

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

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Received 6 November 2012; accepted 7 November 2012; online publish-ahead-of-print 17 January 2013

## 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 m<sup>2</sup>). 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.<sup>1–8</sup> 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.<sup>9–12</sup> Heart failure patients with anaemia have more severe symptoms

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and signs, reduced functional capacity, and higher rates of hospitalization and death, compared with heart failure patients without anaemia.<sup>1–8,13,14</sup> 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.<sup>15,16</sup> One treatment shown to increase haemoglobin in anaemic patients with heart failure is the use of an erythropoiesis-stimulating agent (ESA).<sup>17–22</sup> Studies in experimental animals have also raised the hypothesis that ESAs might also have other potentially beneficial cardiovascular effects.<sup>23–25</sup> 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.<sup>26–28</sup> 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.<sup>29–31</sup> 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.<sup>30</sup> The primary composite outcome is death from any cause or hospitalization for heart failure; change in health-related quality of life, measured using the Overall Summary Score and Symptom Frequency Score from the Kansas City Cardiomyopathy Questionnaire (KCCQ), is a key secondary endpoint.<sup>32</sup>

Briefly, consenting patients aged  $\geq 18$  years, in NYHA functional class II–IV, with an LVEF  $\leq 40\%$  were eligible if their haemoglobin was between 90 and 120 g/L and they were receiving optimal standard heart failure therapy. Major exclusion criteria included transferrin saturation (TSAT)  $< 15\%$ , evidence of bleeding or other correctable causes of anaemia, serum creatinine  $> 265 \mu\text{mol/L}$  ( $> 3.0 \text{ mg/dL}$ ), and blood pressure  $> 160/100 \text{ mmHg}$ . Informed consent was obtained before any study-specific procedure. Patients were randomized 1:1 to double-blind subcutaneous placebo or darbepoetin alfa dosed to a haemoglobin target of 130 g/L (and not exceeding 145 g/L). Randomization was stratified by region and by the presence or absence of an implantable cardioverter defibrillator (ICD), and/or CRT.

### 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:  $\text{eGFR (mL/min/1.73 m}^2) = 175 \times [\text{serum creatinine in mg/dL}]^{-1.154} \times \text{age}^{-0.203} \times 1.212 [\text{if black}] \times 0.742 [\text{if female}]$ .

Descriptive summary statistics are provided using SAS<sup>®</sup> software version 9.2. No statistical comparisons have been made.

## 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).

### 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.<sup>33–36</sup> 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 ( $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ ). 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.<sup>37–40</sup>

### 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 was 56.1 and 59.4, respectively. These are consistent with patients in RED-HF having moderate to severe heart failure.<sup>34,41–44</sup>

### 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

**Table 1** Baseline characteristics and treatment in RED-HF and other recent trials

	<b>EMPHASIS-HF (n = 2737)</b>	<b>SHIFT (n = 6505)</b>	<b>RAFT (n = 1798)</b>	<b>HEAAL<sup>a</sup> (n = 3834)</b>	<b>RED-HF (n = 2278)</b>
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>g</sup>	38	45
Digoxin	27	22	35	42	29
Antithrombotic	–	–	–	33	27

Continued

**Table 1 Continued**

	EMPHASIS-HF (n = 2737)	SHIFT (n = 6505)	RAFT (n = 1798)	HEAAL <sup>a</sup> (n = 3834)	RED-HF (n = 2278)
Vitamin K antagonist	–	–	34 <sup>h</sup>	–	27
Antiplatelet					
Aspirin	–	–	67	51	58
Clopidogrel	–	–	16	–	20
Any	–	–	–	–	66
Antithrombotic or antiplatelet	88	–	–	–	84
Lipid lowering	62	58 <sup>i</sup>	68 <sup>i</sup>	39 <sup>i</sup>	62 <sup>i</sup>
CRT	2	1	–	–	2
ICD	13	4	–	–	14
CRT-D	6	–	–	–	9

ACEi, ACE inhibitor; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NA, not applicable.

<sup>a</sup>Median.

