

Prevalence of anaemia and its clinical management in patients with stages 3-5 chronic kidney disease not on dialysis in Catalonia: MICENAS I study

Aleix Cases-Amenós¹, Alberto Martínez-Castelao², Joan Fort-Ros³, Jordi Bonal-Bastons⁴, M. Pilar Ruiz⁵, Martí Vallés-Prats⁶, Elisabeth Coll-Piera⁷, Josep M. Galcerán-Gui⁸, Investigadores del Estudio Micenas I*

¹ Servicio de Nefrología. Hospital Clínic. Barcelona. (Spain)

² Servicio de Nefrología. Hospital Universitari de Bellvitge. Barcelona. (Spain)

³ Servicio de Nefrología. Hospital Universitari Vall d'Hebron. Barcelona. (Spain)

⁴ Servicio de Nefrología. Hospital Universitari Germans Trias i Pujol. Barcelona. (Spain)

⁵ Servicio de Nefrología. Hospital Moisès Broggi. Sant Joan Despí. Barcelona. (Spain)

⁶ Servicio de Nefrología. Hospital Universitari Josep Trueta. Girona. (Spain)

⁷ Servicio de Nefrología. Fundació Puigvert. Barcelona. (Spain)

⁸ Servicio de Nefrología. Fundació Althaia Manresa. Barcelona. (Spain)

[Nefrologia 2014;34\(2\):189-98](#)

doi:10.3265/Nefrologia.pre2013.Dec.12261

ABSTRACT

Introduction: Anaemia is a common complication of chronic kidney disease (CKD). The aim of this study was to determine the prevalence and clinical management of anaemia in patients with stages 3-5 CKD not on dialysis treated in outpatient Nephrology clinics (OC) in Catalonia. **Methods:** Epidemiological, cross-sectional cohort, multicentre study under routine clinical practice conditions. Data collection by electronic data collection log-book (e-DCL) including personal information and data related to anaemia (haemoglobin, iron status, treatment with erythropoiesis-stimulating agents [ESA] and other anaemia treatments). Anaemia was defined as haemoglobin levels <13.5g/dL in males or <12g/dL in females or patients who receive treatment with ESA. **Results:** We included 504 patients (56.4% male, mean age of 67.8±15.5 years): 61.5% had stage 3 CKD, 30.2% stage 4 and 8.3% stage 5. The main causes of CKD were vascular

and diabetic nephropathy. The prevalence of anaemia was 58.5% (n=295), however, only 14.9% of patients had haemoglobin levels <11g/dL. Mean haemoglobin levels decreased and ESA treatment was more common as CKD progressed, but no significant differences were observed regarding the prescription of iron, according to CKD stages. ESA and intervals most frequently prescribed were darbepoetin alfa with a median dose of 40µg/biweekly, followed by C.E.R.A. with a median dose of 75µg/month and epoetin beta with a median dose of 5,000IU/week. Among the patients with anaemia (n=295), 36.3% (n=107) had iron deficiency and only 53.3% of these patients were treated with iron supplements. **Conclusions:** This study demonstrates the high prevalence of anaemia, which increases as the disease progresses and its good control in a CKD patient population treated in Nephrology outpatient clinics in Catalonia. This control is achieved with moderate doses of ESA and iron supplements prescribed in more than 50% of anaemic CKD patients.

Correspondence: Aleix Cases Amenós

Servicio de Nefrología.
Hospital Clínic. Villarroel, 170. 08036 Barcelona. (Spain).
acases@clinic.ub.es

Keywords: Anemia. Chronic kidney disease. Erythropoiesis-stimulating agents. Iron deficiency.

*Group members:

Investigadores del estudio MICENAS I: los siguientes investigadores también participaron en el presente estudio: Arias M. (Hospital Clínic, Barcelona), Perelló M. (Hospital Vall d'Hebron, Barcelona), Samon R. (Hospital Mollet, Barcelona), Agraz I. (Hospital Vall d'Hebron, Barcelona), Bayes B. (Hospital Germans Trias i Pujol, Barcelona), Cañas L. (Hospital Germans Trias i Pujol, Barcelona), Castellote E. (Hospital de Vic, Barcelona), Craver L. (Hospital Arnau de Vilanova, Barcelona), García R. (Hospital Palamós, Girona), Felip A. (Hospital Mataró, Barcelona), Lauzurica R. (Hospital Germans Trias i Pujol, Barcelona), Pou M. (Hospital Terrassa, Barcelona), Ballarín J. (Fundació Puigvert, Barcelona), Puig J.M. (Hospital del Mar, Barcelona), Puig C. (Hospital d'Igualada, Barcelona), Cao H. (Hospital del Mar, Barcelona), Collado S. (Hospital del Mar, Barcelona), Barbosa F. (Hospital del Mar, Barcelona), Martínez-Vea A. (Hospital Universitari Joan XXIII, Tarragona).

