Incident Anemia in Older Adults with Heart Failure

Rate, Etiology, and Association with Outcomes

Andrew P. Ambrosy, MD[1,2], Jerry H. Gurwitz, MD[3,4], Grace H. Tabada, MPH[2], Andrew Artz, MD MS[5], Stanley Schrier, MD[6], Sunil V. Rao, MD[7,8], Huiman X. Barnhart, PhD[8], Kristi Reynolds, PhD MPH[9], David H. Smith, PhD, RPh[10], Pamela N. Peterson, MD MSPH[11,12,13], Sue Hee Sung, MPH[2], Harvey Jay Cohen, MD[14] and Alan S. Go, MD[2,15,16]

for the RBC HEART Investigators

[1]Department of Cardiology, Kaiser Permanente San Francisco Medical Center, San Francisco, CA, USA; [2]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; [3]Division of Geriatric Medicine, University of Massachusetts Medical School, Worcester, MA, USA; [4]Meyers Primary Care Institute, Worcester, MA, USA; [5]Section of Hematology/Oncology, The University of Chicago, Chicago, IL, USA; [6]Division of Hematology, Stanford University School of Medicine, Stanford, CA, USA; [7]Division of Cardiology, Duke University Medical Center, Durham, NC, USA; [8]Duke Clinical Research Institute, Duke University Medical School, Durham, NC, USA; [9]Division of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA; [10]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA; [11]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA; [12]Denver Health Medical Center, Denver CO; [13]University of Colorado Anschutz Medical Campus, Aurora, CO; [14]Center for the Study of Aging and Human Development, Duke University Medical Center, Durham, NC, USA; [15]Departments of Epidemiology, Biostatistics and Medicine,

University of California at San Francisco, San Francisco, CA, USA; [16]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA

Corresponding Author:

Alan S. Go, MD

Division of Research

Kaiser Permanente Northern California

2000 Broadway

Oakland, CA 94612-2304

Email: alan.s.go@kp.org

Telephone: 510-891-3422

Fax: 510-891-3508

ABSTRACT

Aims: Limited data exist on the epidemiology, evaluation, and prognosis of otherwise unexplained anemia of the elderly in HF. Thus, we aimed to determine the incidence of anemia, to characterize diagnostic testing patterns for potentially reversible causes of anemia, and to evaluate the independent association between incident anemia and long-term morbidity and mortality.

Methods and Results: Within the Cardiovascular Research Network (CVRN), we identified adults age ≥65 years with diagnosed HF between 2005-2012 and no anemia at entry. Incident anemia was defined using World Health Organization (WHO) hemoglobin thresholds (<13.0 g/dL in men; <12.0 g/dL in women). All-cause death and hospitalizations for HF and any cause were identified from electronic health records. Among 38,826 older HF patients, 22,163 (57.1%) developed incident anemia over a median (interquartile range) follow-up of 2.9 (1.2, 5.6) years. The crude rate (95% Confidence Interval [CI]) per 100 person-years of incident anemia was 26.4 (CI:26.0-26.7) and was higher for preserved ejection fraction (EF) (29.2 [CI:28.6-29.8]) compared with borderline EF (26.5 [CI: 25.4-27.7]) or reduced EF (26.6 [CI: 25.8-27.4]). Iron indices, vitamin B12 level, and thyroid testing were performed in 21.8%, 14.9% and 40.2% of patients, respectively. Reduced iron stores, vitamin B12 deficiency, and/or hypothyroidism were present in 29.7%, 3.2% and 18.6% of tested patients, respectively. In multivariable analyses, incident anemia was associated with excess mortality (hazard ratio [HR] 2.14, CI:2.07-2.22) as well as hospitalization for HF (HR 1.80, CI:1.72-1.88) and any cause (HR 1.77, CI:1.72-1.83).

Conclusion: Among older adults with HF, incident anemia is common and independently associated with substantially increased risks of morbidity and mortality. Additional research is

necessary to clarify the value of routine evaluation and treatment of potentially reversible causes of anemia.

Keywords: heart failure, ejection fraction, anemia, iron deficiency, outcomes

INTRODUCTION

Anemia is a very common comorbidity in older adults with an estimated ~10% of patients ≥65 years meeting World Health Organization (WHO) anemia thresholds (i.e., hemoglobin [Hgb] <13.0 g/dL in men and <12.0 g/dL in women).[1] Of these, approximately one-third have clearly definable causes, one-third are associated with chronic diseases, and one-third have no definable cause (also referred to as unexplained anemia of the elderly [UAE]). Notably, anemia is significantly higher in older adults with heart failure (HF) than in the general population, with more than 40% of ambulatory patients with HF having prevalent anemia within a large integrated healthcare delivery system.[2] Furthermore, even after adjusting for underlying chronic kidney disease (CKD) and other known risk factors, there was a graded, independent association between baseline Hgb level <13.0 g/dL and risks of death and hospitalization for HF irrespective of degree of systolic dysfunction.[2]

Despite the high prevalence of anemia, limited data exist about the incidence of anemia among older outpatients with HF. Prior studies have largely been conducted in single center tertiary referral centers and selected landmark clinical trial cohorts, which have limited the generalizability of their findings.[3-5] In addition, rates of evaluation of incident anemia in these patients is unclear, hence, the underlying contributing factors and associated prognosis in this setting remain unknown. Within a large, diverse, multicenter cohort of ambulatory patients with HF without baseline anemia, we aimed to determine the incidence of anemia, to characterize diagnostic testing patterns for potentially reversible causes of anemia, and to evaluate the independent association between incident anemia and long-term morbidity and mortality.

