Course of Vascular Access and Relationship with Treatment of Anemia

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Background and objectives: Maintenance of the vascular access is a crucial factor in hemodialysis, but large studies of factors that are predictive of thrombosis are lacking.

Design, setting, participants, & measurements: This prospective, multicenter study investigated a cohort to describe the management of vascular access and establish the influence of anemia as a risk factor. The cohort included 1710 patients (aged 64.4 yr; 60% men) who were followed every 3 mo at 119 centers during 12 mo. On inclusion, 9.6% had a catheter, 80.3% had a native arteriovenous fistula, and 10.1% had a polytetrafluoroethylene graft.

Results: Low baseline hemoglobin increased the risk for vascular access events. The risk was higher with a polytetrafluoroethylene graft and a catheter *versus* arteriovenous fistula. The multivariate model included type of vascular access, previous cardiovascular events, and noncorrected anemia. The likelihood of remaining free of vascular access events 12 mo later was 0.727 (baseline hemoglobin <10.0 g/dl), 0.801 (10.01 to 11.0 g/dl), 0.814 (11.01 to 12.0 g/dl), and 0.833 (>12.0 g/dl), figures similar to those obtained with hemoglobin from the trimester before the event. The Cox model included type of vascular access.

Conclusions: Correcting anemia did not increase the risk for vascular access–related events, and anemia that was resistant to treatment identified a subgroup of patients with higher comorbidity and higher likelihood of a vascular access event.

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The construction and maintenance of vascular access (VA) constitutes one of the habitual problems in hemodialysis (HD). A suboptimal VA can compromise the effectiveness of HD and lead to malnutrition, infections, tolerance-related problems, hospitalization, and other complications with the potential to affect the quality of life of our patients (1). In Europe and the United States, these complications account for 15 to 36% of all hospitalizations, at a cost of >$700 million in the United States (2–4). The magnitude of the problem is such that since 1999, expert committees have proposed in their guidelines for clinical practice that studies be carried out to search for solutions (1,5). The guidelines of the Spanish Society of Nephrology propose as a possible target the reduction in the use of central venous catheters in favor of attempting to create a native arteriovenous fistula (AVF) whenever possible. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend efforts to reduce the rates of thrombosis to 0.5 episodes per year in patients with a polytetrafluoroethylene (PTFE) graft and 0.25 episodes per year in patients with an AVF (1,5). Currently, however, little information is available on the distribution of the various types of VA, rates of thrombosis, and triggering factors because of the scarcity of large, national-level, prospective studies involving hospital and ambulatory centers (6–8).

Clinical guidelines note the factors that may be involved in VA thrombosis, including patient-related (*e.g.*, age, gender, diabetes), management-related (*e.g.*, prospective follow-up, rotation of puncture sites), and treatment-related characteristics such as anticoagulation, degree of control of hyperparathyroidism, and angiotensin-converting enzyme inhibitor use (1). Some authors have proposed that correcting anemia to achieve normal values may favor the appearance of thrombosis (9); however, this issue remains controversial (8).

Moreover, policies that guide the choice of type of VA and its management vary widely across countries. In the United States, the use of PTFE access is much more prevalent than in Spain, and the rates of thrombosis are as high as one episode per year with PTFE grafts (2,9). However, native AVF is the most frequently used option in Spain, and that estimated thrombosis rate is lower (10).

The Morbidity-and-mortality Anemia Renal (MAR) study has followed a cohort of patients on HD to establish the influence of anemia as a risk factor for mortality and morbidity (11,12). As a secondary objective, this study offers a descriptive analysis of VA-related problems and their course and relationship with anemia management.

Materials and Methods

Study Design

This was a descriptive, prospective, open, multicenter study of a representative cohort of patients who had chronic kidney disease from

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any cause, were on HD, and were followed for 12 mo for this analysis. Representativeness of the sample was based on the sampling strategy, which included patients' being followed in both hospitals and other centers from all parts of continental Spain, and was established in earlier publications that compared our sample with other series and with data from the national dialysis registry (11,12). The main objective of this analysis was to establish the influence of anemia as a risk factor for VA events and to describe the management of VA and its course and factors that influence the appearance of complications.

