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Treating Anemia in Older Adults With Heart Failure With a Preserved Ejection Fraction With Epoetin Alfa

Single-blind Randomized Clinical Trial of Safety and Efficacy

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Background—Anemia is a common comorbidity in older adults with heart failure and a preserved ejection fraction and is associated with worse outcomes. We hypothesized that treating anemia with subcutaneous epoetin alfa would be associated with reverse ventricular remodeling and improved exercise capacity and health status compared with placebo.

Methods and Results—Prospective, randomized, single-blind, 24-week study with blinded end point assessment among anemic (average hemoglobin of 10.4±1 g/dL) older adult patients (n=56; 77±11 years; 68% women) with heart failure and a preserved ejection fraction (ejection fraction=63±15%; B-type natriuretic peptide=431±366 pg/mL) was conducted. Treatment with epoetin alfa resulted in significant increases in hemoglobin (P<0.0001). Changes in end-diastolic volume (−6±14 versus −4±16 mL; P=0.67) at 6 months did not differ between epoetin alfa and placebo, but declines in stroke volume (−5±8 versus 2±10 mL; P=0.09) without significant changes in left ventricular mass were observed. Changes in 6-minute walk distance (16±11 versus 5±12 m; P=0.52) did not differ. Although quality of life improved by the Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure Questionnaire in both cohorts, there were no significant differences between groups.

Conclusions—Administration of epoetin alfa to older adult patients with heart failure and a preserved ejection fraction compared with placebo did not change left ventricular end-diastolic volume and left ventricular mass nor did it improve submaximal exercise capacity or quality of life.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00286182.

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Key Words: aging ■ anemia ■ heart failure

Half of heart failure (HF) patients residing in the community have a preserved left ventricular ejection fraction (HFPEF).[1] These patients are often older adult women with hypertension[2] and several extra cardiac comorbidities, including diabetes mellitus, obesity, anemia, and chronic kidney disease, among others.[3] These comorbid conditions have been associated with altered pressure volume relationships and pump function in HFPEF[4] and confer an adverse prognosis in patients with HFPEF.[1,5,6] Because large-scale clinical trials for this population[7–9] have not demonstrated effectiveness of any specific therapy in HFPEF and in light of the high prevalence of important comorbidities and their strong relationship to adverse outcomes, identification and aggressive treatment of these conditions have been proposed as an effective strategy for HFPEF, while awaiting for new HFPEF-specific therapies to emerge.[10]

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Among the comorbidities prevalent in subjects with HFPEF, anemia has been shown to be highly prevalent, strongly associated with morbidity and mortality, often because of underlying chronic renal disease and among the most modifiable pharmacologically. Accordingly, the purpose of the current study was to evaluate whether treating anemia with subcutaneous epoetin alfa (ESA) in patients with HFPEF would be associated with reverse ventricular remodeling and changes in noninvasively determined pressure volume relationships, significant improvements in exercise capacity, and improved health status, compared with placebo.

Methods

Study Design

This was a single-center, prospective randomized (with 1:1 allocation), single-blind, 24-week study among community-dwelling older adult patients with anemia and HFPEF who received either ESA or placebo. To limit chance imbalances in a trial of this size and because of the differences in hemoglobin levels between sexes and the strong association of renal function with hemoglobin levels, randomization was stratified by sex and baseline renal function (dichotomized by cut point of an estimated creatinine clearance of 40 mL/min). Study subjects were blinded to treatment assignment, which was maintained throughout the study, by providing weekly injections of ESA or placebo in unmarked syringes. End points were performed by study personnel blinded to the result of randomization.

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Study Subjects

The diagnosis of HF was based on the National Health and Nutrition Examination Survey - Congestive Heart Failure criteria with a score >3,[11] and study participants were considered to have a preserved EF if 3-dimensional echocardiographically determined EF was >40%. Anemia was defined as hemoglobin <12 g/dL.[12] Patients were excluded from the study if they had uncontrolled hypertension (systolic blood pressure >160 mm Hg and diastolic blood pressure >90 mm Hg), resting heart rate >120 beats per minute, baseline 6-minute walk >450 m, valvular heart disease greater than mild stenotic or greater than moderate regurgitant lesions by transthoracic echocardiography, infiltrative cardiac disease, such as hemochromatosis and amyloidosis, hypertrophic cardiomyopathy, chronic pulmonary disease (forced expiratory volume in one second <60% predicted), renal failure (glomerular filtration rate <15 mL/min), hemoglobin <9 g/dL, exercise limited by angina, claudication or neurological diseases, severe liver dysfunction, cardiac surgery >3 months prior, known iron deficiency anemia from chronic blood loss, significant alcohol or illicit drug use, known hypercoagulable state, or an active hematologic disease. Patients were also excluded if they had a history of deep venous thrombosis or pulmonary embolus within 12 months before study entry, had a history of cerebrovascular accident or transient ischemic attack within 6 months or an acute coronary syndrome within 6 months of study entry, had an allergy or sensitivity to human serum albumin, or had a known hypersensitivity to mammalian cell–derived products. The study was approved by the Institutional Review Board of the Columbia University Medical Center. Informed consent was obtained from all subjects.

