Clinical policies on the management of chronic kidney disease patients in Italy

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Abstract

Background. Recent studies have indicated that the implementation of international guidelines for the management of renal patients is suboptimal in Italy. The Italian Society of Nephrology (SIN) decided to undertake a multicentre study to obtain a clear picture of clinical policies on chronic kidney disease (CKD) in Italy.

Methods. A 76-item structured questionnaire, designed to evaluate the organization of clinical care, was administered to the director of each participating centre, within the context of a large observational trial in 100 Italian nephrology centres, collecting information on newly diagnosed CKD patients (K/DOQI stage 3–5) on conservative treatment. This paper reports the questionnaire results related to management of anaemia and bone metabolism disorders; assessment of renal function; creation of a vascular access for dialysis and referral of patients to a nephrologist.

Results. Clinical policies at the centre level deviated from guideline recommendations in 70\% (timing of vascular access creation) to 25\% (assessment of iron deficiency) of centres. Assessment of renal function differed from the recommended approach in 30\% of centres; clinical policies related to anaemia and bone disease did not coincide with guideline standards in 50 and 40\% of centres, respectively. Directors of renal unit estimates indicate that the creation of a vascular access occurs very late in 38\% of patients and that referral to a nephrologist is late in \textldots; 40\% of cases.

Conclusion. This survey in Italy highlights important deviations of clinical policies at the centre level from guideline recommendations.

Keywords: chronic kidney disease; guidelines; Italy; management

Introduction

Recent studies have indicated that the implementation of international guidelines for the management of patients with renal diseases is suboptimal in Italy. Less than 20\% of patients had target blood pressure levels in the Target Blood Pressure Levels in Chronic Kidney Disease (TABLE-CKD) study performed in Italian patients with mild to advanced CKD regularly followed-up by nephrologists [1,2]. The dialysis outcomes and practice patterns study (DOPPS), which was carried out in five European countries, including Italy, has shown that the implementation of international guidelines is suboptimal in terms of a number of important issues, such as anaemia and abnormal mineral metabolism [3,4]. The analysis of the data related to the 20 participating Italian centres was consistent with the European results [5]. Despite its clinical relevance, few studies have addressed the issue of the causes of differences between guideline standards and achieved treatment goals. Potential causes include (i) patient-related factors (poor compliance), (ii) insufficient attention by the doctors or (iii) inadequate clinical policies at the centre level that differ from actual guideline recommendations. The Italian Society of Nephrology (SIN) decided to perform a large observational multicentre study, called SIR-SIN (‘Studio Italiano indicatori di Risultato multipli – epidemiologica dell’insufficienza renale cronica in Italia’ della Societ`a Italiana di Nefrologia, ‘Italian study on multiple predictors of outcome–epidemiology of chronic renal insufficiency in Italy’ sponsored by the Italian Society of Nephrology), to obtain a clear picture of clinical practice in Italy related to the diagnosis and management of CKD.

Within this project, a structured questionnaire designed to evaluate local clinical policies was administered to directors of participating centres. This paper reports the results related to the management of the two complications that were found to be managed suboptimally in the DOPPS, namely anaemia and abnormal mineral metabolism. Furthermore, we assessed clinical policies related to the evaluation of renal function and we asked for information on the timing of vascular access creation and patterns of referral to a nephrologist.
Methods

One hundred Italian nephrology centres belonging to the Italian National Health Service were involved in the SIR-SIN project with the aim of creating a national database containing information on the demographic and clinical features, diagnostic work-up, treatment, hospitalisation and survival of 2500 newly diagnosed CKD patients (K/DOQI stage 3–5) on conservative treatment, to be followed up for 3 years or until 200 cases of doubling of serum creatinine were collected; their clinical outcome was to be correlated with clinical practice. The 100 centres were randomly selected from the SIN centre database (363 renal units overall). The project was started in June 2004 and is still ongoing.

One of the SIR-SIN substudies consisted in the administration of a 76-item structured questionnaire by the directors of participating centres, designed to evaluate the organization of clinical care in each centre from the subjective perspective of the investigator. The questionnaire included open, closed and multiple-choice questions subdivided into eight sections: facilities, clinical practice, training and organization of medical and other healthcare staff, IT networking, treatment, diagnostic investigations and laboratory tests available at the centre, prevention and treatment of concomitant diseases and continuous education of medical and other healthcare staff.

This paper summarizes the answers given to a series of questions related to clinical policies implemented at the centre level, in detail:

(a) The management of anaemia, i.e. multiple-choice questions regarding the most commonly used test to establish iron deficiency, the haemoglobin (Hb) cut-off value for starting treatment with erythropoiesis-stimulating agents, their preferred route of administration, how their dosage is calculated and the target Hb levels.

