

## Importance of IV Iron during Predialysis Period in Incident Hemodialysis Patients

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### Abstract

**Background:** An unacceptably high number of patients start dialysis with pronounced anaemia. The aim of this retrospective study was to provide insights into the impact of the pre-dialysis correction of anaemia (using an ESA) and iron deficiency (using oral or IV iron) on the hematological and cardiovascular parameters both at time of onset dialysis as well as for the next 12 months.

**Methods:** Out of the 102 patients, mean age 58.5 (15.9) years, at time of first dialysis in the unit, 70% being males, and 27% having diabetes, 33 patients received IV iron and ESA in the pre-dialysis period versus 69 patients treated with ESA (alone or with oral iron).

**Results:** Patients, in the IV iron group during the pre-dialysis period, commenced dialysis with higher hemoglobin concentrations: 11.1 (1.3) versus 10.4 (1.5) g/dL, ( $p < 0.01$ ), higher iron levels measured by TSAT at 50.0 (19.2) versus 30.1 (15.2)%, ( $p < 0.001$ ), and required lower ESA doses, 0.58 (0.28) versus 0.82 (0.37)  $\mu\text{g}/\text{kg}/\text{week}$ , ( $p < 0.01$ ). There were also differences in the cardiovascular functions with lower left ventricular mass at 116(34) versus 134(39)  $\text{g}/\text{m}^2$ , ( $p < 0.02$ ), improved left ventricular ejection fraction 64.7 (4.4) versus 61.4(8.7)% ( $p < 0.02$ ) and lower MAP at 104.7 (80) vs. 109(13.2) mmHg ( $p < 0.02$ ), and had fewer hospitalizations, during the first year of dialysis.

**Conclusions:** This observational study is the first to suggest hematological, cardiovascular, and other clinical benefits in the first 12 months of dialysis with the early (pre-dialysis) correction of iron deficiency and anemia using IV iron (and ESA) compared to ESA alone or with oral iron.

**Keywords:** Anemia; Hemodialysis; Darbepoetin alfa; Iron therapy

### Introduction

Anaemia is a common phenomena in patients with chronic kidney diseases (CKD), beginning mostly in stage 3-4 of the disease [1]. Moreover, patients with CKD present a high risk for cardiovascular diseases [2]. Anaemia has been suggested as an independent factor for impaired cardiovascular pathology [3], and may be partly corrected by the addition of iron and Erythropoiesis-Stimulating Agents (ESA), as it was recently underlined by the KDIGO guidelines [4] and the European Renal Best Practice Position Statement [5]. In chronic heart failure, a recent pooled analysis of over 1500 pts, suggested that iron deficiency has a greater predictive power than anaemia for mortality [6].

However, the level of correction of anaemia and the target hemoglobin (Hb) and/or iron levels, in order to prevent or correct a cardiovascular pathology and to improve the vital prognosis of these patients is not clearly defined [7]. The impact of such a decision is important, when considering that in the United States 116,946 incident patients started dialysis with a Hb level of 10.57 g/dL and only 25 % of them received pre-dialysis treatment with an ESA [8]. In France, about 10,000 patients started dialysis each year, with Hb concentrations of  $10.2 \pm 1.7$  g/dL and 50% of them received ESA during the pre-dialysis period. Unfortunately no information was available for the iron use [9], although it is the building block for erythropoiesis and essential in numerous other processes, including oxygen utilization, and as such an important factor in the management of our patients.

Numerous large randomized prospective clinical studies were performed in the past years especially in pre-dialysis patients [10-12] demonstrating that pushing for a high haemoglobin target could be deleterious, notably in patients with underlying cardiovascular diseases [13]. None of these studies considered iron therapy as an important factor for the patients: CREATE [10] and CHOIR [11] recommended oral iron, and very seldom intravenous (IV) use, whilst in the TREAT study [12] both groups received oral iron in approximately 67% of the

included patients. Of note, 20.4% of the patients in the placebo group received IV iron compared with only 14.8% in the ESA treated group. In the dialysis setting, the NHCT study [14] demonstrated that the group with the highest Hb target received more IV iron dextran than the group with the lowest Hb target.

