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The Predictive Value of Short-Term Changes in Hemoglobin Concentration in Patients Presenting With Acute Decompensated Heart Failure

Peter van der Meer, MD,* Douwe Postmus, PhD,* Piotr Ponikowski, MD,† John G. Cleland, MD,‡ Christopher M. O'Connor, MD,§ Gad Cotter, MD,‖ Marco Metra, MD;¶ Beth A. Davison, PhD,‖ Michael M. Givertz, MD,# George A. Mansoor, MD,** John R. Teerlink, MD,†† Barry M. Massie, MD,†† Hans L. Hillege, MD,* Adriaan A. Voors, MD*

Groningen, the Netherlands; Wroclaw, Poland; Kingston upon Hull, England; Durham, North Carolina; Brescia, Italy, Boston, Massachusetts; Rahway, New Jersey; and San Francisco, California

Objectives The study sought to investigate the clinical correlates and prognostic role of anemia and changes in hemoglobin in patients hospitalized for acute decompensated heart failure (AHF).

Background Anemia is related to a poor outcome in patients with heart failure. In addition, an increase in hemoglobin during hospitalization might be a sign of effective decongestion and therefore related to improved outcome.

Methods This is a post hoc analysis of the PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study in 1,969 patients with AHF and mild to moderate impaired renal function. Hemoglobin levels were measured daily for the first 4 days and at day 7. The endpoint was 180-day all-cause mortality.

Results Anemia at baseline was observed in 50.3% of the patients. During follow-up, 359 patients (18.2%) died. Hemoglobin increased in 69.1% and was associated with a better renal function at baseline and more weight loss, but was associated with a deterioration of renal function ($p = 0.01$), whereas total dose diuretics was lower in patients with hemoconcentration ($p < 0.01$). Interaction analysis showed that greater weight loss and better baseline renal function were associated with a more rapid increase in hemoglobin concentration ($p < 0.01$ for both). The absolute change in hemoglobin (g/dl) independently predicted outcome (hazard ratio: 0.66; 95% confidence interval: 0.51 to 0.86; $p = 0.002$), whereas baseline hemoglobin levels did not.

Conclusions Patients with AHF and preserved renal function are decongested better, as shown by an increase in hemoglobin. A rapid increase in hemoglobin during the first week is independently associated with a favorable outcome, despite a slight decrease in renal function. (J Am Coll Cardiol 2013;61:1973–81) © 2013 by the American College of Cardiology Foundation

From the *University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; †Klinika Kardiologii, Wroclaw, Poland, ‡University of Hull, Kingston upon Hull, United Kingdom; §Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; ‖Momentum Research, Inc., Durham, North Carolina; ¶University of Brescia, Brescia, Italy; #Brigham and Women's Hospital, Boston, Massachusetts; **Merck Research Laboratories, Rahway, New Jersey; and the ††University of California, San Francisco, San Francisco Veterans Affairs Medical Center, San Francisco, California. Dr. Ponikowski has received honoraria from Merck; consulting fees from Vifor Pharma and Amgen, Inc., honoraria from Vifor Pharma; and travel/accommodation expenses covered by Vifor Pharma and Amgen, Inc. Dr. Cleland was on the Steering Committee for the study; served on the advisory board for MSD; and received payments for both. Dr. O'Connor is a consultant to Merck and Amgen. Dr. Davison and Dr. Cotter are employees of Momentum Research Inc, which was contracted to perform work on the project by Merck. Drs. Metra and Massie have received honoraria and reimbursements from NovaCardia, sponsors of the study, and from Merck, which purchased the rights to rolofylline after completion of the PROTECT pilot study. Dr. Givertz has received institutional research support and served on a scientific Advisory Board for Merck. Dr. Mansoor is an employee of Merck. Dr. Teerlink has received research funds and consulting fees from Merck, the makers of rolofylline for the conduct of this study and has also received research funds and consulting fees from Abbott, Amgen, Biogen Idec, Corthera, Cytokinetics, Johnson & Johnson/Scios, Novartis, Relypsa, and Solvay for research in related areas. Dr. Voors has received speaker and consultancy fees from Merck. All other authors have reported that they have no relationships relevant to the contents of this paper to report.

