

ORIGINAL ARTICLE

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

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ABSTRACT

BACKGROUND

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Patients with systolic heart failure and anemia have worse symptoms, functional capacity, and outcomes than those without anemia. We evaluated the effects of darbepoetin alfa on clinical outcomes in patients with systolic heart failure and anemia.

METHODS

In this randomized, double-blind trial, we assigned 2278 patients with systolic heart failure and mild-to-moderate anemia (hemoglobin level, 9.0 to 12.0 g per deciliter) to receive either darbepoetin alfa (to achieve a hemoglobin target of 13 g per deciliter) or placebo. The primary outcome was a composite of death from any cause or hospitalization for worsening heart failure.

RESULTS

The primary outcome occurred in 576 of 1136 patients (50.7%) in the darbepoetin alfa group and 565 of 1142 patients (49.5%) in the placebo group (hazard ratio in the darbepoetin alfa group, 1.01; 95% confidence interval, 0.90 to 1.13; $P=0.87$). There was no significant between-group difference in any of the secondary outcomes. The neutral effect of darbepoetin alfa was consistent across all prespecified subgroups. Fatal or nonfatal stroke occurred in 42 patients (3.7%) in the darbepoetin alfa group and 31 patients (2.7%) in the placebo group ($P=0.23$). Thromboembolic adverse events were reported in 153 patients (13.5%) in the darbepoetin alfa group and 114 patients (10.0%) in the placebo group ($P=0.01$). Cancer-related adverse events were similar in the two study groups.

CONCLUSIONS

Treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure and mild-to-moderate anemia. Our findings do not support the use of darbepoetin alfa in these patients. (Funded by Amgen; RED-HF ClinicalTrials.gov number, NCT00358215.)

*Investigators in the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial are listed in the Supplementary Appendix, available at NEJM.org.

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ANEMIA IS COMMON IN PATIENTS WITH heart failure, and patients with both heart failure and anemia have a lower functional capacity, worse quality of life, and higher rates of hospitalization and death¹⁻³ than those without anemia.^{4,5} The cause of anemia in patients with heart failure is often unknown but may be related to an absolute or relative deficiency of, or resistance to, erythropoietin. Anemia in such patients is associated with impaired renal function, inflammation, and use of renin-angiotensin system blockers.^{6,7}

Small studies have suggested that increasing the hemoglobin level with the use of an erythropoiesis-stimulating agent (ESA) may improve functional capacity⁸⁻¹³ and reduce hospitalization in patients with heart failure and anemia, but the evidence is not robust.^{14,15} Furthermore, ESAs have not improved cardiovascular outcomes in patients with chronic kidney disease who had anemia, with or without diabetes, and treatment aimed at a high hemoglobin target has increased the risk of atherothrombotic events.¹⁶⁻¹⁸ The aim of our study, the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial, was to determine whether treatment with darbepoetin alfa improves clinical outcomes in patients with chronic systolic heart failure and anemia that is not due to iron deficiency.

METHODS

STUDY DESIGN AND OVERSIGHT

The study design has been reported previously.¹⁹ The executive committee and steering committee designed and oversaw the conduct of the trial, including data analysis, in collaboration with representatives of the sponsor (Amgen). The ethics committee at each study center approved the trial design. Data were collected and managed by the sponsor. The University of Wisconsin Statistical Data Analysis Center (SDAC) prepared unblinded reports for the independent data and safety monitoring committee, which met approximately every 3 months to oversee patient safety. The trial results were analyzed by the sponsor according to a predefined statistical analysis plan, and the analyses were replicated by SDAC. The manuscript was prepared by an academic publications committee, whose members had unrestricted access to the data, and was subsequently revised by all the authors. All the authors participated in

the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data, as well as for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

STUDY PATIENTS

Patients were eligible for the study if they had New York Heart Association (NYHA) functional class II, III, or IV heart failure; a left ventricular ejection fraction of 40% or less; and a hemoglobin level of 9.0 to 12.0 g per deciliter and if they were receiving guideline-recommended heart-failure therapy. Major exclusion criteria were a transferrin saturation of less than 15%, evidence of bleeding or other correctable causes of anemia, a serum creatinine level of more than 3 mg per deciliter (265 μ mol per liter), and a blood pressure of more than 160/100 mm Hg. All patients provided written informed consent.

STUDY PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive either darbepoetin alfa or placebo. Randomization was stratified according to region and whether patients were receiving therapy with an implantable cardioverter-defibrillator, cardiac resynchronization, or both.

