Effects of Early and Late Intervention with Epoetin α on Left Ventricular Mass among Patients with Chronic Kidney Disease (Stage 3 or 4): Results of a Randomized Clinical Trial

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Abstract. It is not known whether prevention of anemia among patients with chronic kidney disease would affect the development or progression of left ventricular (LV) hypertrophy. A randomized controlled trial was performed with 155 patients with chronic kidney disease (creatinine clearance, 15 to 50 ml/min), with entry hemoglobin concentrations ([Hb]) of 110 to 120 g/L (female patients) or 110 to 130 g/L (male patients). Patients were monitored for 2 yr or until they required dialysis; the patients were randomized to receive epoetin α as necessary to maintain [Hb] between 120 and 130 g/L (group A) or between 90 and 100 g/L (group B). [Hb] increased for group A (from 112 ± 9 to 121 ± 14 g/L, mean ± SD) and decreased for group B (from 112 ± 8 to 108 ± 13 g/L) (P < 0.001, group A versus group B). On an intent-to-treat analysis, the changes in LV mass index for the groups during the 2-yr period were not significantly different (2.5 ± 20 g/m² for group A versus 4.5 ± 20 g/m² for group B, P = NS). There was no significant difference between the groups in 2-yr mean unadjusted systolic BP (141 ± 14 versus 138 ± 13 mmHg) or diastolic BP (80 ± 6 versus 79 ± 7 mmHg). The decline in renal function in 2 yr, as assessed with nuclear estimations of GFR, also did not differ significantly between the groups (8 ± 9 versus 6 ± 8 ml/min per 1.73 m²). In conclusion, maintenance of [Hb] above 120 g/L, compared with 90 to 100 g/L, had similar effects on the LV mass index and did not clearly affect the development or progression of LV hypertrophy. The maintenance of [Hb] above 100 g/L for many patients in group B might have been attributable to the relative preservation of renal function.

Chronic kidney disease (CKD) is widespread in the community, with a prevalence far exceeding previous estimates (1). Many studies examining mortality and morbidity rates among patients with CKD have identified high rates of cardiovascular events. When even mild renal insufficiency is associated with other risk factors for cardiovascular disease, the risk of subsequent cardiovascular events is significantly increased (2–10). The effect of mild renal insufficiency (serum creatinine levels of >124 μM) on cardiovascular risk is possibly also independent of other known risk factors and treatment (11–15). For patients established on dialysis, cardiovascular disease is responsible for up to 50% of the all-cause mortality rate (16,17). It is therefore important to attempt to reduce the incidence of cardiovascular events with risk factor modification before the onset of dialysis.

Left ventricular (LV) hypertrophy (LVH) is recognized as a powerful independent predictor of death and morbidity in the dialysis population, together with anemia, hypertension, malnutrition, hyperparathyroidism, and an elevated calcium-phos-
phate product (18–22). Clinically significant anemia, in particular, is often present when creatinine clearance decreases to <40 ml/min (stage 3 or 4) (23) and is closely associated with the development of LVH, which is often manifest before the commencement of dialysis (24–26).

In addition to the standard management of modifiable risk factors, it is currently not known whether avoidance of anemia could reduce or reverse the development of LVH in the CKD (i.e., predialysis) population. This study was designed to assess the effects of early correction of anemia, with epoetin α, on LV mass among patients with CKD.

Materials and Methods
Patient Selection and Study Design

This was an open-label, randomized, prospective, multicenter trial conducted in Australia and New Zealand. The ethics committees of the participating centers approved the protocol, and written informed consent was obtained from all patients.

A research nurse or investigator approached all identifiable predialysis patients at each participating center for study inclusion. Patients were required to be between 18 and 75 yr of age, to have demonstrated a decrease in hemoglobin concentration ([Hb]) of ≥10 g/L within the 12 mo before enrollment, and to have reached a level of 110 to 130 g/L (male patients) or 100 to 120 g/L (female patients). Patients were also required to have estimated creatinine clearances of 15 to 50 ml/min [derived from serum creatinine levels with the Cockcroft-Gault equation (27), adjusted for gender and body mass index].

