Left Ventricular Geometry Predicts Cardiovascular Outcomes Associated with Anemia Correction in CKD

Kai-Uwe Eckardt,* Armin Scherhag,[†‡] Iain C. Macdougall,[§] Dimitrios Tsakiris,[‖] Naomi Clyne,[¶] Francesco Locatelli,** Michael F. Zaug,[†] Hans U. Burger,[†] and Tilman B. Drueke[††]

*Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany; [†]Pharmaceutical Division, F. Hoffmann-La Roche, Basel, Switzerland; [‡]Medical Clinic, Mannheim University Hospital, University of Heidelberg, Heidelberg, Germany; [§]Department of Renal Medicine, King's College Hospital, London, United Kingdom; [‖]Department of Nephrology, General Hospital of Veria, Veria, Greece; [¶]Department of Nephrology, University Hospital of Lund, Lund, Sweden; **Department of Nephrology, Dialysis and Renal Transplantation, Ospedale A. Manzoni, Lecco, Italy; and [††]INSERM Research Unit 507 and Division of Nephrology, Necker Hospital, Paris, France

ABSTRACT

Partial correction of anemia in patients with chronic kidney disease (CKD) reduces left ventricular hypertrophy (LVH), which is a risk factor for cardiovascular (CV) morbidity, but complete correction of anemia does not improve CV outcomes. Whether LV geometry associates with CV events in patients who are treated to different hemoglobin (Hb) targets is unknown. One of the larger trials to study the effects of complete correction of anemia in stages 3 to 4 CKD was the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial. Here, we analyzed echocardiographic data from CREATE to determine the prevalence, dynamics, and prognostic implications of abnormal LV geometry in patients who were treated to different Hb targets. The prevalence of LVH at baseline was 47%, with eccentric LVH more frequent than concentric. During the study, LVH prevalence and mean left ventricular mass index did not change significantly, but LV geometry fluctuated considerably within 2 yr in both groups. CV event-free survival was significantly worse in the presence of concentric LVH and eccentric LVH compared with the absence of LVH ($P = 0.0009$ and $P \leq 0.0001$, respectively). Treatment to the higher Hb target associated with reduced event-free survival in the subgroup with eccentric LVH at baseline ($P = 0.034$). In conclusion, LVH is common and associates with poor outcomes among patients with stages 3 to 4 CKD, although both progression and regression of abnormal LV geometry occur. Complete anemia correction may aggravate the adverse prognosis of eccentric LVH.

Left ventricular hypertrophy (LVH) is considered an important risk factor for adverse cardiovascular (CV) outcomes in patients with chronic kidney disease (CKD).[1] The prevalence of LVH rises with the progression of CKD, ranging from approximately 26% in patients with creatinine clearances of 50 to 75 ml/min to 75% in patients starting dialysis.[2–4] Whereas the presence of LVH is predictive of poor CV prognosis in patients receiving dialysis treatment,[2,5–8] fewer data on the prognostic impact of LVH are available in patients with earlier stages of CKD.

Hemoglobin (Hb) levels have been found to predict the degree of LVH in long-term dialysis patients,[9,10] with each 1 g/dl decrease in Hb being

associated with an approximately 50% increase in the risk for LV dilation and systolic dysfunction.[9] Anemia has also been identified as a risk factor for LV growth and adverse outcomes in patients with less severe kidney disease[3,11] and in the absence of CKD.[12] Because anemia leads to a compensatory increase in cardiac output, this increase in cardiac workload may enhance LV growth and LV dilation in the context of additional risk factors and metabolic abnormalities associated with CKD.[13,14] Of note, eccentric LVH is more frequent than concentric LVH in patients with CKD, indicating that volume overload may be of particular relevance in the pathogenesis of LVH in these patients.[3]

Several small studies in patients with stages 4 to 5 CKD showed reduced LV mass index (LVMI) with partial correction of severe anemia by recombinant human erythropoietin (epoetin)[15–18]; however, randomized, controlled trials (RCTs) that compared partial with complete anemia correction in patients with moderate anemia at baseline did not show an improvement of LVH.[19–25] Moreover, the four trials enrolling >500 patients to test the effects of Hb normalization each failed to show a benefit of target Hb levels above 13 g/dl on CV outcomes.[22,23,26,27] Two of these studies even indicated adverse cardiovascular consequences of randomly assigning patients to a higher Hb target.[26,27]

One of these four larger trials, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial, was performed to compare the effects of complete correction of anemia (target Hb 13.0 to 15.0 g/dl; group 1) with those of partial correction (target Hb 10.5 to 11.5 g/dl; group 2) in patients with stages 3 to 4 CKD.[23] More than 95% of patients who enrolled in CREATE underwent echocardiography at baseline and then annually during the course of the study. We previously reported that there was no difference in LVMI between the two treatment arms.[23] Here we report a detailed analysis of the echocardiographic parameters with the objective to describe the prevalence, dynamics, and prognostic implications of abnormalities in LV geometry in nondialysis patients with CKD in the absence of severe heart failure and to determine whether anemia correction affects CV events, depending on cardiac structure and function.

RESULTS

Study Population and Baseline Characteristics
Of the 603 patients who were included in the intention-to-treat analysis of CREATE, 580 (96%) had baseline echocardiograms, and in 451 (74.8%), these were assessable for LVMI (219 in group 1 and 232 in group 2). The number of patients for whom echocardiograms were assessable for LVMI decreased after 1, 2, and 3 yr to 171, 136, and 74 and to 186, 146, and 81, respectively (Supplemental Table), but there was no difference between groups 1 and 2.

Comparison of the baseline characteristics between the overall CREATE study population and the patients with baseline echocardiograms revealed that this group was a representative subcohort. The only statistical differences were a slightly lower age (57.1 versus 59.0 yr) and a less frequent use of diuretics in the echocardiogram group (42.0 versus 63.5%).

