CJASN ePress. Published on August 16, 2019 as doi: 10.2215/CJN.01380219

Article

Cardiovascular Safety and All-Cause Mortality of Methoxy Polyethylene Glycol-Epoetin Beta and Other Erythropoiesis-Stimulating Agents in Anemia of CKD: A Randomized Noninferiority Trial

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Abstract

Background and objectives Erythropoiesis-stimulating agents correct anemia of CKD but may increase cardiovascular risk. We compared cardiovascular outcomes and all-cause mortality associated with monthly methoxy polyethylene glycol-epoetin beta with those of the shorter-acting agents epoetin alfa/beta and darbepoetin alfa in patients with anemia of CKD.

Design, setting, participants, & measurements We conducted a multicenter, open-label, noninferiority trial in which patients were randomized to receive methoxy polyethylene glycol-epoetin beta or reference erythropoiesis-stimulating agents, stratified by maintenance or correction treatment status and C-reactive protein level. The trial had a prespecified noninferiority margin of 1.20 for the hazard ratio (HR) for the primary end point (a composite of all-cause mortality, nonfatal myocardial infarction or stroke, adjudicated by an independent blinded committee). This trial is registered with ClinicalTrials.gov, number NCT00773513.

Results In total, 2818 patients underwent randomization, received methoxy polyethylene glycol-epoetin beta or a reference agent, and were followed for a median of 3.4 years (maximum, 8.4 years). In the modified intention-to-treat analysis, a primary end point event occurred in 640 (45.4%) patients in the methoxy polyethylene glycol-epoetin beta arm, and 644 (45.7%) in the reference arm (HR 1.03; 95% confidence interval [95% CI], 0.93 to 1.15, P=0.004 for noninferiority). All-cause mortality was not different between treatment groups (HR 1.06; 95% CI, 0.94 to 1.19). Results in patient subgroups on dialysis or treated in the correction or maintenance settings were comparable to the primary analysis.

Conclusions In patients with anemia of CKD, once-monthly methoxy polyethylene glycol-epoetin beta was noninferior to conventional, shorter-acting erythropoiesis-stimulating agents with respect to rates of major adverse cardiovascular events or all-cause mortality.

CJASN 14: ●●●–●●●, 2019. doi: https://doi.org/10.2215/CJN.01380219

Introduction

Anemia is a common complication of advanced CKD (1,2). Up to 80% of patients with ESKD have significant anemia associated with relative erythropoietin insufficiency and/or absolute or functional iron deficiency (2). Severe anemia in CKD increases the need for transfusions, significantly impairs quality of life, and is associated with higher cardiovascular risk and shorter survival (1,3–5).

Recombinant human erythropoietins epoetin alfa and beta have been used since 1989 for treatment of anemia in patients with CKD, with dosing up to three times per week. Targeting hemoglobin levels of >13 g/dl does not improve outcomes in patients with anemia of CKD (6–9) and has been shown to correlate with increased cardiovascular and thrombosis risk (7–9), particularly in patients who require higher doses of erythropoiesis-stimulating agents (ESAs) (9,10). Hence, current guidelines do not recommend normalization of hemoglobin levels in patients with anemia of CKD (2,11).

The $t_{1/2}$ of epoetins has been extended through modification of the carbohydrate moiety (darbepoetin alfa) or attachment of a large methoxy polyethylene glycol polymer chain. These modifications permit less frequent administration schedules of every 1–2 weeks for darbepoetin alfa (or every 4 weeks in nondialysis patients) or monthly for methoxy polyethylene glycol-epoetin beta, reducing treatment burden for patients and health care providers.

In clinical development studies of methoxy polyethylene glycol-epoetin beta, no safety issues unexpected for ESAs were identified. In a pooled analysis of 11 studies, five related cardiac events were identified in 1789 patients treated with methoxy polyethylene glycol-epoetin beta compared with none in

948 patients treated with reference ESAs (12). In the context of uncertainty regarding the cardiovascular safety of ESAs, particularly when targeting higher hemoglobin levels, the US Food and Drug Administration and the European Medicines Agency mandated a postapproval safety study (MIRCERA PASS) of methoxy polyethylene glycol-epoetin beta as part of the risk management plan for the drug. A noninferiority design, used in many trials of this type, was agreed to be appropriate in this setting. The MIRCERA PASS trial was conducted to determine whether methoxy polyethylene glycol-epoetin beta was noninferior to the reference agents epoetin alfa/beta and darbepoetin alfa with regard to all-cause mortality and cardiovascular morbidity when targeting hemoglobin levels of 10–12 g/dl in patients with anemia and CKD.

Materials and Methods

Study Design

We conducted a multicenter, randomized, open-label, noninferiority trial. The funder (F. Hoffmann-La Roche Ltd.) was responsible for the trial design (in consultation with the regulatory authorities in the United States and Europe), conduct, monitoring, data collection, storage, and analysis of the final results. An independent data safety and monitoring committee monitored the trial and had access to the unblinded data. Statistical analyses were performed for the committee by an independent statistical group (International Drug Development Institute, Louvain-la-Neuve, Belgium).

The academic authors of the present article drafted the manuscript, had full access to the final trial data, and vouch for the accuracy and completeness of the data and the analyses, as well as for the fidelity of the trial to the protocol. The study was conducted in accordance with the Declaration of Helsinki and the appropriate national and institutional regulatory authorities and ethics committees approved the trial design.

