Intravenous Erythropoietin in Patients With ST-Segment Elevation Myocardial Infarction

REVEAL: A Randomized Controlled Trial

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Context Acute ST-segment elevation myocardial infarction (STEMI) is a leading cause of morbidity and mortality. In experimental models of MI, erythropoietin reduces infarct size and improves left ventricular (LV) function.

Objective To evaluate the safety and efficacy of a single intravenous bolus of epoetin alfa in patients with STEMI.

Design, Setting, and Patients A prospective, randomized, double-blind, placebo-controlled trial with a dose-escalation safety phase and a single dose (60 000 U of epoetin alfa) efficacy phase; the Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction (REVEAL) trial was conducted at 28 US sites between October 2006 and February 2010, and included 222 patients with STEMI who underwent successful percutaneous coronary intervention (PCI) as a primary or rescue reperfusion strategy.

Intervention Participants were randomly assigned to treatment with intravenous epoetin alfa or matching saline placebo administered within 4 hours of reperfusion.

Main Outcome Measure Infarct size, expressed as percentage of LV mass, assessed by cardiac magnetic resonance (CMR) imaging performed 2 to 6 days after study medication administration (first CMR) and again 12±2 weeks later (second CMR).

Results In the efficacy cohort, the infarct size did not differ between groups on either the first CMR scan (n=136; 15.8% LV mass [95% confidence interval {CI}, 13.3-18.2% LV mass] for the epoetin alfa group vs 15.0% LV mass [95% CI, 12.6-17.3% LV mass] for the placebo group; $P=.67$) or on the second CMR scan (n=124; 10.6% LV mass [95% CI, 8.4-12.8% LV mass] vs 10.4% LV mass [95% CI, 8.5-12.3% LV mass], respectively; $P=.89$). In a prespecified analysis of patients aged 70 years or older (n=21), the mean infarct size within the first week (first CMR) was larger in the epoetin alfa group (19.9% LV mass; 95% CI, 14.0-25.7% LV mass) than in the placebo group (11.7% LV mass; 95% CI, 7.2-16.1% LV mass) ($P=.03$). In the safety cohort, of the 125 patients who received epoetin alfa, the composite outcome of death, MI, stroke, or stent thrombosis occurred in 5 (4.0%; 95% CI, 1.31%-9.09%) but in none of the 97 who received placebo ($P=.04$).

Conclusions In patients with STEMI who had successful reperfusion with primary or rescue PCI, a single intravenous bolus of epoetin alfa within 4 hours of PCI did not reduce infarct size and was associated with higher rates of adverse cardiovascular events. Subgroup analyses raised concerns about an increase in infarct size among older patients.

Trial Registration clinicaltrials.gov Identifier: NCT00378352

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Despite advances in the management of ST-segment elevation myocardial infarction (STEMI), it remains a significant cause of morbidity, mortality, and disability,[1,2] particularly among older persons.[3] Patients who survive STEMI are at risk for developing infarct expansion (the process of myocardial thinning and infarct zone dilation that begins soon after coronary occlusion)[4] and left ventricular (LV) remodeling (the topographical and functional changes in the in-

For editorial comment see p 1908.

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farct zone and the noninfarcted myocardium).[5] Both are strongly associated with heart failure and death.[6] Risk factors for infarct expansion and LV remodeling include infarct size, extent of apoptosis, anterior location of the infarction,[7] severe microvascular obstruction,[8] and older age.[9] Given the global burden of ischemic heart disease and heart failure, therapies that limit infarct size and attenuate or reverse LV remodeling are needed.

Erythropoietin is a 165-amino acid glycoprotein hormone whose production and secretion are regulated by tissue oxygen levels. Beyond its effects on red blood cell production, erythropoietin exhibits pleiotropic effects in cells and tissues, including stimulation of angiogenesis and protection against apoptosis.[10] Furthermore, erythropoietin receptors have been identified on endothelial cells and cardiomyocytes.[11] Preclinical studies have shown that erythropoietin plays a cardioprotective role in various experimental models of myocardial ischemia and ischemia reperfusion.[12-17] In these investigations, erythropoietin was associated with significant reductions in infarct size and improvements in LV function that were partly attributed to its antiapoptotic and angiogenic properties.

To determine whether erythropoietin has similar cardioprotective effects in a clinical setting, we performed the Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction (REVEAL) trial, which evaluated the safety and effect on infarct size of a single intravenous bolus of recombinant human erythropoietin (epoetin alfa) in patients with STEMI who have undergone successful primary or rescue percutaneous coronary intervention (PCI).

METHODS

The REVEAL trial was a multicenter, phase 2, randomized, double-blind, placebo-controlled clinical trial that evaluated the safety and efficacy of a single intravenous bolus of epoetin alfa in patients with STEMI. The design and rationale of the REVEAL trial have been published.[18] Briefly, the study consisted of a dose-escalation phase and an efficacy phase (FIGURE 1). During the dose-escalation phase, 3 doses of epoetin alfa (15 000 U, 30 000 U, and 60 000 U) were sequentially evaluated. These doses were chosen with guidance from the US Food and Drug Administration to balance safety concerns with the relatively high doses of erythropoietin used in preclinical studies. Patients were randomly allocated in a 2 to 1 ratio to each dose of epoetin alfa or placebo, respectively. Dose escalation was guided by an independent data and safety monitoring board, which reviewed clinical and safety data at 2 time points for each dose cohort.[18]

Based on the study design, the highest planned dose of epoetin alfa that was deemed acceptable by the data and safety monitoring board was used in the efficacy phase, in which participants were randomly allocated in a 1 to 1 ratio to epoetin alfa or placebo. The REVEAL study was reviewed and approved by the MedStar Research Institute's institutional review board and by the respective institutional review boards of the participating sites. Written informed consent was obtained from all participants or their legally authorized representatives.

In accordance with guidelines from the National Institutes of Health, self-reported information on race and ethnicity was collected from all study participants. Categories were defined by the study investigators and consisted of Hispanic/Latino or non-Hispanic/Latino for ethnicity and American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, other (which were later condensed into 1 category), white, or black/African American for race.

Eligibility Criteria, Randomization, and Study Medication

Study eligibility criteria are listed in eTable 1 at http://www.jama.com. Briefly, patients were eligible if they had acute STEMI with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 to 1 in a major epicardial artery or large branch vessel during index angiography and underwent successful primary or rescue PCI within 8 hours of onset of ischemic symptoms. To minimize confounding of the measurement of infarct size, patients with a history of LV dysfunction (LV ejection fraction [LVEF] ≤50%), MI, coronary artery bypass grafting, or revascularization in the territory of the culprit artery were excluded.

