FP378

ASSOCIATION OF OUTCOMES AND MAINTENANCE OF TARGET Hb LEVELS IN CKD PATIENTS: FINDINGS FROM A POOLED ANALYSIS OF 23 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 the 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 to target haemoglobin (Hb) levels above 13 g/dL,[5–9] although these results have given rise to controversy.[10]
- We explored the relationship between stable maintenance of Hb levels and clinical outcomes in a pooled database of 23 prospective ESA studies in patients with CKD.

METHODS

- Safety data were pooled from CKD patients treated with Mircera, darbepoetin alfa, epoetin alfa or epoetin beta in the Hb maintenance setting of 23 RCTs, 13 of Hb maintenance and data from the follow-up period of 10 studies performed in anaemia correction.
- Cox proportional hazards regression models of time to first event (unadjusted and adjusted for baseline risk factors) were developed 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 maintenance of Hb levels (average Hb during the study minus individual baseline Hb), defined in three Hb categories:
  - maintained within ± 1 g/dL of baseline
  - increased >1 g/dL from baseline
  - decreased >1 g/dL from baseline
- Analyses were performed for all maintenance setting subjects, maintenance setting subjects on dialysis and maintenance setting subjects not on dialysis.
- Kaplan-Meier curves of the time to first occurrence of the outcomes of interest are displayed by category of the deviation from baseline Hb.
- Hazard ratios (HRs) for each outcome in each category of deviation from baseline Hb relative to the defined reference category, adjusting for all risk factors, are presented for all subjects, diabetic and non-diabetic subjects, as well as those on dialysis and those not on dialysis, along with 95% confidence intervals (CIs).

RESULTS

- In 5729 patients analysed in the Hb maintenance setting, baseline co-morbidities and cardiovascular risk factors were highly prevalent (92.0% of patients) and characteristic of the CKD population; 80.0% were on dialysis. Baseline demographic characteristics, co-morbidities and cardiovascular risk factors are presented in **Table 1**.
- In the time-to-first-event analysis, 653 patients had an event of the composite endpoint, 333 suffered a fatal adverse event, 312 a cardiovascular event and 146 a cerebrovascular event.
- Incidence was approximately double in diabetic as compared with non-diabetic patients and in dialysis as opposed to non-dialysis patients (**Table 2**).
- The Kaplan-Meier display in **Figure 1** demonstrates the time to first occurrence of the composite endpoint and shows that event-free survival was lower in the category with a decrease from baseline Hb greater than 1 g/dL.
- Similarly, event-free survival was lower in the category with a decrease from baseline Hb greater than 1 g/dL for all-cause mortality, cardiovascular events and cerebrovascular events (**Figures 2–4**).
- **Tables 3–6** show increased risk (expressed as HRs) of the composite endpoint, all-cause mortality, cardiovascular events and cerebrovascular events with a decrease from baseline Hb greater than 1 g/dL in the all-subject population, diabetic and non-diabetic subjects, those on dialysis and those not on dialysis.

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

	All subjects N = 5729	Diabetic N = 1845	Non-diabetic N = 3884	Dialysis N = 4614	Non-dialysis N = 1115
Age, mean, SD (years)	59.3 (15.42)	63.7 (12.12)	57.2 (16.34)	58.3 (15.54)	63.1 (14.29)
Sex, male (%)	55.1	56.2	54.6	56.6	48.9
Region, ex-US (%)	85.7	75.6	90.6	84.6	90.3
Weight, mean, SD (kg)	70.8 (16.80)	78.0 (18.09)	67.3 (14.96)	69.5 (16.62)	76.1 (16.51)
Cause(s) of Renal Disease					
Hypertension (%)	26.8	29.3	25.7	26.2	29.5
Diabetes (%)	25.6	79.5	0.0	22.8	37.2
Glomerulonephritis (%)	19.6	5.9	26.1	20.7	15.0
Other (%)	40.9	13.4	53.9	42.3	34.8
Not known (%)	0.9	0.2	1.2	1.1	0.0
Co-morbidities					
Diabetes (%)	32.2	100	0.0	29.0	45.3
History of ...					
hypertension (%)	85.8	92.2	82.7	83.6	94.9
hyperlipidaemia (%)	36.3	55.1	27.3	32.2	52.8
coronary artery disease (%)	24.9	37.1	19.1	25.1	23.9
congestive heart failure (%)	15.2	22.8	11.6	14.4	18.5
peripheral vascular disease (%)	14.3	25.3	9.1	14.7	12.6
cerebrovascular disease (%)	9.9	14.5	7.7	9.5	11.6
Baseline Hb, mean, SD (g/dL)	10.88 (1.687)	11.21 (1.342)	10.73 (1.808)	10.87 (1.829)	10.92 (0.882)
Ferritin, median, range (mg/mL)	345 (0.8; 7520)	347.5 (1.1; 7520)	345 (0.8; 7320)	412 (0.8; 7520)	145 (6.0; 2153)
Parenteral iron supplementation, (%)	44.3	45.4	0.1	52.6	9.8
Baseline albumin, median, range (g/L)	39.4 (1.6; 90.0)	39.0 (1.6; 90.0)	40.0 (14.5; 76.6)	39.0 (1.6; 76.6)	40.6 (20.2; 90.0)
Systolic blood pressure, mean, SD (mmHg)	141 (22.8)	146 (23.3)	139 (22.2)	143 (23.7)	136 (17.8)
Diastolic blood pressure, mean, SD (mmHg)	78 (13.3)	75 (13.2)	79 (13.2)	78 (13.8)	76 (11.0)

