Anaemia management in non-dialysis chronic kidney disease (CKD) patients: a multicentre prospective study in renal clinics

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Keywords: anaemia, chronic kidney disease, ESA, iron deficiency, iron therapy

ABSTRACT

Background. Knowledge on anaemia management in non-dialysis chronic kidney disease (ND-CKD) patients regularly followed in renal clinics is scarce although being essential to identifying areas of therapeutic improvement.

Methods. We prospectively evaluated anaemia management in two visits, performed 6 months apart, in 755 prevalent ND-CKD stage 3b-5 patients followed in 19 nephrology clinics from ≥6 months. Anaemia was defined as severe (Hb <11 g/dL) or mild (Hb: 11–13.5 in males and 11–12 g/dL in females); iron deficiency (ID) was defined as transferrin saturation (TSAT) <20% and/or ferritin <100 ng/mL. Primary endpoint was the change of anaemia and ID prevalence between baseline and 6-month visit. Secondary endpoint was the prevalence of clinical inertia to either ESA or iron supplementation, that is, the lack of ESA or iron prescription despite Hb <11 g/dL or ID.

Results. Age was 69 ± 13 years and GFR 27.5 ± 10.0 mL/min/1.73 m2; male gender, diabetes and prior cardiovascular disease were 57.2, 30.1 and 30.1%, respectively. Prevalence of severe and mild anaemia was 18.0 and 44.0% at baseline and remained unchanged at Month 6 (19.3 and 43.2%). ID was prevalent at both visits (60.1 and 60.9%). Clinical inertia to ESA was similar at baseline and at Month 6 (39.6 and 34.2%, respectively, P = 0.487) and it was less frequent than clinical inertia to iron therapy (75.7 and 72.0%, respectively).

Conclusions. This study shows that anaemia prevalence is unexpectedly high in the setting of tertiary nephrology care. This was due to a persistent clinical inertia in the anaemia management, remarkable for iron supplementation and less critical, but still significant, for ESA treatment.

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INTRODUCTION

Non-dialysis chronic kidney disease (ND-CKD) is a major area to focus on for nephrologists to delay ESRD and reduce the associated high cardiovascular risk [1–3]. Noteworthy, in diabetic patients with moderate-to-severe CKD, mortality is lower in those steadily followed in nephrology clinics than in patients regularly followed by either a cardiologist or endocrinologist, likely because of better control of traditional and non-traditional risk factors [4]. In this picture, anaemia emerges as a main independent modifiable risk factor of cardiovascular and renal damage [5–9]. Despite the clinical relevance of this issue, very few studies have extensively assessed how anaemia is managed in renal clinics [10–12]. The need for updated and comprehensive information on anaemia management is further supported by three reasons. First, strategies for guidelines implementation require the knowledge of how anaemia is currently managed in clinical practice. This is particularly important for physicians when findings derived from selected cohorts of randomized clinical trials (RCTs) have to be implemented in an unselected CKD population requiring individualization strategy, based on the patient’s comorbidities, life activity and symptoms [13]. Secondly, a prescription pattern of anti-anaemic drugs is rapidly changing in response to the negative findings of RCTs on anaemia control [14–16]. Indeed, data from USRDS have recently evidenced a progressive reduction in Hb levels since 2006, in the presence of reducing ESA prescription and increasing iron use [17], and an increased risk of blood transfusion and hospitalization [18–20]. The implementation of the more restrictive KDIGO recommendations [13] could exacerbate this trend. Thirdly, knowledge of anaemia medication patterns use allows identifying opportunities for improving care. Moreover, identification of anaemia treatment patterns in nationally representative outpatient nephrology settings may also help to design an evidence-based algorithm by identifying the variations in physician prescriptions for ND-CKD and the reasons for such variations.

We, therefore, studied a prospective cohort of prevalent ND-CKD patients under nephrology care from at least 6 months prior to baseline in 19 Italian renal clinics. Data were collected in two visits with a 6-month interval to evaluate current management of renal anaemia in CKD and to identify potential areas of therapeutic improvement in terms of ESA and iron use.