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Abbreviations and Acronyms

AHF = acute decompensated heart failure

eGFR = estimated glomerular filtration rate

EV = extracellular volume

HF = heart failure

NT-proBNP = N-terminal pro–B-type natriuretic peptide

NYHA = New York Heart Association

WHO = World Health Organization

Anemia is frequently observed in patients with chronic heart failure (HF) (1). Prevalence of anemia depends both on the severity of HF and diagnostic criteria used to define it, but may be as high as 50% in selected patient cohorts. In a recent meta-analysis, we found that anemia was associated with a 2-fold increased mortality rate in patients with *chronic* HF (2). The etiology of anemia in HF is diverse, including hematinic deficiencies, inflammation, bone marrow dysfunction, renal failure, and hemodilution (3–7). In patients with *acute* decompensated heart failure (AHF) the prevalence and consequences of anemia are less well studied, and hemodilution may play a more prominent role. Testani et al. (8) measured changes in intracardiac pressures in 336 patients with AHF and related this to hemoconcentration. They found that an increase in hematocrit was associated with a significant decline in renal function, but resulted in a better survival. Davila et al. (9) recently studied the role of hemoconcentration in 295 patients with AHF. Hemoconcentration was significantly associated with higher dose of diuretics, greater weight loss, and increased risk of worsening renal function during hospitalization. Hemoconcentration was significantly associated with mortality in univariable analysis, but not in multivariable analysis. However, in both studies only baseline and discharge hemoglobin levels were studied. The aim of the present study was to evaluate the impact of changes in hemoglobin levels on outcome in a large well-defined cohort of 2,033 patients with AHF, with hemoglobin levels measured at multiple pre-defined time points. Therefore, we studied the hemoglobin trajectory of patients during the first week after admission for AHF, including baseline hemoglobin values, absolute changes in hemoglobin, and the slope of the trajectory at baseline and related this to clinical variables and outcome.

See page 1982

Methods

Study population. The PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study was a multicenter, double-blind, placebo-controlled study randomizing patients with AHF and mild to moderate renal dysfunction (estimated creatinine clearance 20 to 80 ml/min, using the Cockroft-Gault formula) to intravenous rolofylline or placebo within 24 h of admission (10). For entry, patients were required to have dyspnea at rest or minimal exertion, evidence of fluid overload requiring intravenous loop diuretics, and elevated natriuretic peptides (N-terminal pro–B-type natriuretic peptide [NT-proBNP] ≥2000 pg/ml or BNP ≥500 pg/ml). The exclusion criteria have been published previously in the design paper (11). Patients with hemoglobin levels <8 g/dl or hematocrit <25% or the need for blood transfusion were excluded. Physical examination for HF signs, including rales, edema, and jugular venous pressure were performed prior to the initial study drug administration, daily through discharge, and on day 7. Blood samples for measurements of hemoglobin were taken at the time of enrollment (day 1) and on days 2, 3, 4, and 7. Patients not surviving the first 7 days after inclusion in the study and patients with no hemoglobin levels measured at any time point were excluded from this analysis. This resulted in a total study population of 1,969 patients. The primary outcome of interest for this non-prespecified analysis of PROTECT was all-cause mortality by day 180. The present study was conducted according to the principles stated in the Declaration of Helsinki. The study protocol was approved by the ethics committee and institutional review boards for each participating site, and all patients signed the informed consent form before participation in the study.

Statistical analysis. For analysis of repeated hemoglobin measurements, we used linear mixed-effects models (12). Such models assume that the evolution of a patient's hemoglobin concentration over time can be described by a linear regression model where some of the regression coefficients are population specific (fixed effects) and others are subject specific (random effects). Visual inspection of the mean hemoglobin levels at each time point suggested that the average evolution of hemoglobin over time was best described by means of a quadratic function. The fixed-effect structure therefore included an intercept, a slope for the linear time effect, and a slope for the quadratic time effect. The random-effect structure also included subject-specific intercepts and slopes for the linear as well as quadratic time effect. All analyses were on the basis of direct maximization of the observed data likelihood, meaning that missing values of hemoglobin were assumed to be missing at random. To explore whether sex, age, estimated glomerular filtration rate (eGFR), change in weight, and treatment with rolofylline were associated with the average evolution of hemoglobin over time, we subsequently fitted a model that included the main effects of these clinical covariates as well as their interactions with the 2 time effects. This full model was then, in a hierarchical way, starting with the higher order interaction terms, reduced to a more parsimonious one by stepwise eliminating those terms that were nonsignificant. Patients with missing covariate values were excluded, resulting in a sample size of 1,687 patients for the interaction analysis.