(b) The management of bone mineral metabolism disorders, i.e. the method used for the measurement of parathyroid hormone (PTH) levels and how often PTH is measured; whether the centre has a target range for PTH and if so, what the range is; whether X-rays and/or bone biopsies are performed to detect osteodystrophy and if so, how often; whether patients are prescribed vitamin D and if so, what criteria are adopted for its introduction.

(c) Glomerular filtration rate (GFR): multiple-choice questions related to the method adopted for its measurement and how often it is measured.

(d) Permanent vascular access; timing of creation of vascular access before initiation of dialysis.

(e) Furthermore, the directors were asked to make an estimate of the timing of patient referral to their units, i.e. the interval between referral and implementation of dialysis.

Questionnaire data were analysed both by pooling all questionnaires and by subdividing them into geographical areas according to the criteria of the Italian National Institute of Statistics (ISTAT): the Northwest regions (Piedmont, Valle d’Aosta, Liguria and Lombardy), the Northeast regions (Veneto, Trentino-Alto-Adige, Friuli-Venezia Giulia and Emilia Romagna), the Central regions (Tuscany, Umbria, Marche and Latium), the Southern regions and the Islands (Abruzzo, Molise, Campania, Basilicata, Apulia, Calabria, Sicily and Sardinia). The number of centres per million inhabitants was calculated for each geographical area, according to the resident population in 2001 (ISTAT census in 2001).

A descriptive analysis of the data was performed, providing frequency distributions of categorical variables in both absolute numbers and percentages, and the usual descriptive parameters (mean ± SD, median, range and quartiles, i.e. Q1 and Q3).

Results

Ninety-six directors answered the questionnaire. Geographical areas were covered in proportion to the resident population: 25 dialysis units came from the Northwest, 13 from the Northeast, 21 from the Central regions and 37 from the South and the Islands. The number of centres per million inhabitants was fairly homogeneous, ranging from 1.2 in the Northeast to 1.9 in the central regions versus 1.7 in the whole of Italy.

Anaemia

Centre directors declared that in their units one (37.9%) to four tests (25.3%) were actually implemented to establish iron deficiency. Serum ferritin and transferrin saturation were the most applied methods for the detection of iron deficiency (76 and 74% of centres, respectively). Serum iron was used in 50.5% and Total Iron Binding Capacity (TIBC) in 32.6%. Only 3% of centres used bone marrow criteria, i.e. hypochromic red cell percentage or Hb content in reticulocytes.

In the majority of nephrology centres (52%), the threshold for starting ESA treatment was set at values <11 g/dl (mean 10.3 ± 0.7 g/dl, median 10.5; min 8.0; Q1 10.0; Q3 11.0; max 12.0). Treatment targets (Table 1) were set in a range larger than the 11 to 12 g/dl recommended by guidelines: the desired lower limit (mean ± SD) was 10.4 ± 0.9 g/dl (median 10.5; min 7.0; Q1 10.0; Q3 11.0; max 12.0) and the desired upper limit was 12.4 ± 0.8 g/dl (median 12.0; min 9.0; Q1 12.0; Q3 13.0; max 14.5).

The ESA dose was calculated on the basis of body weight in 74% of centres and in haemodialysis patients, the intravenous route was the preferred option in 69.5%.

Table 1. Percent distribution of preferred target haemoglobin (Hb) levels; relative to the common practice guidelines lower limit of 11 g/dl and upper limit of 12 g/dl (to convert Hb in g/dl to g/l, multiply by 10)

<table>
<thead>
<tr>
<th>Hb level</th>
<th>Lower limit (%)</th>
<th>Upper limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>≥11 &lt;12</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>≥12 &lt;13</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>≥13</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Policies and guidelines on CKD in Italy

**Table 2. Timing of PTH measurements in CKD patients on conservative treatment**

<table>
<thead>
<tr>
<th>Based on the individual needs (%)</th>
<th>Every month (%)</th>
<th>Every 3 months (%)</th>
<th>Every 6 months (%)</th>
<th>Every year (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>4</td>
<td>20</td>
<td>40</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 3. Timing of bone X-rays evaluation**

<table>
<thead>
<tr>
<th>Based on the individual needs (%)</th>
<th>Never (%)</th>
<th>Every 6 months (%)</th>
<th>Every 12 months (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>2</td>
<td>4</td>
<td>42</td>
<td>5</td>
</tr>
</tbody>
</table>

**Bone mineral metabolism**

PTH serum levels were measured mainly with the intact PTH assay (93% of centres); no centres used C-terminal PTH and only one used N-terminal PTH. The few remaining centres used the CAP/CIP ratio, bioactive PTH or intact PTH solid phase with chemoluminescence. In the majority of centres PTH was monitored at fixed 3–6 month intervals, but in a substantial number of centres a flexible approach tailored to the needs of the patient was adopted (Table 2).