Eligible patients were randomly assigned to epoetin alfa or matching placebo according to the allocation ratio for each dosing cohort. Randomization was performed with a fixed-block randomization scheme using a Web-based application (WebEZ, Almac, Durham, North Carolina) fully integrated with drug supply management information. Randomization was stratified according to age (<70 years or ≥70 years) and infarct location (left anterior descending or non–left anterior descending coronary artery).

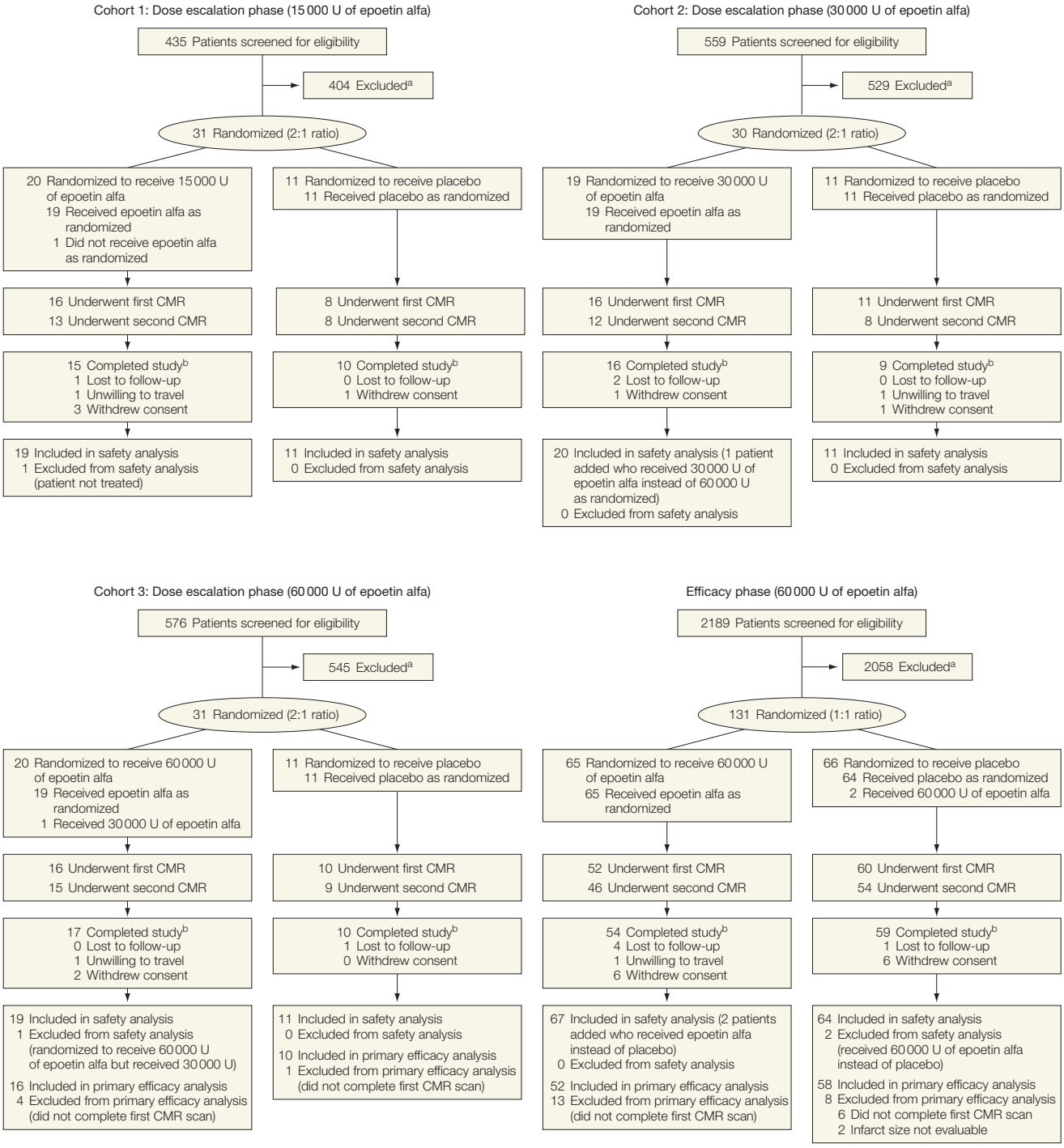
Study medication (epoetin alfa or matching saline placebo) was administered within 4 hours of successful primary or rescue PCI, defined as time of restoration of TIMI flow grade of 2 or greater in the infarct-related artery. During the initial phase of the REVEAL trial, epoetin alfa and matching placebo were provided free of charge by Centocor Ortho Biotech Clinical Affairs (Bridgewater, New Jersey). However, during the efficacy phase, the company elected to cease providing study medication, and the study sponsor (National Institute on Aging) purchased active study medication from Centocor Ortho Biotech and contracted with Florida Biologix, in Alachua, to manufacture matching placebo. All other treatments, including PCI techniques, were at the discretion of the treating physicians, who were encouraged to adhere to guideline recommendations for the management of patients with STEMI.[19]

Cardiac Magnetic Resonance (CMR) Imaging

Patients underwent the first CMR 2 to 6 days after study medication administration and the second CMR 12±2

weeks later. Each CMR examination consisted of (1) a cine CMR for assessment of LV volumes (end-systolic volume and end-diastolic volume), LV mass, and LV function quantified by LVEF and (2) a delayed contrast-enhanced CMR for assessment of infarct size. The values for LV end-systolic volume, LV end-diastolic

Figure 1. Flow of Patients in REVEAL Trial



CMR indicates cardiac magnetic resonance; REVEAL, Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction.
[a] Patients were excluded by sites for reasons beyond failing to meet eligibility criteria such as patients not wanting to participate.
[b] Indicates patients who were followed up for the duration of the study (12±2 weeks), irrespective of whether they underwent the CMR imaging.

volume, and LV mass were indexed to body surface area (BSA). Deidentified CMR studies were analyzed at a core laboratory (Duke Cardiovascular Magnetic Resonance Center, Durham, North Carolina) by investigators masked to treatment assignment and clinical outcomes. Details of the imaging protocol have been published.[18]

Primary and Secondary End Points

The primary efficacy end point of the study was infarct size in the territory of the infarct-related artery, expressed as percentage of LV mass and measured by the first CMR (performed 2-6 days or 48-144 hours) after study medication administration. Secondary end points included infarct size, 3 LV remodeling parameters (LV end-systolic volume, LV end-diastolic volume, and LV mass, each indexed to BSA) and LV function (LVEF) measured by CMR 12±2 weeks after study medication administration (second CMR). The 3 LV remodeling parameters and LVEF measured on the first CMR also were examined.