Prevalencia de anemia y su manejo clínico en la enfermedad renal crónica estadios 3-5 no en diálisis en Cataluña: estudio MICENAS I

RESUMEN

Introducción: La anemia es una complicación frecuente de la enfermedad renal crónica (ERC). El objetivo de este estudio fue conocer la prevalencia de anemia en pacientes con ERC estadios 3-5 no en diálisis atendidos en consultas externas (CCEE) de Nefrología en Cataluña y su manejo clínico. **Metodología:** Estudio epidemiológico, de cohorte transversal, multicéntrico, en condiciones de práctica clínica habitual. Recogida de datos mediante un e-CRD que incluía datos de filiación y aquellos relacionados con la anemia (hemoglobina, estatus férrico, tratamiento con agentes estimuladores de la eritropoyesis [AEE] y con otros coadyuvantes). Se definió anemia como unos niveles de hemoglobina $< 13,5$ g/dl en varones o < 12 g/dl en mujeres o pacientes que recibieran tratamiento con AEE. **Resultados:** Se incluyeron 504 pacientes (56,4 % varones, edad media de $67,8 \pm 15,5$ años): 61,5 % presentaban ERC estadio 3, 30,2 % estadio 4 y 8,3 % estadio 5. Las principales causas de ERC fueron la vascular y la nefropatía diabética. La prevalencia de anemia fue del 58,5 % ($n = 295$); sin embargo, solo un 14,9 % de los pacientes tenían niveles de hemoglobina < 11 g/dl. Los niveles medios de hemoglobina disminuían y el tratamiento con AEE era más frecuente a medida que progresaba la ERC, pero no se observaron diferencias significativas respecto a la prescripción de hierro, según estadios. Los AEE e intervalos más frecuentemente prescritos fueron darbepoetina alfa con una dosis mediana de 40 μ g/bisemanal, seguida por C.E.R.A., con una dosis mediana de 75 μ g/mensual y epoetina beta con una dosis mediana de 5000 U/sem. De los pacientes con anemia ($n = 295$), un 36,3 % ($n = 107$) presentaban ferropenia y de ellos solo un 53,3 % recibía tratamiento con suplementos de hierro. **Conclusiones:** Este estudio demuestra la alta prevalencia de anemia, la cual aumenta a medida que progresa la enfermedad, así como el buen control de la misma en la población de pacientes con ERC atendidos en CCEE de Nefrología en Cataluña. Este control se consigue con dosis moderadas de AEE y prescripción de suplementos de hierro en más del 50 % de los pacientes anémicos.

Palabras clave: Anemia. Enfermedad renal crónica. Agentes estimuladores de la eritropoyesis. Ferropenia.

INTRODUCTION

Chronic kidney disease (CKD) affects around 11% of the Spanish adult population, according to data from the EPIRCE study,¹ and is associated with high morbidity and mortality, particularly as a consequence of cardiovascular disease.^{2,3} Furthermore, CKD is related to a series of complications, including anaemia,⁴ which has been linked to higher morbidity and mortality and CKD progression.

The presence of anaemia is already observed in early stages of CKD (stage 3), but its prevalence increases as renal failure progresses to more advanced stages.⁵ The main cause of anaemia in CKD patients is an erythropoietin deficiency, although a decrease in the half-life of red blood cells, iron and vitamin deficiency and other factors have also been involved.⁵

Since the introduction of recombinant human erythropoietin, erythropoiesis-stimulating agents (ESA) have become the cornerstone of CKD anaemia treatment and have reduced requirements for transfusion, improved the quality of life and reduced left ventricular hypertrophy and morbidity and mortality in these patients.⁶⁻¹⁰ However, target haemoglobin has been the subject of debate in recent years due to recent randomised studies and meta-analyses that have demonstrated that total anaemia correction with ESA is not associated with better survival or a significant improvement in quality of life, while it is associated with a potential increase in adverse cardiovascular effects.¹¹⁻¹⁶

In light of these results, the 2010 European guidelines recommended target haemoglobin of between 11 and 12g/dl, without intentionally exceeding 13g/dl¹⁷ and the EMA (European Medicines Agency) advises not exceeding haemoglobin levels of 12g/dl in patients treated with ESA (Ref. EMEA/188068/2007).¹⁸

The objective of this study was to establish the prevalence of anaemia in patients with stages 3, 4 and 5 CKD not on dialysis treated in outpatient Nephrology clinics in Catalonia, and know its therapeutic management (haemoglobin levels achieved, prescription of ESA, iron therapy and other concomitant treatments) in clinical practice.

MATERIAL AND METHOD

Study design and data collection

This is an epidemiological, cross-sectional, multicentre study under routine clinical practice conditions.

The study data were collected during 2010. All Nephrology Services in Catalonia were invited to participate and we conducted a feasibility survey on all candidates. Nineteen centres were included in the study (90.47% of those invited), of which 17 recruited patients (80.95% of those invited). Two of the centres invited did not participate in the study. Participant centres contributed data from all patients visited consecutively in outpatient Nephrology clinics who met the inclusion and exclusion criteria and who gave their consent to participate in the study over a week, with the aim of including the highest possible number of patients. The data were collected using an electronic data collection

log-book (e-DCL), which was developed specifically for the study. We compiled patients' demographic data (age, gender, weight, height, CKD stage, CKD diagnosis time) and data corresponding to anaemia (haemoglobin levels, ferritin levels, transferrin saturation index [TSI], treatment with ESA, iron, folic acid or vitamin B¹²). We also estimated the glomerular filtration rate (eGFR) using the MDRD-4 formula.

