Stability of Target Hemoglobin Levels during the First Year of Epoetin Treatment in Patients with Chronic Kidney Disease

Luca De Nicola,* Giuseppe Conte,* Paolo Chiodini,† Bruno Cianciaruso,‡ Andrea Pota,‡ Vincenzo Bellizzi,§ Giuseppina Tirino,* Deborah Avino,* Fausta Catapano,* and Roberto Minutolo*

*Nephrology Division and †Department of Biostatistics, Second University of Naples-Santa Maria del Popolo degli Incurabili Hospital-Azienda Sanitaria Locale Napoli 1, and ‡Department of Nephrology, University Federico II, Naples, and §Nephrology Division, County Hospital, Solofra, Italy

Background and Objectives: Instability of hemoglobin levels during epoetin therapy is a new problem in hemodialysis. We evaluated extent and correlates of time in target, that is, the time spent with hemoglobin ≥11 g/dl during the first year of epoetin and its association with renal survival.

Design, Setting, Participants, & Measurements: Data were collected in 917 visits for 12.0 mo in 119 patients with chronic kidney disease; thereafter, patients started renal survival analysis for 10.1 mo. At baseline, hemoglobin was 10.0 ± 0.8 g/dl and GFR was 22.1 ± 14.2 ml/min per 1.73 m².

Results: Hemoglobin target, reached in 1.5 mo, was steadily maintained in only 24% of patients. Time in target was not merely due to differences in time to target; after first achievement of target, in fact, a reduction of hemoglobin <11 g/dl occurred in 51% of patients. At multivariate analysis, male gender, basal GFR and hemoglobin levels, first epoetin dose, and iron supplementation were directly associated with length of time in target. A lower risk for renal death (dialysis n = 53; death n = 8) was detected in the higher tertile of time in target (11.3 mo) versus lower tertile (3.2 mo). This difference persisted at Cox analysis after adjustment for age, gender, GFR, BP, and proteinuria.

Conclusions: In chronic kidney disease, time in target during the first year of epoetin therapy is frequently short depending not only on time to target but also on post-target hemoglobin reductions, correlates with male gender, timing, and intensity of initial therapy and is coupled with better renal survival.


In patients who have chronic kidney disease (CKD) and are not yet on hemodialysis (HD), anemia has a significant prevalence, rising from approximately 15 to 70% in stages 3 to 5 (1–4), and acts as an independent risk factor for cardiovascular disease (2,5–8) and ESRD (8–10). These findings have led to the recommendations, recently reiterated by European (European Best Practice Guidelines) and US (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines (11,12), to prescribe erythropoiesis-stimulating agents (ESA) to maintain hemoglobin ≥11 g/dl in all patients with CKD. A conclusive recommendation on the upper limit was not given, but recent studies suggest that pursuing normalization of hemoglobin levels does not ameliorate cardiorenal outcome (13–16). In the real world of clinical practice, however, even a partial correction of anemia is infrequently observed in patients with CKD, regardless of the country where they live, mainly because of omission of ESA and iron therapy (1–4,17–19).

Noteworthy, an emerging additional problem is that maintenance of target hemoglobin levels may not be an easy task even in treated patients. Observational studies in HD have in fact demonstrated that, during ESA therapy, hemoglobin levels are characterized by marked intrapatient variability over time and that amplitude and duration of hemoglobin fluctuations in the individual patient are predictors of hospitalization and mortality independent from mean hemoglobin levels (20–23). Conversely, no study has analyzed stability of hemoglobin levels in treated pre-HD patients. A retrospective study in a large cohort of patients with CKD showed that lower time-averaged hemoglobin levels are coupled with worse cardiorenal outcome (8); however, in that study, women were not included and no therapeutic information was provided.

In this observational study of clinical practice patterns, we evaluated patients with CKD during the first year of ESA treatment to gain insights into extent and clinical correlates of time in target, that is, the time spent with hemoglobin ≥11 g/dl by each individual patient. In addition, we analyzed the association of time in target with renal survival in view of the fact

Received April 11, 2007. Accepted June 19, 2007.
Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Prof. Luca De Nicola, Cattedra di Nefrologia, Dip. Gerontologia, Geriatria, Mal. Metabolismo, Seconda Università di Napoli, Piazza Miraglia, 80131 Napoli, Italia, Phone/Fax: +39-081-2549409; E-mail: luca.denicola@unina2.it

Copyright © 2007 by the American Society of Nephrology

ISSN: 1555-9041/205–0938
that in HD patients, the protective effects of anemia correction depend not only on the achievement of hemoglobin target but also on its steadiness over time (20–23).