The reference population was prevalent patients who were on HD, were older than 18 yr, began treatment during the period from January 1999 to March 2001, and had not received a kidney transplant. The 4-mo recruitment period lasted from March 2001 to July 2001, and the follow-up period lasted for 12 mo. The final sample consisted of 1710 patients (929 hospital patients and 781 patients followed at dialysis centers), for which we estimated an absolute sampling error of ±0.03 at a 95% confidence interval (CI). Centers were urged to apply the recommendations of the European Clinical Guidelines for the optimal management of anemia in patients with chronic kidney failure (13), although not all patients in this study were receiving treatment with erythropoietin (EPO).

This study was conducted in accordance with the recommendations of the Declaration of Helsinki, and informed consent was obtained from all participating patients. Data were recorded in case report form notebooks by staff physicians every 3 mo for events, changes in treatment, and results. Patient data included age, gender, comorbidity, date when HD was started, cause, and cardiovascular risk factors. Disease management data included HD parameters, management of anemia, cardiovascular risk factors, and HD targets (monocompartmental kT/V) (14). Vascular access events noted were hospitalizations and events that did not require hospitalization (12). For this analysis we considered "combined events" to include thrombosis, graft repair, and hospitalization for a diagnosis related with VA. We used the EPO resistance index (ERI), as an indicator of the response to treatment of anemia with EPO. ERI was calculated every 3 mo as current dosage in U/kg per wk divided by hemoglobin (Hb) in g/dl.

Sample Characteristics

The final sample comprised 1710 patients who were followed at 119 centers and had a mean time on HD of 15.9 ± 11.1 mo. These patients represented 18% of all incident patients during 1999 and 2000, according to the national register. Slightly more than half (54.3%) of the patients received HD at a hospital; the remaining patients were treated at private centers supported by the national health system. Mean age was 64.4 ± 13.6 yr (range 18 to 92 yr), and 60% were men. Cause of chronic kidney disease was diabetes (22.3%), glomerular (15.8%), vascular (13.0%), interstitial (9.9%), polycystic (8.6%), unknown (21.8%), and other causes (7.1%). Mean Charlson comorbidity index (15) was 6.53 ± 2.3, with 30.7% scoring 5 or lower, 36.9% scoring 6 or 7, and 32.4% scoring 8 or more. Slightly more than one third (36.7%) of the patients were on the waiting list for kidney transplantation. All patients received three weekly sessions lasting a total of 11.1 ± 1.3 h/wk, and a high-flux membrane (coefficient >20 ml/h per mmHg) was used for 39.8% of the patients. At the time of inclusion, 75.8% of the patients had hypertension, 16.7% had coronary disease, 13.9% had some degree of heart failure, 11.6% had arrhythmia, 2.0% and antecedents of acute cerebrovascular accident, and 5.5% had peripheral artery disease. The sample has been described in detail elsewhere (11), and we summarize in Table 1 the characteristics of our cohort.

Statistical Analyses

We calculated estimated percentage values or position and dispersion parameters (mean, median, SD, and range) depending on the type of variable. The comparisons reported here are based on the χ^2 test (for categorical variables), ANOVA, t test, and the Mann-Whitney U test. The association of previous factors with subsequent events was established with logistic regression analysis. For survival studies (time to event), we used Kaplan-Meier analysis for univariate and stratified comparisons and Cox regression for multivariate analysis. The database was built and the analysis was performed with SPSS 10.0 software (SPSS, Chicago, IL).

Results

Description of VA and Course

At the time of inclusion, 9.6% of the patients had a catheter, 80.3% had a native AVF, and 10.1% had a PTFE graft. At the end of the study period, these proportions were 9.4, 79.7, and 10.8%, respectively. The most relevant characteristics of the sample, grouped according to type of VA at the start of the study, are shown in Table 1.

The mortality rate was 12%, and 45% of the patients were hospitalized during the 12-mo study period (1.42 admissions per hospitalized patient). The cumulative rate of admission per year for VA problems was 18.2% for patients with a catheter, 6.3% for those with an AVF, and 23.1% for those with a PTFE graft ($P < 0.01$). Figure 1 shows survival to the first VA event according to type of access. The rate of thrombosis was 0.09 episodes per year at risk for patients with a native AVF and 0.44 episodes per year at risk for patients with a PTFE graft. The rate of any event (thrombosis or reparation by any cause) was 0.29 episodes per year at risk for patients with a native AVF and 1.04 episodes per year at risk for patients with a PTFE graft.

