A single dose of erythropoietin in ST-elevation myocardial infarction

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Aims
Cardioprotective effects of erythropoietin (EPO) have been shown in experimental and smaller clinical studies. We performed a prospective, multicentre, randomized trial to assess the effects of a single high dose of EPO after primary coronary intervention (PCI) for an ST-elevation myocardial infarction (STEMI).

Methods and results
Patients with a successful PCI for a first STEMI were randomized to receive either standard medical care alone, or in combination with a single bolus with 60 000 IU i.v. of epoetin alfa within 3 h after PCI. Primary endpoint was left ventricular ejection fraction (LVEF) after 6 weeks, assessed by planar radionuclide ventriculography. Pre-specified secondary endpoints included enzymatic infarct size and major adverse cardiovascular events.

A total of 529 patients were enrolled (EPO n = 263, control n = 266). At baseline (before EPO administration), groups were well-matched for all relevant characteristics. After a mean of 6.5 (± 2.0) weeks, LVEF was 0.53 (± 0.10) in the EPO group and 0.52 (± 0.11) in the control group (P = 0.41). Median area under the curve (inter-quartile range) after 72 h for creatinine kinase was 50 136 (28 212–76 664) U/L per 72 h in the EPO group and 53 510 (33 973–90 486) U/L per 72 h in the control group (P = 0.058). More major adverse cardiac events occurred in the control than in the EPO group (19 vs. 8; P = 0.032).

Conclusion
A single high dose of EPO after a successful PCI for a STEMI did not improve LVEF after 6 weeks. However, the use of EPO was related to less major adverse cardiovascular events and a favourable clinical safety profile. Clinical Trial Registration Information: NCT00449488; http://www.clinicaltrials.gov/ct2/show/NCT00449488?term=voors&rank=2.

Keywords
ST-elevation myocardial infarction • Erythropoietin • Left ventricular function • Cardiovascular events • Infarct size

Introduction
Erythropoietin (EPO) is commonly known as an effective treatment for anaemia, partly caused by an inadequate production of endogenous EPO in patients with renal disease. Experimental studies have suggested cardioprotective effects of EPO, which might be beneficial in the setting of a myocardial infarction.1 In an ischaemia—reperfusion model, mice lacking an EPO receptor in the heart developed larger infarcts compared with wild-type mice.2 In addition, a number of animal studies provided consistent evidence for a reduced infarct size and improved left ventricular function caused by EPO administration.3–10

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In the last 2 years, few studies have investigated the effects of EPO in patients with a myocardial infarction. In a first safety and feasibility study from our group, a single high-dose bolus of EPO (60 000 IU) in patients with a first ST-elevation myocardial infarction (STEMI) resulted in a 200-fold increase in serum EPO levels, without hypertension, thrombotic, or other adverse events (AEs). Ferrario et al. demonstrated a significant reduction in CK-MB release in 30 myocardial infarction patients treated with EPO (33 000 IU before primary coronary intervention (PCI), and 24 and 48 h after admission), but effects on left ventricular function were not reported. Binbrek et al. showed a small and non-significant effect of a single bolus of 30 000 IU EPO on infarct size in 236 myocardial infarction patients, although effects on left ventricular function were again not reported. In 138 STEMI patients, 30 000 IU of EPO administered during the first 3 days did not improve left ventricular function after 6 months, although these data have as yet not been published. We present data from a multicentre, prospective, randomized trial on the effects of a single high dose of EPO in 529 patients after a successful angioplasty for a first STEMI.

Methods

Patients and study design

HEBE III is a prospective, randomized, open-label trial with blinded endpoints. HEBE I and II studied novel techniques to improve left ventricular function after a STEMI, but data have not been published so far. A detailed design of HEBE III has been published elsewhere. In brief, patients were eligible for the study if they had a successful primary PCI [thrombolysis in myocardial infarction (TIMI) flow 2/3 after the procedure, TIMI flow 0/1 before] for a first STEMI. Myocardial infarction was defined as described before, by (i) suggestive chest pain; (ii) symptom onset 12 h before hospital admission or 24 h in case of ongoing ischaemia; (iii) electrocardiogram (ECG) with ST-T-segment elevation ≥ 1 mV in two or more leads or new left bundle branch block. The most important exclusion criteria were a previous myocardial infarction, haemoglobin levels > 17.1 g/dL before PCI, anticipated additional revascularization within 6 weeks, a history of persistent or permanent atrial fibrillation, cardiogenic shock, and a serum creatinine > 2.5 mg/dL.

