Anemia and erythropoietin in cardiovascular disease

Kleijn, Lennaert

Chapter 7

Long term effects of epoetin alfa in patients with ST-Elevation myocardial infarction

Lennaert Kleijn
Marieke L. Fokkema
Peter van der Meer
Anne M. Belonje
Sandra K. Achterhof
Hans L. Hillege
Arnoud van t Hof,
J. Wouter Jukema
Hans O. Peels
José P. Henriques
Jurriën M. ten Berg
Jeroen Vos
Wiek H. van Gilst
Dirk J. van Veldhuisen
Adriaan A. Voors

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Abstract

Purpose

The HEBE III trial showed that epoetin alfa administration in patients with a first ST-elevation myocardial infarction (STEMI) did not improve left ventricular function at 6 weeks after primary percutaneous coronary intervention (PCI). The long term effects of erythropoiesis- stimulating agents on cardiovascular morbidity and mortality are unknown, therefore we evaluated clinical events at 1 year after PCI.

Methods

A total of 529 patients with a first STEMI and successful primary PCI were randomized to standard optimal medical treatment (N = 266) or an additional bolus of 60,000 IU epoetin alfa administered intravenously (N = 263) within 3 hours after PCI. Analyses were performed by intention to treat.

Results

At 1 year after STEMI, 485 patients had complete follow-up. The rate of the composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and/or heart failure was 6.4% (N = 15) in the epoetin alfa group and 9.6% (N = 24) in the control group (p = 0.18). Thromboembolic events were present in 1.3% (N = 3) of patients in the epoetin alfa group and 2.4% (N = 6) in the control group. There was no evidence of benefit from epoetin alfa administration in subgroups of patients.

Conclusions

Administration of a single bolus of epoetin alfa in patients with STEMI does not result in a reduction of cardiovascular events at 1 year after primary PCI. There was a comparable incidence of thromboembolic complications in both treatment groups, suggesting that epoetin alfa administration is safe at long term.

Introduction

Preclinical studies have suggested that erythropoiesis- stimulating agents (ESA) have a cardioprotective effect after myocardial reperfusion. Subsequently, several clinical studies investigated the effects of ESA administered in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) to reduce myocardial infarct size and to improve left ventricular function.[1-9] However, the majority of these studies did not show a beneficial effect of ESA on left ventricular function. One of these studies even reported an increase in thromboembolic events in the ESA treated patients.[7] In addition, results suggested that ESA administration might have an adverse effect on infarct size among STEMI patients aged 70 years or older.[7] However, the number of STEMI patients in the clinical ESA trials was often small.

The HEBE III study was the largest, prospective study randomizing 529 STEMI patients to a single bolus of epoetin alfa or to standard medical care after primary PCI.[2] The primary endpoint of the HEBE III study was left ventricular function at 6 weeks after myocardial infarction. The single high dose of epoetin alfa failed to show an effect on the primary endpoint. However, patients receiving epoetin alfa had a lower 6-weeks incidence of adverse cardiovascular events. The aim of this follow-up study of HEBE III was to evaluate the effect of epoetin alfa on clinical outcome during the first year after myocardial infarction.

Methods

Population

The HEBE III study was a multicenter, randomized, open-label trial with blinded evaluation of the primary end point. The detailed study design and the first results of the primary end point at 6 weeks have been previously published.2,10 The aim of the study was to investigate the effect of high dose epoetin alfa administration after primary PCI on left ventricular function in patients with STEMI. Between January 2007 and June 2009, 529 patients were enrolled.

In short, patients were eligible for participation if they presented with a first STEMI with thrombolysis in myocardial infarction (TIMI) flow 0 or 1 on the coronary angiogram before the PCI procedure and underwent a successful primary PCI with TIMI flow 2 or 3 after PCI. STEMI was defined as chest pain suggestive of cardiac ischemia with symptom onset < 12 h before hospital admission or < 24 h in case of ongoing ischemia, an electrocardiogram with ST-T segment elevation > 0.1 mV in ≥ 2 or more leads or a new left bundle branch block. The most important exclusion criteria were a previous myocardial infarction, hemoglobin levels > 17.1 g/dL before PCI, anticipated additional

revascularization within 6 weeks after primary PCI, a history of persistent or permanent atrial fibrillation, cardiogenic shock and a serum creatinine > 2.5 mg/dL.