On the flip side, the addition of iron, especially IV iron results in a reduction in the required ESA dose to achieve Hb target level [15]. The latest KDIGO guidelines hence recommend IV iron supplementation for HD patients (with confirmed iron deficiency), and IV iron in the pre-dialysis patients if an initial three months trial course of oral iron is ineffective [4]. The transition period between both however remains unclear, and only one study has tried to quantify the use of iron and ESA in patients with CKD at different stages of CKD, discriminating between patients on ESA with and without IV iron [16].

Hence this retrospective data analysis aims to provide initial insights on the clinical benefits during the first 12 months of haemodialysis, for correction of anaemia (using an ESA) and iron deficiency (oral or IV iron) prior to dialysis. We assessed clinically relevant outcomes such as hospitalization rates and changes in the cardiovascular structure (measured through echocardiography) in addition to the usual hematological parameters.

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## Patients and Methods

### Inclusion criteria

Our unit (center hemodialysis and self care unit) records the data on a routine basis using database software (Hemodial- PHP Development). A co-morbidity index (Charlson index) is applied to all patients at initiation of dialysis. Most patients, before dialysis were followed by the physicians of the unit for a period between 3 months and 22 years. Pre-dialysis data (including ESA/iron use) as well as information since the first dialysis to the end of the first year of dialysis was available for 102 patients in our database. All of these patients were included in this analysis, independent of outcomes or results, and grouped into a cohort that received ESA and oral iron (Cohort I: 69 patients) or ESA and IV iron (Cohort II: 33 patients) during pre-dialysis period. Choice of oral or IV iron therapy was physician depending, one of these physicians preferring oral iron, as IV iron required, at that time, hospitalization.

### Methods

All patients were treated on the same protocol described elsewhere [17]. Our target Hb level is 11.5 to 12 g/dL and our iron targets are transferring saturation (TSAT) of 30-45% and a serum ferritin level between 400-600 µg/L [18].

IV DA is administered during the first dialysis session every other week, and a patient is considered to have achieved therapeutic goal when the Hb values are within the target range for 75% or more of the observational time (one year) [19]. IV iron injections are performed once weekly during the last hour of the mid-week session. Iron parameters (serum ferritin and TSAT) were measured at initiation and thereafter every three months. Modalities of adaptation depends on the levels of TSAT and ferritin as follows: for a TSAT < 10% and a serum ferritin < 100 µg/L, then a dose of 100 mg iron is administered; if TSAT is < 20% and serum ferritin < 200 µg/L a dose of 50 mg is injected; and if TSAT is between 30 and 40% and serum ferritin < 400 µg/L a dose of 25 mg is injected [18]. We do not use oral iron in any patients during dialysis.

The above procedure for ESA and IV iron were applied to all patients included in the current analysis and hence the treatment after commencing dialysis was the same for all patients in the 2 cohorts analyzed. We also routinely measure parameters such as albumin levels, CRP and PTH (same technical procedure over the time). Additionally, all transfusions during HD sessions and hospitalizations are recorded in detail within our clinic database for all patients.

### Cardiovascular follow-up

Relevant cardiovascular parameters were recorded prior to the first dialysis session (M0), and then again after 12 continuous months of dialysis (M12). Assessments included the mean arterial pressure [MAP] before the session, and the number of hypotensive drugs prescribed (mainly Angiotensin Converting Enzyme Inhibitors [ACEI], and angiotensin II receptor agonists [ARAI]). Cardiovascular conditions were evaluated by the same cardiologist during the entire period: clinical examination was performed along with an electrocardiogram, and an echocardiography measuring left ventricular mass index (LVMI), and left ventricular ejection fraction (LVEF) per methods described by Bellanger et al. [20].

### Statistical analysis

Statistical analysis of the data was performed using S.A.S version 9.1. Descriptive data were given as mean and Standard Deviation (SD) or as median. Comparisons were done by Wilcoxon sign-rank

tests for quantitative variables, or independence chi-square<sup>2</sup> tests for qualitative variables. Variance analysis for Hb levels, DA and iron doses were performed using Student-t test: p value <0.05 was considered as statistically significant.

