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Evaluation and determinants of underprescription of erythropoiesis stimulating agents in pre-dialysis patients with anaemia.

Data from the French REIN registry

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Short title: Adequacy of anaemia correction in ESRD patients

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Abstract

Background: Inadequate anaemia correction (haemoglobin (Hb) < 11 g/dL without receiving erythropoiesis-stimulating agent (ESA)) is common in pre-dialysis patients, but little is known about its determinants. We used data from the French end-stage renal disease (ESRD) registry to investigate these determinants and the patients' anaemia status one year after starting dialysis.

Methods: Pre-dialysis anaemia care was studied in 6,271 incident ESRD patients from 13 regions, who were first treated between 2003 and 2005. Data included pre-dialysis Hb measure and ESA use, patient's condition and modalities of dialysis initiation. Anaemia status at one year was studied in 925 patients from four regions who started dialysis in 2003 and 2004, were still on dialysis one year later, and had completed the annual registry data form.

Results: Overall, 34.7% of the patients had inadequate pre-dialysis anaemia correction, with variations across regions from 21.1 to 43.2%. Inadequate anaemia correction decreased from 38.0% in 2003 to 33.2% in 2005. It was less likely in patients with diabetic or polycystic kidney disease and more likely in those with malignancy, unplanned haemodialysis, and low glomerular filtration rate or low serum albumin at dialysis initiation. One year after starting dialysis, inadequate correction concerned only 2.6% of the patients. Hb level had risen from 10.3 g/dL in pre-dialysis to 11.7 g/dL, but remained lower in those with inadequate pre-dialysis correction.

Conclusion: Despite improvement over time, inadequate correction with ESAs remains high in pre-dialysis patients in contrast with those on dialysis. As the timing of dialysis initiation is uncertain, continuous management of anaemia is requested.

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Introduction

Anaemia is a major complication appearing early in the course of chronic kidney disease (CKD) and affecting nearly all end-stage renal disease (ESRD) patients. The introduction of erythropoiesis-stimulating agents (ESAs) in 1989 offered a new way to manage renal anaemia. Numerous benefits have been associated with anaemia correction in CKD, including lower morbidity and mortality [1] and reduced occurrence of cardiovascular complications [2]. An haemoglobin (Hb) level of at least 11 g/dL in all CKD patients is recommended by several clinical practice guidelines [3,4], but the maintenance of levels above 13 g/dL appear to be unsafe in these patients according to recent randomized control trials [5,6]. Studies in both pre-dialysis [7-13] and dialysis patients [14-17], however, show that ESA therapy is far from being prescribed to all those who would need it, although anaemia management tends to improve over time [8,17].

Clinical performance measures to assess the quality of anaemia management are commonly based on the prevalences of both anaemia and ESA use [18]. However, to monitor more straightforwardly continuous quality improvement in ESRD patients, we defined "inadequate anaemia correction" as an Hb level lower than 11 g/dL in those not prescribed ESAs. Inadequate anaemia correction refers to failure to adhere to guidelines recommending initiation of ESA therapy whenever the Hb level is under 11 g/dL. Non-prescription of ESAs in CKD patients without anaemia is indeed adequate practice. Moreover, below-target Hb level in patients prescribed ESAs, due to either insufficient ESA dose or hyporesponse to ESAs, are related to other determinants and different interventions.

With the exception of economic constraints, little is known about the determinants of underprescription of ESAs. They are interesting to study in France where these constraints are limited thanks to full reimbursement of ESAs for the treatment of anaemia in all CKD patients since 1996. We therefore used data from the French ESRD registry to investigate pre-dialysis anaemia

correction with ESAs and the determinants of inadequate correction. We also studied the patients' anaemia status one year after starting dialysis according to pre-dialysis anaemia care.

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Patients and Methods

Setting

The French Renal Epidemiology and Information Network (REIN) registry began in 2002 to provide a tool for public health decision support, evaluation and research related to ESRD. It is progressively spreading throughout the country and is aiming for nationwide coverage (that is, all 22 regions and 4 overseas districts). The design and methods have been described in details previously [19].

