Mortality and Cardiovascular Morbidity Associated with Haemoglobin Levels: A Pooled Analysis of Randomised Controlled Trials

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Key Words

Anaemia · Cardiovascular events · Chronic kidney disease · Erythropoiesis-stimulating agent · Haemoglobin target · Methoxy polyethylene glycol-epoetin beta

Abstract

Background/Aims: Several randomised controlled trials (RCTs) have raised concerns about potential harm associated with erythropoiesis-stimulating agents (ESAs) in chronic kidney disease patients, especially when haemoglobin (Hb) levels above 13 g/dl were targeted. We report the relationship between Hb levels and outcomes in the methoxy polyethylene glycol-epoetin beta RCT programme. **Methods:** We assessed the association between Hb and a composite end point, as well as its components [all-cause mortality, myocardial infarction (MI) or cerebrovascular events (CVE)], in multiple post hoc analyses of 9 prospective RCTs (3,405 chronic kidney disease patients). Mean Hb levels over time and deviation from target were analysed using a Cox regression model. Time-adjusted average Hb, deviation from target, the last Hb, Hb slope and within-patient Hb variability preceding an event were analysed using a time-dependent Cox model. Hazard ratios and 95% confidence intervals were calculated. **Results:** Average Hb <10 g/dl, decrease from stable baseline Hb >1 g/dl, last Hb <10 g/dl, Hb decline >1.5 g/dl/4 weeks and increased Hb variability were associated with a higher

risk of the composite end point and all-cause mortality. An increased risk for CVE and MI was found with a last Hb <10 g/dl and with a decrease from baseline >1 g/dl in the preceding month. **Conclusion:** In multiple analyses from a large programme of prospective clinical trials of ESA treatment, risk of all-cause mortality and cardiovascular morbidity risk was consistently higher at Hb <10 g/dl and in patients whose Hb fell below target.

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Introduction

Since their introduction in 1989, erythropoiesis-stimulating agents (ESAs) have been a mainstay in the supportive care of patients with the anaemia of chronic kidney disease. Documented clinical benefits include improved physical performance and quality of life, as well as reduced need for blood transfusions [1–3]. However, randomised controlled trials (RCTs) which failed to demonstrate improved cardiovascular morbidity and mortality have raised concerns about potential harm associated with ESA administration, especially to high target haemoglobin (Hb) levels above 13 g/dl [4–8]. In one of these studies, poor outcome was associated with failure to achieve target Hb in both the high and low Hb target groups [9]. Given the complexity and expense of RCTs, it is appropriate to

Table 1. Design of randomised controlled studies

Study	Design	n	CKD population	Route of administration	Hb target range, g/dl	Duration
Levin et al. [10]	Maintenance	666	Dialysis	IV	10.0–13.5 (1–36) 11.0–13.0 (37–52)	52 weeks
Sulowicz et al. [11]	Maintenance	571	Dialysis	SC	10.0–13.5 (1–36) 11.0–13.0 (37–52)	52 weeks
Klinger et al. [12]	Correction	181	Dialysis	IV	11.0–13.0	52 weeks
Macdougall et al. [13]	Correction	323	Not on dialysis	SC	11.0–13.0	52 weeks
Canaud et al. [14]	Maintenance	309	Dialysis	IV	10.0–13.5 (1–36) 11.0–13.0 (37–52)	52 weeks
Spinowitz et al. [15]	Maintenance	333	Dialysis	IV/SC	10.0–13.5	36 weeks
Carrera et al. [16]	Maintenance	489	Dialysis	IV	11.0–13.0	52 weeks
Roger et al. [17]	Correction	305	Not on dialysis	SC	10.0–12.0	28 weeks
US National Institutes of Health [18]	Maintenance	228	Not on dialysis	SC	10.0–12.0	9 months

CKD = Chronic kidney disease; IV = intravenous; SC = subcutaneous. Figures in parentheses indicate treatment periods in weeks.

explore all available clinical information in order to gain insights into the association between Hb and outcomes.

To this end, we performed retrospective analyses of the relationship between Hb and mortality and cardiovascular morbidity in anaemic chronic kidney disease patients, using data from all RCTs in the methoxy polyethylene glycol-epoetin beta development programme.