## Results

### Baseline characteristics

Baseline characteristics of both cohorts are presented on Table 1: cohort I included 69 patients who did not receive IV iron during the pre-dialysis period (with all of them receiving at least one daily dose of oral iron), whilst Cohort II included 33 patients who all received IV iron in the 12 months preceding the commencement of dialysis. Medical history and various treatments at onset of dialysis were similar between cohorts. There were no statistical differences in sex, age, primary renal disease, first use of AV fistula, previous use of ESA. Global Charlson index was equivalent but there were significantly more patients with cardiac insufficiency, at time of commencing dialysis in the patients who didn't receive IV iron during the pre-dialysis period (Cohort I).

As most of the patients were regularly followed by a nephrologist, during the pre-dialysis time, 90 (88%) of them started dialysis with a native arteriovenous fistula and 12 of them with a transient catheter (3 in Cohort II) for less than 2 months for 8 of them. The IV modalities of administration of iron sucrose during the pre-dialysis period were identical for the 33 patients in Cohort II. Each patient had their iron needs calculated via the Ganzoni formula and then received 2 to 5

Characteristics	Cohort I: 69 Pts without IV Iron during pre-dialysis	Cohort II: 33 Pts with IV Iron during pre-dialysis	Differences C. I & C. II
Sex M/F, n (%)	48 / 21 (70/30)	23 / 10 (70/30)	NS
Age, years, mean(SD)	58.7 (15.5)	58.1 (16.9)	NS
BMI, kg/m <sup>2</sup> , mean (SD)	22.90 (3.90)	22.72 (4.38)	NS
<b>Primary Cause Renal Failure, n (%)</b>			
Diabetes	17(24.5)	10 (30.3)	0.41
Hypertension	16(23)	3 (9)	0.09
Glomerulonephritis	17(24.5)	6 (18.1)	0.49
Interstitial Nephritis	12 (17)	9 (27.2)	0.23
Polycystic Kidney	7 (11)	5 (15.4)	0.74
<b>Co-Morbidities, n (%)</b>			
Hypertension	64 (92)	28 (85)	0.72
Heart Failure NYHA I, II, III, IV	52 (75.3)	17 (51.5)	0.021
Coronary artery disease	9 (13)	5 (15)	0.56
Stroke	9 (13)	4 (12)	0.75
Hepatitis	17 (24.5)	9 (27)	0.62
Cancer	7 (10)	5 (15)	0.52
Charlson index, mean (SD)	7.36 (3.60)	7.21 (3.39)	0.83
<b>Vascular access at initiation, n (%)</b>			0.74
Native AV Fistula	60 (87)	30 (90)	
Transient Catheter	9 (13)	3 (10)	
Concomitant Treatment, n (%)			
ACE I	19 (27)	15 (45)	
ARA II	27 (39)	10 (30)	
Previous ESA Trtt, YES, n (%)	61 (88)	28 (85)	NS
Iron Treatment, n: IV	0	33	
Oral	69	0	

**Table 1:** Characteristics of the incident patients: Cohort I: 69 patients and Cohort II: 33 patients.

infusions of 200 to 300 mg of iron sucrose. The iron infusions were diluted in 125 ml saline solution and administered in the hospital over two to three hours. On average, each patient received a total of 850 mg iron during the pre-dialysis period.

### Hematological Parameters And ESA Dose Requirements

Patients, who received IV iron during the pre-dialysis (Cohort II), started the dialysis period with a higher Hb level: 11.3 (1.4) versus 10.4 (1.5) g/dL. Over the subsequent 12 months of dialysis, these patients had more controlled Hb levels with values within target range (10-12 g/dL) for 85% of the time (versus 59% for Cohort I) (Figure 1). The Cohort II patients also maintained higher TSAT values and subsequently required 40% less DA than Cohort I patients (Table 2) although both groups received the equivalent amount of IV iron during the first year of dialysis. In Cohort II only two patients started dialysis with a Hb level lower than 9 g/dL. The mean cumulative dose of ESA injected was significantly lower in Cohort II versus Cohort

I: 1320 µg/per patient versus 2270 µg (p<0.0001), for one year of treatment (Figure 2).

