

The association of erythropoietin-stimulating agents and increased risk for AV-fistula dysfunction in hemodialysis patients. A retrospective analysis.

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Research article

Keywords: arterio-venous fistula, stenosis, erythropoietin, hemodialysis

Posted Date: April 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-20185/v1>

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Version of Record: A version of this preprint was published on January 18th, 2021. See the published version at <https://doi.org/10.1186/s12882-020-02209-6>.

Abstract

Background

Patients in maintenance hemodialysis (HD) need a patent vascular access for optimal treatment. Recommended first choice is a native arteriovenous fistula (AVF). Complications of AVF are frequent and include thrombosis, stenosis and infections leading to worsening of dialysis efficacy.

Purpose

The aim was to investigate if there are significant variables associated with dysfunctional AVF: s that could be intervened to adjust.

Methods

This retrospective observational study included 153 chronic HD patients referred to a total of 473 radiological investigations due to clinically suspected complications of their native AVF. Another group of chronic HD patients (n=52) who had a native AVF, but were without history of previous complications for at least 2 years were used as controls. Statistical analyses used were ANOVA, logistic regression, parametric and non-parametric methods such as Student's T-test and Mann-Whitney test.

Results

Among Cases at least one significant stenosis (>50% of the lumen) was detected in 348 occasions. Subsequent PTA was performed in (71%, n=248). Median erythropoiesis- stimulating agent (ESA) weekly doses were higher in the Cases than in the Controls (8000 IU vs 5000, p<0.001). Cases received higher doses of intravenous iron/week than the Controls before the intervention (median 50 mg vs 25 mg, p=0.004) and low molecular weight heparin (LMWH, p=0.028). In comparison to the Controls, Cases had a lower level of parathyroid hormone (median 25 vs 20 pmol/L, p=0.009). In patients with diabetes mellitus, HbA1c was higher among Cases than Controls (50 vs 38 mmol/mol, p<0.001). There was no difference between the groups regarding variables such as blood hemoglobin, serum CRP or plasma ferritin.

Conclusion

The study indicated that AVF problems were related to higher doses of ESA, iron administration and LMWH. Optimizing glycemic control in patients with diabetes mellitus may be beneficial.

Introduction

A native arteriovenous fistula (AVF) is the preferred access for patients in chronic hemodialysis [1], while AV graft (AVG) and central dialysis catheters (CDC) are less preferred options [2]. Although thrombosis, stenosis and infections of AVF appear as complications the patency is superior to AVG and CDC [3–6]. The one-year patency of AVF is 50–70% [7–10]. The complex strategy in preparing and creating the AVF includes variables such as the surgical work up with evaluation of vessel quality and the surgical technique to be used. In addition one needs to consider individual circumstances, such as the presence of diabetes mellitus, older age, and female gender, all of which are associated with a worse prognosis [11–14]. Other factors that are considered to hamper AVF function are high levels of plasminogen activator inhibitor type 1, factor VII [15], daily dialysis [16], hypotension [17], smoking [18], disturbed calcium and phosphate balance and increased parathyroid hormone levels [19–22].

Besides individual suffering, the cost due to AVF complications are substantial [5, 23]. A patent AVF improves life expectancy [24]. Therefore, it is important to identify further variables that may be intervened to prevent AVF problems. In addition, if a CDC is necessary it increases the risk for infections [5].

The aim of this study was to investigate if there are other significant risk variables than mentioned above associated with dysfunctional AVF: s that could be considered.

Material And Methods

Since guidelines recommend lower arm AVF [25] the present study focused on researching of risk factors for only these type of patients, thereby excluding those with AVG and those with upper arm placement of AVF. Demographic data and other baseline characteristics are shown in Table 1.

Table 1
Characteristics of the study population at baseline.