Study population

The REIN registry includes all patients on renal replacement therapy for ESRD, whether dialysis or transplant. New (incident) patients are considered from the first day of starting treatment. Those with a diagnosis of acute renal failure are excluded. Overall, 10,234 ESRD patients aged 15 years and older began dialysis in seven regions participating in the registry in 2003, eight regions in 2004 and thirteen in 2005. Data on anaemia care were available in 6,271 of them who were included in this analysis. Those with missing data were mainly from three large regions where initial biological data as a whole were missing in more than half of the patients in the beginning of the registry. It is worth noting, however, that these patients were similar to those included with respect to age, gender, primary renal diseases, and most co-morbidities, except cardiac and vascular diseases, slightly, but significantly more frequent in participants than in non participants, 47% *vs* 44% and 28% *vs* 26%; participants were also more likely to have started renal replacement therapy with unplanned haemodialysis (see definition hereunder), 31% *vs* 28% in non participants.

Information

Data included age, sex, region of care, year of dialysis initiation (2003, 2004 or 2005), body mass index (BMI), primary renal disease, several co-morbidities, and disabilities. Haemoglobin, serum

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creatinine and albumin in the last month before the start of dialysis, as well as pre-dialysis ESA use (yes/no) were also recorded. Other details about anaemia management such as iron supplementation, aluminium levels and inflammatory parameters were not available. Glomerular filtration rate (GFR) was estimated using the simplified modification of diet in renal disease (MDRD) trial equation [20]. Modalities of dialysis initiation were studied as follows: peritoneal dialysis, planned and unplanned haemodialysis. Planned haemodialysis was defined as beginning dialysis with either an arteriovenous fistula or a graft ready for use. Missing data were less than 5% for all variables except BMI and serum albumin which were analyzed as follows: albumin (≥ 3.5 g/dL; < 3.5; "not available" (NA)); BMI (<18.5 kg/m^2; 18.5-24.9; ≥25; NA). GFR was also studied as a dummy with a cut-off point at 10 mL/min/1.73 m^2.

Outcome

The outcome of interest was pre-dialysis inadequacy of anaemia correction, defined as an Hb concentration lower than 11 g/dL in a patient not prescribed ESAs in pre-dialysis. Patients with pre-dialysis Hb level lower than 11 g/dL but prescribed ESAs as well as those with an Hb value of 11 g/dL or greater, were considered as having had adequate anaemia correction.

One-year follow-up

In four regions, annual follow-up was achieved in 1,589 patients who started dialysis in 2003 and 2004. One year after, 69 had received a graft, 319 had died, and 1,201 were still on dialysis. REIN 2004 and 2005 annual data forms were completed, including Hb and ESA use, for 925 patients (77%) from this cohort.

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Statistical analysis

Percentages of pre-dialysis inadequate anaemia correction were first compared between the thirteen regions using Pearson chi-square test. Crude associations between baseline patients' characteristics and inadequate anaemia correction were also studied with Pearson chi-square test. All factors with a *P* value less than 0.15 as well as the region of care were then included in a logistic regression model to provide adjusted odds ratios (OR) of inadequate anaemia correction and 95% confidence intervals (95% CI). Finally, Hb level, ESA use and inadequate anaemia correction were compared before dialysis and one year after using paired chi-square and Student t-test. All analyses were performed with SAS version 8.2 (SAS Institute, Inc., Cary, N.C.)

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Results

Baseline characteristics

Baseline characteristics of the 6,271 incident patients are presented in table 1. Their mean age was 66.6 ± 15.6 years and 61.4% were men. Cardiac diseases and diabetes were the most frequent co-morbidities, and nearly half of the patients had at least two. Nearly one third of the patients started treatment with unplanned haemodialysis and more than two thirds with a glomerular filtration rate lower than 10 ml/mn/1.73 m^2.