Randomization and treatment

After a successful primary PCI with TIMI flow 2 or 3 on the coronary angiogram after PCI, STEMI patients who met eligibility criteria were asked for participation. Patients were randomized (1:1) to optimal standard medical treatment with or without a bolus of 60.000 IU epoetin alfa (Ortho Biotech, a division of Janssen-Cilag B.V.) administered intravenously in 10 minutes. Patients received the bolus of epoetin alfa in the coronary care unit within 3 hours after PCI. Blood pressure, heart rate and ECG were constantly monitored, continuing at regular time points after the infusion up to 48 h after PCI.
All patients received aspirin (500 mg), heparin (5000 IU) and clopidogrel (600 mg) after confirmation of ST-segment elevation on the first ECG. During primary PCI, patients received the glycoprotein IIb/IIIa inhibitor abciximab (0.25 mg/kg) if not contraindicated. The standard treatment after primary PCI consisted of aspirin, clopidogrel (≥ 1 month), β blockers, lipid lowering agents, and angiotensin- converting enzyme inhibitors or angiotensin-II receptor blockers. The patients included in the study provided written informed consent. The research protocol was approved by the central Ethics Committee of the University Medical Center Groningen, and by the local Ethics Committees of each of the participating centers.

Outcomes and definitions

Information on vital status, re-infarction, target vessel revascularization and stroke was collected from hospital records and telephone interviews at 6 weeks and at 1 year after primary PCI. Re-infarction was defined as the onset of recurrent symptoms of ischemia combined with new ST-segment elevations and/or a second increase of serum CK or CK-MB to at least twice the upper limit of the normal range. Target vessel revascularization was defined as PCI or bypass grafting of the infarct-related coronary artery after primary PCI. Other end points included all-cause mortality, stroke and admission for heart failure. The composite end point of cardiovascular events was defined as all-cause mortality, re-infarction, target vessel revascularization, stroke and admission for heart failure. The composite end point of thromboembolic events was defined as re-infarction or stroke.

Statistical analysis

Data were analyzed on an intention to treat basis. Categorical variables are presented

as frequency values and proportions and were compared with the χ^2 test or Fisher's exact test. Continuous normally distributed variables are presented as mean values and standard deviations (SD) and were compared with the 2-tailed Student t test. For skewed distributed variables, median values with interquartile ranges are shown, and the variables were compared with the use of the Mann- Whitney U test. The cumulative incidence of the composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure during the first year was evaluated with the Kaplan Meier method. The clinical outcomes in the treatment groups were compared with the log-rank test. Subgroup analyses were performed for gender, age > 70 years, diabetes, hypertension, smoking and time from symptom onset to PCI > 180 minutes, by means of logistic regression analysis, presenting risk ratios (RR) and corresponding 95% confidence intervals. For all analyses, 2-sided p values of <0.05 were defined as significant. Statistical analyses were performed using the Statistical Package of Social Sciences version 20.0 (SPSS, IBM corporation, Armonk, NY, USA).

Results

Study population

A total of 529 patients were randomized to epoetin alfa (N = 263) or to the control group (N = 266) (Figure 1). A total of 22 patients in the epoetin alfa group and 11 in the control group prematurely withdrew their informed consent, and we were therefore not allowed to report follow-up data of these patients. In 485 patients, 1 year follow-up was available, of which 236 patients were randomized to epoetin alfa and 249 patients

