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Case Report

Impact of Cumulative and/or Combined Effects of ESAs and IV Iron Doses Received During Dialysis on Survival in Hemodialysis Patients

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ABSTRACT

Background: Intravenous iron (IV iron) and Erythropoiesis-Stimulating Agents (ESAs) are key therapies for anemia management during hemodialysis (HD). Studies suggest adverse outcomes with cumulative high exposure to either IV Iron or ESAs but may not reflect clinical situations where iron and ESAs are combined. This study retrospectively assesses the impact on mortality of different dosing strategies.

Methods: All patients attending for HD between Jan04 - Dec12 were included. Data was assessed at 1000, 2000 and 3000 days across 9 cohorts based on a matrix combination of low, mid or high dosing of ESA and IV iron. Survival is estimated using Kaplan-Meier methodology and cohorts analyzed via multivariate model.

Results: 370 incident patients, (69% male) were treated over 140,509 HD sessions and achieved target hematological parameters with mean (SD) Hb of 11.55 (0.77) g/dL, TSAT at 37.1 (8.5) %, and ferritin of 562 (322) µg/L. The low, mid and high dose values were 0-8.5µg, 8.6-14 µg and >14.1 µg and 0-15 mg, 15.1-25 mg and >25.1 mg per session for ESA and iron respectively. The highest risk group for mortality received high doses of both ESA and IV iron (survival at 1000, 2000 and 3000 days was 67, 31 and 0%) whilst cohort receiving low doses of ESA had survival at 3000 days of 70, 87 and 75% for the low, mid and high dose iron groups. In the cohorts receiving mid or high doses of ESA, patients had progressively poorer outcomes as the concomitant IV iron doses increased.

Conclusions: Patients receiving doses <8.5 µg per session of ESA appear to have no negative consequences from receiving concomitant IV iron. Conversely, patients receiving mid-high doses of ESA (i.e., >8.6 µg per session) appear to have increased risk of mortality with the impact exacerbated as IV iron doses are increased.

INTRODUCTION

Anemia develops in most patients with end-stage renal disease treated by HD [1] although appropriate management is still challenging [2]; important and severe anemia is correlated with increased morbidity and mortality [3-6].Concomitantly correcting anemia may ameliorate ventricular hypertrophy [7-9], reduce mortality and the risks of hospitalization [10,11] and improve the quality of life [12,13].

Optimal medical strategy for management of anemia is a fine balance between Erythropoiesis-Stimulating Agents (ESAs) and Intravenous (IV) iron. Initial guidelines targeted Hb>11 g/dL[14] which often necessitated increased ESAs administration. However randomized trials comparing Hb targets on mortality and vascular events [7,15] showed unexpectedly that higher Hb targets appeared to increase the risk of death [16] and major cardiovascular events [17] raising the possibility that the association may be secondary to higher ESAs doses [17]. ESAs doses in HD patients in the United States [18,19] and in Europe [20] have decreased since the addition of a black box warning to the labeling and the introduction of a bundled payment methodology in 2011 in United States [21,22] and in 2013 in France [23].

Administration of IV iron complements ESA therapy, helps to maintain target Hb levels, and lowers ESA requirements [24]. Recently, the use of IV iron has increased and is likely related to reductions in ESA use [25]. However IV iron use also requires a careful balance between intended clinical effects and uncertain risks of toxicities [26] and concerns have been raised regarding the potential for IV iron to cause oxidative stress, inflammation, endothelial dysfunction and immune dysfunction as such prompting calls for caution regarding the potential hazards of high exposure to IV iron [27-29].

Recent studies suggest adverse outcomes from cumulative exposure to either IV iron [30-37] or ESA [38-44] although they do not assess the combination of both IV iron and ESA (and differing doses) in HD patients as reflects routine clinical practice. Nevertheless some studies suggest that higher doses IV iron is not associated with higher risk of mortality, infection, cardiovascular events, or hospitalizations in adult patients on dialysis [45].

This retrospective observational study aimed to investigate the impact of combined and total anemia therapy using ESAs and IV iron on all-cause mortality and hospitalization in a cohort of incident HD patients over more than nine years in a single unit.

MATERIAL AND METHODS

Study Design

Retrospective observational single-center study of incident patients undergoing HD in France with data collected between January 2004 and December 2012. Previous period (pre-dialysis period) could not be analyzed.

All patients during this period were included except those that had less than 90 days of retrievable data. Signed consent authorizing the use of their clinical data for research was obtained from all participants, although Ethics Committee approval is not required per French regulations.

Data Collection

Data was extracted from the Hemodial® database. This database was largely used for different publications [46,47]. Demographic and outcome variables collected included gender, age, body mass index, primary renal disease, Charlson Co-morbidity Index (CCI), ethnic origin and morbidity / end of study events (death, transplantation, transfer to other unit) and/or hospitalization including causes and duration. Laboratory data included hemoglobin (Hb), ferritin, transferrin saturation (TSAT), CRP and albumin.