Of the patients who were approached, 296 agreed to enter the study and underwent initial screening. After screening, 155 patients were considered eligible for randomization (Figure 1). Randomization codes were obtained by telephoning a central number. Patients were randomized according to computer-generated stratification tables (based on angiotensin-converting enzyme inhibitor medication use and age of >60 yr), to achieve equal numbers in each group. Order concealment was maintained until the intervention was assigned. Enrolment proceeded from May 1998 to March 2000. Eligible patients were entered into the study immediately after screening. The cause of renal failure for randomized patients included glomerulonephritis (group A, 22 patients; group B, 20 patients), diabetes mellitus (group A, 20 patients; group B, 16 patients), adult polycystic kidney disease (group A, eight patients; group B, 10 patients), drug-induced nephropathy (group A, five patients; group B, seven patients), renovascular disease (group A, five patients; group B, seven patients), congenital or hereditary renal disease (group A, four patients; group B, six patients), other causes (group A, 10 patients; group B, 10 patients), and unknown causes (group A, one patient; group B, four patients).

For group A patients, subcutaneous epoetin α therapy was initiated with a weekly regimen to maintain the [Hb] between 120 and 130 g/L throughout the study period (up to 2 yr after enrollment and/or the onset of renal replacement therapy). For group B patients, epoetin α therapy was initiated if the [Hb] was <90 g/L at two consecutive clinic visits 2 mo apart or was <80 g/L at any visit without a cause other than CKD. [Hb] was then maintained between 90 and 100 g/L for the remainder of the study period.

Before entry into the study, patients did not exhibit iron deficiencies, with serum ferritin levels of >100 μg/L and/or transferrin saturation values of >20%. During the course of the study, patients received orally or occasionally intravenously administered iron polymaltose as required to maintain those levels. Patients with unstable or poorly controlled angina, severe congestive cardiac failure (New York Heart Association grade III or IV), severe chronic respiratory disease, symptomatic peripheral vascular disease, or a created arteriovenous fistula were excluded from the study.

Patients were evaluated monthly for 4 mo and then every 2 mo, with laboratory assessments and BP measurements. The average of

![Figure 1. Patient flow diagram, indicating selection, randomization, and discontinuation according to treatment group.](image-url)
three seated sphygmomanometric BP readings, taken 1 min apart after
5 min of rest, was recorded. The target BP during the study was
<140/90 mmHg, and antihypertensive medication was prescribed
according to investigator preference.

Echocardiograms and GFR measurements were obtained at the
screening visit, 1 and 2 yr after randomization, and before institution
of renal replacement therapy or discontinuation/early withdrawal.
Ideally, at least three echocardiograms were obtained for each patient,
with two-dimensional, guided, M-mode echocardiography with stan-
dard views. Each site obtained its own echocardiograms, with the
assistance of a trained, full-time technician and the use of the same
ultrasonographic system for all studies. All technicians were required
to undergo a full day of procedure standardization training at a core
laboratory, to ensure compliance with the echocardiographic study
protocols defined by the core laboratory (28). All studies were vide-
otaped and sent to the core laboratory; the results were subjected to
initial blinded analysis by a skilled sonographer, with subsequent
blinded verification (with correction of measurements, if necessary)
by an experienced echocardiologist.

Leading edge-to-leading edge measurements were made according
to the recommendations of the American Society of Echocardiogra-
phy (29). The internal diameter of the left ventricle at end diastole
(LVIDD), the thickness of the interventricular septum (IVS), and
the thickness of the posterior wall (PW) were measured at the onset of the
Q wave of the electrocardiogram. The LV mass (LVM) was calculated
with the corrected American Society of Echocardiography cube
formula (30,31), as follows: LVM = 0.8 [(LVIDD + IVS + PW)³
– LVIDD³] + 0.6 g. The LV mass index (LVMi) was calculated by dividing the LV mass by the body surface area.

End Points
The primary end point was the change in LVMi in 2 yr. The aim
was to determine whether maintenance of [Hb] between 120 and 130
g/L (compared with progressive anemia) among patients with CKD
prevented or delayed the progression of LV growth when other
complications of CKD were aggressively managed. LVH was defined
as a LVMi of >125 g/m² for male patients or >100 g/m² for female
patients (32,33). Primary efficacy was evaluated on the basis of the
LVMi.

