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ASSOCIATION OF OUTCOMES AND Hb LEVELS IN CKD PATIENTS: FINDINGS FROM A POOLED ANALYSIS OF 24 PROSPECTIVE STUDIES

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INTRODUCTION AND AIMS

- Since their introduction in 1989, erythropoiesis-stimulating agents (ESAs) have been a mainstay in the supportive care of patients with anaemia of chronic kidney disease (CKD). Clinical benefits include improved physical performance and quality of life, as well as reduced need for blood transfusions.[1–4]
- 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 for target haemoglobin (Hb) levels above 13 g/dL,[5–9] although these results have given rise to controversy.[10]
- We explored the relationship between achieved Hb and outcomes of interest in a pooled database of 24 randomised prospective ESA studies in patients with CKD.

METHODS

- Safety data were pooled from 6273 patients treated with Mircera, darbepoetin alfa, epoetin alfa or epoetin beta in 24 RCTs – 11 studies of anaemia correction and 13 of Hb maintenance.
- Time-dependent Cox regression analyses, unadjusted and adjusted for baseline risk factors, were performed to estimate the risk of each outcome of interest:
  - All-cause mortality
  - Cardiovascular event (defined by the MedDRA Standardised MedDRA Query [SMQ] "Ischaemic heart disease")
  - Cerebrovascular event (MedDRA SMQ "Cerebrovascular disorders")
  - A composite of these components

  in relation to Hb (mean achieved Hb in the 3 months preceding the event) as a continuous variable and as a categorical variable, the latter using four Hb level categories:
  - <10 g/dL
  - ≥10 to <11 g/dL (reference category)
  - ≥11 to <12 g/dL
  - ≥12 g/dL
- Hazard ratios (HRs) for the outcomes of interest in each Hb variable category relative to reference and for each 1 g/dL unit increase in the mean Hb level (in the analysis of Hb as a continuous variable) within the 3 months prior to the event are presented with the corresponding 95% confidence intervals (CIs).
- The association between achieved Hb levels and outcomes of interest was assessed overall and by diabetic status in all subjects, as well as for subjects on dialysis and those not on dialysis. The possible effect of diabetes status on the association between achieved Hb and the risk of outcomes of interest was also explored by adding a mean Hb achieved-by-diabetes status interaction term to the analysis.

RESULTS

- Of 6273 patients, 3884 (61.9%) were from maintenance studies and 2389 (38.1%) from correction studies. Baseline demographic characteristics, co-morbidities and cardiovascular risk factors are presented in **Table 1**.
- Risk factors were highly prevalent (92.0% of patients) and characteristic of the CKD population; 2072 (33.0%) were diabetic, and 4761 patients (75.9%) were on dialysis.
- 982 events occurred in 768 patients; incidence was approximately double in diabetics as compared with non-diabetic patients and in dialysis as opposed to non-dialysis patients (**Table 2**).
- **Table 3** shows analyses of Hb as a categorical variable and demonstrates increased risk of the composite endpoint, all-cause mortality and cerebrovascular events at Hb <10 g/dL; risk of the composite endpoint and all-cause mortality was decreased at Hb ≥12 g/dL.
- Findings were similar in multiple analyses of each of the outcomes of interest when subsets of subjects (diabetic and non-diabetic subjects; those on dialysis and those not on dialysis) were assessed separately (**Tables 4–7**), although event rates in some subsets were small, and CIs did not exclude unity.

Table 1. Baseline demographic characteristics, co-morbidities and cardiovascular risk factors