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

Outcome of Interest	All Subjects N = 5729 n (inc. rate)	Diabetic N = 1845 n (inc. rate)	Non-diabetic N = 3884 n (inc. rate)	Dialysis N = 4614 n (inc. rate)	Non-dialysis N = 1115 n (inc. rate)
Composite endpoint	653 (11.4)	308 (16.7)	345 (8.9)	536 (11.6)	81 (7.3)
All-cause mortality	333 (5.8)	155 (8.4)	178 (4.6)	279 (6.0)	28 (2.5)
Cardiovascular event	312 (5.4)	158 (8.6)	154 (4.0)	256 (5.5)	41 (3.7)
Cerebrovascular event	146 (2.5)	65 (3.5)	81 (2.1)	117 (2.5)	21 (1.9)

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

Figure 1. Composite endpoint

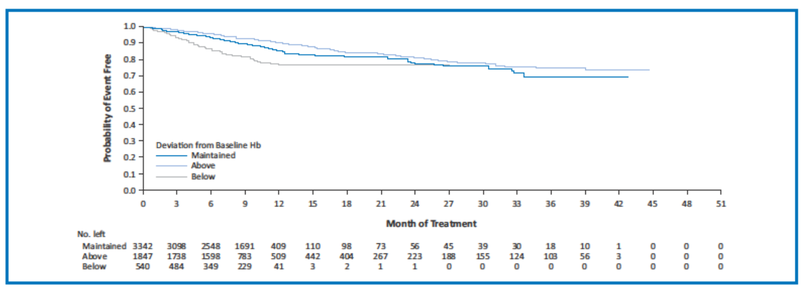

Figure 2. All-cause mortality

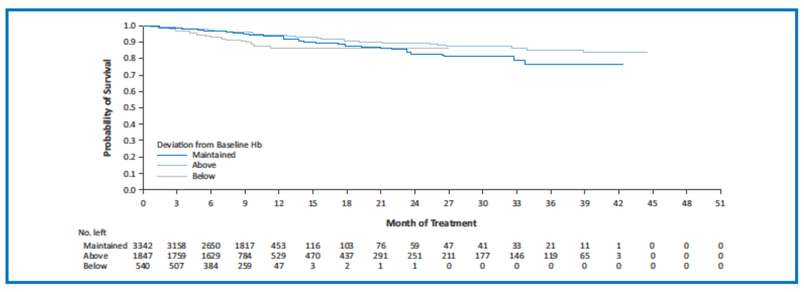

Figure 3. Cardiovascular events

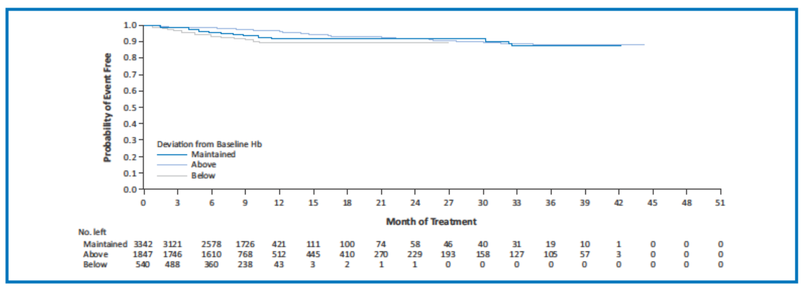

Figure 4. Cerebrovascular events

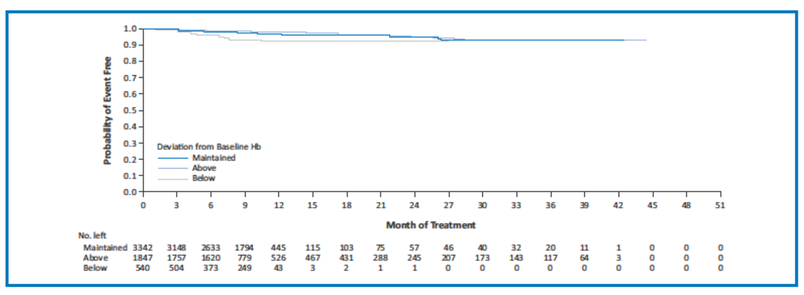

Table 3. Hazard ratios for composite endpoint by subgroup and deviation from baseline Hb