Empirical Bayes inference was applied to estimate the subject-specific hemoglobin trajectories. On the basis of the

intercepts and slopes of these trajectories, patients were classified into different groups on the basis of whether they were anemic or nonanemic and had hemoconcentration or no hemoconcentration. Anemia was defined, according to the World Health Organization (WHO) criteria, as a baseline hemoglobin level (intercept) of <13 g/dl for men and <12 g/dl for women. Hemoconcentration was defined as an increase in hemoglobin levels between baseline and day 7; no hemoconcentration was defined as a hemoglobin level that was stable or decreased between baseline and day 7. Demographic and clinical baseline characteristics, medical history, and medication use within these groups were described as mean ± SD for normally distributed variables, as median (interquartile range) for other continuous variables, and as percentages for categorical variables. The distributions of continuous variables were compared by Student *t* test for normally distributed variables and by Mann-Whitney *U* test for non-normally distributed variables. Chi-square tests were used to compare the distributions of categorical variables.

Kaplan-Meier survival plots were constructed to describe the effect of anemia and hemoconcentration on 180-day mortality, and the observed differences in survival rates were tested for by using the log-rank test. The associations

Table 1 Baseline Characteristics

Variables	Total (n = 1,969)	Nonanemic (n = 978)	Anemic (n = 991)	p Value
Demographics				
Age, yrs	70.0 ± 11.6	68.5 ± 11.9	71.6 ± 11.1	<0.01
Gender (% male)	67.0	63.5	70.5	<0.01
Race (% white)	94.6	96.0	93.1	<0.01
Measurements				
Systolic BP, mm Hg	124.4 ± 17.6	124.9 ± 17.4	124.0 ± 17.9	0.28
Diastolic BP, mm Hg	73.8 ± 11.8	76.0 ± 11.3	71.6 ± 12.0	<0.01
Heart rate, beats/min	80.0 ± 15.4	82.6 ± 15.6	77.4 ± 14.8	<0.01
LVEF,* %	32.2 ± 13	30.9 ± 12.3	33.3 ± 13.5	<0.01
Height, cm	168.5 ± 9.2	168.3 ± 9	168.8 ± 9.5	0.21
Weight, kg	81.8 ± 19.2	81.0 ± 18.8	82.5 ± 19.7	0.08
Laboratory				
Hemoglobin, g/dl	12.7 ± 1.9	14.2 ± 1.3	11.2 ± 1.1	<0.01
Hematocrit, %	40.2 ± 6.1	44.5 ± 4.8	35.9 ± 3.9	<0.01
Albumin, g/dl	3.8 ± 0.4	3.9 ± 0.4	3.8 ± 0.4	<0.01
NT-proBNP,† pg/ml	3,000 (834)	3,000 (294)	3,000 (1410)	0.12
BNP,† pg/ml	1,258 (1398)	1,281 (1293)	1,234 (1451)	0.88
BUN, mmol/l	34.0 ± 17.6	29.3 ± 12.8	38.8 ± 20.2	<0.01
Creatinine, mg/dl	1.5 ± 0.6	1.4 ± 0.5	1.7 ± 0.6	<0.01
eGFR, ml/min	50.6 ± 20.2	55.2 ± 20.2	46.0 ± 19.1	<0.01
Medical history, %				
Heart failure	94.9	94.9	94.9	0.97
Ischemic heart disease	69.5	65.5	73.6	<0.01
Hypertension	79.6	77.1	82.0	<0.01
COPD or asthma	19.8	17.4	22.3	<0.01
Diabetes mellitus	45.8	36.2	55.3	<0.01
Atrial fibrillation	54.1	54.5	53.8	0.77
Treatment before admission, %				
ACEI	61.9	67.1	56.8	<0.01
ARB	16.1	12.7	19.4	<0.01
Beta-blocker	76.7	74.7	78.7	0.04
Aldosterone blocker	44.0	46.3	41.7	0.04
Digoxin	28.4	31.8	25.0	<0.01
Treatment after admission, %				
Total IV loop diuretic‡	280 (434)	240 (340)	320 (520)	<0.01

Values are mean ± SD, proportion (%) or median (interquartile range). *The ejection fraction was reported if it was available within 6 months before admission. Data were available for 944 patients. †Either a brain natriuretic peptide (BNP) level of 500 pg/ml or more or an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 2,000 pg/ml or more was required for enrollment. A point-of-care device for measuring the level of NT-proBNP was provided to study sites if needed, but measurements of more than 3,000 pg/ml were not quantified, which explains the median values of 3,000 pg/ml. The BNP level was measured in 528 patients, and the NT-proBNP level was measured in 1,466 patients. ‡Total dose of intravenous loop diuretics (in furosemide dose equivalents) administered from randomization through day 7 or discharge, if earlier.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; IV = intravenous; LVEF = left ventricular ejection fraction.