<sup>b</sup>Per protocol, all patients had an admission for worsening heart failure within 12 months.

<sup>c</sup>In previous 6 months.

<sup>d</sup>Current AF excluded.

<sup>e</sup>Permanent AF at baseline.

<sup>f</sup>Non-paced.

<sup>g</sup>Spironolactone.

<sup>h</sup>Warfarin.

<sup>i</sup>Statin.

**Table 2 Clinical signs in RED-HF and other heart failure trials**

	Peripheral oedema (%)	Lung crackles/rales (%)	Jugular venous distension (%)	Third heart sound (%)
RED-HF (n = 2278)	36	22	20	14
CARE-HF (n = 813)	18	12	18	20
COMET (n = 3029)	13	9	NR	19
MERIT-HF (n = 3991)	15	11	14	23
CHARM-Added (n = 2548)	23	15 <sup>a</sup>	11 <sup>b</sup>	18
CHARM-Alt. (n = 2028)	26	16 <sup>a</sup>	10 <sup>b</sup>	16

Alt., Alternative; NR, not reported.

<sup>a</sup>Basilar.

<sup>b</sup>> 6 cm.

criteria (Table 1). 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 (Table 4).

## 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 B<sub>12</sub> 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 ( $\geq 15\%$ ).<sup>30</sup> 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

**Table 3** Baseline mean (SD) Kansas City Cardiomyopathy Questionnaire Overall Summary Scores and Clinical Summary Scores in RED-HF and other recent trials

	<b>MADIT-CRT</b> (n = 1820)	<b>HF-ACTION</b> (n = 2331)	<b>SHIFT</b> (n = 6505)	<b>RED-HF</b> (n = 2278)	<b>STICH</b> (n = 1212)	<b>Heart-Mate II</b> (n = 200)
OSS	77	66	65	56 (22.5)	54	27
CSS	81	–	68	59 (22.4)	64	34

CSS, Clinical Summary Score; OSS, Overall Summary Score.

**Table 4** Type of device used by region

	<b>North America</b> (n = 644), n (%)	<b>Latin America</b> (n = 262), n (%)	<b>Western Europe/AUS/RSA/ Israel (n = 609), n (%)</b>	<b>Eastern Europe/Russia</b> (n = 454), n (%)	<b>Asia (n = 309), n (%)</b>
CRT only	8 (1)	4 (2)	19 (3)	3 (1)	4 (1)
CRT-D	133 (21)	1 (<1)	70 (11)	6 (1)	4 (1)
ICD	214 (33)	8 (3)	72 (12)	12 (3)	3 (1)
None	289 (45)	249 (95)	448 (74)	433 (95)	298 (96)

AUS, Australia; RSA, Republic of South Africa; Asia, India and Hong Kong; Latin America, Argentina, Brazil, Chile, and Mexico.

protocol inclusion and exclusion criteria and geographical factors, as well as the time period during which the trial was recruited (as the standard of care changes with time). Nevertheless, there are some differences between patients in RED-HF and those in other trials that almost certainly reflect the impact of anaemia. For example, patients enrolled in RED-HF are older than in most previous trials with a similar inclusion age range, and RED-HF has a much higher proportion of females than previous studies in systolic heart failure. These characteristics are consistent with the finding that anaemia is more common in older subjects and women in general, and in heart failure specifically. Similarly, anaemia is associated with worse functional class (although it is not known which is the 'chicken' and which is the 'egg'). In keeping with this, we found that a higher proportion of patients in RED-HF were in NYHA class III and IV at baseline than in other recent trials. In addition, RED-HF patients had more signs of congestion, particularly peripheral oedema, than reported in previous studies. The KCCQ Overall and Clinical Summary Scores in RED-HF were consistent with generally worse clinical status than in several recent heart failure trials, including MADIT-CRT, SHIFT, and HF-ACTION (although the scores were not as low as in the Heart Mate II trial which enrolled patients with advanced heart failure ineligible for transplantation).<sup>34,41–44</sup>

