A pilot study of chronic, low-dose epoetin-β following percutaneous coronary intervention suggests safety, feasibility, and efficacy in patients with symptomatic ischaemic heart failure

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Received 19 August 2010; revised 4 November 2010; accepted 8 November 2010

Aims
Low-dose epoetin-β improved neo-angiogenesis and cardiac regeneration in experimental models of ischaemic cardiomyopathy without raising haemoglobin. No clinical study has tested this approach to date.

Methods and results
We performed a randomized, placebo-controlled, double-blind, single-centre study of 35 IU/kg body weight epoetin-β given subcutaneously once weekly for 6 months started within 3 weeks after successful percutaneous coronary intervention (PCI). Patients were included if they presented with a lesion within the proximal segment of the left anterior descending artery, the right coronary artery, or circumflex and had symptomatic heart failure. Patients with ST-segment elevation due to an acute myocardial infarct were excluded. The outcome variables were measured at baseline and at 6 months. Primary outcome measure was individual change in ejection fraction; secondary outcome was safety, change in N-terminal pro-brain natriuretic peptide, and peak VO2. Twenty-four patients completed the 6-month treatment course. No adverse event related to the treatment occurred.

Low-dose epoetin-β following PCI significantly improved global ejection fraction as measured by echocardiography (EPO: ΔEF 5.2 ± 2.0%, P = 0.013; placebo: ΔEF 0.3 ± 1.6%, P = 0.851; P = 0.019 for the inter-group difference) and cardiac magnetic resonance (EPO: ΔEF 3.1 ± 1.6%, P = 0.124; placebo: −1.9 ± 1.2%, P = 0.167; P = 0.042 for the inter-group difference). N-terminal pro-brain natriuretic peptide levels decreased in both groups without significant inter-group differences. Peak VO2 levels increased significantly by 3.9 ± 1.1% (P < 0.05) in the EPO group, whereas in the placebo group the increase did not reach statistical significance (Δpeak VO2 3.0 ± 1.6, P = ns). No significant difference regarding peak VO2 was observed between the EPO and placebo groups.

Conclusions
Low-dose epoetin-β treatment following PCI is safe and feasible, and has possible beneficial effects on global ejection fraction and measures of exercise capacity. Extended low-dose epoetin-β treatment warrants further mechanistic studies as well as larger clinical trials.

Clinical Trial Registration Information: NCT00568542

Keywords
Heart failure • Growth substances • Ischaemia

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Introduction

Treatment options and prognosis for patients with heart failure have improved because of revascularization by percutaneous coronary intervention (PCI) or surgical means, drug therapy, and novel device-based treatments. Nevertheless, mortality and morbidity remain high. Heart failure currently accounts for 5% of hospital admissions in Western Europe, making heart failure the commonest cause for emergency department care. Cardiac regeneration could be a future treatment option. Experimental studies and clinical trials suggest that neo-angiogenesis and cardiomyocyte regeneration are feasible. Intra-coronary cell therapy and intra-myocardial bone marrow cell injections have accrued interest in open-label studies; however, randomized trials have shown mixed results.

The use of growth factors has also been promulgated. However, clinical studies of single high doses of granulocyte-colony-stimulating factor (G-CSF) or erythropoietin following acute myocardial infarct were disappointing. Recently, the HEBE III trial investigated the use of a single high dose of epoetin following an acute myocardial infarct. No significant effect on left ventricular (LV) ejection fraction, the primary endpoint, was observed. However, adverse cardiac events, a secondary endpoint, were significantly reduced in the EPO group. Erythropoietin has been studied extensively in patients with anaemia and heart failure. But, aside from smaller surrogate-parameter studies, no large randomized trial has confirmed a benefit in raising haemoglobin levels to >12 mg/dL. In fact, studies aimed at increasing haemoglobin to 14 mg/dL rather than the 12 mg/dL recommended in current guidelines in pre-dialysis patients yielded a neutral heart failure-related outcome.

