CHF. *P = 0.0186 vs NYHA class II; **P = 0.0003 vs NYHA class II.
Relationship Between Hb Concentrations and Outcome

A Cox regression analysis across all 912 subjects was used to establish the relationship between baseline Hb concentrations and mortality or the composite of mortality/CHF hospitalization (Figure 3A and 3B). Mortality was significantly greater in anemic subjects (Hb ≤12.0 g/dL) compared with nonanemic subjects (28% versus 16%, respectively; \(P=0.0172\), log-rank test), as was mortality/CHF hospitalization (56% versus 33%, respectively; \(P<0.0001\), log-rank test) (Figure 3A and 3B and Table 2). Baseline Hb concentration was a significant predictor of both mortality [hazard ratio (HR), 0.842; \(P=0.0009\)] and mortality or CHF hospitalization (HR, 0.858; \(P<0.0001\)). These data suggest that a 1-g/dL increase in Hb concentration is associated with a 15.8% reduction in risk of death and a 14.2% reduction in risk of death/CHF hospitalization. Figure 4A and 4B illustrate that the higher risk for mortality and mortality/CHF hospitalization observed in anemic subjects was seen in all NYHA functional classes. In a multivariate Cox analysis controlling for use of \(\beta\)-blockers, antiarrhythmic drugs, NYHA functional class, baseline diastolic blood pressure, and serum creatinine concentration, baseline Hb concentration remained a significant independent predictor of mortality or CHF hospitalization (HR, 0.915; \(P=0.021\)). Again, this relationship was seen in subjects regardless of whether they received etanercept or placebo.

To examine whether there was a U-shaped relationship between higher Hb concentrations and increased mortality, we calculated the Kaplan-Meier 1-year estimates of survival based on the 10th, 25th, 50th, 75th, and 90th percentiles of baseline Hb. For subjects with Hb <11.8 g/dL, the Kaplan-Meier 1-year estimates of mortality were 24.6%, 20.7%, 13.1%, 13.1%, 12.2%, and 7.9%, respectively, failing to demonstrate a U-shaped relationship between baseline Hb concentrations and mortality.

Finally, 97 of 466 subjects (20.8%) whose Hb concentration remained unchanged or decreased over the 24 weeks of the study compared with baseline had died at 1 year. In comparison, only 62 of 384 subjects (13.9%) whose Hb concentration increased over the 24 weeks of the study compared with baseline had died at 1 year. The Kaplan-Meier estimates of 1-year mortality for these 2 subject groups are 18.1% and 11.4%, respectively (\(P=0.0008\); log-rank test).

Discussion

Results of this study can be summarized as follows. First, anemia is common in CHF and is associated with increasing disease severity, and in general, Hb concentrations change little over time in these patients. Second, a decrease in mean Hb concentration over time is associated with an increase in LVMI. Finally, Hb concentration is an independent risk factor for adverse outcomes, and lower Hb concentrations are associated with higher hospitalization and mortality rates in patients with CHF.

Causes and Pathophysiological Consequences of Anemia

The pathogenesis of anemia in patients with CHF is uncertain and generally referred to as the anemia of chronic disease.\textsuperscript{12} Several mechanisms have been proposed to be contributory, including hematocrit deficiency,\textsuperscript{13} the direct effect of drugs such as ACE inhibitors\textsuperscript{14} and cytokines, which may interfere with erythropoiesis.\textsuperscript{15} We examined the circulating concentrations of a variety of proinflammatory and anti-inflammatory cytokines in subjects with CHF and found that the overall cytokine environment becomes predominantly

The mean±SD LV mass index (LVMI) was 113±33 g/m\(^2\) at baseline and 111±30 g/m\(^2\) after 24 weeks. No difference in change from baseline in LVMI was seen between subjects receiving placebo and those receiving etanercept at week 24 (\(P=0.80\)). Baseline LVMI tended to be lower with higher baseline Hb concentration (\(r=-0.26\), \(P=0.03\)), a trend that was present at 24 weeks, although it was not significant. Figure 2 shows that for subjects whose Hb concentration either remained the same or decreased over the 24 weeks of the study, LVMI increased by 1.6±7.9 g/m\(^2\) (mean ± SD). However, in those subjects who showed an increase in Hb concentration over 24 weeks, LVMI decreased by 7.5±12.1 g/m\(^2\) (\(P=0.0008\)). Further analysis revealed a negative correlation between changes in Hb concentration and LVMI changes at 24 weeks (\(r=-0.32\), \(P=0.0086\)). These data imply that a 1.0-g/dL increase in Hb over a 24-week period is associated with a 4.1-g/m\(^2\) reduction in LVMI. Again, this was seen in subjects regardless of whether they received etanercept or placebo. Among the 66 subjects who had both Hb concentration and cardiac MRI available at baseline, a negative correlation between Hb concentration and EF was suggested (\(r=-0.20\), \(P=0.1138\)). No correlation was found between changes in Hb concentration and changes in LV ejection fraction and end-diastolic or -systolic volume (data not shown).
proinflammatory, especially in more advanced disease (manuscript in preparation). Using the ICD-9 diagnostic coding system, Ezekowitz and colleagues\(^5\) found that 17% of 12,065 patients with CHF were anemic. In 60% of these subjects, no apparent cause for the anemia could be found. The hemodynamic changes accompanying severe anemia include increased preload, reduced peripheral resistance, and increased cardiac output.\(^6\) Vasodilatation may be due to reduced blood viscosity that is mediated in part by enhanced nitric oxide production.\(^7\) These adaptive