Patient Management

All patients included were undergoing HD sessions; these included 95% of high flux dialyzers, 92% of native arterio-venous fistulas, 5% grafts and 3% of permanent central venous catheters, ultrapure dialysate without aluminum and chloramines, and a target Kt/V> 1.4. Regular HD session duration was 4 hours three times a week for 95% of the patients.

ESA use was exclusively Darbepoetin Alfa [DA], during the entire study, injected IV at the end of the dialysis session, once every other week (during the first dialysis session of the week) via the venous injection site before the drip chamber on the venous line [48]. Any change in the DA dosing required a follow-up of four Hb measurements, each performed every two weeks, and the adaptation of the next injected dose was decided by the patient primary physician and decision based on the clinical setting of the dialysis sessions (clotting episodes, hemorrhages, blood losses) and the clinical program of the patient (programmed surgery, specific investigations..); if on the last 4 Hb values, one was outside of the target (11.5-12 g/dL during the entire study) nothing was changed in the DA dosing; if 2 to 3 values were outside of the target, the dosing was adapted depending on the amplitude of the variation. ESA dose requirement was recorded per patient during the entire attendance of the patient in the unit, and expressed as total dose for each patient (µg), dose per session (µg/dialysis session), ESA dose in µg/Kg/week and Erythropoietin

Resistance Index (ERI), calculated by dividing the weekly body-weight-adjusted DA dose by the Hb concentration.

Intravenous iron was exclusively Iron Sucrose (IS) and injected, when necessary, during the six first years once a week during the second dialysis session of the week at a dose ranging from 25 to 100 mg. After a publication developing the synergistic effect of the administration of IV iron and ESA together [49] during the same dialysis session, IV iron was injected for the last three years, once every two weeks simultaneously with DA during the same dialysis session. IV iron was diluted with saline solution (0.9%) up to 20 ml volume and infused over a one-hour period between the second and the third hour of the dialysis session in the arterial line before the dialyzer. The IV iron was titrated according to the most recent values of TSAT, ferritin and CRP, targeting a TSAT level of 40-60% and a serum ferritin of 500-800µg/L [50]. IV iron dose requirement was recorded per patient during the entire study, expressed as total dose for each patient (mg), dose per session (mg/session), and dose per month (mg/month).

Statistical analysis

Data are presented as mean values ±Standard Deviation (SD) for normally distributed variables, or medians for non-normally distributed variables, and percentages (%) for categorical variables. ESA doses and IV doses were compared using Chi-square test for categorical factors and ANOVA for continuous variables. To evaluate the relationships between DA or IS and mortality, Kaplan-Meir survival curves were estimated and compared by the log-rank test. To better appreciate the role of either ESA or IV iron, each dose requirement was expressed as low, middle or high doses. Cox regression was used to estimate the corresponding Hazard Ratios (HRs) with 95% Confidence Intervals (CI), using the low DA and low IS as reference. In addition multivariate Cox model was generated and then added sequentially as co-variables: age, gender, CCI, Hb, ferritin, hospitalization, DA dose and IS dose.

All patients observed in the study were assigned to a cohort based on their ESA and IV iron dosing. To enable assessment of the different ESA and IV iron cohorts, values were selected to generate 3 groups. For ESA, the values of DA for the low, middle or high dose groups were <8.5µg, 8.6 - 14 µg and >14.1 µg per session whilst for the IS administration these were divided into low (<15 mg iron), middle IS (15.1 - 25 mg iron) and high (>25.1 mg iron) per session.

Other variables were assessed including age: (years) <65, >=65; gender: female or male; BMI (kg/m²): <18,5,18.5-25, 25-30, 30-40; CCI: 0-5,5-10,> 10; Hb (g/dL): <11, 11-12, >=12; ferritin (µg/L): <400, 400-700, >=700; number of hospitalization: 0, 1-3, >3.

RESULTS

Baseline characteristics

Three hundred and seventy (370) incident HD patients were included in the 9 year observational period. The majority (69%) were male and the mean age (SD) at initiation of HD was 55.6 (16.2) years with a mean BMI of 22.8 (4.3) kg/m². Primary renal diseases, Co-morbid Charlson Index (CCI), ethnic origin and outcomes are recorded in Table 1. In total, 140,509 dialysis sessions were recorded and the key laboratory data are presented in Table 2. The ESA and IV iron dosing are reported in Table 3.

Table 1: Baseline characteristics of study participants: incident HD patients 2004-2012.