Patients

Patients were eligible for enrollment in the trial if they had CKD (on dialysis or not on dialysis), with anemia defined according to guidelines at the time of study initiation in 2008 (13). Additional criteria for inclusion were a hemoglobin concentration $<$11.0 g/dl in the correction setting and between 10 and 12 g/dl for patients on maintenance treatment and adequate iron status (serum ferritin $\geq$100 ng/ml, or transferrin saturation $\geq$20%). Detailed inclusion and exclusion criteria are provided in Supplemental Table 1. All participants provided written informed consent before the initiation of any study-related procedures.

Randomization and Masking

Randomization was performed centrally by an independent Interactive voice/web Response System (IxRS) provider, following a pre-established randomization list of randomly permuted blocks of size 4 (balanced allocation: 1:1). Randomization was stratified by treatment setting (correction/maintenance) and baseline C-reactive protein category ($\leq$30 or $>$30 mg/L), with 20% of patients specified in the protocol to be in the correction setting at randomization. The study was open label, with both patients and physicians aware of treatment assignment. End points were assessed by an independent adjudication committee whose members were unaware of treatment assignment.

Procedures

Patients were randomly assigned to receive methoxy polyethylene glycol-epoetin beta or a reference agent (epoetin alfa/beta or darbepoetin).

The initial methoxy polyethylene glycol-epoetin beta dose was 0.6 μg/kg every 2 weeks in the correction setting. The dosing interval was changed to once monthly when the target hemoglobin concentration of 10–12 g/dl was achieved. For those in the maintenance setting, patients were switched to methoxy polyethylene glycol-epoetin beta administered at monthly intervals with a starting dose of 120, 200, or 360 μg, determined by the previous weekly ESA dose (see Supplemental Table 2). Patients randomized to the reference group started treatment according to the label if untreated or continued on the same regimen per the label if on a maintenance dose.

Hemoglobin concentrations were assessed monthly in patients on maintenance treatment, and every 2 weeks in previously untreated patients until target levels of 10–12 g/dl were reached, and monthly thereafter. Iron status was monitored every 3 months and supplementation was administered as required, orally or intravenously, to maintain serum ferritin $\geq$100 ng/ml and transferrin saturation $\geq$20%, according to the practice standard of the clinic investigator. Visits occurred monthly throughout the study after randomization and included vital signs, hemoglobin, and platelet counts; serum biochemical testing was conducted according to the schedule in Supplemental Table 3.

Outcomes

The primary composite end point was the time to the first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke (definitions are provided in Supplemental Appendix 1). Secondary end points comprised the individual components of the primary end point. The consistency of effects on the primary end point was explored in a variety of subgroups. Additional safety end points were the occurrence of pure red cell aplasia, thromboembolic events, and gastrointestinal bleeding. The independent central end points committee, the members of which were unaware of the treatment assignment, adjudicated all suspected end point events.

Statistical Analyses

Cox proportional hazards models were used to analyze the time to the first occurrence of primary and secondary end points for all patients who underwent randomization and received treatment. Patients undergoing kidney transplantation were withdrawn from the study and censored at that time if no end points had occurred. A determination of noninferiority of methoxy polyethylene glycol-epoetin beta to the reference ESAs required that the upper bound of the two-sided 95% confidence interval (95% CI) of the