Variable	Cases n = 153	Controls n = 52	p-value
Age, mean (SD)	65.9 (13.5)	65.7 (16.5)	0.565
BMI, mean (SD)	26.5 (4.9)	27.8 (6.1)	0.370
Vintage, mean (SD)	10.3 (33.9)	74.8 (45.1)	< 0.001*
StKt/V, median (quartiles)	2.0 (1.4–2.4)	2.2 (2–2.4)	0.099
Female, n (%)	60 (39%)	13 (25%)	0.064
Tobacco:			
Yes cigarettes, ever	48 (46%)	37 (88%)	< 0.001*
Never	57 (54%)	4 (10%)	
Yes snuff, ever	0 (0%)	1 (2%)	
Missing data	48 (31%)	11 (21%)	
Diagnosis:			
Glomerulonephritis	25 (16%)	12 (28%)	0.433
Diabetes Mellitus	42 (28%)	10 (23%)	
TIN/Tubulointerstitial nephritis	24 (16%)	3 (7%)	
PCKD/Polycystic kidney disease	15 (10%)	3 (7%)	
Nephrosclerosis/Hypertension	35 (23%)	11 (26%)	
Other	11 (7%)	4 (9%)	
Ongoing medication:			
Calcium channel blockers	61 (48%)	19 (43%)	0.608
Alfa-1 receptor blockers	40 (31%)	6 (14%)	0.023*
Furosemides	79 (62%)	26 (59%)	0.758
Beta-blockers	94 (73%)	31 (70%)	0.757
ACE-inhibitors	34 (27%)	11 (25%)	0.839
ARB:s	56 (44%)	12 (27%)	0.054
ASA	69 (54%)	22 (50%)	0.654
Vitamin-K antagonists	9 (7%)	3 (7%)	0.962
Statins	68 (53%)	22 (50%)	0.720
BMI-Body Mass Index. StKt/V-Standard Kt/V-weekly dialysis dose. ASA-Acetylsalicylic acid.			
ACE-Angiotensin Converting Enzyme, ARB: s-Angiotensin II Receptor Blockers.			

The study was a retrospective observational study of patients in chronic hemodialysis (HD) (n = 205) with a native lower arm AVF used for HD. Of these 153 patients were defined as 'Cases' since they had clinical assessed AVF dysfunction that resulted

in referral for radiologic investigation at the local department of Radiology. The Cases performed a total of 473 radiologic examinations of AVFs. Each of these events of investigation were analyzed and defined as an episode of access problems. Besides radiological investigation, this episode included nearest regular laboratory samples both before and after intervention.

Fifty-two chronic HD patients who had not suffered from any AVF complications during (without need of radiology investigation) two years served as controls. Regular laboratory sampling within two months after year one and two respectively, was collected. For all patient's data were collected during the period of 2006 to 2015 from a university hospital and one county hospital.

All patients were over 18 years of age. For the Cases the radiological investigations were performed based on clinical suspicion of insufficient access function due to various reasons such as decline in access blood flow to less than 500 ml/ min or a decline of flow over time or for other clinical reasons (Table 2). Results from radiological interventions of the Cases were collected from medical records and from radiology archives (Table 3).

Table 2

Most common reasons for radiological investigation (n = 473) of the AVF-usually confirmed by measured bloodflow problems.

Clinical finding	Total (%)
High venous pressure	36 (8)
Recirculation	31 (6)
Poor access flow	167 (35)
Swollen AVF area	19 (4)
Prolonged bleeding	24 (5)
Cannulation problems	47 (10)
Preoperative investigation due to access problems	43 (9)
Others	94 (20)
The referrals included several surveillance and monitoring findings to discriminate possible expected clinical findings. "Others" are a blend of worsened dialysis, pain, artery suction and others. Doppler Ultrasound was used as preemptive examination in 307 interventions.	

Laboratory data from the Cases were recorded within one month before every radiological intervention and within one month after the same intervention. Such data were collected at each episode including evaluation of the radiological measurements. Some patients underwent several episodes of interventions, therefore repeated laboratory data was achieved.