Diabetes and impaired renal function are associated with an increased risk of anaemia, and we found both these co-morbidities to be more common in RED-HF than in the other studies described.<sup>1,9,10</sup> Anaemia is also more prevalent in black individuals, and RED-HF has enrolled more black patients than in other recent trials.<sup>1,9,10</sup> This could also reflect the higher proportion of US subjects 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).<sup>1,9,10</sup>

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%.<sup>5,38–40,45</sup> 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 IV and with a firm indication for an MRA.<sup>34</sup> The majority were also enrolled in Europe and none in the USA; MRA use is generally lower in the USA compared with Europe (and RED-HF enrolled a high proportion of patients in the USA). The higher prevalence of renal dysfunction in RED-HF may also have limited use of MRAs.

One other recent trial also makes for an interesting comparison with RED-HF. FAIR-HF enrolled 459 patients with NYHA functional class II or III heart failure, an LVEF  $\leq$  40% (for patients with NYHA class II) or  $\leq$  45% (for NYHA class III), iron deficiency (defined as a ferritin level  $<$  100  $\mu$ g/L or between 100 and 299  $\mu$ g/L, if the TSAT was  $<$  20%), and a haemoglobin level of 9.5–13.5 g/dL.<sup>46</sup> Patients were randomized 1:2 to i.v. saline or i.v. iron. At baseline, the mean level of ferritin in FAIR-HF was 55  $\mu$ g/L (compared with 156  $\mu$ g/L in RED-HF), TSAT 17.4% (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<sup>2</sup>) compared with those in RED-HF (50 mL/min/1.73 m<sup>2</sup>).

**Table 5** Baseline laboratory measurements in RED-HF

Measurement	Median (Q1, Q3)
<b>Haematology</b>	
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)
<b>Iron indices</b>	
Serum iron ( $\mu\text{mol/L}$ )	12.2 (9.8, 15.8)
TIBC ( $\mu\text{mol/L}$ )	50.5 (44.8, 56.7)
Ferritin ( $\mu\text{g/L}$ )	102 (53, 194)
TSAT (%)	24 (19, 31)
<b>Vitamin levels</b>	
Vitamin B <sub>12</sub> (pmol/L)	286 (206, 454)
Serum folate (nmol/L)	24 (14, 56)
<b>Blood chemistry</b>	
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/urea (mmol/L)	10.4 (7.1, 15.0)
Uric acid ( $\mu\text{mol/L}$ )	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)
HbA <sub>1c</sub> (%)	6.0 (5.6, 7.0)
Total cholesterol (mmol/L)	4.1 (3.4, 4.9)

BUN, blood urea nitrogen; HbA<sub>1c</sub>, glycated haemoglobin; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

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.

## Funding

RED-HF is funded by Amgen Inc.

**Conflict of interest:** Glasgow University is compensated for time spent by J.J.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 grant support (research grant to the Brigham and Women's Hospital) for conduct of TREAT and for services to the RED-HF Executive Committee, and received a consulting fee in 2008. M.A., S.C., and D.S. are employees of Amgen, and are currently engaged in research conducted by Amgen. S.D.S. conducts research sponsored by Amgen and has consulted for Amgen. K.S. is a consultant to Amgen and receives research support from Amgen as co-Principal Investigator

of the RED-HF trial. M.T. has received honoraria from Amgen 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.

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Finland (0 patients): V. Harjola, R. Kettunen, M. Kotila.

France (48 patients): F. Bauer, A. Cohen Solal, D. Coisne, J. Davy, P. De Groote, P. Dos Santos, F. Funck, M. Galinier, P. Gibelin, R. Isnard, Y. Neuder, G. Roul, R. Sabatier, J. Trochu.

Germany (99 patients): S. Anker, S. Denny, T. Dreykluff, M. Flesch, S. Genth-Zotz, R. Hambrecht, J. Hein, M. Jeserich, M. John, H. Kreider-Stempfle, U. Laufs, K. Muellerleile, M. Natour, M. Sandri, T. Schäufele, E. von Hohenberg, K. Weyland, B. Winkelmann.