Procedures and treatment

Patients were screened at the cardiac catheterization laboratory of the seven participating centres. In the ambulance, patients received aspirin, clopidogrel, and heparin as per protocol. Before starting the PCI procedure, an ECG was performed and standard medical treatment was initiated. Immediately after the PCI procedure, when TIMI flow 2/3 was confirmed, patients were asked for their oral informed consent by an independent interventional cardiologist and nurse. If they agreed, patients were immediately randomized by means of a computerized program. This system randomly assigned patients to receive optimal standard medical care with or without a bolus of 60 000 IU i.v. of epoetin alfa (Ortho Biotech, a division of Janssen-Cilag B.V.) in 10 min. After randomization, patients were then transported to the cardiac care unit, where written informed consent was signed and a second ECG was acquired. Blood pressure, heart rate, and ECG were monitored according to routine clinical practice at baseline and at regular time points up until 48 h. After 6 weeks, a clinical visit was performed, and blood samples, ECG, and blood pressure were obtained at the outpatient clinic. The research protocol was approved by the central Ethics Committee of the University Medical Center Groningen, and by the local Ethics Committees of each participating centre.

Planar radionuclide ventriculography

Planar radionuclide ventriculography was performed in each of the participating centres to determine left ventricular ejection fraction (LVEF). An injection of 500 MBq of 99mTc-pertechnetate was administered to patients intravenously 20 min after injection of 1 mg stannous chloride. Planar radionuclide ventriculography was obtained on a gamma camera. The camera head was positioned in the best septal left anterior oblique projection. Data acquisition was done using 64 × 64 matrices in a 15% energy window centred on the 140 keV photopeak. Processing was performed on dedicated commercially available computers. In 24 patients (12 EPO and 12 control), a gated 99mTc sestamibi was used instead of planar radionuclide ventriculography. Reproducibility of this measurement was 0.94% LVEF units [confidence interval (CI) 2.7–4.5].

Laboratory measurements

Measurements of CK, CK-MB, troponin, haemoglobin, haematocrit, and creatinine were determined at baseline (immediately before PCI), after 3, 6, 9, 12, 18, 24, 36, 48, 72 h, and 6 weeks after the PCI procedure. At baseline and after 6 weeks, NT-proBNP measurements were performed in plasma using a commercially available electrochemical luminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra- and interassay coefficients of variation were 1.2–1.5 and 4.4–5.0%, respectively, with an analytical range of 5–3 000 pg/mL.

Endpoints and blinding

Primary endpoint of the study was LVEF assessed at 6 weeks after the primary PCI procedure by planar radionuclide ventriculography. Secondary study endpoints were the following:

- Myocardial infarct size: determined by area under the marker curves and peak values of serial computerized measurements of creatinine kinase (CK) and CK-MB and troponin-T.
- Incidence of a cardiovascular event within 6 weeks after PCI: defined as cardiovascular death, re-infarction (any ST-elevation or non-STEMI), emergency re-PCI or coronary artery bypass grafting, stroke, and clear symptoms of heart failure.

Sample size considerations

At the start of the study, no clinical data were available on the effects of EPO on left ventricular function. We assumed an absolute LVEF increase of 3% with EPO as both feasible and clinically relevant. To demonstrate this absolute 3% improvement of LVEF after EPO treatment, with a standard deviation of 11%, a power of 0.8 and a P-value < 0.05, two-sided, 212 evaluable patients per group were needed. From the first 100 patients, we observed that, for several reasons (Figure 1), a primary endpoint could not be obtained in 20% of patients. Therefore, we aimed to include approximately 264 patients...
in each group. Therefore, to obtain 424 evaluable endpoints, a total of 528 patients (264 in each group) had to be included in this study.

**Statistical analysis**

Summaries of quantitative continuous variables are presented as means ± standard deviation or medians and inter-quartile ranges (IQRs) if appropriate. Categorical data are presented as absolute frequencies. Baseline patient characteristics between EPO and control were compared with the use of the χ² test or Fisher’s exact test (binary variables), Student’s t-test (continuous variables), and the Wilcoxon rank-sum (non-Gaussian data). To estimate the treatment effect on the primary endpoint, differences in means and corresponding 95% CI were calculated on the basis of the analysis of variance model. In addition, between-group differences were also computed using three-way ANOVA with terms for group, time, and a group × time to measurement as interaction.