between baseline hemoglobin and outcome and the absolute change in hemoglobin between day 7 and baseline and outcome were subsequently assessed on a continuous scale by including both of these variables as linear terms in Cox regression models (after possible nonlinearity in these relationships were tested for by using fractional polynomials). To explore whether the associations between these 2 features of the subject-specific hemoglobin profiles and 180-day mortality were independent of other variables known to affect outcome in AHF, the following variables were adjusted for in the multivariable analyses: age, creatinine, blood urea nitrogen, systolic blood pressure, albumin, sodium, bicarbonate, pulmonary rales, New York Heart Association (NYHA) functional class 1 month before admission, previous HF hospitalization, glucose, NT-proBNP, weight change between day 4 and baseline, residual congestion (presence of rales and/or edema at day 7), and diuretic dose. NYHA class was included as a categorical variable using dummy coding. Variables that were skewed were log-transformed, and NT-proBNP was additionally truncated at 3,000 pg/ml, the upper detection limit of the point-of-care device that was, if needed, provided to the study sites. Patients with missing covariate values (including all subjects with a BNP measurement) were excluded, resulting in a

Table 2 Characteristics of Patients With and Without Hemoconcentration

Variables	Total (n = 1,969)	No Hemoconcentration (n = 609)	Hemoconcentration (n = 1,360)	p Value
Demographics				
Age, yrs	70.0 ± 11.6	70.3 ± 11.9	69.9 ± 11.4	0.51
Gender (% male)	67.0	66.2	67.4	0.58
Measurements				
Systolic BP, mm Hg	124.4 ± 17.6	124.5 ± 17.3	124.4 ± 17.8	0.92
Diastolic BP, mm Hg	73.8 ± 11.8	73.8 ± 11.7	73.8 ± 11.9	1.0
Heart rate, beats/min	80.0 ± 15.4	79.7 ± 15.9	80.1 ± 15.2	0.63
LVEF, %	32.2 ± 13	32.2 ± 13.4	32.2 ± 12.9	0.99
Height, cm	168.5 ± 9.2	167.9 ± 9.4	168.8 ± 9.1	0.05
Weight, kg (baseline)	81.8 ± 19.2	81.2 ± 19.3	82.0 ± 19.2	0.37
Change in weight,* kg	−2.9 ± 3.2	−2.3 ± 2.9	−3.1 ± 3.3	<0.01
Change in weight,† %	−3.5 ± 3.5	−2.8 ± 3.4	−3.7 ± 3.6	<0.01
Residual congestion, %	45.0	53.2	41.1	<0.01
Laboratory				
Hemoglobin, g/dl (baseline)	12.7 ± 1.9	12.7 ± 2.0	12.6 ± 1.8	0.39
Hemoglobin, g/dl (day 7)	13.0 ± 2.0	12.3 ± 1.9	13.2 ± 1.9	<0.01
Change hemoglobin,‡ g/dl	0.3 ± 0.7	−0.4 ± 0.4	0.6 ± 0.5	<0.01
Hematocrit, % (baseline)	40.2 ± 6.1	41.2 ± 6.3	39.7 ± 6.0	<0.01
Hematocrit, % (day 7)	41.1 ± 6.5	38.3 ± 6.1	42.4 ± 6.3	<0.01
Change hematocrit,‡ %	2.4 ± 10.1	−6.2 ± 6.5	6.8 ± 8.7	<0.01
Albumin, g/dl (baseline)	3.8 ± 0.4	3.9 ± 0.5	3.8 ± 0.4	<0.01
Albumin, g/dl (day 7)	3.9 ± 0.5	3.7 ± 0.4	3.9 ± 0.4	<0.01
Change albumin,‡ %	1.2 ± 11.2	−3.9 ± 8.2	3.6 ± 11.7	<0.01
Creatinine, mg/dl (baseline)	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.6	<0.01
Creatinine, mg/dl (day 7)	1.6 ± 0.7	1.6 ± 0.7	1.6 ± 0.7	0.15
Change creatinine,‡ %	5.3 ± 26.0	3.1 ± 26.4	6.4 ± 25.8	0.01
eGFR, ml/min (baseline)	50.6 ± 20.2	48.3 ± 19.5	51.6 ± 20.4	<0.01
BUN, mmol/l (baseline)	34.0 ± 17.6	36.5 ± 18.9	32.9 ± 16.8	<0.01
NT-proBNP, pg/ml (baseline)	3,000 (834)	3,000 (1,071)	3,000 (697)	0.51
BNP, pg/ml (baseline)	1,258 (1,398)	1,303 (1,469)	1,237 (1,386)	0.41
Treatment before admission, %				
ACEI	61.9	63.1	61.4	0.50
ARB	16.1	15.3	16.4	0.52
Beta-blocker	76.7	77.3	76.5	0.67
Aldosterone blocker	44.0	40.6	45.5	0.04
Digoxin	28.4	27.4	28.8	0.52
Treatment after admission (%)				
Total IV loop diuretics§	280 (434)	300 (492)	260 (380)	<0.01
Rolofylline, %	66.8	64.7	67.8	0.18

Values are mean ± SD, proportion (%) or median (interquartile range). *Change in weight between day 4 and baseline (absolute change). †Change in weight between day 4 and baseline (as % from baseline). ‡Change between day 7 and baseline. §Total dose of intravenous loop diuretics (in furosemide dose equivalents) administered from randomization through day 7 or discharge, if earlier.