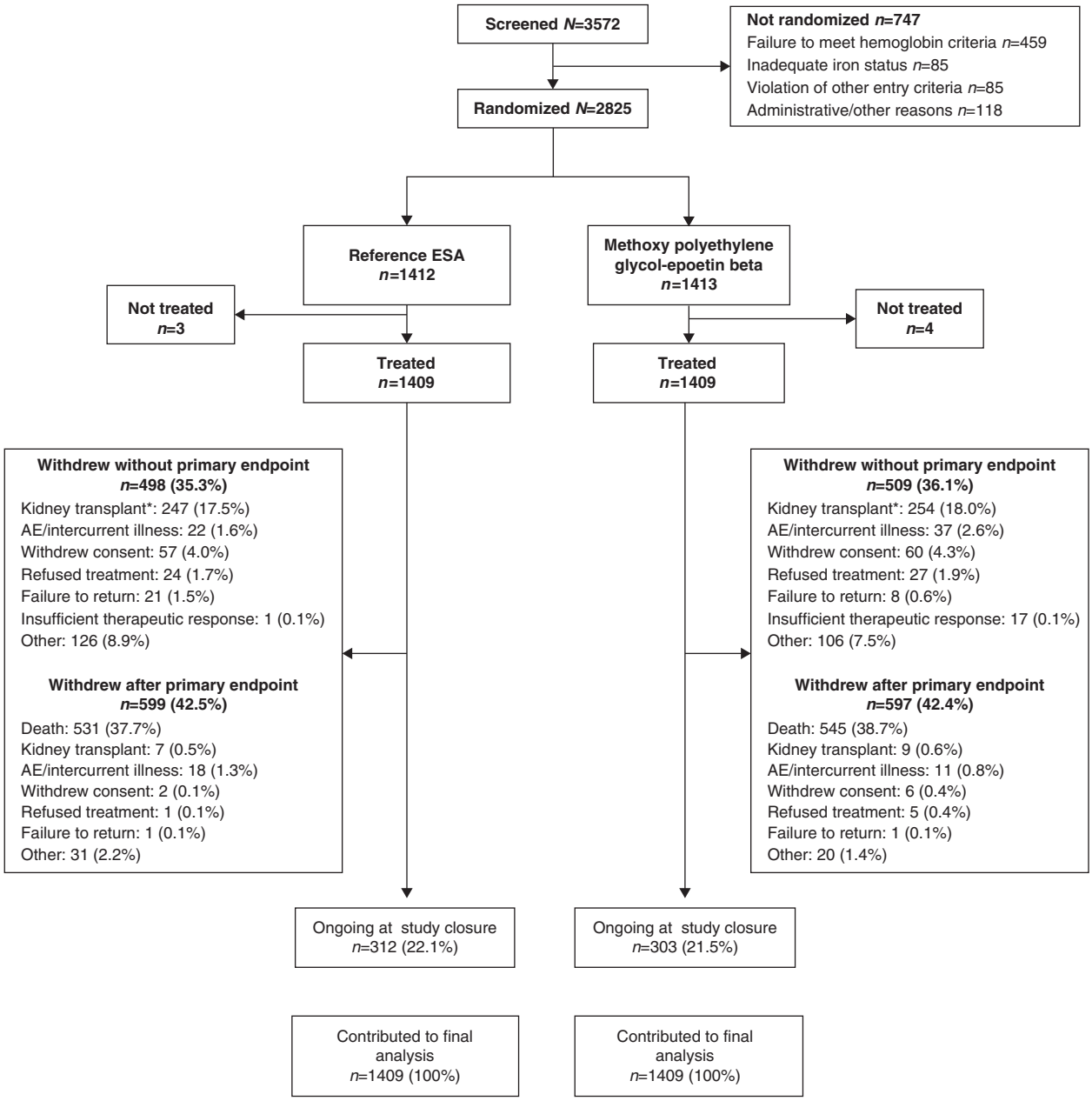

Figure 1. | **Patient disposition.** The most common reason for discontinuation in patients in the 'other' category was the patient moving away from participating dialysis units. *Kidney transplant was a prespecified reason for withdrawal from the trial.

hazard ratio (HR) for the primary end point be <1.20. The number and percentage of patients with a primary end point event were tabulated for predefined subgroups. The HR (methoxy polyethylene glycol-epoetin beta versus the reference ESAs) was calculated within each subgroup. Exploratory analyses using Cox models including time-dependent variables for hemoglobin and dose, averaged over the preceding 3 months before end point events, were performed. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

The trial was designed to accrue 1264 primary end point events for assessing the noninferiority criteria under the assumption of a true HR of 1.0 and 90% power. On the basis of a projected 20% composite event rate, assuming linear recruitment over 30 months and a follow-up time of 18 months after randomization of the last patient, a sample size of 2800 patients, representing approximately 7700 patient-years of exposure, was estimated to be adequate. A lower than expected event rate required a protocol amendment in 2015 to extend the anticipated study duration from an expected 4 years to 8–10 years (Amendment D to the protocol, available in Supplemental Appendix 1). This trial is registered with Clinicaltrials.gov under identifier NCT00773513 (date of registration October 16, 2008).

The data monitoring committee reviewed the safety data when approximately 25%, 50%, and 75% of the events had occurred, making recommendations concerning study

Table 1. Baseline characteristics of the patients

Characteristic, *n* (%)	Reference ESA (*n*=1409)	Methoxy Polyethylene Glycol-Epoetin Beta (*n*=1409)
Median age, yr (interquartile range)	65 (53–74)	64 (53–74)
Men	828 (59)	805 (57)
Region		
Europe	1038 (74)	1039 (74)
Asia	162 (11)	150 (11)
Australia	73 (5)	75 (5)
Latin America	136 (10)	145 (10)
Treatment condition		
Correction	273 (19)	273 (19)
Maintenance	1136 (81)	1136 (81)
On dialysis	1173 (83)	1194 (85)
Years receiving dialysis	*n*=1173	*n*=1194
<1	290 (25)	288 (24)
1–3	432 (37)	429 (36)
>3	451 (38)	477 (40)
Dialysis modality	*n*=1173	*n*=1194
Peritoneal dialysis	81 (7)	91 (8)
Hemodialysis	1092 (93)	1103 (92)
Cardiovascular risk factors and history		
Ischemic heart disease	420 (30)	376 (27)
Peripheral vascular disease	234 (17)	200 (14)
Cerebral vascular disease	137 (10)	131 (9)
Congestive heart failure	202 (14)	192 (14)
NYHA class I	54 (4)	47 (3)
NYHA class II	121 (9)	112 (8)
NYHA class III	30 (2)	41 (3)
NYHA class IV	10 (1)	15 (1)
Unknown	5 (0)	0 (0)
Venous thrombosis	165 (12)	164 (12)
Hypertension	1267 (90)	1268 (90)
Hyperlipidemia	776 (55)	759 (54)
Diabetes	495 (35)	496 (35)
C-reactive protein ≤30 mg/L	1288/1386 (93)	1283/1379 (93)

There were no significant differences between the two arms with regard to any baseline characteristics. ESA, erythropoiesis-stimulating agent; NYHA, New York Heart Association.

conduct or potential interruption or termination. Because of the length of the study, an additional meeting was convened 1 year after the 75% of events review.