The baseline characteristics of patients who were included in the echocardiographic analyses separated by treatment arm are depicted in Table 1. Demographic and clinical characteristics were similar between both groups, except that the proportion of men was slightly higher in group 1. As shown in Table 2, echocardiographic parameters at baseline were also similar between both groups, except that the overall proportion of patients with normal LV geometry was slightly higher and the proportion with concentric remodeling was slightly lower in group 1 than in group 2 (39.0 versus 33.2% and 11.9 versus 18.5%, respectively). Almost half of the patients in either group had LVH at the outset of the study, but the prevalence of systolic dysfunction was very low.

Effects of Anemia Correction on LVMI and Prevalence of LVH
The mean LVMI values over time for all patients for whom echocardiograms were interpretable at baseline and at years 1, 2, and 3 are illustrated in Figure 1 (top). LVMI did not change significantly over time in either of the two study groups. After 1, 2, and 3 yr, the mean changes in LV volume were -2.83 ± 15.9, -0.69 ± 16.4, and $3.34 \, \text{g/m}^2 \pm 24.3$ and 3.15 ± 15.5, 2.62 ± 18.6, and $4.05 \pm 19.1 \, \text{g/m}^2$, and the mean changes in LVMI were -5.06 ± 24.8, -6.58 ± 26.9, and -1.30 ± 36.0 and -2.87 ± 25.2, -7.59 ± 25.6, and -7.53 ± 34.4 in group 1 and group 2, respectively. Considering only patients who had echocardiograms at baseline and after 3 yr, the mean change in LVMI was -3.3 ± 26.5, -3.3 ± 27.5, and -1.3 ± 36.0 and -1.3 ± 23.2, -11.1 ± 27.0, and -7.5 ± 34.4 at baseline and after years 1, 2, and 3 in group 1 ($n = 74$) and group 2 ($n = 81$), respectively. Figure 1 (bottom) shows that there was a trend toward a decreasing overall prevalence of LVH over time in both treatment groups between baseline and year 2, but the prevalence in those remaining in the study at year 3 was virtually identical to that in the whole cohort at baseline. The prevalence of LVH was not different at any time between groups 1 and 2.

To determine whether changes in LVMI occurred in subgroups of patients with different LVMI at study entry, we stratified patients by baseline LVMI ranges. Because of the reduced number of observations in each category after stratification, a meaningful analysis was possible only until year 2. As shown in Figure 2, in patients with a baseline LVMI $<100 \, \text{g/m}^2$, no significant changes from baseline to year 1 or 2 were observed, and there were no differences between treatment groups; however, in patients with a baseline

Table 1. Demographics and baseline characteristics of the population with baseline echocardiograms

Characteristic	Group 1 (n = 219)	Group 2 (n = 232)
Body weight (kg; mean ± SD)	73.7 ± 15.2	71.4 ± 14.1
BMI (mean ± SD)	26.2 ± 4.2	26.2 ± 4.8
Age (yr; mean ± SD)	57.8 ± 14.5	56.6 ± 13.5
Male gender (n [%])	128 (58)	113 (49)
eGFR (ml/min; mean ± SD)[a]	25.0 ± 6.1	24.3 ± 6.0
Cause of CKD (n [%])		
glomerulonephritis	53 (24)	58 (25)
hypertensive renal disease	51 (23)	38 (16)
diabetic nephropathy	41 (19)	48 (21)
polycystic kidney disease	28 (13)	32 (14)
pyelonephritis	14 (6)	18 (8)
interstitial nephritis	17 (8)	14 (6)
other	45 (21)	45 (19)
Diabetes (n [%])	55 (25)	60 (26)
insulin-dependent	11 (5)	9 (4)
Dyslipidemia (n [%])	83 (38)	74 (32)
Hypertension (n [%])	205 (94)	207 (89)
SBP (mmHg; mean ± SD)	139 ± 18	139 ± 16
DBP (mmHg; mean ± SD)	80 ± 10	80 ± 9
Receiving at least one antihypertensive (n [%])[a]	210 (96)	209 (90)
Antihypertensive agents prescribed		
ACE inhibitors	110 (50)	111 (48)
angiotensin II inhibitors	45 (21)	46 (20)
β blockers	98 (45)	83 (36)
calcium channel blockers	119 (54)	119 (51)
α-adrenergic receptor antagonists	42 (19)	31 (13)
loop diuretics	97 (44)	93 (40)
thiazides and other diuretics	25 (11)	20 (9)
Preexisting CVD (n [%])	209 (95)	212 (91)
chronic heart failure[b]	66 (31.6)	57 (26.9)
previous MI[b]	2 (1.0)	2 (0.9)
cerebrovascular disease[b]	8 (3.8)	5 (2.4)
CAD[b]	8 (3.8)	8 (3.8)
peripheral vascular disease[b]	6 (2.9)	4 (1.9)
NYHA class (n [%])[c]	121 (65.4)	118 (67.0)
0	26 (14.1)	30 (17.0)
I	38 (20.5)	28 (15.9)
II		
Hb (g/dl; mean ± SD)	11.5 ± 0.6	11.5 ± 0.6
Serum ferritin (µg/L)		
mean ± SD	174.1 ± 151.0	193.5 ± 163.0
median	132	130
Transferrin saturation (%)		
mean ± SD	25.9 ± 9.6	42.5 ± 22.5
median	24.3	25.6

ACE, angiotensin-converting enzyme; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic BP; eGFR, estimated GFR; NYHA, New York Heart Association; MI, myocardial infarction; SBP, systolic BP.
[a]Percentages and numbers are based on available data, with single data missing.
[b]Expressed as a percentage of patients with preexisting CV disease, excluding hypertension.
[c]Percentages are based on n = number of valid values (185 in the full correction group and 176 in the partial correction group).

LVMI between 100 and 130, between 131 and 160, or >160 g/m^2, significant decreases were observed after 1 and 2 yr when compared with baseline, with more pronounced changes and lower P values in patients with higher baseline LVMI; however, no significant differences were observed between the treatment arms.