Intervention

Erythropoietin alfa (Epoetin alpha, Ortho Biotec, Inc) was administered weekly by subcutaneous injection using a prespecified dosing algorithm[13] that made weekly adjustments based on the rate of rise of the hemoglobin during a 1-week period, as well as the absolute hemoglobin value. Subjects were monitored every week, and dose adjustments were made to avoid rapid increases in hemoglobin (>0.4 g/dL) in any given weekly interval. All subjects randomized to active treatment initially received 7500 U of ESA given weekly by subcutaneous injection, whereas placebo subjects received the same injection volume of normal saline. All subjects were given oral iron (ferrous gluconate 325 mg orally BID). Placebo injection volumes were changed based on the study algorithm during the study to give the appearance that dose adjustments were occurring in the placebo group. Hemoglobin was measured weekly on a venous sample obtained in the patient's home by a point of care system (Hemocue Inc, Sweden), which was shown to be highly correlated with a hospital laboratory.[14]

Weekly Home Visits

Blood pressure by an automated cuff sphygmomanometer (Omron, Kyoko City, Japan) and weight by a digital scale (SECA, Hamburg, Deuschland) were measured weekly in the subject's home by a trained research personnel (S.T.). During home visits, subjects also had brief review of symptoms, targeted physical examinations to evaluate weight, blood pressure, and volume status, along with careful review of all medications, including type, dose, and frequency. Blood was obtained via venipuncture to assess weekly hemoglobin values that were used to determine dose of study drug.

Two- and 3-Dimensional Echocardiography

Standard 2-dimensional transthoracic echocardiography was performed on each subject. End-diastolic measurements of left ventricular (LV) internal dimension, interventricular septal thickness, and LV posterior wall thickness were acquired according to the standards of the American Society of Echocardiography.[15] Doppler indices of the mitral inflow pattern, including peak E-wave velocity, peak A-wave velocity, and isovolumetric relaxation time, as well as lateral mitral annual velocities (e′), were recorded for 3 beats and averaged. LV filling pressures were estimated by the following formula: end-diastolic pressure=11.96+0.596·E/e′.[16]

The equipment and procedures of freehand 3-dimensional transthoracic echocardiography have been previously described in detail.[17,18] Three-dimensional transthoracic echocardiography was performed using a conventional real-time echocardiograph, 3-dimensional acoustic spatial locater, personal computer, and custom software. The data derived include LV chamber end-diastolic volume (EDV), myocardial volume, stroke volume, and the EF (EF=stroke volume/EDV). Myocardial volume was multiplied by 1.05 g/dL to determine ventricular mass. Echocardiograms were performed by a study personnel blinded (S.H.) to clinical information.

Functional Assessment

A 6-minute walk test was performed in all subjects, and a cardiopulmonary exercise test was performed in subjects able to exercise. Testing was performed at baseline and after 3 and 6 months of treatment. The total distance walked was recorded. Patients performed an upright bicycle exercise test, by study personnel blinded to treatment assignment, with the workload increased every 3 minutes by 25 W to a patient-limited maximum level after 3 minutes of rest. Expired gas analysis was performed continuously with a Metabolic Cart (Medical Graphics). Peak Vo_2 was defined as the highest value of Vo_2 achieved in the final 30 seconds of exercise.

Quality of Life, Depression, and Pain

The Kansas City Cardiomyopathy Questionnaire (KCCQ)[19] and the Minnesota Living with Heart Failure Questionnaire[20] were used as 2 valid, reliable, self-administered disease-specific assessments of quality of life (QOL) in patients with HF. Finally, we used the 30-item geriatric depression scale[21] and the Western Ontario and McMaster Universities Osteoarthritis Index[22] to assess depressive symptoms and pain, respectively. All questionnaires were administered at baseline and after 3 and 6 months of follow-up.

Blood Volume Analysis

Blood volume was determined at baseline and after 6 months of therapy by intravenous administration of iodine^{131}-labeled albumin (Volumex, Daxor Corp, New York, NY) as previously described.[23] Plasma volume was determined as the volume of distribution of the radiolabeled albumin obtained by semilogarithmic extrapolation of values measured from at least 3 samples drawn 12 minutes after injection at 6-minute intervals. Plasma radioactivity of each sample was measured in a semiautomated counter (BVA-100 Blood Volume Analyzer; Daxor Corp). Blood volume and red blood cell volumes were calculated from the plasma volume measurement and then compared with normal values for age, sex, height, and weight based on the subject's ideal weight to determine the percent deviation from normal.[24]

Statistical Analyses

SAS for Windows (version 9.1.3, SAS Institute Inc, Cary, NC) was used for all analyses. Results are expressed as mean±SD unless otherwise noted. The primary end point was the change in LVEDV measured by 3-dimensional echocardiography. This was selected as the primary end point because: (1) anemia can result in a high-output state characterized by increases in LV volumes [25]; (2) previous data show that LV size was actually increased in subjects with HFPEF, and this was associated with several comorbid conditions, including anemia [3]; (3) pilot data had demonstrated efficacy of ESA with regard to this end point[26]; and (4) given the highly accurate and reproducible nature of measuring LV volumes with freehand 3-dimensional echocardiography, the sample size required to test the hypothesis was feasible to recruit in a single-center study. Secondary end points included New York Heart Association class, submaximal exercise capacity as assessed by 6-minute walk, maximal exercise capacity as assessed by cardiopulmonary exercise testing with cycle ergometry, QOL as assessed by the KCCQ and Minnesota Living with Heart Failure Questionnaire, and blood volume measurements.

The power calculation for this longitudinal study involving 3 time points (baseline, 3 months, and 6 months) was based on the method by Diggle et al.[27] According to this method, given an anticipated dropout rate of 15% and assuming a high correlation of serial EDV measured by freehand 3-dimensional echocardiography (r=0.98), 28 subjects per group would ensure at least 80% power to detect a reduction in EDV of 20 mL (≈20% decline) in subjects receiving ESA compared with placebo after 6 months of therapy at the usual 2-sided 5% level of significance.

Comparisons between subjects randomized to ESA and placebo regarding baseline demographic and clinical characteristics were evaluated by χ^2 test for dichotomous variables, by unpaired Student t test for continuous variables having a normal distribution, or by Kruskal-Wallis test for non-normally distributed continuous variables.