When asked if they had PTH target values, 12% of the directors did not report any. Amongst the directors who reported them, target PTH values were the following: desired lower limit (mean ± SD) 123 ± 62 pg/ml (median 120; min 12; Q1 80; Q3 150; max 300); desired upper limit 255 ± 97 pg/ml (median 250; min 30; Q1 200; Q3 300; max 500). Remarkably, in non-dialysed CKD patients, 48% of the directors set a lower limit >120 pg/ml and 49% a higher limit >250 pg/ml.

Bone X-rays were performed once a year in 41.9% of centres and in 46.2% according to the patient’s needs (Table 3). The vast majority of directors (76%) declared that bone biopsies are never performed in their centres.

Vitamin D is systematically given to the patients on conservative treatment in more than half of the centres (52.2%). All centres prescribe it specifically for the treatment of secondary hyperparathyroidism, 62.8% for complications of bone disease, such as fractures, and 54.2% for the prevention of bone disease.

**Assessment of renal function**

The two most popular methods for the assessment of renal function (GFR) are serum creatinine + 24-h urine collection and serum creatinine only, with the application of Cockcroft and Gault’s formula. These two methods are simultaneously adopted by nearly half of the centres (49%) and are adopted separately by 22 and 21% of centres, respectively. Renal function is assessed using these two methods by nearly all Italian centres (92%) at every visit (66%) or at fixed intervals (33%); this means that GFR is measured on average at intervals ranging from 2 to 6 months (Table 4).

**Vascular access**

In all centres a permanent vascular access [arteriovenous (AV) fistula, graft or tunnelled catheter] is eventually created in nearly all patients (99%) starting haemodialysis, although in 10 centres 5 to 20% of patients are treated with temporary catheters for chronic dialysis. The permanent access is usually created before dialysis in the majority of patients, but the interval between surgery and beginning of dialysis is rather variable, as follows:

- At least 8 weeks in advance: 30 ± 28% (median 20; min 0; Q1 5; Q3 50; max 100);
- 2–8 weeks in advance: 32 ± 25% (median 25; min 0; Q1 15; Q3 50; max 100);
- 0–2 weeks in advance: 14 ± 12% (median 10; min 0; Q1 5; Q3 20; max 70);
- after starting dialysis: 22 ± 20% (median 20; min 0; Q1 7; Q3 30; max 90);
- no permanent access (use of temporary catheters): 1.3 ± 4.1% (median 0; min 0; Q1 0; Q3 0; max 20).

**Referral to the nephrologist**

Directors estimated that more than half of the patients were referred in good time, i.e. referred at least 6 months before dialysis is required (Table 5).

Among the remaining patients, 29% of the total number of patients were specifically referred for initiating dialysis or they came directly from the emergency room needing dialysis: 12% had an established diagnosis of chronic renal insufficiency but without previous nephrology care, 11% arrived with no diagnosis but with advanced CKD and 6% of patients had acute renal insufficiency that did not resolve.

**Overall compliance with guidelines**

We compared the questionnaire results with the suggestions of the K/DOQI and European guidelines [6–11]. A summary of the level of compliance of clinical policies with the guidelines currently in force is provided in Table 6.

**Table 4. Timing of assessment of renal failure by GFR measurement**

<table>
<thead>
<tr>
<th>2 months (%)</th>
<th>3 months (%)</th>
<th>4–6 months (%)</th>
<th>&gt;6 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>36</td>
<td>39</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 5. Patterns of referral to the nephrologist**

<table>
<thead>
<tr>
<th>At least 6 months before HD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>57%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 6 months before HD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43%→29% of whom directly referred for dialysis or coming from the emergency room</td>
</tr>
<tr>
<td>Irreversible acute renal failure</td>
<td>6%</td>
</tr>
<tr>
<td>Unknown CKD stage 5</td>
<td>11%</td>
</tr>
<tr>
<td>Known advanced CKD never referred to a nephrologists</td>
<td>12%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Haemodialysis.
Table 6. Compliance with guidelines in force (K/DOQI and/or European Best Practice Guidelines)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determination of iron deficiency:measurement of ferritin and TSAT</td>
<td>75</td>
</tr>
<tr>
<td>Cut-off value for introduction of erythropoietin stimulating agents</td>
<td>62</td>
</tr>
<tr>
<td>Target Hb values &gt;11 g/dl</td>
<td>50</td>
</tr>
<tr>
<td>PTH target values</td>
<td>48</td>
</tr>
<tr>
<td>Assessment of renal function</td>
<td>70</td>
</tr>
<tr>
<td>Timing of creating of vascular access</td>
<td>30</td>
</tr>
</tbody>
</table>