Results

Patients

We enrolled 2825 patients from 186 sites in 27 countries between December 12, 2008 and November 9, 2011. Seven patients never received treatment, which left 2818 patients in a modified intention-to-treat analysis (Figure 1). The two treatment groups were well balanced with regard to all baseline characteristics (Table 1, Supplemental Table 4). The median doses of ESAs administered (calculated as equivalent weekly dose for each of the first 7 years of the study) were 18.8–28.0 μg methoxy polyethylene glycol-epoetin beta, 13.3–23.3 μg darbepoetin alfa, and 3604–5345 IU epoetin alfa/beta (Supplemental Figure 1A).

Over the 8.5-year study period, 1007 patients (36%) across both arms withdrew from the trial without experiencing a primary end point event, and approximately half of these were protocol-mandated withdrawals due to kidney transplantation (501 patients). The median time on treatment in the trial was 3.1 years (interquartile range [IQR], 1.3–5.7) in the methoxy polyethylene glycol-epoetin beta arm and 3.6 years (IQR, 1.6–5.9) in the reference arm. A higher proportion of withdrawals (without experiencing a primary end point) was observed in the first year in the methoxy polyethylene glycol-epoetin beta arm (19%) compared with the reference arm (12%). After the first year, rates of withdrawal during the trial were comparable. Considering separately patients who withdrew during the first year (without an event) or who remained on study after the first year, in each group baseline characteristics, including hemoglobin, transferrin saturation, and dialysis modality, were comparable between arms (Supplemental Table 5).

Hematologic and Biochemical Effects

Median hemoglobin concentration was maintained at 10–12 g/dl throughout the study and was similar between treatment arms (Figure 2A). Overall, the mean proportion of time that patients spent within the therapeutic range was 67% for methoxy polyethylene glycol-epoetin beta and 68% for the reference arm. Median serum ferritin levels were ≥100 ng/ml and were comparable for the treatment arms (Figure 2B), whereas median transferrin saturation levels remained ≥20% throughout the study in both arms (Figure 2C). Median transferrin saturation increased and remained approximately 5% higher in the methoxy

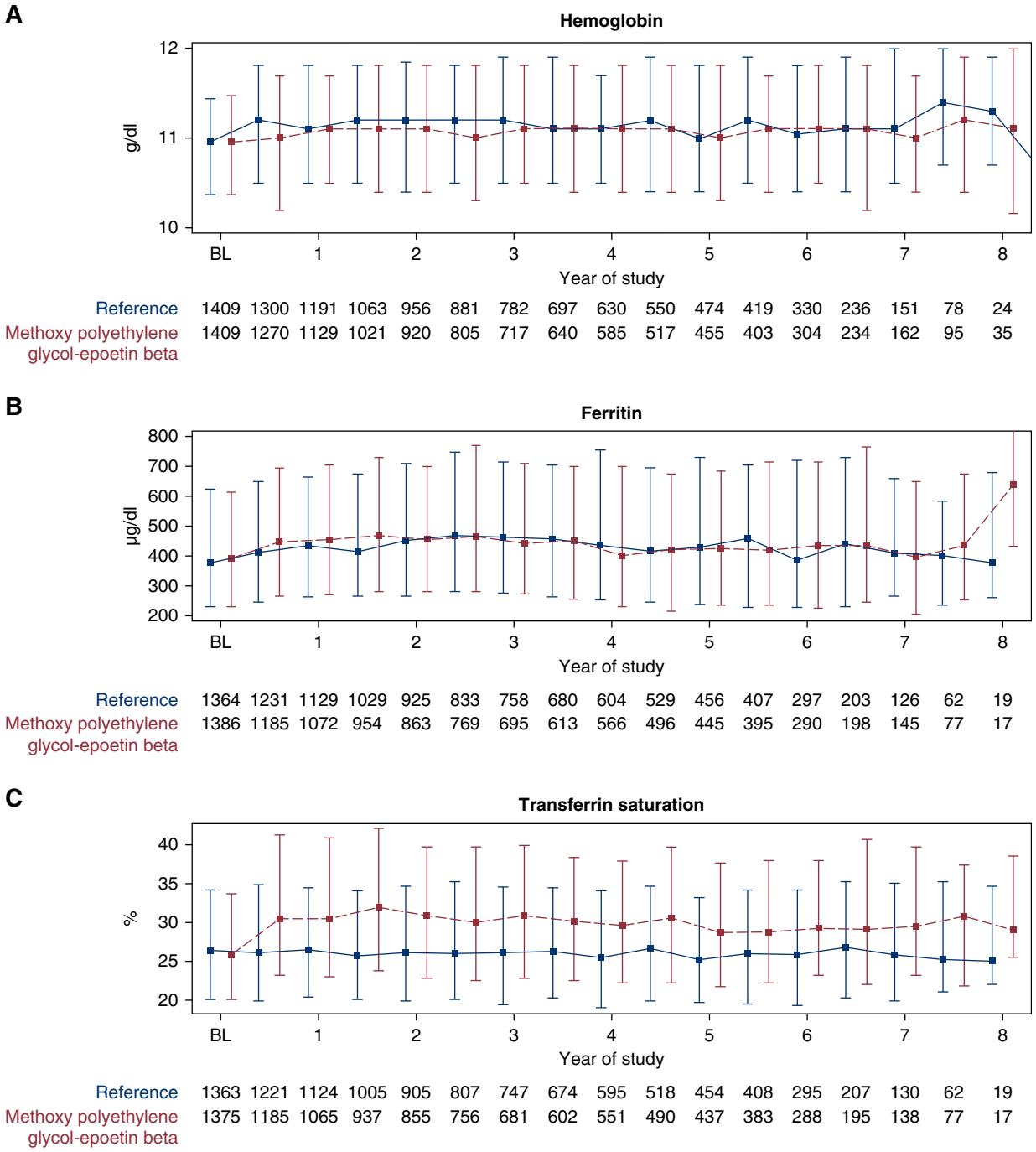

Figure 2. | **Hematologic and iron parameters during the study.** (A) Hemoglobin, (B) ferritin, and (C) transferrin saturation. Values shown are median with IQRs.

polyethylene glycol group than the reference group during the entire study. Iron supplementation (iron salt, route of administration) showed no notable differences between groups (Supplemental Table 6). Median C-reactive protein concentrations and median systolic BP were similar between arms (Supplemental Figure 1, B and C).

