Effect of Hemoglobin Levels on Cardiovascular Outcomes in Patients with Isolated Systolic Hypertension and Left Ventricular Hypertrophy (From the LIFE Study)

Marianne L. Smebye[a], Emil K. Iversen[a], Aud Høieggen, MD[a], Arnljot Flaa, MD[a], Ingrid Os, MD[a], Sverre E. Kjeldsen, MD, PhD[a,b], Michael Hecht Olsen, MD, PhD[c], Arghya Chattopadhyay, PhD[d], Darcy A. Hille, MS, EMBA[d], Paulette A. Lyle, BS[d], Richard B. Devereux, MD[e], Björn Dahlöf, MD, PhD[f].

From [a]Departments of Nephrology and Cardiology, University of Oslo Ullevaal Hospital, Oslo, Norway; [b]Department of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA; [c]Glostrup University Hospital, Glostrup, Denmark; [d]Merck Research Laboratories, Upper Gwynedd, Pennsylvania, USA; [e]Department of Cardiology, Weill Medical Center of Cornell University, New York, New York, USA; and [f]Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

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Correspondence to Aud Høieggen, Department of Nephrology, University of Oslo Ullevaal Hospital, N-0407, Oslo, Norway. Telephone: 472 211 9101. Fax: 472 211 9181. E-mail: aud.hoieggen@ioks.uio.no

Running title: LIFE hemoglobin and ISH

Abstract

The optimal hemoglobin level in patients with hypertension or heart failure is not yet defined. The aim of the present investigation was to examine the relation of hemoglobin with cardiovascular outcomes in high-risk patients with isolated systolic hypertension (ISH) and left ventricular hypertrophy (LVH). In 1326 patients with ISH in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, hemoglobin and cardiovascular outcomes were examined using Cox proportional hazard models. Baseline hemoglobin was negatively related to the rate of cardiovascular death (hazard ratio 0.81 [95% CI 0.67-0.98] per 1 g/dL, p = 0.032) after adjusting for baseline Framingham risk score (FRS), LVH, treatment, and estimated glomerular filtration rate (eGFR). Hemoglobin decreased slightly during the study and the decline was more pronounced in the losartan group (13.9 ± 1.3 g/dL to 13.6 ±1.4 g/dL) than in the atenolol group (13.9 ± 1.2 g/dL to 13.8 ± 1.4 g/dL). Hemoglobin as a time-varying covariate was negatively associated with the rate of cardiovascular death (hazard ratio 0.75 [0.63-0.90], p < 0.001) and stroke (hazard ratio 0.84 [0.72-0.99], p = 0.040), after adjusting for baseline FRS, LVH, treatment, and eGFR. In conclusion, in this high-risk population with ISH and LVH, lower hemoglobin at baseline was associated with higher probability of cardiovascular death, and fall in hemoglobin over time was associated with higher probability of cardiovascular death or stroke and this effect was attenuated by treatment with losartan.

Key words: cardiovascular risk, hemoglobin, hypertension, isolated systolic hypertension, left ventricular hypertrophy

Introduction

Hemoglobin can effect peripheral vascular resistance in 2 ways according to the Poiseuille-Hagen equation: primarily by influencing the viscosity of blood,[1] and secondarily by affecting the caliber of peripheral arterioles.[2] High hemoglobin levels have been related to increased cardiovascular risk[3] and may induce left ventricular hypertrophy (LVH) in patients with hypertension.[4] On the other hand, low hemoglobin levels are also associated with cardiovascular risk. The potentially harmful effect of anemia has been shown in the general population[5] and in patients with heart failure.[6] Little is known about hemoglobin levels and cardiovascular outcome in the hypertensive population. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the effects of losartan were compared with atenolol in the context of comparable blood-pressure lowering.[7] The aim of the present study was to investigate the relation between hemoglobin and cardiovascular outcomes in this prespecified group of well-characterized hypertensive subjects with high cardiovascular risk.

Methods

Study design and organization: The LIFE study was a prospective, multinational, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group study. The primary objective was to evaluate the long-term effects of losartan- compared with atenolol-based antihypertensive therapy in patients with hypertension and electrocardiographically (ECG) documented LVH on the incidence of cardiovascular morbidity and mortality. The LIFE study design, organization, clinical measures, endpoint definitions, basis for choice of comparative agents, statistical power calculations, recruitment details, baseline characteristics, 1-year follow-up, and primary results have been published.[7-11] Hemoglobin levels were obtained at baseline

immediately prior to randomization and at annual clinic visits. The trial protocol was approved by local ethics committees and performed in accordance with the Declaration of Helsinki. The study was overseen by an independent data and safety monitoring board. All participants gave written informed consent.