However, low-dose, long-term epoetin not aimed at increasing haemoglobin could have beneficial effects on cardiac remodelling by several mechanisms, including the promotion of angiogenesis. Epoetin-β, administered at doses as low as 30 IU/kg per week, mobilized endothelial progenitor cells from the bone marrow and increased functionally active endothelial progenitor cells in peripheral blood. Interestingly, epoetin increases circulating endothelial progenitor cell levels by itself; however, improved microvascularization depends on the additional presence of local ischaemia. Thus, chronic, low-dose epoetin-β treatment following PCI for macrovascular ischaemia may exert beneficial effects on LV function beyond the effects of PCI alone.

Methods

Patient population

Patients were eligible if they presented with symptomatic heart failure NYHA ≥II, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (>2 × upper norm) and a significant stenosis in the proximal segment of the right coronary artery, the left anterior descending artery, or the circumflex artery. Patients were screened after successful revascularization by PCI for the stenotic lesion. The patients were required to demonstrate globally reduced ejection fraction or at least a regional wall motion defect in the area of the stenotic lesion. During screening, wall motion defects were detected by LV angiography, echocardiography, or cardiac magnetic resonance imaging (cardiac MRI) at the time of PCI. Patients with acute ST-segment elevated infarct or unprotected left main were excluded. Patients with elevated troponin T as a marker of an acute coronary syndrome were allowed to enter the trial if they did not present with any other exclusion criteria.

These inclusion criteria resulted in a heterogeneous group of patients in terms of ejection fraction. However, all patients also demonstrated elevated LV end-diastolic pressure >15 mmHg. All patients received an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker and a β-blocker if not intolerant to the drugs. Within 3 weeks following successful PCI of a major coronary vessel, patients were asked for informed consent if they fulfilled the inclusion criteria and did not exhibit any of the following exclusion criteria: valvular heart disease, contraindication for cardiac MRI (pace-maker, implantable cardioverter, metal implants, and claustrophobia), uncontrolled hypertension (resting blood pressure >180/100 mmHg), haemoglobin >16 mg/dL, or thrombocytosis. Patients aged >75 years and pre-menopausal women were not included. Patients with active malignancy, severe renal dysfunction (serum creatinine >3.0 mg/dL), chronic liver disease, or indication for open-label epoetin treatment were also excluded. We excluded patients with iron deficiency (ferritin <50 mg/mL and/or transferrin saturation <20%) or anaemia (Hb <12 mg/dL) and patients with neurological diseases, including a prior stroke. Serum vitamin B12 levels were required to be within the normal range. We also excluded patients with earlier in-stent restenosis or stent thrombosis.

The ethics committee of Berlin as well as the BfArM (Bundesamt für Arzneimittel und Medizinprodukte) regulatory agency approved the study and written informed consent was obtained (Eudra-CT 2004-002646-35; ClinicalTrials.gov NCT00568542).

Study protocol

Following informed consent, patients underwent measurement of LV function, laboratory values including NT-proBNP, and exercise capacity. The measurements were performed around day 13.4 ± 3.2 after PCI. No measurement was made within the first 7 days or later than 21 days after PCI. Subjects received either weight-adjusted subcutaneous epoetin-β (35 IU/kg) or placebo once a week for 6 months by self-injecting with a pen (NeoRecomiron®). The clinical trials unit at Charité Campus Virchow randomized the patients and provided them with vials for loading the injection pen. Patients were trained to self-inject epoetin-β or placebo. Patients, doctors, and study nurses were blinded to the investigational product; compliance was checked by inspecting the vial when patients returned for exchange. Data were entered on-site into a centralized database with regular external monitoring (Figure 1). The primary endpoint was change from baseline to 6 months in cardiac MRI and echocardiographically determined global ejection fraction. Secondary endpoints were changes in exercise capacity, NT-proBNP, and regional wall motion. Safety endpoints were adverse events, laboratory values, blood pressure, and repeat revascularization.