Safety end points included vital signs, hemoglobin level, reticulocyte count, markers of cardiac injury, and clinical events including death, recurrent MI, unplanned PCI, arterial thrombotic events (stent thrombosis), venous thrombotic events (deep venous thrombus, pulmonary embolus), heart failure, and neurological events (stroke, transient ischemic attack).

Table 1. Baseline Characteristics of Study Patients[a]

	Total Cohort (N = 222)[b]		Efficacy Cohort (n = 138)	
	Epoetin Alfa (n = 123)	Placebo (n = 99)	Epoetin Alfa (n = 68)	Placebo (n = 70)
Demographics				
Age, mean (SD), y	56.8 (12.4)	58.8 (12.5)	55.6 (12.6)	57.4 (11.9)
Female sex	23 (18.7)	21 (21.2)	7 (10.3)	14 (20.0)
Race[c]				
Black	14 (11.4)	14 (14.1)	6 (8.8)	8 (11.4)
White	104 (84.6)	81 (81.8)	59 (86.8)	61 (87.1)
Other[d]	5 (4.1)	4 (4.0)	2 (2.9)	1 (1.4)
Ethnicity[e]				
Hispanic	4 (3.3)	7 (7.1)	4 (5.9)	2 (2.9)
Non-Hispanic	119 (96.7)	92 (92.9)	64 (94.1)	68 (97.1)
Weight, mean (SD), kg	(n = 122) 89.9 (18.6)	(n = 99) 87.4 (16.0)	(n = 68) 89.3 (16.8)	(n = 70) 87.1 (15.3)
Height, mean (SD), cm	(n = 122) 174.4 (9.2)	(n = 99) 173.2 (9.7)	(n = 68) 174.6 (8.3)	(n = 70) 173.7 (9.5)
Comorbid Conditions				
Hypertension[f]	58 (47.2)	53 (53.5)	28 (41.2)	34 (48.6)
Current smoker[g]	(n = 121) 47 (38.8)	(n = 99) 42 (42.4)	(n = 67) 27 (40.3)	(n = 70) 32 (45.7)
Hyperlipidemia[h]	50 (40.7)	43 (43.4)	24 (35.3)	30 (42.9)
Diabetes[i]	14 (11.4)	25 (25.3)[j]	6 (8.8)	17 (24.3)[j]
Baseline Medication Use				
Clopidogrel	118 (95.9)	94 (94.9)	66 (97.1)	66 (94.3)
Aspirin	110 (89.4)	93 (93.9)	62 (91.2)	64 (91.4)
Heparin[k]	108 (87.8)	86 (86.9)	60 (88.2)	60 (85.7)
Glycoprotein IIb/IIIa inhibitor	88 (71.5)	71 (71.7)	46 (67.6)	45 (64.3)
Patient Subgroups				
Age category, y				
<70	103 (83.7)	81 (81.8)	57 (83.8)	59 (84.3)
≥70	20 (16.3)	18 (18.2)	11 (16.2)	11 (15.7)[l]
Infarct-related artery				
Nonanterior	89 (72.4)	72 (72.7)	48 (70.6)	51 (72.9)
Anterior	34 (27.6)	27 (27.3)	20 (29.4)	19 (27.1)

(continued)

Statistical Analysis

The primary comparison was infarct size measured by the first CMR between participants who received the highest dose of epoetin alfa deemed safe by the data and safety monitoring board and those who received placebo. The sample size for the 3 patient cohorts in the dose-escalation phase was fixed (n=30 per cohort) as agreed on by the REVEAL study investigators and the US Food and Drug Administration. Because the distribution of infarct size data is consistently nonnormal, the sample size for the efficacy phase was determined with an empirical approach that used available infarct size data from studies carefully matched to the conditions of our investigation (mean [SD] infarct size of 19.5 [10.6]). The power values were estimated by simulations that suggested a sample size of 55 patients per group in the efficacy phase and 30 patients from the corresponding dose-escalation phase would provide more than 80% power to detect a difference of 20% or greater in infarct size between the 2 treatment groups. The REVEAL trial continued to accrue patients until 110 participants received study medication and competed their first CMR scan in the efficacy phase.

Efficacy data were analyzed on a modified intention-to-treat basis, which excluded 1 patient who was randomized but did not receive study medication. The efficacy cohort comprised all patients from the efficacy phase plus all patients from the 60 000 U cohort of the dose-escalation phase who received study medication and underwent their first CMR.

Baseline differences between the epoetin alfa and placebo groups were evaluated using the Fisher exact test with a mid-*P* value adjustment for categorical variables and the Wilcoxon rank sum test for continuous variables. Spearman rank correlation coefficients and scatterplots were used to evaluate the relationship between in-

farct size and time from symptom onset to study drug administration and between infarct size and time from study drug administration to first CMR. The primary outcome variable, infarct size expressed as percentage of LV mass measured on the first CMR, was compared between the 2 groups using the log-rank test,[20] both with and without adjustment for age group (<70 vs ≥70 years), infarct-related artery location (left anterior descending vs non–left anterior descending), and enrollment phase.

Between-group comparisons for all other cardiac variables assessed by CMR were performed with analysis of variance for unadjusted analyses and with analysis of covariance for adjusted analyses. The adjusted analyses controlled for age group, infarct-related artery location, and enrollment phase. Adjustment for enrollment phase was performed to control for implicit differences that may exist between patients recruited in the dose-escalation phase and patients recruited in the efficacy phase. For cardiac variables measured on the second CMR, the adjusted models controlled for values of the same variables obtained on the first CMR. In addition, post hoc comparisons of changes from the first CMR to the second CMR in LV end-systolic volume, LV end-diastolic volume, and LV mass, each indexed to BSA, were performed with analysis of variance. The primary and secondary end points were further analyzed within the prespecified subgroups of patient age (<70 vs ≥70 years) and infarct-related artery location (left anterior descending vs non–left anterior descending).