From previous studies (24,25), a SD of 30 g/m² was assumed for
the change in LVMi (26). A sample size of 75 patients per treatment
arm was needed to detect a difference in LVMi of 15 g/m² at a
two-sided significance level of 5%, with a power of 80% and an
attrition rate of 20%. The study was therefore powered to randomize
150 eligible patients in a ratio of 1:1 (group A/group B).

Secondary end points included renal function, cardiac performance,
and quality of life. Renal function was assessed to determine whether
maintenance of a higher [Hb] affected the rate of decline of renal
function. Renal deterioration was assessed on the basis of the time to
the onset of renal replacement therapy, the calculated creatinine
clearance, and nuclear estimations of GFR (in milliliters per minute
per 1.73 m²) as either ⁵¹Cr-EDTA or ⁹⁹mTc-diethylenetriamine penta-
acetic acid clearance. Effects on cardiac performance were assessed
on the basis of systolic (fractional shortening and ejection fraction)
and diastolic (E-A wave relationships) function. Quality of life was
measured with two standardized questionnaires, the SF-36 Health
Survey and the Renal Quality of Life Profile.

Statistical Analyses
Analyses and data presented are based on an intent-to-treat
approach, with all patients being analyzed in the treatment group to
which they were randomized. In addition, a per-protocol analysis was
performed for patients who achieved protocol targets within 3 mo of
the end of the study, i.e., [Hb] of 120 to 130 g/L (group A) or 90 to
100 g/L (group B).

The changes in LVMi in 2 yr were compared between groups with
ANOVA techniques. Clinical and echocardiographic variables were
appraised primarily in relation to the LVMi changes. Other statistical
analyses included t tests, stepwise linear regression analyses, Kaplan-
Meier survival analyses, and Pearson correlation coefficient analyses,
as appropriate. In addition to the primary analyses, a regression model
incorporating all available echocardiograms was constructed to deter-
mine treatment differences with respect to changes in LVMi. This
allowed adjustment for any differences in the time at which the LVMi
was measured.

Results are expressed as mean ± SD or 95% confidence intervals
(CI), unless otherwise indicated. The statistical software package
SPSS version 11.0 (SPSS, Inc., Chicago, IL) was used for analyses.

Results
Clinical Parameters
The initial clinical parameters were similar for the groups.
The use of angiotensin-converting enzyme inhibitors and/or
other antihypertensive agents did not differ significantly be-
tween the groups at the end of the study. Angiotensin II
receptor antagonists were not used during the study. Estimates
of body surface area, weight, and height (2,7) were equal
between the groups at study commencement and did not
change during the study (Table 1).

Unadjusted systolic and/or diastolic BP values at each time
point were comparable for groups A and B for the majority of
the study, but diastolic BP values were significantly higher for
group B at 18 and 21 mo (Figure 2). Postrandomization BP
values were also analyzed with a repeated-measures analysis,
for assessment of whether, on average during the 2-yr period,
there was a difference between the treatment groups.
There was no difference in either systolic or diastolic BP between
the groups, inasmuch as there was no difference in the calculated
2-yr unadjusted mean arterial BP (100 ± 7 versus 98 ± 8
mmHg) or pulse pressure (60 ± 13 versus 58 ± 13 mmHg)
(Table 2).

Analyses were then performed with the corresponding base-
line systolic or diastolic BP fitted as a covariate to adjust for
each patient’s starting BP. In all repeated-measures analyses, a
Toeplitz correlation structure, which allows for the correlation
between time points to be less when the time points are not
adjacent, was used to account for the inpatient variations. In
these analyses, the 2-yr adjusted mean systolic BP did not
differ between the groups (140 and 138 mmHg for groups A
and B, respectively; 95% CI, −1.3 to 5.4; P = NS) but a
significantly higher mean diastolic BP was observed for group
A (81 versus 78 mmHg; 95% CI, 0.6 to 4.2; P = 0.009).

