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## Randomized Double-Blind Trial of Darbepoetin Alfa in Patients With Symptomatic Heart Failure and Anemia

Jalal K. Ghali, MD; Inder S. Anand, MD, FRCP, DPhil; William T. Abraham, MD; Gregg C. Fonarow, MD; Barry Greenberg, MD; Henry Krum, MD; Barry M. Massie, MD; Scott M. Wasserman, MD; Marie-Louise Trotman, MS; Yan Sun, MS; Beat Knusel, PhD; Paul Armstrong, MD; on behalf of the Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group

**Background**—Substantial evidence suggests that anemia is an independent risk factor for worse outcomes in patients with heart failure (HF). The Study of Anemia in Heart Failure Trial (STAMINA-HeFT) is the largest multicenter, randomized, double-blind, placebo-controlled trial to date evaluating the effect of treating anemia in HF.

**Methods and Results**—Patients (N=319) with symptomatic HF, left ventricular ejection fraction  $\leq 40\%$ , and hemoglobin  $\geq 9.0$  g/dL and  $\leq 12.5$  g/dL were randomized (double-blind) to placebo (N=157) or darbepoetin alfa (N=162) subcutaneously every 2 weeks for 1 year (target hemoglobin,  $14.0 \pm 1.0$  g/dL). The primary end point was change from baseline to week 27 in treadmill exercise time. Secondary end points were change from baseline in New York Heart Association class and quality of life at week 27. An additional prespecified efficacy analysis included the time to death by any cause or first HF-related hospitalization by 1 year. At baseline, the median (interquartile range) hemoglobin was 11.4 (10.9, 12.0) g/dL. At week 27, darbepoetin alfa treatment increased median (interquartile range) hemoglobin by 1.8 (1.1, 2.5) g/dL (placebo, 0.3 [−0.2, 1.0] g/dL;  $P < 0.001$ ). Of the patients treated with darbepoetin alfa, 85% achieved 2 consecutive hemoglobin levels of  $14.0 \pm 1.0$  g/dL during the study and experienced a hemoglobin increase of  $\geq 1.0$  g/dL from baseline. By intent-to-treat analysis, darbepoetin alfa treatment did not significantly improve exercise duration, New York Heart Association class, or quality of life score compared with placebo. A nonsignificant trend was observed toward a lower risk of all-cause mortality or first HF hospitalization in darbepoetin alfa-treated patients compared with placebo (hazard ratio, 0.68; 95% CI, 0.43, 1.08;  $P = 0.10$ ). Occurrences of adverse events were similar in both treatment groups.

**Conclusions**—In this study of patients with symptomatic HF and anemia, treatment with darbepoetin alfa was not associated with significant clinical benefits. Darbepoetin alfa treatment was well tolerated and effectively raised hemoglobin. A trend of lower risk of morbidity and mortality was observed. (*Circulation*. 2008;117:526-535.)

**Key Words:** anemia ■ exercise ■ heart failure ■ hemoglobin ■ trials

In patients with heart failure (HF), anemia is common and is associated with more severe symptoms, lower functional status,<sup>1-3</sup> worse exercise capacity,<sup>1,4,5</sup> cognitive impairment,<sup>6</sup> and worse quality of life.<sup>7</sup> Importantly, anemia has been identified as a powerful independent risk factor for morbidity and mortality in HF patients.<sup>1,2,8-13</sup> Because of its potential contribution to both the symptoms and progression of HF,

anemia has recently emerged as a potential target for HF therapy.<sup>1,2,4,8-11</sup>

### Clinical Perspective p 535

Preliminary, single-center, open-label studies in HF patients have shown that treatment of anemia with erythropoiesis-stimulating agents (ESAs) in patients with HF

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The online-only Data Supplement, which contains a complete list of STAMINA-HeFT Study Group investigators, is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.698514/DC1>.

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Clinical trial registration information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00049985.

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may improve exercise capacity<sup>14</sup> and cardiac and renal function and reduce the need for hospitalization and diuretic use.<sup>3,15</sup> Although encouraging, these small studies were relatively short in duration and not designed to provide conclusive data on the safety or clinical efficacy of ESA treatment. Nonetheless, together with the strong association of anemia with poor outcomes, these data support the hypothesis that treatment of anemia might improve functional status and clinical outcomes in HF patients.

The Study of Anemia in Heart Failure Trial (STAMINA-HeFT) was designed as a proof-of-concept study to examine the clinical impact of anemia treatment in a symptomatic, anemic HF population with darbepoetin alfa, a long-acting ESA that stimulates erythropoiesis in the same manner as endogenous erythropoietin.<sup>16</sup> To date, STAMINA-HeFT is the largest randomized, double-blind, placebo-controlled study to evaluate the tolerability and efficacy of treatment of anemia in HF patients.

## Methods

### Study Population

Study participants were  $\geq 21$  years of age and had symptomatic HF for  $\geq 3$  months at the time of enrollment. Key inclusion criteria were as follows: treadmill exercise duration at baseline (based on at least 2 screening tests), with the use of a modified Naughton protocol,<sup>17</sup> between 2 and 14 minutes (for patients aged  $\leq 60$  years) and between 2 and 12 minutes (for patients aged  $> 60$  years), with a rating of perceived exertion of  $\geq 13$  ("somewhat hard") on the Borg scale<sup>18</sup>; left ventricular ejection fraction  $\leq 40\%$  within the previous 12 weeks; a mean of 2 screening hemoglobin concentrations of  $\geq 9.0$  and  $\leq 12.5$  g/dL; transferrin saturation  $\geq 15.0\%$ ; serum vitamin B<sub>12</sub> and folate levels at or above the lower limit of the normal range; treatment for HF with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, unless not tolerated, for  $\geq 8$  weeks, without dose change for  $\geq 4$  weeks; and, if used,  $\beta$ -blocker treatment for  $\geq 8$  weeks, without dose change for  $\geq 4$  weeks.