Materials and Methods

Patients

We conducted in two Italian academic outpatient renal clinics (Second University of Naples and University Federico II of Naples) a retrospective analysis of consecutive adult nondialysis patients who had CKD with anemia (hemoglobin <11 g/dl in two consecutive visits with interval >15 d) and started for the first time ESA therapy between April 30, 2002, and April 30, 2005. To evaluate properly changes over time of hemoglobin levels, we excluded patients with hemoglobin levels measured after the first dose of ESA for a period <10 mo and/or at intervals between consecutive hemoglobin determinations >2 mo. Additional exclusion criteria were incomplete data collection, neoplastic or infectious disease, hemoglobinopathies, and bleeding or blood transfusion in the last 3 mo before study.

The two centers shared the following features: Presence of outpatient clinic dedicated to the conservative care of CKD with in-house analysis of blood and urinary samples and ESA therapy dispensed by the hospital pharmacy; presence of clinical and laboratory standardized protocols, including measurement of creatinine by modified kinetic Jaffe reaction, hemoglobin by Coulter counter, and proteinuria by pyrogallol red-molybdate method; hemoglobin target = 11 g/dl; and criteria for starting dialysis (GFR <7.0 ml/min per 1.73 m² or development of life-threatening complications).

Data Collection

Three nephrologists (G.T., D.A., and F.C.) extracted the data from clinical charts at each available visit within the first year of ESA therapy. Diagnosis of underlying renal disease was derived from clinical history and, when available, from renal biopsy. In particular, diabetic nephropathy was defined by history of persistent albuminuria and severe diabetic retinopathy at fundus oculi and/or fluorangiography, whereas diagnosis of hypertensive nephrosclerosis was made in patients with a long history of hypertension, associated retinopathy, relatively normal urine sediment, and no other renal disease.

Data from basal visit, when the first dose of ESA was prescribed, and from the subsequent six consecutive visits are reported. Information on ESA therapy was verified by analysis of in-hospital pharmacy records. After the end of the first year of ESA therapy, all patients started a follow-up that lasted until February 28, 2007, only to ascertain renal death.

Calculations

We estimated GFR by means of the four-variable Modification of Diet in Renal Disease (MDRD) equation and protein intake by standard formula (3). Iron deficiency was defined by serum ferritin <100 ng/ml and/or transferrin saturation <20%. Malnutrition was defined by presence of albumin <3.5 g/dl and body mass index <20 kg/m².

Hemoglobin was considered at target when ≥11 g/dl. Accordingly, time in target was calculated, in each single patient, as the difference between the extent of initial period of follow-up (first year of ESA therapy) and the portion of this time spent with hemoglobin <11 g/dl. This latter “no target” period is in turn represented by the sum of time to target (interval between basal visit and first-time achievement of hemoglobin target) plus time below target (period spent with hemoglobin <11 g/dl) subsequent to the first-time achievement of target; (Figure 1). Specifically, Time below target was calculated for each interval between two consecutive visits by assuming that hemoglobin trend in this period was linear. The same assumption was made to estimate length of time to target.

Time below target was calculated as follows:

1. If the two hemoglobin values both were below target (<11 g/dl), then time below target corresponded to the interval between two consecutive visits.
2. If both hemoglobin values were at target (≥11 g/dl), then time below target was assumed to be equal to zero.
3. If only the first hemoglobin was at target, then the formula was [(T2 – T1) – (11 – Hb1)/[(Hb2 – Hb1)/(T2 – T1)], where Hb1 and Hb2 are the hemoglobin values of the two consecutive visits and T1 and T2 are the dates of the two visits.
4. If only the second hemoglobin value was at target, then the formula was (11 – Hb1)/[(Hb2 – Hb1)/(T2 – T1)].

We applied 1 and 4 to estimate time to target.