Access blood flow and recirculation (% of return of exit blood flow from the extracorporeal dialyzed circuit to the inlet blood flow) was measured using a Transonic® device. The weekly administered dose of low molecular weight heparin (LMWH, U/week), the erythropoiesis- stimulating agents (ESA, U/week), and intravenously administered iron during the end of the HD (mg/week) were recorded. Dialysis efficacy was estimated by calculating weekly stKt/V based on calculations of urea removal. The time spent in dialysis (hours/week) as well as body mass index (BMI) were registered.

Laboratory values included blood hemoglobin (reference 100–120 g/L), platelets (reference 165–387 × 10⁹/L) serum values of albumin (reference 36–45 g/L), calcium (reference 2.10–2.50 mmol/L), phosphate (reference 0.60–1.5 mmol/L), ferritin (reference 7-120 µg/L), parathyroid hormone (reference 1.5–7.6 pmol/L), C-reactive protein (reference < 5 mg/L, data < 5 mg/L are given as 4.99 mg/L), HbA1c (reference 31–46 mmol/mol-IFCC), p-fibrinogen (reference 2–4 g/L), cholesterol (reference 3.9–7.8 mmol/L). Since we lacked information about weight in numerous patients a rough estimate of ESA responsiveness/resistance (ESA/Hb) was calculated using the ESA doses (U/week) divided by the hemoglobin value (g/L). This was a modified estimate of ESA resistance based on the Erythropoietin Resistance Index by Santos et al [26]. Similarly,

the iron administration in mg/w was related to the hemoglobin level (Iron/Hb). Vintage, dialysis efficacy and present drug administration such as antihypertensives and anticoagulants are given in Table 1.

Statistical analyses were done with statistical package SPSS v25. Descriptive statistics were expressed as means (SD) and medians (range). Analysis of categorical data was done with Chi 2 test, and group statistics were performed with Student t-test, ANOVA and Mann-Whitney test. Paired statistics were performed with the non-parametric Wilcoxon rank test. A multiple logistic regression analysis (stepwise model) was performed with group (Cases vs. Controls) as outcome including the variables gender, age, C-reactive protein (CRP), prescriptions of ESA, calcium-phosphate product, albumin, standard Kt/V (stKt/V), iron administration/week, low molecular weight heparin (LMWH) in thousands of units/week, alfa-, beta-, calcium-channel and angiotensin receptor- blockers, angiotensin converting enzyme inhibitors, and furosemide. Odds ratio (OR) and 95% confidence intervals (CI) are presented to quantify association between the variables and groups. A two-tailed significance level of $p < 0.05$ was used if not otherwise mentioned.

Results

A radio-cephalic (RC) fistula was present in 90% of the Cases, with a dominance for end to side anastomosis. The remaining 10% had a mid-arm placement. All Cases had been investigated by either percutaneous transluminal angiography, PTA (mostly) or phlebography due to impaired fistula function (Table 3). At least one significant stenosis ($> 50\%$) was detected in 348 investigations and a subsequent PTA was performed in 248 of these. Thrombolysis was performed in another 14 Cases (total $n = 262$). In 211 of the examinations no radiological intervention was performed. In 40 of these, there was no abnormality and the remainder underwent surgical adjustment or were referred for another more suitable radiological investigation/intervention (Table 3).

Table 3
For the Cases, the most common findings of radiological investigations ($n = 473$) and measures taken.

Findings	Total (%)
Significant stenosis	348 (74)
No abnormality detected	40 (8)
No measures taken	196 (41)
Additional radiological investigation	32 (7)
Aneurysm	17 (4)
PTA -dilatation \pm stent	248 (52)
Thrombolysis	14 (3)
N.B. Some patients have been registered for several findings since subsequent investigations and measures may have been made at the same, or another event, based on the results received. PTA- Percutaneous Transluminal Angioplasty.	

