Hyporesponsiveness to erythropoiesis-stimulating agents and renal survival in non-dialysis CKD patients

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Abstract

Background. Lower responsiveness to erythropoiesis-stimulating agents (ESA-R) predicts cardiovascular (CV) events. Whether ESA-R also affects the risk of end-stage renal disease (ESRD) is unknown.

Methods. We evaluated ESA-R in 194 consecutive chronic kidney disease (CKD) patients, regularly seen in outpatient nephrology clinics, who started erythropoiesis-stimulating agent (ESA) therapy between 2002–06. Exclusion criteria were causes of anaemia other than CKD or recent transfusion. ESA-R was calculated as \((\text{Hb}_1 - \text{Hb}_0)/\text{time}/\text{ESA dose (g/dL/month)}/(10 \text{ µg/week of ESA})\). Patients were classified, from lower to higher tertile of ESA-R, as poor, intermediate and good responders. Time to ESRD was the primary outcome.

Results. Age was 64 ± 16 years, 48% were male, 34% had diabetes and 32% had CV disease, glomerular filtration rate (GFR) 24 ± 13 mL/min/1.73 m² and proteinuria 0.6 g/dL (interquartile range 0.2–1.9). First ESA dose was 23.7 ± 10.8 g/week; haemoglobin (Hb) increased from 9.9 ± 0.8 g/dL to 11.0 ± 1.2 g/dL at first control, obtained after 1.4 ± 0.4 months. These changes corresponded to an ESA-R of 0.37 ± 0.38 g/dL/month/10 µg/week of ESA and tertiles limits were 0.17 and 0.47. Poor responders were younger and had lower GFR and higher proteinuria than intermediate and good responders. During the first 6 months of ESA therapy, poor responders showed lower Hb levels and sustained longer periods of Hb level <11 g/dL. During follow-up (median 3.0 years), 99 patients reached ESRD. At multivariable Cox’s analysis, poor responsiveness was associated with higher risk of ESRD (hazard ratio 2.49, 95% confidence interval 1.28–4.84).

Conclusion. ESA-R predicts renal prognosis in CKD patients followed in nephrology practice, where ESRD is the predominant outcome and ESA is commonly used at low dose.

Keywords: Anaemia; CKD; erythropoietin; ESA responsiveness; ESRD

Introduction

Several studies in haemodialysis populations have emphasized the importance to identify patients with low responsiveness to erythropoiesis-stimulating agents (ESA-R) for clinical and economical reasons. In this setting, in fact, hyporesponsive patients are at greater risk of all-cause death and cardiovascular (CV) events [1–6], and they consume more than half of the total amount of erythropoiesis-stimulating agent (ESA) used [7]. Conversely, very limited data are available in the setting of non-dialysis chronic kidney disease (CKD) even though the prevalence of hyporesponders to ESAs (~15%) is very close to that estimated among haemodialysis patients [7, 8].

The independent effect of ESA-R on outcome has been specifically addressed in a recent secondary analysis of the TREAT trial [9]. Solomon et al. [9], in fact, found that lower response to the first two (fixed weight-based) doses of darbepoetin was associated with an increased risk of fatal and non-fatal CV events and all-cause death. The proposed mechanisms for this negative association included the toxicity related to high ESA dose, patient-level factors accounting for the hyporesponse or a combination of both [7, 10]. However, results of the TREAT trial cannot be reliably translated to daily clinical practice; indeed, in the real world of nephrology clinics, non-diabetic patients are prevalent, and haemoglobin (Hb) normalization, which was the target of therapy in the active arm of TREAT, is not commonly pursued. In addition, ESA doses prescribed in the TREAT trial are ~2-fold greater than those used in clinical practice [11, 12] and in particular in European countries [13–18]. Therefore, whether the association between ESA-R and adverse outcome holds true also for the lower ESA dosages commonly administered in daily practice is unknown. However, of similar importance is the gap in knowledge on the relationship between ESA-R and progression of CKD towards end-stage renal disease (ESRD), which is often the natural fate of patients under stable nephrology care [11, 19, 20]. Again, to date no information is
available on the association between ESA-R and renal outcome.

This is a historical prospective study aimed at assessing the prognostic role of ESA-R on renal survival in diabetic and non-diabetic patients with CKD Stages 3–5 regularly followed-up in nephrology clinics.