In each individual patient, time in target and yearly mean hemoglobin were calculated as summary measures of serial measurements (24). For analysis of determinants of time in target, we standardized the dosage of darbepoetin in micrograms to international units by using the conversion factor of 1 µg = 200 IU, in accordance with the manufacturer’s recommendations within the European Union.

Statistical Analyses

Continuous variables were reported as means ± SD or median (range) and compared with unpaired t test or with Mann-Whitney test, respectively. ANOVA for repeated measurements was used to evaluate changes over time. Spearman correlation was also used.

To identify the correlates of time in target, we used multiple linear regression analysis. The model was built by identifying a priori the main potential determinants; reliability of model assumptions was tested by normal probability plot on residuals and plot of fitted values versus residuals.

For survival analysis, the primary composite end point was time to renal death defined as time from the end of the first year of ESA therapy to all-cause death or dialysis or renal transplantation, whichever occurred first. We analyzed the unadjusted association of time in target, categorized in three groups by tertiles, with time to renal death by using Kaplan-Meier survival curves compared by log-rank test.

Figure 1. Hemoglobin changes across the target value (≥11 g/dl) during first year of therapy with erythropoiesis-stimulating agents (ESA) in 79-yr-old female patients with CKD and without diabetes, graphically showing time to target, time in target, and time below target (see Materials and Methods for details).
Multivariate Cox proportional-hazards model was used to estimate hazard ratio (HR) for tertile of time in target and the corresponding 95% confidence intervals (CI), adjusted for the effect of potentially confounding variables. Same analyses were run by including, as end point, time to dialysis instead of time to renal death. We also reran survival analysis by including yearly mean of individual hemoglobin levels, categorized in three groups by tertiles, instead of time in target.

Data were analyzed using SPSS version 12.0 (SPSS, Chicago, IL). \( P < 0.05 \) was considered statistically significant.

**Results**

We identified by inclusion criteria 164 patients; because 45 met exclusion criteria (short follow up, \( n = 17 \); prolonged interval between two hemoglobin determinations, \( n = 24 \); incomplete data, \( n = 4 \)), 119 white patients were studied. Patient characteristics that did not differ from those of excluded individuals are shown in Table 1. In women, age was slightly lower than in men (59 ± 18 versus 64 ± 14 yr; \( P = 0.102 \)), with 29% of them being of reproductive age (<50 yr). At baseline, iron deficiency was found in 47% of the entire cohort. Malnutrition was rare (5%), and control of azotemia was adequate. Mean protein intake was 0.86 ± 0.25 g/kg per d. Prevalence of Ca × P >55 mg²/dl² was of 6%. Most patients were treated with multiple antihypertensive therapy, including at least one inhibitor of the renin-angiotensin system (RAS); at baseline, BP was <130/80 mmHg in 21%, and no patient had BP >160/100 mmHg.

Table 1. Basal characteristics of the 119 patients with CKD studieda

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.3 ± 15.9</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>48.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 ± 4.9</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>32.8</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>29.2</td>
</tr>
<tr>
<td>Renal disease (%)</td>
<td></td>
</tr>
<tr>
<td>chronic glomerulonephritis</td>
<td>15.1</td>
</tr>
<tr>
<td>diabetic nephropathy</td>
<td>22.7</td>
</tr>
<tr>
<td>hypertensive nephrosclerosis</td>
<td>17.6</td>
</tr>
<tr>
<td>polycystic kidney disease</td>
<td>8.4</td>
</tr>
<tr>
<td>other/unknown</td>
<td>36.2</td>
</tr>
<tr>
<td>CKD stage 3/4/5 (%)</td>
<td>23/40/37</td>
</tr>
<tr>
<td>Nephrology follow-up (mo)</td>
<td>21 ± 42</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>53 ± 19</td>
</tr>
<tr>
<td>Ca × P (mg²/dl²)</td>
<td>41 ± 9</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>176 ± 151</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td>Proteinuria (g/d)</td>
<td>0.9 (0 to 10.4)</td>
</tr>
<tr>
<td>Antihypertensive drugs (n/patient)</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>70</td>
</tr>
</tbody>
</table>

aQuantitative variables are means ± SD, categorical variables are %. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease.

