Anemia Is Common in Heart Failure and Is Associated With Poor Outcomes

Insights From a Cohort of 12 065 Patients With New-Onset Heart Failure

Justin A. Ezekowitz, MBBCh; Finlay A. McAlister, MD, MSc; Paul W. Armstrong, MD

Background—Although previous work has suggested that anemia is associated with an increased mortality in selected patients with congestive heart failure (CHF), little is known about the prevalence and predictors of anemia, or whether anemia is an independent prognostic factor in unselected, community-based patients with CHF.

Methods and Results—We analyzed a population-based cohort of patients with new-onset CHF from a database of patients discharged from 138 acute-care hospitals in Alberta, Canada, between April 1993 and March 2001. Logistic regression, Kaplan-Meier survival analyses, and Cox proportional hazards model were used. Among the 12 065 patients with CHF (median age 78 years), 17% had anemia, 58% of whom had anemia of chronic disease. After adjustment for clinical and demographic variables, patients with anemia were more likely to be older (odds ratio [OR] 1.01 per year) and female (OR 1.2 [95% confidence interval 1.1 to 1.3]) and to have a history of chronic renal insufficiency (OR=3.2 [95% confidence interval 2.8 to 3.6]), or hypertension (OR 1.3 [95% confidence interval 1.2 to 1.5]). Hazard ratios for mortality, adjusting for covariates, were 1.34 (1.24 to 1.46) in anemic patients, and 1.36 (1.23 to 1.50) in those patients with anemia of chronic disease.

Conclusions—In this large cohort of community-dwelling patients with CHF, anemia is common and an independent prognostic factor for mortality. Further research into the mechanisms of anemia in CHF and randomized controlled trials to test whether correction of anemia improves prognosis in CHF are needed.

Key Words: anemia ● heart failure ● epidemiology
Clinical Features in 12 065 Heart Failure Patients With Any Anemia, Anemia of Chronic Disease, or No Anemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Anemia (n=2083)</th>
<th>Anemia of Chronic Disease (n=1208)</th>
<th>No Anemia (n=9982)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77.3±12*</td>
<td>77.3±11*</td>
<td>76.4±12</td>
</tr>
<tr>
<td>Male sex</td>
<td>944 (45)*</td>
<td>570 (47)*</td>
<td>4972 (50)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>532 (26)</td>
<td>347 (29)*</td>
<td>2346 (24)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>738 (35)*</td>
<td>452 (37)*</td>
<td>2829 (28)</td>
</tr>
<tr>
<td>COPD</td>
<td>625 (30)</td>
<td>372 (31)</td>
<td>2879 (28)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>78 (4)</td>
<td>58 (5)</td>
<td>349 (4)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>868 (42)*</td>
<td>540 (45)*</td>
<td>3805 (38)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>107 (5)</td>
<td>58 (5)</td>
<td>393 (4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>200 (10)*</td>
<td>117 (10)*</td>
<td>550 (6)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>548 (26)</td>
<td>313 (26)</td>
<td>2460 (25)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>228 (11)*</td>
<td>131 (11)*</td>
<td>536 (5)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>387 (19)*</td>
<td>277 (23)*</td>
<td>674 (7)</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or n (%). Note that the 1208 patients classified as having anemia of chronic disease represent a subset of the 2083 patients with any anemia. COPD indicates chronic obstructive pulmonary disease.

Discussion

The key novel findings of our study are the demonstration among a large population-based cohort of CHF patients that anemia is common, that it is an independent prognostic factor, and that the majority of heart failure patients with anemia have anemia of chronic disease. There are several possible explanations for our findings. First, reduced hemoglobin may merely be a marker for the epiphenomena of advanced heart failure (such as hemodilution due to volume overload, malnutrition from cardiac cachexia, or renal insufficiency). An earlier study in patients with New York Heart Association class III or IV failure demonstrated, however, that hemoglobin was an important prognostic factor independent of the pulmonary capillary wedge pressure, body mass index, serum albumin, or serum creatinine.2 Furthermore, anemia was an independent predictor of mortality independent of serum creatinine in 2 previous studies.1,3 Second, because angiotensin-converting enzyme (ACE) inhibitors may inhibit hematopoietic cell proliferation, it is possible that anemia may be a marker for patients receiving higher doses of ACE inhibitors.7,8 This seems unlikely, however, as the presence of anemia seems to be independent of ACE inhibitor use (and dosing).1,2 Third, although anemia may predispose at-risk patients to myocardial ischemia, the prognostic impact of anemia was independent of a diagnosis of ischemic heart disease in our data. Finally, inflammation, characterized by increases in cytokines such as tumor necrosis factor-α,9 is now thought to be a pathophysiological modulator of heart failure. Hence, we believe it is reasonable to hypothesize that heart failure may cause anemia of chronic disease through cytokine-mediated bone marrow suppression.7

As this is an observational study, some potential limitations deserve discussion. The limitations of administrative data-
bases are well known and described elsewhere. However, previous studies have confirmed the accuracy of our data sources and coding for heart failure. Further, all of our analyses were adjusted for known prognostic factors in heart failure, and we confirmed the robustness of our findings in a sensitivity analysis in the youngest and healthiest subgroup, where unmeasured confounding would presumably be minimized.

We believe efforts to better detect anemia in heart failure patients, discern the pathophysiology of, and test new therapies for anemia in heart failure should be a future priority. Indeed, small open-label studies have shown improvements in functional capacity and ejection fraction with correction of anemia using erythropoietin with intravenous iron. There is clearly a need for an appropriately powered randomized trial with meaningful clinical endpoints, such as hospitalizations and mortality, to evaluate the impact of such therapies in anemic heart failure patients.

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**References**

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