Materials and methods

Study design

We conducted in three Italian academic outpatient nephrology clinics a study of consecutive adult non-dialysis CKD patients with anaemia (Hb <11 g/dL in two consecutive visits with interval >15 days) who started ESA therapy for the first time between 30 April 2002 and 31 December 2006. To properly evaluate changes over time of Hb levels, we excluded patients with Hb levels monitored after the first dose of ESA for <6 months and/or at intervals >2 months. Patients with incomplete data, neoplastic or infectious disease, haemoglobinopathies and bleeding or blood transfusion in the last 3 months before the study were also excluded. Data were collected during the first 6 months of ESA therapy (‘observation period’). Thereafter, and until 30 April 2011, the occurrence of ESRD and death was registered (‘follow-up for ESRD’).

Participating centres are in the same Italian region, belonging to the national public health care system and share the following features: presence of outpatient clinic for the conservative care of CKD with in-house analysis of blood and urinary samples and epoetin dispensed by the hospital pharmacy; presence of clinical and laboratory standardized protocols, including measurement of creatinine by modified kinetic Jaffe reaction, Hb by Coulter counter, proteinuria by pyrogallol red-molybdate method and C-reactive protein (CRP) was quantified by nephelometry by using a BNA II Nephelometer (Dade Behring, Inc., Newark, DE). The three renal clinics are run by eight nephrologists who personally follow the same CKD patients from the first visit to the beginning of substitutive therapy. All the participating nephrologists stated that since 2002 their reference for the conservative care of CKD has been based on the Kidney Disease Outcomes Quality Initiative clinical practice guidelines and successive updates. In particular, ESA treatment is initiated when Hb <11 g/dL in two consecutive control visits and targeted at Hb 11.0–13.0 g/dL.

Parameters

To allow comparison in ESA dose in patients receiving epoetin or darbepoetin, we standardized the dose of epoetin in international units to microgram by using the conversion factor of 200 IU = 1 μg in accordance with the manufacturer’s recommendations within the European Union. ESA-R to the first dose was calculated in each patient as (Hb1 – Hb0)/time/ESA, where Hb0 and Hb1 are the Hb values at baseline and at first control visit after ESA administration, respectively. Time is the period between those visits and ESA is the first weekly dose prescribed; therefore, ESA-R is expressed as gram per decilitre per month standardized to 10 μg/week of ESA. In addition, we calculated the ESA-R in the first 6 months of therapy according to methodology developed by Kilpatrick et al. [3]. In particular, we plotted for each patient the Hb slope for the mean ESA dose administered in the observation period and we calculated the Hb slope using a simple linear regression analysis. Therefore, we divided the Hb slope for the mean ESA dose administered in the observation period (graphic description is reported in Supplementary Figure 1A). In each patient, we also calculated glomerular filtration rate (GFR) by the four variable Modification of Diet in Renal Disease (MDRD) study equation and daily protein intake [21].

Statistical analysis

To assess the effects of ESA-R, we stratified patients by ESA-R tertile. Continuous variables are reported as mean ± SD and compared with paired Student’s t-test, analysis of variance either one-way or for repeated measures with Bonferroni as posthoc test. Variables with a non-normal distribution at Shapiro–Wilk test are reported as median and interquartile range (IQR) and analysed by Wilcoxon or Kruskall–Wallis test. Categorical variables are expressed as percent and analysed by chi-square test. For descriptive purpose, patients were grouped in tertiles of ESA-R; we defined patients in the low tertile as poor responders, those in the middle tertile as intermediate responders and those in higher tertile as good responders. For survival analysis, the primary composite end point was time to ESRD, defined as time from first control visit to dialysis or renal transplantation, whichever occurred first; secondary end point was the time to renal death (death or ESRD). Multivariate Cox’s proportional hazards model was used to estimate adjusted hazard ratio (HR) and the corresponding 95% confidence interval (95% CI). We also tested a further Cox’s regression model for each end point using the same covariates but replacing ESA-R at the first visit with ESA-R in the first 6 months of therapy. We also analysed the sensitivity and specificity of these two parameters in relationship to renal death by using receiver operating characteristic (ROC) curves, including area under the curve (AUC) and their 95% CIs. Data were analysed using SPSS 12.0 (SPSS Inc., Chicago, IL).

Results

Characteristics of cohort

We identified by inclusion criteria 243 patients; 49 met exclusion criteria (monitoring <6 months, n = 8; interval between two Hb determinations >2 months, n = 28; incomplete data, n = 11; recent blood transfusion n = 2). Therefore, 194 Caucasian patients were finally studied.

