European Heart Journal (2006) **27**, 1440–1446
doi:10.1093/eurheartj/ehl012

The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET

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Received 18 August 2005; revised 4 April 2006; accepted 13 April 2006; online publish-ahead-of-print 22 May 2006

KEYWORDS
Heart failure;
Anaemia;
Beta-blockers;
Prognosis

Aims Anaemia is a common comorbidity in chronic heart failure (CHF). The predictors of new onset anaemia (NOA) and its long-term prognostic value, particularly in patients treated with beta-blockers, are not known.

Methods and results In COMET, 3029 patients with CHF in NYHA II–IV and EF $<35\%$ were randomized to carvedilol or metoprolol tartrate and were followed for an average of 58 months. Plasma haemoglobin (Hb) concentrations were measured at a central laboratory at randomization, at four monthly intervals for the first year and annually thereafter. According to WHO criteria, anaemia was defined when Hb measured <13 g/dL for men and <12 g/dL for women. We considered anaemia to be severe when Hb <11.5 g/dL for men and <10.5 g/dL for women. The baseline mean Hb was 14.2 ± 1.5 g/dL ($n = 2996$) and 15.9% of patients had anaemia (males, 16.0%; females, 15.2%). At baseline, severe anaemia was found in 3.3% of patients (males, 3.6%; females, 2.0%). During the study, all-cause mortality (RR 1.47) death or hospitalization (RR 1.28), and heart failure hospitalization (RR 1.43, all $P < 0.0001$) were higher in anaemic when compared with non-anaemic patients. In patients without anaemia at baseline, at the end of the study, the cumulative frequency of NOA was 28.1% in males and 27.0% in females. NOA increased over time from 14.2% at year 1 to 27.5% at year 5. Predictors of NOA were: higher age, diuretic dose, creatinine (all $P < 0.0001$), higher serum potassium, lower serum sodium, body mass index, and use of aldosterone antagonists, carvedilol, and digitalis (all $P < 0.03$). Treatment with carvedilol (vs. metoprolol tartrate) was associated with a 24% increased risk to develop NOA ($P = 0.0047$), but not severe anaemia ($P = 0.18$). Patients with a Hb decrease of >3 g/dL (RR 3.37, $P < 0.0001$) or of 2.0–3.0 g/dL (RR 1.47, $P = 0.011$) from baseline had an increased subsequent mortality when compared with patients having Hb increases of 0–1.0 g/dL.

Conclusion In stable ambulatory CHF patients, development of NOA is frequent and can be predicted by a set of clinical variables. Decreases in Hb over time relate to future increased morbidity and mortality.

Introduction

Anaemia is a common comorbidity in chronic heart failure (CHF), and is associated with impaired functional capacity and cardiac function, renal dysfunction, increased rate of hospitalizations, and poor prognosis[1–8] One study has proposed that the relationship between haemoglobin (Hb) levels and mortality is U-shaped.[4] Another study suggested that the mode of death in CHF differs between patients with low Hb (more circulatory failure) when compared with those having high Hb (more sudden death).[6] It is not known whether changes in Hb levels in general or below a certain threshold predict acute events in patients with CHF. Changes in Hb over time have been studied in one study,[3] but still little is known about the predictors of new onset anaemia (NOA) and its long-term prognostic value, particularly in patients treated with beta-blockers. The Carvedilol or Metoprolol European Trial (COMET) population provides a large, well-controlled, and contemporary population with repeated assessments of Hb levels, blinded adjudication of endpoints, and sufficiently long follow-up to address such issues.[9]

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Methods

Study design and population

The design and primary results of the COMET trial have been published elsewhere.[9] Briefly, 3029 patients were randomized to treatment with carvedilol titrated to a dose of 25 mg twice daily ($N = 1511$) or metoprolol tartrate titrated to a dose of 50 mg twice daily ($N = 1518$). Eligibility for COMET was based on the presence of NYHA class II–IV, optimal background therapy with diuretics and an angiotensin-converting enzyme (ACE)-inhibitor, left ventricular (LV) ejection fraction (EF) (LVEF) $<35\%$, and a previous admission for a cardiovascular reason. Plasma Hb concentrations were measured at a central laboratory at randomization, four monthly intervals for the first year and annually thereafter. A sample was also collected at the end of the study. The study was approved by the centres institutional review boards and all participating subjects gave informed consent.