Doses of darbepoetin alfa and placebo were identical in appearance and packaging. The study drug was administered subcutaneously, with doses adjusted according to hemoglobin level, which was measured in a blinded fashion. Patients in the darbepoetin alfa group received a starting dose of 0.75 μ g per kilogram of body weight once every 2 weeks until a hemoglobin level of 13.0 g per deciliter was reached on two consecutive visits. Thereafter, patients received monthly injections, according to an algorithm¹⁹ that was designed to maintain a hemoglobin level of 13.0 g per deciliter (but not exceeding 14.5 g per deciliter) (Table S1 in the Supplementary Appendix, available at NEJM.org). Patients in the placebo group received dose adjustments to mimic those in the darbepoetin alfa group. Dose assignments in the two groups were performed by an interactive voice-response system.

Blood iron indexes were assessed every 3 months during the trial. If the transferrin saturation fell to less than 20% at any time during the study, oral (and, if necessary, intravenous) iron was admin-

istered as tolerated, according to a specified algorithm (for details, see the Supplementary Appendix). Use of supplemental iron was recorded.

STUDY OUTCOMES

The primary outcome was a composite of death from any cause or first hospitalization for worsening heart failure. The prespecified adjudicated secondary outcomes were death from any cause and the composite of death from cardiovascular causes or first hospitalization for worsening heart failure. Additional secondary outcomes were the change from baseline to 6 months in the Overall Summary Score and Symptom Frequency Score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).²⁰ The KCCQ scores range from 0 to 100, with higher scores indicating better quality of life and fewer symptoms and a change of 5 points considered to be clinically meaningful.²¹ Clinical events were adjudicated according to prespecified definitions (Table S2 in the Supplementary Appendix) by members of an independent committee whose members were unaware of study-group assignments and hemoglobin levels.

STATISTICAL ANALYSIS

We determined that the primary outcome would need to occur in approximately 1150 patients in order to detect a between-group difference of 20 percentage points (assuming an annualized event rate of 25% in the placebo group) with a power of 80% after adjustment for the attenuation of treatment effect. The overall type I error was controlled at a significance level of 0.05. The protocol originally assumed that approximately 2600 patients would be enrolled for the accrual of 1150 events. However, because enrollment took longer than anticipated, 1150 events were expected to accrue before the enrollment target was reached, and recruitment was stopped after 2278 patients had been randomly assigned to a study group.

All patients who underwent randomization were included in analyses of the primary and secondary outcomes. We used the Kaplan–Meier approach and a two-sided stratified log-rank test to perform time-to-event analyses. Hazard ratios and 95% confidence intervals were estimated with the use of stratified Cox proportional-hazards models. We performed a secondary analysis of the primary outcome using a Cox proportional-hazards model that was adjusted for the stratifi-

cation variables, as well as for baseline age, sex, NYHA functional class, hospitalization for heart failure within 6 months before randomization (yes vs. no), diabetes (yes vs. no), log serum creatinine level, ejection fraction, cause of heart failure (ischemic vs. nonischemic), body-mass index, left bundle-branch block (yes vs. no), history of atrial fibrillation or flutter (yes vs. no), and systolic blood pressure.

The consistency of the treatment effect was assessed in an as-treated analysis, which included only the outcomes that occurred on or before the date of the last dose of the study drug plus 30 days. The primary outcome was also analyzed according to age; sex; race or ethnic group; region; treatment with an implantable cardioverter–defibrillator, cardiac resynchronization therapy, or both; and estimated glomerular filtration rate (GFR). The patient-reported secondary outcomes were analyzed with the use of a mixed-effects model after adjustment for the stratification variables and the baseline KCCQ score. We used the *Medical Dictionary for Regulatory Activities*, version 15.1, to identify all adverse events of interest. Query search strategies were specified in the statistical analysis plan. All statistical analyses were performed with the use of SAS software, version 9.2. (Additional information on statistical methods is provided in the Supplementary Appendix.)

RESULTS

PATIENTS

From June 13, 2006, to May 4, 2012, a total of 2278 patients underwent randomization at 453 sites in 33 countries. Of these patients, 1136 were assigned to the darbepoetin alfa group and 1142 to the placebo group (Fig. S1 in the Supplementary Appendix). The study groups were balanced with respect to baseline characteristics²² (Table 1, and Table S3 in the Supplementary Appendix). The median age was 72.0 years; 41% of the patients were women, 65% had NYHA class III or IV disease, the median left ventricular ejection fraction was 31%, and the median estimated GFR was 45.7 ml per minute per 1.73 m² of body-surface area.

