Baseline characteristics of patients in the Reduction of Events with Darbepoetin alfa in Heart Failure trial (RED-HF)

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Aims

This report describes the baseline characteristics of patients in the Reduction of Events with Darbepoetin alfa in Heart Failure trial (RED-HF) which is testing the hypothesis that anaemia correction with darbepoetin alfa will reduce the composite endpoint of death from any cause or hospital admission for worsening heart failure, and improve other outcomes.

Methods and results

Key demographic, clinical, and laboratory findings, along with baseline treatment, are reported and compared with those of patients in other recent clinical trials in heart failure. Compared with other recent trials, RED-HF enrolled more elderly [mean age 70 (SD 11.4) years], female (41%), and black (9%) patients. RED-HF patients more often had diabetes (46%) and renal impairment (72% had an estimated glomerular filtration rate <60 mL/min/1.73 m²). Patients in RED-HF had heart failure of longer duration [5.3 (5.4) years], worse NYHA class (35% II, 63% III, and 2% IV), and more signs of congestion. Mean EF was 30% (6.8%). RED-HF patients were well treated at randomization, and pharmacological therapy at baseline was broadly similar to that of other recent trials, taking account of study-specific inclusion/exclusion criteria. Median (interquartile range) haemoglobin at baseline was 112 (106–117) g/L.

Conclusion

The anaemic patients enrolled in RED-HF were older, moderately to markedly symptomatic, and had extensive co-morbidity.

Keywords

Heart failure • Anaemia

Introduction

Numerous studies have shown that anaemia is common in heart failure and is associated with worse outcomes.1–6 While some patients have specific, correctable causes of anaemia such as iron deficiency, the exact aetiology of anaemia in most patients with heart failure is unknown, although contributing mechanisms may include renal impairment, inflammation, inadequate production of erythropoietin, and unresponsiveness to erythropoietin.9–12 Heart failure patients with anaemia have more severe symptoms...
and signs, reduced functional capacity, and higher rates of hospitalization and death, compared with heart failure patients without anaemia.1–8,13,14 If anaemia is a mediator and not just a marker of poor outcomes, correcting anaemia could become an important and novel therapeutic target to improve long-term outcomes in such patients. As a result, there has been much interest in whether correcting anaemia might improve outcomes in heart failure.15,16 One treatment shown to increase haemoglobin in anaemic patients with heart failure is the use of an erythropoiesis-stimulating agent (ESA).17–22 Studies in experimental animals have also raised the hypothesis that ESAs might also have other potentially beneficial cardiovascular effects.23–25 However, it is not known whether ESAs improve clinical outcomes in heart failure, and they have not been shown to reduce cardiovascular events in patients with chronic kidney disease.26–28 The Reduction of Events with Darbepoetin alfa in Heart Failure trial (RED-HF) is testing the hypothesis that anaemia correction with the ESA darbepoetin will reduce the composite endpoint of death from any cause or hospital admission for worsening heart failure, and improve quality of life and other outcomes.29–31 This report describes the baseline characteristics of the patients randomized in RED-HF and considers them in the context of other recently published heart failure trials.

Methods

Objectives
RED-HF is a randomized multicentre double-blind, placebo-controlled, clinical trial designed to determine whether correction of anaemia with the long-acting ESA darbepoetin alfa improves mortality and morbidity in patients with heart failure and anaemia. The details of the design of RED-HF have been described in detail elsewhere.30 The primary composite outcome is death from any cause or hospitalization for heart failure.31–34 At baseline, patients in RED-HF were older, a much larger proportion were women, and more were black than in the other trials. Patients in RED-HF also had a longer duration of heart failure than reported in previous trials.35–37

Baseline demographics
Table 1 shows the baseline characteristics of the patients in RED-HF compared with those of patients in other recently published heart failure trials.33–36 At baseline, patients in RED-HF were older, a much larger proportion were women, and more were black than in the other trials. Patients in RED-HF also had a longer duration of heart failure than reported in previous trials.

Co-morbidities
Two co-morbidities were more common at baseline in RED-HF, specifically diabetes mellitus and impaired renal function (eGFR < 60 mL/min/1.73 m²). The only other notable difference was the much smaller proportion of current smokers in RED-HF, compared with the other trials. In addition to the co-morbidities shown in Table 1, 8% of patients had a history of cancer.

Functional capacity and heart failure signs
At baseline, a greater proportion of patients in RED-HF were in NYHA functional class III or IV than in the other recent trials. As shown in Table 2, more patients in RED-HF had signs of congestion than those in other trials.