For the separate analyses on the first clinical event, the event-free survival was estimated according to the Kaplan–Meier method and...
compared between the two treatment groups by the log-rank test. For differences in NT-proBNP levels and enzymatic infarct size, the Wilcoxon rank-sum test was used.

Safety was assessed by summarizing incidence and type of AEs during the follow-up duration. All patients were included in the safety assessment. The safety analysis focused in particular on AEs, serious AEs, and mortality. No formal statistical hypothesis testing was performed. Treatment regimens were compared on the incidence of adverse drug reactions.

All analyses were done two-sided with a $P$-value < 0.05 indicating statistical significance. All analyses were based on intention-to-treat principle. With regard to missing data, no replacement of missing data was performed. Statistical analyses were performed using SPSS 16 (SPSS, Inc., Chicago, IL, USA).

All statistical analyses were performed by the Trial Coordination Center of the University Medical Center Groningen, and no commercial entities were involved in the data analysis.

## Results

### Patients

Clinical characteristics of the patients are presented in Table 1. At baseline, groups were well-matched for all relevant characteristics. Mean (± SD) age of the patients was 60.9 (± 11.1) years, and 78% were male. Median (IQR) time from the onset of symptoms to the start of the PCI procedure was 180 (120–270) min. Although

### Table 1 Baseline characteristics of 529 patients with a successful primary coronary intervention for a first ST-elevation myocardial infarction randomized to erythropoietin or control

<table>
<thead>
<tr>
<th></th>
<th>Total cohort, n = 529</th>
<th>EPO, n = 263</th>
<th>Control, n = 266</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agea (years)</td>
<td>60.9 ± 11.1</td>
<td>60.8 ± 10.9</td>
<td>61.0 ± 11.3</td>
</tr>
<tr>
<td>%Male</td>
<td>77.7</td>
<td>75.7</td>
<td>79.7</td>
</tr>
<tr>
<td>BMI® (kg/m²)</td>
<td>27.3 ± 4.2</td>
<td>27.4 ± 4.3</td>
<td>27.3 ± 4.0</td>
</tr>
<tr>
<td>History of hyperlipidaemiab</td>
<td>98 (19.0)</td>
<td>53 (21.0)</td>
<td>45 (17.2)</td>
</tr>
<tr>
<td>Diabetesc</td>
<td>47 (9.1)</td>
<td>25 (9.9)</td>
<td>22 (8.4)</td>
</tr>
<tr>
<td>History of hypertensionb</td>
<td>174 (33.8)</td>
<td>84 (33.2)</td>
<td>90 (34.4)</td>
</tr>
<tr>
<td>Current smokerb</td>
<td>116 (22.7)</td>
<td>58 (23.2)</td>
<td>58 (22.2)</td>
</tr>
<tr>
<td>Family history of CADb</td>
<td>186 (36.1)</td>
<td>95 (37.5)</td>
<td>91 (34.7)</td>
</tr>
<tr>
<td>History of revascularizationb</td>
<td>13 (2.5)</td>
<td>5 (2.0)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Hba at baselinea (g/dL)</td>
<td>14.2 ± 1.37</td>
<td>14.0 ± 1.35</td>
<td>14.3 ± 1.29</td>
</tr>
<tr>
<td>Ht at baselinea (L/L)</td>
<td>0.41 ± 0.04</td>
<td>0.40 ± 0.04</td>
<td>0.41 ± 0.03</td>
</tr>
<tr>
<td>Serum creatininec (mg/dL)</td>
<td>0.86 (0.75–10)</td>
<td>0.85 (0.74–10)</td>
<td>0.87 (0.76–101)</td>
</tr>
<tr>
<td>Systolic BP® (mmHg)</td>
<td>128.5 ± 24.1</td>
<td>127.2 ± 24.9</td>
<td>129.7 ± 23.3</td>
</tr>
<tr>
<td>Diastolic BP® (mmHg)</td>
<td>76.8 ± 14.4</td>
<td>76.3 ± 15.0</td>
<td>77.3 ± 13.8</td>
</tr>
<tr>
<td>Heart ratea (b.p.m.)</td>
<td>74.5 ± 15.8</td>
<td>74.9 ± 15.5</td>
<td>74.2 ± 16.0</td>
</tr>
<tr>
<td>Time from symptom onset to PCIc (min)</td>
<td>180 (120–270)</td>
<td>180 (126–288)</td>
<td>174 (120–251)</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa inhibitorb</td>
<td>411 (77.7)</td>
<td>199 (75.7)</td>
<td>212 (79.7)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of diseased vesselsb</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>348 (66.8)</td>
<td>170 (66.1)</td>
<td>178 (67.9)</td>
</tr>
<tr>
<td>2</td>
<td>131 (25.1)</td>
<td>65 (25.3)</td>
<td>65 (24.8)</td>
</tr>
<tr>
<td>3</td>
<td>42 (8.1)</td>
<td>22 (8.6)</td>
<td>19 (7.3)</td>
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</table>