To evaluate the differences in primary end point of change in EDV over time, a longitudinal data analysis was performed using the generalized estimating equations.[28] A similar strategy was followed for the secondary end points as well. In addition, graphical displays were made for change in EDV, change in hemoglobin, New York Heart Association class, 6-minute walk distance, peak Vo_2, and KCCQ summary score.

For end points that were not specified as primary or secondary but rather were exploratory, P values for these tests were adjusted for multiple testing in the false discovery rate context.[29]

Results

Fifty-six subjects were randomized of the 2971 screened. The major reasons for exclusion were the presence of a reduced EF (n=1145), absence of anemia or too severe anemia (n=909), concomitant cognitive dysfunction making informed consent unobtainable (n=184), significant valve disease (n=113), age <55 years (n=92), and other exclusion criteria (Figure 1). Of those subjects eligible to participate (n=123), 47 declined enrollment, given the requirements of the trial study visits, and an additional 20 who signed consent did not meet criteria for inclusion on more formal evaluation, in large part because their hemoglobin did not meet study criteria.

The cohort studied (Table 1) were older adults (77±11 years, 43% aged >80 years), predominately women with multiple comorbid conditions (hypertension, obesity, coronary artery disease, osteoarthritis, and chronic renal disease) and depressive symptoms, as well as chronic pain, which are characteristic of patients with HFPEF.[3,10,30] Subjects had isolated systolic hypertension with a widened pulse pressure and were taking on average 3.2 antihypertensive medications. At baseline, subjects randomized to ESA compared with placebo were more often diabetic but were well matched regarding other demographic features, clinical symptoms and findings to define HFPEF, comorbid conditions, functional capacity, and QOL (Table 1). The overall EF was preserved (58±10%) in both cohorts, with 46 of the 56 subjects recruited having LVEF >50%. Of those with an LVEF <50%, 5 had EF between 46% and 50% and 5 had LVEF between 40% and 45%. Average tissue Doppler velocities were low (≈6–7 cm/s) and E/E′ ratio was increased compatible with elevated estimated filling pressures (estimated LV end-diastolic pressure of 23 mm Hg). Consistent with this phenotype, B-type natriuretic peptides were elevated in both cohorts and did not differ between them at baseline.

During the course of the trial, weekly hemoglobin rose in both the subjects assigned to ESA and placebo (Figure 2). Subjects assigned to ESA achieved on average increase in hemoglobin of +1.5 g/dL. However, subjects assigned to placebo also had a rise in hemoglobin, P<0.0001 for the difference. The blood volume analysis revealed that subjects randomized to ESA had improvement in their red cell deficit (P=0.07) and declines in plasma volume (P=0.04) compared with those who received placebo, whereas changes in total blood volume did not differ between the cohorts.

There was no significant difference in the primary end point of change in EDV (−6±14 versus −4±16 mL; P=0.67; 95% confidence interval, −43.67 to 39.67) from baseline to 6 months in those assigned to ESA or placebo (Figure 3). Declines in stroke volume (−5±8 versus +2±10 mL; P=0.09) tended to be greater in those receiving ESA without significant changes in LV mass (Table 2). Stroke work declined in subjects treated with ESA compared with placebo after 6 months (−454.5±675 versus +211±896 mL·mm Hg; P=0.09).

The effect of ESA on functional capacity was assessed by evaluating New York Heart Association class, 6-minute walk distance, and peak Vo_2. There were no significant changes in New York Heart Association class during the course of the trial (Figure 4, top left) nor did the changes in 6-minute walk distance at 6 months (+16±11 versus +5±12 m; P=0.52; 95% confidence interval, −20.91 to 42.91) differ between the cohorts (Figure 4, top right). Because of the frail nature of the study population, only a subset of patients (n=19) could perform cardiopulmonary exercise testing at baseline and at 6 months (n=10). The difference in peak oxygen consumption from baseline to 6-month follow-up was greater in subjects receiving ESA compared with placebo (+1.0±0.5 versus −1.2±0.6 mL/kg per minute; P<0.03; 95% confidence interval, 0.67 to 3.73; Figure 4, bottom left).

Measures of QOL improved as assessed by KCCQ (+15±5 and +16±4 points; P<0.01 compared with baseline in those randomized to ESA and placebo, respectively) and the Minnesota Living with Heart Failure Questionnaire (−11±4 and −10±5 points; P<0.05 compared with baseline in ESA and placebo, respectively) in both cohorts without significant differences between groups (Figure 4, bottom right). An analysis of the subgroup of subjects with hemoglobin <11 g/dL at entry did not differ from the overall results.

During the course of the trial, there were 14 subjects with serious adverse events randomized to placebo and 11 subjects with a serious adverse event in subjects randomized to ESA, mainly hospitalizations. Among subjects randomized to placebo, 1 subject died suddenly and 1 subject was newly diagnosed with cancer. There were no thrombotic episodes (eg, stroke, transient ischemic attack, myocardial infarction, pulmonary embolism, or venous thrombosis). The total number of hospitalizations did not differ in those randomized to ESA compared with placebo (19 versus 16) nor did the number of hospitalizations for HF (3 versus 2). Similarly, the number of individual subjects hospitalized during the course of the trial did not differ between those randomized to ESA compared with placebo (11 versus 12).

Discussion

The principal findings of this study are that among older adults with HFPEF, the administration of ESA compared with placebo using the current dosing algorithm was safe, with no differences in serious adverse events between those randomized to active therapy versus placebo but did not change LVEDV.