Abbreviations as in Table 1.

total sample size of 1,046 patients for the adjusted analysis. The increase in added predictive value as a result of adding those elements of the subject-specific hemoglobin trajectories that were significantly associated with 180-day mortality to a Cox regression model containing all the other risk factors was examined by calculating the integrated discrimination improvement.

Results

Patient characteristics. Baseline characteristics of patients with and without anemia are shown in Table 1. According to the WHO guidelines, 50.3% of the patients were anemic. Hemoglobin levels <12.5 g/dl were observed in 48.2% of the patients, whereas 7.4% of the patients were severely anemic (hemoglobin <10.0 g/dl).

Hemoconcentration was seen in 69.1% of the patients. Table 2 shows the clinical characteristics of patients with and without hemoconcentration. Patients with an increase in hemoglobin showed similar patterns in albumin and hematocrit, which both significantly increased after 1 week ($p < 0.01$). Weight decreased during the first 4 days by 2.9 ± 3.2 kg and was more pronounced in patients with hemoconcentration ($p < 0.01$). Absolute change in hemoglobin weakly correlated with absolute weight loss and percentage of weight loss (both $rs = -0.16$, $p < 0.001$). Hemoconcentration was associated with a better renal function at baseline. In patients with hemoconcentration, the deterioration in renal function during the first week was more pronounced compared with patients with no hemoconcentration (percent change in creatinine +6.4 ± 26 vs. +3.1 ± 26; $p = 0.01$). Furthermore, in order to understand which factors play an important role in changes in renal function, we investigated factors associated with changes in renal function. Overall renal function deteriorated during the first week in 46% of the patients. A decrease in renal function was associated with older age ($p = 0.01$) and lower hemoglobin levels at baseline ($p < 0.01$). In addition, patients with a decrease in renal function were characterized by a higher increase in hemoglobin levels during the first week compared to patients with an increase in renal function (+0.38 ± 1.2 vs. +0.16 ± 1.1; $p < 0.01$). Total dose of administered diuretics was lower in patients with hemoconcentration ($p < 0.01$). Patients with hemoconcentration were more often treated with rolofylline (65% vs. 68%); however, this difference was not significant ($p = 0.18$).

Average evolution of hemoglobin over time. Figure 1 shows the average hemoglobin trajectory of the population. During hospitalization, hemoglobin levels increased on average by 0.3 ± 0.7 g/dl during the first week. To explore which clinical variables were associated with changes in the hemoglobin trajectory, we performed an interaction analysis. This revealed that a better baseline renal function was significantly associated with a steeper increase of the hemoglobin trajectory over time ($p = 0.02$ for the interaction between eGFR and the quadratic slope component; $p < 0.01$ for the interaction between eGFR and the linear slope component). Furthermore, a greater decrease in weight during the first 4 days of admission was associated with a steeper increase of the hemoglobin trajectory ($p \leq 0.01$ for both interaction terms). Age, sex, and treatment with rolofylline did not influence the average evolution of hemoglobin over time. We did find that baseline hemoglobin levels were on average 0.41 g/dl higher in male patients compared with female patients ($p < 0.01$).