Safety data were analyzed on an as-treated basis. The safety cohort comprised all patients who received study medication. Composite safety end points were added to the analysis plan at the suggestion of the data and safety monitoring board and were compared using the Fisher exact test with a mid-*P* value adjustment. One prespecified interim test of efficacy was performed using the Haybittle-Peto rule.[21] Due to rounding, the interim analysis did not result in a penalty for the final α level. A 2-sided α level of .05 was considered statistically significant. *P* values were not adjusted for multiple comparisons. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

Table 1. Baseline Characteristics of Study Patients (continued)[a]

	Total Cohort (N = 222)[b]		Efficacy Cohort (n = 138)	
	Epoetin Alfa (n = 123)	Placebo (n = 99)	Epoetin Alfa (n = 68)	Placebo (n = 70)
Clinical Characteristics				
Type of PCI				
Primary	110 (89.4)	82 (82.8)[j]	64 (94.1)	55 (78.6)[j]
Rescue	13 (10.6)	17 (17.2)	4 (5.9)	15 (21.4)
Killip class I	(n = 115) 115 (100)	(n = 96) 91 (94.8)[j]	(n = 62) 62 (100)	(n = 67) 64 (95.5)
Heart rate, mean (SD), beats/min	77.4 (16.1)	76.5 (13.6)	77.0 (14.5)	75.6 (13.2)
Blood pressure, mean (SD), mm Hg				
Systolic	129.5 (17.9)	126.5 (18.8)	132.8 (18.1)	126.7 (19.3)
Diastolic	78.4 (12.7)	76.0 (13.7)	79.9 (12.2)	76.8 (13.4)
Time from event 1 to event 2, mean (SD), min				
Symptom onset to restoration of TIMI 2-3 flow	207.5 (106.8)	208.3 (105.7)	210.9 (98.3)	201.9 (111.2)
TIMI flow restoration to study drug administration	176.3 (77.3)	183.0 (74.1)	172.4 (75.0)	175.5 (75.3)
Randomization to administration of study drug	(n = 122) 47.5 (48.0)	(n = 99) 39.9 (32.9)[j]	(n = 67) 47.9 (32.6)	(n = 70) 39.6 (34.6)[j]

Abbreviations: PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
[a] Values are expressed as number (percentage) unless otherwise indicated.
[b] A total of 223 patients were randomized, but only 222 received study medication.
[c] Self-reported information was collected from all patients. Categories were defined by the study and consisted of the following: American Indian/Alaska Native, Asian, black or African American, Native Hawaiian/Pacific Islander, or white.
[d] Includes patients who self-identified as Asian, Native Hawaiian/Pacific Islander, or American Indian/Alaska Native.
[e] Self-reported information was collected from all patients. Categories were defined by the study and consisted of the following: Hispanic/Latino or non-Hispanic/Latino.
[f] Defined as history of high blood pressure as documented by either (1) hypertension diagnosed and treated with medication, diet, and/or exercise or (2) blood pressure level higher than 140 mm Hg (systolic) or 90 mm Hg (diastolic) on at least 2 occasions.
[g] Determined by patient self-report.
[h] Defined as at least 1 of the following: (1) prior total cholesterol level higher than 200 mg/dL (>5.2 mmol/L), (2) prior low-density lipoprotein cholesterol level higher than 100 mg/dL (>2.7 mmol/L), or (3) treatment with a lipid-lowering agent.
[i] Defined as any history of diabetes, need for antidiabetic agents, or fasting blood glucose level higher than 7 mmol/L (>126 mg/dL).
[j] For between-group comparison, the *P* value was less than .05.
[k] Includes both unfractionated and low–molecular-weight heparin.
[l] One patient did not receive the first cardiac magnetic resonance imaging.

RESULTS

Between October 2006 and November 2009, 223 participants at 22 of 28 US sites were enrolled into the study and randomized; 222 participants received study medication. Of these, 189 had the first CMR performed within 2 to 6 days after study drug administration (24 in the 15 000 U cohort; 27 in the 30 000 U cohort; and 138 in the 60 000 U combined efficacy cohort) (Figure 1). In the entire efficacy cohort, the median time from symptom onset to study drug administration was 6.3 hours (interquartile range, 5.0-7.6 hours) and the median time from study drug administration to first CMR was 66.3 hours (interquartile range, 50.2-118.7 hours). Most participants in this cohort (124/138; 89.9%) underwent follow-up CMR (second CMR) at 12±2 weeks. The last follow-up visit was conducted on February 12, 2010.

The baseline clinical characteristics of the total and efficacy cohorts, stratified by treatment assignment, are summarized in TABLE 1. The active medication (epoetin alfa) group and the placebo group were well matched, al-

though the former had a significantly lower prevalence of diabetes mellitus, less use of rescue PCI, and a longer time from randomization until study drug administration.

Efficacy Analyses

Cardiac variables assessed by CMR in the efficacy cohort are shown in TABLE 2. The number of participants included in each efficacy analysis varied depending on CMR end point availability. The primary study end point of infarct size measured within 2 to 6 days after study medication administration was available for 136 of the 138 patients who underwent CMR and did not differ between the epoetin alfa and placebo groups in either the unadjusted analysis or the adjusted analysis, which controlled for age group, infarct-related artery location, and enrollment phase (Table 2 and FIGURE 2). There was no association between infarct size and time from study drug administration to first CMR ($r = -0.13$, $P = .14$). Infarct size measured at 12 ± 2 weeks after the first CMR did not differ between groups in either the unadjusted or adjusted analyses. Adjusting for baseline clinical characteristics that differed between groups did not affect these findings. As with infarct size, infarct mass did not differ between groups at either time point.

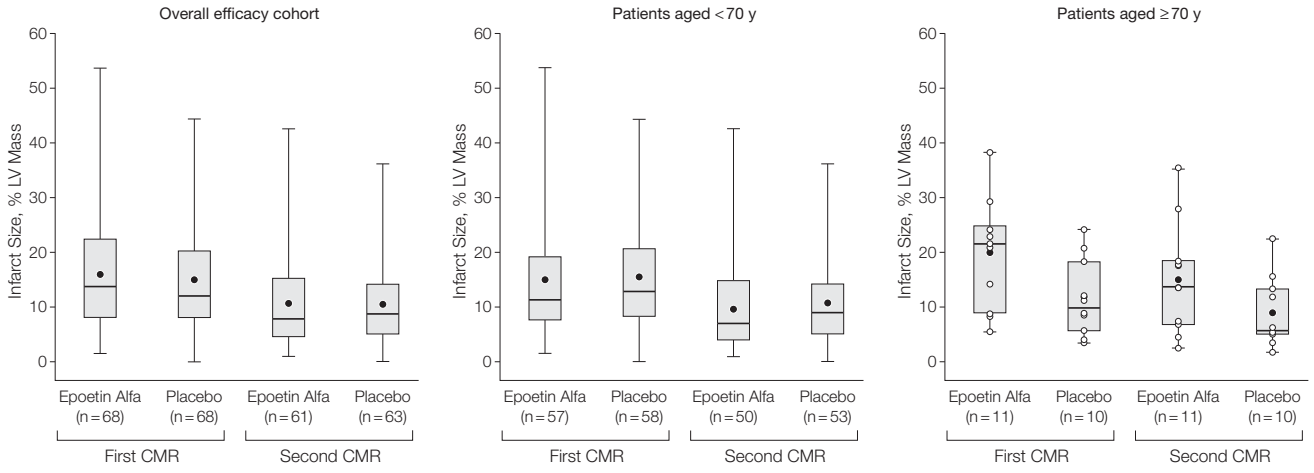
The values for LVEF, LV end-systolic volume indexed to BSA, and LV end-diastolic volume indexed to BSA did not differ between groups in the unadjusted analysis at either time point (Table 2).