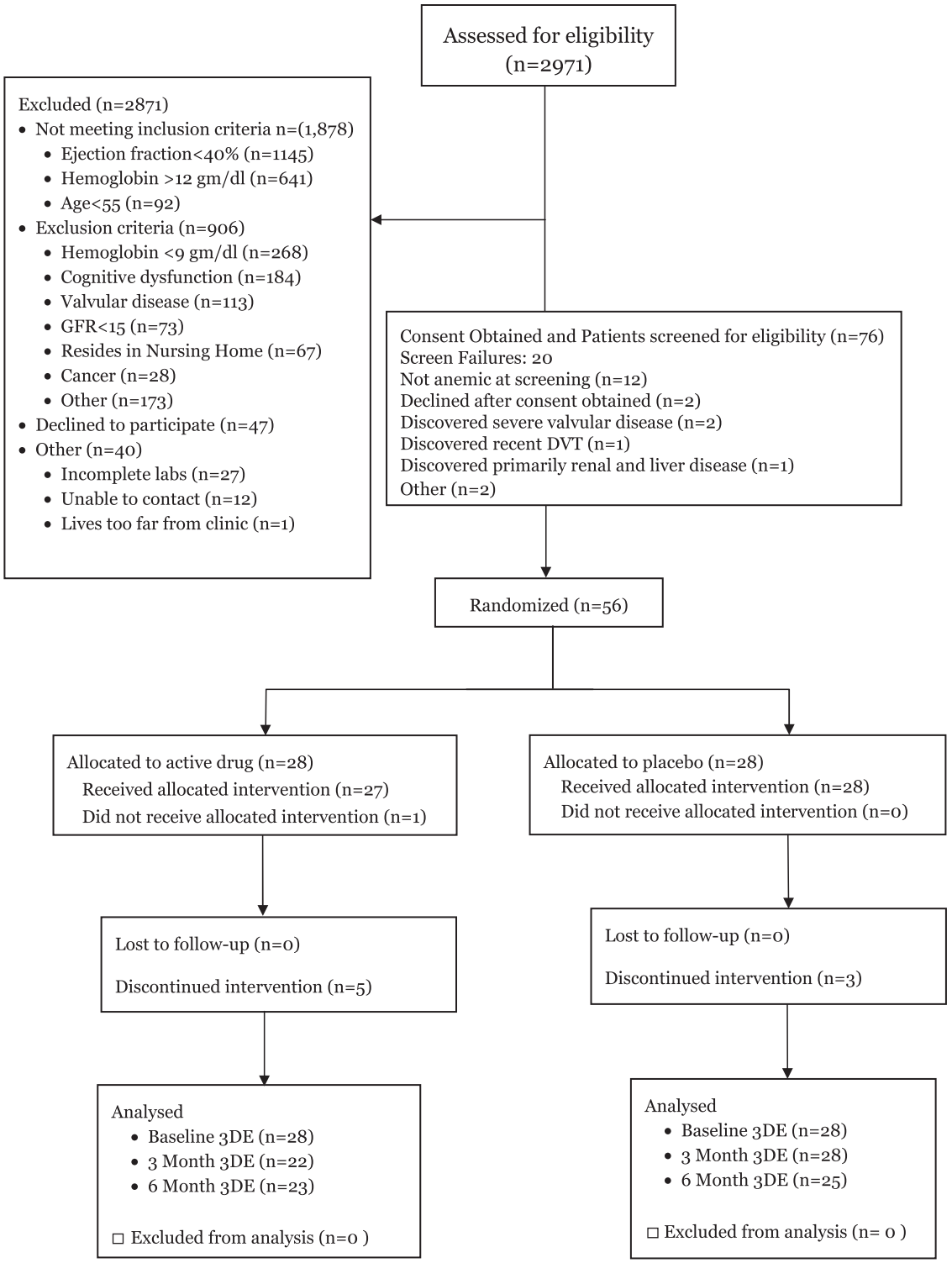

Figure 1. The CCORT chart delineating the flow of patients through the trial. 3DE indicates 3-dimensional echocardiography.

In addition, treatment with ESA did not alter LV mass nor did it improve submaximal exercise capacity as measured by 6-minute walk nor QOL compared with placebo but was associated with increases in peak oxygen consumption in a subset of patients able to exercise.

Previous randomized clinical trials of subjects with HF and a low EF have demonstrated that ESAs are associated with improved exercise tolerance, reduction in symptoms, and have benefits on clinical outcomes in anemic patients with HF, including hospitalizations.[31,32] These encouraging results, coupled with the absence of effective therapies for subjects with HF and a preserved EF and a hypothesis that comorbidities contribute significantly to the phenotype of HFPEF, resulted in the development of the current study. We are not