Discussion

Differences between policies and guideline recommendations, regarding important clinical issues, such as the management of anaemia (assessment of iron status, target Hb levels) and of bone mineral disorders (in particular target PTH levels), which have an impact on the prognosis of CKD patients [3,4], is a matter of concern.

The DOPPS disclosed that the implementation of international guidelines is suboptimal in Europe [3–5]. In DOPPS-Italy, Hb levels were below 11 g/dl in 60% of patients. In this study in CKD, as much as 52% of nephrology directors declared that they start treating anaemia in CKD patients with ESA at a lower threshold than that recommended by current guidelines. In this regard, it is of interest that a recent meta-analysis [12] and the accompanying editorial [13] warn against overcorrection of anaemia in CKD patients. Both DOPPS and our data suggest that in Italian dialysis units, actual clinical policies on anaemia treatment set Hb levels below the guideline target in a significant proportion of centres.

Data in the present study focusing on timing of vascular access creation before the start of dialysis suggest that about 37% of patients do not have a permanent vascular access at least 2 weeks before starting dialysis. This is in agreement with the incident DOPPS data regarding Italian patients, reported by Pisoni et al. [14], which indicated that 38% of patients begin haemodialysis treatment with a central venous catheter (CVC). However, variability among different centres was fairly large, which indicates that there is still considerable room for improvement. Several centres were very well organized with a very low CVC prevalence, but at the same time some centres had a high prevalence of CVC at the beginning of dialysis. It is important to note that the percentage of patients referred late to Italian nephrologists (~30%), very closely matches the percentage of patients starting dialysis with a catheter. This finding suggests that improving late referral patterns might also improve vascular access management in the pre-dialysis period, as previously proposed by Ravani et al. [15].

Bone metabolism assessment patterns also elicit several considerations. According to the K/DOQI guidelines [7], the target range of plasma levels of intact PTH in the various stages of CKD depends on the degree of underlying renal dysfunction. In CKD stage 3 (GFR 30–59 ml/min/1.73 m²) the suggested intact PTH range is 35–70 pg/ml, in CKD stage 4 (GFR 15–29 ml/min/1.73 m²) it is 70–110 pg/ml and in CKD stage 5 (GFR <15 ml/min/1.73 m² or dialysis) it is 150–300 pg/ml. Our results show that such distinction is either unknown or disregarded by Italian nephrologists. The fact that guidelines report a fixed target PTH without taking into account different sensitivities among PTH determination methods is possibly implicated but it is not sufficient to fully explain the apparently scarce attention of Italian nephrologists to PTH targets as related to renal function.

The strength of this study is that the survey was obtained in a large number (100) of nephrology units, representative of all the centres in Italy, as they were randomly selected from the database of the National Association of Nephrologists (SIN). Indeed, geographical allocation showed that all the regions of Italy were adequately represented.

The data represent the local clinical policies declared by 100 directors of nephrology on the investigated issues. We believe that inquiries of this kind are important because these policies ultimately determine the treatment targets at the local level. An important weakness of our study is that we did not specifically inquire how clinical policies were implemented at the centre level, an important issue to investigate in future studies.

In conclusion, our results highlight important differences between clinical policies and clinical practice guideline recommendations. Development and promulgation of practice guidelines is an important advancement of modern medicine. Changing professional behaviour is difficult. It is well recognized that publication of guidelines in professional journals or mailing guidelines to targeted professionals rarely leads to desired changes in professional behaviour [16]. Specific research is needed on barriers hindering guideline implementation at the centre level in renal units. Mechanism(s) governing the behaviour of renal teams and individual doctors are of obvious importance for the achievement of desirable clinical goals. The organizational context (lack of time, reimbursement issues), the social and professional context (old routines hard to remove, personal convictions of team leaders, inadequate update of knowledge base of doctors) may variably contribute to producing unsatisfactory application of guidelines [16].

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Conflict of interest statement. Authors do not have conflicts of interest regarding this study.

Appendix: SIR-SIN Study

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