Hong Kong SAR (10 patients): H. Tse, B. Yan.

Hungary (8 patients): B. Barsi, J. Csikasz, C. Dezsai, I. Edes, T. Forster, P. Karpati, C. Kerekes, E. Kis, I. Kosa, G. Lupkovics, A. Nagy, I. Preda, A. Ronaszeki, J. Tomcsanyi, K. Zamolyi.

India (299 patients): D. Agarwal, V. Bahl, A. Bordoloi, K. Chockalingam, M. Chopda, V. Chopra, J. Dugal, N. Ghaisas, S. Ghosh, P. Grant, S. Hiremath, S. Iyengar, B. Jagadeesa Subramania, P. Jain, A. Joshi, A. Khan, A. Mulasari, S. Naik, A. Oomman, V. Pai, R. Parepally Gopal, K. Parikh,

T. Patel, V. Prakash, B. Sastry, S. Sathe, N. Sinha, V. Srikanthan, P. Subburamakrishnan, H. Thacker, G. Wander.

Israel (37 patients): D. Admon, A. Katz, E. Klainman, B. Lewis, A. Marmor, M. Moriel, M. Mosseri, A. Shotan, J. Weinstein, R. Zimlichman.

Italy (51 patients): P. Agostoni, M. Albanese, G. Alunni, R. Bini, A. Boccanelli, L. Bolognese, C. Campana, E. Carbonieri, C. Carpino, L. Checco, F. Cosmi, G. D'Angelo, M. De Cristofaro, A. Floresta, A. Fucili, M. Galvani, A. Ileva, S. Marra, G. Musca, N. Peccerillo, P. Perrone Filardi, E. Picchio, T. Russo, L. Scelsi, M. Senni, L. Tavazzi.

Latvia (20 patients): A. Erglis, I. Jasinkevica, N. Kakurina, I. Veze, E. Volans.

Lithuania (30 patients): A. Bagdonas, E. Berukstis, J. Celutkiene, A. Dambrauskaite, D. Jarasuniene, D. Luksiene, A. Rudys, G. Sakalyte, S. Sliaziene.

Mexico (97 patients): R. Aguilar-Romero, J. Aspe y Rosas, E. Cardona-Muñoz, J. Castro-Jimenez, J. Chavez-Herrera, E. Chuquiure Valenzuela, G. De la Pena, E. Herrera, J. Leiva-Pons, A. Lopez Alvarado, G. Mendez Machado, G. Ramos-Lopez.

The Netherlands (64 patients): D. Basart, E. Buijs, J. Cornel, M. de Leeuw, R. Dijkgraaf, P. Dunselman, M. Freericks, K. Hamraoui, T. Lenderlink, G. Linssen, P. Lodewick, C. Lodewijks, D. Lok, P. Nierop, E. Ronner, A. Somsen, J. van Dantzig, P. van der Burgh, L. van Kempen, B. van Vlies, A. Voors, A. Wardeh, F. Willems.

Norway (17 patients): K. Dickstein, T. Gundersen, T. Hole, J. Thalamus, A. Westheim.

Poland (92 patients): M. Dabrowski, J. Gorski, J. Korewicki, K. Kuc, P. Miekus, W. Musial, J. Niegowski, W. Piotrowski, P. Podolec, L. Polonski, P. Ponikowski, A. Rynkiewicz, R. Szelemej, M. Trusz-Gluza, M. Ujda, D. Wojciechowski, A. Wysokinski.

Portugal (14 patients): A. Camacho, C. Fonseca, P. Monteiro.

Romania (26 patients): E. Apetrei, I. Bruckner, E. Carasca, I. Coman, M. Datcu, S. Dragulescu, P. Ionescu, D. Iordachescu-Petica, I. Manitiu, V. Popa, A. Pop-Moldovan, M. Radoi, S. Stamate, M. Tomescu, I. Vita.

