

# Target Level for Hemoglobin Correction in Patients With Diabetes and CKD: Primary Results of the Anemia Correction in Diabetes (ACORD) Study

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**Background:** Patients with diabetes and anemia are at high risk of cardiovascular disease. The Anemia CORrection in Diabetes (ACORD) Study aimed to investigate the effect of anemia correction on cardiac structure, function, and outcomes in patients with diabetes with anemia and early diabetic nephropathy.

**Methods:** One hundred seventy-two patients with type 1 or 2 diabetes mellitus, mild to moderate anemia, and stage 1 to 3 chronic kidney disease were randomly assigned to attain a target hemoglobin (Hb) level of either 13 to 15 g/dL (130 to 150 g/L; group 1) or 10.5 to 11.5 g/dL (105 to 115 g/L; group 2). The primary end point was change in left ventricular mass index (LVMI). Secondary end points included echocardiographic variables, renal function, quality of life, and safety.

**Results:** Median Hb level and LVMI were similar in groups 1 and 2 (Hb, 11.9 and 11.7 g/dL [119 and 117 g/L]; LVMI, 113.5 and 112.3 g/m<sup>2</sup>, respectively). At study end, Hb levels were 13.5 g/dL (135 g/L) in group 1 and 12.1 g/dL (121 g/L) in group 2 ( $P < 0.001$ ). No significant differences were observed in median LVMI at month 15 between study groups (group 1, 112.3 g/m<sup>2</sup>; group 2, 116.5 g/m<sup>2</sup>). Multivariate analysis showed a nonsignificant decrease in LVMI ( $P = 0.15$ ) in group 1 versus group 2. Anemia correction had no effect on the rate of decrease in creatinine clearance, but resulted in significantly improved quality of life in group 1 ( $P = 0.04$ ). There were no clinically relevant differences in adverse events between study groups.

**Conclusion:** In patients with diabetes with mild to moderate anemia and moderate left ventricular hypertrophy, correction to an Hb target level of 13 to 15 g/dL (130 to 150 g/L) does not decrease LVMI. However, normalization of Hb level prevented an additional increase in left ventricular hypertrophy, was safe, and improved quality of life.

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**INDEX WORDS:** Diabetes; chronic kidney disease (CKD); left ventricular mass index; quality of life; renal function.

Diabetes has become the most common comorbid condition of end-stage renal disease in Europe and the United States.<sup>1,2</sup> In addition, diabetes is recognized as a major risk factor for cardiovascular disease,<sup>3,4</sup> and the risk is amplified further by the presence of diabetic nephropathy. Accordingly, patients with both end-stage renal disease and diabetes have a worse prognosis than those without diabetes.<sup>5</sup>

Left ventricular hypertrophy (LVH) is observed in approximately 75% of patients entering dialysis therapy, and in addition, other cardiovascular complications, such as chronic heart failure, coronary artery disease, and peripheral arterial disease, are common.<sup>6,7</sup> The burden of cardiovascular disease therefore is greater; consequently, survival rates are worse in patients with diabetes entering dialysis than in those without this condition.<sup>5,8,9</sup>

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Anemia is a common feature of renal disease and is associated with increased mortality in patients with chronic kidney disease (CKD), particularly those with diabetes.<sup>5</sup> Anemia also has an effect on left ventricular mass. For example, in a large prospective Canadian multicenter study, each decrease in hemoglobin (Hb) level of 0.5 g/dL (5 g/L) resulted in an increased odds ratio for left ventricular mass by 32%.<sup>10</sup> Anemia also is an independent predictor of non-elective hospitalization before and after initiation of renal replacement therapy.<sup>11,12</sup>

In patients with end-stage renal disease, treatment of anemia with recombinant human erythropoietin (epoetin) improves overall and cardiovascular event-free survival.<sup>11,13,14</sup> Observational studies suggested that early treatment of anemia in the predialysis stage of CKD has a beneficial effect on mortality after the patients are on dialysis therapy.<sup>15-17</sup> Two uncontrolled observational studies<sup>18,19</sup> and 1 small randomized controlled trial<sup>20</sup> showed that anemia correction with epoetin led to less rapid deterioration in renal function and prevention, or even regression, of LVH<sup>21-23</sup> in patients with advanced CKD. Furthermore, small-scale studies showed that epoetin treatment improved quality of life in patients with diabetes with anemia and early renal disease.<sup>24,25</sup>

In view of these observations, it was proposed that early and complete, as opposed to partial late, anemia correction would have beneficial effects on left ventricular mass index (LVMI), quality of life, and renal function in patients with diabetes with mild to moderate anemia and CKD.

The Anemia CORrection in Diabetes (ACORD) Study is designed to investigate the effects of anemia correction with epoetin beta (NeoRecormon; F. Hoffmann-La Roche Ltd, Basel, Switzerland) on cardiac structure, function, and clinical outcomes in patients with diabetes and CKD not yet on renal replacement therapy. The primary end point was the effect of early versus late treatment strategy for correction of renal anemia on LVH assessed by echocardiographic measurement of LVMI. Secondary objectives included the effect of early and complete anemia correction on left ventricular volumes, left ventricular function, renal function, and various other clinical parameters, including quality of life and, particularly, safety.

## METHODS

### Study Population

ACORD was an international, multicenter, randomized, open-label, parallel-group study involving 64 centers in 16 countries. The study was performed in accordance with the Declaration of Helsinki and guidelines for good clinical practice.<sup>26</sup> The study protocol was approved by the responsible ethical review boards at all participating centers.

The ACORD Study enrolled adult patients with type 1 or type 2 diabetes mellitus, mild to moderate anemia, and early-stage (stages 1 to 3) CKD. Major inclusion and exclusion criteria used to ascertain study eligibility are listed in Table 1. All patients gave written informed consent before inclusion in the study.