Table 2. Left Ventricular (LV) Characteristics Assessed by Cardiac Magnetic Resonance (CMR) Imaging in the Efficacy Cohort[a]

	First CMR (n = 138)[b]			Second CMR (n = 124)[c]		
	Epoetin Alfa	Placebo	*P* Value	Epoetin Alfa	Placebo	*P* Value
Infarct size, % LV mass	(n = 68) 15.8 (10.3) [13.3-18.2]	(n = 68) 15.0 (10.0) [12.6-17.3]	.67	(n = 61) 10.6 (8.6) [8.4-12.8]	(n = 63) 10.4 (7.6) [8.5-12.3]	.89
Infarct mass, g	(n = 68) 24.6 (18.9) [20.1-29.1]	(n = 68) 21.1 (14.5) [17.6-24.5]	.22	(n = 61) 14.9 (13.3) [11.5-18.2]	(n = 63) 12.7 (9.2) [10.4-15.0]	.29
LV ejection fraction, %	(n = 68) 48.2 (9.1) [46.0-50.4]	(n = 70) 48.9 (8.7) [46.8-50.9]	.67	(n = 61) 52.5 (9.3) [50.2-54.8]	(n = 63) 52.0 (8.8) [49.8-54.2]	.76
LV volume indexed to BSA, mL/m^2						
End systolic	(n = 65) 34.7 (14.7) [31.1-38.3]	(n = 68) 32.6 (10.6) [30.1-35.1]	.34	(n = 61) 34.1 (14.0) [30.6-37.6]	(n = 62) 32.0 (11.7) [29.1-34.9]	.36
End diastolic	(n = 65) 65.6 (18.2) [61.2-70.1]	(n = 68) 63.4 (15.4) [59.7-67.0]	.44	(n = 61) 70.0 (17.1) [65.7-74.3]	(n = 62) 66.6 (19.1) [61.8-71.3]	.30
LV mass indexed to BSA, g/m^2	(n = 68) 74.2 (15.2) [70.6-77.8]	(n = 69) 69.2 (13.0) [66.1-72.2]	.04	(n = 61) 67.3 (14.7) [63.7-71.0]	(n = 63) 61.8 (14.1) [58.4-65.3]	.04

Abbreviation: BSA, body surface area.
[a] Values are expressed as mean (SD) [95% confidence interval] unless otherwise indicated. *P* values are from unadjusted analysis.
[b] Performed 2 to 6 days after study medication administration.
[c] Performed 12 ± 2 weeks after first CMR imaging.

Figure 2. Comparison of Infarct Size Between Epoetin Alfa and Placebo Groups



Boxes represent interquartile range, black-filled circles represent means, whiskers represent the minimum and maximum, and horizontal lines represent the median. Individual data points (open circles) are provided for the graph for patients aged 70 years or older due to the low sample sizes. For patients aged 70 years or older, the *P* value is equal to .03 for the comparison of epoetin alfa with placebo for the first cardiac magnetic resonance (CMR) imaging. LV indicates left ventricular.

However, at 12 weeks, the adjusted analysis (which controlled for values of LV end-systolic volume indexed to BSA and LV end-diastolic volume indexed to BSA on initial CMR) showed that adjusted LV end-systolic volume indexed to BSA was 8.1% larger in the epoetin alfa group (n = 61; 34.5 mL/m^2 [95% confidence interval {CI}, 32.2-36.9 mL/m^2]) than in the placebo group (n = 62; 31.7 mL/m^2 [95% CI, 29.3-34.2 mL/m^2]) (P = .04). Furthermore, adjusted LV end-diastolic volume indexed to BSA was 7.2% larger in the epoetin alfa group (n = 61; 70.7 mL/m^2 [95% CI, 67.1-74.3 mL/m^2]) than in the placebo group (n = 62; 65.6 mL/m^2 [95% CI, 61.8-69.4 mL/m^2]) (P = .01). Thus, in post hoc comparisons with the placebo group, the epoetin alfa group had a smaller decrease in LV end-systolic volume indexed to BSA from the first CMR to the second CMR (0.9 mL/m^2 [95% CI, –1.2 to 2.9 mL/m^2] vs –1.9 mL/m^2 [95% CI, –3.7 to 0 mL/m^2], respectively; P = .05) but a greater increase in LV end-diastolic volume indexed to BSA (5.8 mL/m^2 [95% CI, 2.7 to 8.9 mL/m^2] vs 0.9 mL/m^2 [95% CI, –2.4 to 4.1 mL/m^2], respectively; P = .03).

The only end point that differed significantly between groups in the unadjusted analysis was LV mass indexed to BSA (Table 2). On the first CMR, the mean LV mass indexed to BSA was 6.7% higher in the epoetin alfa group than in the placebo group (unadjusted P = .04; adjusted P = .03). This difference persisted at 12 weeks but was due to the difference in LV mass indexed to BSA on the first CMR because the change in LV mass indexed to BSA from the first CMR to second CMR did not differ between treatment groups (–6.2 g/m^2 [95% CI, –8.4 to –4.1 g/m^2] for epoetin alfa vs –6.5 g/m^2 [95% CI, –8.3 to –4.7 g/m^2] for placebo; P = .85).