Russia (105 patients): G. Aroutiounov, M. Ballyuzek, B. Bart, S. Churina, M. Glezer, B. Goloshchekin, A. Ileva, Z. Kobalava, V. Kostenko, Y. Lopatin, A. Martynov, V. Orlov, E. Semernin, Z. Shogenov, B. Sidorenko, A. Skvortsov, G. Storzakov, V. Sulimov, O. Talibov, S. Tereshenko, V. Tsyrlin, V. Zadionchenko, D. Zateyshchikov.

Slovakia (62 patients): A. Dzapina, M. Hranai, J. Kmec, K. Micko, J. Murin, D. Pella, G. Sojka, V. Spisak, P. Vahala, D. Vinanska.

South Africa (25 patients): A. Badat, J. Bayat, S. Dawood, E. Delport, G. Ellis, R. Garda, E. Klug, T. Mabin, D. Naidoo, M. Pretorius, N. Ranjith, L. Van Zyl, H. Weich.

Spain (40 patients): M. Anguita, J. Berrazueta, J. Bruguera i Cortada, E. de Teresa, M. Gómez Sánchez, J. González Juanatey, I. Gonzalez-Maqueda, R. Jordana, J. Lupon, L. Manzano, D. Pascual Figal, L. Pulpón, J. Recio, F. Ridocci Soriano, J. Rodríguez Lambert, E. Roig Minguell, E. Roig Minguell, J. Romero, P. Valdovinos.

Sweden (19 patients): L. Klintberg, T. Kronvall, M. Lycksell, S. Morner, E. Rydberg, K. Swedberg, I. Timberg, G. Wikstrom

Switzerland (0 patients): T.4 Moccetti.

UK (65 patients): J. Ashok, P. Banerjee, G. Carr-White, J. Cleland, E. Connolly, M. Francis, R. Greenbaum, H. Kadr, S. Lindsay, J. McMurray, S. Megarry, A. Memon, D. Murdoch, R. Senior, I. Squire, L. Tan, K. Witte.

USA (601 patients): K. Adams, P. Adamson, A. Adler, L. Altschul, A. Altschuller, H. Amirani, I. Anand, C. Andreou, M. Ansari, M. Antonishen, H. Banchs, S. Banerjee, D. Banish, A. Bank, A. Barbagelata, D. Barnard, R. Bellinger, A. Benn, M. Berk, B. Berry, V. Bethala, S. Bilazarian, J. Bisognano, F. Bleyer, M. Blum, J. Boehmer, A. Bouchard, A. Boyle, B. Bozkurt, C. Brown, B. Burlew, K. Burnham, J. Butler, J. Call, P. Cambier, T. Cappola, R. Carlson, B. Chandler, R. Chandra, P.