Characteristics	Hemodialysis Period 2004-2012
Patients	370
Male (%)	255 (69%)
Female (%)	115 (31%)
Mean Age at start of Dialysis, years (SD)	55.6 (16.2)
Mean BMI at initiation, kg/m² (SD)	22.8 (4.3)
Primary Renal Disease, n (%)	
Glomerulonephritis	99 (26.7)
Diabetes Mellitus	94 (25.4)
Interstitial Nephropathy	84 (22.7)
Hypertension	70 (19.0)
Polycystic Kidney Disease	23 (6.2)
Co-morbidities –Charlson Index	
Mean (SD)	8.16 (3.76)
Ethnic Origin, n (%)	
Caucasian	156 (42.1)
Maghreb	100 (27.0)
Black	94 (25.4)
Asian	20 (5.5)
Outcome of the patients, n (%)	
Living on dialysis	132 (35.6)
Kidney graft	108 (29.1)
Deceased on Dialysis	89 (24.0)
Transfer in other units	39 (10.3)

Patient Status and Overall Outcomes

At the end of the observational period, 132 pts (35.6%) were still on dialysis and the others had achieved outcomes of kidney transplantation (108 patients; 29.1%), were transferred to another unit (39 patients; 10.3%) or died (89 patients; 24%).

The deaths were mainly due to cardiovascular diseases (43.8%), malignancy (15.7%), infection (12.2%) and other reasons (various or unknown origin: 28.3%). The total survival curves are 88% survival at 1000 days (2.7 years), 57% at 2000 days (5.5 years) and 24% at 3000 days (8.2 years).

Overall, 218 (59%) patients had a total of 554 hospitalizations for a total duration of 5511 days (less than 0.2% of the 300,000 days of study period). The reasons for hospitalization were primarily due to cardiovascular disease (25%), infection non-related to vascular access (23%), vascular access related events (21%) and malignancy (15%).

Table 2: Main mean laboratory data of the study.

Characteristics	Hemodialysis Period 2004-2012
Cumulative number of dialysis sessions recorded during the study.	140,509
Hemoglobin at inclusion: g/dL (SD)	9.80 (1.60)
Hemoglobin during the study: g/dL (SD)	11.54 (0.77)
TSAT: % (SD)	36.9 (8.3)
Ferritin: µg/L (SD)	560 (308)
CRP: mg/L (SD)	11.3 (11.9)
Albumin: g/L (SD)	39.5 (3.1)

Table 3: Main parameters about ESA and IV iron during the study (n=370).

ESA: Darbepoetin alfa [DA]
Cumulative DA dose injected: µg 1, 572, 590
Mean dose injected per session, per patient: µg (SD) 12.76 (9.60)
Median dose per session: µg 10.89
Geometric mean: µg 10.15
Mean dose in µg/kg/week/patient (SD): 0.59 (0.41)
Mean ERI (SD): UI/kg/Week/g Hb: 11.02 (9.90)
IV Iron: Iron Sucrose [IS]
Cumulative IS dose injected: mg 2, 285, 700
Mean dose injected per session, per patient: mg (SD) 20.39 (10.81)
Median dose per session: mg 18.21
Mean dose per month: mg 265

ESA and IV iron

During the observational period, 1,572,590 µg of DA was injected with a mean dose per patient and per session of 12.76 (9.6) µg and a median dose of 10.89 µg. Concomitantly, 2,285,700 mg iron (IS) was injected with a mean dose per session of 20.39 (10.81) mg and a median dose of 18.21 mg iron. A comparison of the average doses of either ESA or IV iron indicated poorer survival for pts in the higher dose group (ESA adjusted model: HR=2.426, 95% CI 1.09-2.04, Figure 1A; IV iron adjusted model: HR=2.10; 95% CI 1.13-2.35, Figure 1B).

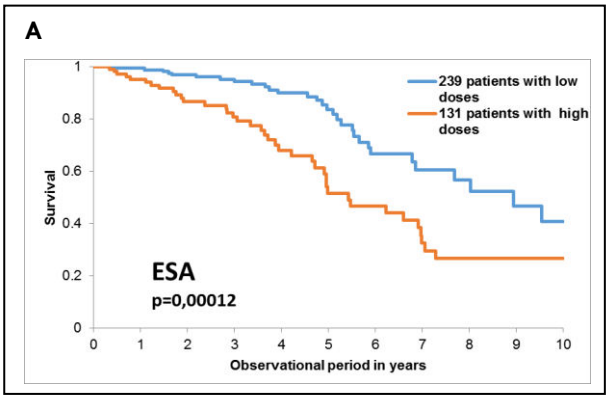

Figure 1: A survival according to ESA administration: -low doses of DA (less than 13µg/session), - high doses of DA (over 13 µg/session).

B survival according to IV iron administration: - low doses of IS (less than 20 mg/session), - high doses of IS (over 20 mg/session).