Statistical methods

Several analyses for Hb are presented. Rather than to present second order or above complex statistical models, it was decided *a priori* that a categorical approach would be presented as this is more understandable and clinically useful. According to the criteria of the World Health Organisation (WHO), anaemia or NOA was defined when Hb measured <13 g/dL for men and <12 g/dL for women.[10] We considered severe anaemia when Hb measured <11.5 g/dL in men and Hb <10.5 g/dL in women. In addition, it was of clinical interest to consider high levels of Hb, and hence we split patients into six non-equal groups based on their Hb values, with the lowest two groups combined being equivalent to the WHO definition of anaemia. In males, these were Group 1: <11.5 g/dL; Group 2: 11.5–13.0 g/dL; Group 3: 13.0–14.0 g/dL; Group 4: 14.0–15.0 g/dL; Group 5: 15.0–16.5 g/dL; and Group 6: ≥ 16.5 g/dL. In females, Group 1: <10.5 g/dL; Group 2: 10.5–12.0 g/dL; Group 3: 12.0–13.0 g/dL; Group 4: 13.0–14.0 g/dL; Group 5: 14.0–15.5 g/dL; and Group 6: ≥ 15.5 g/dL. For analysis purposes, we considered patients in Group 1 to have severe anaemia and patients in Group 2 to have moderate anaemia. The choice of cut-points does not affect the conclusions and sensitivity analyses are given below.

Differences between these six groups were assessed using ANOVA for continuous data, χ^2 for categorical data, and Cox regression analysis for survival data. To assess the multivariable significance of anaemia on outcome, we generated a multivariable model based on 14 clinically important baseline characteristics together with randomized therapy. These variables were age, gender, NYHA classification, systolic blood pressure (BP), body mass index (BMI), duration of HF, LVEF, diabetes, ischaemic aetiology, serum creatinine, serum sodium, concomitant use of aspirin, anticoagulants, and lipid-lowering drugs. NT-proBNP was not included as this was only available in approximately half the patients. However, sensitivity analyses including NT-proBNP were performed.

We used Bootstrap methods to determine which baseline factors affected NOA in patients who were not anaemic at baseline. We produced 200 Bootstrap samples (with replacement) from our database and ran backward stepwise Cox regression analyses on each. We calculated how many times each variable appeared in the final model. The entry/exit threshold probability for this analysis was 0.05. The most frequently occurring variables were included in our model for NOA. We then used 200 further Bootstrap samples to assess the magnitude of the parameter estimates for our model.

To assess the impact of changes in Hb levels on outcome, we undertook a time-dependent Cox regression analysis, adjusted for the standard set of baseline covariates, in which Hb was included as a time-dependent covariate. When assessing the impact of changes in Hb observed, a distinction between reductions in Hb level and increases was made. Patient adherence to the visit schedule was excellent, and missing data was low (406 Hb readings missing/14 890 samples collected at appropriate timepoints = 2.7%). No interpolation or extrapolation for missing values were performed and patients were included in this analysis as far as data allowed. For the Cox regression analyses, Martingale residual plots were used to assess the functional form of the continuous covariates and Schoenfeld residuals plotted to assess the proportional hazards assumptions.

Comparisons between the six groups were made at the 5% significance level. As the interest focused on both low and high Hb, there are multiple comparisons of interest, hence, only assessments with a significance level of 0.01 or below are highlighted.

Results

The baseline mean Hb was 14.2 ± 1.5 g/dL and available in 2996 patients (98.9%). The baseline characteristics of the patients according to the six Hb groups are presented in *Table 1*. At baseline, 15.9% of patients had anaemia according to WHO criteria (males 16.0%; females 15.2%)—3.3% of patients had severe anaemia (Group 1: males 3.6%; females 2.0%) and 12.6% had moderate anaemia (Group 2: males 12.4%; females 13.2%).

Over a median follow-up of 58 months [inter-quartile range (IQR), 54–64 months], 1093 of the 2996 patients died. Kaplan–Meier estimates of the time to all-cause death for each of the six Hb strata are given in *Figure 1*. The relative risk of death in each of the six groups with reference to Group 4 and adjusted for other baseline factors is presented in *Table 2*. When NT-proBNP was included in the multivariable model for both severe (RR = 1.60, 95% CI, 1.05–2.45, $P = 0.0286$) and moderate anaemia (RR = 1.30, 95% CI, 1.01–1.69, $P = 0.0464$) results remained similar. There was no significant interaction between Hb strata and randomized therapy in the model ($P = 0.6551$, *Figure 2*).