METHODS

Source Population

The source population included members from five participating healthcare delivery systems within the Cardiovascular Research Network (CVRN) from 2005-2012.[6] Sites included Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Northwest, Kaiser Permanente Colorado, and Meyers Primary Care Institute. Contributing sites provide care to an ethnically and socioeconomically diverse population across varying practice settings and broad geographic areas. Each site has a Virtual Data Warehouse (VDW) which served as the primary data source for patient identification and characterization.[6, 7] The VDW is a distributed, standardized data resource comprised of datasets at each CVRN site that are populated with linked demographic, administrative, pharmacy, laboratory, and health care utilization (i.e., ambulatory visits and network and non-network hospitalizations with diagnoses and procedures) data for members receiving care at participating sites.

Institutional review boards at participating centers approved the study, and waiver of consent was obtained due to the nature of the study.

Study Sample

We identified all patients age ≥65 years who had a diagnosed HF between 2005-2012, based on either having been hospitalized with a primary discharge diagnosis of HF and/or having ≥3 ambulatory visits coded for HF with at least one visit being with a cardiologist.[8, 9] The date of HF diagnosis is the index date. The International Classification of Diseases, 9th Edition (ICD-9) codes were used as follows: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33,

428.40, 428.41, 428.42, 428.43, and 428.9. Previous studies have shown a positive predictive value of >95% for admissions with a primary discharge diagnosis of HF based on these codes when compared against chart review using Framingham clinical criteria.[2, 10,11] We only included adults aged ≥65 years with at least 12 months of continuous health plan enrollment and pharmacy benefit before the index date to ensure adequate data on covariates.

Anemia status was determined at index date based on WHO thresholds (i.e., Hgb <13.0 g/dL in men and <12.0 g/dL in women) using the most recent Hgb measurement on or up to one year before the index date. Only outpatient, non-emergency department Hgb values were used to determine anemia status. Patient with anemia on or up to one year before the index date were excluded. Other exclusion criteria included organ transplant before or on index date, no evidence of health plan membership after index date, and death on the index date.

Covariates

Assessments of left ventricular EF were obtained for each HF patient based on results of echocardiograms, radionuclide scintigraphy, other nuclear imaging modalities, and left ventriculography found in site-specific databases complemented by manual chart review. The measure closest to the index date, within 2 years prior to, on, or after index date was used. Cardiologist-based qualitative assessments were prioritized over quantitative assessments. Patients were classified into categories of reduced, borderline, or preserved EF. HF with a reduced ejection fraction (HFrEF) was defined either by a reported left ventricular EF ≤40% and/or based on a physician's qualitative assessment of moderate, moderate to severe, or severe systolic dysfunction. HF with a borderline EF (HFbEF) was defined as a reported left ventricular EF between 41-49% and/or physician's qualitative assessment of mildly reduced systolic

function. HF with a preserved EF (HFpEF) was defined as either a reported left ventricular EF ≥50% and/or based on a physician's qualitative assessment of preserved or normal systolic function. Patients with missing or no available left ventricular EF were classified as unknown EF.

Information was ascertained on demographic characteristics and coexisting illnesses based on diagnoses or procedures using relevant ICD-9 codes, laboratory results, or filled outpatient prescriptions from health plan hospitalization discharge, ambulatory visit, laboratory, and pharmacy databases, as well as site-specific cancer registries.[12] Ambulatory blood and urine measurements were obtained from health plan laboratory databases. Iron deficiency was defined as a serum ferritin <40 ng/ml or a ferritin 40-100 ng/ml plus a transferrin saturation (TSAT) <20%.[13, 14] Vitamin B12 deficiency was defined as a vitamin B12 ≤200pg/ml. Hypothyroidism was defined as a thyroid-stimulating hormone (TSH) ≥ 4.1 mIU/L. Medication use at baseline was based on filled prescriptions within 120 days before index date from health plan pharmacy dispensing databases.

Outcomes

Follow-up occurred through December 31, 2013. The primary outcome of interest was development of incident anemia, defined as the first outpatient Hgb measure meeting the WHO threshold for anemia during follow-up. Secondary outcomes included all-cause mortality, HF-specific hospitalization, and hospitalization for any cause. Hospitalizations were comprehensively captured from participating sites' electronic health records, with HF-specific admissions defined using primary discharge diagnosis ICD-9 codes as described previously. Deaths were identified based on electronic health records, administrative databases (i.e.,

including proxy reporting) and Social Security vital status files and state death certificate information, if available.