Adjusted Cox Regression Analyses	Reference category: Hb maintained within ± 1 g/dL of baseline (BL)			
All Hb values included	Decrease from BL >1 g/dL		Increase from BL >1 g/dL	
	HR	95% CI	HR	95% CI
Composite Endpoint				
All subjects	2.31	1.80 – 2.97	0.82	0.60 – 1.12
All diabetic subjects	2.27	1.61 – 3.20	1.05	0.73 – 1.52
All non-diabetic subjects	2.34	1.65 – 3.31	0.61	0.41 – 0.91
All subjects on dialysis	2.35	1.82 – 3.02	0.90	0.59 – 1.37
All subjects not on dialysis	1.82	0.20 – 16.44	0.74	0.40 – 1.39

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 all-cause mortality by subgroup and deviation from baseline Hb

Adjusted Cox Regression Analyses	Reference category: Hb maintained within ± 1 g/dL of baseline (BL)			
All Hb values included	Decrease from BL >1 g/dL		Increase from BL >1 g/dL	
	HR	95% CI	HR	95% CI
All-Cause Mortality				
All subjects	2.44	1.71 – 3.48	0.78	0.50 – 1.23
All diabetic subjects	2.12	1.30 – 3.47	1.00	0.60 – 1.67
All non-diabetic subjects	2.81	1.72 – 4.59	0.57	0.32 – 1.02
All subjects on dialysis	2.35	1.64 – 3.38	1.01	0.56 – 1.84
All subjects not on dialysis	5.03	0.31 – 81.26	4.32	0.84 – 22.16

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

Table 5. Hazard ratios for cardiovascular events by subgroup and deviation from baseline Hb

Adjusted Cox Regression Analyses	Reference category: Hb maintained within ± 1 g/dL of baseline (BL)			
All Hb values included	Decrease from BL >1 g/dL		Increase from BL >1 g/dL	
	HR	95% CI	HR	95% CI
Cardiovascular Events				
All subjects	1.80	1.26 – 2.58	0.74	0.47 – 1.16
All diabetic subjects	1.95	1.23 – 3.09	0.96	0.56 – 1.62
All non-diabetic subjects	1.63	0.95 – 2.80	0.55	0.30 – 0.99
All subjects on dialysis	1.81	1.27 – 2.59	0.59	0.30 – 1.16
All subjects not on dialysis	0.00	0.00	0.84	0.35 – 2.00

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 cerebrovascular events by subgroup and deviation from baseline Hb

Adjusted Cox Regression Analyses	Reference category: Hb maintained within ± 1 g/dL of baseline (BL)			
All Hb values included	Decrease from BL >1 g/dL		Increase from BL >1 g/dL	
	HR	95% CI	HR	95% CI
Cerebrovascular Events				
All subjects	3.39	2.10 – 5.47	0.64	0.33 – 1.25
All diabetic subjects	3.55	1.82 – 6.93	0.70	0.31 – 1.60
All non-diabetic subjects	3.24	1.68 – 6.24	0.58	0.26 – 1.31
All subjects on dialysis	3.60	2.21 – 5.87	0.63	0.23 – 1.74
All subjects not on dialysis	0.00	0.00	0.38	0.12 – 1.16

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

- Results in unadjusted analyses and those adjusted for baseline characteristics were similar.

CONCLUSIONS

- **In a retrospective analysis of a large integrated database comprising 23 prospective RCTs and 5729 CKD patients treated with ESAs in the Hb maintenance setting, risk of a clinically significant event (composite endpoint, fatal adverse events, cardiovascular events and cerebrovascular events) in the all-subjects population and in dialysis subjects, as well as in diabetic subjects, was increased in subjects with a decline from baseline Hb exceeding 1 g/dL.**

ACKNOWLEDGEMENTS

Data presented are from pooled analyses of the following studies: BA16736, BA16738, ML20680, BA16739, BA16740, BA17283, BA17284, BH17847, BH20051, ML21058, ML21060, ML21208, ML21904, BA16169, MA16620, MF3787, MF3981, MF4100, MF4135, MF4173, BA15959, MA17502, MF4169.
This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.
Editorial assistance for this presentation, provided by Health Interactions, was supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

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Presented at the 52nd ERA-EDTA Congress, 28–31 May 2015, London, United Kingdom