The boxes combining ESA and IV iron on survival

Patients were divided into 9 cohorts based on ESA and IV iron dosing and the number of patients (around 50 per group), gender, mean age at start, primary renal disease, Charlson co-morbidity index or BMI were all similar (Table 4). When the nine groups were analyzed for survival (Table 5) survival was poorest in the cohort receiving high doses of both ESA (>14.1 µg per session) and IV iron (>25.1 mg iron per session) with survival rates at 1000, 2000 and 3000 days of 67, 31 and 0% respectively. Conversely, the best results were observed in the cohort receiving low doses of ESA (<8.5µg per session) and IV iron (<15mg iron per session) with survival rates at 1000, 2000 and 3000 days of 100, 96 and 70%. Figure 2 illustrates the survival curve for the three main groups: Low ESA/Low Iron, Mid ESA/Mid Iron, High ESA/High Iron. Patients receiving low

doses of ESA (<8.5µg per session) had little impact of increased IV iron doses on survival at any of the observed time-points. Conversely, mortality was significantly increased in the mid and high ESA dose groups (versus low dose ESA group) and the impact was increased as the dose of IV iron was increased at 2000 and 3000 days.

Table 4: Survival of the nine groups of patients according to the injection dose of DA and IS during the nine years observational study period. The survival of the three groups in yellow are reported on the figure 2 (N=370).

	DA-Low		p	DA-Middle		p	DA-High	
IS-Low	50 patients	LL*	p<0,012	39 patients	ML	p=NS	36 patients	HL
	1000 days	100%		1000 days	91%		1000 days	92%
	2000 days	96%		2000 days	74%		2000 days	61%
	3000 days	70%		3000 days	35%		3000 days	40%
	p= NS		p<0,002	p= NS			p = 0.041	
IS-Middle	39 patients	LM	p<0,001	49 patients	MM	p = NS	31 patients	HM
	1000 days	100%		1000 days	96%		1000 days	88%
	2000 days	90%		2000 days	57%		2000 days	46%
	3000 days	87%		3000 days	24%		3000 days	33%
	p = NS			p< 0,05		p<0.0001	p<0,0019	
IS-High	29 patients	LH	p<0,004	41 patients	MH	p =NS	53 patients	HH
	1000 days	95%		1000 days	93%		1000 days	67%
	2000 days	79%		2000 days	10%		2000 days	31%
	3000 days	75%		3000 days	0%		3000 days	0%

*Initials of group number

Within the bi-variate analysis (Table 6), results suggest higher doses of DA resulted in poorer survival whilst IV iron seems to have a lower impact. Similar observations were observed via the multivariate analysis (Table 7), where the ESA impact was twice as strong as the impact of iron. Age, gender, BMI, Charlson index, ferritin and hospitalization appeared to have no effect. Hb indicates a better survival when the level is between 11 and 12 g/dL.

Overall survival (at 3000 days) was significantly better in the group with low doses (DA <8.5µg and IS <15mg iron per session: 70% survival) compared with the group having mid-range doses (DA 8.6-14 µg and IS 15.1-25mg iron per session: 57% survival; p<0.002) and was worst in the group having high doses of both treatments (0%; p<0.0001). At 1000 days, survival is near identical in combined low and mid-dosing cohorts (100% and 96% respectively) but higher than for the cohort with high doses of both ESA and IV iron (67%).

The improved survival of combined low or mid-dosing groups compared to ESA and IV high groups appeared to be related to age at initiation of HD, Hb concentration (at time of commencing HD) and mean Hb level during the first year of HD [11.7(0.7),compared to 10.8 (0.9), p<0.007]. Additionally, serum ferritin and TSAT were higher at start and during the first year of dialysis supporting the possibility that these patients were previously (during the pre-dialysis period) appropriately iron replete. As expected, ESA dose and IV iron dose are lower in the first two groups compared to the third group however the ESA dose progressively declined in low and mid-dosing groups during the first year (average decrease of 36%) whilst remained effectively stable (decrease of 6%) for the high-dose group (Table 8). Analyzing the mortality (Table 9), death and specifically cardiovascular mortality is increasing with the ESA dose (p< 0.05), while they remain stable when the Iron doses are increasing.

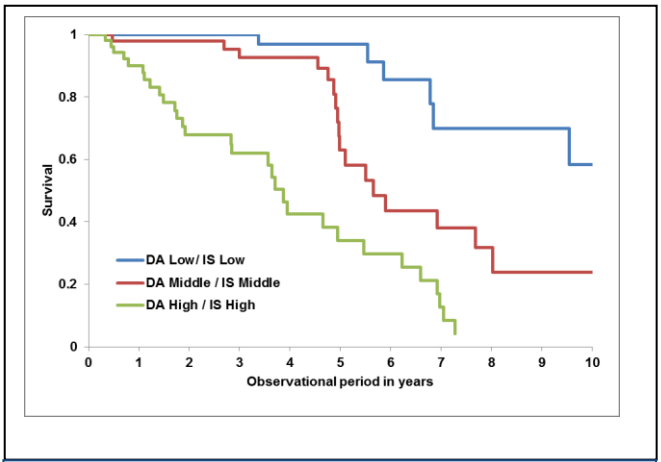

Figure 2: Survival of 3 groups of patients: DA-Low/IS-Low, DA-Middle/IS-Middle, DA-High/IS-High.