At baseline, mean age was 63.7 ± 15.5 years, 52.6% were female, 34% had diabetes and 32% had a history of CV disease. The most frequent causes of CKD were hypertensive nephropathy (31.4%), diabetic nephropathy (20.1%), glomerulonephritis (10.8%) and polycystic kidney disease (8.2%). Daily protein intake was 0.83 ± 0.28 g/kg body weight; mean blood pressure (BP) was 140 ± 21/77 ± 11 mmHg and 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 19.6%, and no patient had BP >170/100 mmHg.

In the whole cohort, basal Hb was 9.9 ± 0.8 g/dL increasing to 11.0 ± 1.2 g/dL at first visit, performed after 1.4 ± 0.4 months on average. Darbepoetin was prescribed in 108 patients (55.7%) at an initial dose of 24.9 ± 10.1 μg/week, with only three patients taking a dose...
>40 μg/week. The remaining 86 patients (44.3%) received either epoietin-α or -β at a mean dose of 4.430 ± 2.319 IU/week, with only six patients taking a dose >8000 IU/week. After conversion from international unit to microgram (ratio 200:1), the mean first ESA dose in the whole cohort was 23.7 ± 10.8 μg/week (median 20 μg/week, IQR 20–30). These features corresponded to an ESA-R of 0.37 ± 0.38 g/dL/month per 10 μg/week of ESA (Supplementary Figure 2A, left panel). Basal characteristics of patients grouped in poor responders (low tertile, ESA-R <0.17), intermediate responders (middle tertile, ESA-R 0.17–0.46) and good responders (high tertile, ESA-R ≥0.47) are reported in Table 1. Good responders were older and they had significantly higher GFR and lower proteinuria (Table 1). No difference was detected in the causes of CKD (Table 1). BP did not differ among the three groups as well as the prevalence of patients receiving at least one RAS inhibitor (80.0, 73.4 and 75.4%, in good, intermediate and poor responders, respectively, P = 0.666). Similarly, achieved protein intake did not differ (0.83 ± 0.31, 0.86 ± 0.31 and 0.81 ± 0.24 g/kg/day, in good, intermediate and poor responders, respectively, P = 0.677).

In good responders, Hb increased at first control visit from 9.7 ± 0.9 to 11.8 ± 1.2 g/dL with an absolute Hb increase of 1.72 ± 0.88 g/dL/month. In this subgroup, darbepoetin dose at first control visit was reduced from 22.0 ± 9.7 to 17.2 ± 9.6 μg/week (P < 0.0001) and remained constant in the following months. In patients with intermediate response, mean Hb increased from 9.9 ± 0.8 to 11.0 ± 0.9 g/dL at first control visit (absolute Hb increase 0.79 ± 0.40 g/dL/month), while in poor responders, Hb did not significantly increase at first control visit (from 10.1 ± 0.7 to 10.2 ± 0.9 g/dL, P = 0.217). In this latter subgroup, Hb increased slowly and reached on average the target at Month 4 (Figure 1). During the observation period (lasting 6.0 ± 0.8 months), mean ESA dose was slightly higher in both intermediate and poor responders.