We performed several sensitivity analyses. First, we used quartiles of Hb, and in these analyses the lowest quartile is Hb ≤ 13.5 g/dL for males and ≤ 12.5 g/dL for females. The adjusted relative risk of death for this group is 1.21 (95% CI: 1.02, 1.43, $P = 0.0333$) when compared with all other patients. Second, we fitted Hb as a continuous covariate. The parameter estimates for a quadratic model are Hb 0.41 (95% CI: 0.27–0.63) and Hb 1.026 (95% CI: 1.01–1.04), which highlights the increased mortality in those with the lowest Hb.[2]

All-cause mortality (RR = 1.47, 95% CI, 1.27–1.71, $P < 0.0001$) death or hospitalization (RR = 1.28, 95% CI, 1.14–1.44, $P < 0.0001$), heart failure hospitalization (RR = 1.43, 95% CI, 1.23–1.68, $P < 0.0001$) were higher in anaemic patients as defined by the WHO (Group $1 + 2$) when compared with non-anaemic patients.

The cause of death by anaemia status at baseline (WHO criterion) is presented in *Table 3*. There are significant differences between patients with and without anaemia for the breakdown of the causes of death ($P = 0.0158$), with less sudden death (37.2 vs. 45.5%) and more circulatory failure (41.4 vs. 30.1%) in those anaemic at baseline. When subgrouping the patients by Hb there was no evidence to suggest that Hb levels affected mode of death ($P > 0.1$, data provided in online supplement).

Table 1 Baseline characteristics of the substudy population according to Hb strata

	Group 1, $N = 99$ (3.3%)	Group 2, $N = 376$ (12.6%)	Group 3, $N = 633$ (21.1%)	Group 4, $N = 830$ (27.7%)	Group 5, $N = 842$ (28.1%)	Group 6, $N = 216$ (7.2%)	*P*-value
Age (years) mean/SD	66.1/13.6	66.0/10.6	63.1/11.2	62.1/10.8	59.5/11.4	58.8/11.3	<0.0001
Gender							
Male, *n* (%)	87 (87.9)	296 (78.7)	516 (81.5)	642 (77.3)	670 (79.6)	179 (82.9)	0.0809
Female, *n* (%)	12 (12.1)	80 (21.3)	117 (18.5)	188 (22.7)	172 (20.4)	37 (17.1)	
BMI (kg/m) mean/SD	25.1/4.4	25.9/4.2	26.4/4.1	27.2/4.2	27.4/4.7	27.5/4.9	<0.0001
Systolic BP (mmHg) mean/SD	124.0/22	123.9/19.3	124.1/19.2	127.5/19.9	126.9/19.1	127.5/18.6	0.0017
Diastolic BP (mmHg) mean/SD	72.0/10.1	74.4/11.3	75.6/10.4	77.8/10.9	78.8/10.4	79.7/11.3	<0.0001
Heart rate (bpm) mean/SD	80.5/13.0	80.3/13.5	79.7/12.9	81.2/13.6	82.0/13.4	83.1/13.7	0.0039
NYHA Class II, *n* (%)	30 (30.3)	144 (38.3)	316 (49.9)	419 (50.5)	444 (52.7)	99 (45.8)	<0.0001
NYHA Class III, *n* (%)	60 (60.6)	201 (53.5)	299 (47.2)	390 (47.0)	371 (44.1)	110 (50.9)	
NYHA Class IV, *n* (%)	9 (9.1)	31 (8.2)	18 (2.8)	21 (2.5)	27 (3.2)	7 (3.2)	
Duration CHF (months)	22.0	22.0	17.5	21.0	22.0	29.0	0.0695
Median (IQR)	(6–55)	(7–68)	(6–57)	(7–58)	(6–63)	(7–66)	
Aetiology							
Ischaemic heart disease, *n* (%)	56 (56.6)	239 (63.6)	345 (54.5)	451 (54.3)	397 (47.1)	84 (38.9)	<0.0001
Hypertension, *n* (%)	14 (14.1)	72 (19.1)	103 (16.3)	154 (18.6)	132 (15.7)	52 (24.1)	0.0490
LVEF Mean/SD	26.2/7.3	25.6/6.5	26.4/7.0	26.2/7.2	26.0/7.5	25.5/7.0	0.5002
NT-proBNP (pg/mL) median	2493	2138	1322	1047	976.7	1257	<0.0001
IQR	(1118–5143)	(927–3894)	(646–2830)	(507–2415)	(385–2116)	(602–2208)	
No. samples	51	214	357	425	407	92	
Previous MI, *n* (%)	45 (45.9)	183 (50.0)	265 (42.8)	344 (42.4)	314 (38.0)	67 (31.5)	0.0001
CAD, *n* (%)	40 (69.0)	163 (69.4)	240 (61.7)	317 (62.2)	289 (51.5)	67 (45.9)	<0.0001
Current angina, *n* (%)	20 (20.2)	103 (27.8)	125 (19.8)	195 (23.6)	161 (19.3)	42 (19.5)	0.0118
HT, *n* (%)	40 (40.4)	135 (36.5)	212 (33.9)	300 (36.7)	310 (37.4)	92 (43.2)	0.2463
Diabetes, *n* (%)	30 (30.3)	106 (28.2)	155 (24.5)	183 (22.1)	196 (23.3)	51 (23.8)	0.1729
Medications							
Diuretics, *n* (%)	98 (99.0)	371 (98.7)	628 (99.2)	817 (98.4)	831 (98.7)	212 (98.1)	0.8034
ACE-inhibitors, *n* (%)	91 (91.9)	346 (92.0)	580 (91.6)	738 (88.9)	778 (92.4)	205 (94.9)	0.0473
Digitalis, *n* (%)	58 (58.6)	214 (56.9)	350 (55.3)	471 (56.7)	531 (63.1)	155 (71.8)	0.0001
Nitrates, *n* (%)	41 (41.4)	165 (43.9)	199 (31.4)	286 (34.5)	238 (28.3)	55 (25.5)	<0.0001
Aldosterone antagonists, *n* (%)	12 (12.1)	48 (12.8)	64 (10.1)	85 (10.2)	92 (10.9)	21 (9.7)	0.7695
Anticoag, *n* (%)	45 (45.5)	173 (46.0)	279 (44.1)	350 (42.2)	399 (47.4)	128 (59.3)	0.0006
Aspirin, *n* (%)	44 (44.4)	150 (39.9)	246 (38.9)	331 (39.9)	269 (31.9)	60 (27.8)	0.0002
Statins, *n* (%)	22 (22.2)	88 (23.4)	125 (19.7)	194 (23.4)	165 (19.6)	36 (16.7)	0.1429
Laboratory analyses							
Serum creatinine (μmol/L)	153.0/113	118.3/44.7	109.4/33.6	102.9/29.9	100.0/26.5	103.5/55.9	<0.0001
Serum sodium (mmol/L)	138.1/5.0	139.2/3.4	139.5/3.2	139.9/3.4	139.7/3.3	139.8/4.2	<0.0001