Discussion

This study assesses the impact on survival of dosing with both ESA and IV iron during dialysis in HD patients. When assessing either product alone, high doses of ESA (>13µg/session) or high doses of IV iron (>25mg/session) suggest a risk for higher mortality. However, when stratifying the groups by ESA and IV iron doses (low, mid or high dosing), the impact of increasing IV iron (when maintaining low ESA doses) appeared to have little / no impact on mortality whilst increasing ESA dose (especially above 8.5µg per session) resulted in increased mortality at 2000 and 3000 days (and the impact was magnified if the dose of IV iron was also increased). The multivariate analysis suggests that the ESA impact on survival is twice as important when compared to IV iron.

Table 5: Main characteristics of each of the nine groups identified.

Characteristics	LL	LM	LH	ML	MM	MH	HL	HM	HH
Number of Patients	50	40	31	39	49	41	36	31	53
Gender: Male %	66	69	76	64	62	62	61	52	62
Female %	34	31	24	36	38	38	39	48	38
Mean age at start, years (SD)	54.6(15.7)	50.2(16.0)	54.3(17.8)	54.5(15.9)	55.8(17.0)	56.4(17.5)	59.5(13.9)	54.2(16.5)	60.6(14.1)
Primary Renal disease: nb(%)									
CGN	13 (26)	14 (35)	6 (20)	13 (34)	14 (28)	12 (29)	8 (22)	7 (22)	13 (24)
Diabetes	13 (26)	7 (18)	10 (34)	12 (30)	11 (23)	12 (29)	9 (25)	5 (16)	16 (28)
Interst. Nephropathy	11 (22)	10 (25)	4 (14)	4 (10)	11 23)	6 (15)	13 (36)	8 (26)	16 (28)
Hypertension	9 (18)	5 (12)	5 (16)	9 (23)	11 (23)	9 (22)	5 (14)	10 (32)	7 (13)
PKD	4 (18)	4 (10)	6 (20)	1 (3)	2 (3)	2(5)	1 (3)	2 (2)	1 (2)
Charlson Index: mean (SD)	7.9 (3.7)	6.9 (3.6)	6.7 (2.7)	8.2 (4.0)	8.7 (3.7)	8.0 (4.0)	8.6 (3.7)	8.1 (3.5)	9.3 (3.8)
BMI:kg/m² (SD)	22 (4)	22.3 (3.6)	23.5 (3.3)	22.2 (4.6)	23 (4)	23.3 (4.9)	22.7 (3.7)	23.6 (5.3)	23.1 (4.3)
Outcomes: nb (%)									
Living on dialysis	23 (46)	14 (35)	11 (36)	15 (38)	14 (29)	15 (37)	21 (58)	7 (22)	15 (28)
Graft	12 (24)	18 (45)	16 (53)	9 (23)	13 (26)	14 (34)	5 (14)	9 (29)	8 (15)
Deceased	6 (12)	1 (2.5)	2 (7)	11 (28)	18 (37)	7 (17)	8 (22)	12 (37)	25 (47)
Transferred	9 (18)	7 (17.5)	1 (4)	4 (11)	4 (8)	5 (12)	2 (6)	4 (12)	5 (10)
Nb of Dialysis sessions	24184	24215	9960	17196	19440	8750	14107	12159	10498
Nb of Hospitalization	53	47	24	78	87	38	87	47	93
Total duration, days	513	328	142	718	929	423	974	672	812
Mean Hb at start: g/dL (SD)	11.0 (1.4)	11.1 (1.4)	11.3 (1.2)	10.6 (1.8)	10.6 (1.3)	10.6 (1.3)	10.4 (2.2)	10.4 (1.3)	9.8 (1.3)
Mean Hb : g/dL (SD)	11.9 (0.7)	12.0 (0.7)	12.0 (0.7)	11.4 (0.5)	11.6 (0.5)	11.7 (0.4)	11.0 (0.6)	11.0 (0.4)	10.9 (0.8)
Mean TSAT: % (SD)	40.6 (9.2)	38.5 (6.5)	35.1 (6.7)	37.2 (8.4)	38.3 (8.1)	36.5 (8.5)	33.2 (6.7)	38.1 (7.4)	33.9 (8.8)
Mean Ferritin: µg/L (SD)	725 (552)	503 (255)	477 (242)	598 (224)	621 (185)	473 (206)	578 (266)	562 (194)	462 (288)
Mean CRP: mg /L (SD)	8.5 (9.7)	7.2 (7.4)	11.5(14.3)	12.1(14.4)	11.6(12.8)	9.1 (7.3)	16.3(14.7)	12.6(12.3)	13.9(11.9)
Mean Albumin : g/L (SD)	40.7 (2.7)	41.3 (3.9)	39.5 (3.3)	39.1 (2.9)	39.8 (3.4)	39.9 (3.1)	38.6 (2.8)	38.6 (2.8)	38.0 (3.9)
Mean DA dose/session: µg	5.2 (2.8)	5.3 (2.1)	5.4 (2.0)	10.8 (1.9)	10.8 (3.3)	11.1 (1.8)	19.6 (7.0)	20.0 (5.8)	25.1(14.7)
Mean DA dose: µg/kg/week	0.33(0.26)	0.28(0.17)	0.25(0.10)	0.55(0.17)	0.53(0.22)	0.48(0.16)	0.94(0.40)	0.90(0.46)	1.01(0.52)
Mean ERI	4.66	4.25	4.10	9.28	9.30	8.6	17.5	17.7	22.4
Mean IS dose/session: mg	12.4 (4.3)	20.0 (2.5)	31(12)	11.1 (5.3)	20.4 (3.4)	30.3 (6.2)	9.0 (4.5)	19.7 (2.4)	32.5(11.9)