<table>
<thead>
<tr>
<th>Infarct-related arteryb</th>
<th>LAD</th>
<th>RCA</th>
<th>RCx</th>
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</thead>
<tbody>
<tr>
<td>209 (40.1)</td>
<td>226 (43.4)</td>
<td>85 (16.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication at follow-upb</th>
<th>Aspirin</th>
<th>Oral anticoagulants</th>
<th>Clopidogrel</th>
<th>Beta-blockers</th>
<th>ACE-inhibitors</th>
<th>ARB</th>
<th>Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>468 (94.6)</td>
<td>33 (6.7)</td>
<td>425 (85.9)</td>
<td>460 (92.9)</td>
<td>348 (70.3)</td>
<td>37 (7.5)</td>
<td>478 (96.6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean ± SD.</th>
<th>(%).</th>
<th>Median (IQR).</th>
</tr>
</thead>
</table>
baseline haemoglobin was higher in the control group, there were no differences in changes in haemoglobin over the first 48 h between the groups.

Patients were treated according to the guidelines, and had received aspirin, clopidogrel, and heparin in the ambulance as per protocol. After a successful PCI procedure (TIMI flow 2/3), patients were randomized. After randomization, immediately before EPO infusion, a 12-lead ECG was performed. Median (IQR) cumulative ST-segment deviation (ST-elevation and ST-depression) was 5.1 (2.6–8.5) mm in the EPO group and 5.1 (2.7–8.5) mm in the control group ($P = 0.88$).

**Endpoints**

After a mean of 6.5 (± 2.0) weeks, planar radionuclide ventriculography was obtained in 448 patients (85%). Reasons for not being able to obtain the primary endpoint are described in Figure 1. Mean (± SD) LVEF was 0.53 (± 0.10) in the EPO group and 0.52 (± 0.11) in the control group ($P = 0.41$) (Figure 2).

Data on enzymatical myocardial infarct size are presented in Table 2. Overall, myocardial infarct size was slightly larger in the control group compared with the EPO group, although these differences did not reach statistical significance.

Cardiovascular events within 6 weeks after the PCI are presented in Table 3. Overall, 8 patients in the EPO group suffered at least one cardiovascular event, compared with 19 patients in the control group ($P = 0.032$). Figure 3 demonstrates Kaplan–Meier curves of cardiovascular events in the EPO and control groups (log-rank for time to first event: $P = 0.031$).

In a subgroup of 214 patients, NT-proBNP was available at baseline and follow-up. Median (IQR) NT-proBNP increased from 81 (40–394) to 380 (198–853) pg/mL in the EPO group and from 106 (45–286) to 470 (217–1010) pg/mL in the control group ($P$-value for difference in change from baseline to 6 weeks: 0.025).

**Safety analysis**

Overall, 49 serious adverse events (SAEs) were reported in 40 control patients, and 33 SAEs were reported in 29 EPO patients. Heart failure-related events (7 vs. 1; $P = 0.034$) and re-infarctions (all caused by acute stent thrombosis; 7 vs. 2; $P = 0.096$) were found more frequently in the control group. Erythropoietin was well tolerated and there were no reports of malignant hypertension, seizure, or deep-vein thrombosis. Only one pulmonary embolism was reported in the control group and none in the EPO group. In addition, cardiovascular deaths and strokes were comparable between both groups (Table 3). Changes in haemoglobin between baseline and 24 h were available in 201 patients. Mean drop in haemoglobin (± SD) was 0.52 (± 1.09) g/dL in the EPO group and 0.55 (± 1.02) g/dL in the control group ($P = 0.86$). Similarly, there were no differences in the change in haematocrit ($P = 0.73$), leucocyte count ($P = 0.75$), or platelet count ($P = 0.37$) between both groups.