Statistical Analysis

All analyses were conducted using SAS, version 9.3 (Cary, NC, USA) at Kaiser Permanente Northern California. Baseline characteristics were compared by incident anemia status using analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. Due to the large sample size, d-values were reported for standardized mean differences to compare baseline characteristics[15]; a d-value ≥0.10 was considered a meaningful difference.

Time-to-event analyses were used for the primary outcome and secondary outcomes. For time to incident anemia, patients were censored if they died, disenrolled from the health plan, received an organ transplant, or reached the end of study follow-up. Rates (per 100 person-years) and associated 95% confidence intervals (CI) were calculated for the outcome of anemia, overall and stratified by left ventricular EF. Multivariable Cox proportional hazard regression models were conducted to identify independent correlates of developing incident anemia. Baseline variables that have been previously reported to be associated with anemia, as well as those found to be different at index date between those who did or did not develop incident anemia were included in the final model.

For all-cause mortality, patients were censored if they disenrolled from the health plan, received an organ transplant, or reached the end of study follow-up. For all-cause and HF-specific hospitalizations, patients were also censored if they died in addition to the aforementioned reasons. Rates (per 100 person-years) and 95% CI were also calculated for each

secondary outcome, stratified by incident anemia status and by possible etiology of anemia. Extended Cox regression models were performed to examine the independent association between incident anemia and the secondary outcomes after adjustment for potential confounders.

RESULTS

Cohort assembly and incidence of anemia

A total of 114,705 elderly patients with HF were identified from 2005-2012 (**Figure 1**). The primary reasons for exclusion were prevalent anemia (N = 30,672), no available Hgb measurements within the past year (N = 24,152), and age <65 years (N = 19,149). The final analytic cohort included 38,826 older adults with HF and no prevalent anemia at baseline.

During a median (interquartile range) follow-up of 2.9 (1.2, 5.6) years, 22,163 patients (57.1%) met the definition for incident anemia, with a crude rate (95% Confidence Interval [CI]) of 26.4 (95%CI: 26.0-26.7) per 100 person-years overall. Incident anemia was marginally higher for HF patients with a preserved EF (29.2 [95%CI: 28.6-29.8] per 100 person-years) compared with a borderline (26.5 [95%CI: 25.4-27.7] per 100 person-years) or reduced EF (26.6 [95%CI: 25.9-27.4] per 100 person-years).

Patient Characteristics by Incident Anemia Status

Patients developing incident anemia were less likely to be women (48.8% vs 56.3%) (**Table 1**). They also more often had a preserved EF (39.1% vs. 35.0%); a higher burden of risk factors for coronary heart disease (i.e., dyslipidemia [82.5% vs. 77.5%], hypertension [86.2% vs. 82.4%], and diabetes mellitus [38.6% vs. 30.2%]), unstable angina (6.7% vs. 5.3%), and prior revascularization (i.e., percutaneous coronary intervention [9.9% vs. 8.5%] and/or coronary artery bypass surgery [6.0% vs. 3.7%]); a lower prevalence of dementia (4.4% vs. 7.8%); and more often had advanced CKD (56.3% vs. 52.9%) or end-stage renal disease (1.3% vs. 0.9%). Patients with incident anemia were more likely to be prescribed an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (66.2% vs. 60.5%), loop diuretic (51.4% vs. 47.0%), statin (63.1% vs. 55.9%) or other lipid lowering therapy (5.8% vs. 4.0%), oral diabetes

medication (28.4% vs. 20.7%), NSAID (12.0% vs. 10.1%), and intravenous/injectable therapies for anemia including erythropoietin (1.5% vs. 0.5%), iron (1.0% vs. 0.6%), and vitamin B12 (0.7% vs. 0.5%).

Laboratory Evaluation of Incident Anemia

Among 22,163 elderly patients with HF who developed incident anemia, iron studies, vitamin B12, and thyroid function tests were evaluated at or within 90 days after the relevant Hgb test in 21.8%, 14.9%, and 40.2% of patients, respectively (**Table 2**). Testing for all three possible conditions occurred in 5.7% of patients, and 52.1% of patients underwent at least one diagnostic test for a potentially reversible cause of anemia. Among tested patients, criteria for iron deficiency, vitamin B12 deficiency, and/or hypothyroidism, were met in 29.7%, 3.2%, and 18.6% of patients, respectively. At least one potentially reversible cause of anemia was identified in 25.8% of tested patients, and diagnostic criteria for all three possible conditions were met in only 2 (0.02%) patients.