The study was approved by the different ethics committees of participating hospitals and patients had to sign their informed consent to allow data to be taken from their clinical history.

Patient selection

The study's target population was adult patients with CKD and an eGFR of less than 60ml/min/1.73m² who were not on dialysis.

Inclusion criteria:

- Patients 18 years old or older.
- Patients with an established clinical diagnosis of stage 3, 4 or 5 CKD not on dialysis treated in outpatient Nephrology clinics in Catalonia.
- Patients who gave their informed consent in writing to participate in the study.

Exclusion criteria:

- Patients whose clinical history did not include a recent determination of haemoglobin (two months before inclusion).
- Any patient situation or condition that, in the opinion of the researcher, would make them unsuitable for participating in the study.

Statistical analysis

Anaemia was defined as haemoglobin levels <13.5g/dl in males and <12g/dl in females or treatment with ESA. We defined iron deficiency as ferritin levels <100ng/ml and/or TSI <20%.

Categorical variables were described using absolute and relative frequencies, including a 95% confidence interval. For the description of the continuous variables, we used means, standard deviation, medians, the minimum and maximum, including the total number of valid values.

For quantitative variables, we used parametric tests (Student's t-test or Anova) or non-parametric tests (Mann-Whitney or Kruskal-Wallis), as appropriate. For qualitative variables, we performed the χ^2 test.

The results were considered to be statistically significant when the *P* value was less than 0.05.

The statistical analyses were carried out using the SAS version 9.1.3 statistical software.

RESULTS

Study population

We recruited a total of 531 patients, of which we excluded 27 because they did not meet the selection criteria or did not have the data necessary for assessing the main variable, leaving 504 patients included in the study.

The characteristics of patients included are displayed in Table 1. 61.5% had stage 3 CKD, 30.2% had stage 4 CKD and the remaining 8.3% had stage 5 of the disease. The causes of CKD are displayed in Table 1. We observe that the main aetiologies are vascular and diabetic nephropathy, although the aetiologies of a high percentage of patients were unknown.

Table 1. Characteristics of the patients included in the study

N = 504	
CKD stage (3a/3b/4/5)	116 (23%)/194 (38.5%)/152 (30.2%) /42 (8.3%)
Gender (male/female)	56.4%/43.6%
Age (years)	67.8 ± 15.5
BMI (kg/m ²)	28.3 ± 5.2
Aetiology	N (%)
Diabetes	82 (16.3%)
Vascular	126 (25%)
Primary glomerulonephritis	54 (10.7%)
Interstitial nephritis	52 (10.3%)
Polycystic kidney disease	23 (4.6%)
Hereditary/congenital	8 (1.6%)
Systemic disease	11 (2.2%)
Unknown	128 (25.4%)
Other	57 (11.3%)

BMI: body mass index.

Table 2. Laboratory data on anaemia (according to the different stages of chronic kidney disease)

Parameter	Mean	SD	Median	Minimum	Maximum	P
Haemoglobin	12.6	1.6	12.6	8.2	18.8	<0.0001
Stage 3a	13.6	1.6	13.5	10.4	18.8	
Stage 3b	12.9	1.5	13	8.2	17.1	
Stage 4	11.9	1.4	12	8.3	17.3	
Stage 5	11.4	1.2	11.1	9.1	14.7	
Serum iron (µg/dl)	68.5	27.3	66	7.4	169	0.0456
Stage 3a	70.7	28.5	67	8.6	169	
Stage 3b	72.9	26.9	69	11.7	143	
Stage 4	64.9	27.5	61	7.4	157	
Stage 5	60.6	23.5	62	20	133	
Ferritin (ng/ml)	158.4	135.8	118	10	860	0.1564
Stage 3a	123.4	106.5	100	15	490	
Stage 3b	156.7	134.1	118	14.2	726	
Stage 4	175.7	156.6	133.4	14.3	860	
Stage 5	159.5	100.7	128.5	10	443.1	
TSI (%)	24.2	11.7	22	1.5	72	0.3110
Stage 3a	24.2	12.7	20	6	63	
Stage 3b	26.4	13	24.1	5	72	
Stage 4	23	10.4	21	6.3	57.1	
Stage 5	22	10	21.5	1.5	54.7	

TSI: transferrin saturation index.