**Discussion**

A single high-dose i.v. bolus of EPO administered immediately after a successful PCI for a first STEMI did not improve left ventricular function after 6 weeks. However, treatment with EPO resulted in significantly fewer major adverse cardiovascular events.

Four earlier smaller studies have reported on the effects of EPO in myocardial infarction patients.11–14 One of these studies was a pilot study,11 two others did not report the effects on left ventricular function,12,13 and in one (unpublished) study in 138 STEMI

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**Table 2** Secondary study endpoint: enzymatic infarct size, determined by serial CK, CK-MB, and troponin T measurements in 529 acute myocardial infarction patients treated with erythropoietin or control

<table>
<thead>
<tr>
<th></th>
<th>EPO, $n = 263$</th>
<th>Control, $n = 266$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK (U/L)</td>
<td>1750 (895–2970)</td>
<td>1726 (967–3300)</td>
<td>0.293</td>
</tr>
<tr>
<td>AUC CK (U/L per 72 h)</td>
<td>50 136 (28 212–76 664)</td>
<td>53 510 (33 973–90 486)</td>
<td>0.058</td>
</tr>
<tr>
<td>Peak CK-MB (U/L)</td>
<td>214 (116–344)</td>
<td>219 (109–322)</td>
<td>0.955</td>
</tr>
<tr>
<td>AUC CK-MB (U/L per 72 h)</td>
<td>5622 (3487–8204)</td>
<td>5931 (3757–8801)</td>
<td>0.16</td>
</tr>
<tr>
<td>Peak troponin T ($\mu$g/L)</td>
<td>4.30 (1.94–7.89)</td>
<td>5.90 (2.20–8.00)</td>
<td>0.564</td>
</tr>
<tr>
<td>AUC troponin T ($\mu$g/L per 72 h)</td>
<td>157.5 (77.6–257.4)</td>
<td>153.0 (88.3–256.3)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Variables are reported in median (IQR).
patients, intravenous infusion of EPO (3.3 × 10^4 IU of epoietin beta at 3 successive days) did not improve left ventricular function at 6 months. These findings are similar to our study and might be explained by a relatively preserved left ventricular function, since patients were very well treated, and received a successful primary PCI procedure shortly after the onset of symptoms. Therefore, in the current setting, left ventricular function might not be the best marker of cardioprotection of EPO during a myocardial infarction.

Myocardial infarct size was measured with cardiac enzymes, which was one of the pre-specified secondary outcomes in this study. We demonstrated a modest reduction in cardiac enzymes with EPO, although these differences did not reach statistical significance. These results are similar to the results published by Binbrek et al., who only showed a modest and non-significant reduction of EPO treatment on myocardial infarct size in 236 patients who received thrombolysis. In a small study in 30 patients, EPO significantly reduced CK-MB release after an STEMI. In a small pilot study in 51 patients with a non-ST-elevation myocardial infarction, a single intravenous dose of 40 000 IU of EPO had no significant effect on enzymatic infarct size.

The second pre-specified secondary outcome marker in this study was the effect of EPO on pre-defined cardiovascular events. A significant reduction in cardiovascular events was observed in the EPO-treated patients. This difference was primarily caused by significantly fewer cases of heart failure in the EPO group. Interestingly, similar findings of less heart failure events in the EPO group were reported in non-STEMI patients. These findings are further supported by data on NT-proBNP in a subgroup of patients from the present study, which showed that the increase of NT-proBNP from baseline to 6 weeks was significantly smaller in the EPO-treated patients, further supporting the potential cardioprotective effects of EPO in STEMI patients. The NT-proBNP results should however be interpreted with caution, since this was a secondary outcome in a subgroup of patients.