Safety

There were 1284 confirmed primary end point events at the study end. Of these, 925 (72%) were deaths (from any cause) and 359 (28%) were nonfatal myocardial infarction or stroke. Primary end point event rates were not different in the methoxy polyethylene glycol-epoetin beta and reference arms (45% and 46% of patients, respectively), with a median time to event of 5.1 years in the methoxy polyethylene glycol-epoetin beta arm (IQR, 2.3–not evaluable) and 5.1 years in the reference ESA arm (IQR, 2.4–not evaluable) (HR, 1.03; 95% CI, 0.93 to 1.15; P=0.004 for noninferiority) (Figure 3). The overall number of deaths during the study was 558 over a median duration of 5.9 years in the methoxy polyethylene

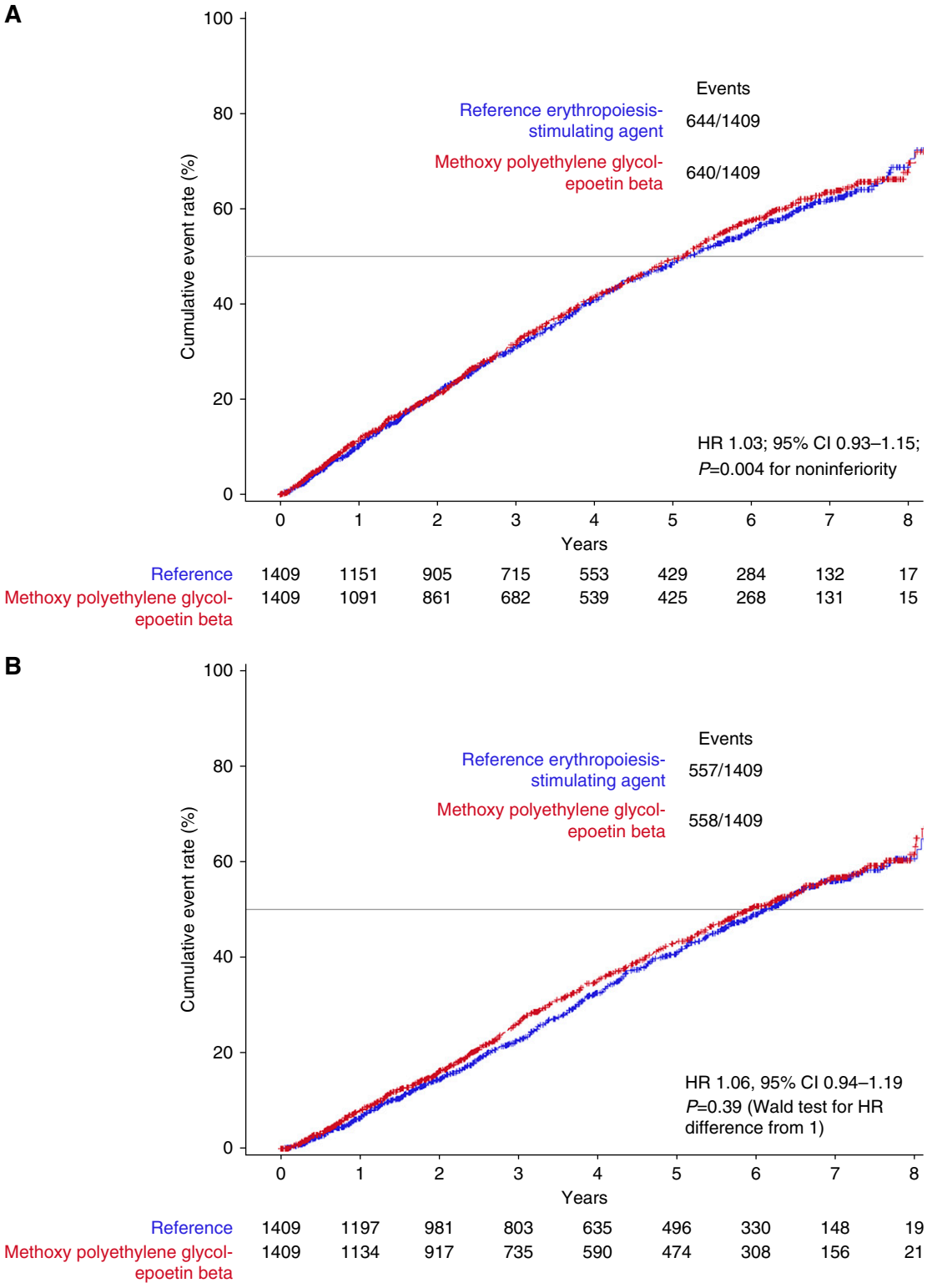

Figure 3. | **Time-to-event curves.** (A) Death from any cause, nonfatal stroke, or nonfatal myocardial infarction (primary end point) and (B) death from any cause.

glycol-epoetin beta arm and 557 over a median duration of 6.1 years in the reference ESA arm, with a HR for all-cause mortality of 1.06 (95% CI, 0.94 to 1.19) (Figure 3B). Rates of nonfatal events (myocardial infarction and stroke) were similar for the two groups (Table 2, Supplemental Figure 2).