Target population and treatment schedule: Persons aged 55 to 80 years with previously treated or untreated hypertension and ECG evidence of LVH were enrolled in the LIFE study. Those with secondary hypertension; myocardial infarction or stroke within the previous 6 months; angina pectoris requiring treatment with β-blockers or calcium antagonists; active heart failure or known left ventricular ejection fraction 40%; or a disorder that, according to the treating physician's opinion, required treatment with open-label study medication or related drugs were excluded. Also excluded were patients with serum creatinine >1.8 mg/dL (160 μmol/L), a solitary kidney, or kidney transplant. Eligible persons were randomly assigned to losartan- or atenolol-based regimens after 1 or 2 weeks of placebo if trough sitting blood pressures were 160-200 mm Hg systolic, 95-115 mm Hg diastolic, or both. In this analysis, the patients had trough sitting blood pressure between 160-200 mm Hg systolic with diastolic pressure <90 mm Hg.[12] From July 6, 1995, through May 2, 1997, a total of 1326 patients with ISH were randomized to treatment in the LIFE study.[12] Patients were followed for 4 or more years with regular visits and upward titration of medication to reach a goal systolic blood pressure of <140 mm Hg. Only 2 patients (0.2%) with ISH were lost to follow-up.

ECG coding and LVH criteria: All ECGs were evaluated at a central core reading center for LVH criteria and Minnesota Codes. ECG-LVH was measured using gender-adjusted Cornell product criteria (RaVL + SV3 [+6 mm in women] x QRS duration) >2440 mm•msec or Sokolow-Lyon voltage (S_{V1} + $RV_{5/6}$) >38 mm.[8, 13-15]

Outcome measures: The primary endpoint was a composite of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction. Other prespecified outcome measures were components of the primary composite endpoint, total mortality, hospitalization for angina pectoris, hospitalization for heart failure, coronary or peripheral revascularization procedures, resuscitated cardiac arrest, and new-onset diabetes mellitus.[7] Routine laboratory tests were performed in 2 central laboratories. The study ran its full course and endpoint follow-up was stopped on September 16, 2001.[7]

Statistical methods: The prespecified data analysis plan for the LIFE study highlighted ISH as being of particular interest and indicated that all endpoint analyses were to be performed in this subgroup. The study of the effect of hemoglobin in the ISH population is post hoc. Hemoglobin level is expressed as mean (standard deviation). All cardiovascular endpoints and blood pressures were analyzed using the intention-to-treat approach. Participants who experienced >1 endpoint were counted as having an event in all relevant endpoint analyses; however, only the first event in a specific category was counted in individual analyses. The associations between hemoglobin and cardiovascular outcomes were examined using Cox proportional hazard models using hemoglobin as a continuous variable or stratified by hemoglobin quintiles. The models were adjusted for Framingham risk score, LVH, treatment, and estimated glomerular filtration rate (eGFR) calculated by using the abbreviated Modification of Diet in Renal Disease study (MDRD) equation.[16] The time-varying hemoglobin analyses included all of the hemoglobin values that were observed before an endpoint and the time between those values as covariates in the Cox regression models.

Results

Patient characteristics: Of the 9193 patients participating in the LIFE study, 1326 fulfilled the criteria necessary for inclusion in this analysis. Patients did not have serious renal dysfunction (baseline mean serum creatinine 0.98 ± 0.23 mg/dL [86.9 ± 20.2 μmol/L]). Compared with the overall LIFE population, patients in the LIFE ISH subgroup were older, had lower diastolic blood pressure, and higher prevalences of coronary heart disease, cerebrovascular disease, peripheral vascular disease, atrial fibrillation, and diabetes at baseline. The mean age was 70 ± 6 years; 60% of patients were women; 92% were white and 6% black; 18% had diabetes; and mean blood pressure was 174 ± 11/83 ± 6 mm Hg. When anemia was defined as hemoglobin <13.8 g/dL for males or <12.1 g/dL for females, the distribution of baseline anemia was significantly different ($p < 0.0001$) between males and females: 23.6% (111 out of 470) of males and 7.6% (55 out of 722) of females had anemia at baseline. Additional baseline characteristics for the ISH subgroup are presented in Table 1, and are similar in the losartan and atenolol groups. Cardiovascular events and treatment effects in the ISH subgroup of LIFE have been published.[12] The treatment benefits of losartan were more pronounced for the primary composite endpoint, cardiovascular death, and stroke than for myocardial infarction.

Hemoglobin and endpoints: Hemoglobin decreased in both treatment groups during the study, more so in the losartan group (13.9 ± 1.3 g/dL to 13.6 ± 1.4 g/dL) than in the atenolol group (13.9 ± 1.2 g/dL to 13.8 ± 1.4 g/dL) (Figure 1).