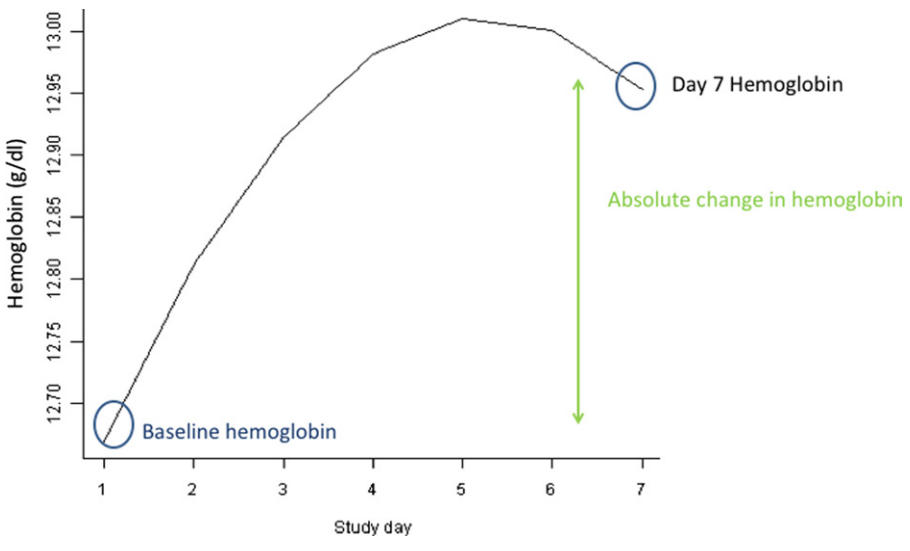
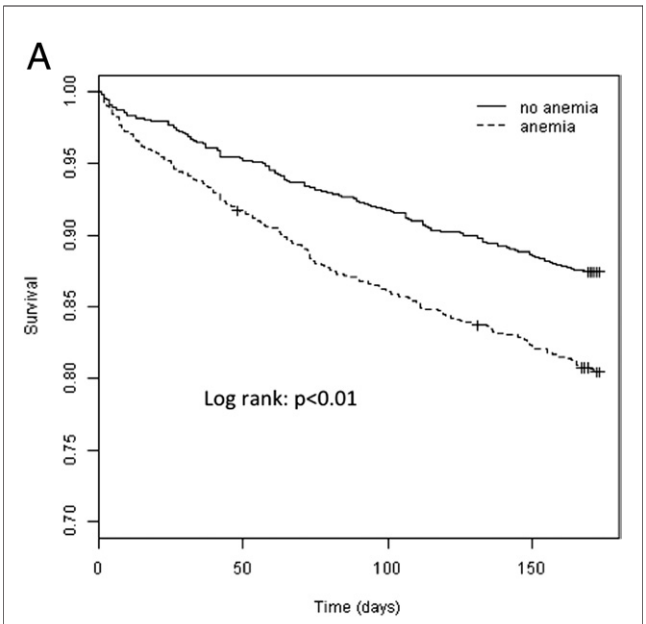


Figure 1 Hemoglobin Changes During the First Week

Linear effects model with the average change in hemoglobin over time for the total cohort.

JACC Vol. 61, No. 19, 2013
May 14, 2013:1973–81



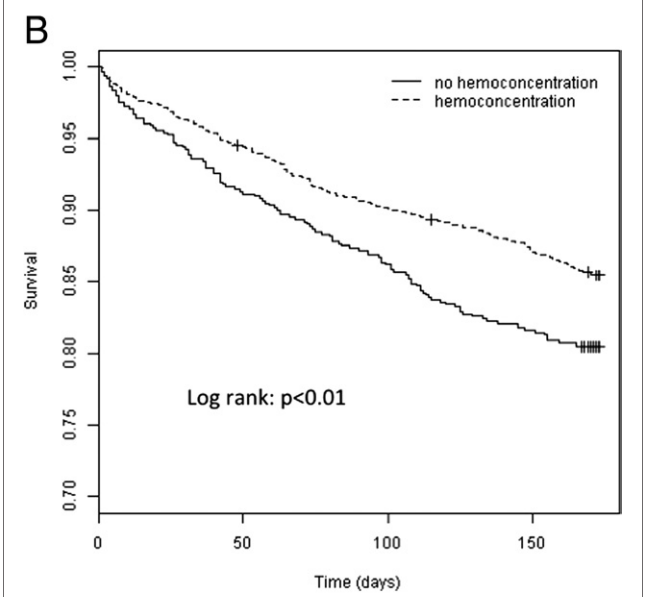


Figure 2 Survival Analysis 180 Mortality

(A) Kaplan-Meier survival curve stratified for anemia at baseline. **(B)** Curve stratified for the absence or presence of hemoconcentration between day 7 and baseline.