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics

Parameter	Placebo (n=28)	Epoetin Alfa (n=28)	*P* Value
Age, y	79 (11)	74 (9)	0.052
Sex, % women	64	71	0.33
Ethnicity, % Hispanic	67	54	0.27
Race			0.59
White, %	68	68	
Black, %	29	32	
Asian, %	4	0	
Body size			
Height, cm	156 (9)	158 (7)	0.27
Weight, kg	75 (15)	83 (19)	0.11
BSA, m^2	1.8 (0.2)	1.9 (0.2)	0.07
BMI, kg/m^2	31 (5)	34 (7)	0.10
Comorbid conditions, %			
Hypertension	100	100	1.0
Diabetes mellitus	50	82	0.01
Chronic obstructive pulmonary disease	11	18	0.45
Coronary artery disease	54	68	0.3
Obesity	54	68	0.3
Chronic kidney disease	50	68	0.2
Hemodynamics			
Systolic BP, mm Hg	140 (15)	146 (17)	0.14
Diastolic BP, mm Hg	65 (11)	67 (11)	0.55
Mean BP, mm Hg	90 (10)	93 (10)	0.37
Pulse pressure, mm Hg	75 (15)	79 (19)	0.41
Heart rate, bpm	74 (14)	67 (13)	0.35
Medications			
ACE inhibitors	14 (50%)	9 (32%)	0.17
ARBs	6 (21%)	11 (39%)	0.15
β-Blockers	22 (79%)	17 (61%)	0.15
Calcium channel blocker	13 (46%)	15 (54%)	0.6
Aldosterone antagonists	4 (14%)	5 (18%)	0.7
Loop diuretics	23 (82%)	19 (68%)	0.2
Thiazide diuretics	4 (14%)	8 (29%)	0.19
Laboratory assessment			
Hemoglobin, g/dL	10.4 (1)	10.6 (1.2)	0.46
Platelet count, ×10(9)/L	232 (64)	233 (68)	0.8
Albumin, g/dL	3.7 (0.5)	3.8 (0.4)	0.5
Potassium, mmol/L	4.5 (0.6)	4.6 (0.5)	0.3
Creatinine, mg/dL	1.51 (0.8)	1.58 (0.7)	0.7
Estimated GFR, mL/min per m^2	48 (18)	46 (19)	0.6
Blood urea nitrogen, mg/dL	37 (16)	33 (17)	0.2
B-type natriuretic peptide, pg/mL	373 (336)	488 (392)	0.2
Iron, μg/dL	60 (38)	61 (49)	0.7
Ferritin, ng/L	85 (73)	87 (79)	0.9
Transferrin saturation, %	20 (13)	20 (14)	0.8
Pain and depression			
Geriatric depression scale, 0–30	7±5	10±7	0.16
WOMAC scale, 0–96	23±16	26±16	0.57

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; bpm, beats per minute; BSA, body surface area; GFR, glomerular filtration rate; and WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

aware of any randomized, prospective clinical trials that have specifically evaluated the treatment of anemia with ESAs in this population. Anemia has been shown to be more prevalent among community-dwelling subjects with HF and a preserved EF than among those with a reduced EF[33] and associated with increased risk of in-hospital mortality,[34] early readmission,[35] and overall mortality,[36] irrespective of EF. Accordingly, we had hypothesized that treatment of anemia would have resulted in significant improvements in ventricular structure and function, functional capacity, and QOL.

However, the results of our study do not support this hypothesis. We were not able to demonstrate any significant effect of ESA on the primary end point of LVEDV in comparison with placebo. Previous studies of ESA have shown statistical reductions in LV mass and volumes and improvements in EF both in patients with chronic kidney disease not on dialysis[37–41] and in those on dialysis.[42,43] Similar results have been shown in patients with systolic HF.[44–46] However, not all trials have demonstrated a clinical effect.[47] Collectively, these trials suggest that the more severe the anemia, the greater the LV mass, the lower the EF, and worse the renal function, the greater the benefit from correction of anemia with ESA therapy. Most of these studies enrolled subjects with more severe anemia than the population studied in this trial, with more significant decrements in renal function and higher LV mass. Most previous investigations did not have imaging performed

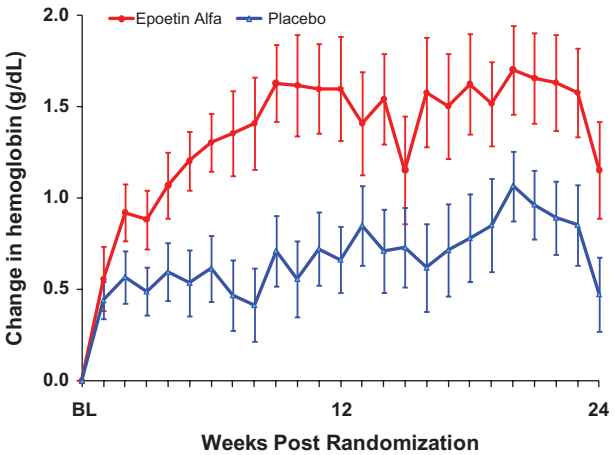

Figure 2. Weekly changes in hemoglobin from baseline during study period in subjects randomized to epoetin alfa (red circles) or placebo (blue triangles). Data represent mean±SE.

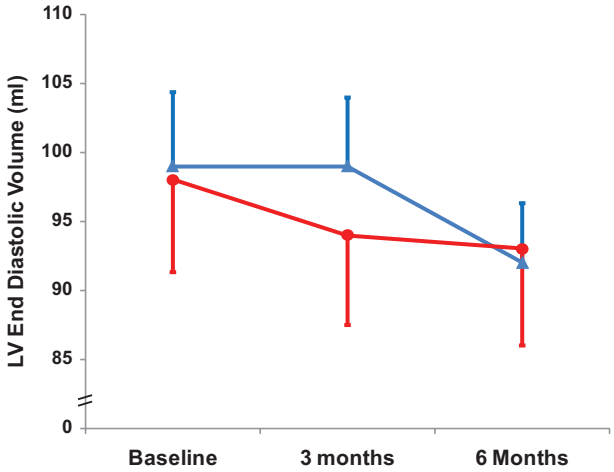

Figure 3. Left ventricular (LV) end-diastolic volume derived from 3-dimensional echocardiography, the primary end point of the study in subjects randomized to epoetin alfa (red circles) or placebo (blue triangles). Data represent mean±SE.

by investigators blinded to the patients' treatment assignment. Also unlike prior studies, both groups received oral iron supplementation, which was used to preserve the blind nature of the trial, but may have impacted on the outcomes. These differences may explain the discrepant results in this trial compared with previous investigations.