Taken together, our findings partly support the concept that EPO might have specific cardioprotective effects. We recently demonstrated that in patients with EPO resistance, mortality was increased. With the discovery of a functional EPO receptor in the heart, it was hypothesized that EPO elicits cardioprotective effects. Exogenous stimulation of these receptors in animal models with human recombinant EPO proved to decrease infarct size and ameliorated ejection fraction. Importantly, in these studies, EPO was given by intraperitoneal infusion, where very high levels of circulating EPO were reached. Also, in our pilot study, serum EPO levels increased by a 150-fold compared with the controls, which was expected to be sufficient. Therefore, we decided to give EPO intravenously instead of directly into the coronary artery. In addition, the beneficial effects of EPO in the experimental studies were present both when given before and after reperfusion, indicating a wide window of opportunity. On the basis of these results, in the present study, we decided to give the bolus of EPO after reperfusion.

The cardioprotective effects of EPO can be explained by two main mechanisms. First, stimulation of the EPO receptor in the heart increases neovascularization through the increase of vascular endothelial growth factor and endothelial progenitor cells homing to the myocardium. Impaired capillary density is thought to be a main pathophysiological mechanism in heart failure. Second, EPO decreased apoptosis in ischaemia–reperfusion models, potentially leading to smaller infarct sizes. The reduction of major adverse cardiac events in the EPO group was observed mainly in the early phase, which might be related to a reduction of apoptosis, although this remains highly speculative. It should be noted that the dose that was used in the animal studies (3000–8000 U/kg) was larger than the dose that was used in the present study. However, a 100-fold lower dose yielded similar results.

Recently, concerns have been expressed regarding safety of the use of EPO, in particular in patients with renal anaemia. In Trial to
Reduce Cardiovascular Events with Aranesp Therapy (TREAT), the use of EPO in patients with renal anaemia was associated with an increased risk of stroke. In addition, EPO treatment in patients with an acute ischaemic stroke was associated with an increased mortality risk. It should be noted however that in each of the studies reporting potentially hazardous effects of EPO, multiple doses were used, and doses were haemoglobin-targeted, in contrast to the present study, where a single dose was used. Also, in a placebo-controlled study in myocardial infarction patients treated with aspirin and clopidogrel, EPO did not alter markers of platelet and endothelial cell activation associated with thrombosis. In the present study, EPO treatment was associated with significantly fewer serious adverse effects, mainly due to fewer heart failure-related events and re-myocardial infarctions due to acute stent thrombosis. Therefore, the present study indicates that the current safety concerns about EPO cannot be translated to single-dose administration in STEMI patients treated with primary angioplasty. However, the current study was not powered for clinical events, and therefore the previous statement should be carefully interpreted.

The present study has limitations. First, we chose an open-label design for practical and safety purposes. Although we did not use a core laboratory, both LVEF and all laboratory values were blinded for both patients and investigators, and all endpoints were adjudicated by a blinded endpoint committee. Second, we failed to meet our primary endpoint. The primary endpoint was based on multiple observations in experimental studies, in which EPO showed a clear improvement in LVEF. However, in the present study, median LVEF after 6 weeks was 0.53, which is only very mildly reduced, and this might explain the absence of an additional effect of EPO. Third, the findings of all pre-specified secondary endpoints should be interpreted with great caution, since the study was only powered to detect a difference in LVEF.

In conclusion, a single high dose of EPO after a successful PCI for a STEMI did not improve LVEF after 6 weeks. However, the use of EPO was related to significantly less major adverse cardiovascular events and a favourable clinical safety profile. A large phase-III clinical trial powered to detect a reduction in hard clinical endpoints should be performed before EPO can be routinely used in this setting.

Funding
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Conflict of interest: S.D.A. received consultancy fees and honoraria for speaking from Amgen Inc, Vifor Pharma, BRAHMS AG and consultancy fees from Nanosphere. D.j.v. received consultancy fees from Amgen Inc.

Appendix

Data Safety Monitoring Board: Professor Dr J.G. Tijssen, Department of Cardiology, Academic Medical Centre Amsterdam, The Netherlands, and Dr M. van den Brand, Erasmus Medical Centre Rotterdam, The Netherlands.

Endpoint Committee: Dr B.J. de Smet and Dr A.F. van den Heuvel, University Medical Center Groningen, The Netherlands. Statistical Support: Dr N. Veeger, Trial Coordination Center, University Medical Centre Groningen, The Netherlands.

References