Chandraratna, R. Chernick, D. Colan, H. Colfer, W. Colucci, T. Connelly, O. Costantini, S. Dadkhah, I. Dauber, J. Davis, S. Davis, S. Denning, M. Drazner, S. Dunlap, L. Egbujiobi, U. Elkayam, J. Elliott, M. El-Shahawy, L. Essandoh, G. Ewald, J. Fang, H. Farhoud, G. Felker, J. Fernandez, R. Festin, G. Fishbein, V. Florea, E. Flores, J. Floro, M. Gabris, M. Garg, R. Gatewood, M. Geller, J. Ghali, W. Ghumman, G. Gibbs, E. Gillespie, R. Gilmore, H. Gogia, L. Goldberg, I. Gradus-Pizlo, T. Grainger, G. Gudmundsson, D. Gunawardena, D. Gupta, T. Hack, S. Hall, G. Hamroff, S. Hankins, M. Hanna, J. Hargrove, W. Haught, P. Hauptman, M. Hazelrigg, C. Herzog, J. Heywood, T. Hill, T. Hilton, H. Hirsch, J. Hunter, H. Ibrahim, M. Imburgia, B. Iteld, B. Jackson, N. Jafarani, D. Jain, A. Jain, M. James, J. Jimenez, E. Johnson, P. Kale, A. Kane-shige, S. Kapadia, D. Karia, R. Karlsberg, R. Katholi, E. Kerut, W. Khoury, R. Kipperman, M. Klapholz, E. Kosinski, M. Kozinn, D. Kraus, S. Krueger, H. Krum, S. Kumar, E. Lader, C. Lee, W. Levy, E. Lewis, K. Light-McGroary, I. Loh, W. Lombardi, C. Machado, F. Maislos, D. Mancini, T. Markus, P. Mather, K. McCants, F. McGrew, B. McLaurin, E. McMillan, D. McNamara, T. Meyer, S. Meymandi, A. Miller, E. Minami, M. Modi, F. Mody, P. Mohanty, R. Moscoso, R. Moskowitz, M. Moustafa, M. Mullen, T. Naz, T. Noonan, T. O'Brien, W. Oellerich, R. Oren, S. Pamboukian, N. Pereira, W. Pitt, C. Porter, S. Prabhu, S. Promisloff, R. Ratkovec, R. Richardson, A. Ross, N. Saleh, M. Saltzberg, S. Sarkar, J. Schmedtje, R. Schneider, G. Schuyler, J. Shanes, A. Sharma, C. Siegel, R. Siegel, D. Silber, V. Singh, N. Singh, J. Singh, J. Sklar, R. Small, A. Smith, E. Smith, E. Smith, D. Smull, R. Sotolongo, C. Staniloae, D. Stapleton, P. Steele, J. Stehlik, M. Stein, W. Tang, U. Thadani, G. Torre-Amoine, B. Trichon, C. Tsai, R. Tummala, A. Van Bakel, R. Vicari, N. Vijay, K. Vijayaraghavan, T. Vittorio, M. Vossler, L. Wagoner, D. Wallis, N. Ward, M. Widmer, J. Wight, C. Wilkins, C. Williams, G. Williams, M. Winchester, E. Winkel, B. Wittmer, D. Wood, D. Wormer, R. Wright, Z. Xu, M. Yasin, R. Zolty.

## References

- O'Meara E, Murphy C, McMurray JJ. Anemia and heart failure. *Curr Heart Fail Rep* 2004;**1**:176–182.
- Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, Burton PB. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004;**110**:149–154.
- Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, Tavazzi L, Latini R, Cohn J. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005;**11**:91–98.
- Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, Chiang YT, Aknay N, Maggioni AP, Opasich C, Latini 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. *Circulation* 2005;**112**:1121–1127.
- O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, Young JB, Solomon SD, Granger CB, Ostergren J, Olofsson B, Michelson EL, Pocock S, Yusuf S, Swedberg K, Pfeffer MA: CHARM. Committees and Investigators. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006;**113**:986–994.
- Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, Remme W, Moullet C, Swedberg K, Cleland JG, Poole-Wilson PA. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006;**27**:1440–1446.
- Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients: a systematic review and meta-analysis. *J Am Coll Cardiol* 2008;**52**:818–827.
- Adams KF Jr, Patterson JH, Oren RM, Mehra MR, O'Connor CM, Piña IL, Miller AB, Chiong JR, Dunlap SH, Cotts WG, Felker GM, Schocken DD, Schwartz TA, Ghali JK; STAMINA-HFP. Registry Investigators. 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. *Am Heart J* 2009;**157**:926–932.
- 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.