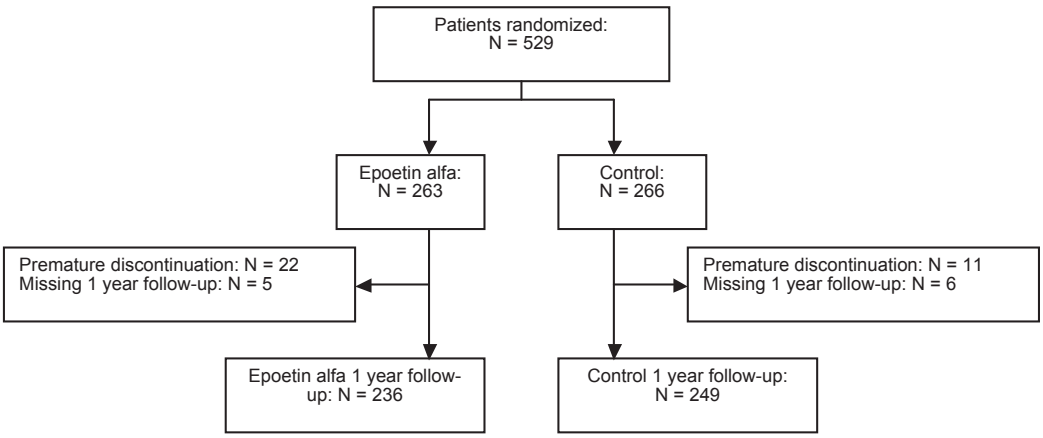

Figure 1. Flow chart. Flow chart of STEMI patients randomized to epoetin alfa or the control group

Table 1. Baseline clinical and angiographic characteristics

	Epoetin alfa N = 236	Control N = 249
Age (years) (± SD)	60.1 (± 10.5)	60.5 (± 11.0)
Male gender	180 (76.3%)	199 (79.9%)
Diabetes	25 (10.6%)	18 (7.2%)
Hypertension	78 (33.2%)	83 (33.3%)
Hypercholesterolemia	51 (21.7%)	43 (17.3%)
Family history CAD	120 (51.1%)	131 (52.6%)
Current smoker	56 (24.0%)	56 (22.5%)
Prior revascularization	5 (2.1%)	8 (3.2%)
Systolic blood pressure (mmHg) (± SD)	127.9 (± 24.8)	129.6 (± 23.6)
Diastolic blood pressure (mmHg) (± SD)	76.7 (± 14.8)	77.1 (± 13.9)
Heart rate (b.p.m.) (± SD)	75.2 (± 15.6)	74.0 (± 16.1)
Haemoglobin at baseline (g/dL) (± SD)	14.0 (± 1.4)	14.3 (± 1.3)
Haematocrit at baseline (%) (± SD)	40.2 (± 3.8)	41.3 (± 3.5)
Serum creatinine at baseline (mg/dL) (IQR)	0.85 (0.74-0.98)	0.87 (0.76-1.00)
Time from symptom onset to PCI (min) (IQR)	180 (126-290)	175 (120-255)
Number of diseased vessels		
1	157 (66.8%)	168 (67.5%)
2	60 (25.5%)	62 (24.9%)
3	18 (7.7%)	19 (7.6%)
Infarct-related coronary artery		
LAD	96 (40.9%)	99 (39.8%)
Cx	38 (16.2%)	42 (16.9%)
RCA	101 (43.0%)	107 (43.0%)

b.p.m = beats per minute, CAD = coronary artery disease, Cx = circumflex coronary artery, IQR = interquartile range, LAD = left artery descending, PCI = percutaneous coronary intervention, RCA = right coronary artery

to the control group. The baseline clinical characteristics were well balanced between the treatment groups (Table 1). The mean age of the patients was 60.1 (±10.5) years in the epoetin alfa group and 60.5 (±11.0) years in the control group, and the proportion of males was 76.3% versus 79.9%. The median time from symptom onset to PCI was 180 (interquartile range 126- 290) minutes in patients receiving epoetin alfa and 175 (interquartile range 120- 255) minutes in patients in the control group. The hemoglobin level at baseline was 14.0 (±1.4) g/dL in the epoetin alfa group and 14.3 (±1.3) g/dL in the control group. The majority of patients presented with 1 vessel disease (66.8% versus 67.5%) on the coronary angiogram.