Measurements

Study visits were undertaken after 4 weeks, 3 months, and 6 months. Assessments performed at baseline and at 6 months included echocardiography, cardiac MRI, serum erythropoietin levels, and NT-proBNP. Haemoglobin, haematocrit, serum creatinine, oscillometric seated blood pressure, and heart rate were assessed at every visit. Echocardiography was performed according to current guidelines; we used the American Society of Echocardiography 16-segment model to assess regional wall motion. Endocardial borders were manually
traced from the apical four- and two-chamber views to calculate per cent ejection fraction using the biplane summation-of-discs method included in current ultrasound machines (Accuson Sequoia, Siemens and Vivid 7, GE Healthcare, München, Germany). Experts, blinded to the treatment, performed the studies and entered the values into the online database. Cardiac MRI regional wall motion was determined by the 17-segment model according to international guidelines. Left ventricular ejection fraction was measured using contiguous short-axis slices according to the validated cardiac MRI laboratory standards. Experts blinded to the treatment allocation performed the image analysis. All data were entered into the central database and regularly monitored.

All patients performed an incremental exercise test until volitional exhaustion on a motorized treadmill (h/p Cosmos Mercury 4.0, Traunstein, Germany) to assess oxygen uptake capacity and power output. Patients breathed through a disposable pneumotach. Exercise was begun at 0 W and increased by 25 W every 3 min until reaching the maximally tolerated workload (Vmax spectra 229D, Sensor Medics, München, Germany).

Statistical analysis

No formal sample size calculation was performed as the trial was conceived as exploratory. All analysed subjects received the treatment to which they were randomly assigned and were retained in the group until endpoint. After completion of the study and final external monitoring, the database was closed and the treatment code opened to perform the statistical analysis. As pre-specified, intra-individual changes in ejection fraction and other endpoints were compared between the two groups with either epoetin-β or placebo treatment. Categorical data were analysed by χ² tests. The Kolmogorov–Smirnov test was applied to detect deviations from normal distribution. We used Levene’s test, which is an inferential statistic used to assess the equality of variance in different samples. Intra-group differences were compared by a one-sided paired t-test and inter-group differences by unpaired t-testing. For variables that were not normally distributed (NT-proBNP), the Mann–Whitney test was applied. A P < 0.05 was considered statistically significant; nominal P-values are presented. All results are reported as mean ± SEM.

Results

Enrolment and baseline characteristics

We recruited 32 patients. Four patients withdrew consent or presented with exclusion criteria during the screening phase after providing informed consent. Of the remaining 28 patients, 14 were assigned to receive placebo and 14 to receive epoetin-β. In the EPO group, one patient dropped out of the study after receiving a cardiac resynchronization device. In the control group, three patients did not finish the 6-month treatment course: two patients withdrew consent for personal reasons and one other patient received an intra-cardiac defibrillator with cardiac resynchronization therapy. The two groups
were well matched in terms of baseline characteristics (Table 1). The EPO group presented with lower end-diastolic pressure at the time of PCI (placebo: 24 ± 2.2 mmHg; epoetin-β: 17.6 ± 2.3 mmHg) as well as reduced LV end-diastolic diameter index (placebo: 115 ± 12.4 mL/m²; epoetin-β: 85 ± 6 mL/m²; Table 1). We considered that a multivariate analysis of the results was not feasible given the low patient numbers in both groups. It is possible that this deviation may have influenced the overall results; however, other parameters such as peak VO₂ showed some discrepancy in favour of the placebo group (placebo: 22 ± 2.9; epoetin-β: 18.8 ± 1.8) and ejection fraction was distributed normally in both groups.

In the placebo group, more patients received a drug-eluting stent; however, the lesion type according to the American College of Cardiology classification was not different. The patients presented with moderate heart failure as judged by ejection fraction, NT-proBNP levels, and peak VO₂ at baseline. All patients also had diastolic dysfunction as shown by elevated LV...
end-diastolic pressure and an elevated $E/E'$ ratio at baseline (see Table 1 for details).

The patients were not anaemic; the baseline haemoglobin and haematocrit values were normal, as were the iron-related values. By chance, the EPO group included two patients with relatively elevated erythropoietin blood levels prior to treatment; this resulted in a borderline higher average level of erythropoietin at baseline ($P = 0.06$) in that group. These two patients presented with haemoglobin values of 14.6 and 14.3 mg/dL and NT-proBNP levels of 210 and 1623 pg/mL, respectively.