Exclusion criteria were as follows: resting blood pressure  $> 160/100$  mm Hg; unstable angina pectoris and/or recent myocardial infarction (within 3 months of randomization); severe uncorrected valvular disease or left ventricular outflow obstruction; major surgery and organ transplantation; likelihood of cardiac transplantation within 6 months after randomization; uncontrolled arrhythmias; active and systemic hematologic diseases; anemia due to acute or chronic bleeding; current malignancy; chemotherapy and/or radiation therapy within 12 weeks; ESA therapy; whole blood or red blood cell transfusion within 12 weeks of intended randomization; serum creatinine  $> 3.0$  mg/dL; and contraindication to iron therapy.

The study protocol was approved by the central institutional review board or the locally appointed ethics committee at each participating study site, and all patients gave their written informed consent. Enrollment started in July 2002; the last patient completed the study in February 2005.

### Study Design

This was a multicenter (65 centers), double-blind, randomized, placebo-controlled phase 2 study. Eligible patients with symptomatic HF and anemia were randomly assigned in a 1:1 ratio to receive darbepoetin alfa (starting dose, 0.75  $\mu\text{g}/\text{kg}$ ) or placebo subcutaneously every 2 weeks for a total of 52 weeks. The randomization scheme was centrally held, computer-generated, and stratified by study center.

The primary study end point was the change in exercise tolerance from baseline to week 27, as measured by treadmill exercise duration. Secondary efficacy end points were the change from baseline to week 27 in New York Heart Association (NYHA) functional classification and health-related quality of life, as mea-

sured by the Minnesota Living with Heart Failure Questionnaire<sup>19</sup> and the Patient's Global Assessment of Change.<sup>20</sup> Additional end points included time to death by any cause or first HF hospitalization. Safety was monitored by the occurrence of adverse events throughout the study, changes in laboratory parameters (including hemoglobin), vital signs at each visit, and seroreactivity to ESAs.

Patients and personnel at the study site were blinded to the treatment. Darbepoetin alfa (Aranesp, 200  $\mu\text{g}/\text{mL}$ ; Amgen Inc, Thousand Oaks, Calif) or matching placebo was provided in single-dose vials. After initial administration, darbepoetin alfa doses were titrated to achieve a gradual rise in hemoglobin concentration. Once hemoglobin had reached  $\geq 13.0$  g/dL and had increased by  $\geq 1.5$  g/dL from baseline, the darbepoetin alfa dose was reduced by 25%. Doses were then adjusted to maintain hemoglobin concentrations within the target range of  $14.0 \pm 1.0$  g/dL. To maintain the blind, doses were adjusted in a similar fashion for placebo patients on the basis of hemoglobin modeling data, independent of the actual blinded hemoglobin concentration during the study. All hemoglobin measurements were made at a central laboratory. An interactive voice response system provided instructions to each site on dose adjustments for darbepoetin alfa and, to maintain the blind, instructions for volume changes for placebo to imitate active dose titration. To maintain the blind, daily elemental oral iron was administered unless baseline ferritin was  $> 800$  ng/mL. Patients continued to receive optimal concomitant therapy for HF during the study.