Quality of life
Table 3 shows KCCQ scores for patients in RED-HF, compared with those of patients in other recently published trials. The baseline Overall Summary Score and Clinical Summary Score for RED-HF patients were 56.1 and 59.4, respectively. These are consistent with patients in RED-HF having moderate to severe heart failure.

Baseline treatment
Overall, the patients were well treated at randomization and the pharmacological therapy at baseline was broadly similar to other recent trials, taking account of study-specific inclusion/exclusion

Results

Enrolment
Between 13 June 2006 and 4 May 2012, a total of 2278 patients were randomized at 453 sites in 33 countries representing all major regions of the world. The three regions with the greatest contribution were North America (n = 644), Western Europe (n = 609), and Central/Eastern Europe (n = 454). The three countries with the largest enrolment were the USA (n = 601), India (n = 299), and Russia (n = 105). The mean number of patients enrolled per site was 5.0 (range per country from 1.3 to 11.1).

Statistical analysis
The RED-HF is an event-driven study, such that assuming an annualized placebo event rate of 25%. Approximately 1150 subjects with primary endpoint events will be needed to detect a 20% difference between treatment groups with 80% power with adjustments for treatment effect attenuation. The protocol originally assumed that the study would enrol approximately 2600 subjects. Because the actual enrolment duration was longer than originally anticipated, 2278 subjects were actually enrolled to accrue the approximately 1150 primary endpoints.

All randomized subjects are included in the present analysis. Descriptive summary statistics in the form of mean and standard deviation (SD) or median and first (Q1) and third quartiles (Q3) are provided for continuous baseline variables, and percentage of total were generated for categorical baseline variables. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) equation for IDMS (isotope dilution mass spectrometry)-calibrated serum creatinine: eGFR (mL/min/1.73 m²) = 175 × [serum creatinine in mg/dL]−1.154 × age−0.203 × 1.212 [if black] × 0.742 [if female].

Descriptive summary statistics are provided using SAS® software version 9.2. No statistical comparisons have been made.
Table 1: Baseline characteristics and treatment in RED-HF and other recent trials

|                      | EMPHASIS-HF (n = 2737) | SHIFT (n = 6505) | RAFT (n = 1798) | HEAAL<sup>a</sup> (n = 3834) | RED-HF (n = 2278) |
|----------------------|------------------------|-----------------|----------------|-----------------------------|------------------|
| Age (mean)           | 69                     | 60              | 66             | 66                          | 70 (11.4)        |
| Female sex (%)       | 22                     | 23              | 17             | 30                          | 41               |
| NYHA class (%)       |                        |                 |                |                             |                  |
| II                   | 100                    | 49              | 80             | 69                          | 35               |
| III                  | 0                      | 50              | 20             | 30                          | 63               |
| IV                   | 0                      | 2               | –              | 1                           | 2                |
| Race (%)             |                        |                 |                |                             |                  |
| White                | 83                     | 89              | –              | 61                          | 68               |
| Black                | 2                      | –               | –              | 1                           | 9                |
| Asian                | 12                     | 8               | –              | 22                          | 14               |
| Other                | 3                      | 3               | –              | 16                          | 9                |
| Heart rate (mean)    | 72                     | 80              | –              | 72                          | 72 (11.2)        |
| BP (mean)            |                        |                 |                |                             |                  |
| Systolic             | 124                    | 122             | –              | 125                         | 120 (18.0)       |
| Diastolic            | 75                     | 76              | –              | 72                          | 69 (11.0)        |
| LVEF (mean)          | 26                     | 29              | 23             | 33                          | 30 (6.8)         |
| QRS duration (mean)  | 122                    | –               | 158            | –                           | 121 (39.4)       |
| BMI (mean)           | 28                     | 28              | –              | 27                          | 27 (5.7)         |
| Principal cause of HF (%) |                     |                 |                |                             |                  |
| IHD                  | 69                     | 67              | 67             | –                           | 72               |
| Non-IHD              | 31                     | 33              | 33             | –                           | 28               |
| Duration of HF (years) | 4.7                   | 3.5             | –              | –                           | 5.3 (5.4)        |
| Medical history (%)  |                        |                 |                |                             |                  |
| Hospitalization for HF | 53                    | 100<sup>b</sup> | 25<sup>c</sup> | –                           | 87 (37'<sup>c</sup>) |
| Hypertension         | 66                     | 67              | 45             | 60                          | 74               |
| Angina pectoris      | 43                     | –               | –              | 65 (IHD)                    | 32               |
| Unstable angina      | –                      | –               | –              | –                           | 21               |
| Myocardial infarction| 50                     | 56              | –              | –                           | 54               |
| PCI                  | 22                     | –               | 24             | –                           | 28               |
| CABG                 | 19                     | –               | 34             | –                           | 28               |
| Atrial fibrillation/flutter | 31                 | 8<sup>d</sup>  | 13<sup>e</sup> | 28                          | 32               |
| LBBB<sup>f</sup>     | 27                     | –               | 72             | –                           | 19               |
| Diabetes mellitus    | 31                     | 31              | 34             | 31                          | 46               |
| Stroke               | 10                     | 8               | –              | –                           | 8                |
| Current smoker       | –                      | 18              | 14             | –                           | 4                |
| Renal function       |                        |                 |                |                             |                  |
| Serum creatinine (μmol/L) | 102                | –              | –              | 97                          | 131 (49.3)       |
| eGFR mL/min/1.73 m<sup>2</sup> (mean) | 71             | 75              | 61             | –                           | 50 (21.3)        |
| eGFR < 60 mL/min/1.73 m<sup>2</sup> (%) | 33            | –              | 50             | –                           | 72               |
| Treatment (%)        |                        |                 |                |                             |                  |
| Diuretic             | 85                     | –               | 85             | 77                          | 91               |
| ACEi                 | 78                     | 79              | –              | NA                          | 63               |
| ARB                  | 19                     | 14              | –              | NA                          | 28               |
| ACEi, ARB, or both   | 94                     | –               | 97             | NA                          | 89               |
| Beta-blocker         | 87                     | 90              | 90             | 72                          | 85               |
| MRA                  | NA                     | 60              | 42<sup>e</sup> | 38                          | 45               |
| Digoxin              | 27                     | 22              | 35             | 42                          | 29               |
| Antithrombotic       | –                      | –               | –              | 33                          | 27               |