STUDY-DRUG ADMINISTRATION AND FOLLOW-UP

Five patients (3 in the darbepoetin alfa group and 2 in the placebo group) did not receive any doses of the study drug and were not included in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Darbeпоetin Alfa (N=1136)	Placebo (N=1142)
Median age (interquartile range) — yr	72.0 (63.0–78.0)	71.0 (63.0–78.0)
Female sex (%)	40.3	42.6
Race (%) †		
White	68.8	67.3
Black	7.8	9.9
Other	23.4	22.8
Median body-mass index (interquartile range) ‡	26.1 (23.3–30.0)	26.3 (23.4–30.2)
New York Heart Association class (%)		
II	32.6	36.9
III or IV	67.4	63.0
Median left ventricular ejection fraction (interquartile range) — %	31.0 (25.0–35.0)	30.0 (25.0–35.0)
Median duration of heart failure (interquartile range) — yr	3.8 (1.3–7.5)	3.5 (1.2–7.7)
Ischemic heart failure (%)	73.2	72.6
Medical history (%)		
Hypertension	73.0	74.1
Diabetes	46.3	46.3
Atrial fibrillation or flutter	33.3	32.3
Stroke (hemorrhagic or ischemic)	7.7	8.0
Hospitalization for heart failure within past 6 mo	35.4	38.4
Cancer §	8.2	6.8
Medication (%)		
ACE inhibitor or ARB	87.9	89.9
Beta-blocker	85.4	84.7
Diuretic	90.5	92.5
Mineralocorticoid-receptor antagonist	43.6	45.8
Median blood pressure (interquartile range) — mm Hg		
Systolic	120.0 (109.0–133.0)	120.0 (108.0–130.0)
Diastolic	70.0 (60.0–80.0)	70.0 (60.0–78.0)
Median heart rate (interquartile range) — beats/min	72.0 (64.0–80.0)	71.0 (64.0–80.0)
Median laboratory values (interquartile range)		
Creatinine — mg/dl	1.40 (1.10–1.80)	1.40 (1.10–1.80)
Estimated glomerular filtration rate — ml/min/1.73 m ²	45.6 (34.0–61.3)	45.8 (34.1–61.6)
Hemoglobin — g/dl	11.15 (10.55–11.60)	11.20 (10.65–11.65)
Transferrin saturation — %	24.0 (19.0–31.0)	24.0 (19.0–31.0)

* There were no significant differences between the two groups except for New York Heart Association class ($P<0.05$). P values were not adjusted for multiple comparisons. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Not included in this category were patients with a history of basal-cell carcinoma, squamous-cell carcinoma, or cervical intraepithelial neoplasia.

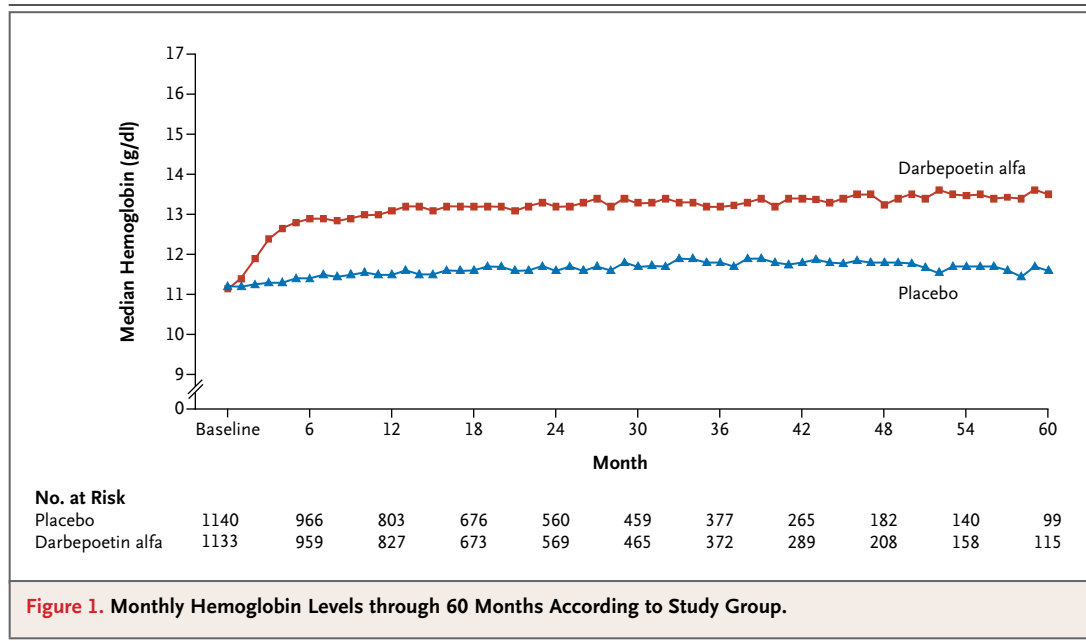


Figure 1. Monthly Hemoglobin Levels through 60 Months According to Study Group.

safety analysis. The study drug was discontinued for reasons other than death in 368 patients (32.4%) in the darbepoetin alfa group and 412 patients (36.1%) in the placebo group (Table S4 in the Supplementary Appendix).