In the current trial, the improvements in QOL were large (11-point declines in the Minnesota Living with Heart Failure Questionnaire and 15-point improvements in the KCCQ) and comparable in magnitude to improvement seen in trials of biventricular pacing for systolic HF[48] and in a trial of treatment for acute decompensated HF.[49] However, there were no differences in the degree of improvement in subjects randomized to ESA or placebo. In addition, the declines observed in plasma volume in subject receiving ESAs were not attributable to differences in the use of diuretics between the 2 cohorts and were similar to that observed in another trial of ESA in HFLEF in which plasma volume was measured by a similar technique.[50] Although the effects of ESAs on plasma volume are poorly understood, they have been observed in dialysis patients as well.[51]

This trial recruited an older adult cohort (mean age, >75 years), predominately women (67%) with multiple comorbidities (including chronic pain and depression), which mimics what is seen in community-based studies of HF, but has, until now, not been replicated in a prospective clinical trial. We did not have formal measures of frailty (eg, handgrip strength, weight loss, physical activity scores), except for gait speed that was 0.67 m/s, well in the range to be considered frail. Given the frail nature of the subjects enrolled and the multiple comorbid conditions that resulted in significant functional limitations attributable to both their underlying HF and mobility limitations related to chronic arthritis, gait instability, and sarcopenia, a majority were unable to perform exercise tests and home visits were considered an essential aspect of study design to ensure adherence. Such novel trial designs may be useful in addressing the knowledge gap that occurs when older adults are not recruited into clinical trials.[30]

The dosing algorithm used in this trial[13] was designed to increase hemoglobin in a small, but safe manner with careful attention to the rate of rise[52] and target hemoglobin.[53] Both of these factors have been shown to be associated with adverse outcomes in subjects receiving erythropoietin-stimulating agents. Indeed, analysis of the Trial to Reduce Cardiovascular Events With Aranesp Therapy suggested that current dosing algorithms for erythropoietin-stimulating agents are of concern because of observed increased risk for cardiovascular outcomes among subjects who are hyporesponsive to therapy.[54] Although the targeted rise in hemoglobin was achieved (≈1.5 g/dL) with relatively low doses of ESA in this trial, the difference between active therapy and placebo averaged ≈0.8 g/dL for the duration of the trial. This was a result of an unanticipated rise in hemoglobin in the placebo arm. The latter may be attributable to several factors. First, the use of oral iron in both cohorts, used to preserve the blinded nature of the study, could have affected increases in hemoglobin. Second, our previous analysis suggests that alterations in diuretic dosages were an independent contributor to hemoglobin values.[13] Accordingly, although the algorithm used was safe and resulted in significant increases in hemoglobin that were associated with improvements in peak Vo_2 as predicted by the Fick equation, the study does not exclude that a different dosing algorithm could be associated with different outcomes. However, given the finding that unresponsiveness to ESAs is associated with an increased risk of adverse outcomes[54] coupled with the fact that subjects with HFPEF share many of the same features of subjects who are hyporesponsive to ESA (female sex, obese, mild anemia), higher doses are not without their risks. Because we did not use different definitions of anemia for men and women, using a hemoglobin ≤12 g/dL, while at the higher end of the abnormal range for women, was a single hemoglobin value that met the definition of anemia and could increase the generalizability of our findings. Such a definition has been routinely used in previous trials of erythropoietin-stimulating agents for systolic HF. Recruiting a population with more severe anemia may have enriched the population with subjects who could have had a favorable response to erythropoietin, but this is not known and our current analysis of this subgroup does not suggest a difference in outcomes evaluated. Accordingly, alternative trial designs for the population may be warranted. Such designs could use a run-in phase to assess for erythropoietin responsiveness before randomization and more carefully define the presence of a true red cell deficit in patients with volume overload states, such as renal dysfunction and HF,[23] in whom a hemodilutional basis of their anemia could be present. Finally, use of iron supplementation may be a more appropriate means of addressing anemia in this population.

The study is limited by its small sample size and the inability to perform several secondary end points (eg, cardiopulmonary exercise test) in a large percentage of subjects. In addition, as diabetes mellitus adversely affects LV remodeling, the higher prevalence of diabetes mellitus in the ESA versus control population could have blunted beneficial effects of epoetin on the primary end point. By including subjects with an EF <50%, some subjects admittedly had EF that were not preserved, but the final mean EF of the