Baseline hemoglobin was negatively related to the rate of cardiovascular death (hazard ratio 0.81 [95% CI 0.67-0.98] per 1 g/dL, $p = 0.032$) after adjusting for baseline Framingham risk score, treatment LVH, and eGFR. Results were also examined by quintiles of baseline hemoglobin level, where the reference group was the lowest quintile of hemoglobin (12.9 g/dL) (Figure 2). There were negative relations between hemoglobin levels at baseline over the range of levels observed in this study and the

primary composite endpoint, cardiovascular death, and stroke, but there was a minimally higher rate of myocardial infarction in the highest hemoglobin quintile (Figure 2). Hemoglobin as a time-varying covariate was negatively associated with the rate of cardiovascular death (hazard ratio 0.75 [0.63-0.90], $p < 0.001$) and stroke (hazard ratio 0.84 [0.72-0.99], $p = 0.040$) after adjusting for baseline Framingham risk score, LVH, treatment, and eGFR (Table 2). These associations were also significant for the unadjusted analysis for cardiovascular death, and for the primary composite endpoint, stroke, and cardiovascular death when adjusted for baseline Framingham risk score and LVH (Table 2).

Discussion

In the present investigation of high-risk patients with ISH and LVH, we found that lower hemoglobin during follow-up was significantly related to a higher rate of the LIFE primary composite endpoint of cardiovascular death, fatal and non-fatal stroke, and fatal and non-fatal myocardial infarction, after adjustment for Framingham risk score and LVH. Lower follow-up hemoglobin was of borderline significance when treatment and eGFR were also added to the model. Lower follow-up hemoglobin was significantly related to cardiovascular death and stroke in both sets of covariate adjustments (i.e., Framingham risk and LVH with or without treatment and eGFR). When considered separately with adjustment for covariates, a 25% lower relative risk of cardiovascular death and a 19% lower risk of stroke was detected per g/dL higher hemoglobin. The association of higher hemoglobin with fewer cardiovascular events did not show a clear threshold level in this population, nor was any U- or J-shaped relation detected. The patients treated with the losartan-based regimen had a larger decrease in hemoglobin than the patients on the atenolol-based regimen, consistent with the results of Robles *et al.*[17]. The statistical significance of benefits associated with losartan-based therapy previously reported in

the LIFE ISH substudy[12] was sustained or even modestly enhanced in the present analyses that also took time-varying hemoglobin into account. In addition, the present results in the subset of the LIFE population with ISH confirm the finding of the association of low hemoglobin with several endpoints, including all-cause mortality, in a preliminary analysis of the entire LIFE study population.[18]

The World Health Organization defines anemia as hemoglobin concentration <13.0 g/dL for men and post-menopausal women, and <12.0 g/dL for pre-menopausal women.[19] Among otherwise healthy individuals, anemia is well tolerated because of compensating mechanisms, and optimal hemoglobin level is a matter of debate. Still, in the Atherosclerosis Risk in Communities (ARIC) study,[5] a clear relation between risk for cardiovascular disease and lower hemoglobin levels in both women and men was revealed. In chronic kidney disease, however, no benefit of complete correction of anemia has been seen.[20-21]

Some limitations to these analyses need to be mentioned. The LIFE study population was of older age and mainly white ethnicity. LIFE enrolled patients with hypertension and ECG-LVH, a population at high risk for cardiovascular events. Analyses of patients with ISH in LIFE are subgroup analyses of the LIFE population, although the ISH group was selected a priori as being of special interest.

In conclusion, while lower hemoglobin at baseline or fall in hemoglobin over time are associated with higher probability of outcomes, this was attenuated by treatment with losartan in the LIFE study. This observation does not suggest that attempting to increase hemoglobin in this cohort is warranted. This analysis confirms previous studies that describe lower hemoglobin, even at the low normal range, as an adverse prognostic sign.

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Figure 1. Summary of hemoglobin level at different time points by treatment.

Figure 2. Results obtained from Cox proportional hazard model with baseline hemoglobin quintiles and with adjustment for baseline Framingham risk score, treatment, and estimated glomerular filtration rate. Comparison is with the lowest quintile of hemoglobin (12.9 g/dL).

CI = confidence interval

Table 1

Baseline characteristics of LIFE patients with isolated systolic hypertension[12]