The study was terminated on September 1, 2012, with a median follow-up of 28 months. Vital status at study termination was unknown for 13 patients (1.1%) in the darbepoetin alfa group and 21 (1.8%) in the placebo group because of loss to follow-up or withdrawal of consent (Fig. S1 in the Supplementary Appendix). If contact could not be made at the time of study termination, data were censored in the analysis at the time of the last contact.

HEMOGLOBIN VALUES

The median hemoglobin level at baseline was 11.2 g per deciliter in the two study groups (Table 1). On the basis of the area under the curve (AUC), the median attained hemoglobin level over time was 13.0 g per deciliter (interquartile range, 12.4 to 13.4) in the darbepoetin alfa group and 11.5 g per deciliter (interquartile range, 10.7 to 12.2) in the placebo group ($P < 0.001$) (Fig. 1).

The between-group difference in the hemoglobin level was significant by 1 month after randomization and remained so throughout the study. In the 1122 patients in each study group who received a study drug and provided a post-

baseline blood sample, the hemoglobin value was 13.0 g per deciliter or more on three consecutive occasions in 807 patients (71.9%) in the darbepoetin alfa group and 241 (21.5%) in the placebo group ($P < 0.001$). The median monthly dose in the darbepoetin alfa group was 167 μg (interquartile range, 105 to 286).

ANEMIA TREATMENTS IN ADDITION TO THE STUDY DRUG

A total of 40 patients (3.5%) in the darbepoetin alfa group and 77 (6.7%) in the placebo group received at least one dose of a nonstudy ESA ($P < 0.001$). There was no significant difference in the proportion of patients who received iron at least once during the study (intravenous iron: 4.9% in the darbepoetin alfa group and 5.6% in the placebo group, $P = 0.47$; oral iron: 72.3% in the darbepoetin alfa group and 73.5% in the placebo group, $P = 0.52$). Among patients who received a study drug, one or more blood transfusions were performed in 123 patients (10.9%) in the darbepoetin alfa group and in 188 (16.5%) in the placebo group ($P < 0.001$).

STUDY OUTCOMES

The primary composite outcome of death from any cause or first hospitalization for worsening heart failure occurred in 576 patients (50.7%) in the darbepoetin alfa group and 565 (49.5%) in the

Table 2. Primary, Secondary, and Other Adjudicated Outcomes.

Outcome	Darbepoetin Alfa (N=1136)	Placebo (N=1142)	Hazard Ratio (95% CI)*	P Value†
	<i>no. of patients (%)</i>			
Primary composite outcome				
Death from any cause or first hospitalization for worsening heart failure	576 (50.7)	565 (49.5)	1.01 (0.90–1.13)	0.87
Death from any cause	474 (41.7)	458 (40.1)	1.04 (0.92–1.19)	0.51
First hospitalization for worsening heart failure	314 (27.6)	311 (27.2)	0.99 (0.85–1.16)	0.92
Secondary composite outcome				
Death from cardiovascular causes or first hospitalization for worsening heart failure	513 (45.2)	506 (44.3)	1.01 (0.89–1.14)	0.92
Death from cardiovascular causes	388 (34.2)	376 (32.9)	1.04 (0.91–1.20)	0.56
Other adjudicated outcomes				
Death from any cause or first nonfatal cardiovascular event‡	607 (53.4)	589 (51.6)	1.04 (0.93–1.17)	0.49
Fatal or nonfatal myocardial infarction§	64 (5.6)	74 (6.5)	0.84 (0.60–1.18)	0.32
Unstable angina	18 (1.6)	12 (1.1)	1.49 (0.72–3.09)	0.28
Fatal or nonfatal stroke¶	42 (3.7)	31 (2.7)	1.33 (0.83–2.12)	0.23
Heart failure during ongoing hospitalization	25 (2.2)	22 (1.9)	1.08 (0.61–1.93)	0.78
Deep venous thrombosis	10 (0.9)	10 (0.9)	1.01 (0.42–2.43)	0.98
Fatal or nonfatal pulmonary embolism	6 (0.5)	2 (0.2)	3.20 (0.64–15.90)	0.13
Resuscitation after cardiac arrest	12 (1.1)	15 (1.3)	0.77 (0.36–1.65)	0.50

* Hazard ratios and 95% confidence intervals were calculated with the use of stratified Cox models.