SUBJECTS AND METHODS

This is a multicentric prospective non-interventional study carried out in 19 Italian outpatient nephrology clinics with a geographic distribution proportional to the size of the population in the four Italian macro-areas. All participating centres were included if they had an outpatient clinic dedicated to the care of ND-CKD patients, that is, not receiving dialysis or transplantation, with the attending patient population seen at least twice per year, and if ≥500 patients were regularly followed in the clinic. One nephrologist in each centre underwent formal training for data entry; case report forms were filled online in a single remote database by keeping the patients’ identity anonymous. Study protocol required collecting data of two visits performed 6 months apart; data were collected in the periods June–November 2010 (baseline visit) and December 2010–May 2011 (6-month visit). We enrolled all consecutive adult patients with ND-CKD stage 3b–5 (four-variable MDRD equation GFR <45 mL/min/1.73 m²), followed by ≥6 months in the renal clinic. Exclusion criteria were renal transplantation, changes in GFR >30% in the previous 6 months, active malignancy, cirrhosis and advanced heart failure (NYHA IV). Study protocol was conducted in adherence to the Declaration of Helsinki and approved by the Ethics Committees of all participating centres; all the patients signed informed consent.

All the participating centres used the same criteria to define existing comorbidities and pathologies [21]. At baseline, for each patient, information covered demographic and medical history; at both visits, blood samples were analysed in hospital laboratories of each participating centre. Furthermore, we collected dietary prescription and pharmacological therapy in the two visits, and the therapeutic targets pursued in each centre (local investigators filled a specific questionnaire on this issue). At 6-month visit, we also recorded intercurrent death, ESRD, transplantation and hospitalizations. The completeness and accuracy of information were assessed by running a set of queries on data recorded and eventual discrepancies were sent to local investigators for revision.

Anaemia and iron deficiency (ID) was defined using the cut-off recommended by International Guidelines on anaemia published before study start [22]. Anaemia was defined as mild if Hb was 11–13.5 g/dL in males and 11–12 g/dL in females; severe anaemia was defined by Hb <11 g/dL, according to Italian policy that allows starting ESA only below this level. ID was defined as transferrin saturation (TSAT) <20% and/or serum ferritin <100 ng/mL. We also measured the prevalence of severe anaemia and ID using the specific cut-off provided by each local investigator (Supplementary data Table S1). At both study visits, we assessed clinical inertia to ESA defined as the lack of ESA prescription in patients with Hb levels below the centre-specific cut-off, after excluding patients reporting non-compliance to ESA therapy. Similarly, clinical inertia to iron therapy was defined as the lack of iron prescription in patients with either TSAT or ferritin below the centre-specific cut-off, after excluding patients reporting non-compliance to iron therapy. Primary endpoint was the change in anaemia and ID prevalence between baseline and Month 6. Secondary endpoints were (i) the change of clinical inertia prevalence to either ESA or iron supplementation and (ii) the relationship between severe anaemia/ID and all-cause hospitalization.

Statistical analysis

Continuous variables are reported as means ± SD and compared with either paired or unpaired Student’s t-test. Variables with a non-normal distribution are reported as median (interquartile range, IQR) and analysed by the Wilcoxon or Mann–Whitney test. Categorical variables are expressed as per cent and analysed by either the McNemar test (paired data) or the Chi-square test (unpaired data). To evaluate the effects of basal
variables on Hb at Month 6, we performed a regression analysis by using the General Linear Model. We included a priori into the model age, gender, diabetes, prior cardiovascular disease (CVD), smoking, diagnosis of polycystic kidney disease, albumin, GFR, low TSAT, low ferritin, PTH, proteinuria, C-reactive protein (CRP) and prescription of renin–angiotensin system (RAS) inhibitors all measured at baseline. PTH, proteinuria and CRP, being non-normally distributed, were log-transformed before inclusion into the model. Baseline Hb levels were not added in the model because of its high correlation ($r = 0.75$) with the 6-month value (dependent variable).

We analysed the association of anaemia and ID with the all-cause hospitalization (considering the first event occurring) in Cox proportional hazards models. Patients were stratified in four groups according to the presence/absence of anaemia (Hb <11 g/dL) and ID (TSAT <20% or ferritin <100 ng/mL). The multivariable model was adjusted for those variables significantly associated with hospitalization at univariate analysis (CVD, serum albumin, proteinuria, PTH and GFR) except that age and gender that were forced into the model. This approach was used due to the limited number of events (66 first hospitalizations) in order to avoid over-fitting of the model. Data were analysed using SPSS 12.0 (SPSS, Inc., Chicago, IL, USA); $P$-values <0.05 were considered significant.