Prognostic Factors for the Appearance of VA Events

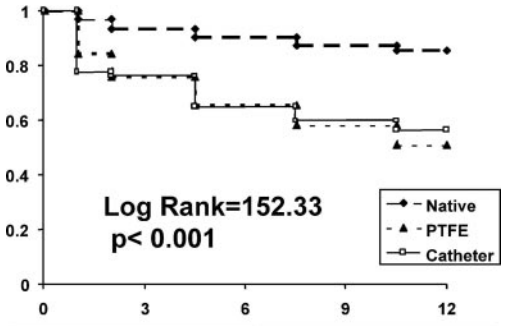
This analysis aimed to identify prognostic factors for combined VA event (any VA event regardless of whether the patient was hospitalized). The risk for VA event was 1.32 (95% CI 1.05 to 1.74) for patients with Hb concentrations <11.0 g/dl *versus* those with Hb concentrations ≥11.0 g/dl. The risk for VA event was higher in patients with baseline Hb <10.0 g/dl (1.66; 95% CI 1.12 to 2.44) than in those with baseline Hb ≥10.0 and <12.0 g/dl (1.05; 95% CI 0.78 to 1.41) in comparison with the reference category Hb ≥12.0 g/dl. The relative risk for VA event decreased 0.87 (95% CI 0.79 to 0.96) per 1-g/dl increase in Hb value. The risk for an event was higher in patients with a PTFE graft (5.7; 95% CI 3.9 to 8.49) and in those with a catheter (4.58; 95% CI 3.07 to 6.84) in comparison with the reference category of native AVF. Comorbidity increased the risk for a VA event: 1.12 (95% CI 1.03 to 1.22) per point increase in the Charlson index and 1.86 (95% CI 1.33 to 2.6) in patients with a history of cardiovascular events. The model that was obtained with multivariate analysis by logistic regression included type of access, comorbidity, and anemia. Type of access was the main predictor of VA events, with an odds ratio (OR) of 5.48 in patients with a PTFE graft and 4.01 in patients with a catheter (*versus* native AVF, $P = 0.0001$), followed by comorbidity (history of cardiovascular events), with an OR of 1.86 ($P = 0.03$)

Table 1. Initial characteristics of the sample[a]

Characteristic	Catheter (n = 139)	PTFE Graft (n = 171)	Native AVF (n = 1366)	Total Cases	P
Men (%)	46.3	46.2	63.1	60.0	<0.001[b]
Age (yr)	69.1 (10.6)	66.6 (12.5)	63.6 (13.9)	64.3 (13.6)	<0.001[b]
Time on HD (mo)	13.9 (7.2)	16.0 (6.9)	15.5 (7.0)	15.4 (7.0)	<0.03[c]
BMI	25.4 (5.1)	25.9 (4.8)	25.3 (4.3)	25.3 (4.4)	NS
Diabetes (%)	38.1	37.4	23.2	25.9	<0.001[b]
Charlson index	7.6 (2.4)	7.1 (2.4)	6.4 (2.2)	6.5 (2.3)	<0.001[b]
Kt/V Daugirdas (mean [SD])	1.58 (0.34)	1.76 (0.35)	1.66 (0.43)	1.66 (0.42)	<0.01[d]
% with kT/V >1.3	78.5	93.8	84.3	84.7	<0.005
Serum albumin (g/L; mean [SD])	36.1 (4.3)	37.7 (4.1)	38.2 (4.4)	38.0 (4.4)	<0.005[e]
iPTH >400 pg/dl (%)	13.2	13.4	14.1	14.0	NS
Anemia					
baseline Hb (mean [SD])	11.4 (1.5)	11.6 (1.5)	11.7 (1.4)	11.6 (1.4)	<0.03[f]
Hb >12.0 g/dl (%)	37.6	42.3	39.8	39.9	
Hb >10.0 and <12.0 g/dl (%)	42.8	41.8	47.5	46.5	
Hb <10.0 g/dl (%)	19.6	15.9	12.7	13.6	
Ferrokinetics					
ferritin >100 ng/ml (%)	86.7	89.3	89.8	89.5	NS
TSI >20% (%)	68.6	76.0	77.4	76.6	NS
Fe^{2+} treated intravenously (%)	80.6	83.0	78.6	79.2	NS
EPO					
treated (%)	96.4	97.1	94.4	94.8	NS
U/kg per wk	125.5 (69.3)	120.4 (74.9)	109.1 (70.6)	111.7 (71.1)	<0.02[f]
ERI	11.5 (6.9)	10.9 (7.7)	9.8 (7.1)	10.1 (7.2)	<0.02[f]