### Study Design

The ACORD Study design is shown in Fig 1. Eligible patients who fulfilled the stipulated inclusion and exclusion criteria were randomly assigned to receive either early and complete anemia correction to attain normal Hb levels (target Hb, 13 to 15 g/dL [130 to 150 g/L]; group 1) or partial anemia correction (target Hb, 10.5 to 11.5 g/dL [105 to 115 g/L]; group 2).

Randomization was performed centrally into 2 treatment groups by using a block-size randomization procedure stratified by country and use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. Patients in group 1 were started immediately on subcutaneous epoetin beta treatment to reach a target Hb level of 13 to 15 g/dL (130 to 150 g/L) within approximately 3 months. Patients in group 2 were started on subcutaneous epoetin beta treatment only when their Hb level had decreased to less than 10.5 g/dL (<105 g/L) on 2 consecutive visits at an interval of 2 weeks or if their Hb level decreased to less than 10 g/dL (100 g/L) at a single determination. The starting dose of subcutaneous epoetin beta in both groups was 2,000 IU once weekly, self-administered using the Reco-Pen (F. Hoffmann-La Roche Ltd) delivery device.

All patients had a clinical assessment at 6 weeks and 3 months after starting treatment and at 3-monthly intervals thereafter. In addition, during the correction phase of treatment, patients must have returned to the clinic every 2 weeks for assessment of Hb and any adjustment to epoetin beta dose necessary to achieve a rate of increase in Hb not exceeding 1 g/dL (10 g/L) every 4 weeks. The study was scheduled to end after each patient had completed 15 months of follow-up.

### Role of the Funding Source and Study Committees

The trial was designed, implemented, and overseen by a Study Steering Committee, together with representatives of the sponsor, F. Hoffmann-La Roche Ltd. The sponsor identified participating centers together with the Steering Committee and was responsible for monitoring the centers, data collection, and data cleaning. The statistical analysis plan was agreed with the Steering Committee before database closure. The Steering Committee was granted access to all study data. Interpretation of all study data was done in close collaboration between the Steering Committee and the sponsor.

**Table 1. Major Inclusion and Exclusion Criteria for the ACORD Trial****Major inclusion criteria**

Adults ( $\geq 18$  years) not yet requiring renal replacement therapy  
 Hb level of 10.5 to  $< 13$  g/dL at screening  
 Creatinine clearance  $\geq 30$  mL/min at screening  
 Diabetes mellitus (type 1/type 2) with stable glycemic control for at least 3 mo  
 One serum creatinine determination  $\geq 3$  mo before enrollment (in addition to screening)  
 Documented diabetic nephropathy (ie, by proteinuria, renal biopsy, or albuminuria and target-organ microangiopathy)  
 SBP  $\leq 140$  mm Hg, DBP  $\leq 90$  mm Hg at screening

**Major exclusion criteria**

Rapid progression of chronic renal failure (eg,  $> 20\%$  increase in serum creatinine in the 3 mo before enrollment)  
 Need for renal replacement therapy expected within 6 mo after enrollment  
 Documented evidence of nondiabetic renal disease; nephrotic syndrome  
 Chronic heart failure (New York Heart Association class III-IV)  
 Myocardial infarction, unstable angina, or stroke in the 3 mo before enrollment  
 Evidence of clinically significant valvular disease  
 Hemolysis  
 Vitamin B<sub>12</sub> or folic acid deficiency  
 Serum ferritin  $< 50$  ng/mL  
 Blood transfusions within the 3 mo before enrollment

*Note:* To convert Hb in g/dL to g/L, multiply by 10; ferritin in ng/mL to  $\mu$ g/L, multiply by 1; creatinine clearance in mL/min to mL/s, multiply by 0.01667.

Patient safety in the study was overseen by an independent data safety committee, which reviewed the data regularly. The data safety committee consisted of 3 experienced clinicians and an independent statistician (Appendix 1).

**Study End Points**

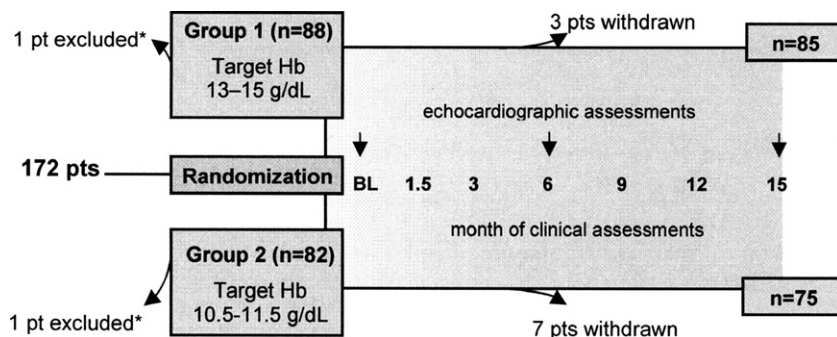
The primary end point of ACORD was change from baseline in LVMI at 15 months. Secondary end points included additional echocardiographic and clinical variables, such as left ventricular end-systolic and end-diastolic volumes, left ventricular ejection fraction (LVEF), and fractional shortening. Other echocardiographic variables, such as geometry of the left ventricle and effects on concentric or eccentric LVH, also were examined. Exploratory analyses included assessment of renal function at each scheduled visit and quality of life, assessed by using a self-administered 36-Item Short-Form Health Survey (SF-36) questionnaire at baseline and study end.<sup>27,28</sup> Renal function was assessed by estimating glomerular filtration rate by using the Cockcroft-Gault and simplified 4-variable Modification of Diet in Renal Disease formulae.<sup>27-30</sup> Echocardiographic measure-

ments were performed in accordance with recommendations of the American Society of Echocardiography at baseline, after 6 months, and at study end<sup>31</sup> (for details, see Appendix 2) and were assessed blinded for treatment by an independent central echocardiographic core laboratory (Cardio Analytics Ltd, Plymouth, UK).