The increased risk for either single product is reflected in the literature with numerous studies suggesting adverse outcomes from cumulative exposure to either IV iron [30-37] or ESA's [38-44]. Whilst our data support these findings (when looking at either product alone, Figure 1) our data also suggest that it is more important to assess both ESA and IV iron dosing together to understand the relative negative impact of the combined therapy (and then the individual products within the combination). The same approach was evocated by Ellis and Brookhart[51] in a setting with two concurrent treatments: IV iron treated concurrently with ESA in hemodialysis patients. That said, a recently reported abstract [52], conducted in a similar manner to our study, on 1086 patients but a short period of three years, concluded that high doses of ESA and iron are significantly associated with higher risks of cardiovascular disease and death. But regarding the combined effect of both ESA and IV iron, their conclusions are the opposite of our: regardless of ESA dose a higher dose of iron is significantly associated with a higher risk. This differs from our finding and warrants further (ideally prospectively controlled studies) to further elucidate the best management strategies.

Table 6: Bi-variate analysis of the nine groups.

Category	Initials	Pr>Khi-2	Hazard Ratio	95% Hazard Ratio Confidence Limits
DA-Low/IS-Low	LL	1	-	-
DA-Low/IS-Mid	LM	0.2432	0.283	0.034 – 2.356
DA-Low/IS High	LH	0.7006	1.371	0.275 – 6.844
DA-Mid/IS-Low	ML	0.0361	2.912	1.072 – 7.914
DA-Mid/IS-Mid	MM	0.0049	3.830	1.501 – 9.769
DA-Mid/IS-High	MH	0.0001	9.250	2.961 – 28.894
DA-High/IS-Low	HL	0.0412	2.596	0.898 – 7.501
DA-High/IS-Mid	HM	0.0058	3.980	1.493 – 10.611
DA-High/IS-High	HH	<.0001	11.836	4.770 – 29.368

In relation to ESA, many questions have been raised since the Food and Drugs Administration revised the prescribing instructions for ESA [21,53]: toxicity of ESA, dose and consequences of hyporesponsiveness, ERI, hemoglobin target (which was stable all over the study), increased risk of cardiovascular related mortality. Alone, ESA does not appear to be a toxic drug, however there are no randomized studies to prove/disprove this. Various mathematical approaches appear in the literature: Perez-Garcia et al uses a propensity score matching for each patient by modeling the probability of receiving > or 8000 IU/week using logistic regression model [44]: in his model the fifth quintile (>8127 IU/week) is an independent predictor of mortality. Streja et al using a marginal structural model defines that there is a dose-

dependent positive association between weekly ESA dose >18000 IU (30µg/session of DA) and mortality risk [54]. The Netherlands Cooperative Study on the Adequacy of Dialysis using a sequential Cox approach and inverse probability of censoring weight conclude that pts with ESA over 6000 IU/week have 1.2-1.5 increased mortality risk [55]. Kouroulidis et al conduct a meta-analysis using the data from 31 trials, report that higher ESA dose (>10000IU/ week [16.6µg/session]) during the first three months of dialysis is correlated with all cause of mortality irrespectively of the Hb levels [56]. Our own data support the same conclusions: middle DA dose (10.8 µg/session of DA [6480 IU/week]) or high doses (25.1µg /session of DA [15000 IU/week]) have a poor survival compared to lower doses and a dose of 12000 IU/week during the first trimester give also a pejorative effect.

A second parameter that may predict mortality of patients receiving ESA is (hypo) responsiveness. They are multiple causes of hyporesponsiveness including iron deficiency, non-controlled hyperparathyroidism, central venous catheters and its blood losses [57], aluminum toxicity, malnutrition, and some other drugs. Some authors state that ESA responsiveness, rather than dose, is the major determinant of adverse events in HD pts[41,58-60].If the patient has malnutrition, it may be beneficial to try to improve the nutritional status (at least increase the albumin level) of those in malnutrition to avoid more dose of ESA and iron administration [61] Is Erythropoietin Resistance Index (ERI) a good indicator for the degree of responsiveness to ESAs ?; ERI is related to mortality even in our study with a cut off at 10 UI/kg/week/g Hb with a survival of 87% at 5 years when ERI is under 10, and of 48% at 5 years when ERI is over 10 ($p<0.00001$). However this index has some limitations: by the definition ERI is strongly related to ESA dose and weight [62]. When the ESA dose is changed, ERI is also modified without information about the mechanism of resistance. If the Hb level increased, independently of the ESA administration, ERI is also impacted. Chait et al conclude that ERI is not an adequate independent measure of ESA resistance [62], when Okazaki et al suggest that ERI is a good index [63].