After the basal visit, complete data were collected in 798 visits for a median period of 12.0 mo (10.7 to 13.6). Overall, the median number of visits per patient was seven (seven to 12), with seven visits available in 78 patients, eight in 18, nine in nine, and ≥10 in 14 patients. The main clinical features during follow-up are described in Table 2. BP and number of antihypertensive drugs remained unchanged during follow-up. Similarly, ferritin levels, which were higher in men than in women at baseline (197 ± 158 versus 136 ± 107 ng/ml, respectively; \( P = 0.014 \)), did not vary. Serum albumin levels and body weight remained unchanged, thereby excluding development of malnutrition. Number of prescriptions of darbepoetin and β-epoetin did not differ. All patients received ESA subcutaneously. First ESA dose (25 ± 10 µg/wk for darbepoetin and 4524 ± 2486 IU/wk for β-epoetin) did not change subsequently. Hemoglobin levels >13 g/dl were infrequently detected (86 [11%] of 798 visits); in these cases, ESA therapy was generally maintained, being temporarily stopped in only five of 86 visits with high hemoglobin. No bleeding or blood transfusion was reported; only six patients required hospitalization, but they continued ESA. Iron and folate supplementation were always given by oral route.

Figure 2 describes hemoglobin changes. Hemoglobin increased to target, at least in one visit, in all patients but four who constantly had hemoglobin <11 g/dl. Rate of hemoglobin increase between baseline and first control was 0.56 g/dl per mo (−2.3 to 4.3) and correlated with first ESA dose (\( r = 0.250, P = 0.006 \)); hemoglobin declined in 15 patients, whereas 65% showed an increment <1 g/dl per mo and only eight had an increment >2 g/dl per mo. No correlation was found between hemoglobin increments and concomitant BP changes (\( r = 0.106, P = 0.252 \)). The median time required to reach target (time to target) was 1.5 mo (0.2 to 10.7). Thereafter, target was on average maintained; however, only 29 (24.3%) patients had hemoglobin at target from first control after starting ESA to the 12-mo visit.

The median value of time in target of the whole cohort was 8.2 mo (0 to 12.8). At multiple regression analysis (Table 3), male gender, basal GFR and hemoglobin levels, first dose of ESA, and initial iron supplementation all were directly associated with length of time in target. When patients were categorized in three tertiles of time in target, 40 had hemoglobin at target only for 3.2 mo (0 to 6.2 [lower]), 40 for 8.2 mo (6.5 to 10.3 [middle]), and 39 for 11.3 mo (10.3 to 12.8 [higher]). In the lower and middle tertiles, extent of time in target was similarly determined by duration of time to target and length of the period with hemoglobin <11 g/dl after first-time achievement of target (Figure 3). Within the latter period, in fact, a reduction of hemoglobin <11 g/dl became apparent in at least one visit in 82.5 and 65.0% of patients of the lower and middle tertiles, respectively, whereas it occurred in only 10.3% of the higher tertile.

As depicted in Table 4, patients in the three tertiles differed for gender distribution and mean hemoglobin values during first year of ESA. Number of visits was similar; indeed, visit frequency was not associated with time in target, as attested by the NS correlation coefficient at Spearman correlation test (\( r = \).
Table 2. Main clinical and therapeutic features during the first year of ESA therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal</th>
<th>Month 2</th>
<th>Month 4</th>
<th>Month 6</th>
<th>Month 8</th>
<th>Month 10</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb ≥11 g/dl (%)</td>
<td>—</td>
<td>46.2</td>
<td>75.6</td>
<td>70.6</td>
<td>67.2</td>
<td>68.1</td>
<td>69.7</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>22.1 ± 14.2</td>
<td>21.2 ± 12.7</td>
<td>20.6 ± 12.0</td>
<td>20.2 ± 12.0</td>
<td>19.2 ± 11.7</td>
<td>19.5 ± 12.6</td>
<td>18.3 ± 12.3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137 ± 20</td>
<td>139 ± 20</td>
<td>141 ± 20</td>
<td>138 ± 18</td>
<td>142 ± 23</td>
<td>141 ± 21</td>
<td>140 ± 20</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78 ± 11</td>
<td>79 ± 11</td>
<td>79 ± 11</td>
<td>79 ± 10</td>
<td>81 ± 13</td>
<td>78 ± 11</td>
<td>77 ± 11</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>26.3 ± 13.3</td>
<td>21.3 ± 11.5</td>
<td>26.1 ± 17.0</td>
<td>32.8 ± 34.7</td>
<td>26.4 ± 12.4</td>
<td>25.1 ± 10.4</td>
<td>26.0 ± 12.6</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>162 ± 154</td>
<td>162 ± 187</td>
<td>118 ± 110</td>
<td>174 ± 162</td>
<td>193 ± 215</td>
<td>146 ± 150</td>
<td>151 ± 147</td>
</tr>
<tr>
<td>Darbepoetin/β-epoetin (n)</td>
<td>61/58</td>
<td>61/58</td>
<td>65/51</td>
<td>63/52</td>
<td>63/55</td>
<td>60/57</td>
<td>58/53</td>
</tr>
</tbody>
</table>