Pre-dialysis haemoglobin level, ESA use and inadequacy of anaemia correction

The average level of pre-dialysis Hb was at 10.3 ± 1.8 g/dL and 63.6% of the patients had an Hb value lower than 11 g/dL. This Hb level was at 10.6 ± 1.7 g/dL among patients with pre-dialysis ESAs as compared with 9.9 ± 1.7 g/dL (P<0.0001) among those without pre-dialysis ESAs. Overall, 50.4% of the patients were prescribed ESAs in pre-dialysis and more than one patient out of three (34.7%) had inadequate anaemia correction. Among the subset of patients having an Hb level less than 11 g/dL in pre-dialysis, 68% were not prescribed ESAs.

Pre-dialysis anaemia correction, by region

Inadequate anaemia correction varied from 21.1% to 43.2% according to the region of care (Figure 1). Overall, 15% of the patients had an Hb greater than 11g/dL without receiving ESAs. Among those receiving ESA therapy, 5 % of the patients had an Hb level greater than 13 g/dL. After adjusting for patients' characteristics and modalities of dialysis initiation, regional variations in pre-dialysis inadequate anaemia correction remained strongly significant (P<0.0001).

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Determinants of inadequate pre-dialysis anaemia correction

In the crude analysis, inadequacy of pre-dialysis anaemia correction was neither related to age nor gender (Table 2). It was significantly lower in 2005 as compared to 2003. Inadequate anaemia correction was also more frequent in patients with active malignancy, but not in those with other co-morbidities, including diabetes. It was not related to BMI level, but was more frequent in patients with missing BMI data. Patients with inadequate anaemia correction were more likely to start renal replacement therapy with haemodialysis at a low GFR levels (GFR < 10 mL/min/1.73 m^2) and with a serum albumin < 3.5 g/dL or missing and less likely to have polycystic kidney disease. Half of the patients with polycystic kidney disease had an Hb lower than 11 g/dL at the dialysis initiation, as compared with 65% for patients with diabetic nephropathy or other primary renal disease (P<0.0001). After adjustment, factors independently associated with inadequate pre-dialysis anaemia correction included malignancy, unplanned first haemodialysis, low GFR and serum albumin, as well as missing BMI or serum albumin value. Polycystic kidney disease and diabetes as the primary cause of ESRD were associated with its decrease, independent of GFR and mode of dialysis initiation. Improvement of care in 2005 as compared to 2003 was also still statistically significant independent of patients' case mix and region.

Anaemia status one year after starting dialysis according to pre-dialysis anaemia care

As compared with the 925 patients who remained on dialysis one year after starting treatment and whose anaemia status was known, their 276 counterparts with missing data did not significantly differ with respect to either pre-dialysis inadequacy of anaemia correction or any of its determinants except malignancy more frequent in them (data not shown). The mean Hb level rose from 10.3 g/dL in pre-dialysis to 11.7 g/dL one year after, and the proportion of patients receiving ESAs from 50.0% to 88.5% (Table 3). Overall, inadequate anaemia correction as defined in this study was only 2.6% one year after beginning dialysis. However, 28.5% of the patients had still an Hb level lower

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than 11 g/dL. This percentage was significantly higher in patients with inadequate pre-dialysis anaemia correction as compared with those with adequate correction (34.9% *vs* 25.0%). Anaemia status at one year was related to pre-dialysis Hb level and anaemia correction; the better the pre-dialysis anaemia status, the higher the haemoglobin level and the better the adequacy of anaemia correction one year later.

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Discussion

This study showed that pre-dialysis anaemia correction with ESAs is suboptimal in France, although it tended to improve over time. Several risk factors for ESAs' underprescription were identified including the co-existence of malignancy with ESRD, unplanned first haemodialysis, a GFR less than 10 mL/min/1.73 m^2 and serum albumin less than 3.5 g/dL at dialysis initiation, non-diabetic and non-polycystic kidney diseases. Some regions also seemed to perform better in achieving the recommended goal than others. In contrast with the pre-dialysis period, anaemia correction with ESAs one year after starting dialysis, was adequate with respect to the used definition, in nearly 100% of the patients, but almost 30% of them remained with an Hb level lower than 11 g/dL.