	All subjects N = 6273	Diabetic N = 2072	Non-diabetic N = 4201	Dialysis N = 4761	Non-dialysis N = 1512
Age, mean, SD (years)	59.3 (15.53)	63.9 (12.19)	57.0 (16.47)	58.0 (15.68)	63.4 (14.30)
Sex, male (%)	54.5	55.9	53.8	56.5	48.4
Region, ex-US (%)	86.8	77.7	91.2	85.0	92.1
Weight, mean, SD (kg)	70.7 (16.73)	77.6 (17.95)	67.2 (14.95)	69.3 (16.56)	75.0 (16.55)
Cause(s) of Renal Disease					
Hypertension (%)	27.3	29.9	26.0	25.7	32.3
Diabetes (%)	26.3	79.7	0.0	22.3	39.0
Glomerulonephritis (%)	19.1	5.6	25.8	20.6	14.4
Other (%)	40.7	13.3	54.2	43.2	32.8
Not known (%)	0.9	0.2	1.2	1.2	-
Co-morbidities					
Diabetes (%)	33.0	100.0	0.0	28.5	47.2
History of ...					
hypertension (%)	85.9	92.5	82.6	82.9	95.1
hyperlipidaemia (%)	37.3	56.7	27.8	31.5	55.8
coronary artery disease (%)	25.1	37.1	19.2	24.9	25.8
congestive heart failure (%)	15.3	22.7	11.7	14.2	18.8
peripheral vascular disease (%)	14.0	24.4	8.9	14.4	12.9
cerebrovascular disease (%)	9.9	14.5	7.7	9.4	11.6
Baseline Hb, mean, SD (g/dL)	10.74 (1.724)	11.03 (1.407)	10.60 (1.845)	10.78 (1.894)	10.62 (1.011)
Ferritin, median, range (mg/mL)	330 (1.1 – 8230)	329 (1.1 – 7520)	330.2 (3.0 – 8230)	406 (1.1 – 8230)	168.5 (6.0 – 2586)
Parenteral iron supplementation at baseline, yes (%)	41.6	41.6	41.6	51.9	9.1
Baseline albumin, median, range (g/L)	39.7 (1.6 – 90.0)	39.0 (1.6 – 90.0)	40.0 (14.0 – 76.6)	39.0 (1.6 – 76.6)	41.0 (20.2 – 90.0)
Systolic blood pressure, mean, SD (mmHg)	141 (22.6)	144 (23.1)	139 (22.2)	143 (23.8)	136 (17.5)
Diastolic blood pressure, mean, SD (mmHg)	77 (13.3)	74 (13.0)	79 (13.2)	78 (13.9)	75 (10.8)

Table 2. Events and event rates by endpoint and analysis subgroup

Outcome of Interest	All Subjects N = 6273 n (inc. rate)	Diabetic N = 2072 n (inc. rate)	Non-diabetic N = 4201 n (inc. rate)	Dialysis N = 4761 n (inc. rate)	Non-dialysis N = 1512 n (inc. rate)
Composite endpoint	768 (13.31)	352 (20.01)	416 (10.37)	597 (15.28)	132 (8.24)
All-cause mortality	400 (6.64)	176 (9.40)	224 (5.40)	319 (7.83)	49 (2.95)
Cardiovascular event	360 (6.17)	184 (10.31)	176 (4.35)	278 (7.05)	68 (4.20)
Cerebrovascular event	169 (2.83)	71 (3.83)	98 (2.38)	128 (3.16)	32 (1.94)

n, number of subjects with at least one event
inc. rate = incidence rate, number of subjects with at least one event per 100 PEY

Table 3. Hazard ratios for outcomes by Hb category

Achieved Hb (g/dL)	<10	≥10 to <11	≥11 to <12	≥12
HR [95% CI]				
Composite endpoint	1.52 [1.01 – 2.29]	Ref	0.80 [0.60 – 1.07]	0.74 [0.56 – 0.98]
All-cause mortality	2.30 [1.44 – 3.66]	Ref	0.87 [0.60 – 1.26]	0.44 [0.29 – 0.66]
Cardiovascular event	0.89 [0.43 – 1.81]	Ref	0.74 [0.49 – 1.12]	0.79 [0.53 – 1.18]
Cerebrovascular event	2.97 [1.29 – 6.87]	Ref	0.94 [0.47 – 1.90]	1.51 [0.79 – 2.89]

Red shading indicates HRs above 1 where the 95% CIs exclude unity.
Yellow shading indicates HRs below 1 where the 95% CIs exclude unity.

Table 4. Hazard ratios for composite endpoint by Hb category and subgroup

Adjusted Time-Dependent Cox Analyses	Reference category: Hb ≥10 – <11 g/dL					
All Hb values included	Hb <10 g/dL		Hb ≥11 – <12 g/dL		Hb ≥12 g/dL	
	HR	95% CI	HR	95% CI	HR	95% CI
Composite Endpoint						
All subjects	1.52	1.01 – 2.29	0.80	0.60 – 1.07	0.74	0.56 – 0.98
All diabetic subjects	1.20	0.64 – 2.27	0.86	0.58 – 1.27	0.76	0.52 – 1.12
All non-diabetic subjects	1.79	1.05 – 3.06	0.74	0.48 – 1.12	0.71	0.48 – 1.06
All dialysis subjects	1.98	1.27 – 3.09	0.84	0.61 – 1.17	0.75	0.53 – 1.04
All subjects not on dialysis	0.00	0.00	0.47	0.24 – 0.90	0.45	0.25 – 0.84

Red shading indicates HRs above 1 where the 95% CIs exclude unity.
Yellow shading indicates HRs below 1 where the 95% CIs exclude unity.