Effects of Anemia Correction on LV Volume, LV Diameters, and LV Function

No significant changes in LV volume (LVV), LV end-diastolic diameter, LV end-systolic diameter, LV ejection fraction (LVEF), and fractional shortening (FS) from baseline to year 1 or year 2 were observed within or between the two treatment groups (Table 3). Of note, LVEF remained stable throughout the study.

Dynamics of LV Geometry over Time

To determine a possible influence of target Hb on the dynamics of LV geometry over time, we determined separately the proportion of patients who were within a certain category of LVM and geometry at baseline and remained within this category or changed to another category for group 1 and group 2 patients who had interpretable echocardiograms at baseline and year 2.

As shown in Tables 4 and 5, there were no significant differences between group 1 and group 2, but both groups revealed significant fluctuations between categories. Among patients whose LV geometry was normal at baseline, 61.7 to 64.9% maintained normal geometry after 2 yr, whereas 17.0 to 17.5% showed concentric remodeling and 15.8 to 21.3% developed LVH (nearly all eccentric). Among those with LVH at baseline, 56.5 to 63.2% continued to show LVH after 2 yr, whereas 25.0 to 32.2% were normalized and 9.7 to 10.3% regressed to concentric remodeling. Moreover, by the end of year 2, 33.3 to 42.3% of those with concentric LVH at baseline had eccentric LVH, but only 8.8 to 9.5% of those with eccentric LVH at baseline showed concentric LVH.

Table 2. Baseline echocardiographic findings

Finding	Group 1 (n = 219)	Group 2 (n = 232)	P
Continuous parameters (mean ± SD)			
LVEDD (cm)	5.05 ± 0.67	4.91 ± 0.68	0.091
LVESD (cm)	2.85 ± 0.58	2.74 ± 0.66	0.067
septal wall thickness (cm)	1.18 ± 0.24	1.20 ± 0.28	0.960
posterior wall thickness (cm)	1.05 ± 0.17	1.05 ± 0.17	0.853
relative wall thickness	0.42 ± 0.08	0.43 ± 0.09	0.359
LVV	67.73 ± 19.20	65.11 ± 19.24	0.166
LV muscle mass index (g/m²)	120.32 ± 35.03	117.97 ± 34.34	0.442
FS (%)	43.67 ± 7.12	44.67 ± 7.86	0.128
Discrete parameters (n [%])[a]			
normal LV geometry	85 (39.0)	77 (33.2)	0.218
LVH	105 (47.9)	108 (46.6)	0.802
LVH, concentric	43 (19.7)	42 (18.1)	0.704
LVH, eccentric	61 (28.0)	66 (28.4)	0.953
LV dilation	26 (11.9)	21 (9.1)	0.357
concentric remodeling	26 (11.9)	43 (18.5)	0.060
systolic dysfunction	1 (0.5)	1 (0.4)	0.762

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.
[a]Percentages and numbers are based on available data, with single data missing.

Determinants of Baseline LVH and LV Growth

The results of multivariate analyses of determinants of baseline LVH and of LV growth in patients with echocardiographic data at year 2 are shown in Tables 6 and 7. For LVH, only race and baseline systolic BP were significant. Trends were observed for female gender, diabetes, and baseline diastolic BP. There were no significant determinants of LV growth.

Effects of Baseline LV Status on the Occurrence of CV Events

Kaplan-Meier CV event-free survival curves in the two treatment groups, stratified by LV status at baseline, are shown in Figure 3. The probability of experiencing a CV event was significantly greater in the presence than in the absence of LVH at baseline. It was significantly higher in patients with eccentric LVH than in those with concentric LVH. The treatment arms did not differ in risk for CV events in the subgroups with no LVH or concentric LVH at baseline, but among those with eccentric LVH at baseline, treatment toward a normal Hb level led to a significant worsening of event-free survival as compared with treatment toward a subnormal Hb target.

DISCUSSION

This echocardiographic analysis of patients enrolled in CRE-ATE confirms that LVH is a frequent complication in stages 3 to 4 CKD and is associated with an increased frequency of CV events. Moreover, the study shows that LV geometry plays an important role in predicting CV events in such patients, because the prognosis was worst in those with eccentric LVH and intermediate in those with concentric LVH (Figure 3). This suggests that an increase in myocardial wall thickness may be a beneficial adaptive response under conditions of increased cardiac workload. The relative importance of LVM and LVV for patient prognosis was previously studied in patients who were on dialysis.[28] Remarkably, there was a clear-cut association between baseline LVH and subsequent CV events in CREATE, even though patients with severe heart failure (New York Heart Association stages III and IV) were excluded from the trial, BP was reasonably controlled (136/79 and 135/77 mmHg at study end in groups 1 and 2, respectively), and the use of potentially protective CV medication was high (approximately 50% of patients were on angiotensin-converting enzyme inhibitors, approximately 20% were on angiotensin receptor blockers, and more than one third were on β blockers).[23] A comparatively low CV morbidity is also reflected by the overall first CV event rate, which was only approximately half of what had been predicted (7.8% per year). Apparently, however, LVH predicts CV events irrespective of the absolute overall risk.