#### RESULTS

**Characteristics of cohort**

The mean number of patients (all Caucasian) enrolled in each single centre was 40 ± 23 (range: 10–90). The study flow chart is depicted in Figure 1 and baseline characteristics of patients are reported in Table 1. Of the 755 enrolled patients, 43.6, 42.8 and 13.6% had CKD at Stage 3b, 4 and 5, respectively. Previous follow-up in nephrology was 3.0 years (IQR: 1.2–5.0).

When compared with baseline, no significant change was detected at Month 6 for GFR, calcium, phosphorus, PTH, CRP, cholesterol, albumin and use of RAS inhibitors, while proteinuria increased from 0.34 (IQR: 0.15–1.00) to 0.40 g/day (IQR: 0.15–1.10) ($P = 0.001$). The interval between two study visits was 6.1 months (IQR: 5.9–6.4). During the follow-up, no patient received a blood transfusion.

#### Prevalence of anaemia and ID

Anaemia prevalence did not change between two visits (Figure 2A) nor did Hb distribution (Supplementary data, Figure S1). The proportion of patients developing severe anaemia (9.4%) was similar to that of patients showing recovery of severe anaemia (8.1%). Severe anaemia development occurred more frequently for patients with CKD stage 5 (Supplementary data, Table S2) and in the presence of a greater ESA use at month 6; conversely, ESA doses and intervals of administration did not change (Table 2). In the whole cohort, 502 patients (66.5%) did not receive any ESA during the follow-up; in this subgroup, severe anaemia was present in 7.0% at baseline and 9.8% at month 6 ($P = 0.04$). In patients steadily treated with ESA ($n = 187, 24.8$%), severe anaemia was present in 7.0% at baseline and 9.8% at month 6 ($P = 0.04$). In patients steady treated with ESA ($n = 187, 24.8%$), severe anaemia was

| Table 1: Demographic and clinical characteristics of patients at baseline |
|-----------------------------|------------------|------------------|
| Age (years)                | 69.2 ± 13.3      | Male gender (%)  | 432 (57.2)       |
| Male gender (%)            |                   | Diabetes (%)     | 227 (30.1)       |
| Active smoking (%)         |                   | Body mass index (kg/m²) | 27.6 ± 5.4 |
| Renal disease (%)           |                   | Left ventricular hypertrophy (%) | 347 (50.2) |
| Renal disease (%)           |                   | Prior CV disease (%) | 227 (30.1)       |
| Hypertension               | 214 (28.3)       | Glomerulonephritis | 130 (17.2)       |
| Glomerulonephritis         | 130 (17.2)       | Diabetic nephropathy | 101 (13.4)       |
| Diabetic nephropathy       | 101 (13.4)       | TIN/pyelonephritis | 35 (4.6)         |
| TIN/pyelonephritis         | 35 (4.6)         | Autosomal polycystic kidney disease | 22 (2.9) |
| Other                      | 62 (8.2)         | Unknown          | 191 (25.3)       |
| Unknown                    | 191 (25.3)       | GFR (mL/min/1.73 m²) | 27.5 ± 10.0     |
| GFR (mL/min/1.73 m²)       | 27.5 ± 10.0      | Calcium (mg/dL)  | 9.3 ± 0.6        |
| Calcium (mg/dL)            | 9.3 ± 0.6        | Phosphorus (mg/dL) | 3.7 ± 0.7       |
| Phosphorus (mg/dL)         | 3.7 ± 0.7        | PTH (pg/mL)      | 104 (69–172)    |
| PTH (pg/mL)                | 104 (69–172)     | Cholesterol (mg/dL) | 183 ± 42      |
| Cholesterol (mg/dL)        | 183 ± 42         | Albumin (g/dL)   | 4.1 ± 0.5       |
| Albumin (g/dL)             | 4.1 ± 0.5        | C-reactive protein (mg/L) | 3.02 (0.53–3.78) |
| C-reactive protein (mg/L)  | 3.02 (0.53–3.78) | Proteinuria (g/day) | 0.34 (0.15–1.00) |
| Proteinuria (g/day)        | 0.34 (0.15–1.00) | Systolic/diastolic blood pressure (mmHg) | 136 ± 18/77 ± 10 |