Safety was assessed by continuous monitoring and collection of adverse events throughout the study. Vital signs and laboratory parameters (including complete hematology and blood chemistry test results) were collected at week 6, month 3, and every 3 months until study end.

**Statistical Analysis**

All primary, secondary, and exploratory analyses were based on the intent-to-treat principle. In addition, per-protocol analyses, which excluded major protocol violators, were conducted for the main efficacy variables. The primary end point (change in LVMI from baseline to study end) was analyzed by using analysis of covariance with treatment group as the main factor and baseline LVMI as covariate. For analysis of secondary echocardiographic end points,



**Figure 1.** Study design and patient (pt) disposition. \*Two patients from 1 center were excluded from all analyses because source verification for the laboratory could not be performed and the center was closed.

such as left ventricular end-systolic and end-diastolic volumes, LVEF, and fractional shortening, a similar covariance model was used with treatment group as the main factor and the respective baseline value as covariate.

For quality of life, mean total score on the SF-36 subscales at the end of the study were calculated, and analysis of covariance was performed using baseline as an independent cofactor. Other variables were analyzed qualitatively. Percentages of patients with stable Hb levels, as well as other comparisons between groups, were done by using chi-square test. All values are reported as mean  $\pm$  SD or median value with the respective range or interquartile range (IQR).

Sample-size calculation for ACORD was based on the primary outcome variable, LVMI. The expected mean change in LVMI from baseline to follow-up between the 2 study groups was 20 g/m<sup>2</sup>. With a sample size of at least 64 assessable patients per treatment arm, ACORD would have had 80% power to show this difference between study groups. Assuming a 20% dropout rate during the course of the study, it was calculated that recruitment of at least 160 patients (80 per treatment arm) was needed.

## RESULTS

### Patients and Baseline Characteristics

One hundred seventy-two patients were randomly assigned to the 2 treatment arms (group 1, 89 patients; group 2, 83 patients), of which 160 completed the study as planned (group 1, 85 patients; group 2, 75 patients; Fig 1). Two patients from a single center were randomly assigned, but were excluded from all analyses because the center was closed due to major violation of Good Clinical Practice guidelines.

Patient baseline characteristics are listed in Tables 2 and 3. In general, baseline characteristics were similar in the 2 groups. However, median body weight, body mass index, and creatinine clearance were significantly greater in group 1 compared with group 2. Furthermore, a greater

**Table 2. Patient Characteristics at Baseline**

	Group 1 Target Hb, 13-15 g/dL (n = 88)	Group 2 Target Hb, 10.5-11.5 g/dL (n = 82)	P
Sex (% men)	51	50	0.941
Age (y)	58 (49-69)	57 (47-66)	0.366
Weight (kg)*	75.6 (50.0-106.1)	70.0 (41.5-110.0)	0.009
Body mass index (kg/m <sup>2</sup> )	28.5 (24.9-30.7)	25.6 (23.1-29.5)	0.005
SBP (mm Hg)	134 (126-140)	133 (126-139)	0.886
DBP (mm Hg)	78 (70-80)	80 (71-80)	0.188
Type 1 diabetes (%)	27	35	0.291
Time since diagnosis (y)	20 (17-30)	24 (21-31)	0.174
Type 2 diabetes (%)	73	65	0.291
Time since diagnosis (y)	16 (11-21)	14 (9-19)	0.256
Diabetic retinopathy (%)	84	83	0.917
HbA <sub>1c</sub> (%)	8.2 (7.2-9.2)	7.9 (6.8-8.7)	0.078
Hematology/iron variables			
Hb (g/dL)	11.9 (11.3-12.2)	11.7 (11.3-12.0)	0.151
Ferritin (ng/mL)	99 (69-163)	125 (62-212)	0.687
Transferrin saturation (%)	22 (17-31)	22 (18-29)	0.435
Renal function			
Urine protein excretion (g/24 h)	1.3 (0.5-3.1)	0.8 (0.4-2.9)	0.322
Creatinine clearance (mL/min)	51 (39-67)	46 (35-55)	0.020
Serum creatinine (mg/dL)	1.58 (1.21-1.93)	1.63 (1.26-2.17)	0.334
Lipid variables			
Low-density lipoprotein cholesterol (mg/dL)	116 (89-143)	124 (104-159)	0.110
High-density lipoprotein cholesterol (mg/dL)	50 (39-66)	50 (43-62)	0.828
Total cholesterol (mg/dL)	197 (166-236)	201 (174-232)	0.377
Triglycerides (mg/dL)	151 (97-204)	133 (97-213)	0.502
Statin treatment (%)	46	35	0.208
Fibrate treatment (%)	7	9	0.779

*Note:* Values expressed as percent or median (IQR) unless noted otherwise. To convert Hb in g/dL to g/L, multiply by 10; ferritin in ng/mL to  $\mu$ g/L, multiply by 1; creatinine clearance in mL/min to mL/s, multiply by 0.01667; serum creatinine in mg/dL to  $\mu$ mol/L, multiply by 88.4; low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol in mg/dL to mmol/L, multiply by 0.02586; triglycerides in mg/dL to mmol/L, multiply by 0.01129.

\*Median (range).