HT, hypertension; Medications, at randomization; Anticoag, anticoagulants for Hb groups see methods section.

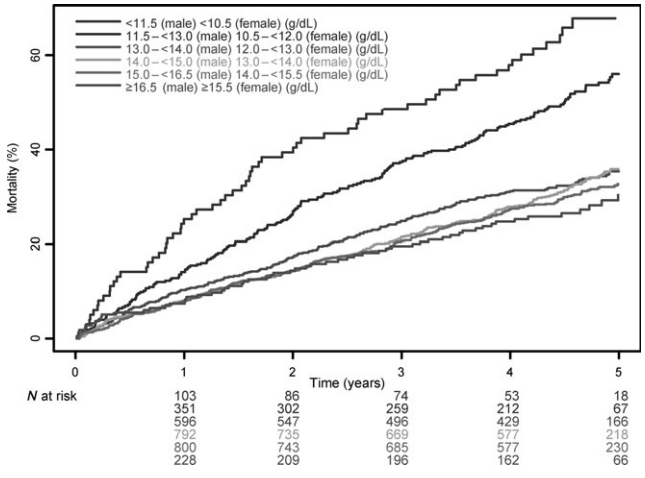

Figure 1 Kaplan–Meier survival curve by Hb strata (all-cause mortality). See online supplementary material for a colour version of this figure.

Relationship between baseline Hb and hospitalization

Compared with Hb Group 4 when adjusted for the standard set of baseline factors, patients with severe anaemia (Group 1) had increased risk of all-cause hospitalization (RR = 1.72, 95% CI, 1.34–2.21, $P < 0.0001$), death or hospitalization (RR = 1.76, 95% CI, 1.39–2.23, $P < 0.0001$), hospitalization for worsening HF (RR = 1.70, 95% CI, 1.22–2.36, $P = 0.0018$), and death or hospitalization for worsening HF (RR = 1.71, 95% CI, 1.31–2.25, $P = 0.0001$). For patients with moderate anaemia (Group 2) the corresponding relative risks were 1.22 (95% CI, 1.05–1.42, $P = 0.0096$), 1.19 (95% CI, 1.03–1.38, $P = 0.0188$), 1.47 (95% CI, 1.21–1.80, $P = 0.0001$), and 1.39 (95% CI, 1.18–1.63, $P = 0.0001$).