All Controls had a radio-cephalic (RC) fistula, with a dominance for end-to-side anastomosis. The 52 Control patients were considered for up to 124 measurements.

Table 1 shows that there were no differences between the groups in age, nor between the prevalence of various diagnoses considered responsible for kidney failure. The Controls had a history of a longer vintage and more tobacco users, whereas current users were similar between groups. The Cases had a higher prevalence of administered alfa-receptor blockers ($n = 40$, 31% vs. $n = 6$, 14%, $p = 0.023$).

Fibrinogen values were analyzed to estimate bleeding risk for 158 occasions before intervention in the Cases. The mean value was 4.5 g/L (SD \pm 1.3) and 70% had a value above the upper reference value.

The prescriptions differed insofar that the Cases received a higher dose of weekly ESA compared to the Controls (Table 4), iron and LMWH both before and after intervention.

The ESA doses did not differ between genders. The Cases with glomerulonephritis or nephrosclerosis received higher doses of ESA than those with other diagnoses (p -value < 0.01). In the Controls, the ESA doses were lower for all diagnoses compared to the Cases.

At follow-up the Controls with diabetes mellitus had an increase in HbA1c while other values remained unchanged. In the Cases hemoglobin was lowered after intervention, most probably due to bleeding during the intervention. Indirect measures of the more effective AVF flow after intervention can be the increased blood pump speed, $stKt/V$ and HD hours/week and the decreased recirculation.

Among the Cases, the ESA/Hb correlated with fibrinogen ($r = 0.292$, $p = 0.002$), Iron/Hb ($r = 0.215$, $p = 0.001$), CRP ($r = 0.163$, $p = 0.003$), and dialysis time/week ($r = 0.18$, $p = 0.001$), but did not correlate with the other factors.

Multiple logistic regression analysis revealed that besides female gender ($p = 0.042$), higher prescription of ESA (OR 1.17, 1.09–1.26, $p < 0.001$) and LMWH (OR 1.06, 1.0–1.12, $p = 0.04$), and the use of alfa-receptor blockers, (OR 3.5, 1.36–9, $p = 0.009$) remained as statistically significant factors for the performance of AVF intervention.

Table 4.

Table 4

shows that in regard to baseline laboratory values the Cases had a higher dose of weekly iron administered and a lower parathyroid hormone (PTH) level than the Controls. However, the calcium-phosphate product did not differ between groups.

For the patients suffering from diabetes nephropathy, the Cases had a higher HbA1c. This difference was not there after intervention. When comparing the first data for the Controls (n = 117) and the data before intervention in the Cases (n = 397), the median values of CRP did not differ (Controls; 6 mg/L, quartiles: 5–14 vs Cases: 6 mg/L, quartiles 5–14).

Variable	Controls				Cases				Group comparison	
	First data	Data < 8w later	n	p-value	Before intervention	After intervention	n	p-value	Parametric Controls vs Cases p-value	Nonparametric Controls vs Cases p-value
Calcium, mmol/L	2.34 (0.41)	2.35 (0.41)	117	0.674	2.35 (0.17)	2.35 (0.17)	417	0.736	0.729	0.737
Phosphate, mmol/L	1.60 (0.43)	1.57 (0.41)	117	0.548	1.65 (0.45)	1.66 (0.49)	413	0.873	0.193	0.214
Calcium x phosphate product	3.7 (1.0)	3.7 (1.0)	117	0.197	3.9 (1.1)	3.9 (1.2)	433	0.158	0.197	0.261
Albumin, g/L	36.9 (5.0)	37.4 (5.4)	118	0.107	36.5 (4.6)	36.2 (4.6)	407	0.052	0.308	0.432
Platelets, (x10 ⁹)	246 (88)	250 (95)	117	0.340	237 (76)	241 (82)	379	0.253	0.253	0.396
Hemoglobin, g/L	114 (12)	114 (12)	118	0.531	114.7 (11.9)	112.9 (12.3)	427	0.001*	0.261	0.23
PTH, pmol/L	33 (27)	34 (25)	100	0.740	27 (25)	34 (106)	349	0.253	0.022*	0.009*
Cholesterol mmol/L	3.89 (0.79)	3.78 (0.83)	10	0.547	4.2 (1.5)	3.8 (0.9)	30	0.169	0.231	0.524
HbA1c*, mmol/mol	49 (20)	54 (20)	17	0.039*	58 (17)	58 (16)	101	0.448	0.033*	0.037*
Ferritin, µg/L	449 (244)	510 (489)	104	0.133	467 (255)	486 (251)	313	0.095	0.701	0.871
Drug prescriptions:										
ESA, U/W	4667 (3654)	4673 (3701)	78	0.975	7063 (387)	6982 (382)	333	0.153	p < 0.001	p < 0.001