Subject-specific hemoglobin trajectories and outcome. During 180 days follow-up, 359 patients (18.2%) died. Kaplan-Meier curves revealed that no anemia at baseline and hemoconcentration were both associated with significantly lower 180-day mortality (Figs. 2A and 2B, respectively). There was no significant difference between outcome in patients with moderate (hemoglobin: 10 to 12.5 g/dl) and severe anemia (hemoglobin <10 g/dl; p = 0.16). Baseline hemoglobin levels and the absolute change in hemoglobin between day 7 and baseline were associated with a reduction in 180-day mortality in univariable Cox-regression analysis (Table 3). After including both components of the subject-specific hemoglobin trajectories in a multivariable model and correcting for other known risk factors in AHF, only the absolute change in hemoglobin predicted 180-day mortality (hazard ratio: 0.66; 95% confidence interval: 0.51 to 0.86; p = 0.002), whereas baseline hemoglobin concentration did not. Baseline hemoglobin lost its predictive power after adjustment for renal function and age. Figure 3 shows the plot of the mortality risk against the change in hemoglobin relative to a patient with stable hemoglobin levels. In order to study the incremental predictive value, we added change in hemoglobin to the final model (age, creatinine, blood urea nitrogen, systolic blood pressure albumin, sodium, bicarbonate, pulmonary rales at baseline, NYHA functional class 1 month before admission, previous HF hospitalization, glucose, NT-proBNP, change in weight, residual congestion, and diuretic dose). Absolute change in hemoglobin improved the integrated discrimination improvement significantly by 1.2% (p = 0.033).

Discussion

In patients admitted with AHF and renal dysfunction, anemia at presentation is not related to a poorer outcome, but a larger increase in hemoglobin during hospitalization is related to improved 180-day survival. Most of the data on anemia in heart failure are derived from cohorts of patients with chronic HF (1, 2, 13). From these studies, we know that anemia is common, with percentages ranging from 15% to 50% depending on the severity of HF and the definition of anemia. In a meta-analysis comprising 34 studies and more than 150,000 patients, one-third of the patients were considered anemic (2). Only a few studies have analyzed the prevalence and consequences of anemia in patients with AHF. Prevalence of anemia, in all studies defined as hemoglobin <12 g/dl, ranged from 31% in the study of Tarantini et al. (14) to 50% in the study of Young et al. (15). The results of the present study are comparable to these findings. Taken together, it is clear that anemia is more prevalent in patients presenting with AHF, compared with patients with chronic HF. However, there are discrepancies between the different studies regarding the prognostic value of anemia. Silva et al. (16) found that anemia in patients with AHF is not associated with an impaired outcome, whereas both Young et al. (15) and Tarantini et al. (14) found an independent association with in hospital mortality and HF readmissions. In the present study, baseline hemoglobin levels were not independently associated with 180-day mortality. Baseline hemoglobin concentration lost its statistical power after adjustment for renal function and age, emphasizing that these factors determine prognosis to a larger extent. The reason for these differences might be related to the endpoint, in hospital mortality versus 180-day mortality, or the more sensitive statistical approach, hemoglobin as a continuous variable versus a dichotomous analysis and the inclusion of the hemoglobin trajectory in the

Table 3 Unadjusted and Adjusted HRs for 180-Day All-Cause Mortality

	Unadjusted			Adjusted		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Hemoglobin, per g/dl (baseline)	0.87	0.82–0.92	<0.001	0.99	0.90–1.09	0.88
Change hemoglobin,* per g/dl	0.62	0.52–0.73	<0.001	0.66	0.51–0.86	0.002

*Change in hemoglobin between day 7 and baseline. Adjusted hazard ratios (HRs) are after correction of age, creatinine, blood urea nitrogen, systolic blood pressure, sodium, bicarbonate, albumin, glucose, New York Heart Association functional class 1 month prior to index hospitalization, heart failure hospitalization in the last year, pulmonary rales, residual congestion, N-terminal pro–B-type natriuretic peptide total intravenous diuretic dose.
CI = confidence interval.

statistical model. In contrast, findings of the recent study by Waldum et al. (17) are in line with our findings. They observed that in patients with severe heart failure (NYHA functional class IIIb or IV), baseline anemia did not predict outcome. Their population might be more comparable with the present study.

The differences in prevalence of anemia in chronic HF versus AHF might be related to the etiology of anemia. The role of fluid overload in the etiology of anemia has been established in patients with chronic HF. For example, Westenbrink et al. showed that anemic chronic HF patients have an elevated extracellular volume (ECV), which is related to lower hemoglobin levels (18), especially in the setting of impaired renal function. Impaired renal perfusion in chronic HF causes activation of the renin-angiotensin system, resulting in salt and fluid retention and consequently increases in ECV. Furthermore, elevated levels of antidiuretic hormone may lead to fluid retention. This retention of fluid in chronic HF causes hemodilution, which may result in pseudoanemia. This pseudoanemia might even carry a worse prognosis than in patients with true anemia (anemic patients in which ECV levels are within the normal range) (19). In these studies, anemic HF patients received higher doses of diuretics but nevertheless displayed elevated ECV. Importantly, although fluid retention was related to anemia, signs and symptoms of fluid retention were absent. Thus, hemodilution seems to precede the clinical presentation of fluid overload.