Despite the association of echocardiographic findings at baseline with subsequent CV events, we did not find a progressive increase of LVM or observe a progressively increasing prevalence of LVH in the entire study population during the 3-yr study period (Figures 1 and 2). On the contrary, in patient subgroups with elevated LVMI at baseline, mean LVM decreased during the course of the investigation in both treatment arms. A similar observation was made in a previous, smaller study testing the effect of Hb normalization on the progression of LVH.[20] Conversely, several other studies suggested that LVH in patients with CKD is progressive. Thus, cross-sectional studies reported an increasing prevalence of LVH with increasing severity of CKD[3,4] and an observational study of nondialysis patients with CKD demonstrated progressive LV growth.[11] A large RCT of incident hemodialysis patients with normal baseline LVMI levels, allocated to lower and higher Hb targets, also demonstrated an increase in LVMI in both treatment groups during a follow-up of 2 yr.[22] Because in our study the patient population for which interpretable echocardiograms were available decreased with study time, our observations may to some extent be prone to survival bias. Nevertheless, enrollment in the trial seemed to stabilize the overall progression of LVH, possibly owing to the absence of hemodynamic changes associated with dialysis in conjunction with improved patient surveillance, BP control, the use of CV medications, and the avoidance of progressive anemia. Clearly, however, there was no difference between early anemia correc-
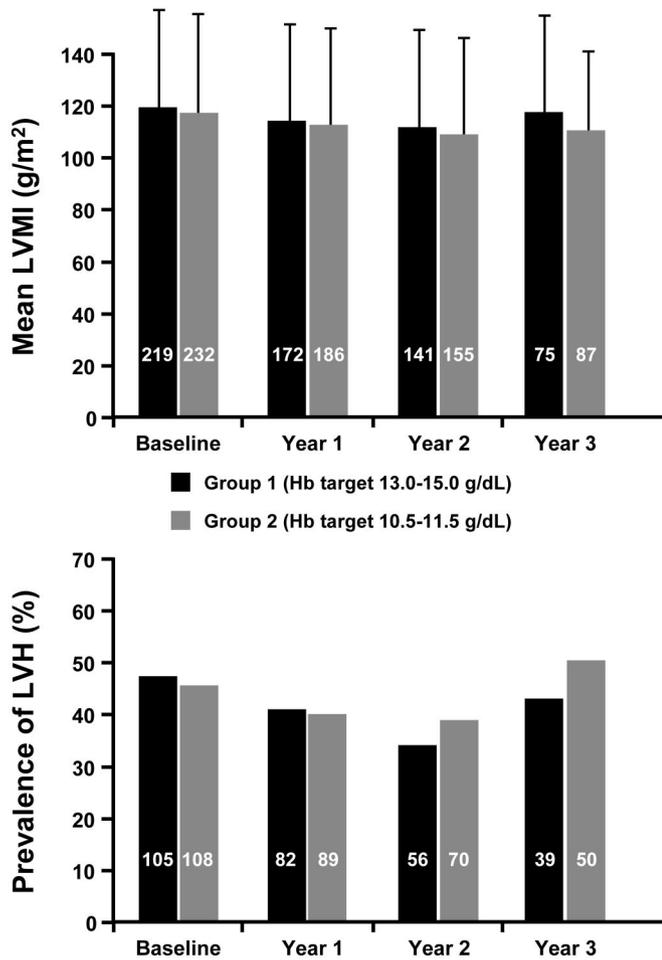
Figure 1. Mean LVMI (top) and prevalence of LVH (bottom) from years 1 to 3 in group 1 (full Hb correction; ■) and group 2 (partial Hb correction; ▦). Numbers within the bars refer to numbers of patients still in the study with interpretable echocardiograms.
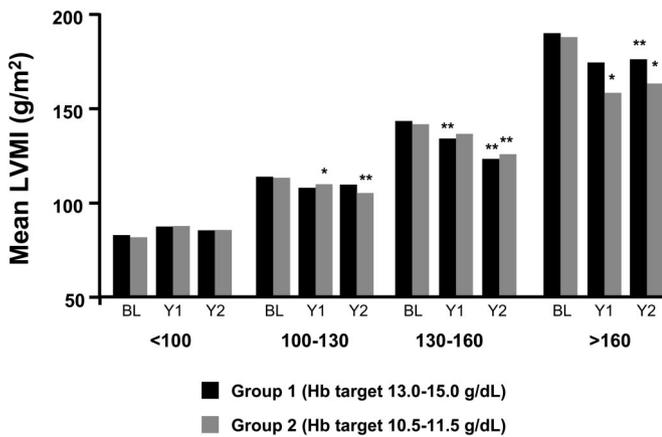
Figure 2. Mean LVMI over time in patients stratified according to baseline LVMI range. BL, baseline; Y1, year 1; Y2, year 2. $*P < 0.05$, $**P < 0.01$ *versus* baseline.

tion with a normal Hb target (group 1) and later correction toward a subnormal Hb target (group 2). The same conclusion was recently derived from a meta-analysis of other trials comparing Hb targets >12 g/dl with conventional targets in patients with moderate anemia at baseline.[29] One of the limitations of CREATE and other studies conducted so far is the lack of a control group without anemia correction, which would have been necessary to assess the impact of avoiding severe anemia.

Although the natural history of the development of LVH is complex, concentric remodeling (*i.e.*, an increase in relative wall thickness in the absence of LVH) is considered an early stage of cardiac adaptation to increased cardiac workload. Further progression may lead to concentric hypertrophy, whereas eccentric hypertrophy often reflects dilation of a ventricle that previously showed signs of concentric remodeling and/or hypertrophy or a direct consequence of volume overload.[30,31] Despite the overall stability of mean LVM and LVH prevalence, a detailed analysis of the patients stratified according to echocardiographic categories revealed marked fluctuations between categories within a 2-yr observation period (Tables 4 and 5). The absence of an overall change in mean LVM therefore reflects a neutral net balance between factors stimulating progression and factors favoring regression of LVH, rather than halted progression of poorly reversible cardiac abnormalities. Differences observed can be caused at least in part by effects of regression to the mean. Nevertheless, the striking changes over time revealed by our analysis may add to the discussion about the validity and variability of echocardiographic measurements.[32,33] In particular, in patients undergoing hemodialysis, extracellular volume status can significantly influence echocardiographic parameters; however, although CREATE did not censor patients at the onset of dialysis, >75% of patients in the 2-yr follow-up had not yet started dialysis (Supplemental Table); therefore, changes in volume status related to the dialysis schedule cannot account for the observed variability in the echocardiographic results. Long-standing abnormalities of cardiac structure and function in CKD can also improve significantly after kidney transplantation,[34,35] which further supports the reversibility of myocardial abnormalities. Targeting a normal as compared with a subnormal Hb concentration in patients with moderate anemia, however, does not seem to be effective in improving the net balance between progression and regression of LV growth and dilation.