ESA schedule (n)
withdrawn — — 3 4 1 2 8
2/wk 4 4 2 0 4 3 2
1/wk 106 95 91 88 82 78 72
1/2 wk 9 20 21 25 27 33 35
1/4 wk 0 0 2 2 4 3 2
Darbepoetin (µg/kg per wk) 0.39 ± 0.16 0.38 ± 0.17 0.40 ± 0.18 0.39 ± 0.19 0.37 ± 0.24 0.39 ± 0.25 0.38 ± 0.25
β-epoetin (IU/kg per wk) 66 ± 38 63 ± 42 58 ± 33 61 ± 34 61 ± 34 61 ± 36 64 ± 37
Supplementation (%) iron 72 79 81 70 70 71 64
folate 47 41 44 44 47 45 47

+aQuantitative variables are means ± SD, categorical variables are % or absolute frequencies. In the case of multiple visits in the same 2-mo period, data were aggregated for descriptive analysis. DBP, diastolic BP; eGFR, estimated GFR; ESA, erythropoiesis-stimulating agents; Hb, hemoglobin; SBP, systolic BP; TSAT, transferrin saturation.

Discussion

Significant fluctuations of hemoglobin levels have been found, depending on the definition used, in 30 to 90% of HD patients (20–23). Proposed key determinants of this intrapatient variability of hemoglobin are intercurrent comorbidities and frequent changes of ESA therapy, which are two common features in HD. Ample fluctuations of hydration status, again typical in HD, also contribute to hemoglobin cycling (25). Therefore, hemoglobin stability during ESA may profoundly differ between HD and non-HD patients.

This study provides first-time evidence on durability of target hemoglobin levels in ESA-treated patients with CKD. Only 24% of patients had hemoglobin at target throughout the first year of ESA therapy. Extent of time in target was determined not only by the length of the period spent to reach target but also by the subsequent hemoglobin fluctuations (Figure 3). Specifically, among patients of the lower and middle tertiles of time in target, 74% showed at least one reduction of hemoglobin <11 g/dl subsequent to the visit at which the target was detected for the first time.
We studied patients who had been followed in renal clinics for an average of almost 2 yr before the study and had multiple visits during follow-up. Indeed, we observed a low incidence of cardiovascular events, absence of malnutrition and Ca/P abnormalities, and large use of RAS inhibitors. In particular, BP control was adequate because uncontrolled hypertension was not found and prevalence of target BP (130/80 mmHg) was double that observed in a national survey carried out in patients who had CKD and were undergoing regular nephrology care (3).