### TABLE 2. Mortality and CHF Hospitalization by Baseline Hb Concentration

<table>
<thead>
<tr>
<th>Baseline Hb Concentration, g/dL</th>
<th>Mortality, % (n)</th>
<th>Kaplan-Meier 1-y mortality rate, % (95% CI)*</th>
<th>Mortality or CHF hospitalization rate, % (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12.0 (n=108)</td>
<td>27.8 (30)</td>
<td>24.0 (15.4–32.6)</td>
<td>55.6 (60)</td>
</tr>
<tr>
<td>12.0 to &lt;13.7 (n=319)</td>
<td>18.2 (58)</td>
<td>15.9 (11.5–20.4)</td>
<td>36.1 (115)</td>
</tr>
<tr>
<td>13.7 to &lt;14.9 (n=255)</td>
<td>17.3 (44)</td>
<td>13.0 (8.3–17.7)</td>
<td>35.3 (90)</td>
</tr>
<tr>
<td>≥14.9+ (n=230)</td>
<td>11.7 (27)</td>
<td>10.2 (5.9–14.6)</td>
<td>27.0 (62)</td>
</tr>
</tbody>
</table>

*95% CI, log-rank test comparing the 4 Hb categories for mortality (P=0.020).
**95% CI, log-rank test comparing the 4 Hb categories for mortality or CHF hospitalization (P=0.0001).
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responses may ultimately lead to an increase in LV mass, a significant factor for poor prognosis for cardiovascular and overall outcomes. Anemia has been demonstrated to result in eccentric hypertrophy in rats accompanied by increased capillary proliferation, abnormal diastolic wall stress, and interstitial fibrosis. Whether similar mechanisms operate in patients with CHF remains to be determined. In a study of 448 subjects with renal disease, 25% were found to increase their LVMI significantly over a 12-month period. In multivariate analysis, a decrease in Hb concentration emerged as an independent predictor of increasing LV size. We found that a 1-g/dL increase in Hb concentration was associated with a 4.1-g/m² decrease in LVMI over a 24-week period. These results suggest that, at least in patients with CHF, even relatively small decreases around a normal Hb value may have deleterious effects on myocardial remodeling and contribute to worsening CHF. These data are among the first to suggest a causal relationship between anemia and worse outcome in patients with CHF.

Impact of Anemia on Outcome in Subjects With Heart Failure

The study described here confirms and expands the findings of previous reports linking anemia to adverse outcome in patients with CHF. We found that lower Hb concentrations were associated with higher mortality and hospitalization rates. For every 1-g/dL reduction in Hb concentration, the risk of mortality increased by ~16%, which is in line with other published studies. The risk of death or hospitalization for CHF was increased by 14.2%. This increase in both mortality and morbidity at lower Hb concentrations was seen in all subjects independent of NYHA functional class, a finding not previously reported. We did not find any evidence to support a J- or U-shaped relationship between higher baseline Hb concentrations and higher mortality. Furthermore, we also found that, compared with patients with an increase in Hb, patients with a decrease or no change in Hb concentration over time (24 weeks) were associated with a higher mortality rate at 1 year, a finding potentially linked to the increase in LVMI described above. Treatment with etanercept had no effect on Hb concentrations, and outcome was the same in anemic and nonanemic subjects regardless of the use of etanercept. It is difficult to explain why Hb concentration does change in some subjects over time. Possibilities include the use of erythropoietic stimulating proteins, blood transfusion, or alteration in medications that may contribute to the development of anemia, along with the development of fluid overload and hemodilution. Do these data imply that treatment of anemia in patients with CHF may be beneficial? In an open-label trial using erythropoietin to correct anemia in CHF patients, Silverberg and colleagues demonstrated significant improvements in NYHA class, EF, visual analog score, and hospitalization events after treatment. Mancini and colleagues treated anemic CHF patients with erythropoietin and showed significant improvements in peak oxygen consumption, exercise duration, performance in the 6-minute walk test, and quality of life. Larger randomized trials are required to fully investigate this hypothesis.

Study Limitations

This was a retrospective analysis of a small number of patients who underwent cardiac MRI and cytokine analysis in the RENAISSANCE trial. Larger, prospectively designed clinical studies are required to validate these findings.

Acknowledgments

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References

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