The differences observed for mortality between the Hb groups, leading to shorter average follow-up for those with anaemia, would have impacted on the mean lengths of hospitalization during the study. Even so, the median lengths of hospitalization during the study of patients with severe and

Table 2 Multivariable Cox proportional hazard model for all-cause mortality ($N = 2996$)

	Relative risk	95% CI	*P*
Hb Group 1 vs. Group 4	1.558	1.145, 2.121	0.0048
Hb Group 2 vs. Group 4	1.405	1.16, 1.703	0.0005
Hb Group 3 vs. Group 4	0.942	0.783, 1.134	0.529
Hb Group 5 vs. Group 4	1.025	0.859, 1.222	0.7873
Hb Group 6 vs. Group 4	0.828	0.615, 1.114	0.2117
Carvedilol vs. Metoprolol	0.835	0.737, 0.946	0.0047
Increasing age (per 1 year)	1.028	1.021, 1.035	<0.0001
Systolic BP >120 mmHg vs.≤120 mmHg	0.757	0.664, 0.864	<0.0001
NYHA class III vs. II	1.497	1.309, 1.713	<0.0001
NYHA class IV vs. II	1.917	1.453, 2.529	<0.0001
Increasing creatinine (per 1 μM/L)	1.002	1.001, 1.003	<0.0001
Increasing sodium (per 1 mM/L)	0.945	0.929, 0.962	<0.0001
Increasing BMI (per 1 kg/m^2)	0.968	0.953, 0.984	0.0001
Diabetes	1.325	1.152, 1.525	0.0001
Increasing duration of HF (per month)	1.002	1.001, 1.003	0.0002
Aetiology ischaemic vs. non-ischaemic	1.313	1.138, 1.515	0.0002
LVEF >25% vs. LVEF≤25%	0.807	0.709, 0.917	0.0011
Lipid-lowering agent	0.764	0.647, 0.902	0.0015
Female vs. male	0.816	0.692, 0.962	0.0154
Anticoagulants	1.17	1.002, 1.367	0.0473
Aspirin	1.123	0.953, 1.323	0.1659

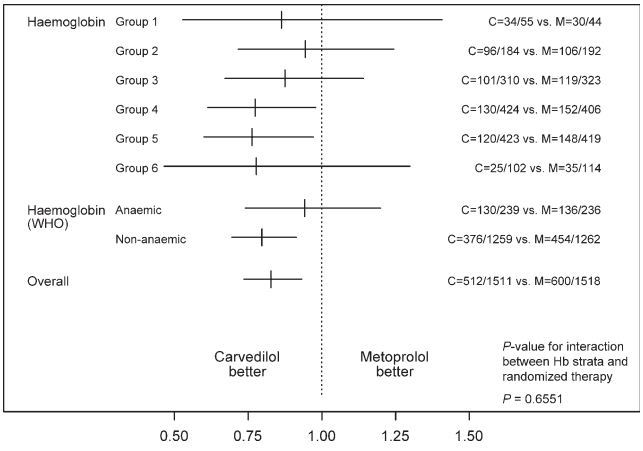

Figure 2 Relative risk of all-cause mortality by Hb strata. C, carvedilol, M, metoprolol.

moderate anaemia were 24 (IQR, 10–60) and 23 ± (9–60) days, respectively, approximately 10 days longer than those with higher Hb ($P < 0.0001$). They also had the longest median length of stay in hospital for worsening heart failure at 5 (IQR, 0–21) and 4 (0–20) days, respectively ($P = 0.0027$).

Changes in Hb over time

In patients without anaemia at baseline, at the end of the study, the cumulative frequency of NOA was 28.1% in males and 27.0% in females. NOA increased significantly over time from 14.2% at year 1 to 27.5% at year 5. The factors affecting NOA are provided in *Table 4*. Variables which appeared in at least 70% of the Bootstrap samples are included in the final model. Treatment with carvedilol was associated with a 22% increased risk to develop NOA (RR = 1.22, 95% CI, 1.05–1.41, $P = 0.0102$).

Table 3 Cause of death according to WHO definition of anaemia at baseline (absolute number of patients and percentages)

	WHO anaemic	WHO non-anaemic
Non-cardiovascular (%)	30 (11.3)	106 (12.8)
Sudden death (%)	99 (37.2)	378 (45.5)
Circulatory failure (%)	110 (41.4)	250 (30.1)
Stroke (%)	11 (4.1)	38 (4.6)
Other cardiovascular (%)	7 (2.6)	38 (4.6)
Unable to assign (%)	9 (3.4)	20 (2.4)
Total	266	830

Overall test of column homogeneity, $P = 0.0158$.