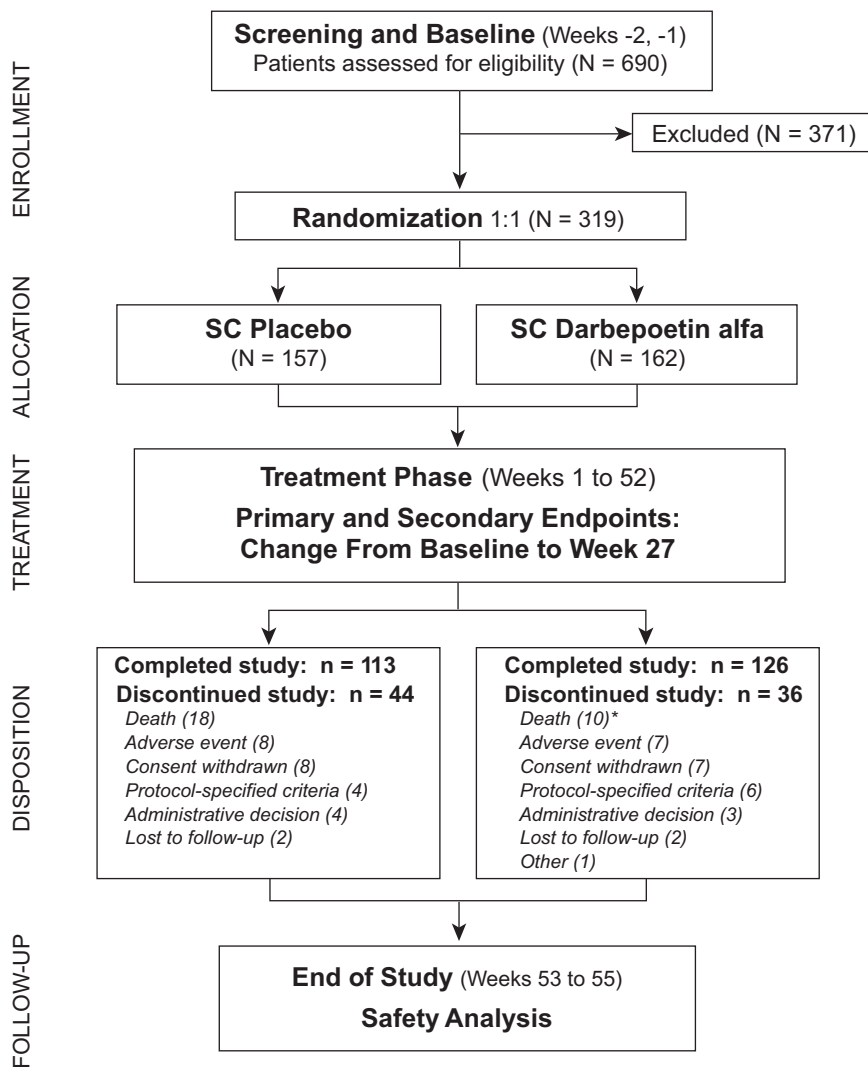
### Study Assessments

Hemoglobin concentrations were measured weekly during screening and for the first 12 weeks of treatment and until 4 consecutive hemoglobin measurements were in the target range; every 2 weeks thereafter; and at the end-of-study visit (2 weeks after the last dose at week 53 or on withdrawal). Exercise duration was measured weekly during screening and at weeks 13 and 27, with the use of a modified Naughton protocol.<sup>17</sup> The level of exertion was recorded with the use of the rating of perceived exertion scale (from 6 to 20; light to hard).<sup>18</sup> Hematology, blood chemistry, serum iron, total iron-binding capacity, transferrin saturation, and ferritin were measured by a central laboratory at screening; at weeks 9, 17, 27, and 39; and at the end-of-study visit (study week 53). NYHA class was assessed at study weeks 1, 9, 13, 17, 27, 39, and at the end-of-study visit; QOL assessments occurred at study weeks 1, 13, 27, and 53. Adverse events were recorded throughout the study. A telephone follow-up for mortality was conducted at week 55 after patients terminated the study. Reported deaths and hospitalizations were adjudicated by an independent end point adjudication committee. Anti-erythropoietic seroreactivity assays were performed before administration of the first dose of study drug (week 1), at week 27, and at the end-of-study visit.

### Statistical Analysis

The sample size of 300 patients provided  $> 80\%$  power to detect a treatment effect of  $\geq 60$  seconds for the primary end point of change from baseline in exercise duration at week 27, assuming an SD of 150 seconds, a 20% dropout rate, and a 5% 2-sided significance level. Efficacy analyses were based on the intent-to-treat analysis set (all patients randomly assigned to a treatment group). The analysis of quality of life parameters was based on available data without imputation. Safety analyses included all randomly assigned patients who received at least 1 dose of study drug.

The primary analysis compared change from baseline at week 27 in exercise duration between the darbepoetin alfa and placebo groups. A repeated-measures ANCOVA mixed-effects model was applied with the use of available data with no imputation; treatment was the main effect, baseline exercise duration was a covariate, and a random patient intercept and unstructured covariance matrix were used. Although randomization was stratified by study center, this variable was not included as a fixed effect in the model because of the small number of patients at many centers. However, sensitivity analyses including pooled center as a fixed or random effect in the model showed similar results. For continuous secondary end points, comparisons between the darbepoetin alfa and placebo groups were



**Figure 1.** Study design and patient disposition. \*One additional patient died 1 day after discontinuing the study early because of an adverse event with fatal outcome; this death was included in all safety and efficacy analyses. SC indicates subcutaneous.

made with ANCOVA, adjusted for baseline value unless otherwise indicated. For categorical variables, a logistic regression model was fitted, or a 2-group  $\chi^2$  test of equal proportions between treatment groups was performed. The analysis of time to death by any cause or first HF hospitalization was performed with a 2-sided log-rank test. Hazard ratios and their CIs were estimated with a Cox proportional hazards model. Results are presented without adjustment for baseline covariates. Similar results were observed after adjustment for baseline covariates. Standard summary statistics were calculated for each variable. Results were considered to be nominally statistically significant if  $P < 0.05$ .

A post hoc exploratory analysis of change from baseline in exercise tolerance by change in hemoglobin was performed with a repeated-measures, mixed-effects model adjusted for baseline exercise duration, and Pearson correlation coefficients were calculated. These analyses were performed on a subset of patients who participated in the study for at least 17 weeks.

All data are held by the study sponsor (Amgen Inc). The authors had full access to and take responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

## Results

### Study Cohort

Three hundred nineteen patients were randomized, 157 patients to placebo and 162 to darbepoetin alfa (Figure 1). Treatment groups were generally balanced with respect to

measures of demographics and baseline characteristics (Table 1). Most patients were white (81%), male (63%), had NYHA class III HF (61%), and received comprehensive HF treatment including  $\beta$ -blockers (78%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (90%), and diuretics (91%). The prevalence of ischemic heart disease was 75% and of hypertension was 66%. The mean (SD) duration of HF was 6 (6) years. Median values for iron parameters (serum iron, ferritin, total iron-binding capacity, transferrin saturation) were within the normal ranges in patients of both treatment groups at baseline (Table 1) and did not change significantly throughout the study in either treatment group. Median and interquartile range (IQR) concentrations for each of these measures at weeks 27 and 53 for the placebo and darbepoetin alfa groups, respectively, were as follows: serum iron concentration 13.0 (10.0, 15.0)  $\mu\text{mol/L}$  and 12.0 (9.0, 15.0)  $\mu\text{mol/L}$  (placebo) and 14.0 (10.5, 18.0)  $\mu\text{mol/L}$  and 15.0 (12.0, 19.0)  $\mu\text{mol/L}$  (darbepoetin alfa); ferritin 134 (80, 241)  $\mu\text{g/L}$  and 135 (70, 283)  $\mu\text{g/L}$  (placebo) and 114 (61, 192)  $\mu\text{g/L}$  and 150 (91, 242)  $\mu\text{g/L}$  (darbepoetin alfa); total iron-binding capacity 51.0 (45.0, 58.0)  $\mu\text{mol/L}$  and 51.0 (46.0, 58.0)  $\mu\text{mol/L}$  (placebo) and 53.0 (46.5, 61.0)  $\mu\text{mol/L}$  and 50.0 (45.0, 57.0)  $\mu\text{mol/L}$  (darbepoetin alfa);