### Cardiovascular parameters

Patients who received IV iron during the pre-dialysis period (Cohort II) commenced the dialysis period with better cardiovascular conditions (Table 2): LVMI is lower, LVEF is better, MAP lower despite similar

### Concomitant medication: Other outcomes

The overall mortality rate was very low at the end of the first year of dialysis: 3 patients (all in Cohort I) died due to cancer, hyperkalemia or cardiac insufficiency. Seven patients were transplanted (5 in Cohort I and 2 in Cohort II), with two of these occurring in the twelfth month of dialysis, (and included in the analysis). Ninety four patients completed the first year on dialysis. Forty three patients (42%) were hospitalized during this period (31 in Cohort I and 12 in Cohort II) for 58 episodes (41 in Cohort I and 17 in Cohort II, p<0.05) with reasons including

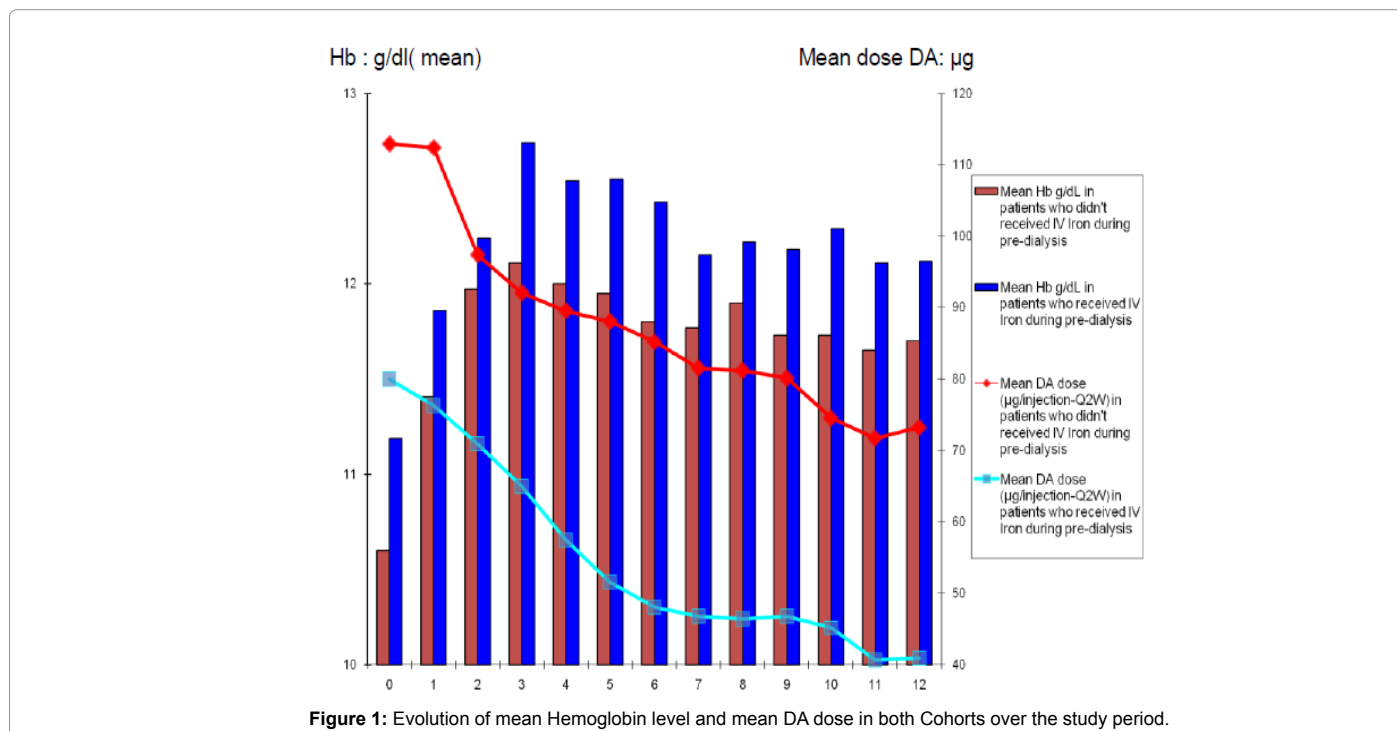
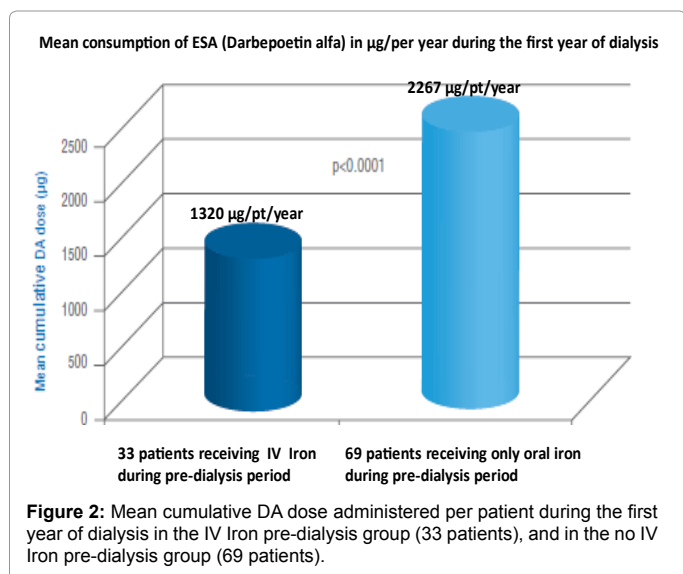