Clinical outcomes

A total of 6 patients died during 1 year follow-up after primary PCI, 1 patient in the epoetin alfa group and 5 in the control group (Table 2). The composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure occurred in 6.4% (N = 15) of patients in the epoetin alfa group and 9.6% (N = 24) of

Table 2. Clinical events at 1 year follow-up

	Epoetin alfa N = 236	Control N = 249	p value
All -cause mortality	1 (0.4%)	5 (2.0%)	0.12
Re- infarction	1 (0.4%)	5 (2.0%)	0.12
Target vessel revascularization	10 (4.2%)	13 (5.2%)	0.61
Stroke	2 (0.8%)	1 (0.4%)	0.53
Heart failure	1 (0.7%)	4 (2.6%)	0.19
Composite end point	15 (6.4%)	24 (9.6%)	0.18
Thromboembolic complications	3 (1.3%)	6 (2.4%)	0.35
Major bleeding	8 (3.4%)	10 (4.0%)	0.72

The composite end point includes all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure. Thromboembolic complications include re-infarction and stroke

patients in the control group (p = 0.18) during the first year after primary PCI (Table 2, Figure 2). Thromboembolic events were present in 1.3% (N = 3) of patients in the epoetin alfa group and 2.4% (N = 6) in the control group. Major bleeding occurred in 3.4% (N = 8) and 4.0% (N = 10) of patients, respectively.

Subgroups

In the subgroups of gender, age (>70 years), diabetes, hypertension, smoking and time from symptom onset to primary PCI (>180 minutes), there was no significant difference in the incidence of the composite end point between the epoetin alfa group and the control group (Figure 3).

Discussion

The 1 year follow-up results of this randomized trial on epoetin alfa in 485 STEMI patients showed no significant difference in the composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure between STEMI patients randomized to a single high dose epoetin alfa or to standard optimal medical treatment after primary PCI. In addition, the incidence of thromboembolic complications was comparable between the treatment groups.

Erythropoietin is a hematopoietic hormone produced by the kidneys in response to hypoxia. It stimulates the production of red blood cells by inhibition of apoptosis of progenitor cells, causing an increase of the hemoglobin level. In clinical practice, exogenous erythropoietin is often administered in anemic patients with a reduced erythropoietin production.[11]ESA are mainly used in anemic patients with chronic kidney disease and cancer, and in these patients chronic administration effectively raises hemoglobin leading to a reduction in symptoms. However, this is not associated with a favorable ef-

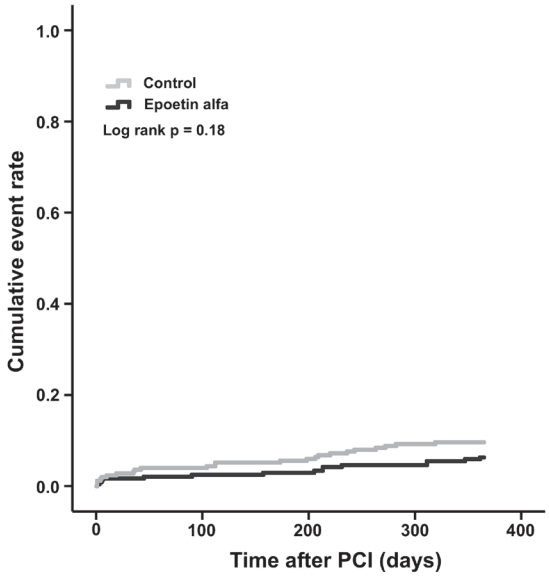

Figure 2. Cumulative incidence of the composite end point all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure. Cumulative event rate of STEMI patients randomized to epoetin alfa or the control group during the first year after primary PCI

fect on outcome.[12-14] Long-term use of ESA have also been investigated in patients with chronic heart failure. In these patients, it reduced symptoms and increased exercise capacity,[15,16] but it also did not improve outcome.[17]