Data are means ± SD, median (IQR) or number (%). TIN, tubulointerstitial nephritis.
Hb, TSAT and ferritin targets pursued in each participating centre are reported in the Supplementary data, Table S1 and Appendix. The low threshold of Hb target was 11 g/dL in 16/19 centres (605/775 patients). TSAT <20% and ferritin <100 ng/mL were considered as low threshold in 79.1 and 76.8% of patients, respectively. When using the centre-specific cut-off values for defining severe anaemia and ID, we found similar results. Indeed, severe anaemia was 16.0% at baseline and 16.4% at 6-month visit and ID was 64.1% at baseline and 64.3% at Month 6. Advanced age, female gender and prescription of RAS inhibitors were associated with significantly lower Hb at Month 6, while smoking habit, higher albumin and higher GFR predicted an increase of Hb at month 6 (Table 3). Interestingly, we found that a TSAT <20% at baseline significantly predicted a subsequent Hb decline of 0.36 g/dL, whereas low ferritin at baseline did not influence Hb at Month 6.

**Treatment of anaemia**

Potential areas of improvement in anaemia management were evidenced in Figure 3 by evaluating the lack of ESA prescription in patients stratified for Hb levels (Figure 3A) or the lack of iron supplementation for Hb levels (Figure 3B), as well as the lack of iron supplementation in patients stratified for TSAT (Figure 3C) and ferritin levels (Figure 3D). The prevalence of ESA-untreated patients at baseline was constantly high (from 36 to 47%). At 6-month visit, fewer patients were left without ESA therapy especially in the subgroups with more severe anaemia. We found ID in a substantial portion of the four Hb subgroups (in Hb <9.5, 9.5 to <10, 10 to <10.5 and 10.5 to <11, ID was present in 82, 72, 47 and 67% at baseline and 75, 84, 66 and 59% at Month 6). However, missed iron therapy was common (Figure 3B). When compared with ESA therapy, iron supplementation was omitted in a larger number of patients independently from the degree of ID both at baseline and at 6-month visit (Figure 3C and D). Indeed, 54% of patients with TSAT <12 and 66% of those with ferritin <30 ng/mL and did not receive iron supplementation. Further insights were obtained by classifying the 734 patients with complete data of Hb, TSAT and ferritin in four subgroups, according to the presence/absence of severe anaemia and ID (Table 4). In comparison with controls (no anaemia/no ID), patients with either severe anaemia or ID or both did not differ for age, GFR, diabetes, history of CVD, whereas the prevalence of females was higher (ranging from 48 to 57 versus 30% in controls, P < 0.001). In the control group (n = 245), we observed a significant decline at Month 6 of Hb, TSAT and ferritin; this was associated with the development of severe anaemia and ID in 10.6 and 27.3% of patients, respectively. In anaemic patients without ID (n = 47), Hb increased and anaemia resolved in 42.6% of patients. In this subgroup, ID developed at Month 6 in ~45% of patients due to the slight decline of TSAT and the significant reduction of ferritin. In the subgroup with isolated ID (n = 355), no significant improvement of TSAT and ferritin was detected and resolution of ID was evidenced in only 18.4% of the patients. Furthermore, 12.1% of the patients developed anaemia at month 6. Finally, the patients with both anaemia and ID (n = 87) showed a significant increase in Hb (anaemia correction in...
44.8% of patients) but no changes of TSAT and ferritin (ID correction in 19.5% of patients). When considering prescription of anaemia drugs (Table 4), we found a significant increase of ESA use in patients with no ID/no anaemia and in those with both ID and anaemia while no significant change occurred in iron use for any subgroup.

**Therapeutic inertia to anaemia drugs**

In anaemic patients, non-compliance to ESA treatment was reported in 14 subjects (5.5% of those receiving ESA prescription). After excluding these patients, clinical inertia to ESA, that is, lack of ESA prescription despite Hb lower than centre-specific cut-off as reported in Supplementary data, Table S1, occurred in 39.6% of anaemic patients at baseline and 34.2% at Month 6 (\(P = 0.512\)). In patients with clinical inertia to ESA, iron was prescribed in 38.6% at baseline and 21.1% at Month 6 (\(P = 0.138\)). Non-compliance to iron supplementation was reported in 100 patients, 91% of which had ID. After excluding non-compliant patients, we evaluated clinical inertia to iron therapy, that is, the lack of iron prescription despite low TSAT and/or ferritin according to centre-specific cut-off reported in the Supplementary data, Table S1A; this phenomenon occurred frequently in iron-deficient patients both at baseline (75.7%) and month 6 (72.0%) (\(P = 0.276\)). Therapeutic inertia to iron therapy was also detected among ESA-treated patients (45.9% at baseline and 44.1% at month 6) (\(P = 0.925\)).