[a]Data for subgroups according to type of vascular access (VA), and comparisons between subgroups according to ANOVA (continuous variables) and comparison of proportions. AVF, arteriovenous fistula; BMI, body mass index; EPO, erythropoietin; ERI, erythropoietin resistance index; HD, hemodialysis; iPTH, intact parathyroid hormone; PTFE, polytetrafluoroethylene graft; TSI, transferrin saturation index.

Bonferroni/Tahmane tests for multiple comparisons: [b]Native AVF *versus* all others, [c]catheter *versus* native AVF, [d]PTFE graft *versus* all others, [f]catheter *versus* all others, [e]catheter *versus* all others.



VA Patency probability	1st Trimester	2nd Trim.	3rd Trim.	Year
Catheter	0,762	0,637	0,597	0,564
PTFE	0,762	0,658	0,581	0,508
Native AV	0,936	0,905	0,877	0,858

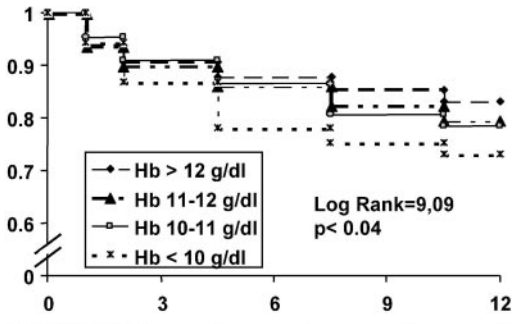
Figure 1. Kaplan-Meier survival curves to first vascular access (VA) event, according to type of VA on inclusion. PTFE, polytetrafluoroethylene graft.

and anemia (Hb concentration <11.0 g/dl), with an OR of 1.1 (P = 0.07).

Our survival analysis also showed that type of VA was the best predictor of VA events, with a likelihood of remaining free of events after 12 mo of 0.564 for patients with a catheter, 0.508 for patients with a PTFE graft, and 0.858 for those with a native AVF (log rank test = 152.33, Kaplan-Meier test $P < 0.001$; Figure 1). Survival analysis according to baseline Hb value established a likelihood of remaining free of events after 12 mo of 0.727 for Hb <10.0 g/dl, 0.801 for Hb 10.01 to 11.0 g/dl, 0.814 for Hb 11.01 to 12.0 g/dl, and 0.833 for Hb >12.0 g/dl (log rank test = 9.09, Kaplan-Meier test $P < 0.04$). Survival analysis according to Hb value measured in the trimester before the event yielded a similar pattern, as shown in Figure 2. Because type of VA was associated with other prognostic factors and management of anemia, we used multivariate analysis to obtain the corresponding Cox model, which included type of VA, cardiovascular events before creation of the access, and Hb value in the trimester before the VA event. The OR (95% CI) were 3.63 (2.65 to 4.98) for PTFE graft and 3.29 (2.34 to 4.63) for catheter *versus* native AVF, 1.63 (1.23 to 2.16) for previous cardiovascular event, and 1.11 (1.02 to 1.21) per 1-g/dl decrease in Hb concentration before the event.

Correction of Anemia and VA

The type of VA also influenced how anemia was managed and the response to treatment of anemia. When we compared



VA Patency probability	1st Trimester	2nd Trim.	3rd Trim.	Year
Hb < 10 g/dl	0,868	0,781	0,753	0,727
Hb 10-11 g/dl	0,91	0,865	0,807	0,801
Hb 11-12 g/dl	0,899	0,86	0,825	0,814
Hb > 12 g/dl	0,909	0,879	0,856	0,833

Figure 2. Kaplan-Meier survival curves before VA event, according to hemoglobin (Hb) concentration.

patients according to type of VA, we found that the dosage of EPO needed was 109.1 ± 70.6 U/kg per (up to 545.5) in patients with an AVF, 120.4 ± 74.9 U/kg per (up to 415.1) in those with a PTFE graft, and 125.5 ± 60.3 U/kg per (up to 381) wk in those with a catheter ($P < 0.002$) to obtain Hb values of 11.7 ± 1.4, 11.6 ± 1.5, and 11.4 ± 1.5 g/dl, respectively ($P < 0.03$). The EPO dosages of patients with VA events were higher than those of patients with complete follow-up and without VA events (Table 2). The relative risk for failing to achieve appropriate control of anemia (Hb <11.0 g/dl) was 1.55 (95% CI 1.08 to 2.22) in patients with a catheter and 1.24 (95% CI 0.89 to 1.73) in those with a PTFE graft, compared with the native AVF reference group (Table 1).