ESA have also been investigated in acute ischemic conditions in patients without anemia. In these patients, single doses of ESA were used with the aim of protection against ischemia. In patients with acute cerebral ischemia early studies suggested potentially beneficial effects of ESA.[18] However, a subsequent much larger study indicated that ESA were not beneficial in these patients.[19] In comparison, more studies have been conducted in patients with acute cardiac ischemia and myocardial infarction as compared to acute cerebral ischemia. In preclinical studies, administration of ESA showed cardioprotective effects in cardiac ischemia.[20] Administration of exogenous erythropoietin resulted in a reduction of cardiac cell apoptosis in different animal models in rats and rabbits during ischemia, and after the onset of reperfusion.[21-23] Administration of ESA even resulted in a reduction in cardiomyocyte loss and a decreased infarct size after induced ischemia in rats and dogs.[21,24,25] In addition, ESA may contribute to a reduction in the inflammatory response induced after myocardial reperfusion and have a positive effect on neovascularization.[25,26]

After these encouraging pre-clinical studies, clinical trials have evaluated the effect of ESA administration in patients with STEMI undergoing PCI.[1-9] In 2 small clinical stud-

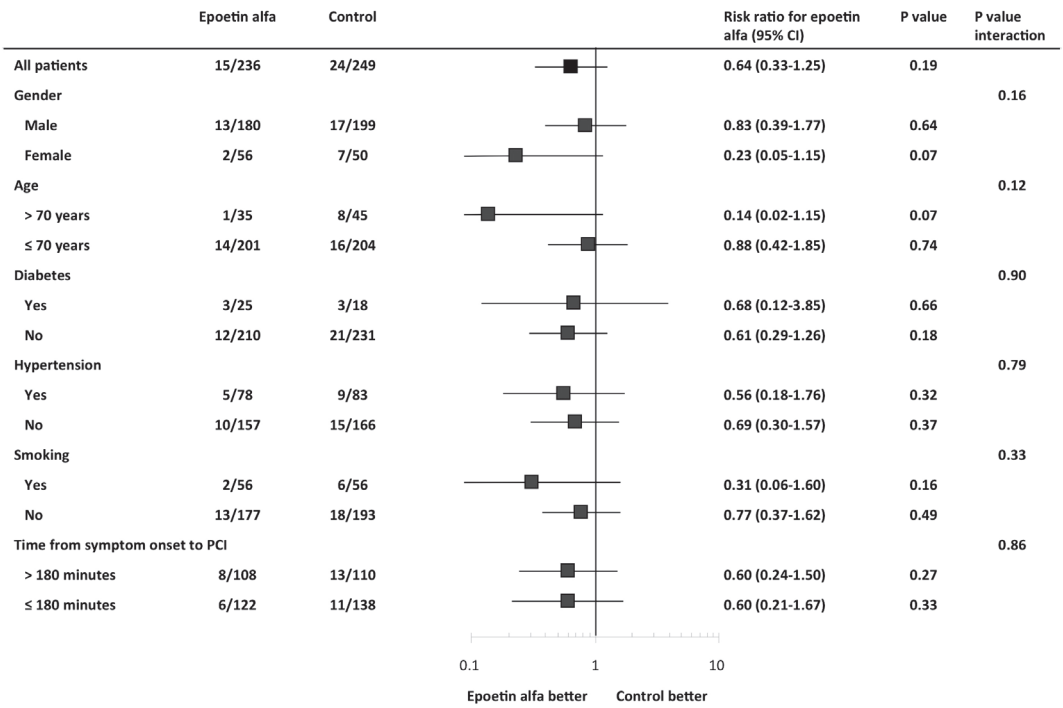

Figure 3. Subgroup analysis Subgroup analysis of the composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure

ies, the investigators observed an improvement in left ventricular function over time in STEMI patients receiving ESA, and not in the control group.[4,5] Although the results of preclinical studies were promising, ESA administration did not result in a reduction of infarct size or an improvement in left ventricular function between the treatment groups in most clinical trials. We performed the largest randomized clinical trial investigating the effect of epoetin alfa in STEMI patients so far. Epoetin alfa did not result in an improvement of left ventricular function at 6 weeks after primary PCI. However, we observed a reduction in cardiovascular events at 6 weeks in the epoetin alfa group compared to the control group, although numbers were low (8 vs 19, p = 0.032). In the current study we can report that one year after PCI, the initial differences in cardiovascular events disappeared.