In an analysis by subgroups, the results with regard to the primary end point showed an interaction only for patients

Table 2. Major safety end points

End Point	Reference ESA (n=1409)	Methoxy Polyethylene Glycol-Epoetin Beta (n=1409)	Hazard Ratio (95% CI)	P Value	
	No. of Patients (%)	No. of Patients (%)		For Noninferiority[a]	For Difference[b]
Primary end point (composite of all-cause death, nonfatal MI, and nonfatal stroke)	644 (46)	640 (45)	1.03 (0.93 to 1.15)	0.004	0.54
Secondary end point					
Death	557 (40)	558 (40)	1.06 (0.94 to 1.19)		0.36
Nonfatal MI or stroke	191 (14)	168 (12)	0.91 (0.74 to 1.12)		0.39
Fatal or nonfatal MI	158 (11)	143 (10)	0.95 (0.76 to 1.19)		0.66
Fatal or nonfatal stroke	98 (7)	89 (6)	0.94 (0.70 to 1.25)		0.66

ESA, erythropoiesis-stimulating agent; 95% CI, 95% confidence interval; MI, myocardial infarction.
[a]P value for the test for noninferiority at a hazard ratio of 1.20 (primary endpoint only).
[b]P value from the Wald test for hazard ratio difference from 1.

with a history of congestive heart failure (Figure 4). As anticipated, patients not receiving dialysis at the initiation of the trial had a longer time to a primary end point event than those on dialysis at the start of the trial (Supplemental Figure 3).

Other Analyses

Causes of Death. Among the adjudicated causes of death, noncardiovascular death, and death sudden etiology unknown were the most prevalent classifications (Supplemental Table 7). A greater number of deaths sudden etiology unknown occurred in the methoxy polyethylene glycol-epoetin beta arm (185 versus 136), whereas a greater number of noncardiovascular deaths occurred in the reference arm (264 versus 223). No association was found between causes of death and patient baseline characteristics.

Hemoglobin Concentrations and ESA Doses before an End Point Event. Exploratory analyses of the on-study 3-month average hemoglobin concentrations demonstrated that hemoglobin concentrations <10 g/dl were associated with an almost three-fold higher risk of experiencing a primary end point event (HR, 2.76; 95% CI, 2.41 to 3.17) compared with the reference category of 10–11 g/dl. In patients with hemoglobin 11 to ≤12 or ≥12 g/dl, the risk was significantly less than the reference category (Supplemental Table 8). The risk of a primary end point was also greater in patients receiving higher doses of ESAs (Supplemental Table 8). There was no association found between causes of death and hemoglobin levels or doses of ESAs received.

Other Safety Data

The percentage of patients with gastrointestinal bleeding (11.7% in the methoxy polyethylene glycol-epoetin beta group versus 11.1% in the reference group) and thromboembolic events (32.8% in the methoxy polyethylene glycol-epoetin beta group versus 34.5% in the reference group) were similar. No cases of antibody-mediated pure red cell aplasia occurred in the trial. Adverse events occurring in ≥5% of patients are shown in Supplemental Table 9.

Discussion

In the MIRCERA PASS trial, treatment with methoxy polyethylene glycol-epoetin beta resulted in rates of major cardiovascular events and mortality that were similar to rates with the reference ESAs among patients with anemia associated with CKD. The results of the analysis of the individual components of the primary end point (mortality, nonfatal myocardial infarction, and nonfatal stroke) and of analyses of deaths from any cause were consistent with those of the primary composite end point. The similar rates of the primary end point in the methoxy polyethylene glycol-epoetin beta and reference ESA groups were observed in the context of comparable hemoglobin levels.

The primary results of the MIRCERA PASS trial, which has the longest duration of follow-up of any study of anemia treatment in CKD, are consistent with the results from other pooled analyses of trials in the development program of methoxy polyethylene glycol-epoetin beta (14,15), as well as a Cochrane systematic review specifically analyzing the safety of methoxy polyethylene glycol-epoetin beta compared with the other available ESAs (16).

ESAs are effective in correcting anemia and maintaining hemoglobin concentrations in the majority of patients with CKD, although safety concerns have been raised about both higher cardiovascular and thrombotic risks when these agents are administered at higher doses or when the hemoglobin target is >13 g/dl (6–9). At the time the MIRCERA PASS study was initiated in December 2008, several studies had failed to demonstrate that correction of anemia to a target hemoglobin >13 g/dl in patients with CKD reduced the risk of cardiovascular events (6,7,9). MIRCERA PASS was not designed to look at different target hemoglobin levels, but exploratory analyses suggest that risk of cardiovascular events or all-cause death was highest in patients with low hemoglobin