Subgroup Analyses

Infarct size did not differ between treatment groups according to infarct-related artery location in either the unadjusted or adjusted analysis within 2 to 6 days (first CMR) or at 12 weeks (second CMR). The interaction between treatment assignment and age group (P = .08) suggests that age group may modify the effect of epoetin alfa on infarct size. Infarct size did not differ between groups among patients younger than 70 years (Figure 2). However, among patients aged 70 years or older, the mean infarct size on the first CMR was 41.2% larger in the epoetin alfa group (19.9% LV mass [95% CI, 14.0-25.7% LV mass]) than in the placebo group (11.7% LV mass [95% CI, 7.2-16.1% LV mass]; n = 21; unadjusted P = .03; adjusted P = .02) (Figure 2). These results were unchanged when the analyses were further adjusted for presence of diabetes mellitus, which was the only characteristic that significantly differed between the 2 groups (prevalence of 9.1% in the epoetin alfa group and 54.5% in the placebo group). Among patients aged 70 years or older, infarct size on the second CMR remained 40.0% larger in the epoetin alfa group (15.0% LV mass [95% CI, 9.1-20.9% LV mass]) than in the placebo group (9.0% LV mass [95% CI, 4.9-13.0% LV mass]), although this difference was not statistically significant (unadjusted P = .12). The observed difference was mainly due to the difference in infarct size on the first CMR (adjusted P = .07 when controlling for infarct-related artery location and enrollment phase; adjusted P = .88 when controlling for the previously mentioned items plus the first CMR value of infarct size).

Safety Analyses

Participants who received epoetin alfa had a higher incidence of adverse events (69/125 [55.2%; 95% CI, 46.05%-64.10%]) than those who received placebo (40/97 [41.2%; 95% CI, 31.33%-51.69%]; P = .04) (TABLE 3). These

Table 3. Clinical Adverse Events in the Total and Efficacy Cohorts[a]

	Total Cohort			Efficacy Cohort		
Events	Epoetin Alfa (n = 125)	Placebo (n = 97)	*P* Value	Epoetin Alfa (n = 86)	Placebo (n = 75)	*P* Value
Death	1 (0.8) [0.02-4.38]	0	.72	0	0	
Myocardial infarction (MI)[b]	2 (1.6) [0.19-5.66]	0	.35	1 (1.2) [0.03-6.31]	0	.73
Unstaged PCI	6 (4.8) [1.78-10.15]	0	.02	4 (4.7) [1.28-11.48]	0	.08
CABG	0	1 (1.0) [0.03-5.61]	.22	0	1 (1.3) [0.03-7.21]	.23
Stroke	1 (0.8) [0.02-4.38]	0	.72	0	0	
Stent thrombosis	3 (2.4) [0.50-6.85]	0	.17	2 (2.3) [0.28-8.15]	0	.36
LV thrombus	3 (2.4) [0.50-6.85]	2 (2.1) [0.25-7.25]	.83	2 (2.3) [0.28-8.15]	0	.36
New or worsening CHF	5 (4.0) [1.31-9.09]	2 (2.1) [0.25-7.25]	.36	2 (2.3) [0.28-8.15]	1 (1.3) [0.03-7.21]	.80
Any adverse event[c]	69 (55.2) [46.05-64.10]	40 (41.2) [31.33-51.69]	.04	49 (57.0) [45.85-67.61]	31 (41.3) [30.08-53.30]	.05
Any serious adverse event[d]	25 (20.0) [13.38-28.09]	10 (10.3) [5.06-18.14]	.05	14 (16.3) [9.20-25.80]	6 (8.0) [2.99-16.60]	.12
Death, MI, stroke, or stent thrombosis	5 (4.0) [1.31-9.09]	0	.04	2 (2.3) [0.28-8.15]	0	.36
Death, MI, or stroke	4 (3.2) [0.88-7.99]	0	.08	1 (1.2) [0.03-6.31]	0	.73

Abbreviations: CABG, coronary artery bypass graft; CHF, congestive heart failure; LV, left ventricular; PCI, percutaneous coronary intervention.
[a] Values are expressed as number (percentage) [95% confidence interval] unless otherwise indicated. Number of participants for cohorts given according to treatment received.
[b] Does not include index event.
[c] Includes events that occurred during the period between randomization and discharge or day 7, whichever came first.
[d] Includes events that occurred during the period between randomization and the second CMR.

participants also had a higher incidence of serious adverse events (25/125 [20.0%; 95% CI, 13.38%-28.09%]) than those who received placebo (10/97 [10.3%; 95% CI, 5.06%-18.14%; *P*=.05). Of the 125 patients who received epoetin alfa, the composite outcome of death, MI, stroke, or stent thrombosis occurred in 5 (4.0%; 95% CI, 1.31%-9.09%) but in none of the 97 who received placebo (*P*=.04). Descriptions of these clinical events can be found in the eAppendix at http://www.jama.com.

There were no clinically meaningful differences between treatment groups in hemoglobin levels, reticulocyte counts, or blood pressure at the various time points assessed after administration of study medication (eTable 2 at http://www.jama.com), which likely reflects the fact that only a single infusion of epoetin alfa was administered. Similarly, there were no clinically meaningful differences between treatment groups in the changes in the levels of these variables from baseline or from the preceding time point.

COMMENT

In the REVEAL trial, a single bolus of intravenous epoetin alfa in patients with STEMI who underwent successful primary or rescue PCI failed to demonstrate a reduction in infarct size. There was a significant increase in infarct size in prespecified analyses among older patients. There was also a significant increase in the composite of cardiovascular adverse events that included stent thrombosis. Clinical interest in the use of erythropoietin as a cardioprotective agent emanated from a growing body of experimental evidence showing that erythropoietin's nonerythropoietic effects include anti-inflammatory, antiapoptotic, and angiogenic properties.[10,22] In preclinical models, erythropoietin promotes neovascularization and induces mobilization of endothelial progenitor cells from bone marrow.[23] In animal models of ischemic myocardial injury, erythropoietin was shown to reduce apoptotic cells,[12,17] diminish cardiomyocyte loss,[16] improve functional recovery,[14] decrease infarct size,[16,17] and attenuate infarct expansion.[17]

Other Clinical Trials

Previous clinical studies evaluating the effects of erythropoietin on infarct size have yielded conflicting results. In 5 of these studies, infarct size was indirectly estimated from serial measurements of enzymatic markers of cardiac injury. In the HEBE III trial, a single dose of erythropoietin (60 000 U) within 3 hours of primary PCI in patients with STEMI reduced enzymatic infarct size by 6.7% (*P*=.06) but did not improve LVEF at 6 weeks.[24] In a small pilot study, a single dose of erythropoietin (33 000 U) reduced enzymatic infarct size by 30%.[25] However, in 3 other trials (1 in patients with non-STEMI, 1 in patients with STEMI who were treated with fibrinolysis, and 1 in patients with STEMI who underwent PCI), a single dose of erythropoietin (40 000 U, 40 000 U, and 50 U/kg, respectively) did not reduce enzymatic infarct size.[26-28]

In 2 small studies that assessed infarct size with contrast-enhanced CMR (a powerful, validated tool that allows accurate and reproducible measurement of infarct size[29,30]), erythropoietin did not affect infarct size at 4 days[28] or at 6 months.[25] Using CMR, the REVIVAL-3 (Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells) study found that 3 daily doses of erythropoietin (33 000 U each) did not reduce infarct size at 5 days or at 6 months[31]; 6-month LVEF also remained unimproved.