### Table 1. Basal characteristics of patients by tertiles of ESA-R

<table>
<thead>
<tr>
<th>Tertiles of ESA-R</th>
<th>Higher (ESA-R ≥0.47)</th>
<th>Middle (ESA-R 0.17–0.46)</th>
<th>Lower (ESA-R &lt;0.17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65</td>
<td>64</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.4 ± 14.9</td>
<td>63.4 ± 14.0</td>
<td>59.4 ± 16.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>44.6</td>
<td>53.1</td>
<td>60.0</td>
<td>0.080</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 ± 6.0</td>
<td>27.6 ± 5.5</td>
<td>26.7 ± 4.7</td>
<td>0.661</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>32.3</td>
<td>40.6</td>
<td>29.2</td>
<td>0.712</td>
</tr>
<tr>
<td>CV disease (%)</td>
<td>32.3</td>
<td>32.8</td>
<td>30.8</td>
<td>0.851</td>
</tr>
<tr>
<td>Renal disease</td>
<td>40.0</td>
<td>32.8</td>
<td>21.5</td>
<td>0.360</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>20.0</td>
<td>20.3</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>6.2</td>
<td>10.9</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7.7</td>
<td>4.7</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>26.2</td>
<td>31.3</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>141 ± 20</td>
<td>141 ± 22</td>
<td>137 ± 21</td>
<td>0.536</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76 ± 10</td>
<td>76 ± 12</td>
<td>78 ± 11</td>
<td>0.513</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>9.7 ± 0.9</td>
<td>9.9 ± 0.8</td>
<td>10.1 ± 0.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.6</td>
<td>0.574</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>4.3 ± 0.9</td>
<td>4.2 ± 0.8</td>
<td>4.5 ± 0.9</td>
<td>0.086</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>116 (79–170)</td>
<td>135 (64–220)</td>
<td>109 (63–226)</td>
<td>0.876</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.74 (0.35–1.08)</td>
<td>0.52 (0.31–0.91)</td>
<td>0.47 (0.31–0.82)</td>
<td>0.258</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>27.2 ± 13.2</td>
<td>22.1 ± 14.0</td>
<td>21.6 ± 11.5</td>
<td>0.026</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0.5 (0.1–1.3)</td>
<td>0.6 (0.2–1.8)</td>
<td>1.1 (0.3–2.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>23.2 ± 9.7</td>
<td>21.6 ± 8.4</td>
<td>24.0 ± 7.8</td>
<td>0.275</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>115 (48–225)</td>
<td>105 (50–205)</td>
<td>110 (63–226)</td>
<td>0.748</td>
</tr>
<tr>
<td>Iron supplementation (%)</td>
<td>63.1</td>
<td>75.0</td>
<td>75.4</td>
<td>0.213</td>
</tr>
<tr>
<td>ESA dose (μg/week)</td>
<td>22.0 ± 9.7</td>
<td>25.5 ± 12.3</td>
<td>23.5 ± 10.3</td>
<td>0.175</td>
</tr>
</tbody>
</table>

*Higher, middle and lower ESA-R tertiles correspond to good, intermediate and poor responders, respectively. Values are mean ± SD or median [interquartile range]. PTH, parathyroid hormone; TSAT, transferrin saturation.

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Fig. 2. Cumulative incidence of ESRD in good, intermediate and poor responders to ESA therapy. These subgroups correspond to higher, middle and lower tertiles of ESA-R.
(23.9 ± 9.8 and 23.5 ± 11.9 μg/week, respectively) than in good responders subgroup (17.6 ± 8.2 μg/week). The large majority of patients (92.3%) received a dose of ESA ≤40 μg/week; the highest ESA dose prescribed in good, intermediate and poor response subgroups was 60 μg/week (in three patients), 80 μg/week (in one patient) and 100 μg/week (in one patient), respectively. No patient received ESA at dose >1.5 μg/kg/week. During the observation period, ESA-R was 0.15 ± 0.13 g/dL/month per 10 μg/week of ESA (Supplementary Figure 1A, left panel) and strictly correlated with ESA-R measured at first control visit (r = 0.341, P < 0.0001).

No bleeding or blood transfusion was reported during the 6-month observation period. Four patients required hospitalization because of non-fatal CV events (one among good responders and three among intermediate responders); these patients did not require an interruption of or change in dosage of ESA during their hospital stay.

**Survival analysis**

During the follow-up subsequent to the first control visit (median 3.0 years IQR 1.5–5.5), 35 patients died and 99 reached ESRD; incidence rate of ESRD markedly increased from higher to lower responsiveness subgroups (10.5, 14.2 and 23.4/100 patient-year) (Figure 2). After adjustment for potential confounders, poor responsiveness to ESA increased the risk of ESRD by 2.5-fold (Table 2).

Table 2. Cox analysis of determinants of ESRD*

<table>
<thead>
<tr>
<th>Parameter Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.00 (0.98–1.10)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.40 (0.91–2.17)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.86 (0.53–1.39)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>0.89 (0.87–0.92)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>1.10 (1.01–1.21)</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>1.11 (0.86–1.45)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.05 (0.83–1.31)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>1.24 (0.97–1.59)</td>
</tr>
<tr>
<td>Tertiles of ESA-R at first visit</td>
<td></td>
</tr>
<tr>
<td>Higher (good responders)</td>
<td>Ref</td>
</tr>
<tr>
<td>Middle (intermediate responders)</td>
<td>1.07 (0.59–1.97)</td>
</tr>
<tr>
<td>Lower (poor responders)</td>
<td>2.49 (1.28–4.84)</td>
</tr>
</tbody>
</table>

*ESA-R, ESA responsiveness at first control visit.