Adequacy of anaemia correction with ESAs measures the level of adherence to the K/DOQI and ERA-EDTA guidelines recommending the use of ESA therapy in CKD patients whenever the Hb level is less than 11 g/dL. This goal was not reached in 68% of incident ESRD patients who were not prescribed ESAs before starting dialysis despite clear indication. The present results are quite similar in comparison with practices in other settings, where this percentage range from 70 to 80% [7,9,11], and confirm the need for improvement in healthcare delivery for CKD patients in the pre-dialysis period. Conversely, only 5 % of the patients receiving an ESA therapy had an Hb level greater than 13 g/dL, a target level recently appeared to be unsafe according to 2 large clinical trials including CKD patients before dialysis [21].

In the REIN registry, unplanned first dialysis session is used as a surrogate for late nephrology referral. The increased percentage of inadequate anaemia correction when the first dialysis was unplanned is consistent with previous studies showing that the timing of referral to a nephrologist is associated with the quality of pre-dialysis care, including anaemia [22,23]. In France, only

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physicians employed on staff in hospitals and dialysis centres, mainly nephrologists, were authorized to prescribe ESA therapy, so that access to these drugs rested as much on timely referral to nephrologists as on nephrologists' clinical practice. It is worth noting, however, that the percentages of inadequate correction in those starting dialysis with planned haemodialysis or peritoneal dialysis were far from being negligible, 28 and 24% of the patients, respectively. Therefore, attributing non-adherence to guidelines to non-nephrologists alone may be too hasty, as a large number of patients with pre-dialysis nephrology care were also not prescribed ESAs. GFR level is strongly related to that of anaemia: the greater the severity of renal insufficiency, the greater the degree of anaemia [10,24]. Consequently, our finding that inadequate correction was independently associated with lower GFR at dialysis initiation was not surprising. The same argument can be used to explain the relationship between low serum albumin and inadequate practices. Indeed, associations between low GFR, hypoalbuminaemia and anaemia are well established [25].

Our data showed that, in patients with polycystic kidney disease and diabetic nephropathy, inadequacy of anaemia correction was 25% and 17% lower, respectively, than in those with other primary renal disease. Polycystic patients have been reported as having higher Hb levels than other CKD patients at a comparable degree of renal dysfunction [15]. In our study, only half of them had an Hb lower than 11 g/dL at the dialysis initiation, as compared with 65% for patients with other primary renal disease. Moreover, it has been described that, at any level of GFR, anaemia is more severe in patients with than without diabetes [26]. Our results concerning patients with diabetic nephropathy may reflect greater awareness for anaemia care and higher rate of pre-dialysis ESA prescription in this population. In contrast, inadequate correction was more likely in patients with malignancy even after adjustment for several potential confounders. Yet, we may have expected a better management of anaemia in these patients with intensive medical follow-up.

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Inadequate anaemia correction varied across regions from 21 to 43%, which, despite an egalitarian national health system, reveals within-country variations in practices as there are between countries [7,8,14-17]. Obrador *et al.* [8] reported substantial variations in the percentage of patients receiving pre-dialysis ESAs across health service areas in the United States. The question raised is "what differences between regions could explain this variability?" In our study, neither patients' characteristics nor modalities of dialysis initiation explained variations in anaemia correction, as they persisted after controlling for these factors in the multivariate analysis. Clinical practices and organization of CKD care in each region may play a role, disparities in health care services between French regions being important [27]. However, it is worth noting that even the absence of variations at the regional (population) level would not necessarily mean that they are none at the centre or at the individual (physician/patient) level. Indeed, heterogeneity within-region may well be as large as between regions.

Patients who began dialysis in 2003 were 26% more likely to have inadequate correction with ESAs as compared with those who began in 2005. This trend towards improvement of anaemia correction is encouraging and consistent with other studies showing greater pre-dialysis use of ESAs over time [10,28].