Comparison (mean and SD) for Controls after more than 1 year free of AVF problems vs. follow-up within 8 weeks, and for Cases before vs. after intervention. In addition, parametric and non-parametric comparison between Controls first data and Cases pre-intervention values. *HbA1c results are given only for blood samples taken from patients with diabetes mellitus. PTH-Parathyroid hormone, ESA-Erythropoietin stimulating Agent, LMWH Low Molecular Weight Heparin, QB- blood pump speed ml/min, CRP-C-reactive protein. HD- hemodialysis.

Variable	Controls			Cases				Group comparison		
Iron, mg/W	43 (65)	34 (35)	72	0.211	59 (60)	55 (44)	234	0.257	0.073	0.004*
LMWH, U/W	11949 (5062)	12270 (5581)	74	0.282	14225 (8022)	14537 (8174)	227	0.183	0.064	0.028*
HD conditions:										
Blood pump flow, ml/min	307 (28)	308 (20)	61	0.708	288 (48)	299 (46)	185	0.001*	p < 0.001	p < 0.001
Recirculation, %	0.7 (4.5)	0.2 (1.7)	61	0.385	4.7 (11)	0.7 (3.7)	130	< 0.001*	p < 0.001	p < 0.001
Access flow, ml /min	1105 (494)	1090 (497)	61	0.622	631 (446)	866 (512)	158	< 0.001*	p < 0.001	p < 0.001
HD, hours/w	12.2 (2.7)	12.0 (2.3)	78	0.196	12.1 (2.4)	12.3 (2.4)	320	0.009*	0.348	0.61
StKt/V	2.16 (0.53)	2.17 (0.58)	72	0.831	1.88 (0.59)	1.90 (0.59)	257	0.237	p < 0.001	p < 0.001
Venous pressure	137 (23)	140 (29)	62	0.492	133 (28)	131 (31)	121	0.409	0.263	0.295
Comparison (mean and SD) for Controls after more than 1 year free of AVF problems vs. follow-up within 8 weeks, and for Cases before vs. after intervention. In addition, parametric and non-parametric comparison between Controls first data and Cases pre-intervention values. *HbA1c results are given only for blood samples taken from patients with diabetes mellitus. PTH-Parathyroid hormone, ESA-Erythropoietin stimulating Agent, LMWH Low Molecular Weight Heparin, QB- blood pump speed ml/min, CRP-C-reactive protein. HD- hemodialysis.										

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Discussion

In the present study, the remaining risk factors for AVF dysfunction after multiple regression analyses were female gender, prescriptions of higher doses of ESA and LMWH, and the use of alfa-receptor blockers. Univariate analyses also showed a relation to prescription of higher doses of iron to the Cases. There was no obvious reason that the increased ESA doses were due to inflammation since CRP, ferritin and albumin were similar both during the first series and the second (after intervention), although there was a small correlation between ESA/Hb and CRP. The elevated ESA doses in the Cases were also shown in a few previous studies [27–29].