**Table 3. Cardiovascular Diseases at Baseline**

	Group 1 (n = 88)	Group 2 (n = 82)
Chronic heart failure (%)	5	2
Ischemic heart disease (%)	25	14
Previous myocardial infarction	17	7
Coronary artery disease	5	7
Cerebrovascular disease, stroke (%)	6	5
LVH (%)	5	4
Peripheral vascular disease (%)	11	6
Valvulopathies (%)	1	4
Electrocardiogram abnormalities (%)	5	1
Other cardiovascular diseases (%)	13	12

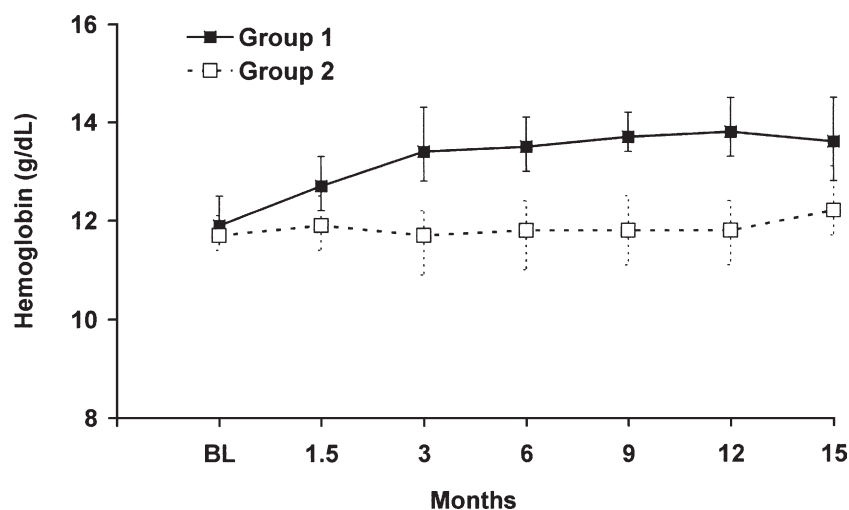
Note: LVH as reported by treating physician.

proportion of patients had type 2 diabetes in group 1 (73%) compared with group 2 (65%). Previous myocardial infarction and peripheral vascular disease were the most commonly observed concomitant cardiovascular diseases (excluding hypertension; Table 3).

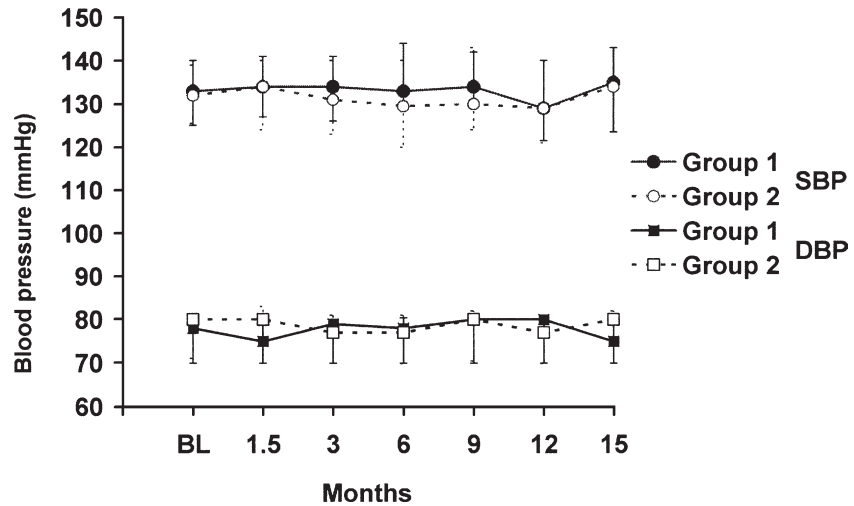
In total, 89% and 84% of patients in group 1 and group 2 received angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers with or without other antihypertensives, respectively. Calcium channel blockers, loop diuretics, and  $\beta$ -blockers were prescribed, with or without angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, in 52%, 38%, and 23% of patients, respectively. Use of multiple antihypertensive medications was common, with only 19.8% of patients receiving monotherapy. Half the patients received 3 or more antihypertensive agents.

### Anemia Correction

At baseline, median Hb levels were 11.9 g/dL (119 g/L) in group 1 and 11.7 g/dL (117 g/L) in group 2 (Table 2). Epoetin beta treatment was administered to all patients in group 1 after randomization and was received at least once by all patients in this group during the study. Thirteen of 82 patients (16%) in group 2 received epoetin beta treatment during the study to maintain their Hb level within the target range of 10.5 to 11.5 g/dL (105 to 115 g/L). Median Hb levels over time in the 2 treatment groups are shown in Fig 2. In accordance with the study protocol, median Hb level was within the target of 13 to 15 g/dL (130 to 150 g/L) in group 1 by study end (13.5 g/dL [135 g/L]) and slightly greater than the target of 10.5 to 11.5 g/dL (105 to 115 g/L) in group 2 (12.1 g/dL [121 g/L]). Changes in median Hb levels from baseline to study end were 1.7 g/dL ([17 g/L]; IQR, 0.8 to 2.6 g/dL [8 to 26 g/L]) in group 1 and 0.3 g/dL ([3 g/L]; IQR, -0.5 to 1.0 g/dL [-5 to 10 g/L]) in group 2, with a significant difference in median Hb level of 1.4 g/dL (14 g/L) at study end between the study groups (chi-square test;  $P < 0.001$ ). Normalization of Hb levels did not lead to an increase in median blood pressure by study end in group 1 (systolic blood pressure [SBP], 134 mm Hg [range, 100 to 184 mm Hg]; diastolic blood pressure [DBP], 76 mm Hg [range, 58 to 100 mm Hg]; Fig 3). Similarly, there was no change in median blood pressure from baseline to study end in group 2 (SBP, 134 mm Hg [range, 100 to 162 mm Hg]; DBP, 80 mm Hg [range, 55 to 107 mm Hg]; Fig 3).



**Figure 2.** Median Hb ( $\pm$  IQR) over time by treatment group. Abbreviation: BL, baseline. \*Significant difference in response rates between groups at study end by chi-square test. To convert Hb in g/dL to g/L, multiply by 10.