Several studies have evaluated the quality of anaemia care either before [7-13] or during maintenance dialysis [14-17]. However, none examined the course of anaemia and ESA use according to pre-dialysis anaemia care. We showed that inadequate correction in the pre-dialysis period, as defined here, was almost inexistent one year after the start of dialysis. Administrative constraints in the delivery of ESAs before dialysis may partly explain this difference; in 2003-05, these were delivered by hospital pharmacies alone and required nurses to inject the drug at home. Therefore, access to ESAs was much more difficult for CKD out-patients than for dialysis patients, in whom ESAs were delivered and directly injected during dialysis sessions. Despite high levels of

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ESA use one year after starting dialysis, however, almost one third of the patients had below-target Hb level. We showed that inability to reach target Hb in these patients seem to be partially related to pre-dialysis inadequate anaemia correction. Efficacy of anaemia management or compliance to treatment as well as hyporesponsiveness to ESAs are other issues that were beyond the scope of this analysis.

Our results should be interpreted in light of two limitations. First, more than one third of all incident dialysis patients had missing data on Hb and/or ESA use. In the REIN registry, only a few items, including demographics, primary CKD and treatment modalities, are mandatory for registering a new patient whereas others, including co-morbidities, biological data and ESA treatment are checked for validity but do not preclude patients' registration [19]. This partly explains why, at the start of the registry, some regions focused on achieving complete registration of patients and mandatory items, but failed to do so for some biological items and ESA use. However, missing information about anaemia was not related to most other baseline characteristics, except unplanned first haemodialysis and cardiovascular disease. This patient cohort can thus be considered as fairly representative of the overall dialysis population from the studied regions. In the same way, as missing anaemia status at one year was neither related to the pre-dialysis adequacy of anaemia correction nor to most patient's baseline characteristics, our findings about the course of anaemia status are applicable to the entire 2003 and 2004 dialysis cohort. Second, collected data concerned Hb level in the last month before starting dialysis and pre-dialysis ESA use. No information was available about treatment history, particularly pre-dialysis ESA duration or doses and possible adjuvant therapy with iron salts. Therefore, we cannot rule out that the group of patients with adequate pre-dialysis anaemia correction include a number of individuals with very short duration of pre-dialysis ESA therapy, which would tend to underestimate inadequacy of care in this cohort.

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Nevertheless, it is worth noting that the mean Hb level among patients with pre-dialysis ESAs was significantly higher than that of those without ESAs.

In conclusion, despite full reimbursement of ESAs for treating CKD anaemia since 1996, this study showed that inadequate anaemia correction remains high in pre-dialysis patients in contrast with those on dialysis. These findings underline the difficulties in managing CKD patients not yet on replacement therapy when optimization of pre-dialysis care is the key to improve ESRD outcomes. Their main implication for public health is that interventions to improve anaemia management should target both nephrologists and non-nephrologists in care of CKD patients, as underprescription of ESAs was mainly observed in late referred patients, as characterized by unplanned first haemodialysis, but was also frequent in those with planned haemo- or peritoneal dialysis. In this respect, the 2006 new regulation about ESA prescription authorizing their delivery by out-of-hospital pharmacists may also help improving anaemia care in these patients.

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Table 1. Baseline characteristics in 6,271 incident dialysis patients

	Percentage or mean ± standard deviation
Men	61.4
Age (years)	66.6 ± 15.6
Dialysis initiation in 2003	19.7
Dialysis initiation in 2004	26.5
Body mass index (kg/m^2)	25.2 ± 5.2
< 18.5	5.2
18.5-24.9	38.9
≥ 25	37.3
NA*	18.6
Cardiac disease[a]	46.9
Vascular disease[b]	28.4
Diabetes	35.1
Respiratory disease	10.4
Active malignancy	7.1
Patients with at least 2 comorbidities[c]	44.6
Disability	9.5
Primary renal disease	
Polycystic disease	6.8
Diabetes	18.9
Other	74.3
Mode of dialysis initiation	
Unplanned hemodialysis	31.0
Planned hemodialysis	53.6
Peritoneal dialysis	15.4
Estimated GFR [d] (ml/min/1.73 m^2)	9.0 ± 5.0
< 10	70.3
Serum albumin (g/dL)	3.4 ± 0.6
< 3.5	38.4
≥ 3.5	27.6
NA	34.0

NA, not available
[a] Cardiac disease = history of congestive heart failure, coronary heart disease, myocardial infarction or dysrhythmia.
[b] Vascular disease = history of peripheral arterial disease or stroke.
[c] Comorbidities include cardiac or vascular diseases, diabetes, respiratory disease, and malignancy
[d] GFR : estimated glomerular filtration rate using the abbreviated MDRD equation