Taken together with the REVEAL trial, these results indicate that no clinical study to date has shown any beneficial effect of erythropoietin on infarct size measured by CMR. Furthermore, the results in the subgroup of participants aged 70 years or older in the REVEAL trial suggest that erythropoietin may adversely affect infarct size in this high-risk population. Although this concerning finding should be interpreted with caution due to the small number of older patients enrolled in the REVEAL trial and the lack of multiplicity adjustment in the analyses, it suggests the need for added vigilance before enrolling older patients in any future trial evaluating erythropoietin in the setting of MI.

In the small pilot study (N=30) that reported a 30% reduction in enzymatic infarct size with erythropoietin, the erythropoietin treatment group had a greater decrease in LV end-systolic volume than the placebo group, and a similar increase in LV end-diastolic volume.[25] Our larger study failed to replicate these observations. Instead, the epoetin alfa group in the REVEAL trial showed a smaller decrease in LV end-systolic volume indexed to BSA and a larger increase in LV end-diastolic volume indexed to BSA than the placebo group, suggesting a greater reliance on the Frank-Starling mechanism to augment stroke volume. Thus, administration of erythropoietin may be associated with adverse LV remodeling at 3 months.

In the REVEAL trial, we also found a significantly increased risk of death, recurrent MI, stroke, or stent thrombosis with erythropoietin, suggesting an increased thrombotic risk with erythropoietin in patients with STEMI. This is consistent with other studies involving erythropoietin in noncardiac populations.[32-34] Chronic administration of erythropoietin can lead to increases in vasoconstriction, blood pressure, blood viscosity,[35] and thrombotic risk.[36] Some previous studies in patients with MI did not detect an increased risk of adverse events with erythropoietin,[25,27,28,37,38] and the HEBE III trial reported a lower risk of major adverse cardiovascular outcomes in patients receiving erythropoietin.[24] On the other hand, REVIVAL-3 observed an increased risk of death, recurrent MI, stroke, or target vessel revascularization in patients who received erythropoietin.[31] Due to these conflicting safety findings, temporary withholding of erythropoietin in patients who are receiving this medication for labeled indications and who sustain an MI merits further study.

Reconciling Animal and Clinical Studies

The promising cytoprotective effects of erythropoietin observed in animal models have not been reproduced in clini-

cal studies of acute MI. It is conceivable that the effects of erythropoietin differ among species. For example, although erythropoietin reduced infarct size in a rodent model of coronary occlusion,[17] it failed to do so in a porcine model.[39] Moreover, the average infarct size in the REVEAL trial (approximately 15%-16%) was smaller than infarct sizes reported in animal studies. However, the average infarct size in the REVIVAL-3 study was approximately 27% to 28%,[31] and erythropoietin still was not effective in reducing infarct size. In addition, the doses of erythropoietin used in animal studies (3000-5000 U/kg) were generally higher than those used in the current and other clinical studies. However, the cardioprotective effects of erythropoietin have been demonstrated at doses as low as 150 U/kg in rodents (when administered ≤4 hours of ischemic injury).[40]

Importantly, animal studies indicate that there is a therapeutic window of time beyond which the tissue-protective effects of erythropoietin are attenuated; furthermore, the duration of this window is directly related to erythropoietin dose.[40] For example, in a rodent model of coronary ligation, the benefits of erythropoietin at 3000 U/kg can still be observed when administration is delayed up to 12 hours (but not 24 hours) after ischemic injury; whereas at 150 U/kg, these benefits are observed only when erythropoietin is administered within 4 hours (but not 8 hours) of ischemic injury. Furthermore, in a rodent model of ischemia reperfusion, an erythropoietin dose of 3000 U/kg was effective in reducing infarct size if administered at the time of reperfusion (after a 2-hour ischemic injury), but not if infused 4 hours later (M. Talan, unpublished data, September 2010).

In the REVEAL trial, erythropoietin was infused more than 6 hours (on average) after symptom onset. Thus, we cannot exclude the possibility that administration of erythropoietin in our study occurred beyond the putative therapeutic window. The delay in study medication infusion was related in part to the design of the REVEAL trial, which required successful PCI before randomization and was mindful of the importance of door-to-balloon times in patients with STEMI. Although it is possible that earlier administration could have affected the results, erythropoietin did not reduce infarct size in the REVIVAL-3 trial,[31] even though it was administered at the time of PCI.

CONCLUSIONS

In summary, a single bolus of 60 000 U of epoetin alfa in patients with STEMI within 4 hours following successful PCI did not reduce infarct size and was associated with higher rates of adverse cardiovascular events. Subgroup analyses in our study raised concerns about an increase in infarct size among the small number of patients who were aged 70 years or older.

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REFERENCES

1. Young JJ, Kereiakes DJ. Pharmacologic reperfusion strategies for the treatment of ST-segment elevation myocardial infarction. *Rev Cardiovasc Med*. 2003;4(4):216-227.
2. McGovern PG, Pankow JS, Shahar E, et al; Minnesota Heart Survey Investigators. Recent trends in