Laboratory data on anaemia and iron status

Data on haemoglobin and iron status are displayed in Table 2, which shows levels of haemoglobin, serum iron, ferritin and TSI according to CKD stage. Anaemia prevalence in the study population was 58.5%, although only 14.9% of patients had haemoglobin levels <11g/dl. The mean haemoglobin of the whole cohort was 12.6±1.6g/dl, although we observed a tendency for haemoglobin levels to decrease as CKD advanced. We observed an inverse correlation between the eGFR and haemoglobin levels (Figure 1). The mean ferritin of the whole study group was 158.4±135.8ng/ml and the mean TSI was 24.2±11.7%, without significant differences for ferritin or TSI being observed according to the stage of the disease. Among anaemic patients (n=295), 36.3% (n=107) had an iron deficiency (ferritin <100ng/ml and/or TSI <20%).

Anaemia prevalence according to demographic data

The patient's profile according to the presence or absence of anaemia is displayed in Table 3, without significant differences being found according to sex, but with there being significant differences according to age (higher anaemia amongst older individuals), CKD aetiology (diabetes and unknown cause

are the most prevalent aetiologies in anaemia), CKD stage (as CKD progresses, a higher presence of anaemia is observed) and eGFR (lower eGFR amongst patients with anaemia).

Treatments prescribed for anaemia

40.5% of all patients were receiving some form of treatment for anaemia at the time of the visit. The data referring to treatment for anaemia are displayed in Tables 4, 5, 6, 7 and 8.

The treatments for anaemia are displayed in Table 4 according to the CKD stage. Of the patients treated, 68.0% (n=136) were receiving an ESA, 14.5% were receiving folic acid and 10.0% were receiving vitamin B₁₂. 66.0% of all patients with chronic renal failure and anaemia were receiving iron supplements at the time of the visit (61% orally and 5% intravenously). We can observe how the percentage of patients treated increases as the CKD stage increases (Table 8). ESA was the most frequent treatment as CKD progressed, while folate and vitamin B₁₂ were prescribed more often in earlier stages, but no significant differences were observed with regard to the prescription of iron supplements according to the stages. There were no statistically significant differences with regard to the prescription of oral and intravenous iron according to

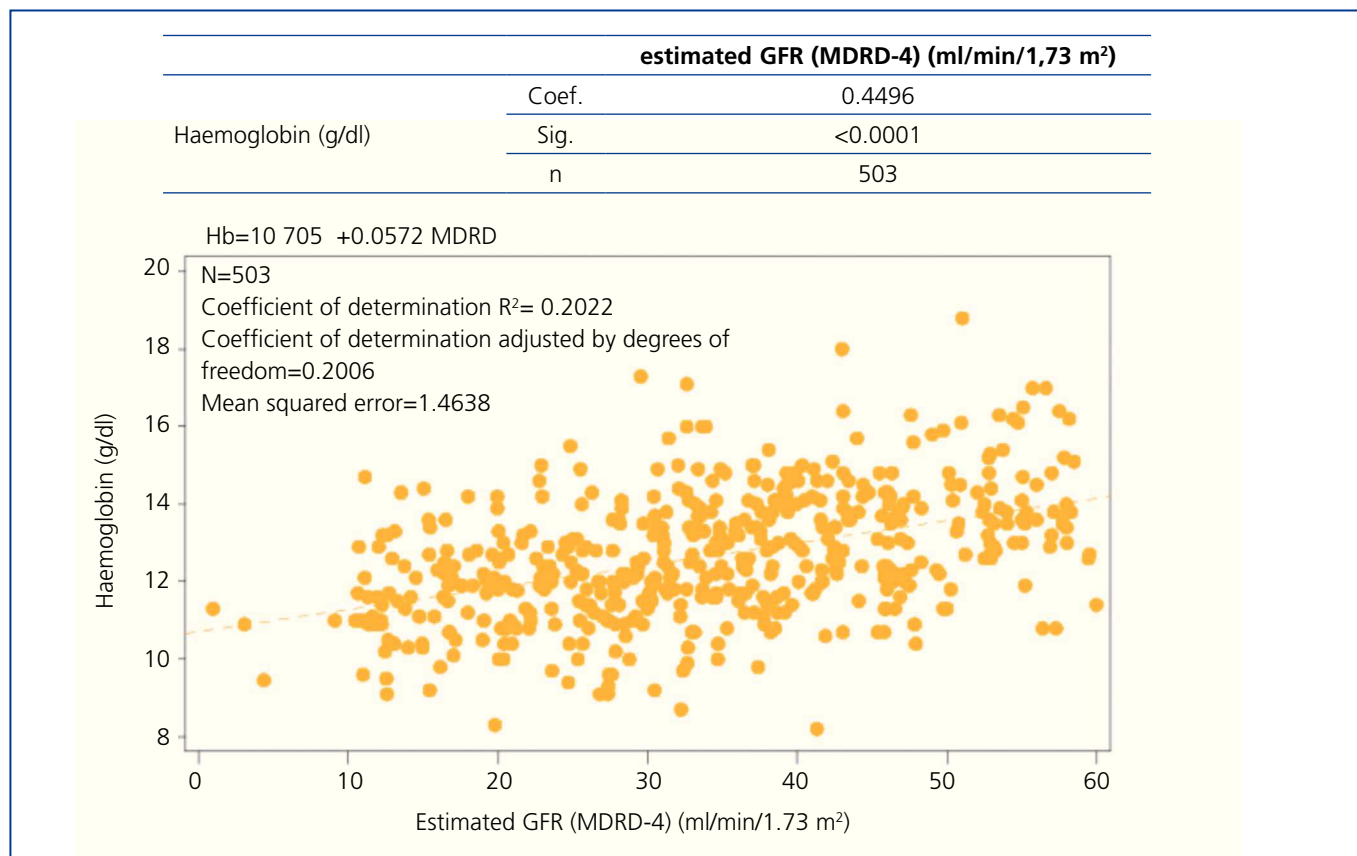


Figure 1. Correlation between the haemoglobin level and the glomerular filtration rate.