† P values were calculated by means of a stratified log-rank test and have not been adjusted for multiple comparisons.

‡ Cardiovascular events included in this category were myocardial infarction, unstable angina, stroke, heart failure during ongoing hospitalization, hospitalization for worsening heart failure, deep venous thrombosis, pulmonary embolism, and resuscitation after cardiac arrest.

§ Myocardial infarctions were fatal in 19 patients in the darbepoetin alfa group and 23 patients in the placebo group.

¶ A total of 15 patients in each study group had a fatal stroke.

|| Pulmonary embolism was fatal only in 1 patient in the placebo group.

placebo group (hazard ratio in the darbepoetin alfa group, 1.01; 95% confidence interval [CI], 0.90 to 1.13; $P=0.87$) (Table 2 and Fig. 2A). The result of the analysis adjusted for baseline characteristics was similar (adjusted hazard ratio, 1.01; 95% CI, 0.90 to 1.13; $P=0.88$), as was the result of the as-treated analysis (hazard ratio, 0.98; 95% CI, 0.86 to 1.13; $P=0.82$). The result for the primary outcome was consistent across all subgroups examined (Fig. S2 in the Supplementary Appendix).

There were 474 deaths (41.7%) in the darbepoetin alfa group and 458 (40.1%) in the placebo group (hazard ratio, 1.04; 95% CI, 0.92 to 1.19; $P=0.51$) (Table 2 and Fig. 2B), corresponding to overall annualized mortality rates of 14.4% and 13.8%, respectively. The number of patients who died from cardiovascular causes or had a first hospitalization for worsening heart failure was

similar in the two study groups, as was the number of patients for each of the components of this composite outcome (Table 2 and Fig. 2). The total numbers of hospitalizations for heart failure (including second and subsequent hospitalizations) were 572 in the darbepoetin alfa group and 695 in the placebo group ($P=0.06$ from a negative binomial model).

Fatal or nonfatal adjudicated stroke occurred in 42 patients (3.7%) in the darbepoetin alfa group and 31 (2.7%) in the placebo group (hazard ratio, 1.33; 95% CI, 0.83 to 2.12; $P=0.23$). All other prespecified adjudicated outcomes are summarized in Table 2.

The least-squares mean changes from baseline to month 6 in the Overall Summary Score of the KCCQ were 6.68 points (95% CI, 5.35 to 8.01) in the darbepoetin alfa group and 4.48 points (95% CI, 3.15 to 5.81) in the placebo group (treatment