Figure 1: Evolution of mean Hemoglobin level and mean DA dose in both Cohorts over the study period.

Mean (SD)	69 Pts without IV Iron during Pre-dialysis		33 Pts with IV Iron During Pre-dialysis		p value at M0	p value at M12
	M0	M12	M0	M12		
Hb g/dL	10,4(1,5)	11,5 (0,8)	11,1(1,3)	12,1 (0,9)	0,016	0,003
TSAT %	30,1(15,2)	37,0 (14,0)	50,0(19,2)	43,8(12,6)	0,00001	NS
Ferritin µg/L	176 (192)	509 (339)	202 (149)	658 (347)	NS	NS
DA Q2W µg/inj	112,4(55,4)	74,2(51,0)	80 (23,8)	42,4(24,4)	0,015	0,002
DA total/Pt/an µg	2267		1320		0,0001	
F.IV QW mg/inj	86 (25)	54,9 (45,9)	90,6(19,8)	60,3(27,8)	NS	NS
CRP mg/L	7.6 (8.2)	9.2 (9.2)	5.1(4.3)	7.1(10.3)	0.03	NS
CV Parameters						
LVMI g/m <sup>2</sup>	134 (39)	99 (22)	116 (34)	92 (16)	0,014	NS
LVEF %	61,4 (8,7)	65,9 (6,6)	64,7 (4,4)	66,9 (4,2)	0,02	NS
MAP mmHg	109,5(13,2)	93,4(12,8)	104,7(8,0)	87,6(13,1)	0,02	0,1
Médications: N(%) ACEI & ARA II	37(54%)	18(26%)	18(54%)	7(21%)	NS	NS
Hospit. days/Pt/year	2,6		2,0		0,05	

Table 2: Main results of both group of patients.



surgery for 28 episodes and medical reasons for 30 episodes. Patients receiving IV iron prior to dialysis (Cohort II) had significantly lower hospitalization rates with 2 days per patient per year versus 2.6 days in Cohort I ( $p < 0.05$ ). Eighteen hospitalizations episodes (12 in Cohort I and 6 in Cohort II) were scheduled at onset of dialysis in order to complete the kidney transplant validation (5 kidney removals, 6 cardiac angiographies and 7 surgical procedures on the vascular access). Mean time between onset of dialysis and the first hospitalization was  $118 \pm 87$  days (median 120 days), with 98 days for Cohort I and 164 days for Cohort II,  $p < 0.05$ . During the first year of dialysis, there were no transfusion during the dialysis sessions and 6 hospitalized patients (5 in Cohort I and 1 in Cohort II) were transfused once.