Laboratory Parameters
The initial [Hb] values for the groups were equal, and the
changes observed during the study are presented in Figure 3.
Although intergroup differences were statistically significant,
the absolute decrease and the rate of decrease for group B
during the 24 mo were slight (Figure 3). Because the [Hb] for group A was maintained at or slightly above 120 g/L, the difference between groups, although statistically significant, was also of marginal clinical significance (Table 2, Figure 3).

Albumin levels and iron parameters did not change significantly during the study (initial, 24-mo, and mean 2-yr values). Initial parathyroid hormone levels were similar for the groups, but the mean 2-yr level was slightly higher for group A, compared with group B ($P = 0.05$). Creatinine levels demonstrated progressive increases for both groups, without a significant intergroup difference at any time point (Table 2).

### Table 1. Anthropometric, demographic, and clinical data, according to group.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53 ± 14 (M), 50 ± 14 (F)</td>
<td>54 ± 12 (M), 50 ± 15 (F)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>38 (51%)/36 (49%)</td>
<td>33 (42%)/45 (58%)</td>
</tr>
<tr>
<td>Body surface area, (m²)</td>
<td>1.87 ± 0.22</td>
<td>1.84 ± 0.19</td>
</tr>
<tr>
<td>Weight, (kg)</td>
<td>78 ± 17</td>
<td>76 ± 14</td>
</tr>
<tr>
<td>Height, (m²)</td>
<td>4.1 ± 0.6</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (24%)</td>
<td>26 (33%)</td>
</tr>
<tr>
<td>Use of ACE Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial</td>
<td>53 (74%)</td>
<td>58 (74%)</td>
</tr>
<tr>
<td>final</td>
<td>47 (71%)</td>
<td>43 (70%)</td>
</tr>
<tr>
<td>Use of other antihypertensive agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial</td>
<td>20 (27%)</td>
<td>24 (31%)</td>
</tr>
<tr>
<td>final</td>
<td>15 (23%)</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>Patients commencing dialysis</td>
<td>24 (32%)</td>
<td>15 (19%)</td>
</tr>
</tbody>
</table>

*Data supplied are absolute numbers, percentages, and/or mean ± SD as indicated. Except where indicated, data represent initial findings. ACE, angiotensin-converting enzyme; M, male; F, female. No between-group comparisons achieved statistical significance.*

During the 24 mo were slight (Figure 3). Because the [Hb] for group A was maintained at or slightly above 120 g/L, the difference between groups, although statistically significant, was also of marginal clinical significance (Table 2, Figure 3).

Albumin levels and iron parameters did not change significantly during the study (initial, 24-mo, and mean 2-yr values). Initial parathyroid hormone levels were similar for the groups, but the mean 2-yr level was slightly higher for group A, compared with group B ($P < 0.05$). Creatinine levels demonstrated progressive increases for both groups, without a significant intergroup difference at any time point (Table 2).

### Echocardiographic Results

**Intention-to-Treat Analysis.** For analyses of group A versus group B, 152 echocardiograms (group A, 74; group B, 78) obtained after randomization were available for analysis. There were 67 and 69 echocardiograms obtained at 1 yr and 63 and 54 echocardiograms obtained at 2 yr for groups A and B, respectively. The initial LVMi values did not differ between the groups (105 ± 23 and 101 ± 23 g/m² for groups A and B, respectively; $P = 0.33$) (Table 2). The change in LVMi in 2 yr for group A was 2.5 ± 20 g/m², compared with 4.5 ± 20 g/m² for group B (95% CI, −8.4 to 4.0; $P = 0.44$). Assuming this rate of change in LVMi during the 2-yr period, a total of 1571 patients would have been required to demonstrate a significant difference ($P < 0.05$) between groups in a post hoc power analysis.

There was no significant difference in LVMi values between groups at the end of the study ($P = 0.65$) (Figure 4), regardless of whether values were calculated according to estimated body surface area or height².7 (data not shown). Except for the initial ventricular septum thickness (10.7 ± 1.5 mm for group A, compared with 10.2 ± 1.5 mm for group B; $P = 0.041$), no significant difference between groups was identified with respect to echocardiographic indices, including LV end-diastolic diameter and volume, end-systolic diameter and volume, and posterior wall thickness (data not shown). Cardiac systolic function was generally good, with the lowest LV ejection fraction being >34%. The mean LV ejection fractions at study end were 59 ± 7 and 61 ± 9% for groups A and B, respectively.