Interestingly, the outcome of patients who had eccentric LVH at baseline and were in the complete anemia correction arm tended to be worse than that of those in the standard correction arm (Figure 3). Although the number of patients in the different subgroups was small and the difference only just statistically significant without correction for multiple comparisons, we believe that this observation generates a new hypothesis about possible adverse effects of Hb normalization. Several mechanisms, which are not mutually exclusive, may contribute. First, stimulation of erythropoiesis toward higher Hb levels increases red cell mass with possible consequences

Table 3. Summary of other echocardiographic parameters at baseline, year 1, and year 2

Parameter	Baseline		Year 1		Year 2	
	Group 1 (n = 219)	Group 2 (n = 232)	Group 1 (n = 171)	Group 2 (n = 186)	Group 1 (n = 136)	Group 2 (n = 146)
LVV (cm^3)	67.7 ± 19.2	65.1 ± 19.2	64.4 ± 16.4	66.4 ± 18.2	65.4 ± 17.6	66.5 ± 22.8
LVEDD (cm)	5.1 ± 0.7	4.9 ± 0.7	4.9 ± 0.6	4.9 ± 0.7	5.0 ± 0.6	4.9 ± 0.7
LVESD (cm)	2.9 ± 0.6	2.7 ± 0.7	2.8 ± 0.6	2.7 ± 0.6	2.8 ± 0.6	2.8 ± 0.7
LVEF (%)	81.3 ± 7.2	81.9 ± 7.7	81.7 ± 7.3	82.4 ± 8.0	81.6 ± 7.5	82.1 ± 7.6
FS (%)	43.7 ± 7.1	44.7 ± 7.9	43.9 ± 7.3	44.7 ± 7.9	44.1 ± 7.7	44.7 ± 7.8

Data are means ± SD.

Table 4. Changes in LV geometry in patients in group 1 (full anemia correction) for whom echocardiograms were interpretable at baseline and after 2 yr (n = 134)

Parameter	Baseline	Year 2 (n [%])					
		Normal LV Geometry	Concentric Remodeling	Concentric LVH	Eccentric LVH	LVH Total	NA
Normal LV geometry	57	37 (64.9)	10 (17.5)	0 (0.0)	9 (15.8)	9 (15.8)	1
Concentric remodeling	16	8 (50.0)	7 (43.8)	0 (0.0)	1 (6.3)	1 (6.3)	
Concentric LVH	27	6 (22.2)	5 (18.5)	6 (22.2)	9 (33.3)	15 (55.6)	1
Eccentric LVH	34	14 (41.2)	1 (2.9)	3 (8.8)	16 (47.1)	19 (55.9)	
LVH total	62	20 (32.2)	6 (9.7)	10 (16.1)	25 (40.3)	35 (56.5)	1

NA, data for categorizing into LV geometry group not available.

Table 5. Changes in LV geometry in patients in group 2 (partial anemia correction) for whom echocardiograms were interpretable at baseline and after 2 yr (n = 144)

Parameter	Baseline	Year 2 (n [%])					
		Normal LV Geometry	Concentric Remodeling	Concentric LVH	Eccentric LVH	LVH Total	NA
Normal LV geometry	47	29 (61.7)	8 (17.0)	1 (2.1)	9 (19.1)	10 (21.3)	
Concentric remodeling	29	18 (62.1)	8 (27.6)	1 (3.5)	2 (6.9)	3 (10.3)	
Concentric LVH	26	6 (23.1)	4 (15.4)	5 (19.2)	11 (42.3)	16 (61.5)	
Eccentric LVH	42	11 (26.2)	3 (7.1)	4 (9.5)	23 (54.8)	27 (64.3)	1
LVH total	68	17 (25.0)	7 (10.3)	9 (13.2)	34 (50.0)	43 (63.2)	1

NA, data for categorizing into LV geometry group not available.

Table 6. Determinants of LVH (by multivariate logistic regression analysis) in patients with 2-yr echocardiographic data (n = 316)

Effect/Covariate Included in the Model	OR	95% CI	P
Age (>60 versus <60 yr)	1.11	0.56 to 2.18	0.767
Gender (female versus male)	1.57	0.88 to 2.80	0.124
Race (white versus other)	0.41	0.19 to 0.91	0.029
Diabetes (yes versus no)	0.47	0.22 to 1.04	0.061
Hypertension (yes versus no)	1.82	0.24 to 13.71	0.562
Baseline SBP (mmHg)	1.03	1.00 to 1.05	0.028
Baseline DBP (mmHg)	0.96	0.92 to 1.00	0.062
Previous CVD	1.43	0.11 to 18.16	0.785
Previous MI	0.71	0.16 to 3.24	0.662
Previous CAD	1.51	0.65 to 3.49	0.334
Baseline eGFR (ml/min per 1.73 m^2)	0.95	0.87 to 1.04	0.295
Baseline eGFR (>25 versus <25 ml/min per 1.73 m^2)	1.69	0.56 to 5.10	0.350
Baseline Hb (g/dl)	1.21	0.76 to 1.94	0.420

CI, confidence interval; OR, odds ratio.

for blood volume. Although small studies in normal volunteers[36] and patients on dialysis[37,38] indicated that total blood volume remains stable after treatment with epoetin, as a result of a compensatory decline in plasma volume, this adaptive reduction in plasma volume presumably requires either normal kidney function or increased ultrafiltration during dialysis. Plasma volume control is compromised in advanced CKD. In fact, the single small study available in nondialysis patients with CKD showed a decline in plasma volume that was insufficient to compensate for the increase in red cell volume, thereby resulting in an increase in total blood volume after anemia correction.[39] Such an increase in blood volume might have a negative impact on cardiac function in patients with eccentric LVH. Second, as per study design, the hematocrit, which influences whole-blood viscosity and peripheral vascular resistance, was higher in group 1 than in group 2. The difference was moderate (approximately 5 percentage points),[23] but blood viscosity is