## Discussion

Recommendations for the appropriate correction of anaemia in patients with CKD both pre-dialysis and during dialysis was recently updated in the KDIGO guidelines [4] and partly amended by ERBP [5]. These guidelines and their recommendations differ from the previous version [21]. In essence, the guidelines increased the targets for iron values (namely serum ferritin and TSAT) and hence recommend the increased use of iron, especially IV iron, whilst being more conservative with target Hb concentrations and subsequent restricting ESA use to minimal dosing to permit effective erythropoiesis and avoid supra-physiological levels for Hb concentrations. Unfortunately, the adoption of the guidelines is still limited as can be seen with about 2/3 of patients still commencing dialysis in an anemic state and with questionable iron reserves that do not appear to be adequately replenished with oral iron [22].

Based on our analysis, the use of IV iron not only prepared enabled patients starting dialysis to have an improved baseline profile, but to also maintain this for the next 12 months achieving target levels on a more frequent basis ultimately requiring less ESA dosing (a key target of the KDIGO guidelines [4]). The correction of the main cardiovascular parameters such as MAP, LVMi, LVEF, and controlled drug prescription was achieved to a higher degree than the cohort not receiving IV iron during the pre-dialysis period, as assessed by the results on first dialysis day. Patients receiving the ESA and IV iron therapies during this pre-dialysis period, therefore started dialysis with a better Hb level, better iron parameters, better cardiovascular conditions, and required 40% less ESA during the first year of dialysis, and had fewer hospitalizations.

Further to the above, we observed very low mortality rates, only 3%, compared with 17.5% as observed in the DOPPS study [23], 17% in the French Registry [9] and 22.6% in the Medicare program [24]. Whilst it is difficult to determine a single point of difference that adequately explains this difference, we postulate this may be related to one or several (or even all) of these following factors: commencing Hb concentration, reduced ESA dose in the first year of dialysis, appropriate iron parameters levels, high percentage of usable AV fistula at time of onset of dialysis and/or the improved cardiac function at this time.

The commencing Hb concentration and/or iron levels at time of dialysis resulted in lower ESA doses being required in our patients (compared with other published literature from observational programs). In France, a mean Hb concentration at onset of dialysis for the 10,000 patients was 10.2(1.7) g/dL [9], whilst 30% of the patients reached dialysis on an emergency status, which was not the case in our unit (3% only). In United States [8] the situation is quite similar with a mean Hb level at onset of dialysis of 10.57 g/dL. The mean ESA dose reached a peak during the second month of dialysis at 28,705 UI per week (almost 150 µg per week) [8]. But recently, under the new bundle payment, the DOPPS Practice Monitor, initiated by the US Centers for Medicare & Medicaid Services reported concomitantly a decline in the median Hb level around 10.9 g/dL and a mean prescribed IV epoetin decreasing from 20,500 U/week to 13,300 U/week in December 2012 (133µg every 2 weeks) [25]. Some similar experiences were reported, notably in Spain, where Perez-Garcia [26] presented in a multicenter study in incident HD patients a mean Hb level of 10.6 (1.7) g/dL, a mean TSAT of 25.3 (3.8) %, and a mean ferritin level of 236 (238) µg/L. In this study 80% of the patients received during the pre-dialysis period ESA, but 50% of them were anemic at onset of dialysis, and 2/3 of them had at the same time an iron deficiency [26].

The consequences of a low hemoglobin level, at start of dialysis, are important, especially in the cardiovascular field, inducing a necessary new approach. Further to the above, the Medicare program [24] introduced the fact that mortality is higher when hematocrit is lower than 30%. Moreover this study also suggested that mortality is reduced when IV iron is used in patients with a low hematocrit whilst the use of ESAs didn't influence significantly the mortality [24].

Whilst correction of anaemia using high doses of ESA and IV iron at start of dialysis has demonstrated a beneficial effect on mortality [27,28], there is also data to suggest that high doses of ESAs could have a deleterious effect, especially in patients with a high incidence of comorbid factors [26,28]. In our study the consumption of EPO is higher by 40% during the first 4 months compared to the last 4 months (and was significantly lower in patients that had received IV iron in the pre-dialysis period). Having a too high Hb target or reaching it too quickly with only ESAs is probably the Achilles' heel.