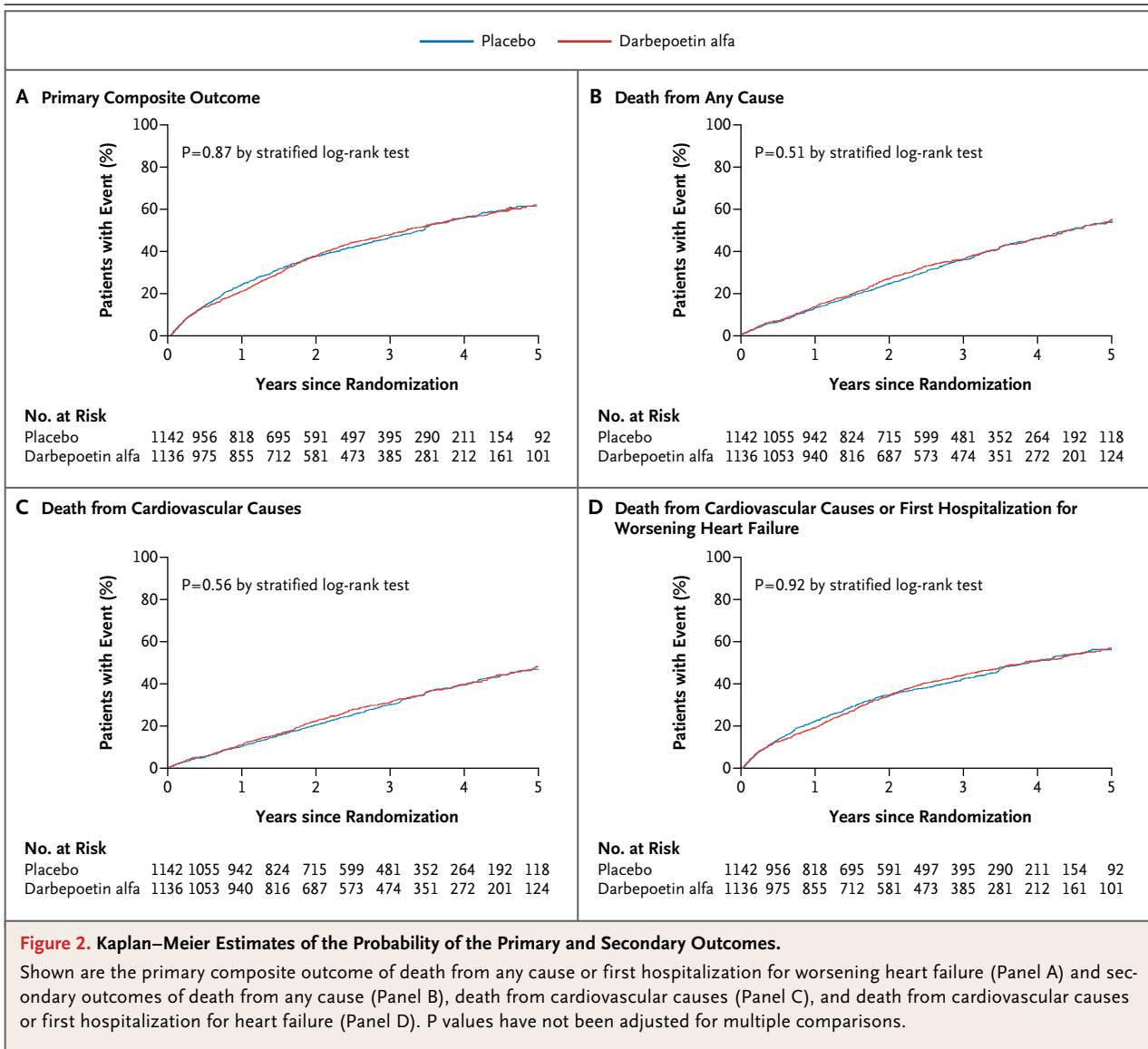


Figure 2. Kaplan–Meier Estimates of the Probability of the Primary and Secondary Outcomes.

Shown are the primary composite outcome of death from any cause or first hospitalization for worsening heart failure (Panel A) and secondary outcomes of death from any cause (Panel B), death from cardiovascular causes (Panel C), and death from cardiovascular causes or first hospitalization for heart failure (Panel D). P values have not been adjusted for multiple comparisons.

difference, 2.20 points; 95% CI, 0.65 to 3.75; P=0.005). The proportions of patients with an improvement in the Overall Summary Score of 5 points or more at 6 months were 53% in the darbeopetin alfa group and 48% in the placebo group (P=0.06). The increases from baseline to 6 months in the Symptom Frequency Score were 6.20 points (95% CI, 4.71 to 7.69) in the darbeopetin alfa group and 3.91 points (95% CI, 2.42 to 5.40) in the placebo group (P=0.01).

ADVERSE EVENTS

In the darbeopetin alfa group, 221 of 1133 patients (19.5%) had an adverse event leading to study-

drug discontinuation, as compared with 229 of 1140 (20.1%) in the placebo group (P=0.73). The most frequent serious adverse events, and those of particular interest, are summarized in Table 3 and in more detail in Table S5 in the Supplementary Appendix. Embolic and thrombotic adverse events were reported in 153 patients (13.5%) in the darbeopetin alfa group and 114 (10.0%) in the placebo group (P=0.01) (Table 3, and Table S6 in the Supplementary Appendix). With respect to serious adverse events, septic shock was reported significantly more frequently in the darbeopetin alfa group than in the placebo group, although there was no excess of other serious adverse events

Table 3. Adverse Events of Interest.*

Adverse Event	Darbeпоetin Alfa (N=1133)	Placebo (N=1140)	Risk Difference (95% CI)†	P Value‡
	no. of patients (%)		percentage points	
Any event of interest	660 (58.3)	662 (58.1)	0.2 (-3.9 to 4.2)	0.93
Cardiac failure	438 (38.7)	459 (40.3)	-1.6 (-5.6 to 2.4)	0.43
Ischemic heart disease	155 (13.7)	164 (14.4)	-0.7 (-3.6 to 2.2)	0.63
Cerebrovascular disorder				
Any	61 (5.4)	45 (3.9)	1.4 (-0.3 to 3.2)	0.10
Hemorrhagic	39 (3.4)	30 (2.6)	0.8 (-0.6 to 2.2)	0.26
Ischemic	51 (4.5)	32 (2.8)	1.7 (0.2 to 3.2)	0.03
Embolic and thrombotic events				
Any	153 (13.5)	114 (10.0)	3.5 (0.9 to 6.1)	0.009
Arterial§	87 (7.7)	73 (6.4)	1.3 (-0.8 to 3.4)	0.24
Venous¶	29 (2.6)	20 (1.8)	0.8 (-0.4 to 2.0)	0.19
Vessel type unspecified and mixed arterial and venous	51 (4.5)	27 (2.4)	2.1 (0.6 to 3.6)	0.005
Hemodialysis-related vascular access thrombosis	1 (0.1)	0	0.1 (-0.1 to 0.3)	0.50
Hypertension	81 (7.1)	69 (6.1)	1.1 (-0.9 to 3.1)	0.29
Cancer	69 (6.1)	68 (6.0)	0.1 (-1.8 to 2.1)	0.90
Convulsions	4 (0.4)	5 (0.4)	-0.1 (-0.6 to 0.4)	1.00
Hypersensitivity reactions	99 (8.7)	96 (8.4)	0.3 (-2.0 to 2.6)	0.79
Antibody-mediated pure red-cell aplasia	0	0	NA	NA