**Epoetin-β treatment**

Patients in the EPO group had significantly increased levels of erythropoietin at 6 months, compared with the placebo group ($P = 0.009$, Figure 2A). No significant change in blood pressure, haematocrit, or haemoglobin was observed in either group (Figure 2B, Table 2). Pharmacological treatment of patients was in accordance with current guidelines; in both groups, >95% of patients received a β-blocker, ACE-inhibitor or AT1-antagonist, statin, and aspirin plus clopidogrel during every planned visit (Table 1). During the study, no stent thrombosis or uncontrolled hypertension was observed. All patients were on dual-antiplatelet therapy throughout the study. One patient of the control group was re-admitted to the hospital for decompensated heart failure that resolved with nitroglycerin and furosemide; this was the only serious adverse effect reported in the study. The episode was judged unrelated to study treatment.

**Quantitative measurement of left ventricular function**

The individual change in ejection fraction between baseline and 6-month follow-up measured by echocardiography and cardiac MRI was greater in the EPO group than in the placebo group. Both methods of LV function measurement performed in the trial, namely cardiac MRI and echocardiography, are reported in a combined fashion due to the low patient numbers. Epoetin-β treatment led to a significant increase (Figure 3A) in echocardiographic ejection fraction ($\Delta EF 5.7 \pm 1.9\%$, $P < 0.05$). Percutaneous coronary intervention treatment alone plus placebo brought about no change in ejection fraction ($\Delta EF 0.3 \pm 1.6\%$, $P = \text{ns}$). The EPO group had slightly higher ejection fractions, compared with placebo at baseline; the difference was not statistically significant. The cardiac MRI measurements (Figure 3B) revealed an upward trend in ejection fraction in the EPO group ($\Delta EF 3.1 \pm 1.6\%$, $P = \text{ns}$), whereas the reverse was the case in the placebo group ($\Delta EF = -1.9 \pm 1.2\%$, $P = \text{ns}$). As a result, the comparisons of the intra-individual $\Delta EF$ baseline vs. 6-month follow-up between the groups reached statistical significance ($P < 0.05$). Due to the low patient numbers, we did not perform a multivariate analysis. No difference in pharmacological treatment, blood

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**Figure 2** Levels of (A) erythropoietin and (B) haemoglobin in both study groups. Following treatment for 6 months, only the EPO treatment group demonstrated increased erythropoietin levels compared with baseline levels. The EPO group by chance had two patients with elevated levels at baseline. No significant increase in haemoglobin was observed in either group.
pressure, or further interventions was observed. No significant change in LV end-diastolic volume was detected. The $\Delta$LVEDV over the 6 months was $<20$ mL in both groups ($\Delta$LVEDV placebo group: $+15 \pm 12.5$ mL, $P = ns$; EPO group: $0.1 \pm 8.4$ mL, $P = ns$). If anything, further ventricular dilation occurred in the placebo group, whereas the EPO group remained stable in terms of diameters and volume. No significant change in recovery of the regional wall motion defect at study entry could be documented by echo or cardiac MRI, probably due to the low patient numbers.

### Table 2  Safety data concerning haemoglobin levels and blood pressure (fiducial limits, mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>EPO group</th>
<th>Significance ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemoglobin (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.9 ± 0.3</td>
<td>14.1 ± 0.3</td>
<td>ns, $P = 0.68$</td>
</tr>
<tr>
<td>4 weeks</td>
<td>13.8 ± 0.3</td>
<td>14.5 ± 0.3</td>
<td>ns, $P = 0.18$</td>
</tr>
<tr>
<td>3 months</td>
<td>14.1 ± 0.2</td>
<td>15.1 ± 0.3</td>
<td>ns, $P = 0.59$</td>
</tr>
<tr>
<td>6 months</td>
<td>14.3 ± 0.2</td>
<td>14.9 ± 0.4</td>
<td>ns, $P = 0.52$</td>
</tr>
<tr>
<td><strong>Blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>121 ± 5.3/67 ± 1.7</td>
<td>122 ± 5.4/70 ± 3.4</td>
<td>ns, $P = 0.85$</td>
</tr>
<tr>
<td>4 weeks</td>
<td>116 ± 5.4/65 ± 2.4</td>
<td>126 ± 5.8/70 ± 3.3</td>
<td>ns, $P = 0.27$</td>
</tr>
<tr>
<td>3 months</td>
<td>122 ± 4.1/68 ± 2.6</td>
<td>123 ± 3.8/71 ± 3.4</td>
<td>ns, $P = 0.80$</td>
</tr>
<tr>
<td>6 months</td>
<td>123 ± 3.6/65 ± 2.2</td>
<td>117 ± 3.8/66 ± 2.6</td>
<td>ns, $P = 0.25$</td>
</tr>
</tbody>
</table>