**Table 1. Demographic and Baseline Characteristics**

Characteristic	Placebo (N=157)	Darbepoetin alfa (N=162)	All Patients (N=319)
Sex, n (%)			
Male	107 (68)	93 (57)	200 (63)
Ethnicity, n (%)			
White	134 (85)	124 (77)	258 (81)
Black	17 (11)	23 (14)	40 (13)
Other	6 (4)	15 (9)	21 (7)
Age, mean (SD), y	69 (10)	68 (12)	69 (11)
NYHA classification, n (%)			
Missing	1 (1)	0 (0)	1 (0)
Class I	3 (2)	1 (1)	4 (1)
Class II	51 (32)	62 (38)	113 (35)
Class III	97 (62)	96 (59)	193 (61)
Class IV	5 (3)	3 (2)	8 (3)
Left ventricular ejection fraction, mean (SD), %	36 (9)	35 (10)	36 (10)
Duration of HF, mean (SD), y	6 (6)	6 (5)	6 (6)
Medical history, n (%)			
Ischemic heart disease	124 (79)	114 (70)	238 (75)
Hypertension	104 (66)	107 (66)	211 (66)
Myocardial infarction	97 (62)	94 (58)	191 (60)
Diabetes	79 (50)	86 (53)	165 (52)
Medications, n (%)			
$\beta$ -Blockers	118 (75)	132 (81)	250 (78)
ACEI and/or ARB	142 (90)	145 (90)	287 (90)
Diuretics	140 (89)	150 (93)	290 (91)
Cardiac glycosides	78 (50)	79 (49)	157 (49)
Vasodilators	63 (40)	82 (51)	145 (45)
Median (IQR) laboratory measurements			
Hemoglobin, g/dL	11.3 (10.7, 11.9)	11.5 (11.0, 12.0)	11.4 (10.9, 12.0)
Serum ferritin, $\mu$ g/L	124 (57, 243)	121 (69, 230)	123 (62, 238)
Serum iron, $\mu$ mol/L	12.0 (10.0, 15.0)	13.0 (10.0, 16.0)	13.0 (10.0, 16.0)
Transferrin saturation, %	23.5 (18.9, 30.1)	23.5 (19.8, 30.9)	23.5 (19.2, 30.5)
Total iron-binding capacity, $\mu$ mol/L	52.0 (46.0, 58.0)	52.0 (45.0, 57.0)	52.0 (45.0, 58.0)
Creatinine, mg/dL	1.4 (1.2, 1.8)	1.5 (1.1, 1.9)	1.5 (1.1, 1.8)
eGFR, mL $\cdot$ min <sup>-1</sup> $\cdot$ 1.73 m <sup>-2*</sup>	47.5 (37.4, 62.3)	47.2 (36.3, 64.6)	47.2 (36.3, 62.9)

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; and eGFR, estimated glomerular filtration rate.

\*Calculated with the use of the Modification of Diet in Renal Disease formula.

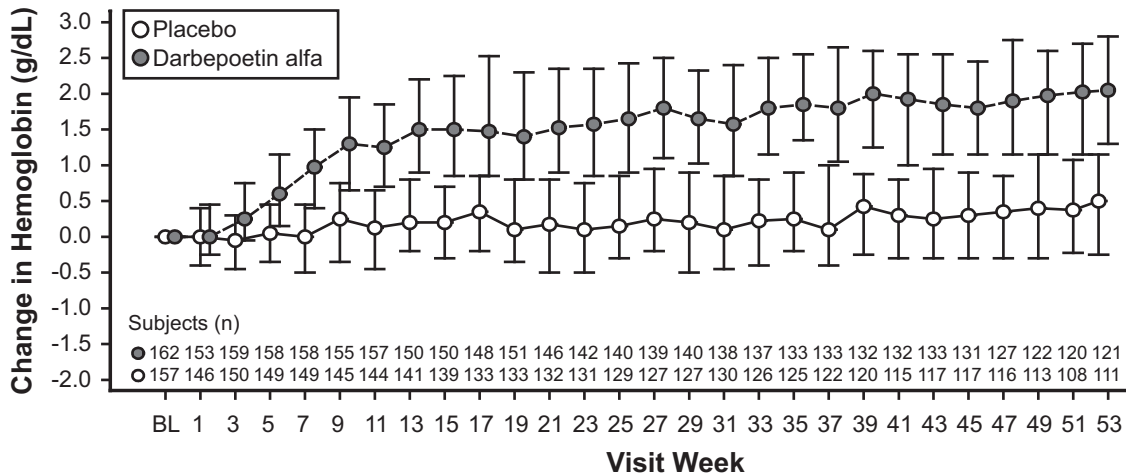
transferrin saturation 24.7% (19.1%, 31.5%) and 23.5% (18.0%, 30.5%) (placebo) and 26.4% (20.0%, 35.5%) and 31.3% (23.3%, 36.7%) (darbepoetin alfa). For each of these iron parameters, the approximate number of patients was 125 (placebo) and 132 (darbepoetin alfa) at week 27 and 113 (placebo) and 123 (darbepoetin alfa) at week 53.

### Change in Hemoglobin

Median (IQR) baseline hemoglobin concentrations were similar in the darbepoetin alfa and placebo groups, respectively

(Table 1). Hemoglobin concentrations were approximately normally distributed; median (IQR) values for change in hemoglobin over time for both treatment groups are shown in Figure 2. In patients receiving darbepoetin alfa, median hemoglobin change from baseline increased gradually, reaching  $\approx$ 1.5 g/dL from baseline by 12 to 14 weeks of treatment. Target hemoglobin concentrations for the darbepoetin alfa-treated patients were sustained for the duration of the study after the hemoglobin titration phase: At week 27, the median (IQR) hemoglobin was 13.4 (12.4, 14.2) g/dL, and the median





**Figure 2.** Median change from baseline in hemoglobin over time (safety analysis set). Vertical lines represent IQR.

(IQR) change from baseline was 1.8 (1.1, 2.5) g/dL compared with 0.3 (−0.2, 1.0) g/dL in the placebo group ( $P < 0.001$ ); at week 53, the median (IQR) hemoglobin was 13.6 (13.1, 14.4) g/dL, and the median (IQR) change from baseline was 2.1 (1.3, 2.8) g/dL compared with 0.5 (−0.3, 1.2) g/dL in the placebo group ( $P < 0.001$ ). Eighty-five percent ( $n = 137$ ) of darbepoetin alfa–treated patients achieved the target hemoglobin range during the study and experienced a hemoglobin increase of  $\geq 1.0$  g/dL from baseline; of those receiving placebo, 19% ( $n = 30$ ) reached the target.