Although instability of target hemoglobin levels may be even greater in patients with late or inadequate nephrology follow-up, the selection criteria used here allowed evaluation of time in target in the absence of confounding factors that can per se significantly affect hemoglobin levels, such as inconsistent ESA administration, poor health status, and inadequate treatment of other main uremic complications (11,12,18,26). Under these conditions, we found a positive correlation between time in target and male gender, basal GFR and hemoglobin level, and intensity of initial therapy of anemia, whereas no predictive role was detected for comorbidities (Table 3). The association between length of time in target and male gender cannot be merely explained by intercurrent menses in younger female patients even though serum ferritin levels were lower in women versus men. Indeed, this relationship remained significant after adjustment for iron status (Table 3). Therefore, gender-related differences in other factors, possibly represented by androgen levels, may play a major additional role in the response to ESA (27). In this regard, it is interesting that in the HD setting, female patients require higher dosages of ESA, independent of iron status and depurative efficiency, to maintain the same hematocrit level of men (28). With regard to the role of basal GFR and hemoglobin, it is reasonable to hypothesize that greater steadiness of hemoglobin target levels is attained in the presence of higher levels of endogenous epoetin because both parameters are indicative of endogenous epoetin production (29). More insights were obtained by the analysis of ther-
apy. Initial iron supplementation was directly correlated to length of time in target. The role of iron therapy becomes obvious when considering that availability of iron is key for optimal erythropoiesis, and almost half of our population started observation with either absolute or relative iron deficiency. The observed large prevalence of iron-deficient patients is similar to that reported in large European surveys and in the 1988 to 1994 US National Survey (1,17,19). Therefore, our data suggest that iron deficiency continues to be a major problem also in renal clinics and, more important, that effectiveness of iron supplementation is not limited to the increase in hemoglobin levels (11,12) but extends to the steadiness of hemoglobin target levels. Similarly, time in target was predicted by the first dose of ESA; this finding is conceivable with the correlation found between first ESA dose and concomitant hemoglobin increment.

A conservative attitude in the therapy of anemia emerged in the subsequent period. ESA dosage, in fact, remained on average unchanged throughout the first year of observation (Table 2). More important, when comparing patients’ characteristics in the tertiles of time in target at the end of the first year of ESA therapy (Table 4), no difference was found in main factors that influence the entity of anemia other than gender, such as prevalence of comorbidities, degree of renal damage, and use of RAS inhibitors. Conversely, tertiles markedly differed for the use of ESA. Whereas in the higher tertile approximately 70% of

**Table 4. Main characteristics of patients, grouped in tertiles of time in target, at the end of the first year of ESA therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower</th>
<th>Middle</th>
<th>Higher</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.7 ± 15.9</td>
<td>61.4 ± 15.6</td>
<td>63.8 ± 16.5</td>
<td>0.773</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>32.5</td>
<td>52.9</td>
<td>61.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30.0</td>
<td>37.5</td>
<td>30.8</td>
<td>0.938</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>25.0</td>
<td>32.5</td>
<td>45.8</td>
<td>0.159</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>16.2 ± 9.7</td>
<td>17.5 ± 10.4</td>
<td>21.2 ± 15.8</td>
<td>0.177</td>
</tr>
<tr>
<td>Mean Hb (g/dl)</td>
<td>10.7 ± 0.5</td>
<td>11.5 ± 0.5</td>
<td>12.5 ± 0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>23.5 ± 10.3</td>
<td>26.6 ± 13.4</td>
<td>26.7 ± 11.4</td>
<td>0.390</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>161 ± 147</td>
<td>143 ± 98</td>
<td>139 ± 85</td>
<td>0.666</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143 ± 22</td>
<td>140 ± 21</td>
<td>137 ± 17</td>
<td>0.374</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79 ± 12</td>
<td>76 ± 11</td>
<td>76 ± 10</td>
<td>0.314</td>
</tr>
<tr>
<td>Proteinuria (g/d)</td>
<td>1.6 ± 1.9</td>
<td>2.2 ± 2.4</td>
<td>1.7 ± 2.2</td>
<td>0.452</td>
</tr>
<tr>
<td>ACEI/ARB (% patients)</td>
<td>65.0</td>
<td>80.0</td>
<td>66.7</td>
<td>0.862</td>
</tr>
<tr>
<td>Visits after first ESA prescription total number</td>
<td>277</td>
<td>269</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td>with expected increase in ESA dosage</td>
<td>181/277 (65%)</td>
<td>62/269 (23%)</td>
<td>14/152 (6%)</td>
<td></td>
</tr>
<tr>
<td>with actual increase in ESA dosage</td>
<td>25/181 (15%)</td>
<td>10/62 (16%)</td>
<td>2/14 (14%)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.** Time to renal death by tertiles of time in target and mean individual hemoglobin levels in the first year of ESA therapy. Tertiles of time in target are higher (11.3 mo; 10.3 to 12.8), middle (8.2 mo; 6.5 to 10.3), and lower (3.2 mo; 0 to 6.2); tertiles of mean hemoglobin are higher (12.4 g/dl; 11.9 to 15.7), middle (11.4 g/dl; 11.1 to 11.9), and lower (10.7 g/dl; 9.7 to 11.1).
patients did not require dosage adjustment because of adequate response to the first ESA dose in terms of achievement and maintenance of target, the vast majority of patients in middle and lower tertiles required therapy intensification; in these patients, however, therapy was increased in only 15% of visits in which intensification was indicated. This occurred even though the rate of hemoglobin increment after initial prescription was in most cases well below the recommended range of 1 to 2 g/dl per mo (11,12). Such an inadequate therapeutic approach cannot be justified by the common fear of treating patients with uncontrolled hypertension or of ESA-related worsening of BP control because basal BP was on average <140/80 mmHg and no correlation was found between hemoglobin and BP changes. We therefore disclosed a “clinical inertia” in the management of anemia that likely influenced stability of hemoglobin target levels. In this regard, we recently showed that clinical inertia in CKD applies to the whole spectrum of the recognized modifiable determinants of cardiorenal risk (3,4); in particular, we found that, in Italy, the majority of anemic patients with CKD do not receive ESA despite prolonged follow-up in nephrology (3). This study adds the evidence that, in the event that patients are treated, therapy is not adjusted in relation to the individual erythropoiesis response.