10. Anand IS. Pathophysiology of anemia in heart failure. *Heart Fail Clin* 2010; **6**:279–288.
11. Westenbrink BD, Voors AA, de Boer RA, Schuringa JJ, Klinkenberg T, van der Harst P, Vellenga E, van Veldhuisen DJ, van Gilst WH. Bone marrow dysfunction in chronic heart failure patients. *Eur J Heart Fail* 2010; **12**:676–684.
12. Van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. *Nat Rev Cardiol* 2011; **8**:485–493.
13. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002; **39**:1780–1786.
14. Falk K, Swedberg K, Gaston-Johansson F, Ekman I. Fatigue and anaemia in patients with chronic heart failure. *Eur J Heart Fail* 2006; **8**:744–749.
15. Felker GM, Adams KF Jr, Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. *J Am Coll Cardiol* 2004; **44**:959–966.
16. Anand IS. Anemia and chronic heart failure implications and treatment options. *J Am Coll Cardiol* 2008; **52**:501–511.
17. Ngo K, Kotecha D, Walters JA, Manzano L, Palazzuoli A, van Veldhuisen DJ, Flather M. Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. *Cochrane Database Syst Rev* 2010; **1**:CD007613.
18. Cleland JG, Sullivan JT, Ball S, Horowitz JD, Agoram B, Rosser D, Yates W, Tin L, Fuentealba P, Burton PB. 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**:155–161.
19. Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymliński R, Ryan E, Wasserman SM, Baker N, Rosser D, Rosen SD, Poole-Wilson PA, Banasiak W, Coats AJ, McDonald K. 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**:753–762.
20. Van Veldhuisen DJ, Dickstein K, Cohen-Solal A, Lok DJ, Wasserman SM, Baker N, Rosser D, Cleland JG, Ponikowski P. 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**:2208–2216.
21. Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, Massie BM, Wasserman SM, Trotman ML, Sun Y, Knusel B, Armstrong P; Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation* 2008; **117**:526–535.
22. Klapholz M, Abraham WT, Ghali JK, Ponikowski P, Anker SD, Knusel B, Sun Y, Wasserman SM, van Veldhuisen DJ. The safety and tolerability of darbepoetin alfa in patients with anaemia and symptomatic heart failure. *Eur J Heart Fail* 2009; **11**:1071–1077.
23. Lipsic E, Westenbrink BD, van der Meer P, van der Harst P, Voors AA, van Veldhuisen DJ, Schoemaker RG, van Gilst WH. Low-dose erythropoietin improves cardiac function in experimental heart failure without increasing haematocrit. *Eur J Heart Fail* 2008; **10**:22–29.
24. Van der Meer P, Lipsic E, van Veldhuisen DJ. Asialoerythropoietin to protect the failing heart: is it possible to run with the hare and hunt with the hounds? *J Am Coll Cardiol* 2010; **56**:1959–1960.
25. Kleijn L, de Boer RA, Voors AA. Should erythropoietin treatment in chronic heart failure be haemoglobin targeted? *Eur J Heart Fail* 2010; **12**:215–216.
26. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**:2085–98.
27. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355**:2071–2084.
28. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Fezy J, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361**:2019–2032.
29. Desai A, Lewis E, Solomon S, McMurray JJ, Pfeffer M. Impact of erythropoiesis-stimulating agents on morbidity and mortality in patients with heart failure: an updated, post-TREAT meta-analysis. *Eur J Heart Fail* 2010; **12**:936–942.
30. McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, Polu KR, Solomon SD, Sun Y, Swedberg K, Tendera M, van Veldhuisen DJ, Wasserman SM, Young JB; RED-HF Committees and Investigators. 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.
31. Van Veldhuisen DJ, McMurray JJ; RED-HF Executive Committee. Are erythropoietin stimulating proteins safe and efficacious in heart failure? Why we need an adequately powered randomised outcome trial. *Eur J Heart Fail* 2007; **9**:110–112.
32. 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**:1245–1255.
33. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364**:11–21.
34. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; **376**:875–885.
35. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; **363**:2385–2395.
36. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; **374**:1840–1848.
37. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Klein W, Tavazzi L; CARE-HF study Steering Committee and Investigators. Baseline characteristics of patients recruited into the CARE-HF study. *Eur J Heart Fail* 2005; **7**:205–214.
38. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; **362**:7–13.
39. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Hertz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000; **283**:1295–1302.
40. McMurray J, Ostergren J, Pfeffer M, Swedberg K, Granger C, Yusuf S, Held P, Michelson E, Olofsson B; CHARM committees, investigators. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail* 2003; **5**:261–270.
41. Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**:1451–1459.
42. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361**:1329–1338.
43. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL; STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011; **364**:1607–1616.
44. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009; **361**:2241–2251.
45. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**:2248–2261.
46. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**:2436–2448.