**Primary End Point: Exercise Tolerance**

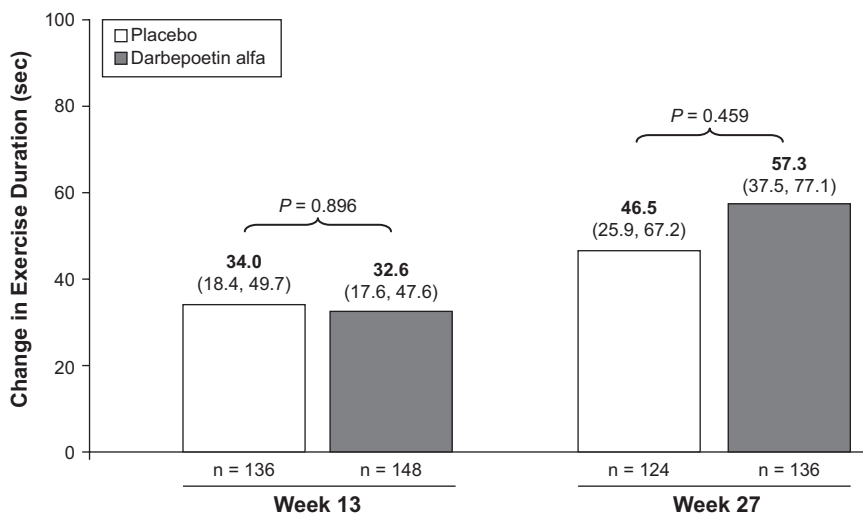
Exercise tolerance was measured by exercise duration with the use of maximal exercise treadmill tests. At baseline, the mean (SD) achieved exercise duration was similar for patients in both treatment groups: 409 (170) seconds in the placebo group ( $N = 157$ ) versus 408 (165) seconds in the darbepoetin alfa group ( $N = 162$ ). At week 27, the mean (SD) change in exercise duration was 45.6 (126.4) seconds in the placebo group ( $N = 124$ ) compared with 58.4 (111.1) seconds in the darbepoetin alfa group ( $N = 136$ ). In the primary analysis with the use of a repeated-measures, mixed-effects model adjusted for baseline exercise duration, there was no

statistically significant difference between the placebo group and the darbepoetin alfa group in the adjusted mean (95% CI) change from baseline in exercise duration at week 27: 46.5 (25.9, 67.2) versus 57.3 (37.5, 77.1);  $P = 0.46$  (Figure 3).

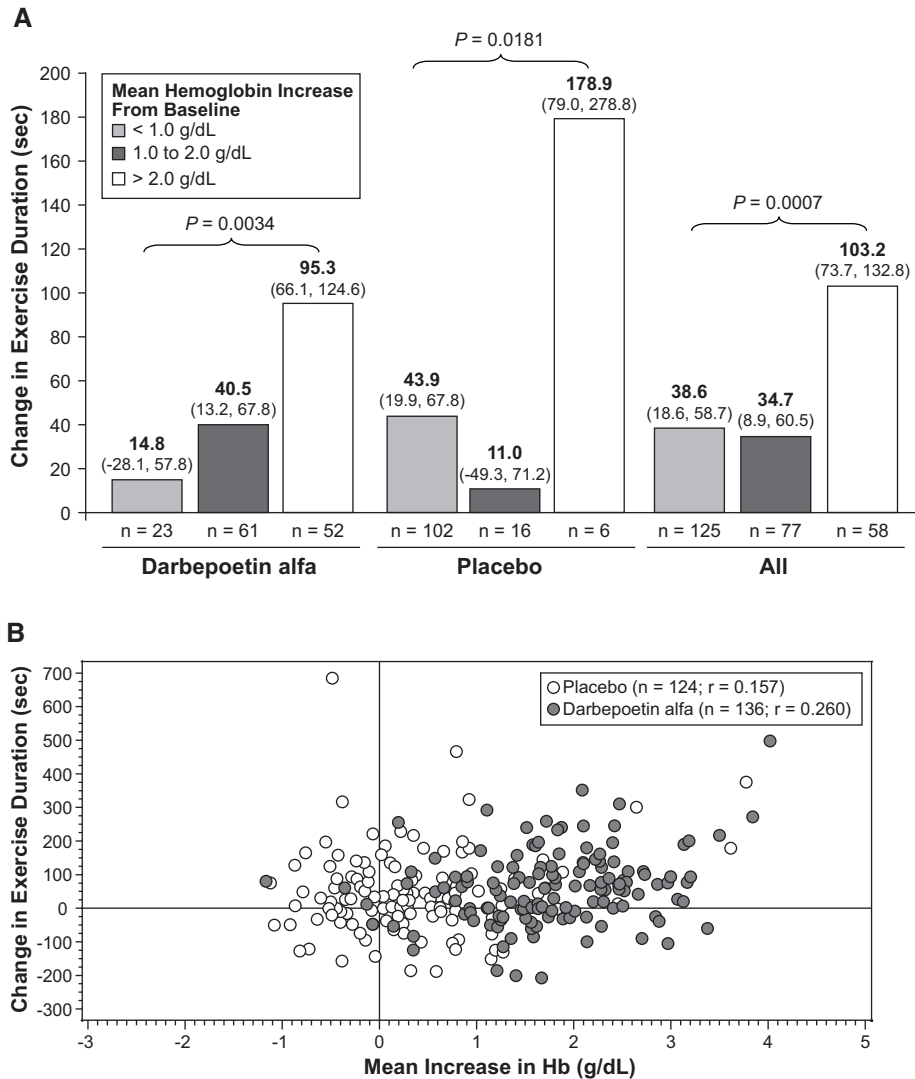
**Secondary End Points: NYHA Class and Health-Related Quality of Life**

There was no statistically significant difference in change of NYHA functional class between darbepoetin alfa and placebo groups. Adjusted mean (SE) changes from baseline at week 27 were −0.19 (0.04) and −0.13 (0.04) in the darbepoetin alfa ( $n = 142$ ) and placebo groups ( $n = 128$ ), respectively ( $P = 0.34$ ).

The same proportion of patients in the darbepoetin alfa ( $n = 115/162$ ) and placebo ( $n = 112/157$ ) groups experienced an improvement in Patient’s Global Assessment of Change at week 27 (71% versus 71%;  $P = 0.95$ ). The Minnesota Living with Heart Failure Questionnaire total score improved over time during the course of the study in both groups (mean [SE] change from baseline at week 27: placebo ( $n = 120$ ), −7.1 [1.9]; darbepoetin alfa ( $n = 136$ ), −9.3 [1.6]), but there was no difference in response between the placebo and active groups ( $P = 0.38$ ,  $t$  test).