The notion of a well and on a long-term Hb level in HD patients is controversial. In our study, the target Hb level remains identical over the nine year period, and is stable since 1999. Low concentration of Hb is associated with an increased mortality risk [64]. The intended Hb target influences the ESA dose. In many units the target changes with years [65,66] and with the new label for ESA by the FDA [52].

Table 7: Cox multivariate model of the different factors (N=370).

Parameter	Category	Pr> Khi-2	HazardRatio	95% Hazard Ratio Confidence Limits
ESA-DA	Low	1	-	-
ESA-DA	Middle	0.0001	4.778	2.150 – 10.619
ESA-DA	High	0.0006	4.225	1.850 – 9.652
IV Iron-IS	Low	1	-	-
IV Iron-IS	Middle	0.4522	1.241	0.707 – 2.176
IV Iron-IS	High	0.0033	2.552	1.365 – 4.769
Age, years	< 65	1	-	-
Age, years	>=65	0.0946	1.512	0.931 – 2.456
Sex	Female	1	-	-
Sex	Male	0.4137	1.252	0.730 – 2.147
BMI Kg /m²	< 18.5	1	-	-
BMI Kg /m²	18.5-25	0.9163	1.040	0.499 – 2.166
BMI Kg /m²	25-30	0.8679	1.081	0.431 – 2.711
BMI Kg /m²	30-40	0.5482	1.423	0.450 – 4.501
Charlson Index	0-5	1	-	-
Charlson Index	5-10	0.1396	3.080	0.692 – 13.700
Charlson Index	>10	0.0736	3.955	0.877 – 17.836
Hb, g/dL	<11	1	-	-
Hb, g/dL	>=12	0.3037	0.674	0.318 – 1.429
Hb, g/dL	11-12	0.0391	0.544	0.305 – 0.970
Ferritin, µg/L	< 400	1	-	-
Ferritin, µg/L	400-700	0.9362	1.028	0.517 – 2.046
Ferritin, µg/L	>=700	0.5888	1.203	0.615 – 2.355
Hospitalization, Nb	0	1	-	-
Hospitalization, Nb	1-3	0.0779	1.860	0.933 – 3.707
Hospitalization, Nb	> 3	0.4811	1.321	0.609 – 2.865

The administration of ESA's could increase the risk of cardiovascular-related mortality. Some events have been correlated to high ESA dose: hypertension, stroke and thrombotic events [16,56,67]. High-dose ESA-treated patients with higher target Hb levels, and poorly controlled hypertension, manifest a high risk of mortality, with a direct ESA effect proposed to be causal [14]. A similar association between ESA dose and an increased risk of stroke has been described, particularly in patients with poorly controlled hypertension, or those with a prior history of stroke [56]. In our study there was a tendency of higher cardio vascular mortality as the ESA dose is increasing, while it was not the case with IV Iron.

Impact of Cumulative and/or Combined Effects of Esas and IV Iron Doses Received During Dialysis on Survival in Hemodialysis Patients. Journal Of Case Reports: Clinical & Medical. 2019; 2(2):135.

Table 8: Differences in characteristics and main biologic parameters between the groups DA Low/IS Low, DA Middle/IS Middle and the group DA High/IS High, at start of dialysis and during the first year of dialysis.

Parameters	Groups LL,MM	GroupHH	p
Number of patients	99	52	
Gender: Male (%) Female (%)	69 (70) 31 (30)	39 (75) 13 (25)	
Age: years, mean (SD)	55.0 (16.2)	60.6 (14)	p=0.02
BMI: kg/m² mean (SD)	22.4 (4.0)	23.2 (4.3)	p=0.2
Charlson Index, mean (SD)	8.32	9.37	p=0.1
Hemoglobin, g/dL, mean (SD) First measurement at start of dialysis Mean Hb during the first year	 10.8 (1.5) 11.7 (0.7)	 9.8 (1.3) 10.8 (0.9)	 p<0.0001 p<0.0001
Ferritin, µg/L, mean (SD) First measurement at start of dialysis Mean level during the first year	 406 (354) 581 (326)	 275 (219) 435 (299)	 p<0.006 p<0.007
TSAT, %, mean (SD) First measurement at start of dialysis Mean level during the first year	 35.2 (15.6) 41.7 (12.1)	 30.4 (14.5) 34.3 (10.1)	 p<0.05 p<0.0001
ESA (DA) dose: µg/Kg/week, mean (SD) First dose at start of dialysis Mean DA dose during the first trimester Mean DA dose during the first year	 0.56 (0.34) 0.47 (0.29) 0.36(0.22)	 0.98 (0.46) 0.88 (0.38) 0.84 (0.51)	 p<0.00001 p<0.00001 p<0.00001
Iron dose (IS), mean (SD) First dose, mg Mean IS during the first trimester: mg/month Mean IS during the first year: mg/month	 67 (39) 266 (161) 274	 96 (36) 384 (145) 352	 p<0.0001 p<0.0001 p<0.0005