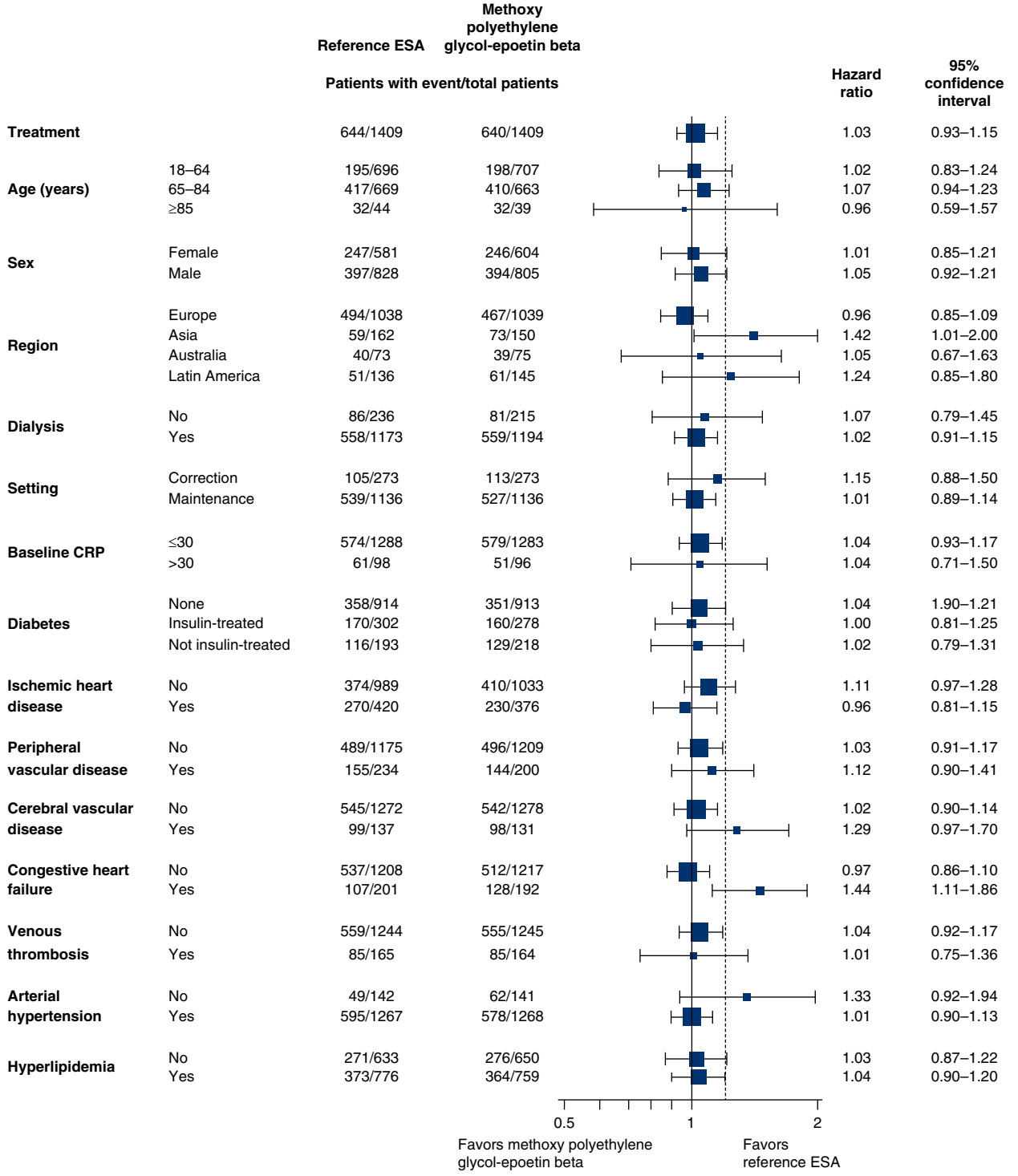

Figure 4. | **Subgroup analysis of the primary end point by baseline patient and disease factors.**

levels on treatment: no relative increases in cardiovascular events or death were observed in patients who had on-treatment values of ≥12 g/dl, whereas those with hemoglobin concentrations of ≤10 g/dl had increased rates of cardiovascular morbidity and all-cause mortality. Although these analyses were exploratory, and the association of low hemoglobin with cardiovascular morbidity and mortality may be confounded by disease factors or comorbidities, the results are consistent with a previous meta-analysis of the development trials of methoxy polyethylene glycol-epoetin beta (15). Higher doses of all ESAs were associated with increased rates of primary end point events. Analysis of prespecified subgroups supported the overall analyses.

More patients in the methoxy polyethylene glycol-epoetin beta arm than the reference arm withdrew during the first

year. This was not unexpected, given that the trial was open label and patients and physicians may have been more cautious when switching from one ESA to another compared with those in the reference arm who continued a treatment regimen with which they were already familiar. Most withdrawals were for nonsafety reasons, with no evidence to suggest that the higher rate of withdrawal during the first year in the methoxy polyethylene glycol-epoetin beta selected a healthier population in one arm versus the other.

Important limitations of the MIRCERA PASS trial include the open-label design, because both the investigator and patient were aware of the treatment randomization. However, patient and investigator blinding would have been unrealistic because of the differences in dosing schedules. The primary end point events (death, myocardial infarction, and stroke) were prospectively adjudicated by an independent end points committee who were blinded to study treatment throughout the trial. This process and the large number of events, long length of follow-up, and a contemporary, representative high-cardiovascular-risk population reflecting clinical practice are important study strengths. Iron supplementation was used as required throughout the study, to maintain iron parameters above the minimum threshold in both treatment groups (serum ferritin ≥100 ng/ml or transferrin saturation ≥20%), with no restriction on dose, formulation, or route of administration. This may be considered both a limitation, as different modalities may affect ESA use differently, and a strength, as it reflects clinical practice.