**Figure 3.** Median blood pressure ( $\pm$  IQR) over time by treatment group. Abbreviation: BL, baseline.

Median weekly epoetin beta dose required to maintain patients in group 1 within the protocol-specified target Hb level range was 46.1 IU/wk/kg ( $\sim$ 3,500 IU/wk). Fifty-eight percent of patients in group 1 and 35.4% in group 2 received at least 1 dose of oral iron supplementation.

**Primary End Point**

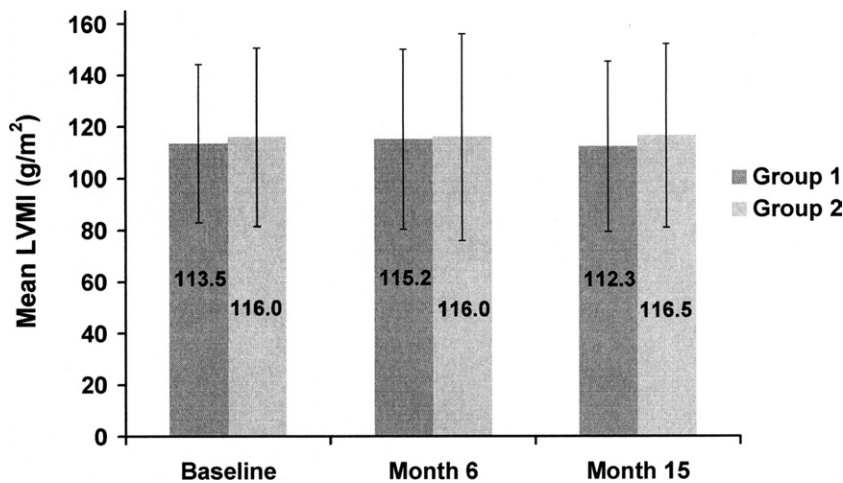
There were no statistically significant differences in LVMI at baseline (mean LVMI: group 1,  $113.5 \pm 30.6$  g/m<sup>2</sup>; group 2,  $116.0 \pm 34.6$  g/m<sup>2</sup>), month 6 (group 1,  $115.2 \pm 34.8$  g/m<sup>2</sup>; group 2,  $116.0 \pm 40.1$  g/m<sup>2</sup>), and month 15 (group 1,  $112.3 \pm 32.9$  g/m<sup>2</sup>; group 2,  $116.5 \pm 35.6$  g/m<sup>2</sup>) between the 2 study groups (Fig 4).

Additional analysis of LVMI by either quartiles (Table 4) or grouping of baseline LVMI

( $<100$ ,  $\geq 100$  to  $<130$ ,  $\geq 130$  to  $<160$ , and  $\geq 160$  g/m<sup>2</sup>; Fig 5) showed a greater numerical decrease in LVMI in patients with LVH at baseline in group 1, a finding also observed in multivariate analysis ( $P = 0.15$ ).

**Other Echocardiographic Parameters**

Echocardiographic variables, such as left ventricular end-systolic and end-diastolic diameters, and posterior and septal wall thickness, LVEF, and fractional shortening were well balanced at baseline in the 2 treatment groups, and there were no significant differences in these parameters from baseline to study end between the 2 study groups (Table 5). Notably, at baseline, the frequency of patients with LVH was greater in group 1 (47%) than group 2 (39%). By the



**Figure 4.** LVMI (mean  $\pm$  SD) by treatment group.

Table 4. LVMI Over Time by LVMI Quartile at Baseline

	Quartile			
	1	2	3	4
Group 1				
Baseline	74.9 ± 11.1	102.5 ± 5.6	121.4 ± 5.32	152.8 ± 16.4
Month 6	83.3 ± 10.4	116.3 ± 38.9	127.5 ± 26.0	138.3 ± 27.0
Month 15	78.6 ± 12.6	108.6 ± 19.7	126.7 ± 28.1	145.7 ± 36.7
Group 2				
Baseline	77.6 ± 7.6	99.1 ± 7.5	123.9 ± 4.9	163.8 ± 23.9
Month 6	82.3 ± 20.25	96.4 ± 13.5	127.5 ± 18.6	150.5 ± 41.3
Month 15	88.1 ± 18.35	96.2 ± 11.2	126.4 ± 18.3	152.9 ± 37.7

Note: Values expressed as mean ± SD.

end of the study, this imbalance in LVH prevalence at baseline was decreased through a greater reduction in LVH prevalence at study end in group 1 (38%) compared with group 2 (35%).

### Renal Function

At baseline, creatinine clearance (Cockcroft-Gault formula) was not significantly different between group 1 and group 2. In group 1, median creatinine clearance was 50.9 mL/min ([0.85 mL/s]; IQR, 38.7 to 67.2 mL/min [0.65 to 1.12 mL/s]), and in group 2, was 45.6 mL/min ([0.76 mL/s]; IQR, 35.1 to 54.8 mL/min [0.59 to 0.91 mL/s]). Urine protein excretion was 1.3 g/24 h (IQR, 0.5 to 3.1 g/24 h) in group 1 and 0.8 g/24 h (IQR, 0.4 to 2.9 g/24 h) in group 2. From baseline to study end, a similar decrease in creatinine clearance was observed in both treatment arms. Median creatinine clear-

ance decreased by  $-5.5$  mL/min ( $[-0.09$  mL/s; IQR,  $-11.5$  to  $-0.3$  mL/min [ $-0.19$  to  $-0.01$  mL/s]) in group 1 and by  $-3.4$  mL/min ( $[-0.06$  mL/s; IQR,  $-11.4$  to  $+2.0$  mL/min [ $-0.19$  to  $+0.03$  mL/s]) in group 2 (by means of Cockcroft-Gault formula; Fig 6). Similar results were observed when the simplified 4-variable Modification of Diet in Renal Disease formula was used for calculation of estimated glomerular filtration rate. In group 1, the decrease was  $-5.1$  mL/min ( $[-0.09$  mL/s; IQR,  $-10.7$  to  $-0.1$  mL/min [ $-0.18$  to  $-0.00$  mL/s]), and in group 2, was  $-3.9$  mL/min ( $[-0.07$  mL/s; IQR,  $-12.1$  to  $+1.8$  mL/min [ $-0.20$  to  $+0.03$  mL/s]). Only 5 patients (2 patients, group 1; 3 patients, group 2) were referred for dialysis during the study period. There also was no change in urine protein excretion in either group by study end (group 1, 1.4 g/24 h [IQR, 0.4 to 3.2 g/24 h]; group 2, 0.9 g/24 h [IQR, 0.4 to 2.2 g/24 h]).