The time spent with hemoglobin at target during the first year of ESA was associated with renal survival (Figure 4). Specifically, risk for renal death was 58% lower in patients who had hemoglobin at target with respect to those who had hemoglobin ≥11 g/dl for only 3 mo (Table 5). As expected, tertiles of time in target differed in the yearly mean of individual hemoglobin levels; we therefore repeated renal survival analysis by including this parameter instead of time in target. Mean hemoglobin value, however, did not have a predictive role. Of note, these results must be interpreted with caution because of the relatively small number of patients studied and short follow-up. Nevertheless, the discrepancy between renal death, being observed in the same cohort of patients, suggests that the association between hemoglobin levels and prognosis is more complex in treated patients than in untreated patients, in whom outcome is consistently predicted by mean hemoglobin levels (2,5–7,9,10). At variance with time in target, in fact, the yearly mean of hemoglobin does not take into account transitory reductions of hemoglobin below target. Therefore, according to these results and previous studies in treated HD patients as well (20–23), to ensure the best outcome in ESA-treated patients with CKD, achievement of target hemoglobin may not be sufficient if not coupled with its maintenance over time. Indeed, in healthy status, stable oxygen delivery to tissues is allowed by the fairly constant maintenance of hemoglobin levels within a narrow range. It is reasonable to hypothesize that the same holds true in CKD, where steadiness of hemoglobin levels is even more important because of the ischemic status typically present at the level of the kidney as of other tissues. In particular, experimental evidence has accumulated that in CKD, the major, although not exclusive, nephroprotective effect of ESA is the reduction of hypoxia, as a result of anemia correction, that diminishes tubular damage and dependent nephron loss (30). To gain full expression of these beneficial effects, BP should be adequately controlled (31–33), as in the case of our patients.

A main limitation of this study is represented by its observational nature; lack of randomization, in fact, cannot allow a proper assessment of cause–effect relationship between time in target and outcome. Nevertheless, observational studies obtained in the real world of clinical practice can be important means to generate and investigate hypothesis, thereby helping investigators to select the interventions that will be more properly assessed by subsequent clinical trials (34,35). Our findings seem useful to plan correctly randomized trials aimed at verifying in a large number of patients with CKD whether greater stability of hemoglobin target translates into better prognosis.

### Conclusions

In patients who have CKD and are followed in renal clinics, length of the period spent with hemoglobin at target during the first year of ESA (1) is frequently short, depending not only on the time required to reach target but also on post-target reductions of hemoglobin; (2) correlates with male gender as well as with timing and intensity of initial therapy; and (3) is probably associated with better renal survival.
Disclosures
None.

References
28. Ifudu O, Urbirari J, Rajwani I, Vlacich V, Reydel K, Delosreyes G, Friedman E: Gender modulates responsiveness to