**Figure 3.** Adjusted mean (95% CI) change from baseline in exercise duration over time. Least-squares mean obtained from repeated-measures, mixed-effects model adjusted for baseline value.



**Figure 4.** Post hoc analysis of change in exercise duration by change in hemoglobin. A, Adjusted mean (95% CI) change from baseline in exercise duration at week 27 stratified by mean increase from baseline in hemoglobin concentration (mixed-effects model). Mean hemoglobin increase from baseline is the mean hemoglobin between week 17 and end of study minus baseline for each patient. B, Scatterplot (including Pearson correlation coefficients) of change from baseline in exercise duration at week 27 by mean hemoglobin increase. Multiple points with the same x and y values are offset in the x dimension by  $\approx 1$  symbol diameter.

**Post Hoc Analysis: Change in Exercise Duration by Hemoglobin Response**

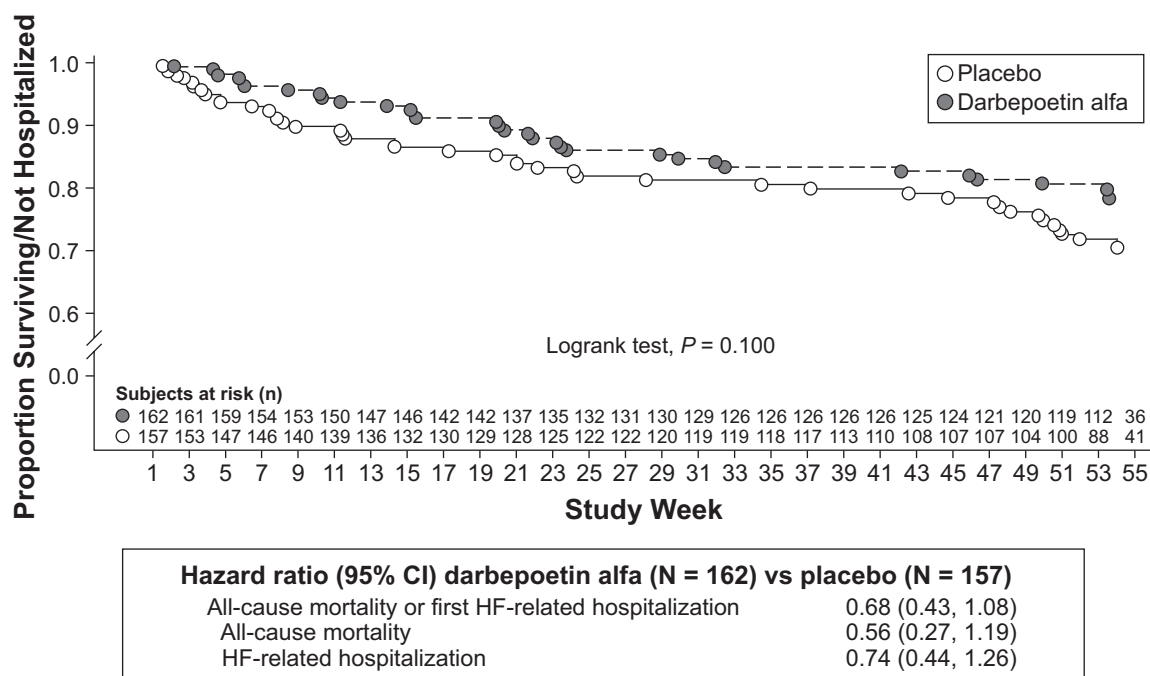
In a post hoc analysis there was a statistically significant, hemoglobin-associated increase in adjusted mean change from baseline in exercise duration at study week 27 that was observed in each treatment group and in the combined group (Figure 4A). Independent of treatment, patients who had a mean rise of hemoglobin concentration  $\geq 2.0$  g/dL between week 17 and the end of the study compared with baseline showed the greatest improvement in exercise duration compared with patients who had a mean rise of hemoglobin  $< 1.0$  g/dL. However, individual subject data (Figure 4B) show that mean increases from baseline in hemoglobin concentration  $\geq 2.0$  g/dL occurred more frequently in the darbepoetin alfa group (n=52) than in the placebo group (n=6) for patients with available exercise data at week 27. The correlation between hemoglobin change and change in exercise duration was weak. In the combined treatment group, when the

ANCOVA model adjusted for baseline exercise duration included hemoglobin response as a continuous variable in the model, a 1.0-g/dL increase in hemoglobin concentration corresponded to a 21-second improvement in exercise duration from baseline to week 27 ( $P=0.002$  for the association).

Corresponding analyses were completed for NYHA class, Patient’s Global Assessment of Change, and Minnesota Living with Heart Failure Questionnaire. With the exception of NYHA class in the darbepoetin alfa group, no statistically significant correlation was seen between hemoglobin change and change in these measurements (data not shown).

**Clinical Outcomes**

During study participation (time from initial study drug administration to end of study), 18 patients (11%) in the placebo group and 11 patients (7%) in the darbepoetin alfa group died from any cause. Although our study was not designed to show differences in the prespecified efficacy



**Figure 5.** Kaplan–Meier plot of all-cause mortality or first HF-related hospitalization (intent-to-treat analysis set).

analysis of time to death by any cause or first HF hospitalization, treatment with darbepoetin alfa was associated with a trend of lower risk for the composite end point (hazard ratio, 0.68; 95% CI, 0.43, 1.08;  $P=0.10$ ), with both individual components contributing to this effect (Figure 5). The study design also included a long-term follow-up for mortality after study termination, during which an additional 7 and 9 deaths were reported for the placebo and darbepoetin alfa groups, respectively, resulting in an overall mortality of 25 (16%) in the placebo group and 20 (12%) in the darbepoetin alfa group. From this follow-up, the overall hazard ratio (95% CI) for all deaths, including deaths after the study was ended early, was 0.68 (0.38, 1.24) when the darbepoetin alfa group was compared with the placebo group.