Table 2. Changes in Parameters During Trial

	Placebo						Epoetin Alfa						Adjusted *P* Value
	n	Baseline	n	Change at 3 mo	n	Change at 6 mo	n	Baseline	n	Change at 3 mo	n	Change at 6 mo	Between-group Comparison*
Hemodynamics													
Systolic BP, mm Hg	28	140 (15)	27	−4.8 (25)	22	−5.86 (22)	28	146 (17)	22	−0.59 (22)	22	−2 (27)	0.81
Diastolic BP, mm Hg	28	65 (11)	27	−3 (13)	22	−0.2 (9)	28	67 (11)	22	−2 (12)	22	2 (11)	0.80
Laboratory													
Hemoglobin, mg/dL	28	10.4 (0.9)	26	+0.7 (1.0)	22	0.5 (1.0)	28	10.6 (1.1)	22	1.7 (1.4)†	21	1.2 (1.2)†	0.03
Creatinine, mg/dL	28	1.5 (0.8)	27	0.03 (0.4)	24	−0.03 (0.4)	28	1.6 (0.7)	22	0.1 (0.3)	22	0.1 (0.4)	0.61
BUN, mg/dL	28	37 (16)	27	−1 (15)	24	−1 (17)	28	33 (17)	22	3 (16)	22	3 (17)	0.66
eGFR, mL/min	28	48 (18)	27	0.4 (18)	24	1.0 (13)	28	46 (19)	22	−3 (9)	22	−2 (9)	0.83
BNP, pg/mL	28	373 (336)	27	−60 (166)	24	−67 (256)	28	488 (392)	22	26 (273)	20	−13 (348)	0.81
Quality of life													
KCCQ	28	62 (22)	27	13 (16)†	24	16 (19)†	27	58 (28)	22	9 (19)†	22	15 (24)†	0.90
MLWFQ	28	32 (22)	27	−12 (16)†	24	−10 (22)†	27	35 (25)	22	−7 (19)†	22	−11 (21)†	0.80
GDS	28	7 (5)	24	−0.5 (4)	24	0.7 (5)	28	10 (7)	22	−1.0 (4)	22	−0.7 (4)	0.95
WOMAC	28	41 (28)	27	−6 (19)	24	−7 (30)	28	44 (29)	22	−7 (17)	22	−7 (21)	0.95
Three-dimensional echocardiography													
LV ejection fraction, %	27	58 (9)	27	3 (7)	23	4 (8)	26	58 (10)	21	1 (7)	20	−2 (8)	0.18
LV end-diastolic volume, mL	27	99 (28)	27	0.03 (10)	23	−4 (16)	26	98 (32)	21	−5 (9)	20	−6 (14)	0.67
Stroke volume, mL	27	56 (13)	27	3.9 (10)	23	3 (9)	26	56 (15)	21	−2 (7)†	20	−5 (8)†	0.09
LV end-systolic volume, mL	27	43 (19)	27	−4 (9)	23	−7 (13)	26	42 (22)	21	−3 (8)	20	−1 (12)	0.61
Mean e′ velocity, cm/s	27	6.5 (2.6)	24	−0.3 (1.9)	21	−1.1 (2.5)	27	6.5 (3.2)	20	0.5 (2.8)	18	−0.7 (3.5)	0.61
E-velocity/e′	27	19 (10)	24	3 (8)	21	3 (7)	26	19 (15)	20	0 (6)	18	−1 (11)	0.61
Pressure volume relationships													
Estimated LVEDP, mm Hg	27	23 (6)	24	1.75 (5)	19	0.3 (4)	26	24 (9)	20	0.35 (4)	18	−0.4 (5)	0.83
Stroke work	27	5161 (1309)	27	333 (839)	23	211 (896)	26	5374 (1610)	21	−120 (615)	20	−455 (675)	0.09
Stroke work/LV mass	27	53 (15)	27	4 (8)	23	2 (13)	26	52 (14)	21	−3 (7)*	20	−4 (7)*	0.32
Functional													
6-Min walk, m	27	239 (102)	26	9 (69)	23	5 (59)	27	242 (97)	21	14 (51)	21	16 (47)	0.50
Vo_2, mL/kg per minute	9	10.3 (2.9)	7	−0.9 (1.8)	6	−1.2 (1.4)	10	9.0 (2.5)	5	0.7 (2.1)	4	1.0 (1)	0.03
Respiratory exchange ratio	9	1.1 (0.1)	7	−0.01 (0.1)	6	−0.04 (0.1)	10	1.0 (0.2)	5	0.04 (0.1)	4	0.03 (0.08)	0.95
VE/VCO_2	9	34 (6)	7	2.1 (7)	6	0.2 (3)	10	38 (16)	5	−0.6 (8)	4	−3 (7)	0.61
Blood volume													
Red cell volume, mL	24	1323 (288)	N/A	N/A	17	58 (237)	20	1454 (433)	N/A	N/A	15	173 (164)	0.13
Plasma volume, mL	24	3264 (701)	N/A	N/A	17	14 (287)	20	3710 (975)	N/A	N/A	15	−206 (299)†	0.04
Total blood volume, mL	24	4586 (950)	N/A	N/A	17	66 (433)	20	5163 (1379)	N/A	N/A	15	−32 (318)	0.40
Red cell volume, %	24	−18 (9)	N/A	N/A	17	2 (13)	20	−18 (17)	N/A	N/A	15	10 (10)	0.07
Plasma volume, %	24	24 (22)	N/A	N/A	17	0 (10)	17	22 (20)	N/A	N/A	15	−6 (10)	0.23
Total blood volume, %	24	8 (15)	N/A	N/A	17	1 (9)	20	10 (18)	N/A	N/A	15	0.3 (5)	0.80

BP indicates blood pressure; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDP, left ventricular end-diastolic pressure; MLWFQ, Minnesota Living with Heart Failure Questionnaire; and WOMAC, Western Ontario and McMasters Arthritis Index.

**P* value for between-group comparisons from generalized estimating equation at 6 months. For all *P* values except for those corresponding to primary and secondary end points, *P* values were adjusted for multiple hypothesis testing in the false discovery rate context.

†Significant difference from baseline within group.

population was solidly normal. Although the study subjects recruited were only a small percentage of the total HF population seen at our institution, the clinical and demographic characteristics of these subjects suggest that they are quite representative of the majority of patients with HFPEF who are older adult women with long-standing hypertension and multiple comorbidities. Indeed, such patients have been traditionally excluded from randomized clinical trials,[30,55] resulting in limited data from which to derive appropriate therapies. In addition, the trial was of a relatively short