The other deviate findings in the Cases are reasonably explained by the impaired blood flow in the AVF before intervention such as the use of a lower blood pump speed, higher recirculation, less effective dialysis (shown by a lower $stKt/V$) and the shortened HD time. All of these variables improved after intervention. Within the frame of the study, other expected risk factors such as tobacco use and calcium, phosphate and PTH levels were similar or even worse in the Controls.

Insulin resistance due to tissue insensitivity is pronounced in uremic patients [30]. Other investigators showed that diabetic patients with AVF problems had a poorer homa-IR index (Homeostasis model assessment). Such metabolic disturbance may impair the vascular endothelium [7, 31]. This is in line with the present study where the Cases with diabetic nephropathy had higher HbA1c values before intervention. The improvement after intervention indicates a causal relationship towards a less uremic state by more effective dialysis, and thereby less insulin resistance.

However, the shorter vintage when AVF problems appear in the Cases compared to the Controls indicate that these patients also have a more general problem that affects their AVF already early on, but also later after placement.

Several Cases in the present study might suffer from hyporesponsiveness to ESA since hemoglobin levels were similar to Controls. Johnson et al. noted that such hyporesponsiveness is present in 5–10% of CKD patients [32]. A few studies have suggested a link between ESA responsiveness and higher morbidity and mortality in end-stage renal disease patients [33, 34] often together with more signs of inflammation [35–37].

Regarding AVF in the present study, there is no indication that the Cases had a higher degree of inflammation than the Controls.

In that ESA increases blood pressure [38], higher ESA doses could explain higher blood pressures and the addition of antihypertensive drugs such as alfa receptor blockers.

The increased ESA doses could be due to a greater loss of blood by increased clotting and to the subsequent waste of blood within the extracorporeal system during each HD.

Such clotting would also explain the use of higher LMWH doses, motivated by a state of thromboembolism based on visual presence of fibrin deposits in the dialyzer during HD.

The activation of coagulation during HD is initiated by the blood membrane contact [39]. This will result in high concentrations of activators in the blood that returns to the AVF, which may favor clotting in this AVF area. Besides a local activation a more general effect seems present since most AVF stenoses and thromboses are present/develop closer to the AVF anastomosis as well as the site where the needle for the inlet to the dialysis circuit is located [14].

A higher ESA dose was related to a higher extent of thromboembolic complications in AVF [40] as well as of cardiovascular diseases in general [40–43].

The present study shows a relation between ESA/Hb and plasma fibrinogen that indicates an association with increased thromboembolic risk. Such data also fit with previous studies that noted in general that treatment with ESA was associated with increased thromboembolic events [41, 44, 45].

Another reason for the increased ESA and intravenous iron doses is that higher LMWH doses inhibit clotting which may increase blood loss at the site of the AVF after termination of the HD.

This may be strengthened by the fact that the higher doses of iron administration did not result in larger deposits of iron stores as indicated by ferritin levels that were similar to those of the Controls. The repeated infusions of iron could have toxic effects on local AVF conditions and lead to negative effects on all-cause mortality [46, 47]. Also, ferritin levels above 400 µg/L have recently raised concern to be associated with higher inflammatory effects on the vascular endothelium with iron-induced oxidative stress and endothelial dysfunction [48]. In the present study ferritin was above 400 µg/L among half of the patients. However, this level was recommended by KDIGO in 2012 [49]. This indicates that lower values may be considered in the future. Maintaining a regular hemoglobin level can be achieved by using regular ESA doses combined with intravenous iron doses adapted to S-ferritin (SF) and transferrin saturation (TSAT) thresholds that are lower than those used in routine practice; this contributes to a reduced risk of iron overload. [50].

Studies have indicated increased morbidity and shortened life expectancy for HD patients that receive ESA above 8100 units/w [51] and iron doses above 800 mg within 6 months [52].

The administration of intravenous ESA might enhance ESA-receptors in the stenotic fistulae, inducing cell proliferation in response to local TGF-β1 expression, resulting in intimal thickening of the vessel wall [53]. This should entail more careful attention when reaching doses beyond 8000 IU/w and subsequent attention to other methods to treat the anemic state of the HD patient.