### Adverse Event Assessments

Darbepoetin alfa was well tolerated, with an adverse event profile similar to placebo (Table 2). Most patients in both treatment groups (placebo, 92%; darbepoetin alfa, 93%) experienced at least 1 adverse event. The most common adverse events in the darbepoetin alfa and placebo groups, respectively, were musculoskeletal and connective tissue signs and symptoms (28% versus 28%), neurological signs and symptoms (25% versus 24%), worsening HF (23% versus 29%), upper respiratory tract infections (22% versus 26%), asthenic conditions (20% versus 26%), and breathing abnormalities (19% versus 22%). There were no differences in serious adverse events or treatment-related events (as considered by the investigator), and there was no difference between treatment groups in the incidence of adverse events of specific interest, defined as those historically associated with ESA treatment, such as thrombotic events, hypertension, and seizures (Table 2). All bioassay tests for neutralizing antibody

to darbepoetin alfa were negative, and no clinically significant changes in laboratory parameters (except for erythrocyte-related hematology data) or vital signs were observed (data not shown).

Most deaths that occurred during the study were due to cardiac disorders: HF (placebo,  $n=8$  versus darbepoetin alfa,  $n=3$ ), ventricular arrhythmias and cardiac arrest ( $n=0$  versus

**Table 2. Summary of Adverse Events**

Category	Placebo (N=157), n (%)	Darbepoetin alfa (N=162), n (%)
Any adverse event	145 (92)	150 (93)
Serious adverse events	81 (52)	76 (47)
Treatment-related adverse events	16 (10)	21 (13)
Related serious adverse events	3 (2)	4 (2)
Related fatal adverse events	1 (1)	0 (0)
Adverse events of specific interest	58 (37)	55 (34)
Worsening heart failure	45 (29)	38 (23)
Hypertension	10 (6)	13 (8)
Myocardial infarction	5 (3)	4 (2)
Stroke	3 (2)	3 (2)
Transient ischemic attack	1 (1)	4 (2)
Subarachnoid hemorrhage	0 (0)	1 (1)
Intracranial hemorrhage	0 (0)	1 (1)
Deep vein thrombosis	2 (1)	0 (0)
Pulmonary embolus	0 (0)	0 (0)
Seizure	2 (1)	1 (1)
Discontinuation due to adverse events	8 (5)	7 (4)
Deaths on study	18 (11)	11 (7)



n=2), ischemia (n=0 versus n=1), and sudden death (n=4 versus n=2). One sudden death was considered to be treatment related by the blinded investigator and occurred in the placebo group.

### Discussion

This is the largest randomized, double-blind, placebo-controlled study to date that examines the safety and efficacy of treatment of anemia with darbepoetin alfa in patients with anemia and symptomatic HF. The study did not meet its primary and secondary end points of improving exercise duration, NYHA class, or health-related quality of life. In this study population, darbepoetin alfa administered every 2 weeks raised and maintained the hemoglobin concentration within the target range of  $14.0 \pm 1.0$  g/dL. Darbepoetin alfa was well tolerated, with an adverse event profile similar to that of placebo. An additional prespecified efficacy analysis showed a trend of lower risk for the composite end point of all-cause mortality or first HF hospitalization in the darbepoetin alfa group compared with the placebo group. This observation is hypothesis generating and is supportive of the conduct of an adequately powered outcomes trial to evaluate the treatment of anemia in HF.

The findings in this large, double-blind, placebo-controlled study contrast with earlier published data.<sup>3,14,15</sup> In a small, single-center, single-blinded study by Mancini and colleagues,<sup>14</sup> anemic HF patients (n=26) who received Epoetin alfa showed a significant improvement in peak  $\dot{V}O_2$  and exercise duration compared with patients receiving placebo. Silverberg and colleagues<sup>15</sup> reported significant improvements in NYHA functional class in patients receiving Epoetin alfa compared with control. In contrast, Ponikowski et al<sup>21</sup> showed improved health-related quality of life and a trend toward increased exercise duration but no improvement in peak  $\dot{V}O_2$  in a double-blind, placebo-controlled trial of HF patients receiving darbepoetin alfa.

There are several possible reasons why the results for primary and secondary study end points presented here were smaller than expected. Performing exercise tests and symptom assessments in a multicenter study adds variability. Compared with the study performed by Mancini and colleagues, patients in STAMINA-HeFT were older, their baseline exercise duration was lower, and the degree of anemia (baseline median hemoglobin, 11.4 g/dL) and hemoglobin correction was more modest. When the patients' age and comorbidities in this study are considered, exercise tolerance may have been limited by factors other than anemia or HF. Study patients at the investigative centers in this study were well treated, receiving standard evidence-based HF medications. Clinically meaningful improvements in quality of life<sup>22</sup> were observed in both placebo- and darbepoetin alfa-treated patients, possibly related to the frequency of physician contact and/or administration of an injectable study drug in this study. Thus, it may be difficult to achieve additional improvements in symptoms and exercise tolerance in such patients. Nevertheless, contrary to earlier suggestions from smaller and less well-controlled studies, the trial reported here did not show that treating mild to moderate anemia in HF patients results in improved exercise duration or symptoms.

Previous retrospective studies have identified anemia as a powerful independent risk factor for morbidity and mortality in HF patients.<sup>1,2,8-13</sup> Although the study presented here was not prospectively designed to evaluate the effect of darbepoetin alfa on clinical outcomes, a prespecified analysis showed a trend for a lower event rate for all-cause mortality or first HF hospitalization in patients receiving darbepoetin alfa. The morbidity and mortality results presented here raise the possibility of a potential benefit of treating anemia in HF despite no significant improvements in exercise duration, NYHA class, or quality of life compared with placebo.