**Figure 3**  Increase in ejection fraction following percutaneous coronary intervention plus low-dose epoetin-β over 6 months compared with percutaneous coronary intervention plus placebo treatment. (A) Echocardiographic data from patients with complete measurements both at baseline and at 6-month follow-up. The comparison between the groups revealed a significant change favouring the EPO treatment arm. (B) Cardiac magnetic resonance imaging data from all patients with complete analysis both at baseline and at 6-month follow-up. The comparison between the groups revealed a significant change favouring the EPO treatment arm.

**Heart failure assessment**

We also analysed other parameters of heart failure, namely blood levels of NT-proBNP and exercise tests. Both parameters improved over the course of the study following PCI, without significant differences between EPO and placebo (Figure 4A and B). Peak VO$_2$ levels increased significantly by $3.9 \pm 1.1\%$, $P < 0.05$ in the EPO group. In the placebo group, we detected no significant change ($\Delta$peak VO$_2$ $3.0 \pm 1.6$, $P = ns$). No difference in the number of hospital admissions due to heart failure related to
study drug assignment was observed during the 6-month follow-up.

The study population was quite heterogeneous regarding individual NT-proBNP levels at study entry, and the reduction during the follow-up period possibly precluded any statistically relevant effects (Table 1, Figure 4B). However, the data on exercise capacity revealed some interesting insights. Patients in both groups had a numerically increased aerobic capacity (EPO: 16.4 ± 1.8 to 20.3 ± 1.9 mL/min/kg, \( P < 0.05 \); placebo: 19.3 ± 1.8 to 22.3 ± 3.4 mL/min/kg, \( P = \text{ns} \) and power output (EPO: 120 ± 16 to 152 ± 17 W, \( P < 0.05 \); placebo: 129 ± 21 to 140 ± 27 W, \( P = \text{ns} \)). The EPO group achieved significance, while the placebo group did not. Moreover, maximum oxygen pulse was enhanced more in the EPO group (25.4%, \( P < 0.05 \)) than in the placebo group (15.7%, \( P = \text{ns} \)). These data suggest that epoetin-β might have indeed improved cardiac function.

At the individual anaerobic threshold, we observed numerical increases for oxygen pulse (EPO: 10.9 ± 1 to 13.3 ± 1.1, \( P < 0.05 \); placebo: 12.7 ± 0.9 to 13.7 ± 1.1, \( P = \text{ns} \)) and power output (EPO: 70.3 ± 10.7 to 80.7 ± 10.1, \( P < 0.05 \); placebo: 65 ± 6.0 to 75.7 ± 14.4, \( P = \text{ns} \)) with only slight changes in oxygen uptake. Again, the EPO group achieved significance, while the placebo group did not. No significant alterations were observed for lactate concentrations, either at individual anaerobic threshold or at volitional exhaustion. The more pronounced adaptations in patients who received EPO compared with the placebo group suggested that improved cardiac function was responsible for these findings rather than metabolic adjustments.