Continued
of note, use of antithrombotic and antiplatelet therapy was not more common in RED-HF than in the other trials. ICD and CRT use was also consistent with other recent trials. However, device use was greater in North America and Western Europe than elsewhere.

**Haematological and other laboratory measurements**

Apart from haemoglobin, haematocrit, and erythrocyte count which were reduced, as expected, the median values for other haematological indices were within the normal range, as were vitamin B₁₂ and folate levels (Table 5). The proportion of women with serum iron, total iron-binding capacity (TIBC), ferritin, and TSAT within the normal range (97, 94, 88, and 97%, respectively) was numerically higher than for men (89, 92, 83, and 73%, respectively). The notable difference in proportion with a normal TSAT reflects the higher lower limit of normal for men (20% vs. 15% in women) and the eligibility TSAT criterion (≥15%).³⁰ Blood chemistry was largely as anticipated, with an elevated urea (blood urea nitrogen) in keeping with the high prevalence of subjects with a low eGFR.

**Discussion**

Comparison of patient baseline characteristics across trials has to be made cautiously because these are partly determined by...
Anaemia is also more prevalent in black individuals, to be more common in RED-HF than in the other studies. The longer average duration of heart failure in patients in RED-HF is also consistent with the notion that anaemia is more common in more advanced heart failure (in addition to the studies shown in Table 1, the duration of heart failure was 3.1 years in BEST and 4.3 years in Val-HeFT)\(^1,9,10\).

Most other characteristics at baseline did not differ strikingly between patients in RED-HF and other study populations. The one exception was the lower prevalence of smoking in RED-HF. Although this could be a chance finding (or due to under-reporting of smoking in certain regions/cultures), review of current smoking rates in five other trials showed a prevalence which ranged from 10.6% to 17.5%.\(^5,38–40,45\) The prevalence of smoking in RED-HF may, therefore, be unusually low, possibly reflecting the association between smoking and higher haemoglobin levels.

Baseline use of an ACE inhibitor (or ARB) and beta-blocker in RED-HF was high and consistent with the use of these drugs in other recent trials. Mineralocorticoid receptor antagonist (MRA) use at baseline was not as high as in SHIFT, but all patients in that trial had recently been hospitalized, i.e. probably recently in NYHA class II or III heart failure, an LVEF ≤ 30%, a haemoglobin level of 9.5–13.5 g/dL. Patients were randomized 1:2 to i.v. saline or i.v. iron. At baseline, the mean ferritin level in FAIR-HF was 55 μg/L (compared with 156 μg/L in RED-HF), TSAT 17.3% (compared with 26.9%), and haemoglobin 11.9 g/dL (compared with 11.0 g/dL). Patients in FAIR-HF had a higher average eGFR at baseline (64 mL/min/1.73 m\(^2\)) compared with those in RED-HF (50 mL/min/1.73 m\(^2\)).
In summary, the patients enrolled in RED-HF exhibit the expected greater functional impairment and co-morbidities found in patients with anaemia in addition to heart failure and are well treated with conventional evidence-based therapy. Therefore, RED-HF is well placed to answer the question of whether or not the addition of darbepoetin alfa to standard therapy will have an incremental benefit in patients with systolic heart failure and anaemia.