Predictors of Incident Anemia

Older age, non-white/European race, Hispanic ethnicity, and a prior history of smoking were significantly associated with incident anemia (**Table 2**, **Supplementary Table 1**). Medical comorbidities significantly associated with incident anemia included a prior history of acute myocardial infarction, valvular heart disease, peripheral artery disease, diagnosed depression, inflammatory arthritis, osteoarthritis, diabetes mellitus, chronic lung disease, chronic liver disease, systemic cancer, and hospitalization for a bleeding event. Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 (vs. 60-89 ml/min/1.73m^2), dipstick proteinuria ≥1+ (vs. group

negative/trace), and systolic blood pressure 130-139 mmHg (vs. ≤120 mmHg) were also significantly associated with anemia.

Incident Anemia and Outcomes

During a median (interquartile range) follow-up of 2.9 (1.2, 5.6) years, the unadjusted death rate (per 100 person-years) for HF patients with and without incident anemia was 18.2 (95%CI:17.9-18.6) and 17.5 (95%CI:17.2-17.9), respectively. During follow-up, the crude all-cause and HF-specific hospitalization rates (per 100 person-years) for HF patients with incident anemia were 64.1 (95%CI: 63.1-65.0) and 13.7 (95%CI: 13.4-14.0), respectively, while the unadjusted all-cause and HF-specific hospitalization rates (per 100 person-years), for HF patients without incident anemia were 37.4 (95%CI: 36.7-38.1) and 9.3 (95%CI: 9.0-9.6), respectively.

After adjusting for potential confounders, incident anemia was associated with an increased risk of all-cause death (adjusted hazard ratio [HR] 2.14, 95% CI:2.07-2.22), all-cause hospitalization (HR 1.77, 95% CI: 1.72-1.83), and HF hospitalization (HR 1.80, 95% CI: 1.72-1.88) (**Figure 2**, **Supplementary Table 2**).

Among potentially treatable causes of anemia, patients with incident anemia meeting our criteria for iron deficiency experienced similar survival and HF-specific hospitalizations but were at increased risk for all-cause hospitalization (HR 2.04, 95% CI 1.85-2.26) compared with patients with incident anemia tested for but not found to be iron deficient (HR 1.65, 95% CI 1.55-1.76). In contrast, patients with incident anemia and vitamin B12 deficiency were at increased risk of death (HR 1.50, 95% CI 1.16-1.95) compared with patients without incident anemia but had a somewhat better prognosis compared to patients tested for but not found to be vitamin B12 deficient (HR 2.10, 95% CI 1.98-2.22). A similar trend was observed for all-cause

or HF hospitalization among patients with incident anemia diagnosed with vitamin B12 deficiency. Finally, patients with incident anemia diagnosed with hypothyroidism were at increased risk of death (HR 2.32 95% CI 2.15-2.50 vs. HR 1.99, 95% CI 1.90-2.08), all-cause hospitalization (HR 1.82, 95% CI 1.66-2.01 vs. HR 1.67, 95% CI 1.60-1.75), and HF-specific hospitalization (HR 2.17, 95% CI 1.95-2.41 vs. HR 1.77, 95% CI 1.67-1.87) compared with patients tested for but not found to be hypothyroid.

DISCUSSION

Among older adults with HF who had a baseline Hgb within the normal range, the incidence of subsequent anemia approached 60% over a median follow-up of approximately three years. Patients with incident anemia were more likely to be men, had a higher prevalence of cardiac and non-cardiac comorbidities, and were more likely to be taking NSAIDs. Although uncommon overall, these patients were also more likely to have previously received intravenous/injectable therapies for anemia (i.e., erythropoietin, iron, and vitamin B12). Yet, only slightly more than half of patients were evaluated for potentially reversible causes of anemia (e.g. iron deficiency, vitamin B12 deficiency, and hypothyroidism) within 90 days. However, when documented testing occurred, close to 20-30% of patients were found to be iron deficient and/or hypothyroid. Finally, although HF universally portends a poor prognosis, incident anemia was associated with an increased risk of morbidity and mortality regardless of the underlying etiology of anemia and independent of traditional risk factors.

The prevalence of anemia is significantly higher in older adults with HF than in the general population but estimates have varied widely depending on duration and severity of HF (i.e., recent-onset vs. advanced), current clinical status (i.e., stable vs. decompensated), and care setting (i.e., inpatient vs. outpatient).[1, 2, 16] However, to our knowledge, this is the first study to comprehensively and longitudinally describe the rate, etiology, and outcomes of incident anemia in ambulatory patients with HF across the spectrum of EF. Despite excluding patients with prevalent anemia at baseline, on average, clinicians would only need to follow 100 patients for a single year to diagnose incident anemia in 25-30 patients. Furthermore, we observed that the incidence of anemia is higher based on targeted demographic features, clinical characteristics, and medication exposure. The high incidence of detected anemia over a relatively brief

timeframe has important surveillance implications. Physicians treating HF patients should consider screening for anemia regularly in accordance with the most recent guideline recommendations.[17, 18]

Although incident anemia was common, relatively few patients underwent a documented systematic evaluation for targeted possible contributors to anemia. Thyroid function tests were checked in ~40% of patients but the exact reasoning for ordering these labs is unknown, and it is likely that the majority of thyroid function tests were obtained as part of a general medical evaluation or ongoing care of known thyroid disease unrelated to anemia among this older cohort. In contrast, iron indices and vitamin B12 levels were only checked in ~15-20% of patients. In aggregate, these data suggest that upwards of 50% of patients developing incident anemia may not undergo a purposeful short-term diagnostic work-up for selected possible contributors to anemia. Hence, given the diagnostic yield for iron studies and thyroid function tests was approximately 20-30%, it may be feasible and cost-efficient to routinely evaluate and treat these potentially reversible causes of anemia, although additional evidence is needed to demonstrate that this is associated with improved overall outcomes in HF.