acute coronary heart disease—mortality, morbidity, medical care, and risk factors. *N Engl J Med*. 1996; 334(14):884-890.
3. Maggioni AP, Maseri A, Fresco C, et al; Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2). Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. *N Engl J Med*. 1993;329(20):1442-1448.
4. Eaton LW, Weiss JL, Bulkley BH, Garrison JB, Weisfeldt ML. Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. *N Engl J Med*. 1979; 300(2):57-62.
5. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. *Circulation*. 1990; 81(4):1161-1172.
6. Weiss JL, Marino PN, Shapiro EP. Myocardial infarct expansion: recognition, significance and pathology. *Am J Cardiol*. 1991;68(14):35D-40D.
7. Weisman HF, Healy B. Myocardial infarct expansion, infarct extension, and reinfarction: pathophysiologic concepts. *Prog Cardiovasc Dis*. 1987;30 (2):73-110.
8. Ezekowitz JA, Armstrong PW, Granger CB, et al. Predicting chronic left ventricular dysfunction 90 days after ST-segment elevation myocardial: an Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) substudy. *Am Heart J*. 2010;160(2): 272-278.
9. Yang Y, Ma Y, Han W, et al. Age-related differences in postinfarct left ventricular rupture and remodeling. *Am J Physiol Heart Circ Physiol*. 2008; 294(4):H1815-H1822.
10. Chong ZZ, Kang JQ, Maiese K. Angiogenesis and plasticity: role of erythropoietin in vascular systems. *J Hematother Stem Cell Res*. 2002;11(6):863-871.
11. Anagnostou A, Liu Z, Steiner M, et al. Erythropoietin receptor mRNA expression in human endothelial cells. *Proc Natl Acad Sci U S A*. 1994;91 (9):3974-3978.
12. Tramontano AF, Muniyappa R, Black AD, et al. Erythropoietin protects cardiac myocytes from hypoxia-induced apoptosis through an Akt-dependent pathway. *Biochem Biophys Res Commun*. 2003;308(4): 990-994.
13. Wright GL, Hanlon P, Amin K, Steenbergen C, Murphy E, Arcasoy MO. Erythropoietin receptor expression in adult rat cardiomyocytes is associated with an acute cardioprotective effect for recombinant erythropoietin during ischemia-reperfusion injury. *FASEB J*. 2004;18(9):1031-1033.
14. Cai Z, Manalo DJ, Wei G, et al. Hearts from rodents exposed to intermittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. *Circulation*. 2003;108(1):79-85.
15. Parsa CJ, Matsumoto A, Kim J, et al. A novel protective effect of erythropoietin in the infarcted heart. *J Clin Invest*. 2003;112(7):999-1007.
16. Calvillo L, Latini R, Kajstura J, et al. Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. *Proc Natl Acad Sci U S A*. 2003;100 (8):4802-4806.
17. Moon C, Krawczyk M, Ahn D, et al. Erythropoietin reduces myocardial infarction and left ventricular functional decline after coronary artery ligation in rats. *Proc Natl Acad Sci U S A*. 2003;100(20):11612-11617.
18. Melloni C, Rao SV, Povsic TJ, et al. Design and rationale of the Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction (REVEAL) trial. *Am Heart J*. 2010; 160(5):795-803, e2.
19. Antman EM, Hand M, Armstrong PW, et al; Canadian Cardiovascular Society; American Academy of Family Physicians; American College of Cardiology; American Heart Association. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2008;51(2):210-247.
20. Dudley RA, Harrell FE Jr, Smith LR, et al. Comparison of analytic models for estimating the effect of clinical factors on the cost of coronary artery bypass graft surgery. *J Clin Epidemiol*. 1993;46(3):261-271.
21. Jennison C, Trunbull BW. *Group Sequential Methods With Applications to Clinical Trials.* Boca Raton, FL: Chapman & Hall; 2000.
22. Lipšic E, Schoemaker RG, van der Meer P, Voors AA, van Veldhuisen DJ, van Gilst WH. Protective effects of erythropoietin in cardiac ischemia: from bench to bedside. *J Am Coll Cardiol*. 2006;48(11):2161-2167.
23. Bahlmann FH, De Groot K, Spandau JM, et al. Erythropoietin regulates endothelial progenitor cells. *Blood*. 2004;103(3):921-926.
24. Voors AA, Belonje AM, Zijlstra F, et al; HEBE III Investigators. A single dose of erythropoietin in ST-elevation myocardial infarction. *Eur Heart J*. 2010; 31(21):2593-2600.
25. Ferrario M, Arbustini E, Massa M, et al. High-dose erythropoietin in patients with acute myocardial infarction: a pilot, randomised, placebo-controlled study. *Int J Cardiol*. 2011;147(1):124-131.
26. Liem A, van de Woestijne AP, Bruijns E, et al. Effect of EPO administration on myocardial infarct size in patients with non-STE acute coronary syndromes: results from a pilot study. *Int J Cardiol*. 2009;131 (2):285-287.
27. Binbrek AS, Rao NS, Al Khaja N, Assaqqaf J, Sobel BE. Erythropoietin to augment myocardial salvage induced by coronary thrombolysis in patients with ST segment elevation acute myocardial infarction. *Am J Cardiol*. 2009;104(8):1035-1040.
28. Suh JW, Chung WY, Kim YS, et al. The effect of intravenous administration of erythropoietin on the infarct size in primary percutaneous coronary intervention [published ahead of print March 1, 2010]. *Int J Cardiol*. doi:10.1016/j.ijcard.2010.02.002.
29. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999;100(19):1992-2002.
30. Kim RJ, Albert TS, Wible JH, et al; Gadoversetamide Myocardial Infarction Imaging Investigators. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation*. 2008;117(5):629-637.
31. Ott I, Schulz S, Mehilli J, et al; REVIVAL-3 Study Investigators. Erythropoietin in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a randomized, double-blind trial. *Circ Cardiovasc Interv*. 2010;3(5):408-413.
32. Ehrenreich H, Weissenborn K, Prange H, et al; EPO Stroke Trial Group. Recombinant human erythropoietin in the treatment of acute ischemic stroke. *Stroke*. 2009;40(12):e647-e656.
33. Singh AK, Szczech L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006; 355(20):2085-2098.
34. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA*. 2008;299(8):914-924.
35. Smith KJ, Bleyer AJ, Little WC, Sane DC. The cardiovascular effects of erythropoietin. *Cardiovasc Res*. 2003;59(3):538-548.
36. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998; 339(9):584-590.
37. Lipšic E, van der Meer P, Voors AA, et al. A single bolus of a long-acting erythropoietin analogue darbepoetin alfa in patients with acute myocardial infarction: a randomized feasibility and safety study. *Cardiovasc Drugs Ther*. 2006;20(2):135-141.
38. Ozawa T, Toba K, Suzuki H, et al; EPO/AMI-I Pilot Study Researchers. Single-dose intravenous administration of recombinant human erythropoietin is a promising treatment for patients with acute myocardial infarction: randomized controlled pilot trial of EPO/AMI-1 study. *Circ J*. 2010;74(7):1415-1423.
39. Kristensen J, Maeng M, Rehling M, et al. Lack of acute cardioprotective effect from preischaemic erythropoietin administration in a porcine coronary occlusion model. *Clin Physiol Funct Imaging*. 2005; 25(5):305-310.
40. Moon C, Krawczyk M, Paik D, Lakatta EG, Talan MI. Cardioprotection by recombinant human erythropoietin following acute experimental myocardial infarction: dose response and therapeutic window. *Cardiovasc Drugs Ther*. 2005;19(4):243-250.