Methods

Data Source

All 9 RCTs in the development programme for methoxy polyethylene glycol-epoetin beta (Mircera®; F. Hoffmann-La Roche, Basel, Switzerland) were included in this analysis (table 1). Eligibility criteria, Hb targets and dose adjustment guidance were very similar for all of the studies, providing an adequate basis for pooling. Patients entered the maintenance studies with stable Hb values in a range from 10.0 to 13.0 g/dl and were required to maintain Hb within 1 g/dl of their individual value at study entry (baseline value). Hb measurements were performed at least once monthly in every patient, with the majority having weekly determinations. All studies were performed in accordance with applicable institutional and national ethical standards and with the Helsinki Declaration of 1975, as revised in 2000.

Data for methoxy polyethylene glycol-epoetin beta and reference ESAs (epoetin alfa, epoetin beta, darbepoetin alfa) were pooled, as the analyses explored the relationship between clinical events and Hb levels, regardless of the ESA used to achieve them.

Clinical Outcome Measures

The primary outcome of interest was the first occurrence of a composite end point comprising all-cause mortality, cerebrovascular events (CVE) and myocardial infarction (MI). Individual components of the composite were also analysed. The Standardised MedDRA Query ‘Cerebrovascular disorders (narrow)’ was used to identify CVE and the Standardised MedDRA Query ‘Myocardial infarction (narrow)’ for MI; CVE and MI were not adjudicated.

Statistical Analyses

To explore the relationship between outcomes and Hb over the complete study, time from first dose of ESA to first event was displayed using Kaplan-Meier curves for each Hb category and analysed using a Cox proportional-hazards regression model, adjusted for baseline characteristics [age, gender, race, region, body weight, smoking status, comorbidities (hypertension, hyperlipidaemia, diabetes, ischaemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease), systolic and diastolic blood pressure, parenteral iron supplementation, ferritin, albumin, C-reactive protein]. Hazard ratios (HRs) and 95% confidence intervals (CIs) were presented. Each patient’s postbaseline Hb measurements were summarised as a time-adjusted average value. Deviation from target was calculated by subtracting the baseline value from this average Hb value.

An extension of the Cox model, including a time-dependent Hb variable, was used to explore the relationship between end points and Hb within the preceding month. HRs and 95% CIs were presented. The analyses explored time-adjusted average Hb value, deviation from target, the last Hb value, Hb slope and within-patient variability (expressed as standard deviation, SD) of Hb.

Table 2. Baseline patient characteristics

<i>All patients (n = 3,405)</i>		Albumin, g/l	39.0 ± 4.9
Age, years	62.5 ± 14.9	C-reactive protein	
Male gender	1,915 (56.2)	≤ 3 mg/l	1,091 (32.9)
Race		> 3 to < 6.6 mg/l	979 (29.6)
Caucasian	2,580 (75.8)	≥ 6.6 mg/l	1,242 (37.5)
Black	492 (14.4)	ESA dose at baseline, IU/week ^b	
Other	333 (9.8)	Mean ± SD	8,793 ± 9,406
Region		Median	6,000 [4,000–10,850]
USA	831 (24.4)	<i>Maintenance patients (n = 2,596)</i>	
Ex-USA	2,574 (75.6)	Hb, g/dl	11.8 ± 0.7
Body weight, kg	74.0 ± 17.9	10 to < 11 g/dl	313 (12.1)
Smokers	348 (10.2)	11 to < 12 g/dl	1,193 (46.0)
Aetiology of CKD ^a		≥ 12 g/dl	1,090 (42.0)
Hypertension/large vessel disease	1,264 (37.1)	<i>Correction patients (n = 809)</i>	
Diabetes	1,168 (34.3)	Hb, g/dl	9.8 ± 0.8
Glomerulonephritis	559 (16.4)	< 10 g/dl	466 (57.6)
Interstitial nephritis/pyelonephritis	327 (9.6)	10 to < 11 g/dl	332 (41.0)
Polycystic kidney disease	178 (5.2)	11 to < 12 g/dl	11 (1.4)
Other	621 (18.2)	<i>Patients not on dialysis (n = 847)</i>	
Comorbidities		Glomerular filtration rate, ml/min/1.73 m ²	27.0 ± 11.8
Hypertension	3,152 (92.6)	<i>Patients on haemodialysis (n = 2,478)</i>	
Hyperlipidaemia	1,834 (53.9)	Blood pressure, mm Hg	
Diabetes	1,408 (41.4)	Systolic	143 ± 23.9
Ischaemic heart disease	1,062 (31.2)	Diastolic	76 ± 13.9
Congestive heart failure	630 (18.5)	<i>Patients not on haemodialysis (n = 927)</i>	
Peripheral vascular disease	615 (18.1)	Blood pressure, mm Hg	
Cerebrovascular disease	360 (10.6)	Systolic	135 ± 18.3
Mode of dialysis		Diastolic	73 ± 11.1
Haemodialysis	2,478 (72.8)		
Peritoneal dialysis	71 (2.1)		
Not on dialysis	856 (25.1)		
Parenteral iron supplementation	1,694 (49.8)		
Transferrin saturation, %	27.2 [21.6–34.4]		
Ferritin, µg/l	366 [193–605]		

Values are means ± SD, numbers with percentages in parentheses or medians with interquartile ranges in square brackets.