A similar result was obtained using ESA-R as continuous variable; indeed, for each unit of decrease in ESA-R, the risk for ESRD increased by 2.2-fold (HR 2.22, 95% CI 1.01–4.89). Finally, we repeated the same multivariable Cox’s analysis by replacing ESA-R at first control visit (dotted line) and ESA-R calculated in the first 6 months (solid line) of ESA therapy for prediction of ESRD.

To evaluate the relationship between the risk associated to responsiveness and severity of renal impairment (expressed as proteinuria and GFR), we repeated the Cox analysis by excluding proteinuria and GFR from the model. The risk for ESRD in poor responders remained unchanged (HR 2.31, 95% CI 1.21–4.46). In addition, we did not find any significant interaction in predicting ESRD between categories of ESA-R and either GFR or proteinuria (P = 0.103 and P = 0.205, respectively). Same results were obtained when ESA-R was included in Cox models as continuous variable (data not shown).

**Discussion**

This is the first study evaluating the association between hyporesponsiveness to ESA and renal survival. Indeed, secondary analysis of TREAT trial focused exclusively on...
CV events (fatal and non-fatal) and on all-cause mortality, but no information was provided on the role of ESA-R in predicting the risk of progressing to ESRD [9]. The results of the present study complement the conclusions of the TREAT analysis as they further support the notion that ESA-R is a useful parameter which should also be considered in the management of renal anaemia in non-dialysis CKD patients seen in nephrology practice, outside the setting of randomized clinical trials.

Potential mechanisms of this association are not readily apparent. Indeed, ESA-R is the combination of two factors that is, Hb level and dose required to reach that level and therefore, hyporesponsive patients may be at increased risk because they are exposed to either high ESA dose or a low Hb concentration. The first determinant can be reasonably excluded being our hyporesponsive patients treated with an initial ESA dose (median 20 μg/week) that is approximately one-third of that used in the low responders in TREAT trial (median 58 μg/week) [9]. The same holds true when considering the first 6 months of therapy: during the observation period, in fact, only 2.6% of patients received ESA at a dose >40 μg/week. Similarly, the ESA dosage in our patients was one-fifth of that found to be associated with adverse CV outcome in the secondary analysis of the CHOIR study (20 000 IU/week) [22]. The prescription of a lower dose of ESA in our patients is not surprising considering that in clinical practice, nephrologists are not ‘forced’ by protocol to reach a specific Hb value; the target Hb they pursue is a range of values which includes Hb levels lower than that of randomized trials on the effects of complete anaemia correction. In this regard, it is interesting to note that the difference in ESA dosing between US and European patients persists also when treatment is aimed to reach the same Hb level. Indeed, normalization of Hb levels is attained with much lower doses of ESA (4.347 IU/week, on average) in non-US patients [13–18, 23, 24], that is, about one-third with respect to the doses prescribed in the CHOIR and TREAT trials which involved almost exclusively US patients [9, 22]. Overall, these regional differences of ESA consumption in the conservative phase of CKD, and the similar data reported in haemodialysis [25], may mirror a different burden of CV co-morbidities/inflammation in US patients versus European patients.

The second factor influencing ESA-R is Hb level. We cannot rule out that the persistence of poor anaemia control may have influenced renal outcome since most hyporesponsive patients spent the majority of the observation period with Hb <11 g/dL as compared with intermediate responders and good responders (Figure 1). In this regard, we previously demonstrated that in non-dialysis patients, the lower is the time-in-target and the higher is the risk of renal death [26, 27]. We can speculate that persistence of anaemia could have induced a faster renal disease progression secondary to the hypoxia-mediated tubulointerstitial fibrosis [28–30].