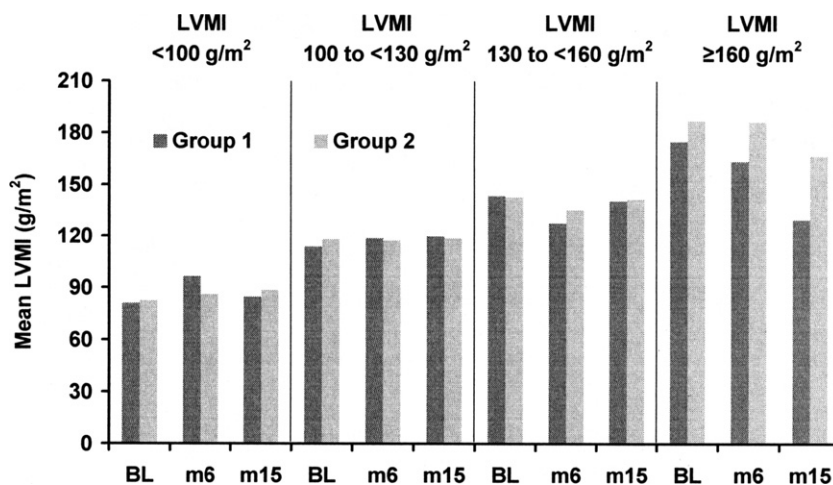


Figure 5. LVMI (mean ± SD) over time by degree of LVH at baseline. Abbreviation: BL, baseline.

**Table 5. Mean Change From Baseline to Study End in Secondary Echocardiographic and Other Clinical Variables by Treatment Group**

Mean Change	Group 1	Group 2
Left ventricular end-systolic volume index (mL/m <sup>2</sup> )	3.95	3.90
Left ventricular end-diastolic volume index (mL/m <sup>2</sup> )	1.73	3.65
LVEF (%)	-5.03	-3.92
Fractional shortening (%)	0.83	2.42
Left ventricular end-systolic diameter (cm)	-0.01	-0.10
Left ventricular end-diastolic diameter (cm)	0.05	0.01
Left ventricular posterior wall thickness (cm)	-0.02	0.00
Left ventricular septal wall thickness (cm)	-0.03	0.01

### Quality of Life

Quality of life (by means of SF-36 for general health) was significantly better in patients who received early and complete anemia correction (group 1) compared with patients receiving partial and late anemia correction (group 2). Mean change in general health score from baseline to study end was +5.33 in group 1 compared with -0.33 in group 2 ( $P = 0.04$ ).

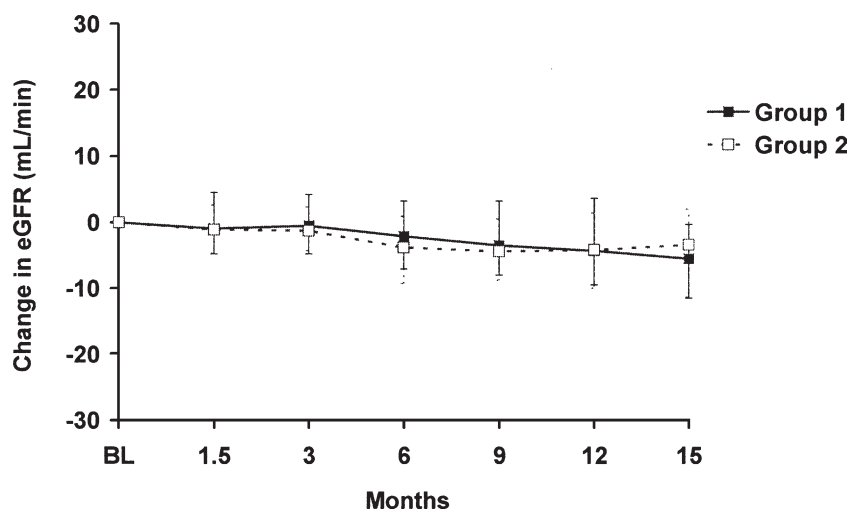
### Safety

There were no differences in adverse-event rates between the 2 study groups. The most frequently reported adverse events were vascular disorders (group 1, 23%; 20 patients; group 2, 16%; 13 patients). Of these, hypertension was reported as the most frequent adverse event by 15 patients (17%) in group 1 (1 patient with hypertensive crisis) and 9 patients (11%) in group 2. No difference in cardiac adverse events was observed between the 2 study groups (group 1, 7%; 6 patients,

including 2 patients with myocardial infarction, 1 patient with angina pectoris; group 2, 6%; 5 patients, no patient with myocardial infarction, 1 patient with unstable angina pectoris). The annualized cardiac event rate was approximately 4%. One patient in group 2 presented with ischemic stroke. Deep vein thrombosis was reported in 2 patients in group 1. Other observed vascular events included intermittent claudication (2 patients in group 2), flushing (1 patient in group 1), and hypotension, thrombophlebitis, and vasculitis (1 patient per event in group 2).