All-cause mortality was the largest component of the primary end point. Over half of all deaths were adjudicated as having a clear noncardiovascular cause, with the second largest category being "sudden death etiology unknown;" by definition, this category included all cases where the cause of death was unclear. Although there were some differences between treatment arms in the cause of death categorizations, this is not likely to be explained in terms of a differential effect of methoxy polyethylene glycol-epoetin beta, in the context of having a similar number of deaths overall.

Since completion of the MIRCERA PASS study, an observational cohort study from Japan has reported a 13% higher rate of 2-year mortality in patients on dialysis receiving long-acting ESAs compared with shorter-acting ESAs (17). The study population of MIRCERA PASS was diverse, including patients from several countries and both nondialysis and dialysis subgroups. Importantly, results obtained from a large randomized trial with several years of follow-up, with prospective adjudication of all cardiovascular events blinded to treatment assignment, remain the most robust form of evidence available for the safety of the ESAs used in patients with CKD. The data from the large observational study reported by Sakaguchi *et al.* (17), despite propensity matching and statistical adjustments, are hampered by indication bias and residual confounders that make direct comparisons between the two studies difficult.

In conclusion, among patients with anemia of CKD, treatment with monthly methoxy polyethylene glycol-epoetin beta resulted in overall rates of major cardiovascular events, all-cause mortality, and other serious adverse events that were similar to those associated with conventional reference ESAs administered more frequently.

Data-sharing statement

Qualified researchers may request access to individual patient-level data for use in further research studying the medicine or disease that was researched in the original studies through the clinical study data request platform (www.clinicalstudydatarequest.com). An independent panel reviews any research requests and allows access to the data through the platform where the proposal is appropriate. A signed Data Sharing Agreement is required before data access can be provided, as part of this the researchers commit to publish the results of the analysis in a scientific journal (or open-access journal/platform) within 1 year of analysis completion. Data will be available after the medicine studied has been approved by regulators for the indication in both the United States and European Union and at least 18 months after completion of the study report. Data can be shared where Roche have the legal authority to provide the data and consider it feasible to anonymize the data without compromising the privacy and confidentiality of research participants, amongst other criteria. Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available at https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Acknowledgments

We thank all the study investigators and patients who participated in the trial (for a full list of study investigators, please see Supplemental Appendix 2). All authors received medical writing support from F. Hoffmann-La Roche Ltd., furnished by Dr. John Carron of Health Interactions. The study was sponsored by F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Dr. Locatelli and Dr. Oguey were involved in design of the study. Dr. Locatelli and Dr. Hannedouche collected data. Dr. Oguey collated, analyzed, and interpreted the data. Ms. Morgan was responsible for the statistical analysis. Dr. White was chair of the cardiovascular end points committee throughout the trial. Dr. Locatelli, Dr. Fishbane, Dr. Hannedouche, and Dr. White drafted and edited sections of the manuscript. All authors approved the final submitted manuscript.

Disclosures

Dr. Fishbane reports research support from AstraZeneca, Keryx, Corvidia, and Akebia and having been a consultant for AstraZeneca and Corvidia. Dr. Locatelli reports having received personal fees from Akebia, Astellas, and Astra Zeneca as a consultant and speaker and having received personal fees from Amgen, Roche, and Vifor-Fresenius Medical Care as a consultant. Dr. Locatelli also reports having served on advisory boards for Akebia, Amgen, Astellas, AstraZeneca, GSK, and Roche. Ms. Morgan and Dr. Oguey are employees of F. Hoffmann-La Roche Ltd. Dr. White reports personal fees from a position as member of steering committee of the trial at Relypsa Inc. Dr. White and Dr. Fishbane report having served on the endpoint adjudication committee in the current trial for F. Hoffmann-La Roche Ltd. All authors report medical writing support from F. Hoffmann-La Roche Ltd.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01380219/-/DCSupplemental.

Supplemental Appendix 1. Cardiovascular end point definitions.

Supplemental Appendix 2. List of investigators.

Supplemental Table 1. Inclusion and exclusion criteria.

Supplemental Table 2. Starting dose of methoxy polyethylene glycol-epoetin beta according to previous ESA treatment when switching from another ESA.

Supplemental Table 3. Schedule of assessments.

Supplemental Table 4. Additional baseline characteristics.

Supplemental Table 5. Concomitant iron supplementation.

Supplemental Table 6. Selected baseline parameters by withdrawal in the first year.

Supplemental Table 7. Adjudicated causes of death.

Supplemental Table 8. Time-dependent Cox regression models for hemoglobin level and dose prior to the event.

Supplemental Table 9. Adverse events experienced by ≥5% of patients.

Supplemental Figure 1. Doses of erythropoiesis-stimulating agents, C-reactive protein levels, and systolic BP during the study.

Supplemental Figure 2. Time-to-event curves for time to myocardial infarction and time to stroke.

Supplemental Figure 3. Time-to-event curves for death from any cause, nonfatal stroke, or nonfatal myocardial infarction, for patients on dialysis or not on dialysis.

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Received: February 1, 2019 **Accepted:** July 10, 2019

Published online ahead of print. Publication date available at www.cjasn.org.