**Hospitalization risk**

During the follow-up, we recorded 74 hospitalizations in 66 patients (hospitalization rate 1.49/100 patients-month), due to cardiovascular events (34%), metabolic complication (34%), surgery (23%) and preparation of vascular access (9%). Incidence of hospitalization was significantly higher in anaemics (17.8%) than in non-anaemics (6.6%), while it was similar in patients with and without ID (10.2 and 7.2%, \(P = 0.166\)). Multivariable Cox analysis showed that adjusted hospitalization risk was higher in patients with anaemia irrespective of the iron status (Figure 4). Indeed, hazard ratios were higher in
Table 3. General linear model estimating the effect of demographic and clinical parameters on haemoglobin level at month-6 visit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>10.37</td>
<td>8.42 to 12.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (10 years)</td>
<td>−0.15</td>
<td>−0.26 to −0.04</td>
<td>0.006</td>
</tr>
<tr>
<td>Female gender</td>
<td>−0.84</td>
<td>−1.13 to −0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Active smoking (yes versus no)</td>
<td>0.82</td>
<td>0.37 to 1.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus (yes versus no)</td>
<td>−0.16</td>
<td>−0.45 to 0.13</td>
<td>0.276</td>
</tr>
<tr>
<td>History of CVD (yes versus no)</td>
<td>−0.03</td>
<td>−0.33 to 0.27</td>
<td>0.848</td>
</tr>
<tr>
<td>APKD (yes versus no)</td>
<td>0.05</td>
<td>−0.72 to 0.82</td>
<td>0.896</td>
</tr>
<tr>
<td>GFR (5 mL/min/1.73 m²)</td>
<td>0.28</td>
<td>0.20 to 0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>0.42</td>
<td>0.10 to 0.73</td>
<td>0.010</td>
</tr>
<tr>
<td>Transferrin saturation &lt;20% (yes versus no)</td>
<td>−0.36</td>
<td>−0.66 to −0.07</td>
<td>0.017</td>
</tr>
<tr>
<td>Ferritin&lt;100 ng/mL (yes versus no)</td>
<td>−0.19</td>
<td>−0.48 to 0.09</td>
<td>0.180</td>
</tr>
<tr>
<td>Log-PTH (pg/mL)</td>
<td>0.04</td>
<td>−0.35 to 0.43</td>
<td>0.845</td>
</tr>
<tr>
<td>Log-proteinuria (g/day)</td>
<td>−0.04</td>
<td>−0.29 to 0.22</td>
<td>0.777</td>
</tr>
<tr>
<td>Log-CRP (mg/L)</td>
<td>−0.02</td>
<td>−0.10 to 0.05</td>
<td>0.511</td>
</tr>
<tr>
<td>Prescription of RAS inhibitors (yes versus no)</td>
<td>−0.31</td>
<td>−0.61 to −0.003</td>
<td>0.048</td>
</tr>
</tbody>
</table>

The value of intercept represents the Hb value from which it is possible to estimate the Hb changes predicted by variables reported in the model. CVD, cardiovascular disease; APKD, autosomal polycystic kidney disease; RAS, renin–angiotensin system.