In the present study, the rate of hemoconcentration was clearly associated with a greater weight loss in the first 4 days and a better renal function at baseline. The finding that absolute levels of hemoglobin in patients with AHF do not predict outcome suggests that anemia itself in AHF might be mostly driven by fluid overload and that response to

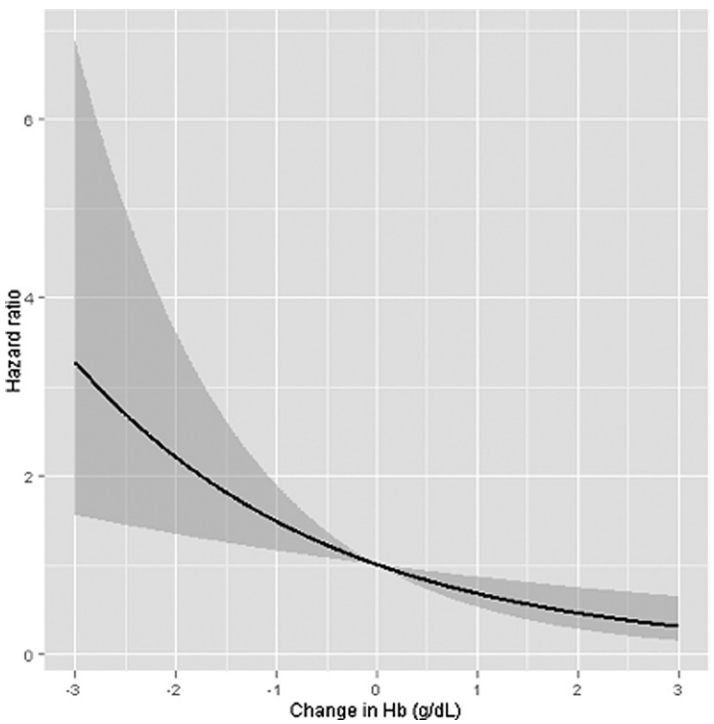


Figure 3 Mortality and Changes of Hemoglobin Levels

Plot of the mortality hazard ratio **(solid line)** and 95% confidence interval **(dark gray area)** against the change in hemoglobin relative to a patient with stable hemoglobin levels.

JACC Vol. 61, No. 19, 2013
May 14, 2013:1973–81

diuretics explains the finding that absolute change in hemoglobin predicts outcome. Adenosine A1 receptor antagonists have been studied in patients presenting with AHF. Initial studies showed a beneficial effect on diuresis and renal protection. In 2 post hoc studies of the PROTECT trial, it was observed that treatment with rolofylline, an adenosine A1 receptor antagonist, was associated with more weight loss compared with placebo (20,21). However, despite a greater weight loss, randomization to rolofylline was not associated with an increased rate of hemoconcentration.

Study limitations. The etiology of anemia in heart failure is diverse, and we do not have data on hematinic deficiencies or measurements of extracellular volume. We only assessed hemoglobin levels during the first week. Whether hemoglobin levels remain relatively stable after this period is unknown. Natriuretic peptides were only measured at baseline and not during follow-up. We have no data on feeding status of the patients. It is known that fasting or a very low calorie diet leads to natriuresis, which may have an effect on hemoconcentration and weight change (22). Furthermore, we performed a post hoc analysis of the PROTECT trial that was designed to study the effect of rolofylline in AHF patients with renal impairment. Therefore, it remains unknown if our findings are applicable to all patients with AHF.

Conclusions

From the clinical perspective, besides hemoglobin measurements, other bedside variables of volume status are available, including weight change and urinary output minus intake. The latter is notoriously unreliable in the clinical setting. In addition, fluid balance and weight changes both reflect intravascular as well as extravascular fluid status. In contrast, hemoconcentration itself gives information specifically on intravascular fluid status and one might speculate that it is this component that in part drives the slight decrease in renal function during decongestion. The present study emphasizes that this moderate decrease in renal function during decongestion does not negatively impact prognosis. These findings are in line with the results of the DOSE (Diuretic Optimization Strategies Evaluation) trial, which investigated the effect of high- versus low-dose diuretics in AHF (23). In this trial, more aggressive decongestion was associated with a slight decrease in renal function, but resulted in a greater relief of dyspnea and fewer serious adverse events. However, long-term effects from this study are unknown. The finding of our study that hemoconcentration is associated with an improved outcome, despite a slight decrease in renal function, adds to this.

Patients with AHF and preserved renal function are decongested better, as shown by an increase in hemoglobin. A rapid increase in hemoglobin during the first week is independently associated with a favorable outcome, despite a small decrease in renal function.

Reprint requests and correspondence: Dr. Adriaan A. Voors, Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands. E-mail: a.a.voors@umcg.nl.

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