Finally, we found that incident anemia was associated with higher mortality and hospitalization (HF-specific and all-cause) independent of traditional risk factors. This is in contrast to prevalent anemia in patients with HF where the relationship with clinical outcomes has been variable after adjusting for volume status and degree of kidney dysfunction.[19-23] This discrepancy can likely be explained by the fact that anemia in HF patients can broadly be divided into two categories: an absolute reduction in red blood cell content vs. a relative dilution with preserved red blood cell content and excess intravascular volume. The present analysis likely selected preferentially for the former (i.e., *true anemia*) and not the later (i.e., *pseudoanemia*) by

restricting the study population to stable, ambulatory patients with HF without baseline anemia who subsequently developed incident anemia. Thus, these patients likely suffered from true anemia with a corresponding reduction in red blood cell content and diminished oxygen carrying capacity. However, it remains to be seen if anemia is merely a surrogate marker of a poor prognosis or a potential mediator of clinical outcomes. Several early phase clinical trials have shown that HFrEF patients with iron deficiency receiving IV ferric carboxymaltose experienced an early and sustained improvement in signs and symptoms, quality of life, and exercise capacity.[24-26] In response, the guidelines for the management of HF were recently updated and recommend that IV iron supplementation be considered to improve quality of life and functional status in symptomatic HFrEF patients with iron deficiency (Class of Recommendation IIb, Level of Evidence B-R).[17, 18] However, prior studies have been underpowered to assess objective clinical endpoints and there are several ongoing pivotal trials of IV iron supplementation in HF patients with iron deficiency irrespective of anemia status (ClinicalTrials.gov **NCT03036462**, **NCT03036462**, and **NCT03037931**).

Our study did have several limitations. First, more than 20% of patients were excluded because of a missing Hgb measurement at baseline, which may affect the generalizability of the results. However, the participating health care delivery systems collectively provide care to a large, ethnically and socioeconomically diverse population across a wide range of practice settings and broad geographic areas, which bolsters the study's generalizability. Second, not all patients were systematically evaluated for potentially reversible causes of anemia, and the diagnostic yield may vary if all patients were tested in real-world practice. Third, laboratory values were processed locally and were not validated at a central laboratory, although all testing was performed in a Clinical Laboratory Improvement Amendments-approved facility. Fourth,

cutoffs used to define iron deficiency, especially in HF, remain controversial, with some data suggesting a worse prognosis in HF patients with a ferritin as high as 100-300 ng/mL in conjunction with a TSAT <20%.[27-32] Fifth, we are not able to further characterize the potential work-up for occult gastrointestinal bleeding (i.e., a referral for evaluation by a gastroenterologist, flexible sigmoidoscopy/colonoscopy, and/or fecal occult blood testing) as these data elements largely exist as unstructured free text in the electronic health record and it is not feasible to reliably and accurately extract this information for the nearly 40,000 patients included in the final analytical cohort. Finally, as with all observational studies, we cannot fully exclude unmeasured or residual confounding.

In conclusion, among older ambulatory HF patients without baseline anemia, the annual incidence of documented anemia was approximately 25-30%. High-risk features for the development of incident anemia include older age, male gender, a high burden of comorbid conditions, and receipt of antiplatelet therapy and/or NSAID use. Despite the high short-term rate of incident anemia and the promising diagnostic yield of laboratory studies, only a small proportion of patients underwent a comprehensive work-up for anemia. Finally, incident anemia was independently associated with excess morbidity and mortality in HF across the spectrum of EF. Future research is necessary to clarify the effectiveness of routine evaluation and treatment of potentially reversible causes of anemia in older outpatients with HF.

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CONFLICT OF INTEREST

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Figure Legends

Figure 1. A consort diagram showing the derivation of the final analytic cohort of older adults with heart failure.

Figure 2. Multivariable association of incident anemia and anemia type with (A) all-cause mortality, (B) all-cause hospitalization, and (C) heart failure-specific hospitalization based on status and underlying etiology of incident anemia. The reference group was no incident anemia in all models.

Table

Table 1. Baseline characteristics of older adults with heart failure, overall and by incident anemia status.