Changes in pooled LVMi estimates ($n = 117$) during the 2-yr period demonstrated no correlation with BP indices, parathyroid hormone levels, albumin levels, GFR, age, diabetes mellitus, or the use of antihypertensive medications. In a regression model that incorporated all echocardiograms obtained during the 2-yr period, there was a nonsignificant increase in...
Table 2. Initial, 1-yr, 2-yr, and mean values during the study period for echocardiographic, clinical, and laboratory data, according to group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>1 yr</th>
<th>2 yr</th>
<th>2-yr Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>105 ± 23</td>
<td>101 ± 23</td>
<td>105 ± 22</td>
<td>104 ± 21</td>
</tr>
<tr>
<td>Change in LVMi (g/m²)</td>
<td>0 ± 17</td>
<td>2 ± 17</td>
<td>2.5 ± 20</td>
<td>4.5 ± 20</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139 ± 19</td>
<td>137 ± 18</td>
<td>142 ± 19</td>
<td>137 ± 20</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 ± 11</td>
<td>81 ± 10</td>
<td>82 ± 10</td>
<td>80 ± 12</td>
</tr>
<tr>
<td>[Hb] (g/L)</td>
<td>112 ± 9</td>
<td>112 ± 8</td>
<td>124 ± 11</td>
<td>110 ± 13</td>
</tr>
<tr>
<td>GFR, (ml/min per 1.73 m²)</td>
<td>26 ± 11</td>
<td>25 ± 11</td>
<td>24 ± 11</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>Creatinine, (mM)</td>
<td>0.28 ± 0.09</td>
<td>0.33 ± 0.15</td>
<td>0.32 ± 0.14</td>
<td>0.48 ± 0.28</td>
</tr>
<tr>
<td>PTH, (pM)</td>
<td>21 ± 19</td>
<td>18 ± 16</td>
<td>22 ± 24</td>
<td>24 ± 23</td>
</tr>
<tr>
<td>Albumin, (g/L)</td>
<td>40 ± 4</td>
<td>40 ± 5</td>
<td>38 ± 4</td>
<td>39 ± 4</td>
</tr>
<tr>
<td>Ferritin, (µg/L)</td>
<td>188 ± 176</td>
<td>192 ± 216</td>
<td>188 ± 161</td>
<td>224 ± 324</td>
</tr>
<tr>
<td>Transferrin saturation, (%)</td>
<td>26 ± 9</td>
<td>26 ± 8</td>
<td>27 ± 11</td>
<td>27 ± 9</td>
</tr>
</tbody>
</table>

* Results are expressed as mean ± SD. LVMi, left ventricular mass index; PTH, parathyroid hormone; [Hb], hemoglobin concentration.

log LVMi (adjusted for height²) of 0.7%/yr for group A patients, compared with 3.6%/yr for group B patients (P = 0.09).

Patients with LVH in baseline assessments were also studied. At the commencement of the study, 21 of 74 patients in group A and 25 of 78 in group B demonstrated echocardiographic evidence of LVH. When patients were divided into groups with or without LVH at the commencement of the trial (irrespective of treatment group), those with preexisting LVH demonstrated a significant decrease in LVMi (from 127 ± 18 to 122 ± 26 g/m², n = 33, P < 0.001) in 2 yr. Those with normal initial LVMi values exhibited an increase in LVMi (from 93 ± 16 to 99 ± 21 g/m², n = 84, P < 0.001); however, the changes were not related to [Hb]. The difference in the changes in LVMi in 2 yr between patients with and without LVH in baseline assessments was also significant (−3.9 ± 19 versus 7.0 ± 19 g/m², P = 0.006).

Figure 3. [Hb] (mean ± SD) measured at 3-mo intervals during the study. All comparisons between groups indicated significant differences, except for the initial values (P < 0.001). The numbers of patients remaining in the study at 6-mo intervals are indicated. ◆, group A; ■, group B.