The type of ESAs could not be analyzed in our study, as Darbepoetin alfa was all over the study the single ESA used in our unit [68]. In a recent study Sakaguchi et al compared mortality risk of users of short-acting ESAs with those of long-acting ESAs (like Darbepoeitin) [69]. Using Cox proportional hazards models the authors found that the relative risk of death was 13% higher among long-acting ESA users compared with short-acting ESA users. The use of IV iron was not studied and our survival at two years (Figure 1) is much better in any case that in the Japanese study [69]. The same difference in survival was estimated by Wilhelm-Leen et al [70] and observed without any significance by Winkelmayer et al [71].

Optimal treatments for anemia (in 2018) include ESA and iron therapy, with the later mostly comprised of IV iron [73,73]. Our study underlines this fact in that only four pts out of the 370 did not receive a single dose of IV iron (two of them in relation with hypersensitivity during the pre-dialysis period, and two of them for genetic hemochromatosis). However, with changes in ESA label combined with reimbursement policies [21-23], average IV iron doses rose from 210 mg per month in 2009 to 332 mg per month in 2011 but then back to 290 mg per month in 2013 and have remained stable since [74]. Despite its established effectiveness, there have been concerns about the safety of IV iron supplementation [75]. Hypersensitivity reactions have been a concerning complication of IV iron administration: first an anaphylactic reaction can be life-threatening if not immediately addressed; second the immediacy of the reaction is traumatic for both patients and staff. However, it appears that the absolute incidence of adverse hypersensitivity is low [75].

Table 8: Differences in characteristics and main biologic parameters between the groups DA Low/IS Low, DA Middle/IS Middle and the group DA High/IS High, at start of dialysis and during the first year of dialysis.

Characteristics	Low ESA	Middle ESA	High ESA	Low Iron	Middle Iron	High Iron	Total
Number of Patients	120	130	120	125	121	124	370
Deaths:	9	35	45	25	30	34	89
Number %	7.5%	27%	38%	20%	25%	27%	24%
Cardiovascular deaths:	3	13	24	10	14	17	41
Number %	33%	37%	53%	40%	46%	50%	46%
Infection related deaths:	0	2	4	2	1	3	6
Number %	0%	6%	9%	8%	4%	9%	7%
Cancer related deaths:	1	2	7	4	3	3	10
Number %	11%	6%	16%	16%	10%	9%	11%

Cardiovascular disease is the leading cause of death among HD pts and there are theoretical concerns that IV iron may increase the risk of CV-related outcomes through inducing increased oxidative stress [28,76]. IV iron has generally not been shown to increase the risks for infection-related mortality. However, a recent study examines the association of 1-month IV exposure with infection-related outcomes [77]: both bolus dosing and >200 mg/month doses are associated with an increased risk of infection-related hospitalization, but not infection related death. Our study finds no clear difference in infectious mortality with other causes of mortality.

Additionally, high iron dosing is associated with higher iron stores [27,78]: 84% of the HD patients have an iron overload (severe in 36%) based on the use of magnetic resonance imaging to measure hepatic iron. Both monthly IV iron dose and cumulative dose correlate with hepatic iron and current practices of IV iron prescriptions can result in significant hepatic iron overload.

The present study has several strengths and limitations: the prospective recruitment of all patients starting dialysis treatment over a nine years period, with various ethnic origin,

various age, and various primary renal diseases, and a clearly report of ESA and IV iron prescriptions allow evaluation and follow-up over a long observational period without significant loss of data. Hb level, ESA and IV iron dosing management has been maintained stable over this long period. Modifications in the dosing of both drugs are realized in the same manner. However, it is a single center observational study with only 370 patients and lacked control groups that were not treated with IV iron or ESA (and groups were not stratified or randomized in any manner).

In conclusion, patients receiving doses <8.5 µg per session of ESA appear to have fewer negative consequences from receiving low, mid or high doses of concomitant IV iron versus patients that receive higher doses of ESA. When receiving mid to high doses of ESA (i.e., >8.6 µg per session), patients may be at increased risk of mortality with this impact further exacerbated by increasing IV iron doses. We recommend that minimum doses of ESA (ideally <8.5 µg per session) are used when managing anemia with IV iron dosing as required to maintain serum ferritin and/or TSAT values per guidelines. If higher doses of ESA are required then the IV iron dose should be maintained <15mg per session wherever feasible.

CONFLICT OF INTEREST STATEMENT

The study design was elaborate by JR. JR receives presentation fees by Amgen and Vifor. The data were analyzed by CE and AL. TC and HI participates to the redaction of the paper.

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