Patient Characteristics	Overall N = 38,826	Incident Anemia N = 22,163	No Anemia N = 16,663	d-value[1]
Mean (SD) age, yr	78.6 (7.6)	78.1 (7.2)	79.2 (8.0)	0.15
Women, n (%)	20,204 (52.0)	10,826 (48.8)	9378 (56.3)	0.15
Race, n (%)				
White / European	31,179 (80.3)	17,638 (79.6)	13,541 (81.3)	0.01
Black / African American	2748 (7.1)	1755 (7.9)	993 (6.0)	
Asian / Pacific Islander	2231 (5.7)	1355 (6.1)	876 (5.3)	
Native American	149 (0.4)	100 (0.5)	49 (0.3)	
Other/ Unknown	2519 (6.5)	1315 (5.9)	1204 (7.2)	
Hispanic, n (%)	4065 (10.5)	2515 (11.3)	1550 (9.3)	0.07
Current or former smoker, n (%)	15,597 (40.2)	8624 (38.9)	6973 (41.8)	0.07
Left ventricular ejection fraction categories, n (%)				0.11
Preserved EF (≥ 50% or Normal)	14,491 (37.3)	8667 (39.1)	5824 (35.0)	
Borderline EF (41% to <50% or Mild)	3596 (9.3)	2143 (9.7)	1453 (8.7)	
Reduced EF (≤40% or Moderate to Severe)	8363 (21.5)	4713 (21.3)	3650 (21.9)	
No EF Available	12,376 (31.9)	6640 (30.0)	5736 (34.4)	
Medical history, n (%)				
Acute myocardial Infarction	4561 (11.7)	2639 (11.9)	1922 (11.5)	0.02
Unstable angina	2364 (6.1)	1474 (6.7)	890 (5.3)	0.14
Coronary artery bypass surgery	1943 (5.0)	1320 (6.0)	623 (3.7)	0.30
Percutaneous coronary intervention	3595 (9.3)	2186 (9.9)	1409 (8.5)	0.10
Ischemic stroke or transient ischemic attack	2879 (7.4)	1520 (6.9)	1359 (8.2)	0.11
Atrial fibrillation or flutter	16,198 (41.7)	8949 (40.4)	7249 (43.5)	0.08
Ventricular tachycardia or fibrillation	1178 (3.0)	676 (3.1)	502 (3.0)	0.01
Mitral and/or aortic valvular disease	9671 (24.9)	5833 (26.3)	3838 (23.0)	0.11
Peripheral artery disease	2494 (6.4)	1562 (7.0)	932 (5.6)	0.15
Dyslipidemia	31,196 (80.3)	18,289 (82.5)	12,907 (77.5)	0.19
Hypertension	32,833 (84.6)	19,103 (86.2)	13,730 (82.4)	0.17
Diabetes mellitus	13,593 (35.0)	8554 (38.6)	5039 (30.2)	0.23
Hospitalized bleeding	2049 (5.3)	1230 (5.5)	819 (4.9)	0.08
Hyperthyroidism	1950 (5.0)	1128 (5.1)	822 (4.9)	0.02
Hypothyroidism	8579 (22.1)	4790 (21.6)	3789 (22.7)	0.04
Dementia	2262 (5.8)	965 (4.4)	1297 (7.8)	0.37
Depression	6618 (17.0)	3697 (16.7)	2921 (17.5)	0.04
Infectious arthritis	107 (0.3)	70 (0.3)	37 (0.2)	0.21
Inflammatory arthritis	1578 (4.1)	1028 (4.6)	550 (3.3)	0.21
Osteoarthritis	12,514 (32.2)	7339 (33.1)	5175 (31.1)	0.06