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Table 2. Determinants of inadequate pre-dialysis anaemia correction in 6,271 incident patients*

		Inadequate anaemia correction (%)	Crude analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value
Gender : Men		35.5	1			
Women		33.3	0.91 (0.81-1.01)	0.073		
Age (year)	≥ 80	32.8	1			
	66 – 79	34.8	1.09 (0.9 5-1.26)	0.265		
	≤ 65	35.5	1.13 (0.98-1.31)			
Year of dialysis start	2005	33.2	1		1	
	2004	35.1	1.09 (0.96-1.23)	0.009	1.13 (0.97-1.32)	0.027
	2003	38.0	1.24 (1.08-1.41)		1.26 (1.06-1.50)	
Body mass index (kg/m^2)						
18.5 - <25		34.0	1		1	
< 18.5		37.6	1.17 (0.92-1.49)	0.0002	1.15 (0.88-1.50)	0.006
≥ 25		32.4	0.93 (0.83-1.05)		0.95 (0.83-1.09)	
NA		39.7	1.28 (1.11-1.48)		1.28 (1.08-1.52)	
Cardiac disease [a]						
No		35.2	1			
Yes		34.2	0.95 (0.86-1.06)	0.376		
Vascular disease [b]						
No		35.1	1			
Yes		33.8	0.94 (0.84-1.06)	0.331		
Diabetes						
No		34.9	1			
Yes		34.5	0.99 (0.88-1.10)	0.796		
Respiratory disease						
No		34.5	1			
Yes		36.5	1.09 (0.92-1.29)	0.321		
Active malignancy						
No		34.0	1		1	
Yes		44.6	1.56 (1.29-1.90)	<0.0001	1.30 (1.01-1.61)	0.021
At least 2 comorbidities [c]						
No		34.7	1			
Yes		34.8	1.00 (0.90-1.11)	0.967		
Disability						
No		34.7	1			
Yes		37.3	1.12 (0.94-1.34)	0.206		
Primary renal disease						
Other		35.9	1		1	
Polycystic disease		25.7	0.62 (0.49-0.77)	<0.0001	0.75 (0.58-0.96)	0.009
Diabetes		33.2	0.89 (0.78-1.02)		0.83 (0.72-0.97)	
Mode of dialysis initiation						
Peritoneal dialysis		24.1	1		1	
Unplanned haemodialysis		51.4	3.34 (2.81-3.97)	<0.0001	3.16 (2.61-3.82)	<0.0001
Planned haemodialysis		27.9	1.22 (1.04-1.44)		1.16 (0.97-1.39)	
Estimated GFR ≥10		30.3	1		1	
< 10		36.5	1.32 (1.17-1.48)	<0.0001	1.34 (1.17-1.52)	<0.0001
Serum albumin (g/dL)						
≥ 3.5		26.4	1		1	
< 3.5		40.3	1.86 (1.63-2.13)	<0.0001	1.73 (1.49-2.00)	<0.0001
NA		35.3	1.52 (1.32-1.74)		1.51 (1.29-1.78)	

OR, odds ratio; CI, confidence interval; NS, not significant; NA, not available; GFR : estimated glomerular filtration rate
[a] Cardiac disease = history of congestive heart failure, coronary heart disease, myocardial infarction or dysrhythmia.
[b] Vascular disease = history of peripheral arterial disease or stroke.
[c] Comorbidities include cardiac or vascular diseases, diabetes, respiratory disease, and malignancy

* Results adjusted for the region of care

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Table 3. Anaemia status before and one year after starting dialysis according to pre-dialysis anaemia care in 925 incident patients from four regions