* Adverse events of interest were identified with the use of the prespecified Standard MedDRA (*Medical Dictionary for Regulatory Activities*) Query (SMQ) search strategies, as specified in the statistical analysis plan. Patients could have more than one event in each overall category. Data are for patients who received at least one dose of a study drug. NA denotes not applicable.

† The risk difference for each event was calculated as the percentage of patients with the event in the darbepoetin alfa group minus the percentage of patients with the event in the placebo group. The 95% Wald asymptotic confidence intervals for the risk difference were calculated.

‡ P values were calculated with the use of Pearson's chi-square test, except for hemodialysis-related vascular access thrombosis and convulsions, for which Fisher's exact test was used. P values have not been adjusted for multiple comparisons.

§ Included in the arterial-events category are the following preferred terms: acute myocardial infarction, amaurosis fugax, carotid-artery occlusion, cerebrovascular insufficiency, coronary arterial stent insertion, coronary-artery occlusion, ischemic stroke, lacunar infarction, myocardial infarction, percutaneous coronary intervention, peripheral arterial occlusive disease, peripheral-artery thrombosis, peripheral embolism, retinal-artery occlusion, and transient ischemic attack.

¶ Included in the venous-events category are the following preferred terms: deep-vein thrombosis, jugular-vein thrombosis, pulmonary embolism, retinal-vein occlusion, thrombophlebitis, superficial thrombophlebitis, and limb venous thrombosis.

|| Included in the unspecified events are the following preferred terms: bone infarction, cerebral infarction, cerebral ischemia, cerebrovascular accident, coronary-artery thrombosis, embolism, hemorrhagic stroke, hemiparesis, hemiplegia, heparin-induced thrombocytopenia, intestinal infarction, intracardiac thrombus, shunt occlusion, splenic infarction, thrombosis, thrombosis in device, mesenteric-vessel thrombosis, and thrombosis prophylaxis.

related to infection in the darbepoetin alfa group (Table S7 in the Supplementary Appendix). A history of cancer at baseline was reported by 93 patients in the darbepoetin alfa group and 78 in the placebo group. Of these patients, 44 in the darbepoetin alfa group and 36 in the placebo group died; the deaths were attributed to cancer in 4 and

6 of the patients, respectively, with no significant between-group differences. There was no significant between-group difference in systolic blood pressure during the study, but the diastolic blood pressure was 1 mm Hg higher (median AUC) in the darbepoetin alfa group than in the placebo group (P=0.03).

DISCUSSION

We evaluated the effect of correcting anemia in patients with systolic heart failure by adding darbepoetin alfa to contemporary therapy, with a target hemoglobin level of 13.0 g per deciliter. As compared with placebo, darbepoetin alfa treatment led to an early and sustained increase in the hemoglobin level. Despite this improvement, the use of darbepoetin alfa did not reduce the risk of the primary outcome of death or hospitalization for worsening heart failure. None of the other adjudicated outcomes differed significantly between the two study groups. The lack of effect of darbepoetin alfa was consistent across all prespecified subgroups.

From a safety perspective, more patients had fatal or nonfatal strokes in the darbepoetin alfa group than in the placebo group. Although the difference was not significant, this observation is in keeping with the findings of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT),¹⁶ a study of darbepoetin alfa in patients with diabetes, chronic kidney disease, and anemia. As has been noted in other populations,^{17,18} there was a significant increase in investigator-reported arterial and venous thromboembolic events in patients receiving darbepoetin alfa.

Although the rate of clinical events was not reduced in the darbepoetin alfa group, treatment of anemia did improve the Overall Summary and Symptom Frequency Scores on the KCCQ. However, the average between-group difference and the difference in the proportion of patients with a clinically meaningful improvement in these scores were of questionable importance.