The use of IV iron and ESA in our study clearly indicates beneficial consequences on not only anaemia management but also on the cardiovascular conditions of these patients. Similar signals of the combined IV iron (and ESA) use during pre-dialysis period was observed during TREAT study [11]. In this study, 68.6% of the patients received oral iron, but only 10.4% in the ESA group received IV iron, whilst 20.4% received IV iron in the placebo group. The use of IV iron is likely an important factor for the increase of Hb level from 10.4 to 11.3 g/dL in the placebo arm. In other studies the use of IV iron in CKD ND patients seems to be limited: IV iron alone for 8% of the patients, and IV iron and ESA for 12% in the States [29]. Our policy especially for the Cohort II indicates that IV iron and low doses of ESA could be beneficial also for the cardiovascular conditions, which

were decried with the use of high doses of ESA during the TREAT study [11].

In this study we are reporting on two critical factors: the level of Hb, and the cardiovascular conditions of the patients. These patients started dialysis with a higher Hb level at 11.1(1.3) g/dL versus 10.4(1.5),  $p < 0.003$ , and required 40% less ESA during the first year of dialysis, but the same amount of IV iron. The second substantial advantage is these patients, well matched with the other group, presented at onset of dialysis less cardiac insufficiency, MAP better controlled, (104.7 versus 109.5 mmHg,  $p < 0.02$ ) without more use of antihypertensive agents, and at least better echocardiographic conditions: lower LVMI, better LVEF. These improvements appear to have also resulted in less hospitalization during the first year of dialysis for patients that had optimized ESA and IV iron in the pre-dialysis period.

In a recent meta-analysis on the same subject Parfrey [30] pointed out that the correction of anaemia leads to a reduction of LVMI, but often for an Hb level over 12 g/dL. Suzuki [31] also noted that in 77 non dialyzed patients receiving ESA an improvement in the LVMI from 121.3(25.8) to 114.0(25.1)g/m<sup>2</sup> ( $p = 0.12$ ) correlated with the Hb level ( $p = 0.011$ ). Another study, in patients with chronic heart failure and iron deficiency, that were receiving IV iron (ferric carboxymaltose), demonstrated to significantly improve disease symptoms, functional capacity and overall capacity of life [32]. In our study IV iron and ESA induced a better cardiovascular condition at onset of dialysis compared to those receiving only oral iron and ESA: 116(34) versus 134(39) g/m<sup>2</sup>,  $p < 0.014$ .

Hence, whilst our study indicates a role for appropriate iron correction prior to dialysis, there are numerous research questions that remain unanswered including “what is appropriate pre-dialysis target iron levels and how long before dialysis should these be achieved?”, “can appropriate anaemia and iron management in pre-dialysis period delay onset of dialysis?”, and “does early iron repletion have a positive impact on mortality over a longer term?”. These and many other questions may therefore constitute potential endpoints of future studies in this important area of our patient care. However based on these data and the most recent guidelines, it appears that optimizing early the iron parameters as well as avoiding anaemia is an important factor in caring for CKD patients.

## Conclusions

Despite the fact that this study is retrospective and monocentric, it clearly confirms the importance of pre-dialysis care. This study underlined the fact that even in well controlled patients (pointed out by the presence in 88% of the patients an AV fistula for the first dialysis), patients are commencing dialysis with anaemia and iron deficiency. Whilst at the onset of dialysis the correction of anaemia is realized by good dialysis, high doses of ESAs and high doses of IV iron the required doses to achieve appropriate management might be avoided with earlier intervention. Our study suggests a strong role for the use of IV iron and ESA to achieve optimized pre-dialysis values. Such practices may then aid in decreasing the number of first year dialysis mortality cases, reducing deleterious cardiovascular conditions, and number of hospitalizations, and likely provide financial benefits due to a reduced dosing in first year of dialysis of ESA (as well as reduced hospitalization).

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