Coef.: Pearson's correlation coefficient (bivariate); GFR: glomerular filtration rate; Hb: haemoglobin; n: number of patients; Sig: Pearson's correlation test significance.

the CKD stage. In the anaemic patient subgroup we observed similar results to those of the overall population, although they were not significant for vitamin B₁₂ and folic acid (Table 5). The ESA and intervals most frequently prescribed in our population were darbepoetin alfa with a median dose of 40 µg/biweekly, followed by C.E.R.A (*Continuous Erythropoietin Receptor Activator*) with a median dose of 75 µg/month, followed by epoetin beta with a median dose of 5000 IU/week. The prescription of epoetin alfa to the study population was rare.

Table 6 displays treatment with iron supplements in the anaemic, iron-deficient patient subgroup; 53.3% received treatment with iron, 12.1% did not receive iron supplements and in the rest of the patients, it was not specified in the e-DCL. The prescription of iron to anaemic and iron-deficient patients was more common in patients with stage 5 CKD than in earlier stages.

Table 7 displays treatment for anaemia according to haemoglobin levels, and we observed that 67.9% of patients with haemoglobin levels <11 g/dl received ESA and/or iron therapy and 33.3% received both. Likewise, in patients with haemoglobin >12 g/dl, 18% received ESA, as well as 8.2%

of those with haemoglobin >13 g/dl. Of those treated with ESA, 43.4% had haemoglobin levels >12 g/dl and 12.5% had haemoglobin levels >13 g/dl.

DISCUSSION

This study shows a high prevalence of anaemia in patients with stages 3-5 CKD not on dialysis and a suitable control of the latter in patients treated in 17 Nephrology Service outpatient clinics in Catalonia.

The prevalence of anaemia in this patient population with stages 3-5 CKD not on dialysis was 58.5%, however only 14.9% had haemoglobin of less than 11 g/dl, that is, that 85.1% of patients would exceed the low haemoglobin margin established by the European guidelines.¹⁷ In the MERENA observational multicentre study, conducted on 1129 patients with stages 3 and 4 CKD tested in outpatient Nephrology clinics in Spain, anaemia prevalence was somewhat lower than that of this study (51.3% compared to 58.5%), although it must be borne in mind that this study did not include patients with stage 5 CKD and it is possible that recently published referral criteria may have resulted in patients who are currently treated in outpatient

Table 3. Patient profile according to the presence of anaemia

N=504	Presence of anaemia	Absence of anaemia	P
CKD stage (3a/3b/4/5)	35.3%/52.1%/73.7%/97.5%	64.7%/47.9%/26.3%/2.4%	<0.05
Gender (male/female)	59.9%/59.3%	40.1%/40.7%	ns
Age (years)	70±14.9	64.7±15.7	<0.0001
BMI (kg/m ²)	28.7±5.4	27.7±5.4	ns
eGFR (ml/min/1.73m ²)	29.7±12.1	31.9±12.8	<0.0001
Time since CKD diagnosis (years)	6.2±7.5	7.1±8	ns
CKD aetiology	N (%)	N (%)	
Unknown	29.2%	20.1%	0.02
Vascular	24.4%	25.8%	ns
Diabetes	19.7%	11.5%	0.01
Primary glomerulonephritis	9.5%	12.4%	ns
Pyelonephritis	7.8%	13.9%	0.02
Polycystic kidney disease	3.7%	5.7%	ns
Systemic disease	2%	2.4%	ns
Hereditary/congenital	1%	2.4%	ns
Other	11.2%	11.5%	ns

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, BMI: body mass index, ns: not significant.

Nephrology clinics having higher comorbidities, including anaemia, than in previous studies, such as MERENA.¹⁹ The prevalence of anaemia in 1058 patients with CKD not on dialysis in Italy was 16%, 32% and 51% in stages 3, 4 and 5 respectively, although the definition of anaemia in this study would require lower levels of haemoglobin (haemoglobin <12g/dl in males and <11g/dl in females).²⁰ In a recent Spanish prospective study of 439 non-anaemic patients with CKD, followed up over three years, 35% developed anaemia, and they had a quicker progression of CKD and a higher risk of hospitalisation, cardiovascular events and mortality.²¹