Figure 3: Prevalence of missed ESA (A) and iron (B) prescription in anaemic patients stratified for Hb levels, and the prevalence of missed iron prescription in iron-deficient patients stratified for TSAT (C) or ferritin values (D) at baseline (white bars) and month-6 visit (grey bars). TSAT and ferritin thresholds were selected on the basis of their distribution (values closest to inter-quartile limits).
Table 4. Basal and 6-month anaemia management in patients stratified according to the presence of anaemia and iron deficiency at baseline

<table>
<thead>
<tr>
<th></th>
<th>No iron deficiency/no anaemia</th>
<th>No iron deficiency/anaemia</th>
<th>Iron deficiency/no anaemia</th>
<th>Iron deficiency/anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Month 6</td>
<td>Baseline</td>
<td>Month 6</td>
</tr>
<tr>
<td><strong>Haemoglobin (g/dL)</strong></td>
<td>13.1 ± 1.4</td>
<td>12.8 ± 1.5*</td>
<td>10.2 ± 0.7</td>
<td>10.8 ± 1.3*</td>
</tr>
<tr>
<td><strong>Anaemia (%)</strong></td>
<td>—</td>
<td>10.6</td>
<td>100</td>
<td>57.4</td>
</tr>
<tr>
<td><strong>TSAT (%)</strong></td>
<td>29.4 ± 7.4</td>
<td>26.8 ± 9.5*</td>
<td>29.6 ± 8.8</td>
<td>28.6 ± 14.9</td>
</tr>
<tr>
<td><strong>Ferritin (ng/mL)</strong></td>
<td>188 (136–261)</td>
<td>179 (119–265)*</td>
<td>239 (158–343)</td>
<td>209 (126–304)*</td>
</tr>
<tr>
<td><strong>TSAT &lt;20%</strong></td>
<td>—</td>
<td>21.6</td>
<td>—</td>
<td>31.9</td>
</tr>
<tr>
<td><strong>Ferritin &lt;100 ng/mL</strong></td>
<td>—</td>
<td>11.8</td>
<td>—</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>Iron deficiency (%)</strong></td>
<td>—</td>
<td>27.3</td>
<td>—</td>
<td>44.7</td>
</tr>
<tr>
<td><strong>ESA use (%)</strong></td>
<td>22.4</td>
<td>26.1*</td>
<td>63.8</td>
<td>70.2</td>
</tr>
<tr>
<td><strong>Iron use (%)</strong></td>
<td>10.2</td>
<td>14.3</td>
<td>34.0</td>
<td>29.8</td>
</tr>
</tbody>
</table>

Data are means ± SD, median (IQR) or per cent.

*Anaemia is defined as Hb <11 g/dL. Iron deficiency is defined as either TSAT <20% or ferritin <100 ng/mL.

*P < 0.05 versus baseline.
ID. ESA doses were in the low range and similar to previous
tached to modality of ESA prescription, under-use of ESAs or
The lack of improvement in anaemia control rates could be as-
mented is lacking in the literature; however, when compared
r with a suf-
in ESA use at the 6-month visit without change in dosage and
s increased hospitalization risk (1.70, 95% CI: 0.85–3.39).

DISCUSSION

This study provides an in-depth evaluation of anaemia man-
agement in a heterogeneous prospective cohort ND-CKD
patients receiving long-lasting care in Italian nephrology
clinics. The previous studies evaluating anaemia management
in ND-CKD were either limited to diabetics [10], or those
with advanced CKD [23], or to cross-sectional data [10, 11,
23, 24]. This latter aspect is relevant because cross-sectional
evaluation of Hb and iron indices could be misleading since it
captures as ‘uncontrolled’ also abnormal data at their first
occurrence in outpatient clinics and, moreover, it does not allow
appreciating eventual intervention of nephrologist for controlling
these parameters. Our study, being based on two visits
with a sufficient lag-time (6 months) and including a complete
prescription pattern, provides a unique tool for estimating
anaemia control rate, adherence to guidelines and therapeutic
approach of nephrologists to anaemia.