Figure 4. Initial, 12-mo, and 24-mo estimates of left ventricular mass index (LVMi) (mean ± SD) for group A (higher [Hb]) (■) and group B (lower [Hb]) (□). There were no significant differences between or changes within groups during the study.
Table 3. Initial clinical and laboratory data and 2-yr echocardiographic results for “protocol objective-achieved” patients in their respective groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 37)</th>
<th>Group B (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53 ± 11</td>
<td>54 ± 14</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>18/19</td>
<td>8/7</td>
</tr>
<tr>
<td>[Hb] (g/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial</td>
<td>112 ± 11</td>
<td>108 ± 6</td>
</tr>
<tr>
<td>final</td>
<td>130 ± 8</td>
<td>92 ± 5</td>
</tr>
<tr>
<td>2-yr mean</td>
<td>123 ± 5</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial</td>
<td>27 ± 11</td>
<td>22 ± 7</td>
</tr>
<tr>
<td>final</td>
<td>19 ± 9</td>
<td>15 ± 6</td>
</tr>
<tr>
<td>2-yr mean</td>
<td>23 ± 9</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial</td>
<td>108 ± 23</td>
<td>101 ± 28</td>
</tr>
<tr>
<td>1-yr</td>
<td>106 ± 24</td>
<td>108 ± 24</td>
</tr>
<tr>
<td>2-yr</td>
<td>107 ± 26</td>
<td>115 ± 36</td>
</tr>
</tbody>
</table>

* Data are expressed as mean ± SD. M, male; F, female.
* P < 0.001, for 2-yr change, group A versus group B.
* P = 0.019, for 2-yr change, group A versus group B.

Protocol Objective-Achieved Analysis. Relatively few patients in either group achieved the planned protocol objectives of [Hb] of ≥120 g/L (group A) or ≤100 g/L (group B) within 3 mo of the end of the study (37 and 15 patients, respectively). The changes in [Hb] during the study for both groups are presented in Table 3. There was no difference between groups (protocol objective achieved) with respect to age, gender, or GFR throughout the study. However, a significant difference was observed between groups for the change in LVMi (from baseline values) at 2 yr (P = 0.019), as well as a greater 2-yr LV end-diastolic volume for group B (106 ± 27 ml, n = 32, for group A versus 128 ± 26 ml, n = 8, for group B; P = 0.04). Trends toward similar effects were also observed for the changes in LV end-diastolic diameter and volume during the 2-yr period (data not shown). No other differences in echocardiographic parameters were observed.

Renal Function

Measured GFR at 12 and 24 mo progressively decreased from baseline values (P < 0.001) (Table 2), although no significant difference in renal function between the groups was evident at those times. The decreases in GFR in 2 yr were 8 ± 9 ml/min per 1.73 m² for group A and 6 ± 8 ml/min per 1.73 m² for group B. Calculated creatinine clearance values exhibited similar results (data not shown). Although a trend toward a higher rate of dialysis commencement for group A was evident (Table 1), a significant overall positive, rather than negative, correlation between [Hb] and GFR was observed (r = 0.299, P = 0.002; data not shown).

Quality of Life

The SF-36 Health Survey scores indicated moderate health at study commencement for both groups. Physical health scores were estimated as 54 ± 11 for group A and 59 ± 11 for group B. There was no difference between the two treatment groups in the changes in scores from baseline to study termination (−2 ± 14 for group A versus −1 ± 13 for group B; 95% CI, −5.4 to 3.0). The initial mental health scores were similar for the two groups (56 ± 11 for group A versus 55 ± 12 for group B); and the changes in scores at the end of the study were also small (0 ± 14 versus −3 ± 11; 95% CI, −1.7 to 6.4). The Renal Quality of Life Profile total scores were similar for the two groups at study commencement (32 ± 21 for group A, compared with 26 ± 16 for group B). There was little change in scores at the end of the study and no significant difference between groups (7 ± 17 versus 5 ± 14; 95% CI, −3.4 to 6.6).