Table 5. Hazard ratios for all-cause mortality by Hb category and subgroup

Adjusted Time-Dependent Cox Analyses	Reference category: Hb ≥10 – <11 g/dL					
All Hb values included	Hb <10 g/dL		Hb ≥11 – <12 g/dL		Hb ≥ 12 g/dL	
	HR	95% CI	HR	95% CI	HR	95% CI
All-Cause Mortality						
All subjects	2.30	1.44 – 3.66	0.87	0.60 – 1.26	0.44	0.29 – 0.66
All diabetic subjects	2.14	1.08 – 4.22	0.97	0.58 – 1.63	0.58	0.33 – 1.00
All non-diabetic subjects	2.42	1.29 – 4.54	0.77	0.45 – 1.32	0.31	0.17 – 0.57
All dialysis subjects	3.00	1.77 – 5.08	0.95	0.61 – 1.46	0.51	0.31 – 0.84
All subjects not on dialysis	0.00	0.00	0.53	0.22 – 1.31	0.21	0.08 – 0.55

Red shading indicates HRs above 1 where the 95% CIs exclude unity.
Yellow shading indicates HRs below 1 where the 95% CIs exclude unity.

Table 6. Hazard ratios for cardiovascular events by Hb category and subgroup

Adjusted Time-Dependent Cox Analyses	Reference category: Hb ≥10 – <11 g/dL					
All Hb values included	Hb <10 g/dL		Hb ≥11 – <12 g/dL		Hb ≥12 g/dL	
	HR	95% CI	HR	95% CI	HR	95% CI
Cardiovascular Events						
All subjects	0.89	0.43 – 1.81	0.74	0.49 – 1.12	0.79	0.53 – 1.18
All diabetic subjects	0.48	0.14 – 1.63	0.70	0.41 – 1.18	0.69	0.41 – 1.15
All non-diabetic subjects	1.43	0.57 – 3.61	0.80	0.41 – 1.56	0.96	0.52 – 1.78
All dialysis subjects	1.16	0.55 – 2.44	0.77	0.48 – 1.22	0.73	0.46 – 1.17
All subjects not on dialysis	0.00	0.00	0.40	0.14 – 1.11	0.54	0.21 – 1.38

Table 7. Hazard ratios for cerebrovascular events by Hb category and subgroup

Adjusted Time-Dependent Cox Analyses	Reference category: Hb ≥10 – <11 g/dL					
All Hb values included	Hb <10 g/dL		Hb ≥11 – <12 g/dL		Hb ≥12 g/dL	
	HR	95% CI	HR	95% CI	HR	95% CI
Cerebrovascular Events						
All subjects	2.97	1.29 – 6.87	0.94	0.47 – 1.90	1.51	0.79 – 2.89
All diabetic subjects	3.67	0.73 – 18.35	2.13	0.61 – 7.45	2.97	0.89 – 9.92
All non-diabetic subjects	2.66	1.00 – 7.06	0.54	0.22 – 1.33	1.02	0.47 – 2.21
All dialysis subjects	4.25	1.64 – 11.04	1.22	0.53 – 2.79	1.80	0.81 – 3.98
All subjects not on dialysis	0.00	0.00	0.36	0.09 – 1.48	0.71	0.22 – 2.26

Red shading indicates HRs above 1 where the 95% CIs exclude unity.

- In analyses of Hb as a continuous variable, risk of a composite endpoint and all-cause mortality was decreased with each 1 g/dL unit increase from baseline in mean Hb, while the CIs of the HR for cardiovascular and cerebrovascular events included unity (**Table 8**).

Table 8. Hazard ratios for outcomes in relation to Hb as continuous variable

Endpoint	HR associated with mean Hb increase of 1g/dL (continuous variable)
HR [95% CI]	
Composite endpoint	0.87 [0.80 – 0.95]
All-cause mortality	0.68 [0.60 – 0.76]
Cardiovascular event	0.96 [0.84 – 1.10]
Cerebrovascular event	0.99 [0.83 – 1.19]

Yellow shading indicates HRs below 1 where the 95% CIs exclude unity.

- Results in unadjusted analyses and those adjusted for baseline characteristics were similar.
- In general, tests for mean Hb achieved-by-diabetes status interaction had p-values >0.1, suggesting no difference between diabetic and non-diabetic subjects in the association between mean Hb achieved and risk of outcomes.

CONCLUSIONS

- **In an analysis of a large integrated database comprising 24 prospective RCTs enrolling 6273 CKD patients treated with ESAs, risk of a clinically significant event decreased with increasing Hb; greatest risk was observed at Hb levels below 10 g/dL and lower risk at Hb values at or above 12 g/dL.**
- **Multiple analyses of various aspects of Hb in relation to clinical outcomes have shown a consistent association between Hb levels below the reference range of 10–11 g/dL and unfavourable prognosis for a composite endpoint, all-cause mortality and cerebrovascular events, as well as an association of Hb values above the reference range with a lower risk of these events.**
- **The occurrence of cardiovascular events appeared to be independent of Hb values. Findings for dialysis and non-dialysis subjects were similar to those in all subjects. While the risk of events is higher in diabetic subjects, the analyses suggest that the association between Hb and outcomes was independent of diabetes status.**

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