We found that uncontrolled anaemia (Hb <11 g/dL) in-
olved about one patient out six at baseline and this prevalence
did not change within the next 6 months (Figure 2A). ESA
prescription pattern disclosed a slight but significant increase in
ESA use at the 6-month visit without change in dosage and
doing intervals (Table 2); this increase in ESA use was par-
ticularly evident in patients with Hb <10.5 g/dL (Figure 3A).
The lack of improvement in anaemia control rates could be as-
cribed to modality of ESA prescription, under-use of ESAs or
ID. ESA doses were in the low range and similar to previous
observation in Italian outpatient nephrology clinics [5]. Com-
parison with other surveys is not possible since this information
is lacking in the literature; however, when compared with RCTs, we found that the dosage prescribed in our cohort
was similar to those prescribed in European trials [18, 25–27],
but much lower than those used in US trials [16, 17]. Why this
occurs is beyond the scope of this study, but this information
is relevant to correctly implement the individualization of ESA
therapy recommended by the guidelines. Use of ESA at impro-
perly extended dosing interval could have also contributed to
less effective erythropoiesis and, therefore, to a low success
rate of therapy [28]; however, this phenomenon was limited to
only a minority of patients using short-acting epoetin (~7%),
in which the mean interval between doses was 11–12 days on
average. Conversely, the lack of ESA prescription in anaemic
patients could have had a greater impact on anaemia control.
Indeed, clinical inertia to ESA therapy was frequent in our
anaemic patients. This point represents a critical area of
improvement considering that therapeutic inertia is associated
with a worse renal survival of non-dialysis CKD patients [29].
A larger degree of inertia was found when examining iron pre-
scription, being present in about two-thirds of iron-deficient
patients. It is expected that non-anaemic patients will not
receive iron supplements until anaemia develops; however,
over 40% of iron-deficient patients did not receive any iron
despite Hb <11 g/dL.

Our results disclose a high prevalence of ID not only in
women (68.6%), but also in men (53.8%), where ID is less fre-
fently expected. The high frequency of ID and the relatively
low prescription of iron compounds can be multifactorial.
Indeed, elevated hepcidin levels, scarce patient compliance,
fear of side-effects of oral administration and suboptimal iron
supplementation [30, 31] can all contribute to ID. In particu-
lar, several publications have highlighted the role of hepcidin,
an acute-phase protein synthesized in the liver, as a main regu-
lator of iron metabolism in CKD; high-circulating levels of this
protein, in fact, reduce absorption of iron from the gut and
impede the release of iron from reticulo-endothelial sites [32].
In ND-CKD patients, hepcidin levels are usually elevated
because of impaired renal function or sustained inflammatory
state; the latter, however, can be reasonably excluded in our
cohort on the basis of the low CRP levels. Regardless the
potential mechanisms, high-hepcidin levels may have contrib-
uted both to the low TSAT and ferritin concentrations found
in our cohort and to an impaired efficacy of oral iron therapy.
However, this hypothesis cannot be verified because hepcidin
levels were not available in the real-life setting of this study.
In our cohort, nephrologists reported that non-compliance to
oral iron therapy occurred only in ~13% of patients, a fre-
quency remarkably lower than that described in the literature
(20–46%) [30, 33]. The discrepancy with other studies may
underline the importance of stable tertiary care in motivating
CKD patients. On the other hand, the low frequency of poor
adherence also suggests that other causes accounted for the
persistent high ID rates. Besides the above-mentioned role of
hepcidin, one further possibility is that the prescribed daily
amount of elemental iron was too low (~90 mg/day on
average) considering current recommendations (~200 mg/
day) [13]. In our opinion, an increased use of i.v. iron (occur-
ing in only 3% of iron-treated patients) would be desirable to
obtain a more effective supplementation leading to better
control rates of anaemia with less need of ESA, administered

FIGURE 4: Unadjusted (grey circles) and case-mix adjusted (black circles) hazard ratios for hospitalization in 734 CKD patients stratified in four subgroups according to the presence of severe anaemia (Hb <11 g/dL) and iron deficiency (either TSAT <20% or ferritin <100 ng/mL) at baseline. The multivariable model is adjusted for age, gender, CVD, serum albumin, proteinuria, PTH and GFR.
at lower doses [34, 35]. However, this approach exposes patients to a greater risk of compromising veins for future vascular access [36] and increases the burden of patient out clinics. Newer iron compounds that ensure adequate iron supplementation with very few venipunctures, such as iron carboxymaltose or ferumoxytol [37, 38], may reduce this problem but they are not available in Italy yet.

The greater attention of nephrologists to ESA therapy rather than iron supplementation was further supported by the observation that at Month 6, iron supplementation did not increase in spite of the presence at baseline of ID, whereas ESA use increased significantly in patients with anaemia independently from the presence of ID (Table 4). On the other hand, as depicted in Figure 3, iron supplementation was less frequent at both visits in patients with low TSAT and/or ferritin (26–28%) than in those with low Hb (41–50%), suggesting that the decision of prescribing iron is driven more by low Hb levels rather than by the specific indices of ID. Overall these findings suggest that in clinical practice the lack of iron supplementation remains a main limitation for effectively managing anaemia and reducing ESA use despite available evidence and recommendations [35, 39, 40].