Discussion

When this study began, it was not known whether prevention or early partial correction of anemia with epoetin α would affect LV growth among patients with CKD. Findings from this study did not indicate a clear benefit for maintenance of nearly physiologic [Hb] with respect to this question, because of the comparable findings for the primary end point for the treatment groups. The most relevant confounding factor, which might have influenced the results, was the relative closeness of the [Hb] values for the two groups. The 2-yr mean [Hb] did not decrease substantially for group B, probably because renal function remained relatively well preserved, and values were maintained at the lower limit of the target range for group A. Comparable BP control between groups might also have mitigated the potential development of LVH. In contrast, for patients who did achieve the protocol targets, changes in LVMi were consistent with findings of previous studies that identified anemia as an independent predictor of LVH (19,34), with changes in volume-based parameters possibly being of particular importance as determinants of LV growth. Therefore, there is some evidence that avoidance of anemia, together with control of BP and volume status, might favorably affect LV growth among patients with advanced CKD. Greater numbers of patients and/or longer study duration might have helped clarify these issues in this study.

The prevalence of LVH among all patients at the commencement of the study was 30%, which is consistent with cross-sectional studies of patients with equivalent levels of renal dysfunction (26,35). Two small uncontrolled studies demonstrated reductions in LVH with changes in [Hb] among patients with CKD. Portoles et al. (36), in an uncontrolled study, reduced the LVMi from 178 to 147 g/m² (P < 0.05) for 11 patients in 6 mo by increasing [Hb] from 9.0 to 11.7 g/L. In the second study, Hayashi et al. (37) compared partial hematocrit correction (30%) with normalization (40%) among nine subjects. After 12 mo, hematocrit normalization resulted in a greater reduction in LVMi than did partial correction (111 versus 127 g/m²), compared with baseline values (141 g/m², P < 0.05). Changes in LVMi in our study among patients initially with or without LVH were not related to treatment group randomization. In addition, there was not a predominance of one treatment group among patients who developed LVH.
during the course of the study. It is likely that this finding is related to the small difference in [Hb] between treatment groups, but the finding also suggests that maintenance of [Hb] at or near 110 g/L, compared with 120 g/L, has a small differential effect on LVMi in general, and particularly LVH, in advanced CKD. Whether this finding is also partly related to the absolute [Hb] is unclear, although earlier studies did suggest that the absolute [Hb] becomes more important as values decrease below 90 g/L (38).

Prevention or correction of anemia may have benefits that extend beyond the effects on LVH. Recent studies demonstrated benefits among patients with renal impairment and severe resistant heart failure, with improved New York Heart Association symptoms, improved exercise capacity, and stabilization of the rate of decrease of GFR (39–41). Small studies among dialysis patients also demonstrated benefits of [Hb] normalization on sleep (42), neurologic function (43), exercise capacity, and well being (44,45). Quality of life has also been demonstrated, in a variety of controlled and uncontrolled studies, to be related to [Hb] among dialysis patients (20,45,46). The fact that we were unable to observe a difference in quality of life between groups in this study is likely to be related to the small overall difference in [Hb], rather than an intrinsic difference between dialysis and nondialysis patients.

Early correction of uremic anemia in CKD must be performed with caution. Epoetin-induced hypertension after correction of uremic anemia is a recognized complication of treatment (47,48). Nephrologists have increasingly recognized the importance of tight BP control in slowing the rate of progression of CKD. Schrier et al. (49) recently highlighted the importance of rigorous aggressive treatment of hypertension (target of <120/80 mmHg) among predialysis patients with adult-onset polycystic kidney disease and LVH; LVMi was normalized for 71% of patients during a 7-yr period. Interestingly, the decrease in LVMi was continuous and progressive during the 7-yr period, raising the possibility that prospective trials (such as this study) may demonstrate greater effects if extended longer. It should be remembered that LV mass is determined by modifiable factors other than [Hb] and efforts to address these additional factors remain important.

In summary, maintenance of [Hb] values between 120 and 130 g/L did not have a conclusive effect on LVH in this study, although the difference in [Hb] values between the groups was small and a longer follow-up period might have been required. Even modest BP control (to levels higher than the currently recommended target values) seemed to result in a relatively slow rate of decline in renal function, which might also have affected the rate of the decrease in [Hb]. Renal function was not adversely affected in the group randomized to the higher [Hb], and no detectable difference in the quality of life between groups was evident during the treatment period.

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