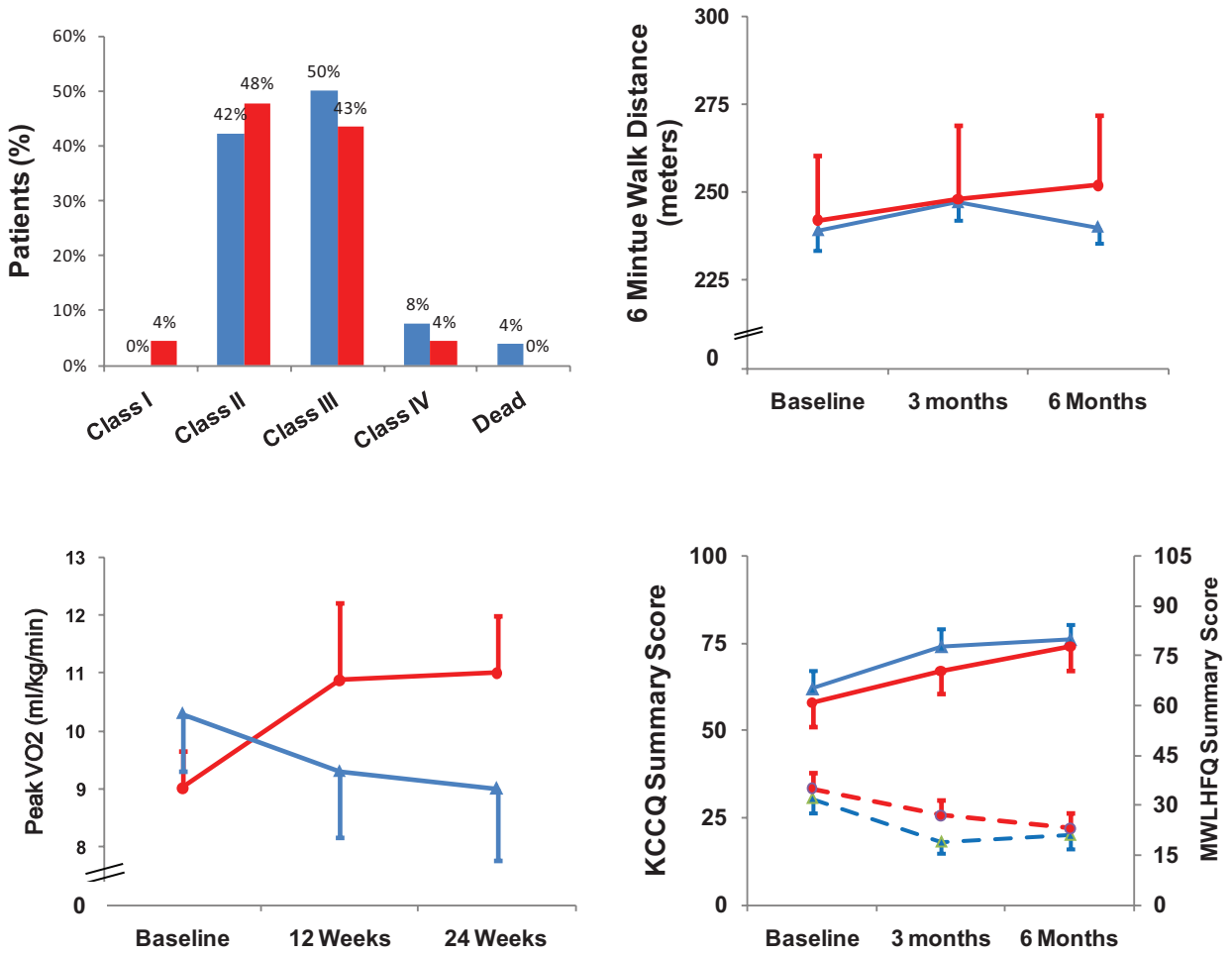

Figure 4. Distribution of New York Heart Association class after 6 mo in epoetin alfa (ESA) (red bars) and placebo (blue bars; **top left**); 6-minute hall walk distance in ESA (red circles) and placebo (blue triangles; **top right**); peak Vo_2 in ESA (red circles) and placebo (blue triangles; **bottom left**) and quality of life measures for Kansas City Cardiomyopathy Questionnaire (KCCQ) (solid lines) and Minnesota Living with Heart Failure Questionnaire (MLWFQ) (dashed lines; **bottom right**) at baseline and after 3 and 6 months of therapy.

duration of 6 months. However, we included multiple end points focusing on ventricular function measured with tomographic reconstruction, functional capacity measured with multiple modalities, and QOL evaluated in distinct domains.

In conclusion, administration of ESA to older adult patients with HFPEF compared with placebo did not change cardiac structure nor did it improve submaximal exercise capacity or QOL.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Among more than half of patients with heart failure who have a preserved ejection fraction, treatment is largely empirical and predominately focused on the cardiovascular phenotype. A majority of patients with heart failure who have a preserved ejection fraction are older adult women with hypertension and several other comorbidities, including obesity, renal dysfunction, diabetes mellitus, and anemia, among others. Whether treating these comorbidities will have clinical benefits has been suggested but as yet has not been subject to rigorous study. Accordingly, we conducted a prospective, randomized, single-blind clinical trial of treating anemia with epoetin alfa in older adults with heart failure who have a preserved ejection fraction. The trial recruited an older adult cohort (mean age, >75 years), predominately women (67%) with multiple comorbidities (including chronic pain and depression), which mimics what is seen in community-based studies of heart failure, but has, until now, not been replicated in a prospective clinical trial. Despite increasing hemoglobin in a safe manner using a prespecified dosing algorithm, epoetin alfa was not associated with ventricular remodeling nor was it associated with improvements in submaximal exercise capacity or quality of life compared with placebo. These data suggest that for the rapidly rising population of heart failure who have a preserved ejection fraction, treatment with erythropoietin as prescribed in this trial is not associated with meaningful clinical benefits. Furthermore, these data demonstrate that randomized clinical trials can be carried out in the population by using novel approaches (eg, nonprinciple visits being conducted in the subject's home) and provide an evidence base for informing clinicians caring for this vulnerable population.