**Discussion**

We performed a double-blind, placebo-controlled pilot study to evaluate the effects of low-dose epoetin-β administered subcutaneously, once a week for 6 months, on cardiac function in heart failure patients following PCI for significant coronary disease. Heart failure was defined by dyspnoea, elevated NT-proBNP levels, and measures of diastolic dysfunction (LV end-diastolic pressure and \( E/E' \)). We used epoetin-β doses that did not influence haemoglobin or haematocrit in these non-anaemic patients. All patients had a regional wall motion defect in the territory of the coronary artery subjected to PCI. This pilot study found low-dose epoetin-β treatment to be feasible. Furthermore, we found evidence of improved LV function following epoetin-β treatment by means of two different imaging techniques, with intra-individual changes in ejection fraction analysed by expert readers blinded to the treatment allocation. Furthermore, we found evidence of improved cardiac performance with exercise following epoetin-β treatment over 6 months. This is therefore
Erythropoietin has been tested in anaemic patients with heart failure leading to an ongoing, multi-centre, randomized trial of darbepoetin in heart failure (RED-HF). This trial is aimed at correcting the anaemia often observed in association with severe heart failure. Anaemia is associated with increased mortality in heart failure but a causal relationship has not been established. Large studies in pre-dialysis patients have failed to show a benefit of normalizing haemoglobin levels to >14 mg/dL, compared with a lower target of 12 mg/dL. Earlier studies of erythropoietin in heart failure solely identified significant changes of exercise capacity rather than parameters of LV remodelling. While in our study no significant differences in peak VO₂ were observed between the groups, echocardiography and cardiac MRI both confirmed attenuation of LV remodelling. The exercise test revealed no significant effect on peak VO₂ but a significant effect on power output, which is a finding also in line with improved cardiac function rather than metabolic adjustments by oxygen uptake.

We found that low-dose epoetin-β treatment for 6 months was safe. Larger doses of erythropoietin to avoid blood transfusions in patients with chronic kidney disease or malignant disease may be harmful. Some studies suggest that erythropoietin treatment could be an option to reduce in-stent restenosis by accelerating re-endothelialization of the injured endothelium. However, other studies have implied thrombocyte activation. Our study was small, but we nonetheless observed no stent thrombosis. Recent studies have reached the same conclusion regarding single high-dose darbepoetin, a longer-acting erythropoietin analogue, following PCI after acute myocardial infarction. The HEBE III trial confirmed this finding regarding safety and reported less cardiac events including stent thrombosis. Here, we excluded patients with an acute myocardial infarction. In addition, darbepoetin administered >26 weeks in patients with anaemia and chronic heart disease aimed at a target haemoglobin of 14 ± 1.0 g/dL has also been shown to be safe.

Several small studies have supported the idea that erythropoietin could exert pro-angiogenic effects by mobilizing endothelial progenitor cells even at low doses. In addition, the functional capacity of these endothelial progenitor cells, as measured by their migration capacity, is enhanced especially with chronic treatment. Improving endothelial function and neo-angiogenesis in ischaemic myocardial tissue has been shown to be a valid strategy to attenuate LV remodelling by preventing a mismatch between perfusion and cardiac hypertrophy. Interestingly, ischaemia is necessary for erythropoietin to increase myocardial expression of vascular, endothelial growth factor, thereby stimulating homing and local proliferation of endothelial progenitor cells. This effect is specific to erythropoietin, while in principle mobilization of endothelial progenitor cells is also achieved by other growth factors such as G-CSF. However, G-CSF lacks any effects on homing and local proliferation of endothelial progenitor cells. Therefore, the negative results of recent clinical trials analysing the effect of G-CSF in patients following myocardial infarction cannot be extrapolated to erythropoietin treatment.

Our pilot study is limited by its small sample size, the lack of a power calculation, and variations in patient baseline data. Nonetheless, the patient characteristics were similar in both treatment arms, and treatment as well as data acquisition and analyses were conducted in a strict double-blind fashion. Retrospectively, differences in LV end-diastolic pressure at the time of PCI as well as LV end-diastolic diameter index were observed. This may have influenced the outcome over the 6-month treatment course, although dimensions did not change significantly over the treatment course.

We believe that the reported findings provide an improved perspective for heart failure patients after coronary intervention. Percutaneous coronary intervention alone in elective patients with symptoms of heart failure does not necessarily improve heart function. Once-weekly low-dose epoetin-β treatment in addition to PCI is feasible, and the data suggest that the treatment may be effective. Larger trials confirming this approach are warranted to reproduce this result and possibly to introduce this concept into clinical practice in heart failure patients undergoing macrovascular revascularization.

Acknowledgements
The authors thank the Franz-Volhard Clinical Research Center team at Charité Campus Buch and the Pharmacy at Charité Campus Virchow for expert help throughout the study.

Funding
This study was supported by a grant from the Roche Foundation of Anemia Research (RoFAR). The study was solely investigator initiated; the granting agency played no role in the study or in the report preparation.

Conflict of interest: none declared.

References