^a Several aetiologies possible for 1 patient.

^b Darbepoetin alfa expressed in international units after multiplication of microgram dose by 200.

Results

Study Population

Analyses were based on pooled data from 9 phase III RCTs involving 3,405 patients treated with ESAs; cumulative exposure was 2,826 patient-years. Patient characteristics are displayed in table 2.

End Point Events

In total, 330 patients (9.7%) experienced a composite end point, 210 (6.2%) a fatal event (giving a death rate of 7.4 per 100 patient-years), 100 (2.9%) at least 1 non-fatal or fatal CVE and 93 patients (2.7%) an MI.

Relationship of End Points to Hb over the Complete Study

Patients with an average Hb < 10 g/dl had a higher risk of a composite end point compared to patients in the reference range (10 to < 11 g/dl), while patients with average Hb in the range from 11 to < 12 and ≥ 12 g/dl had a lower risk compared to reference (fig. 1). Comparable results were observed for all-cause mortality, but not for CVE (fig. 2). As in all results presented below, findings in the unadjusted analyses were similar to those adjusted for baseline characteristics. The full set of results can be found in the online supplementary material (suppl. tables 1–9; see www.karger.com/doi/10.1159/000366478 for all online suppl. material).

Fig. 2. Relationship between end points and average Hb (n = 3,405).

Maintenance patients whose Hb decreased by more than 1 g/dl compared to their individual baseline value experienced a composite end point more frequently than patients whose Hb remained within the target range (fig. 3). Similar results were observed for all-cause mortal-

ity and CVE, though not for MI (fig. 4). Patients whose Hb increased by more than 1 g/dl compared to baseline experienced a similar rate of the composite end point to those who remained within the target range.

Fig. 3. Kaplan-Meier plot of the relationship between composite end point and deviation from Hb target (n = 2,596).

Fig. 4. Relationship between end points and deviation from Hb target (n = 2,596).

Fig. 5. Relationship between end points and average Hb in the preceding month (n = 3,405).

Relationship of End Points to Hb within the Preceding Month

An average Hb of <10 g/dl within the month prior to an event was associated with a higher risk for the composite end point compared to reference (Hb 10 to <11 g/dl; fig. 5). Higher Hb values in the month preceding the event were associated with a lower risk. A comparable pattern was observed for all-cause mortality. Findings were generally similar for these two end points when subgroups of patients (correction and maintenance; dialysis and non-dialysis; diabetics and non-diabetics) were analysed separately (online suppl. table 4).

In the maintenance studies, Hb values that decreased by more than 1 g/dl compared to baseline within the month before an event were associated with a higher risk of a composite end point than were values within the target range (fig. 6). The same pattern was observed for individual components of the end point. The risk of an end point was similar with Hb values that increased by more than 1 g/dl and those maintained within ± 1 g/dl of baseline.

A last Hb value of <10 g/dl within the month before an event was associated with a higher risk of each end point compared to reference (10 to <11 g/dl; fig. 7). Last Hb

values in the categories ≥ 11 g/dl in the month preceding an event were associated with a lower risk of all-cause mortality but not of the other end points.

Compared to the reference range (-0.5 to 0.5 g/dl/4 weeks), a calculated Hb decline >1.5 g/dl in the 4 weeks before an event was associated with a higher risk for the composite end point and all-cause mortality, but not for CVE and MI (fig. 8).

When last Hb value and calculated rate of Hb change were included in the same model, the association between the last Hb value of <10 g/dl within the month before the event and the increased risk of each of the end points remained, independent of the calculated rate of Hb change, with the exception of all-cause mortality, which remained independently associated with both the highest rate of decline and the lowest last Hb value. A last Hb value ≥ 12 g/dl prior to the event was associated with the lowest risk of all-cause mortality, independent of the calculated rate of Hb change (online suppl. table 8).

In maintenance studies, within-patient variability (SD) of Hb in the month before the event was associated with the composite end point after adjustment for baseline risk factors and Hb level (online suppl. table 9). For each increase of 0.1 g/dl in the within-patient SD, the risk

Fig. 6. Relationship between end points and deviation from Hb target in the preceding month (n = 2,596).