The mean profile for Hb over time by carvedilol and metoprolol is presented in *Figure 3A*. Carvedilol was associated with a significantly lower mean Hb throughout the follow-up period. At year 1, for instance, the reduction in Hb plasma concentration was −0.2 g/dL (95% CI, 0.36–0.1 g/dL, $P = 0.0003$). *Figure 3B* presents the proportion of patients experiencing NOA over time. Carvedilol was associated with an increased incidence of anaemia ($P = 0.0180$) but not of severe anaemia ($P = 0.18$).

Changes in Hb and outcome

A total of 2678 patients (89.4%) had follow-up Hb measures available for analyses. *Figure 4* shows the impact of Hb on mortality when adjusted for the standard set of baseline covariates in a time-dependent multivariable Cox regression analysis. The risks associated with moderate and severe anaemia at baseline are increased further when the repeated Hb assessments are included. In a time-dependent

Table 4 Multivariable Cox proportional hazard model for the predictors of anaemia (Hb $<$ 13 g/dL males, $<$12 g/dL females) in patients without anaemia at baseline (Hb $\geq$ 13 g/dL males, $\geq$12 g/dL females) at baseline ($N = 2521$)

	Frequency (%)[a]	Relative risk	95% CI	*P*	Bootstrap estimate[b]
Carvedilol vs. metoprolol	78.0	1.216	1.048, 1.412	0.0102	1.224
Increasing age (per 1 year)	100	1.027	1.02, 1.035	$<$0.0001	1.026
Diuretic ($>$80 vs. $\leq$80 mg furosemide equivalent)	90.5	1.409	1.186, 1.674	0.0001	1.381
Increasing creatinine (per μmol/L)	99.5	1.405	1.121, 1.762	0.0032	1.005
Aldosterone antagonists	85.5	0.967	0.947, 0.989	0.003	1.375
Increasing sodium (per mmol/L)	73.5	1.265	1.074, 1.489	0.0048	0.967
Increasing potassium (per mmol/L)	74.0	1.004	1.002, 1.005	$<$0.0001	1.256

[a]The frequency each variable occurred in 200 Bootstrap samples using backward stepwise methods.
[b]The mean parameter estimate obtained from 200 Bootstrap samples using the final model.

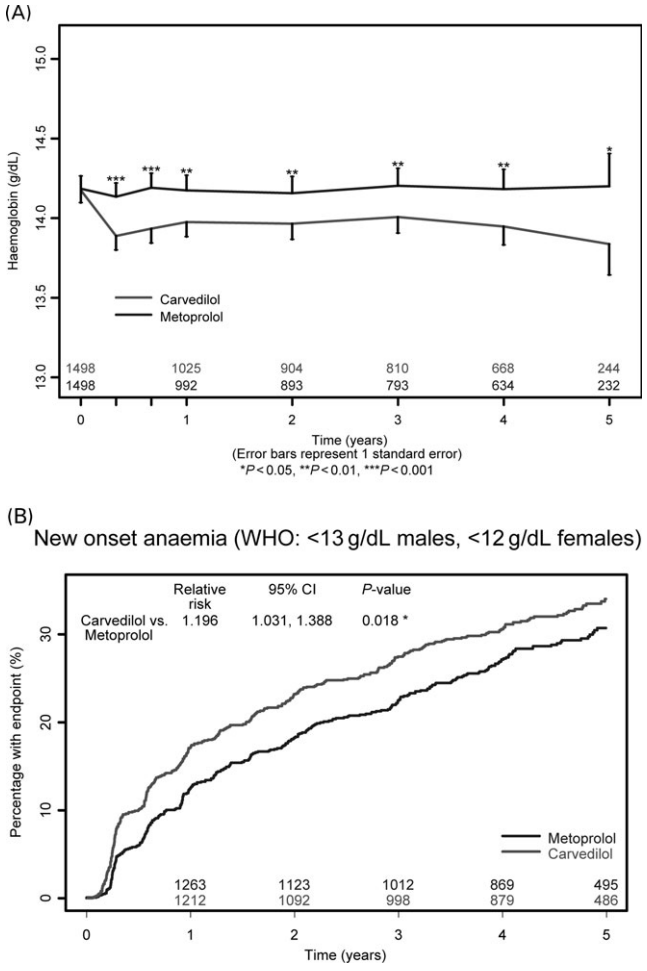

Figure 3 (*A*) Change in Hb over time in the two treatment arms. See online supplementary material for a colour version of this figure. (*B*) Proportion of patients with NOA over time in the two treatment arms. See online supplementary material for a colour version of this figure.