### DISCUSSION

ACORD is the first prospective study to evaluate in patients with diabetes and CKD stages 2 to 3 the effects of early and complete anemia correction versus conventional partial anemia correction, as suggested by current guidelines.<sup>14,32</sup> Despite differences in body weight, body mass index, creatinine clearance, and frequency of



**Figure 6.** Median change ( $\pm$  IQR) in estimated glomerular filtration rate (eGFR) from baseline over time by treatment group, calculated from creatinine clearance by means of the Cockcroft-Gault formula. Abbreviation: BL, baseline. To convert eGFR from creatinine clearance in mL/min to mL/s, multiply by 0.01667.



type 2 diabetes at baseline, there were no major imbalances at baseline between study groups. In group 1, anemia correction with epoetin beta resulted in a significant increase in Hb level ( $P < 0.001$ ) compared with group 2. However, the initial hypothesis of this study, namely, that early and complete anemia correction to an Hb target level of 13 to 15 g/dL (130 to 150 g/L; group 1) would result in a significant decrease in LVMI at month 15 compared with maintaining patients at a lower Hb target level of 10.5 to 11.5 g/dL (105 to 115 g/L; group 2), was not confirmed. As shown in Fig 4, mean LVMI was stable in both study groups across the entire observation period. In line with the primary efficacy parameter (LVMI), there were no statistically significant differences in any of the secondary or other exploratory echocardiographic parameters between the 2 study groups.

The finding for the primary end point of this study contrasts with previous reports in which partial reversal of LVH was seen with epoetin treatment.<sup>33,34</sup> Importantly, in these previous studies, Hb values at baseline were markedly lower and mean LVMI values were markedly higher compared with the present study enrolling patients with mild to moderate anemia (inclusion criterion, Hb level of 10.5 to 12.5 g/dL [105 to 125 g/L]) and well-controlled blood pressure. Comparison of mean LVMI in this study with the classification of the American Society of Echocardiography (“moderately abnormal”: in women, 101 to 112 g/m<sup>2</sup>; in men, 117 to 130 g/m<sup>2</sup>)<sup>35</sup> shows that in the present study, mean LVMI was only moderately abnormal, possibly pointing to slowly improving management of patients with diabetes with renal failure, although we cannot exclude a selection artifact. At any rate, the chance of seeing reversal thus was lessened. One also might argue that despite a clinically meaningful ( $\sim 1.4$  g/dL [14 g/L]) and statistically significant difference in median Hb levels ( $P < 0.001$ ) between the 2 study groups, the difference might have been insufficient to have a significant impact on LVMI.

The primary result of this study adds additional evidence to results of 3 recent studies reported by Roger et al,<sup>36</sup> Parfrey et al,<sup>37</sup> and Levin et al.<sup>38</sup> In all 3 studies conducted in highly selected and well-controlled predialysis<sup>36,38</sup> or dialysis patients<sup>37</sup> who had no severe LVH at

baseline, no significant effects of Hb level increase by epoetin treatment on LVMI was observed. Our finding of no significant regression of LVH in patients without increased LVMI and only moderate degrees of anemia at baseline also is in line with previous observations of Foley et al<sup>39</sup> and McMahon et al.<sup>40</sup>

When we assessed patients with increased LVMI at baseline in a subanalysis, a decrease in LVMI was observed that was more pronounced in group 1 with early and complete anemia correction (Table 4; Fig 5). Regression of LVMI was seen in the recent open-label intervention trial of Ayus et al<sup>41</sup> investigating patients with or without diabetes and comprising a high proportion of patients with LVH (68.3%). In this study, epoetin was administered only if Hb level was less than 10 g/dL ( $< 100$  g/L), with the objective to increase Hb to values greater than 12 g/dL ( $> 120$  g/L). In patients receiving epoetin, mean Hb level increased from 9.1 g/dL (91 g/L) to 11.3 g/dL (113 g/L;  $P < 0.001$ ), and mean LVMI at baseline significantly decreased from  $157 \pm 55.7$  to  $142 \pm 55.7$  g/m<sup>2</sup> ( $P < 0.007$ ) within 6 months.

In contrast to the overall neutral finding for the primary and secondary echocardiographic parameters, quality of life improved significantly in patients for whom anemia was corrected early and completely ( $P = 0.04$ ). With respect to renal function, no difference in estimated glomerular filtration rate was observed between the 2 study groups. Importantly, there was no difference in adverse events between groups and the annual cardiac event rate was remarkably low, ie, 4%.

Baseline data from the ACORD Study show that a substantial proportion of the enrolled patients failed to meet treatment targets recommended by current practice guidelines for preventing cardiovascular disease in patients with diabetes.<sup>42</sup> The recommended targets were exceeded for median SBP ( $< 130$  mm Hg) in approximately 67% to 72%, for low-density lipoprotein cholesterol level ( $< 96.7$  mg/dL [ $< 2.5$  mmol/L]) in 53% to 66%, and for HbA<sub>1c</sub> level (6.1%) in 84% to 88% of patients.

Although in principle, all patients were eligible for treatment with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, only 84% to 89% were administered these agents.  $\beta$ -blockers, proved to reduce cardiovascular mortality and morbidity,<sup>43-45</sup> were

largely underprescribed, with only 23% of patients receiving these agents.

Despite the reported benefits of statin treatment for reducing low-density lipoprotein cholesterol levels and reducing the risk of cardiovascular events in patients with diabetes,<sup>42,46,47</sup> only 35% to 46% were administered statins and 53% to 66% had low-density lipoprotein cholesterol levels greater than those recommended by the European guidelines (96.7 mg/dL [2.5 mmol/L]).<sup>42</sup>

Assessment of quality-of-life parameters using the SF-36 scale showed that early and complete anemia correction was associated with a significantly greater improvement from baseline to study end in general health compared with partial anemia correction. Although not significant, there also was greater improvement from baseline in vitality in group 1 compared with group 2. These improvements were similar to those observed by Rossert et al.<sup>48</sup> Both studies showed the beneficial impact that early and complete anemia correction can have on patient quality of life.