Fig. 7. Relationship between end points and last Hb in the preceding month (n = 3,405).

Fig. 8. Relationship between end points and Hb slope in the preceding month (n = 3,405).

of a composite end point increased by 9% (adjusted HR = 1.09, 95% CI = 1.06–1.12). Similar patterns were observed for all-cause mortality and MI.

Discussion

A small number of RCTs have demonstrated benefits of Hb levels above 13 g/dL in terms of quality of life or transfusion avoidance but have failed in every case to demonstrate improved survival [4–8, 19]. Although rates of major clinical events such as death, cardiovascular death and MI were not significantly different in individual studies, a meta-analysis of RCTs comparing lower versus higher Hb has shown that stroke, hypertension

and vascular access thrombosis were more common when higher Hb levels were targeted, while mortality, MI and serious cardiovascular events were not [20]. The significantly increased stroke risk in the meta-analysis resulted from addition of data from the largest RCT by far, in which the incidence of stroke was doubled in patients assigned to complete correction of anaemia with darbepoetin alfa [8]. This finding has given rise to a discussion of the appropriate use of ESAs in clinical practice, treatment guidelines and product labelling [21–24].

In the context of this controversy, we analysed clinical outcomes in relation to Hb using a large integrated database in the methoxy polyethylene glycol-epoetin beta clinical development programme. Since eligibility criteria and protocol guidance for Hb management were very

similar for the 9 prospective RCTs, pooling of safety findings from patients treated to a range of Hb targets was appropriate in retrospective analyses of the relationship of Hb to the occurrence of death, CVE and MI.

These analyses showed that all-cause mortality was associated with Hb below 10 g/dl, decrease from stable baseline Hb by more than 1 g/dl, Hb decline >1.5 g/dl/4 weeks and increased Hb variability. Conversely, a lower mortality risk was found with Hb in the categories 11 to <12 and ≥ 12 g/dl. The greatest risk for CVE and MI was found with a decrease from baseline >1 g/dl in the month preceding the event as well as with a last Hb value <10 g/dl before the event. There was no evidence of an increased or decreased risk of CVE or MI in Hb categories 11 to <12 and ≥ 12 g/dl.

Findings were consistent in unadjusted models and in analyses adjusted for baseline characteristics.

The composite end point comprised fatal adverse events in roughly two-thirds of cases. Results linking low Hb or Hb decline and all-cause mortality observed in these analyses have been reported in publications based on large registries [25–27] and two prospective observational studies [28, 29], neither of which assigned patients to specified Hb targets. In the latter, higher achieved Hb was associated with decreasing all-cause mortality, a finding similar to those in our analyses, which showed the lowest risk for death associated with last Hb value, average Hb in the preceding month and Hb during the complete study period in the categories 11 to <12 and ≥ 12 g/dl.

The primary limitation of our analysis is its retrospective and exploratory nature, which does not allow conclusions on a causal relationship between Hb levels and outcomes, since patients were not assigned to Hb categories by randomisation. It should also be clear that HRs with CIs including 1 do not constitute evidence that there is no relationship between a given Hb level and outcome; it is equally possible that a low number of events resulting in wide CIs may have obscured a true relationship. Additionally, the mortality rates in the 9 RCTs included in this analysis are lower than those encountered in the general population of patients with advanced chronic kidney disease, and the absolute numbers of MI and CVE are low.

In these analyses, most HRs greater than 1 and with a CI excluding 1, indicating increased risk, were in the Hb category <10 g/dl. There were no HRs greater than 1 and with a CI excluding 1 in the Hb category ≥ 12 g/dl. However, the results of the TREAT study showing a 2-fold increase stroke in patients assigned to a target Hb >13 g/dl (achieved Hb 12.5 g/dl) mandate special care in treating patients at risk of stroke. In a post hoc analysis of the TREAT study, Skali et al. [30] found that independent

predictors of stroke included history of stroke, more proteinuria and known cardiovascular disease. As a result, current guidelines and expert opinion [24, 31] propose individualisation of ESA treatment and advise great caution in patients with a history of stroke.

In summary, although these results do not constitute a demonstration of a causal relationship between low Hb values and unfavourable outcomes, they do provide consistent evidence to support the association. They also suggest a lower risk of all-cause mortality and cardiovascular morbidity with Hb values >11 g/dl in a relatively large number of patients enrolled in RCTs.

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