Discussion

Evolution of VA

The data from this study provide an accurate estimate of VA use in Spain. The representativeness of our sample was discussed in a previous publication (11), but it is worth recalling that this study included >15% of all patients who started HD between 1999 and 2000 and >8% of all prevalent patients at the end of 2000. Distribution across age groups, gender, causes, and prevalence of diabetes was similar to the distribution reflected in the national register (11,12). We previously described the differences between our patients and the data from the US Renal Data System register in terms of comorbidity, survival, management of anemia, and particularly the use and maintenance of various types of VA (11). Notably, the distribution of patients by type of VA was stable during our 12-mo follow-up period and was similar to the distribution reported in previous studies in Spain of patients who were seen in hospital and outpatient settings (6,7) and in patients who were seen only in ambulatory centers (8).

The rate of access thrombosis was 0.14 per year in patients who were at risk with an AVF, and 0.44 per year in patients who were at risk with a PTFE graft. These figures are within the target values recommended by the National Kidney Foundation K/DOQI guidelines and are lower than the rates published for the US Renal Data System register (2). Despite these encouraging results, much remains to be done to achieve the ideal VA that yields appropriate dialysis performance, comfort, and convenience for the patient and a good prognosis throughout the period when the patient needs HD.

Anemia and Other Prognostic Factors in the Maintenance of VA

We found that the type of VA (PTFE *versus* native fistula) had the greatest influence on the prognosis for survival, as found in previous studies (1,3,16,17). This analysis looked specifically into the role of anemia and its treatment in the incidence of thrombosis and found that Hb level was associated with the course of the VA. The better the control of anemia, the more favorable the course of VA during the subsequent 12 mo. However, some clinical trials have reported a higher rate of thrombosis when target of Hb reaches normal value levels (9). The study by Besarab *et al.* (9) was a clinical trial in a selected population, with two treatment objectives (normalization of hematocrit *versus* maintenance of hematocrit at 30%), and their intention-to-treat analysis showed a higher rate of thrombosis in the normalization group. The authors suggested that the mechanism could include high blood viscosity as a result of the hemoconcentration (with higher post-HD hematocrit) and low blood flow as a result of the postdialysis hypotension. Both may favor VA thrombosis, especially in patients with a PTFE graft. However, patients who had thrombosis did not have higher Hb levels. A recent Cochrane systematic review of controlled trials that compared various targets of Hb in EPO treatment concluded that there were no significant differences in the risk for VA thrombosis between low and high Hb groups (18).

Our study was observational in nature and involved a nonselected population for whom clinical guidelines for the treatment of anemia were recommended. The patients were later

Table 2. Initial EPO dosages of patients with or without VA events[a]

Access	With VA Events	Without VA Events	*P*
Global	122.9 (76.4)	111.5 (70.8)	0.031
Native AVF	113.8 (70.6)	110.6 (71.2)	NS
PTFE Graft	131.1 (87.6)	116.0 (72.4)	NS
Catheter	135.3 (76.2)	124.2 (65.2)	NS

[a]Data for subgroups according to type of vascular access and comparisons between subgroups according (ANOVA). Data are means (SD) in U/kg per wk (patients with complete follow-up $n = 1328$).

stratified according to the results. Thus patients who remained anemic may represent a subgroup in which the response to treatment was smaller, comorbidity was greater, and inflammation was more frequent. In fact, the subgroup of patients whose anemia responded least favorably to treatment received EPO and iron therapy (at high dosages in some patients) but comprised patients who had more comorbidity and more often had a catheter (and least often had a native AVF). Moreover, efficacy of HD and nutritional status were compromised often in this subgroup. These comorbidity factors, along with possible inflammation associated with catheter use, might have resulted in suboptimal access performance and a less favorable course of the VA, as suggested in a previous study (19).