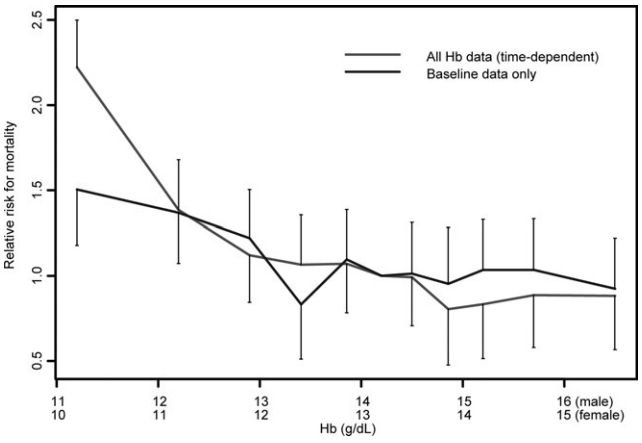

Figure 4 Adjusted relative risk of all-cause mortality by Hb over the course of the study. See online supplementary material for a colour version of this figure.

multivariable analysis for absolute Hb, based on the six categories used before, the relative risk of mortality for severe anaemia was 2.52 (95% CI, 1.97–3.22, $P < 0.0001$) when compared with reference Group 4. Patients with moderate anaemia had an increased relative risk of 1.49 (95% CI, 1.23–1.80, $P < 0.0001$).

Change in Hb over the study was split into eight non-equal groups as follows: <-3; -3 to -2; -2 to -1; -1 to 0; 0 to 1; 1 to 2; 2 to 3; and >3 g/dL. *Table 5* presents the relative risk of death for each of these groups relative to those patients with a small increase in Hb over the study (0 to 1 g/dL). Patients with a large decrease in Hb (≤ -3 g/dL) had an increased risk of death of 3.37 (95% CI, 2.46–4.61, $P < 0.0001$), compared with the reference group. There were 196 (7.3%) patients who had a decrease of this magnitude at one or more timepoints. Increases in Hb did not affect prognosis.

Discussion

In this *post hoc* analysis of data from COMET, we confirm that anaemia is common in patients with CHF and of independent prognostic value. Significantly and independently, anaemia predicts an increased risk of all-cause mortality, all-cause mortality or hospitalizations, hospitalizations for heart failure, higher hospital readmission rates for heart failure, and longer hospital stays for any reason. NOA was common during follow-up occurring in 14% of previously non-anaemic patients at 1 year and in 27.5% of patients at 5 years, similarly in men and women, and it developed more frequently in patients treated with carvedilol than with metoprolol tartrate. NOA was associated with increased subsequent risk, particularly in patients with decreases of Hb >3 g/dL.

Table 5 Multivariable time-dependent Cox proportional hazard model for the influence of change in Hb on mortality

	Relative risk	95% CI	*P*
ΔHb≤3 vs. >0 to 1 g/dL	3.37	2.464, 4.611	<0.0001
ΔHb > −3 to −2 vs. >0 to 1 g/dL	1.466	1.092, 1.969	0.0109
ΔHb > −2 to −1 vs. >0 to 1 g/dL	1.178	0.944, 1.471	0.1474
ΔHb > −1 to 0 vs. >0 to 1 g/dL	1.005	0.831, 1.215	0.9595
ΔHb >1 to 2 vs. >0 to 1 g/dL	0.982	0.753, 1.281	0.8923
ΔHb >2 to 3 vs. >0 to 1 g/dL	1.178	0.775, 1.791	0.4421
ΔHb >3 vs. >0 to 1 g/dL	1.144	0.661, 1.978	0.6314

Adjusted for randomized therapy, age, gender, NYHA classification, systolic BP, BMI, duration of HF, LVEF, diabetes, ischaemic aetiology of CHF, serum creatinine, serum sodium, concomitant use of aspirin, anticoagulants, and lipid-lowering drugs.

Anaemia and outcome

Our findings confirm and expand previous reports[2–8] on the link between anaemia and poor outcome in the context of long follow-up (5 years) and presence of beta-blocker therapy in all patients. Our study confirms that anaemia remains common and does not resolve, indicating that modern therapy has limitations in this subset of patients. In previous studies including patients only partially treated with beta-blockers, it was suggested that high Hb levels were associated with increased morbidity and mortality.[6] We did not find a U-shape relationship in COMET and do not confirm this finding in patients treated with beta-blockers.