A post hoc analysis of exercise duration by hemoglobin response showed a statistically significant hemoglobin-associated increase in exercise duration between baseline and study week 27 in each treatment group and in the combined group. Two observations are key here. First, it is not surprising that a large increment in hemoglobin may be necessary to affect exercise time. Second, an association between exercise duration and hemoglobin was also seen in the placebo group; however, it occurred less frequently because these patients rarely showed spontaneous, significant increases in hemoglobin. Anemia and/or change in hemoglobin in these study patients may be both a reflection and a determinant of their clinical status. It is important to note that it is unclear at this point whether the observed increase in exercise duration by hemoglobin response represents a true mechanistic effect, a mere association, or a marker of overall health.

The results presented here are in support of a proof of concept and encourage the need for larger outcomes trials such as the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) Trial, which will evaluate the safety and potential benefit of treatment of anemia with darbepoetin alfa in patients with symptomatic HF.<sup>23</sup>

### Study Population

In regard to the patient cohort, there were more women (37%) than are typically enrolled in HF trials.<sup>2,9,24</sup> However, the definition of anemia applied in this study (hemoglobin  $\geq 9.0$  and  $\leq 12.5$  g/dL for both men and women) may have contributed in part by not including men who are anemic according to the definition of the World Health Organization (hemoglobin  $< 13.0$  g/dL). In a retrospective analysis by Ezekowitz and colleagues,<sup>25</sup> 40% of men and 35% of women with HF were anemic according to World Health Organization guidelines. However, anemia predicted mortality in men but not in women, suggesting that gender-specific anemia definitions and stratification by sex may be important issues in the design of randomized outcomes trials evaluating the treatment of anemia in HF patients. As mentioned above, the median hemoglobin in the STAMINA-HeFT population was 11.4 g/dL at baseline. The selection of HF patients with mild to moderate anemia was intentional and based on the association of mild to moderate anemia with poor outcomes in the aforementioned studies.

Other characteristics of this study cohort include comprehensive medical treatment for HF, older age, and a longer history of HF. The renal function (median estimated glomerular filtration rate,  $47.2 \text{ mL} \cdot \text{min}^{-1} \text{ per } 1.73 \text{ m}^{-2}$ ; mean estimated glomerular filtration rate,  $52.4 \text{ mL} \cdot \text{min}^{-1} \text{ per } 1.73 \text{ m}^{-2}$ ).

1.73 m<sup>-2</sup>) in the STAMINA-HeFT population is slightly lower than typically seen in HF trials,<sup>26</sup> which may represent the older age, the higher percentage of women in this study, or the likely contributory role of renal dysfunction as the cause of anemia in some patients. Patients with severe renal insufficiency were excluded in STAMINA-HeFT, and although chronic renal insufficiency is likely a factor contributing to the development of anemia in patients with HF,<sup>27</sup> the degree of renal insufficiency suggests that the etiology of anemia in this study population is multifactorial.

### Adverse Event Profile

Over the years, concerns have emerged about the safety of ESA treatment in patients with cardiac diseases. Two recent studies, Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta (CREATE), in patients with chronic kidney disease randomized to receive epoetin alfa or beta, respectively, to achieve either a higher (up to 15.0 g/dL) or a lower (up to 11.5 g/dL) target hemoglobin showed that a higher hemoglobin level may be associated with increased risk of morbidity and mortality.<sup>28,29</sup> An earlier study with Epoetin alfa comparing the effect of high (42%) versus low (30%) hematocrit maintenance in hemodialysis patients with HF or ischemic heart disease was terminated early because there was a trend toward increased mortality and a significantly higher incidence of thrombosis in patients randomized to the higher hematocrit level.<sup>30</sup> It has been speculated that high doses of ESAs, rather than high hemoglobin concentrations, may lead to adverse outcomes.<sup>31</sup> In the study reported here, fewer deaths occurred in the darbepoetin alfa group than in the placebo group. Darbepoetin alfa treatment was generally well tolerated and was associated with a similar number and incidence of adverse events compared with the administration of placebo. No incidences of deep vein thrombosis or pulmonary emboli occurred in the darbepoetin alfa treatment group, and the number and frequency of other adverse events of special interest, such as hypertension, myocardial infarction, stroke, subarachnoid hemorrhage, intracranial hemorrhage, and seizure, were similar between the darbepoetin alfa and placebo groups. There were 4 transient ischemic attacks in the darbepoetin alfa group compared with 1 in the placebo group, whereas the number and frequency of worsening HF episodes were higher in the placebo group. These findings in this HF population, which included many patients with underlying atherosclerotic disease, are reassuring as they relate to future investigation.

### Conclusion

In this study, treatment of anemia with darbepoetin alfa in patients with anemia and symptomatic systolic HF was well tolerated and gradually raised and maintained hemoglobin concentrations within the target range. The adverse event profile was very similar for the groups treated with darbepoetin alfa or placebo. Darbepoetin alfa treatment did not improve the primary end point of exercise tolerance or secondary end points of NYHA functional class or health-related quality of life compared with placebo. However, a trend toward lower risk for all-cause mortality or first HF

hospitalization was observed. The safety findings and the observed efficacy trend support the conduct of a larger trial to determine the potential benefit of treatment of anemia with darbepoetin alfa on clinical outcomes in patients with anemia and systolic HF.

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### CLINICAL PERSPECTIVE

Anemia is common in heart failure (HF) patients and is associated with worse symptoms and outcomes. Several early studies suggested that anemic HF patients may benefit from therapy with erythropoiesis-stimulating agents. In this 1-year, prospective, randomized, double-blind, placebo-controlled trial in patients with symptomatic HF and anemia, treatment with the erythropoiesis-stimulating agent darbepoetin alfa effectively raised hemoglobin concentration compared with placebo. There were no clinically or statistically significant differences between treatment groups in exercise time, New York Heart Association class, quality of life, or adverse event profile. A prespecified analysis showed a nonsignificant trend toward lower risk of all-cause mortality or first HF hospitalization with darbepoetin alfa treatment. The contrast between results of earlier studies, which demonstrated improvements in exercise capacity, New York Heart Association class, and quality of life, and our study highlights the equipoise that clinicians face regarding the management of anemia in HF and the importance of conducting rigorous, well-powered trials. These observations regarding long-term outcomes require further investigation in an adequately powered outcomes trial that will provide the direction that the medical community needs and deserves for the appropriate treatment of anemia in HF.