Demographic factors that influence the presence of anaemia in the study population include CKD stage (greater prevalence of anaemia as the glomerular filtration rate decreases), age (greater prevalence of anaemia in older patients, probably related to a lower eGFR) and the aetiology of CKD (greater prevalence of anaemia in diabetic nephropathy and lower prevalence in interstitial nephritis). These results coincide with previous studies that demonstrate that anaemia is more common and severe at any eGFR level in diabetic patients, compared with non-diabetic patients.^{22,23}

Table 4. Treatment of anaemia according to the chronic kidney disease stage

Treatment	Stage 3a (n=114)	Stage 3b (n=192)	Stage 4 (n=146)	Stage 5 (n=42)	Total	P
Some form of treatment	19 (16.7%)	60 (31.3%)	85 (58.2%)	36 (85.7%)	200 (40.5%)	<0.0001
ESA	6 (31.6%)	31 (51.7%)	66 (77.6%)	33 (91.7%)	136 (68%)	<0.0001
Iron	13 (68.4%)	38 (63.3%)	56 (65.9%)	25 (69.4%)	132 (66%)	ns
Folic acid	10 (52.6%)	10 (16.7%)	6 (7.1%)	3 (8.3%)	29 (14.5%)	0.035
Vitamin B ₁₂	2 (10.5%)	12 (20%)	4 (4.7%)	2 (5.6%)	20 (10%)	0.013

ESA: erythropoiesis-stimulating agents, ns: not significant.

Table 5. Treatment of anaemia according to the chronic kidney disease stage in anaemic patients

Anaemic patients	Stage 3a (n=41)	Stage 3b (n=101)	Stage 4 (n=112)	Stage 5 (n=41)	Total (n=295)	P ^a
Some treatment	15 (36.6%)	52 (51.5%)	72 (64.3%)	35 (85.4%)	174 (59.0%)	<0.0001
ESA	5 (12.2%)	22 (21.8%)	52 (46.4%)	30 (73.2%)	109 (36.9%)	<0.0001
Iron	10 (24.4%)	34 (33.7%)	48 (42.9%)	24 (58.5%)	116 (39.3%)	0.9916
Folic acid	7 (17.1%)	8 (7.9%)	6 (5.4%)	3 (7.3%)	24 (8.1%)	0.0502
Vitamin B ₁₂	1 (2.4%)	8 (7.9%)	4 (3.6%)	2 (4.9%)	15 (5.1%)	0.2496

ESA: erythropoiesis-stimulating agents.

^aχ² test.

Mean haemoglobin of CKD patients was relatively high (12.6g/dl), bearing in mind that 40.5% of patients were receiving some form of treatment for anaemia. Of the 187 patients treated for anaemia, 72.7% (136 patients) were treated with ESA at the time of the study.

In earlier stages of CKD, only 16.7% of patients with stage 3a CKD and 31.3% with stage 3b CKD received some form of treatment for anaemia, with mean haemoglobin levels of 13.6g/dl and 12.9g/dl being observed, respectively. As CKD progressed, the percentage of patients who received some form of treatment for anaemia increased to 85.7% in stage 5 with mean haemoglobin of 11.4g/dl being observed.

In the most advanced stages of CKD (4 and 5), anaemia was controlled by more frequent use of ESA, notably ESA with a longer half-life, which allow them to be administered biweekly or monthly. This facilitates compliance, it is more comfortable for the patient and it improves haemoglobin stability. Furthermore, monthly doses of agents with a longer half-life (darbepoetin or C.E.R.A.) were lower than equivalent doses of erythropoietin, although given the cross-sectional nature of the study, these data should be interpreted with caution. It should also be highlighted from this study that anaemia control is achieved with relatively low doses of ESA (80µg/month darbepoetin,

75µg/month C.E.R.A.) with respect to other studies with darbepoetin or C.E.R.A.^{13,24-26} This is important because high doses of ESA have been associated with higher mortality²⁷ and the guidelines advise considering the ESA doses necessary for achieving the haemoglobin levels.¹⁷

In our study, 43.4% of anaemic patients who received ESA had haemoglobin >12g/dl and 12.5% had haemoglobin >13g/dl, which suggests overtreatment with ESA in a significant percentage of them. Additionally in our study, we observed that 24 patients (32.0% of whom had haemoglobin <11g/dl) did not receive any treatment for anaemia.

Although the mean values of ferritin and TSI of the whole group were above the minimum values advised in the guidelines, 36.3% of anaemic patients had an iron deficiency. With regard to iron therapy, 53.3% of iron-deficient patients received treatment with iron supplements (most as oral iron supplements), 12% did not receive iron and there was no data available for 34.5%. Assuming that where no data was contributed the patients did not receive iron, this suggests an aspect of improvement in anaemia treatment in these patients, as indicated by recommendations by experts and the new KDIGO (Kidney Disease Improving Global Outcomes)

Table 6. Treatment with iron supplements in anaemic and iron-deficient patients according to the chronic kidney disease stage

Iron-deficient patients	Stage 3a n = 14	Stage 3b n = 32	Stage 4 n = 44	Stage 5 n = 17	P ^a
Without iron	0 (0%)	3 (9.4%)	9 (20.5%)	1 (5.9%)	0.0420
With iron	7 (50%)	14 (43.8%)	22 (50%)	14 (82.4%)	
Not specified	7 (50%)	15 (46.9%)	13 (29.5%)	2 (11.8%)	

^aχ² test.