In the Cardiovascular Risk Reduction in Early Anaemia Trial with Epoetin beta (CREATE) study, earlier start of dialysis treatment was noted in some patients randomly assigned to a higher Hb level target.<sup>49</sup> In the present study, serum creatinine concentration was monitored regularly. Creatinine clearance and doubling of serum creatinine level were not significantly different in the 2 treatment groups, suggesting a similar rate of progression of CKD. Similarly, there was no difference between treatment groups in frequency of patients requiring dialysis (group 1, 2 patients; group 2, 3 patients). Findings with respect to renal function confirm the observation of Rossert et al,<sup>48</sup> who found no significantly greater decrease in glomerular filtration rate in patients randomly assigned to an Hb target level of 13 to 15 g/dL (130 to 150 g/L).

Importantly, safety profiles of the 2 study groups were very similar in terms of frequency of adverse events. In contrast to previous reports, although the most frequent adverse event was hypertension, there were no significant differences in blood pressure until study end.

A remarkably low annual cardiovascular event rate of approximately 4% was observed, with no differences between study groups. This cardiovascular event rate is much less than cardiac event

rates reported in previous studies, eg, 15% in a Canadian cohort study examining patients with mild to moderate renal insufficiency.<sup>10</sup> The low cardiovascular event rate observed in our study may be explained by excluding patients with severe anemia. Furthermore, an Hb level decrease to less than 10.5 g/dL (<105 g/L) was prevented by protocol. In addition, use of such cardioprotective agents as  $\beta$ -blockers, statins, aspirin, and angiotensin-converting enzyme inhibitors may have contributed to the low cardiovascular event rate.

In conclusion, this study is designed to investigate the effect of early and complete versus late and partial anemia correction in patients with diabetes with mild to moderate anemia and CKD stages 2 to 3. Overall, no significant decrease in LVMI was seen in the overall study population. This finding is explained most plausibly by the strict inclusion criteria of the study, resulting in enrollment of a study population with only moderately increased LVMI. Of note, early and complete anemia correction was associated with a significant improvement in quality of life and did not result in increased cardiac risk or accelerated renal progression.

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#### APPENDIX 1: STUDY ORGANIZATION

Study Steering Committee: Professor E. Ritz, Department of Internal Medicine, University of Heidelberg, Heidelberg, Germany; Professor M. Laville, Department of Nephrology, Université Claude Bernard, Lyon, France; Professor R. Bilous, Education Centre, James Cook University Hospital, Middlesbrough, UK; Dr D. O'Donoghue, Department of Renal Medicine, Hope Hospital, Salford, UK; Dr F. de Alvaro, Servicio de Nefrología, Hospital Universitario

La Paz, Madrid, Spain; Professor Dr A. Scherhag (nonvoting member), F. Hoffmann-La Roche Ltd, Basel, Switzerland, and I. Medical Clinic, University Hospital Mannheim, Germany.

Data and Safety Monitoring Board: An independent Data and Safety Monitoring Board consisting of 2 experienced clinicians (1 nephrologist and 1 diabetologist) and 1 independent biostatistician was appointed to review safety data at regular intervals. In the event of unacceptable safety findings, the Data and Safety Monitoring Board had the authority to suggest discontinuation of the trial to the Steering Committee and the sponsor.

Sponsor: F. Hoffmann-La Roche Ltd, Basel, Switzerland.

## APPENDIX 2: ECHOCARDIOGRAPHIC METHODS

Echocardiographic assessments were performed at screening (baseline), month 6, and end of study according to the recommendations of the American Society of Echocardiography.<sup>31</sup> All echocardiographic examinations were documented on videotape or similar recording media. The standard formulae used for calculation of the reported echocardiographic parameters are given next. Presence of LVH was defined as LVMI greater than 100 g/m<sup>2</sup> in women and greater than 130 g/m<sup>2</sup> in men.

### Primary End Point

LVMI (g/m<sup>2</sup>):

$$\text{LVMI [g/m}^2\text{]} = \frac{0.8 [1.04\{(\text{LVEDD} + \text{IVS} + \text{PWT})^3 - (\text{LVEDD})^3\}] + 0.6}{\text{BSA}} \quad (1)$$

### Secondary Echocardiographic End Points

Left ventricular (LV) end-systolic and end-diastolic volume (mL/m<sup>2</sup>) and indices (left ventricular end-systolic [LVESVI] and end-diastolic volume index [LVEDVI] in mL/m<sup>2</sup>):

$$\text{LV volume [mL/m}^2\text{]} = \frac{7}{2.4 + \text{LVEDD}} (\text{LVEDD})^3 \quad (2)$$

LVESVI (mL/m<sup>2</sup>):

$$\text{LVESVI} = \frac{\text{LVESV}}{\text{BSA}} \quad (3)$$

LVEDVI (mL/m<sup>2</sup>) after 15 months, defined as:

$$\text{LVEDVI} = \frac{\text{LVEDV}}{\text{BSA}} \quad (4)$$

LVEF (%):

$$\text{LVEF} = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}} \times 100\% \quad (5)$$

LVFS (%):

$$\begin{aligned} \text{Fractional shortening [\%]} \\ = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}} * 100 \quad (6) \end{aligned}$$

Other abbreviations used in formulas:

LVEDD = left ventricular end-diastolic diameter (cm)

LVESD = left ventricular end-systolic diameter (cm)

IVS = interventricular septal wall thickness in diastole (cm)

PWT = left ventricular posterior wall thickness in diastole (cm)

BSA = body surface area (m<sup>2</sup>)

LVESV = left ventricular end-systolic volume (mL)

LVEDV = left ventricular end-diastolic volume (mL)

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