Regarding the overwhelming effects in animal models of acute myocardial infarction, how can the discrepancy with the clinical situation be explained?[27] A first explanation may be that the cardioprotective effect of ESA in animals cannot be translated to humans, probably as a consequence of differences in coronary anatomy, and differences in infarct sizes and ESA dose compared with clinical studies. Secondly, the timing of epo-

etin alfa administration may not have been optimal, as epoetin alfa was administered after myocardial reperfusion.[28] The higher ESA doses used in animals compared to humans could have contributed to the observed differences in treatment effects. However, it seems that the dose of epoetin alfa was high enough to have effects on serum levels, as a previous pilot study showed a 200-fold increase of serum erythropoietin levels after administration of high dose darbepoetin alfa.[29] Third, a single bolus dose of epoetin alfa may not have been sufficient. However, it should be taken into account that increases in hemoglobin levels may cause unwanted side effects.[30] Fourth, we included patients with a first STEMI who were reperfused early after symptom onset. As a consequence of the small infarct sizes in a majority of patients, the possible effects of epoetin alfa may not have been observed. Finally, the number of included patients may have been too small to observe an effect on clinical outcome.

Safety

Administration of high dose ESA has raised safety concerns in patients with anemia and chronic kidney disease receiving high ESA doses. In a study of patients with diabetes, chronic kidney disease and anemia, high ESA doses resulted in an increased risk of stroke in patients receiving darbepoetin alfa compared to placebo.[14] In addition, some randomized trials in STEMI patients observed a trend towards a higher incidence of re-infarction, target vessel revascularization and stroke in patients treated with ESA compared to placebo, but numbers were low.1,7 In the present larger follow-up study of HEBE III, the incidence of cardiovascular events did not significantly differ between patients randomized to epoetin alfa or the control group at 1 year after primary PCI. This is also supported by the results of a meta-analysis of randomized trials investigating the effect and safety of ESA in patients with myocardial infarction.[31] However, this was performed on study level rather than with individual patient data.

Subgroups

Najjar et al. observed that in patients ≥ 70 years the mean infarct size was larger in the ESA group than in the placebo group on the first cardiac magnetic resonance imaging.7 We did not observe a higher incidence of adverse cardiovascular events in patients ≥ 70 years receiving ESA compared to the control group. In addition, none of the investigated subgroups showed a significant difference in cardiovascular events between the treatment allocations.

Limitations

Several limitations should be taken into account. This study was powered on an estimated improvement of left ventricular ejection fraction at 6 weeks after PCI. Therefore, the number of patients may have been too small to investigate a difference in clinical outcome and cardiovascular events at 1 year after PCI. In addition, the number of events was small, making it difficult to observe differences in effect between the treatment allocations. Furthermore, the population of STEMI patients included in this study was a selective population with better clinical outcomes than expected in a general STEMI population. This makes it more difficult to translate our results to real world clinical practice. Finally, the study was not blinded for treatment allocation.

Conclusion and implications

The administration of epoetin alfa in patients with STEMI did not result in a reduction of cardiovascular events at 1 year after primary PCI. However, the higher incidence of thromboembolic complications, as observed in some previous studies, was not observed in patients receiving epoetin alfa in this study. This may suggest that a single dose of epoetin alfa administration is safe at the long term. However, whether serial ESA administration in STEMI patients is safe and effective should be investigated in an adequately powered trial with clinical end points.

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