Table 7. Determinants of LV growth (by multivariate logistic regression analysis) in patients with 2-yr echocardiographic data ($n = 316$)

Variable	OR	95% CI	P
Age (>60 *versus* <60 yr)	0.76	0.34 to 1.67	0.493
Gender (female *versus* male)	1.60	0.81 to 3.15	0.176
Race (white *versus* other)	0.54	0.23 to 1.26	0.153
Diabetes mellitus (yes *versus* no)	0.96	0.39 to 2.37	0.932
Hypertension (yes *versus* no)	1.51	0.16 to 13.95	0.718
Baseline SBP (mmHg)	1.02	0.99 to 1.04	0.221
Baseline DBP (mmHg)	0.99	0.94 to 1.04	0.714
Previous CVD	0.91	0.06 to 13.64	0.947
Previous CAD	1.50	0.56 to 4.02	0.422
Baseline eGFR (ml/min per 1.73 m^2)	0.95	0.85 to 1.06	0.336
Baseline eGFR (>25 *versus* <25 ml/min)	1.65	0.47 to 5.84	0.437
Baseline Hb (g/dl)	1.22	0.71 to 2.12	0.473

exponentially related to hematocrit.[40] Although the precise hemodynamic consequences are difficult to predict, it is possible that they have more impact in patients with eccentric LVH than in those without. Third, treatment with epoetin has been associated with an increase in BP, and both hemodynamic as well as nonhemodynamic mechanisms have been implicated. Although there was no difference in BP between groups 1 and 2 in CREATE, hypertension was a more frequently reported adverse event in patients targeted to the higher Hb level,[23] and patients with eccentric LVH at baseline could be more sensitive to BP increases. Finally, nonerythropoietic adverse effects of epoetin might also play a role, as suggested by a recent secondary analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study.[41]

Irrespective of the underlying mechanisms, the observation that targeting toward a normal Hb concentration aggravates the increased risk for patients who already show signs of established cardiac overload may also explain differences in outcomes among the four largest RCTs that have so far compared the effect of partial *versus* complete anemia correction. Two of these trials, the study by Parfrey *et al.*[22] of incident dialysis patients and CREATE, found no increase in CV risk in the overall study population, whereas the study by Besarab *et al.*[27] and CHOIR[26] reported trends toward increased mortality in the higher Hb arms. Although in the latter two studies no echocardiography was done, the characteristics of enrolled patients suggest that the proportion of patients with eccentric LVH and the severity of LV dilation were higher in these two trials than in the two others. Parfrey *et al.*[22] excluded patients with ventricular dilation, whereas Besarab *et al.*[27] enrolled only patients with clinical evidence of congestive heart failure or ischemic heart disease. CHOIR also enrolled patients with a high CV burden, with hypertension and diabetes being much more frequent causes of CKD than in CREATE.

In conclusion, in patients with stages 3 to 4 CKD, LVH is frequent and associated with poor outcomes. Both progression and regression of abnormal LV geometry can be observed, pointing toward opportunities for intervention. Although targeting toward a normal Hb level as compared with a subnor-

mal level in patients with moderate anemia at baseline did not result in differences in LVM and LV geometry, it may further aggravate the adverse prognosis of eccentric LVH.

CONCISE METHODS

Study Population and Design

Details of the CREATE study protocol and population are described elsewhere.[23,42] In brief, the CREATE trial enrolled patients with CKD from 94 centers in 22 countries. Major inclusion criteria were an estimated GFR of 15 to 35 ml/min per 1.73 m^2 body surface area (Cockcroft-Gault), mild to moderate renal anemia (Hb 11.0 to 12.5 g/dl), systolic BP ≤170 mmHg, and diastolic BP ≤95 mmHg. Patients with New York Heart Association stages III and IV congestive heart failure or whose renal insufficiency was rapidly progressive and/or expected to result in the requirement for renal replacement therapy within 6 mo were excluded.

CREATE was designed as an open-label, parallel-group study in which patients were randomly assigned (1:1) to receive epoetin beta (NeoRecormon; F. Hoffmann-La Roche Ltd., Basel, Switzerland), starting at 2000 IU subcutaneously once weekly, either beginning immediately, to a target Hb level of 13.0 to 15.0 g/dl (group 1), or beginning only when Hb levels had fallen below 10.5 g/dl, to a target Hb level of 10.5 to 11.5 g/dl (group 2). The primary end point was time to a first CV event (a composite of sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, unstable angina, manifestation of peripheral vascular disease, or severe cardiac arrhythmias). Secondary end points included the echocardiographic assessments of LVMI, LVH, and LV function from baseline to follow-up in each study group and respective comparisons between the two study arms.

All patients provided written informed consent. The study protocol was approved by local ethics committees. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Echocardiographic Assessments