Other authors have reported findings similar to ours (7,18). Foley *et al.* (20) investigated the role of anemia in patients with left ventricular hypertrophy and reported as an ancillary finding that normalization of Hb levels (13.0 to 14.0 g/dl) did not increase the risk for thrombosis compared with a group of patients with low Hb levels (9.5 to 10.5 g/dl). A recent study by Garrancho *et al.* (8) analyzed a large cohort of patients who were on HD and followed exclusively at outpatient centers and found similar rates of access survival in patients with mean a Hb of 12.0 to 13.0 g/dl and in the reference group of patients with a mean Hb of 10.0 to 12.0 g/dl. Moreover, these authors found a NS trend toward a higher rate of thrombosis at Hb levels <10.0 g/dl. However, their analysis was based on mean Hb value for the entire study period, which might have confounded the results because of reverse causality bias. In patients who have a VA event, suboptimal dialysis, hospitalization, and surgical procedures that can contribute to lower Hb values are often associated.

To avoid this confounding factor (cause by effect), we analyzed our data with three different approaches. First, we used mean Hb level for the entire study period (as described previously) and found that appropriate correction of anemia was not associated with a worse course of the VA. In previous analyses, we found a linear association between appropriate control of anemia and lower mortality and between the former and lower global hospitalization rate—results that confirmed some of the findings of the Dialysis Outcomes and Practice Patterns Study (DOPPS) (21). Second, the results were similar when Hb levels on inclusion were used instead of mean Hb for the entire study period, because we detected no increase in the risk for a VA event in patients with Hb >12.0 g/dl. Finally, we repeated the analysis with a time-dependent variable—Hb concentration measured in the trimester before the VA event—with the same results.

The factors that contribute to poor survival of VA are frequently associated. Type of VA was the most powerful predictor of VA survival, and the choice of type of VA depends on these comorbidity factors. As we have shown, patients with a PTFE graft were older, had a higher prevalence of diabetes and obesity, had more frequent comorbidity factors, and were more often women than patients with a native AVF. Multivariate analysis with type of VA and comorbidity (recalling that age was included in the comorbidity index) essentially ruled out the influence on survival of all other factors. Other studies have established a low serum albumin value as a marker of increased risk for thrombosis (19), through the role of inflammation in the obstruction of PTFE grafts. However, serum albumin is also a nutritional marker associated with greater comorbidity and other risk factors; consequently, albumin dropped out of our multivariate model (the greater the comorbidity, the lower the albumin concentration). Recent studies have confirmed the influence of age and diabetes (both included in the Charlson index) on VA prognosis but have also found a role for hyperparathyroidism or angiotensin-converting enzyme inhibitor. In our cohort, we were not able to confirm the influence of these last two factors on VA prognosis.

Type of VA and Treatment of Anemia

The type of VA seems to act as a risk marker for inadequate response to treatment for anemia. This effect was clearest in patients with a central venous catheter, who needed larger dosages of EPO to achieve smaller corrections in anemia. The ERI was higher in patients with a catheter than in those with a PTFE graft and was higher in the latter group when compared with patients with a native AVF. Our data showed that the effect was maintained despite that ferrokinetics values were within the normal range. We found less favorable dialysis outcomes, nutritional indicators, and serum albumin levels in the group of patients with a catheter. These patients had factors predictive of a poor response to treatment of anemia, and these factors, together with the inflammatory stimulus of the catheter itself, contributed to the partial or complete resistance to treatment with EPO.

Conclusions

Correcting anemia within the limits proposed by current guidelines did not seem to increase the risk for VA events. Moreover, anemia that was refractory to treatment in observational studies identified a subgroup of patients with more comorbidity, in whom the likelihood of VA events was greater. This analysis provides an estimate of the distribution of types of VA in a Spanish population of patients on dialysis and the difference in clinical course between various types of VA. In addition, we were able to identify age and comorbidity as the main prognostic factors of VA events. HD with a central venous catheter required the use of more EPO-stimulating agents and was associated with a less satisfactory correction of anemia and less favorable nutrition and dialysis parameters. The most beneficial VA for patients, in terms of clinical course, rate of events, efficacy, and response to treatment of anemia, was the native AVF, and this type of access should be encouraged with appropriate preparation and follow-up to minimize the rate of events.

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Disclosures

None.

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