Variable	Losartan (n = 660)	Atenolol (n = 666)	All (n = 1326)
Age (years)	70.2 (6.4)	70.4 (6.3)	70.3 (6.3)
Female	388 (58.8%)	408 (61.3%)	796 (60.0%)
Ethnic origin			
White	606 (91.8%)	617 (92.6%)	1223 (92.2%)
Black	44 (6.7%)	37 (5.6%)	81 (6.1%)
Hispanic	5 (0.8%)	9 (1.4%)	14 (1.1%)
Asian	4 (0.6%)	2 (0.3%)	6 (0.5%)
Other	1 (0.2%)	1 (0.2%)	2 (0.2%)
Blood pressure (mm Hg)	174.2/83.0 (10.7/5.4)	174.5/82.3 (11.0/6.2)	174.4/82.6 (10.9/5.8)
Heart rate (beats/min)	71.5 (10.3)	71.5 (11.3)	71.5 (10.8)
Body mass index (kg/m^2)	27.2 (4.6)	27.7 (5.2)	27.5 (4.9)
Cornell voltage-duration product (mm•msec)	2771.9 (1077.8)	2820.2 (1157.0)	2795.6 (1118.1)
Sokolow-Lyon (mm)	30.8 (10.5)	31.4 (10.6)	31.1 (10.6)
Framingham risk score	0.230 (0.103)	0.238 (0.098)	0.232 (0.101)
Current smokers	95 (14.4%)	102 (15.4%)	197 (14.9%)
Previously untreated	233 (35.3%)	211 (31.7%)	444 (33.5%)
Coronary heart disease	158 (23.9%)	140 (21.0%)	298 (22.5%)
Cerebrovascular disease	70 (10.6%)	86 (12.9%)	156 (11.8%)
Peripheral vascular disease	57 (8.6%)	55 (8.3%)	112 (8.4%)
Atrial fibrillation	28 (4.2%)	39 (5.9%)	67 (5.1%)
Diabetes	103 (15.6%)	131 (19.7%)	234 (17.6%)
Hemoglobin (gm/dL)	13.86 (1.27)	13.90 (1.21)	13.88 (1.24)
Serum creatinine (micromol/L)	89.13 (22.27)	87.50 (19.91)	88.31 (21.12)
eGFR (mL/min/1.73 m^2)	70.21 (16.09)	70.36 (15.57)	70.29 (15.82)

eGFR = estimated glomerular filtration rate

Table 2

Effect of time-varying hemoglobin on cardiovascular endpoints

	Unadjusted HR (95% CI)	Adjusted for baseline FRS + LVH HR (95% CI)	Adjusted for baseline FRS + LVH+ treatment + eGFR HR (95% CI)
Primary composite endpoint	0.95 (0.84-1.07)	0.89 (0.79-1.00)	0.90 (0.80, 1.01)
	p=0.371	p=0.046	p=0.077
Cardiovascular death	0.83 (0.70-0.99)	0.79 (0.67-0.93)	0.75 (0.63-0.90)
	p=0.034	p=0.005	p=0.001
Stroke	0.87 (0.74-1.02)	0.83 (0.71-0.97)	0.84 (0.72-0.99)
	p=0.093	p=0.020	p=0.040
Myocardial infarction	1.08 (0.89-1.31)	1.02 (0.84-1.24)	1.02 (0.83-1.25)
	p=0.437	p=0.831	p=0.854

CI = confidence interval; eGFR = estimated glomerular filtration rate; FRS = Framingham risk score; HR = hazard ratio per g/dL of hemoglobin.

Figure 1. Summary of hemoglobin level (mean ± SD) at different time points by treatment

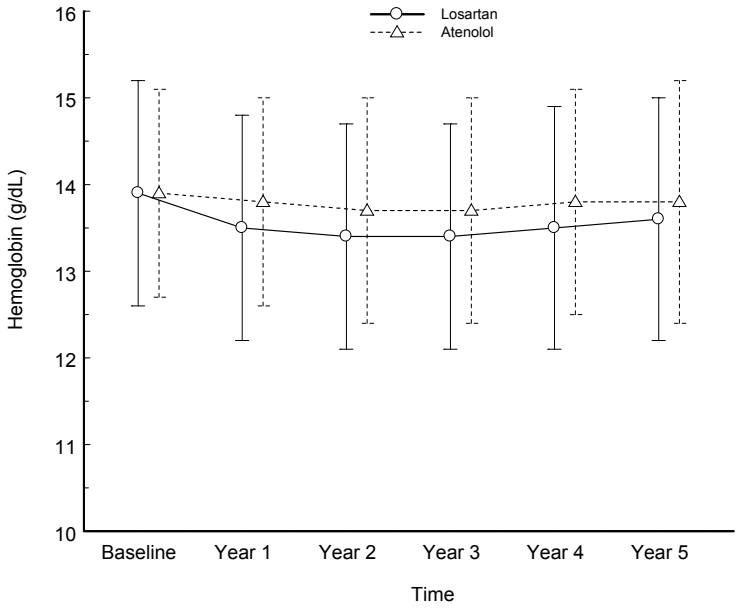

Figure 2. Results obtained from Cox proportional hazard model with baseline hemoglobin quintiles and with adjustment for baseline Framingham risk score, treatment, and estimated glomerular filtration rate. Comparison is with the lowest quintile of hemoglobin (12.9 g/dL).