Patient Characteristics	Overall N = 38,826	Incident Anemia N = 22,163	No Anemia N = 16,663	d-value[1]
Arthritis unspecified	3366 (8.7)	1969 (8.9)	1397 (8.4)	0.04
Chronic lung disease	15,682 (40.4)	9022 (40.7)	6660 (40.0)	0.02
Chronic liver disease	944 (2.4)	560 (2.5)	384 (2.3)	0.06
Systemic cancer	3871 (10.0)	2283 (10.3)	1588 (9.5)	0.05
Laboratory values				
Estimated glomerular filtration rate, ml/min/1.73 m^2, n (%)				0.10
90-150	1339 (3.4)	721 (3.3)	618 (3.7)	
60-89	15,590 (40.2)	8577 (38.7)	7013 (42.1)	
45-59	11,174 (28.8)	6342 (28.6)	4832 (29.0)	
30-44	7559 (19.5)	4535 (20.5)	3024 (18.1)	
15-29	2375 (6.1)	1479 (6.7)	896 (5.4)	
<15	180 (0.5)	120 (0.5)	60 (0.4)	
Dialysis	423 (1.1)	280 (1.3)	143 (0.9)	
Missing	186 (0.5)	109 (0.5)	77 (0.5)	
Dipstick Proteinuria, n (%)				0.05
Negative or trace	23,567 (60.7)	13,565 (61.2)	10,002 (60.0)	
1+	3309 (8.5)	1952 (8.8)	1357 (8.1)	
2+	1866 (4.8)	1144 (5.2)	722 (4.3)	
3+	817 (2.1)	538 (2.4)	279 (1.7)	
Missing	9267 (23.9)	4964 (22.4)	4303 (25.8)	
Baseline hemoglobin, g/dL				
Mean (SD)	13.9 (1.2)	13.7 (1.1)	14.2 (1.3)	0.42
Systolic blood pressure, mmHg				
Mean (SD)	128.0 (20.2)	129.0 (20.4)	127.0 (20.0)	0.10
Diastolic blood pressure, mmHg				
Mean (SD)	70.1 (11.8)	69.4 (11.8)	70.8 (11.8)	0.12
HDL cholesterol, g/dL				
Mean (SD)	49.7 (15.1)	49.3 (15.1)	50.2 (15.0)	0.06
LDL cholesterol, g/dL				
Mean (SD)	96.3 (32.4)	95.2 (31.9)	97.8 (33.1)	0.08
Baseline medication use, n (%)				
ACE inhibitor/angiotensin II receptor blocker	24,747 (63.7)	14,663 (66.2)	10,084 (60.5)	0.15
Aldosterone receptor antagonist	2639 (6.8)	1538 (6.9)	1101 (6.6)	0.03
Beta-blocker	25,787 (66.4)	15,005 (67.7)	10,782 (64.7)	0.08
Calcium channel blocker	12,394 (31.9)	7378 (33.3)	5016 (30.1)	0.09
Digoxin	7181 (18.5)	4106 (18.5)	3075 (18.5)	0.00
Diuretic (loop)	19,225 (49.5)	11,386 (51.4)	7839 (47.0)	0.11
Diuretic (thiazide)	9366 (24.1)	5374 (24.2)	3992 (24.0)	0.01
Nitrates	8442 (21.7)	5119 (23.1)	3323 (19.9)	0.11
Statins	23,300 (60.0)	13,984 (63.1)	9316 (55.9)	0.18
Other lipid lowering drugs	1957 (5.0)	1291 (5.8)	666 (4.0)	0.24
Antiplatelet	3962 (10.2)	2376 (10.7)	1586 (9.5)	0.08

Patient Characteristics	Overall N = 38,826	Incident Anemia N = 22,163	No Anemia N = 16,663	d-value[1]
Anticoagulant	11,473 (29.5)	6676 (30.1)	4797 (28.8)	0.04
Diabetes therapy	9737 (25.1)	6285 (28.4)	3452 (20.7)	0.25
NSAIDs	4336 (11.2)	2653 (12.0)	1683 (10.1)	0.12
Erythropoietin	432 (1.1)	342 (1.5)	90 (0.5)	0.64
Iron	318 (0.8)	211 (1.0)	107 (0.6)	0.24
Vitamin B12 injection	241 (0.6)	153 (0.7)	88 (0.5)	0.16

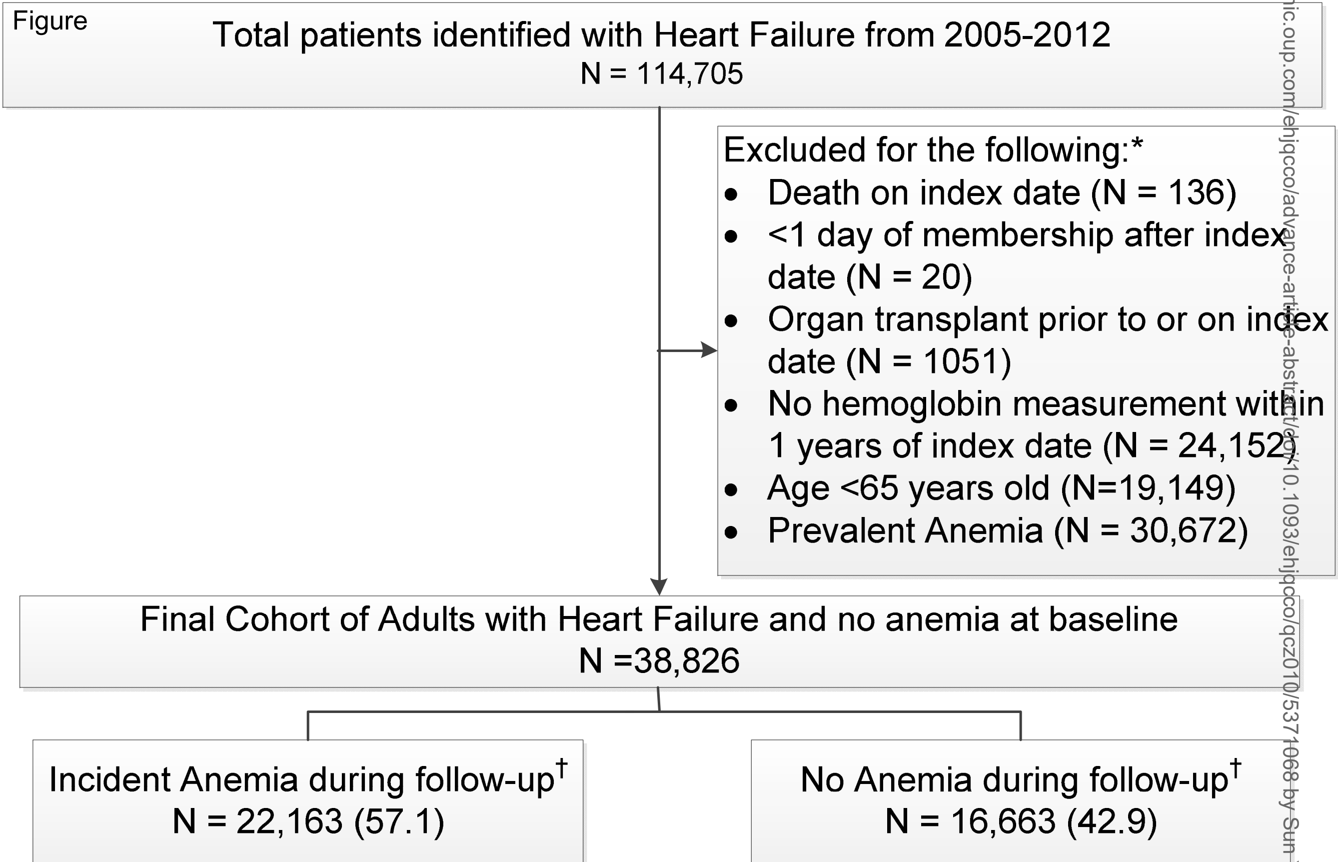
[1]d-value ≥0.10 was considered a meaningful difference