Recently, it has been proposed that the increased risk of adverse outcome associated to ESA resistance may reflect either unknown or unmeasured innate or other patient characteristics [7, 10]. The most important of the known factors are the severity of illness, iron deficiency, inflammatory state, malnutrition and hyperparathyroidism [8, 31–33]. In addition, other factors, such as diabetes, proteinuria and low GFR, are associated with lower erythropoietin and/or Hb levels and may increase the susceptibility of patients to ESA resistance [34–37]. In our study, no difference was detected among tertiles in the prevalence of diabetes and previous CV disease as well as for iron status and supplementation, body mass index (BMI), parathyroid hormone and CRP levels (Table 1). In particular, CRP was on average in the low level range likely because we do not prescribe ESA in the presence of acute inflammatory states; under these circumstances, we tolerate a mild degree of anaemia and ESA are prescribed once acute illness causing inflammation has resolved and therefore, CRP returned towards normal values. Conversely, patients with low ESA-R had more pronounced renal damage, as testified by lower GFR and higher proteinuria which possibly accounted for hyporesponsiveness. These factors are strong predictors of faster progression of renal disease towards ESRD; however, the inclusion of GFR and proteinuria in the Cox model, even though significantly associated with ESRD, did not reduce the prognostic role of low ESA-R (Table 2); sensitivity analyses confirmed this finding. Alternatively, we can speculate that poor ESA-R may reflect individual biological response to ESA unrelated to the ‘traditional’ determinants of ESA resistance. In this regard, it is noteworthy that the secondary analysis of the TREAT trial found differences in some factors affecting ESA resistance (iron status, BMI and CRP) [9], but when Authors tested the ability to predict a poor initial response to ESA from a model incorporating as many as 92 baseline characteristics, they found that such a model did not improve the prediction of the outcome. However, outcome was better predicted by including ESA response rather than 92 baseline covariates (7% for death and CV composite outcome) [9].

One additional interesting finding of our study is that the predictive value of ESA-R calculated at first control visit is comparable with that measured after the 6-month observation period. These two parameters, in fact, similarly predicted ESRD and ROC curve analysis did not show any difference in AUC (Figure 3 and 4). This information is clinically relevant as it allows clinicians to obtain the same prognostic information some months earlier, that is, after 1.4 months rather than 6.0 months. This result conflicts with beliefs that in haemodialysis patients, misclassification of hyporesponsive patients may occur when ESA-R is calculated from data over 1 or 2 months due to the presence of transient Hb cycling within a 6-month period [7]. However, the phenomenon of Hb cycling occurs more frequently in haemodialysis patients (91%) than in non-dialysis subjects (62%) [38, 39].

A main limitation of this study is represented by its observational nature which cannot allow a proper assessment of cause-effect relationship between ESA-R and renal outcome. However, randomized controlled trials on this issue are of difficult design because ESA response cannot be predicted a priori, being a combination of severity of illness and individual sensitivity to the drug. Nevertheless, observational studies obtained in the real world of
Clinical practice can be an important means to generate and investigate hypothesis. In addition, sample size was small; however, to address the issue properly, we had to conduct the study in the relatively limited group of patients with at least one complete evaluation every 2 months.

In conclusion, the present study provides evidence that ESA-R predicts renal prognosis in non-dialysis CKD patients followed in nephrology practice, where ESRD is the predominant outcome and ESA is commonly used at low dose. While the exact mechanism of this association cannot be defined, our results support the suggestion to consider ESA-R as a valuable tool in anaemia management by extending its prognostic usefulness from CV to renal risk.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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Conflict of interest statement. None declared.

References

Myocardial microvascular disease and major adverse cardiovascular events in patients with end-stage renal disease: rationale and design of the MICROCARD study

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Abstract
Background. Myocardial ischaemia, a consequence of coronary artery disease, is a major cause of death in patients with end-stage renal disease (ESRD). The pathophysiology and clinical presentation of coronary artery disease in ESRD patients seem to differ from non-ESRD patients with higher implication of myocardial microvascular disease (MMD), higher mortality, fewer myocardial infarctions, less significant coronary stenosis and low efficacy of well-established drugs such as statin and angiotensin-converting enzyme inhibitors. No study has investigated the presence of MMD and its clinical impact in ESRD patients.

Methods. We designed an observational prospective cohort study to investigate the prevalence of MMD and its association with major adverse cardiovascular events (MACE) in ESRD patients with a positive non-invasive test for myocardial ischaemia. Patients eligible for inclusion are those >18 years old receiving dialysis and/or undergoing investigation for kidney transplantation, who are referred to our renal clinic and meet all the inclusion criteria but none of the exclusion criteria. Patients with a positive test for myocardial ischaemia will be enrolled in the ‘invasive group’. They will be further examined to detect simultaneously epicardial coronary stenosis by coronary angiography and MMD using pressure wire measurement of fractional flow reserve and coronary flow reserve followed by calculation of the index of microcirculatory resistance. Patients with a negative test for myocardial ischaemia will be enrolled in a ‘control group’ designed to verify whether the invasive group is indeed at high risk for MACE. Both groups will be followed up for 2 years to compare the incidence of MACE.

Conclusion. The MICROCARD study will phenotype MMD and will investigate its relation with the incidence of MACE in ESRD patients with myocardial ischaemia. Clinicaltrial.gov NCT01291771.