Although we enrolled patients with mild-to-moderate anemia, they were at high risk for events, and we accrued the number of primary outcome events that were needed to test our hypothesis. Our patients were iron-replete at baseline, had a high use of iron during the study (as dictated by the study protocol), and did not become iron-deficient

during the study. The protocol-defined hemoglobin target of 13.0 g per deciliter was attained in the darbepoetin alfa group, and the median between-group difference in the hemoglobin level was 1.5 g per deciliter (since there was a slight increase in hemoglobin level in the placebo group). Observational studies have shown that outcomes are worse in patients with heart failure who have a hemoglobin level of less than 12.0 g per deciliter than in those with a hemoglobin level of 12.0 g per deciliter or more.^{2,23} Moreover, in these studies, a change of 1 g per deciliter was associated with a difference in all-cause mortality of approximately 15 to 20 percentage points (and a similar difference in a composite of all-cause mortality or heart-failure hospitalization).²³ Consequently, our findings suggest that the hemoglobin level, like other surrogates, is simply a marker of poor prognosis in heart failure rather than a therapeutic target.

A limitation of our study is that we excluded patients with severe anemia (hemoglobin level, <9.0 g per deciliter). Such patients might have a greater increase in hemoglobin values with darbepoetin alfa (with greater separation from the findings in the placebo group). However, severe anemia is uncommon in patients with heart failure. Also, we tested one approach to elevating the hemoglobin level, and other strategies may have different effects.

In summary, we found that the correction of anemia with the use of darbepoetin alfa did not reduce the rate of death or hospitalization among patients with systolic heart failure who were receiving contemporary treatment. Moreover, there was a significant increase in the risk of thromboembolic events among patients receiving darbepoetin alfa. Our findings do not support the use of darbepoetin alfa in patients with systolic heart failure and mild-to-moderate anemia.

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REFERENCES

1. O'Meara E, Murphy C, McMurray JJ. Anemia and heart failure. *Curr Heart Fail Rep* 2004;1:176-82.
2. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004;110:149-54.
3. Maggioni AP, Opasich C, Anand I, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005;11:91-8.
4. O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesar-
- tan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006;113:986-94.
5. Komajda M, Anker SD, Charlesworth A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006;27:1440-6.

6. Anand IS. Pathophysiology of anemia in heart failure. *Heart Fail Clin* 2010;6:279-88.
7. Westenbrink BD, Voors AA, de Boer RA, et al. Bone marrow dysfunction in chronic heart failure patients. *Eur J Heart Fail* 2010;12:676-84.
8. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001;37:1775-80.
9. Cleland JG, Sullivan JT, Ball S, et al. Once-monthly administration of darbepoetin alfa for the treatment of patients with chronic heart failure and anemia: a pharmacokinetic and pharmacodynamic investigation. *J Cardiovasc Pharmacol* 2005;46:155-61.
10. Ngo K, Kotecha D, Walters JA, et al. Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. *Cochrane Database Syst Rev* 2010;1:CD007613.
11. Ghali JK, Anand IS, Abraham WT, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation* 2008;117:526-35.
12. Ponikowski P, Anker SD, Szachniewicz J, et al. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2007;49:753-62.
13. van Veldhuisen DJ, Dickstein K, Cohen-Solal A, et al. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. *Eur Heart J* 2007;28:2208-16.
14. Klapholz M, Abraham WT, Ghali JK, et al. The safety and tolerability of darbepoetin alfa in patients with anaemia and symptomatic heart failure. *Eur J Heart Fail* 2009;11:1071-7.
15. van der Meer P, Groeneweld HF, Januzzi JL Jr, van Veldhuisen DJ. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. *Heart* 2009;95:1309-14.
16. Pfeffer MA, Burdman EA, Chen C-Y, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019-32.
17. Singh AK, Szczec L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
18. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-90.
19. McMurray JJ, Anand IS, Diaz R, et al. Design of the Reduction of Events with Darbepoetin Alfa in Heart Failure (RED-HF): a phase III, anaemia correction, morbidity-mortality trial. *Eur J Heart Fail* 2009;11:795-801. [Erratum, *Eur J Heart Fail* 2010;12:765.]
20. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;35:1245-55.
21. Pettersen KI, Reikvam A, Rollag A, Stavem K. Reliability and validity of the Kansas City cardiomyopathy questionnaire in patients with previous myocardial infarction. *Eur J Heart Fail* 2005;7:235-42.
22. McMurray JJV, Anand IA, Diaz R, et al. Baseline characteristics of patients in the Reduction of Events with Darbepoetin Alfa in Heart Failure trial (RED-HF). *Eur J Heart Fail* 2013;15:334-41.
23. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation* 2005;112:1121-7.

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