In most cases, the origin of anaemia in CHF is uncertain and anaemia of chronic illness is diagnosed.[2] Several mechanisms for the development of anaemia in CHF have been proposed and include impaired erythropoïetin production, erythropoïetin resistance, iron and haematinic deficiencies, inflammation and cytokine activation, and haemodilution.[11] We observed that patients in the lower Hb strata were more often taking aspirin (*Table 1*), which might suggest that concealed bleeding played a role in our population. However, concomitant use of aspirin did not enter the model for prediction of NOA (*Table 4*). Anticoagulation therapy was used less frequently in patients with Hb <12.5 g/dL, and may illustrate the hesitation to use such therapy in anaemic patients or simply mean that anaemic patients were sicker.

NOA outcome and mechanisms

NOA was common during the 5-year follow-up period. There is no clear explanation for the change in Hb over time in CHF. Possibilities include again haematinic deficiency, fluid overload and haemodilution, change in inflammatory status, change in medications that may contribute to Hb concentration such as anticoagulants, aspirin, or ACE-inhibitors. Our multivariable model for NOA (*Table 4*) highlights the following baseline risk factors: increasing age, use of large doses of furosemide, aldosterone antagonists and carvedilol, kidney dysfunction, and high potassium levels (all adverse) as well as high serum sodium levels (protective). We note other factors predicting NOA have been identified in the Val-HEFT trial.[3]

We observed that small changes in Hb did not affect mortality, whereas patients experiencing a large decrease in Hb at any time during follow-up (in time-dependent analyses) had a three-fold increase in mortality. In a short-term substudy of the RENAISSANCE trial investigating the effect of etanercept in patients with CHF, it was suggested that a decrease in Hb over time was associated with an increased LV mass and higher mortality.[7] In a report based on data from the Val-HeFT study,[3] decreases in Hb over 1 year had adverse prognostic value. In Val-HeFT, increases in Hb over 12 months were found to predict improved subsequent prognosis–which we could not find in our study. Recently, using the SOLVD prevention and treatment arms database, it was reported that enalapril increased the odds of developing new anaemia at 1 year by 56% (adjusted model) in both symptomatic and asymptomatic patients with LV dysfunction without anaemia at baseline.[12] However, only a minority of these patients received beta-blocker therapy. The mechanism by which ACE-inhibitors cause anaemia remains unclear but may involve a decrease of circulating angiotensin II which in turn inhibits erythroïd precursors.[13] In our study, we cannot confirm the adverse impact of ACE-inhibitors on NOA. By design, all patients had to be treated with an ACE-inhibitor and/or an angiotensin receptor antagonist, and hence COMET may have lacked power to analyse this issue.

Carvedilol and anaemia development

Interestingly, we found that carvedilol induced a small but significant decrease in Hb when compared with metoprolol, and was a strong predictor of NOA. Similar results are also seen in COPERNICUS and CHRISTMAS when carvedilol is compared with placebo (unpublished data). It has long been known that erythropoietin-secreting cells within the renal parenchyma receive extensive sympathetic innervation, and that erythroïd progenitor cells display β-1, β-2, and α-adrenergic surface receptors.[14] Experimental augmentation of sympathetic activity in animals and humans increases erythropoïesis via an independent enhancement of both erythropoïetin production and erythroïd progenitor cell proliferation. Moreover, specific blockade of β-2 adrenergic receptors, but not β-1 or α-adrenergic receptors, completely abolished both the sympathetically mediated rise in erythropoïetin production and erythroïd progenitor cell proliferation.[15–18] As carvedilol blocks β-1, β-2, and α-adrenergic receptors, whereas metoprolol is a β-1 selective blocker, this might explain the differences observed between the two arms of the COMET trial with respect to changes in Hb concentrations over time.

This effect was not associated with poor outcome. Rather, we observed a 17% reduction in mortality in patients treated with carvedilol when compared with those treated with metoprolol, and there was no statistically significant interaction between Hb strata and treatment effect, suggesting that the potentially harmful effect of a reduction in Hb concentration with carvedilol was completely offset by other beneficial effects of carvedilol on survival.

In conclusion, this study showed that, in COMET, anaemia at baseline was common, associated with a specific clinical profile, increased morbidity and mortality in a large population of patients with mild to moderate heart failure treated with ACE-inhibitors and beta-blockers. The annual incidence of NOA was high over a period of 5 years, and associated with a high risk of death or rehospitalization. Predictors of NOA included age, worsening renal function, and treatment with carvedilol. The latter effect did not offset the benefit observed on mortality with carvedilol.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

This study was supported by F. Hoffmann–La Roche Ltd. We thank Mrs Villareal for her technical support.

Conflict of interest: C.M. is a Roche salaried employee.

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