	N	Haemoglobin (g/dL)	Haemoglobin < 11g/dL (%)	ESA use (%)	Inadequate anaemia correction (%)
Overall anaemia status					
In pre-dialysis	925	10.3 ± 1.7	64.2	50.0	35.7
One year after starting dialysis	925	11.7 ± 1.4	28.5	88.5	2.6
P value		< 0.0001	0.03	0.0005	<0.001
Anaemia status at one year by pre-dialysis anaemia status					
Pre-dialysis haemoglobin					
< 11 g/dL	594	11.6 ± 1.4	31.0	91.1	3.2
≥ 11 g/dL	331	11.8 ± 1.3	24.2	84.0	1.5
P value		0.2012	0.0281	0.0012	0.1218
Pre-dialysis ESA use					
No	463	11.6 ± 1.5	31.8	84.9	4.1
Yes	462	11.8 ± 1.3	25.3	92.2	1.1
P value		0.0097	0.0306	0.0005	0.0039
Pre-dialysis adequacy of anaemia correction					
No	330	11.5 ± 1.5	34.9	88.5	5.5
Yes	595	11.8 ± 1.3	25.0	88.6	1.0
P value		0.0391	0.0016	0.9684	< 0.0001

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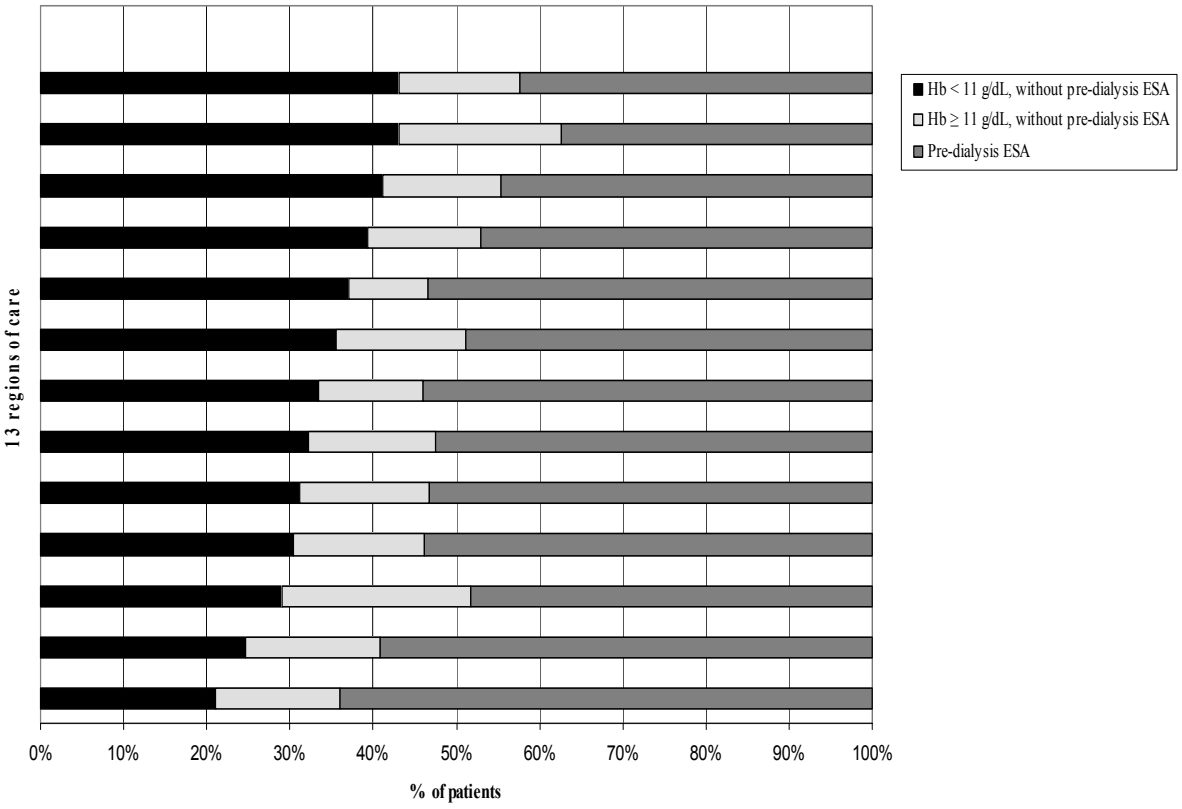

Figure I. Distribution of patients according to pre-dialysis anaemia correction by regions