Table 2. Crude rate and multivariable predictors of incident anemia in older adults with heart failure.

Characteristics	Incident Anemia (per 100 person-years)	Adjusted Hazard Ratio (95% CI)
Ejection fraction		
Preserved	29.16 (28.55-29.78)	**1.04 (1.00-1.08)**
Borderline	26.52 (25.42-27.67)	1.01 (0.96-1.06)
Reduced	26.60 (25.85-27.37)	Reference
Unknown	23.33 (22.77-23.90)	**0.89 (0.86-0.93)**
Index age		
65-74 years		Reference
75-84 years		**1.19 (1.15-1.23)**
≥85 years		**1.32 (1.26-1.38)**
Women		**0.79 (0.77-0.82)**
Race		
White / European		Reference
African American		**1.2 (1.14-1.26)**
Asian / Pacific Islander		1.05 (0.99-1.11)
Native American		**1.22 (1.02-1.47)**
Other / Unknown		**1.11 (1.05-1.19)**
Hispanic ethnicity		**1.06 (1.02-1.11)**
Smoking status		
Never		Reference
Current or former smoker		**1.08 (1.05-1.11)**
Medical history, n (%)		
Acute myocardial infarction		**1.10 (1.05-1.15)**
		1.01 (0.95-1.07)
Coronary artery bypass surgery		
Mitral and/or aortic valvular disease		**1.17 (1.14-1.21)**
Peripheral artery disease		**1.22 (1.15-1.29)**
Dyslipidemia		**0.94 (0.90-0.98)**
Hypertension		**1.08 (1.04-1.13)**
Diabetes mellitus		**1.12 (1.07-1.17)**
Hospitalized bleeding		**1.19 (1.12-1.26)**
Diagnosed depression		**1.05 (1.01-1.09)**
Inflammatory arthritis		**1.39 (1.31-1.49)**
Osteoarthritis		**1.08 (1.05-1.12)**
Chronic lung disease		**1.07 (1.04-1.10)**
Chronic liver disease		**1.18 (1.08-1.29)**
Systemic cancer		**1.21 (1.16-1.27)**
Laboratory results		
Estimated glomerular filtration rate, mL/min/1.73m²		

Characteristics	Incident Anemia (per 100 person-years)	Adjusted Hazard Ratio (95% CI)
90-150		1.03 (0.95-1.11)
60-89 (reference)		Reference
45-59		**1.07 (1.04-1.11)**
30-44		**1.34 (1.29-1.40)**
15-29		**1.94 (1.82-2.06)**
≤15		**2.88 (2.36-3.52)**
Dialysis		**1.91 (1.69-2.15)**
Missing		**1.71 (1.41-2.07)**
Dipstick proteinuria		
Negative/trace/missing (reference)		Reference
1+		**1.08 (1.03-1.13)**
2+		**1.19 (1.12-1.27)**
3+		**1.27 (1.16-1.39)**
Missing		0.99 (0.96-1.03)
Systolic blood pressure, mmHg		
≥180		0.98 (0.94-1.03)
160-179		0.99 (0.95-1.04)
140-159		1.01 (0.97-1.06)
130-139		**1.11 (1.03-1.19)**
121-129		1.10 (0.98-1.25)
≤120 (ref)		Reference
Missing		0.97 (0.92-1.01)

Figure



*exclusions are not mutually exclusive

†based on WHO criteria for anemia (Hemoglobin threshold: Women <12.0 g/dL; Men <13.0 g/dL)

Figure