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Conflict of interest: Glasgow University is compensated for time spent by J.I.V.McM working as a Steering Committee member for the RED-HF and TREAT trials. I.S.A. is a member of the RED-HF Steering Committee. A.P.M and C.O. have no conflicts to declare. M.A.P. has received honoraria for participation in the RED-HF Steering Committee. D.J. van V. has received Board Membership fees and his department has received unrestricted research grants from Amgen. J.B.Y. is a consultant to Amgen and receives research support from Amgen as co-Principal Investigator of the RED-HF trial.

Appendix: RED-HF trial investigators

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Table 5 Baseline laboratory measurements in RED-HF

| Measurement | Median (Q1, Q3) |
|-------------|----------------|
| Haematology |                |
| Haemoglobin (g/L) | 112 (106, 117) |
| Haematocrit (%) | 0.34 (0.33, 0.36) |
| White cells (10^9/L) | 6.5 (5.3, 7.9) |
| Red cells (10^12/L) | 5.3 (4.4, 6.1) |
| Platelets (10^9/L) | 224 (179, 275) |
| Iron indices |                |
| Serum iron (µmol/L) | 12.2 (9.8, 15.8) |
| TIBC (µmol/L) | 50.5 (44.8, 56.7) |
| Ferritin (µg/L) | 102 (53, 194) |
| TSAT (%) | 24 (19, 31) |
| Vitamin levels |                |
| Vitamin B12 (pmol/L) | 286 (206, 454) |
| Serum folate (nmol/L) | 24 (14, 56) |
| Blood chemistry |                |
| Sodium (mmol/L) | 140 (138, 142) |
| Potassium (mmol/L) | 4.5 (4.2, 4.9) |
| Magnesium (mmol/L) | 0.9 (0.8, 1.0) |
| BUN (mmol/L) | 10.4 (7.1, 15.0) |
| Uric acid (µmol/L) | 440 (357, 547) |
| Albumin (g/L) | 39 (36, 42) |
| Calcium (mmol/L) | 2.4 (2.3, 2.5) |
| Phosphorus (mmol/L) | 1.2 (1.1, 1.3) |
| Glucose (mmol/L) | 6.1 (5.3, 8.4) |
| HbA1c (%) | 6.0 (5.6, 7.0) |
| Total cholesterol (mmol/L) | 4.1 (3.4, 4.9) |

BUN, blood urea nitrogen; HbA1c, glycated haemoglobin; TIBC, total iron-binding capacity; TSAT, transferrin saturation.
References

1. O’Meara E, Murphy C, McMurray JJ. Anemia and heart failure. Curr Heart Fail Rep 2004;1:176–182.

2. Anand I, McMurray JJ, Whismore J, Warren M, Pham A, Mcmannish MA, Burton PB. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004;110:149–154.

3. Maggioni AP, Opsich C, Anand I, Barlera S, Carbonieri E, Gonzini L, Tavazzi L. Hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Eur Heart J 2004;25:1440–1446.

4. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. J Cardiovasc Risk 2005;11:91–98.

5. Anand IS, Kuskowlski MA, Rector TS, Flores VG, Glazer RD, Hester A, Chiang YT, Ackray N, Maggioni AP, Opsich C, Latin R, Cohn JN. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Eur Heart J 2005;26:1121–1127.

6. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. J Cardiovasc Risk 2005;11:91–98.

7. Westenbrink BD, de Boer RA, Voors AA, van Gilst WH, van Veldhuisen DJ. Anemia and mortality in heart failure patients a prospective assessment of the occurrence of anemia in patients with heart failure: results from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) Registry. Circulation 2006;113:986–994.

8. Komada M, Arker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A. Anemia and mortality in heart failure patients a prospective assessment of the occurrence of anemia in patients with heart failure: results from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) Registry. Circulation 2006;113:986–994.

9. Westenbrink BD, de Boer RA, Voors AA, van Gilst WH, van Veldhuisen DJ. Anemia in chronic heart failure: etiology and treatment options. Curr Opin Cardiol 2008;23:141–147.