Table 7. Treatment for anaemia according to haemoglobin levels

	Hb < 11 g/dl (n = 75)	Hb ≥ 11-< 12 g/dl (n = 101)	Hb ≥ 12- < 13 g/dl (n = 120)	Hb ≥ 13 g/dl (n = 208)	Total (n = 504)
Only iron	10 (13.3%)	22 (21.8%)	10 (8.3%)	9 (4.3%)	51 (10.1%)
Only ESA	16 (21.3%)	16 (15.8%)	16 (13.3%)	7 (3.4%)	55 (10.9%)
Iron and ESA	25 (33.3%)	20 (19.8%)	26 (21.7%)	10 (4.8%)	81 (16.1%)

ESA: erythropoiesis-stimulating agents, Hb: haemoglobin.

guidelines, which promote iron therapy for optimising erythropoiesis and the response of the ESA treatment.²⁸⁻²⁹

The main limitation of this study for the interpretation of its results is its cross-sectional nature and that the conclusions are obtained from haemoglobin levels and iron parameters from just one laboratory test, and from the dosage of a treatment at one point in time. Another limitation concerns the difference between the valid definition for all the populations (haemoglobin <13.5g/dl in males and <12g/dl in females) and accepted target haemoglobin levels for good control of anaemia in CKD patients, defined as the result of the latest prospective multicentre studies carried out,¹¹⁻¹³ which would be between 10 and 12g/dl, both in males and females. Furthermore, this study did not evaluate other parameters that influence haemoglobin levels and ESA dose, such as the presence of inflammation, nutritional parameters, treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, or intact parathyroid hormone levels. Furthermore, this study cannot be extrapolated to the general CKD patient population, since many are treated in Primary Care, but it can be extrapolated to the patient subgroup treated in outpatient Nephrology clinics, who presumably have more comorbidities, including anaemia.

The main conclusion of this study is that patients with stages 3, 4 and 5 CKD not on dialysis followed up in hospital clinics of Catalonia have a high prevalence but, in general, an adequate control of anaemia. This good control is achieved with a combination of moderate doses of ESA (particularly in advanced stages of CKD) and the prescription of iron in more than 50% of those who require it. Nevertheless, we have observed a significant percentage of patients treated with ESA with haemoglobin levels >12g/dl and a certain undertreatment of iron deficiency, which suggests that there are opportunities for improvement in the treatment of anaemia in our patients.

Acknowledgements

MICENAS I study researchers. The following researchers also participated in this study: Arias M. (Hospital Clínic, Barcelona), Perelló M. (Hospital Vall d'Hebron, Barcelona), Samon R. (Hospital Mollet, Barcelona), Agraz I. (Hospital Vall d'Hebron, Barcelona), Bayes B. (Hospital Germans Trias i Pujol, Barcelona), Cañas L. (Hospital Germans Trias i Pujol, Barcelona), Castellote E. (Hospital de Vic, Barcelona), Craver L. (Hospital Arnau de Vilanova, Barcelona), García R. (Hospital Palamós, Girona), Felip A. (Hos-

Table 8. Patients on treatment with oral iron and intravenous iron according to the chronic kidney disease stage

Anaemic or non-anaemic patients	Stage 3a		Stage 3b		Stage 4		Stage 5		Total		p ^b
	n	% ^a	n	% ^a	n	% ^a	n	% ^a	n	% ^a	
Treatment for anaemia	19	100.0	60	100.0	85	100.0	36	100.0	200	100.0	< 0.0001
Iron	13	68.4	38	63.3	56	65.9	25	69.4	132	66.0	0.9988
Oral	13	68.4	32	53.3	51	60.0	25	69.4	121	60.5	0.1902
Intravenous	1	5.3	11	18.3	14	16.5	2	5.6	28	14.0	0.0771

^a Percentages calculated on the total number of patients being treated for anaemia.

^b χ^2 test/Fisher's exact test.

Note: more than one route of administration may be indicated for a patient who is being treated with iron.

pital Mataró, Barcelona), Lauzurica R. (Hospital Germans Trias i Pujol, Barcelona), Pou M. (Hospital Terrassa, Barcelona), Ballarín J. (Fundació Puigvert, Barcelona), Puig J.M. (Hospital del Mar, Barcelona), Puig C. (Hospital d'Igualada, Barcelona), Cao H. (Hospital del Mar, Barcelona), Collado S. (Hospital del Mar, Barcelona), Barbosa F. (Hospital del Mar, Barcelona), Martínez-Vea A. (Hospital Universitari Joan XXIII, Tarragona).

Conflicts of interest

This study was sponsored by the Societat Catalana de Nefrologia with financing from Roche Pharma in Spain.