The classification of patients according to the presence/absence of anaemia and ID also provides useful data on the dynamics of anaemia and ID occurrence (Table 4). We found that among non-anaemic patients at baseline, 11.5% subsequently developed anaemia (Hb <11 g/dL). Elderly, females and low GFR are all significant factors predicting low Hb during the follow-up, whereas other known pro-anaemic factors (CRP, PTH and proteinuria) did not play a role (Table 3). Perhaps the CRP levels were not sufficiently elevated in this pre-dialysis population to be associated with anaemia severity, as previously suggested for ESA responsiveness [41]. In addition, the significant association of low TSAT but not ferritin with Hb decline confirms the relatively greater importance of functional ID [42–44]. To our knowledge, only one study has recently estimated the rate of anaemia development in ND-CKD patients [45]. The authors found that the onset of anaemia in the first 6 months of follow-up was lower (4.5%) than that we found (11.5%), likely because that study enrolled patients only in CKD stage 3. However, the incidence rate of ID was not reported [45]. Finally, it is important to note that stratifying patients on the basis of anaemia, and ID is also useful to obtain better stratification of hospitalization risk. In this regard, the presence of Hb <11 g/dL, with or without ID, identified patients at an increased risk of hospitalization. Owing to the observational nature of the present study, it is possible that anaemia may simply represent a marker of disease severity.

In conclusion, this study shows a persistent clinical inertia in the nephrology management of renal anaemia. The nephrologists’ failure to modify therapy despite unmet goals was remarkable for iron supplementation (~75% of patients) and less critical, but still significant, for ESA treatment (~35% of patients). This phenomenon was clinically significant being associated with a prevalence of anaemia (~65% of mild-to-severe anaemia) that is unexpectedly high in the setting of patients with low inflammation under steady nephrology care.

**SUPPLEMENTARY DATA**

Supplementary data are available online at http://ndt.oxford-journals.org.

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**CONFLICT OF INTEREST STATEMENT**

R.M. has received consulting fees from Roche and lecture fees from Abbott, Amgen, Roche. F.L. has received payment for board membership from Affymax, Amgen, Roche, Takeda Pharmaceutical, Janssen, and Sandoz and lecture fees from Amgen, Roche, Janssen, Takeda Pharmaceutical, Pharmacosmos, Fresenius Medical Care. M.G. has received lecture fees from Abbott, Amgen, Fresenius Medical Care, Genzyme. R.B.: none. G.F.: none. L.O.: none. G.C. has received lectures fees from Amgen, Roche and payment for board membership from Abbott. L.D.N. has received consulting fees from Amgen and Roche, payment for board membership from Abbott and lecture fees from Abbott, Amgen, Roche.

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Echocardiographical determinants of an abnormal spatial QRS-T angle in chronic dialysis patients

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ABSTRACT

Background. The spatial QRS-T angle describes the relation between ventricular depolarization and repolarization. Having a wide (abnormal) angle is considered an important predictor of arrhythmic events. Given the high incidence of sudden cardiac death in dialysis patients, this parameter is of particular interest in this patient group. The objective of this study was to assess the association of (modifiable) echocardiographic parameters and an abnormal spatial QRS-T angle in dialysis patients.

Methods. A total of 94 consecutive dialysis patients were included. In all patients a 12-lead electrocardiogram (ECG), a two-dimensional echocardiogram and routine blood samples were obtained. The spatial QRS-T angle was then calculated from the 12-lead ECG. An abnormal spatial QRS-T angle was defined as ≥130° in males and ≥116° in females.

Results. An abnormal spatial QRS-T angle was present in 27 (29%) patients. Patients with an abnormal spatial angle had a lower left ventricular ejection fraction (LVEF) of 47 ± 7 versus 55 ± 6% (P < 0.001) and had a higher left ventricular (LV) dysynchrony, with a septal to lateral (S–L) delay of peak systolic velocity of 70 inter quartile range (IQR) (40, 100) ms versus 30 IQR (10, 70) ms (P = 0.001), respectively. Multivariate logistic regression analysis controlling for possible confounders demonstrated that LVEF [odds ratio (OR) 0.82; 95%