Patients underwent echocardiography at baseline and then annually and at the initiation of dialysis, using American Society of Echocardiography standards.[43] Parasternal twodimensional (2D) long-axis view (of at least 15 s), M-mode view, and 2D short-axis view, and apical 2D two-chamber and four-chamber views were recorded. For patients who required hemodialysis, echocardiography was performed 15 to 20 h after a dialysis session. All recordings were interpreted in a blinded manner by an independent echocardio-
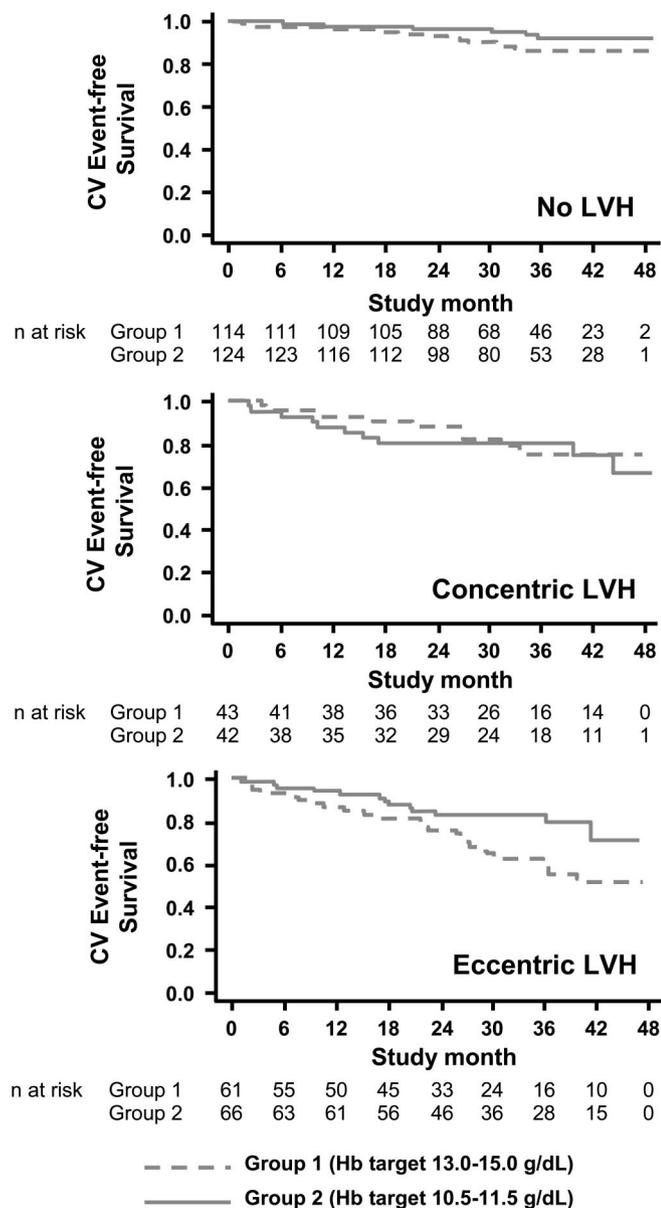
Figure 3. CV event-free survival in both treatment arms in patients without LVH at baseline (top; *n* = 238), patients with concentric LVH at baseline (middle; *n* = 85), and patients with eccentric LVH at baseline (bottom; *n* = 127). Overall event-free survival was significantly worse in the presence of concentric LVH and eccentric LVH as compared with the absence of LVH (log rank test *P* = 0.0009 and *P* < 0.0001). The percentage of events was higher in the patients with eccentric LVH than in the concentric group, but this difference did not reach statistical significance (hazard ratio 1.37; 95% confidence interval 0.78 to 2.38; *P* = 0.27). Moreover, in the presence of eccentric LVH at baseline, event-free survival was significantly worse in group 1 as compared with group 2 (*P* = 0.034).

graphic core laboratory (Cardio-Analytics, Plymouth, UK). All analyses are based on patients with at least one assessable echocardiographic recording at baseline.

Recorded echocardiographic parameters included poste

rior wall thickness, relative wall thickness, intraventricular septal wall thickness, LVMI, LVV, LV end-diastolic diameter, LV end-systolic diameter, FS, and LVEF. According to standard criteria, LVH was defined as an LVMI >100 g/m^2 in women and >131 g/m^2 in men, concentric LVH as LVH with a relative wall thickness >0.45, eccentric LVH as LVH with a relative wall thickness ≤ 0.45, concentric remodeling as a relative wall thickness >0.45 in the absence of LVH, LV dilation as left ventricular volume index >90 ml/m^2, and LV systolic dysfunction as LVEF $<40\%$ and/or FS <0.25.[44] LV growth was defined as an increase in LVMI of at least 20% from baseline or growth of >20 g/m^2. For further details and the respective formulas, see supplementary materials.

Statistical Analysis

All presented analyses were included in a predefined statistical analysis plan. All analyses were secondary objectives in the study; therefore, no correction for multiple corrections was performed and the results are primarily of a hypothesis-generating nature. Echocardiographic variables were analyzed as changes from baseline at 1 and 2 yr after randomization using an analysis of covariance model with the treatment group as the main factor and the baseline value as covariate. Analyses of LVMI over time were performed, including mean, median, minimum, maximum, and SD for LVMI at each time point by treatment group. A covariance model with baseline LVMI and LVH as co-factors was used for LVMI and LVH at 1 yr and for LVMI at 2 yr after univariate analyses for predefined factors of specific interest (together with treatment). Multivariate analyses for all factors significant at 15% α level were performed. A Cox proportional hazard model was used to estimate the relative risks and the corresponding 95% confidence intervals of a CV outcome event.

REFERENCES

1. Schiffrin EL, Lipman ML, Mann JF: Chronic kidney disease: Effects on the cardiovascular system. *Circulation* 116: 85–97, 2007

2. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 47: 186–192, 1995

3. Levin A, Singer J, Thompson CR, Ross H, Lewis M: Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis* 27: 347–354, 1996

4. Nardi E, Palermo A, Mulè G, Cusimano P, Cottone S, Cerasola G: Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. *J Hypertens* 27: 633–641, 2009

5. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE: Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 11: 1277–1285, 1996

6. London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, Metivier F, Adda H, Safar ME: Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: Follow-up of an interventional study. *J Am Soc Nephrol* 12: 2759–2767, 2001

7. Kessler M, Zannad F, Lehert P, Grünfeld JP, Thuilliez C, Leizorovicz A, Lechat P, FOSIDIAL Investigators: Predictors of cardiovascular events in patients with end-stage renal disease: An analysis from the Fosinopril in dialysis study. *Nephrol Dial Transplant* 22: 3573–3579, 2007

8. Silberberg JS, Barre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 36: 286–290, 1989

9. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis* 28: 53–61, 1996

10. Silberberg J, Racine N, Barre P, Sniderman AD: Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. *Can J Cardiol* 6: 1–4, 1990

11. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O: Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 34: 125–134, 1999

12. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, Young JB, Solomon SD, Granger CB, Ostergren J, Olofsson B, Michelson EL, Pocock S, Yusuf S, Swedberg K, Pfeffer MA, CHARM Committees and Investigators: Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: Results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 113: 986–994, 2006

13. Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J Am Soc Nephrol* 16: 1803–1810, 2005

14. Eckardt KU: Cardiovascular consequences of renal anaemia and erythropoietin therapy. *Nephrol Dial Transplant* 14: 1317–1323, 1999

15. London GM, Zins B, Pannier B, Naret C, Berthelot JM, Jacquot C, Safar M, Drueke TB: Vascular changes in hemodialysis patients in response to recombinant human erythropoietin. *Kidney Int* 36: 878–882, 1989

16. Macdougall IC, Lewis NP, Saunders MJ, Cochlin DL, Davies ME, Hutton RD, Fox KA, Coles GA, Williams JD: Long-term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. *Lancet* 335: 489–493, 1990

17. Sikole A, Polenakovic M, Spirovska V, Polenakovic B, Masin G: Analysis of heart morphology and function following erythropoietin treatment of anemic dialysis patients. *Artif Organs* 17: 977–984, 1993

18. Portolés J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A: Cardiovascular effects of recombinant human erythropoietin in predialysis patients. *Am J Kidney Dis* 29: 541–548, 1997

19. Foley RN, Parfrey PS, Morgan J, Barré PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 58: 1325–1335, 2000

20. Roger SD, McMahon LP, Clarkson A, Disney A, Harris D, Hawley C, Healy H, Kerr P, Lynn K, Parnham A, Pascoe R, Voss D, Walker R, Levin A: Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): Results of a randomised clinical trial. *J Am Soc Nephrol* 15: 148–156, 2004

21. Levin A, Djurdjev O, Thompson CR, Barrett B, Ethier J, Carlisle E, Barre P, Magner P, Muirhead N, Tobe S, Tam P, Wadgymar JA, Kappel J, Holland D, Pichette V, Shoker A, Soltys G, Verrelli M, Singer J: Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis* 46: 799–811, 2005

22. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anaemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 16: 2180–2189, 2005

23. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A, CREATE Investigators: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 355: 2071–2084, 2006

24. Macdougall I, Temple RM, Kwan J: Is early treatment of anaemia with epoetin alfa beneficial to predialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomised, comparative group trial. *Nephrol Dial Transplant* 22: 784–793, 2007

25. Ritz E, Laville M, Bilous RW, O'Donoghue D, Scherhag A, Burger U, de Alvaro F: Anemia Correction in Diabetes Study Investigators: Target level for hemoglobin correction in patients with diabetes and CKD: Primary results of the Anemia Correction in Diabetes (ACORD) Study [erratum appears in *Am J Kidney Dis* 49: 562, 2007]. *Am J Kidney Dis* 49: 194–207, 2007

26. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355: 2085–2098, 2006

27. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998

28. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barré PE: The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 5: 2024–2031, 1995

29. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P: Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: A meta-analysis. *Clin J Am Soc Nephrol* 4: 755–762, 2009

30. Hunter JJ, Chien KR: Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med* 341: 1276–1283, 1999

31. Selvetella G, Lembo G: Mechanisms of cardiac hypertrophy. *Heart Fail Clin* 1: 263–273, 2005

32. Zoccali C: How important is echocardiography for risk stratification in follow-up of patients with chronic kidney disease? *Nat Clin Pract Nephrol* 3: 178–179, 2007

33. Mark PB, Patel RK, Jardine AG: Are we overestimating left ventricular abnormalities in end-stage renal disease? *Nephrol Dial Transplant* 22: 1815–1819, 2007

34. Rigatto C, Foley RN, Kent GM, Guttmann R, Parfrey PS: Long-term changes in left ventricular hypertrophy after renal transplantation. *Transplantation* 70: 570–575, 2000

35. Zolty R, Hynes PJ, Vittorio TJ: Severe left ventricular systolic dysfunction may reverse with renal transplantation: Uremic cardiomyopathy and cardiorenal syndrome. *Am J Transplant* 8: 2219–2224, 2008

36. Lundby C, Thomsen JJ, Boushel R, Koskolou M, Warberg J, Calbet JA, Robach P: Erythropoietin treatment elevates haemoglobin concentra-

tion by increasing red cell volume and depressing plasma volume. *J Physiol* 578: 309–314, 2007

37. Abraham PA, Opsahl JA, Keshaviah PR, Collins AJ, Whalen JJ, Asinger RW, McLain LA, Hanson G, Davis MG, Halstenson CE: Body fluid spaces and blood pressure in hemodialysis patients during amelioration of anemia with erythropoietin. *Am J Kidney Dis* 16: 438–446, 1990

38. Lebel M, Kingma I, Grose JH, Langlois S: Hemodynamic and hormonal changes during erythropoietin therapy in hemodialysis patients. *J Am Soc Nephrol* 9: 97–104, 1998

39. Anastassiades E, Howarth D, Howarth J, Shanks D, Waters H, Hyde K, Yin JL, Geary C, Gokal R: Influence of blood volume on the blood pressure of predialysis and peritoneal dialysis patients treated with erythropoietin. *Nephrol Dial Transplant* 8: 621–625, 1993

40. Macdougall IC, Hutton RD, Coles GA, Williams JD: The use of erythropoietin in renal failure. *Postgrad Med J* 67: 9–15, 1991

41. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK: Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 74: 791–798, 2008

42. Eckardt K-U: The CREATE trial: Building the evidence. *Nephrol Dial Transplant* 16[Suppl 2]: 16–18, 2001

43. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 2: 358–367, 1989

44. Huwez FU, Pringle SD, Macfarlane PW: A new classification of left ventricular geometry in patients with cardiac disease based on M-mode echocardiography. *Am J Cardiol* 70: 681–688, 1992