REFERENCES

- Otero A, Gayoso P, Garcia F, de Francisco AL; EPIRCE study group. Epidemiology of chronic renal disease in the Galician Population: results of the pilot Spanish Epirce study. *Kidney Int Suppl* 2005;(99):S16-9.
- US Renal Data System: USRDS 2009 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.
- Rucker D, Tonelli M. Cardiovascular risk and management in chronic kidney disease. *Nat Rev Nephrol* 2009;5:287-96.
- Kazmi WH, Kausz AT, Khan S, Abichandani R, Ruthazer R, Obrador GT, et al. Anemia: an early complication of chronic renal insufficiency. *Am J Kidney Dis* 2001;38:803-12.
- Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia. The Third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2002;162:1401-8.
- Obrador GT, Roberts T, St Peter WL, Frazier E, Pereira BJG, Collins AJ. Trends in anemia at initiation of dialysis in the United States. *Kidney Int* 2001;60:1875-84.
- Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis* 1996;28:53-61.
- Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F. Increasing the hematocrit has beneficial effect on quality of life and is safe in selected haemodialysis patients. Spanish Cooperative Renal Patients Quality of life Study Group of the Spanish Society of Nephrology. *J Am Soc Nephrol* 2000;11:335-42.
- Cody J, Daly C, Campbell M, Donaldson C, Khan I, Rabindranath K, et al. Recombinant human erythropoietin for chronic renal failure anemia in pre-dialysis patients. *Cochrane Database Syst Rev* 2005;(3):CD003266.
- De Nicola L, Chiodini P, Zoccali C, Borrelli S, Cianciaruso B, Di Iorio B, et al.; SIN-TABLE CKD Study Group. Prognosis of CKD patients receiving outpatient nephrology care in Italy. *Clin J Am Soc Nephrol* 2011;6:2421-8.
- Singh AK, Szczec L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al.; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
- Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al.; CREATE investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071-84.
- Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al.; TREAT investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019-32.
- Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010;153:23-33.
- Clement FM, Klarenbach S, Tonelli M, Johnson JA, Manns BJ. The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. *Arch Intern Med* 2009;169:1104-12.
- Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. *Clin J Am Soc Nephrol* 2009;4:755-62.
- Locatelli F, Aljama P, Canaud B, Covic A, De Francisco, Macdougall IC, et al.; Anemia Working group of European Best Practice (ERBP). Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study. *Nephrol Dial Transplant* 2010;25:2846-50.
- Ref. EMEA/188068/2007 European Medicines Agency starts review of the safety of epoetins. Available at: <http://www.halmed.hr/upl/novosti/18806807en.pdf>.
- Martínez-Castelao A, Górriz JL, Portolés JM, De Alvaro F, Cases A, Luño J, et al. Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. *BMC Nephrol* 2011;12:53.
- De Nicola L, Minutolo R, Chiodini P, Zoccali C, Castellino P, Donadio C, et al.; Target Blood Pressure Levels in Chronic Kidney Disease (TABLE in CKD) Study Group. Global approach to cardiovascular risk in chronic kidney disease: reality and opportunities for intervention. *Kidney Int* 2006;69:538-45.
- Portolés J, Górriz JL, Rubio E, de Alvaro F, García F, Alvarez-Chivas V, et al.; NADIR-3 Study Group. The development of anemia is associated to poor prognosis in NKF/KDOQI stage 3 chronic kidney disease. *BMC Nephrol* 2013;14:2.
- Dikow R, Schwenger V, Schomig M, Ritz E. How should we manage anemia in patients with diabetes? *Nephrol Dial Transplant* 2001;17:67-72.
- Bosman DR, Winker AS, Marseden JT, MacDougall IC, Watkins PJ. Anaemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care* 2001;24:495-9.
- Agarwal AK, Silver MR, Reed JE, Dhingra RK, Liu W, Varma N, et al. An open-label study of darbepoetin alfa administered once monthly for the maintenance of haemoglobin concentrations in patients with chronic kidney disease not receiving dialysis. *J Intern Med* 2006;260:577-85.
- Minutolo R, Zamboli P, Chiodini P, Mascia S, Vitiello S, Stanzione

- G, et al. Conversion of darbepoetin to low doses of CERA maintains hemoglobin levels in non-dialysis chronic kidney disease patients. *Blood Purif* 2010;30:186-94.
26. Frimat L, Mariat C, Landais P, Koné S, Commenges B, Choukroun G. Anaemia management with C.E.R.A. in routine clinical practice: OCEANE (Cohorte Mircera patients non-dialyses), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis. *BMJ Open* 2013;3(3):e001888. pii: e001888. doi: 10.1136/bmjopen-2012-001888.
27. Cuevas X, García F, Martín-Malo A, Fort J, Lladós F, Lozano J, et al. Risk factors associated with cardiovascular morbidity and mortality in Spanish incident hemodialysis patients: two-year results from the ANSWER Study. *Blood Purif* 2011;33(1-3):21-9.
28. Besarab A, Coyne DW. Iron supplementation to treat anemia in patients with chronic kidney disease. *Nat Rev Nephrol* 2010;6:699-710.
29. KDIGO. Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl* 2012;2:279-335.