The lower stKt/V, as an estimate of the extent of HD, was still significantly lower for the Cases (compared to the Controls) after intervention of the stenosis, although it was well within the limit of recommendation. Therefore, the present study cannot rule out that extended HD could reduce the need of ESA. This would be in line with other studies [54, 55].

The significant finding of a higher frequency of doxycycline prescription in the Case group may comply with the fact that they receive higher ESA doses. ESA administration increases blood pressure [38], and as a consequence of this is the need of more antihypertensives. On the one hand, doxycycline as an alpha-receptor blocker dilates vessels and may counteract, for example platelet aggregation, having beneficial profibrinolytic effects [56, 57] and counteract coronary constriction [58]. On the other hand, doxycycline may stimulate collagen synthesis [59] and induce edema [60], which would be a disadvantage for the AVF.

The strength of this study was the consecutive inclusion of these numerous episodes of the Cases and the Controls who had a lower arm AVF observed up to a 9-year period.

A weakness of the study was that in some of the patients the phlebography or angiography could not reveal a stenosis, although the AVF access was not considered optimal from a clinical point of view. This could have been due to vasoconstriction or problems to achieve adequate locations of the needles at the insertion sites. On some occasions, it was later found out that the patient had more central stenoses such as at the upper arm or at the exit of the subclavian vein. Some patients suffered from elongated 'non-significant' stenoses that caused an impaired flow [14].

The importance of the results is that the presence of hyporesponsiveness to ESA and iron doses should bring up the question of whether it might be reasonable to keep a lower dose and thereby a hemoglobin level in the lower range. In patients with previous clotting problems, complicated surgical procedures and higher fibrinogen levels favor thromboembolic events and therefore may be considered for a prolonged period of LMWH as prophylaxis for thrombosis, as is also suggested by others [61]. In the present study the relation between ESA/Hb and plasma fibrinogen indicates an association and supports an increased thromboembolic risk. Such data also fit with previous studies showing that treatment with ESA was associated with increased thromboembolic events [41, 44, 45]. Future research should clarify if a more extensive bleeding and/or coagulation occurs when the dialysis is ended and thereby is partly responsible for the prescription of higher ESA doses.

Diabetes patients may benefit from an improved metabolic control to counteract insulin resistance. Rostoker et al. recommend caution when combining high doses of ESA and intravenous iron among diabetics treated with HD, which may contribute to AVF related complications [48]. The present study does not rule out that a similar approach may be helpful also for other groups of patients who suffer from AVF problems.

In conclusion our study showed that AVF problems were related to higher doses of ESA, iron administration and LMWH. Probable reasons are increased bleeding and/or thromboembolic events aside from the hyporesponsiveness to ESA. Further studies should elucidate benefits in reduced targets of hemoglobin, and doses of ESA and iron administration to avoid problems of AVF.

Declarations

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics committee in Gothenburg, Sweden, EPN, DNR, 402-14, 2014-08-22, T-037-15, 2015-01-09. The Ethics committee approved that the informed consent was waived since the study subjects were de-identified and no intervention was induced by the study.

AW, BS and SN analysed and interpreted the data and prepared the manuscript.

AW, BS and HH were responsible for the study concept, design and revising it critically for important intellectual content. All authors discussed the results, contributed to the manuscript and approved the final version.

Obtained funding: The Department of Research and Development at Skaraborg Hospital and Norrlands Njurföreningar supported the study.

Acknowledgements to:

Ursula Hadimeri for valuable comments on the interventional examinations.

Anna Lena Emanuelsson-Loft for valuable comments regarding text configuration.

Malin Skagerlind, RN, PhD, Dept of Public health and Clinical Medicine Umea, for gathering laboratory and intervention results.

Albert Crenshaw, L-A Write Now, for professional and effective language check.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

The authors declare that they have no competing interests.

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