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An Analysis of Vascular Access Thrombosis Events From the Proactive IV irOn Therapy in hemodiALysis Patients Trial

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Introduction: Treatment of anemia in dialysis patients has been associated with increased risk of vascular access thrombosis (VAT). Proactive IV irOn Therapy in hemodiALysis Patients (PIVOTAL) was a clinical trial of proactive compared with reactive i.v. iron therapy in patients requiring hemodialysis. We analyzed the trial data to determine whether randomized treatment arm, alongside other clinical and laboratory variables, independently associated with VAT.

Methods: In PIVOTAL, 2141 adult patients were randomized. The type of vascular access (arteriovenous fistula [AVF], arteriovenous graft [AVG], or central venous catheter [CVC]) was recorded at baseline and every month after randomization. The associations between clinical and laboratory data and first VAT were evaluated in a multivariate analysis.

Results: A total of 480 (22.4%) participants experienced VAT in a median of 2.1 years of follow-up. In multivariable analyses, treatment arm (proactive vs. reactive) was not an independent predictor of VAT (hazard ratio [HR] 1.13, $P = 0.18$). Diabetic kidney disease (HR 1.45, $P < 0.001$), AVG use (HR 2.29, $P < 0.001$), digoxin use (HR 2.48, $P < 0.001$), diuretic use (HR 1.25, $P = 0.02$), female sex (HR 1.33, $P = 0.002$), and previous/current smoker (HR 1.47, $P = 0.004$) were independently associated with a higher risk of VAT. Angiotensin receptor blocker (ARB) use (HR 0.66, $P = 0.01$) was independently associated with a lower risk of VAT.

Conclusion: In PIVOTAL, VAT occurred in nearly 1 quarter of participants in a median of just >2 years. In this *post hoc* analysis, randomization to proactive i.v. iron treatment arms did not increase the risk of VAT.

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VAT is a common occurrence in patients receiving hemodialysis.[1] When this problem occurs, patients are exposed to disruption to their lives and hemodialysis provision, unscheduled hospital care, intervention to either salvage or replace the access, and have adverse morbidity and mortality.[1] As most patients with advanced kidney failure may expect to rely on hemodialysis for some if not most of their time on kidney replacement therapy,[2,3] the impact of this problem is significant.[4]

Each of the main types of vascular access has different risks, reasons, and consequences of thrombosis. AVF thrombosis rates are relatively low and usually caused by vascular stenoses. When thrombosis occurs, there is a high likelihood of irreversible access failure.[5] (CVC: including both tunneled and

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nontunneled) thrombosis rates are higher but the immediacy of access provided by CVC replacement partially offsets the impact of thrombosis.[6] AVG thrombosis occurs most frequently, but restoration of access patency is more often successful than for AVFs.[7]

In addition to differences in the physical characteristics of flow and the vessel wall among AVF, AVG, and CVC access,[8,9] blood rheology has been implicated in VAT. Anemia is associated with increased risk of VAT; greater erythropoietin-stimulating agent (ESA) exposure is found in those with VAT; and when ESA doses have been set to deliver higher levels of hematocrit, an increase in VAT has been found. In the Normal Hematocrit Trial, the incidence of thrombosis of the vascular access sites was significantly higher in patients randomized to the normal hematocrit group.[10–12] The extremes of iron deficiency and iron overload states have been associated with prothrombotic risk.[13,14]

With these issues, VAT was a prespecified secondary safety end point in the PIVOTAL.[15,16] This presented the opportunity to evaluate whether the direct or indirect consequences of proactive and reactive i.v. iron dosing strategies may associate with overall VAT risk. We describe in detail the occurrence of VAT in patients within 12 months of initiating regular hemodialysis, who required treatment with an ESA by vascular access subtype, the variables associated with VAT, and compare the 2 randomized i.v. iron therapy arms on VAT.

METHODS

The design, baseline characteristics, and results of PIVOTAL have been published.[15,16] In brief, 2141 adults within 12 months of initiating regular hemodialysis, who had a ferritin concentration <400 μg per liter, transferrin saturation (TSAT) <30%, and treated with an ESA, were enrolled. Existing iron therapy was stopped, and participants were randomized 1:1 to either high-dose i.v. iron administered proactively or low-dose i.v. iron administered reactively, based on monthly ferritin and TSAT levels. In the high-dose group, 400 mg of iron sucrose was prescribed each month unless ferritin was >700 μg per liter or TSAT >40%. Patients in the low-dose iron group received incremental doses between 0 mg and 400 mg of iron sucrose per month, to maintain ferritin ≥200 μg per liter and TSAT ≥20%. The trial protocol required the use of an ESA in a dose sufficient to maintain hemoglobin 100 to 120 g/l, but otherwise, patients were managed according to usual care.

Baseline and Follow-Up Information Related to Vascular Access

The PIVOTAL electronic case report form had a specific question completed by local investigators about the type of vascular access in use for hemodialysis which was completed at baseline and monthly thereafter.

Clinical Outcomes

The primary outcome of PIVOTAL was the composite of the time to first occurrence of myocardial infarction, stroke, hospitalization for heart failure, or death from any cause. Study end points were classified by an Endpoint Adjudication Committee. VAT was a prespecified safety outcome, hence not adjudicated, although incidence of VAT was reviewed by the Independent Data Monitoring Committee.

Statistical Analysis

Baseline characteristics were summarized as means and SDs, medians, and lower and upper quartiles or counts and percentages as appropriate. The development of a first VAT was analyzed in relation to variables captured at baseline and in relation to variables captured on a monthly basis throughout the trial (time-varying covariates).

Baseline variables analyzed for an association with VAT included the following: age, sex, ethnicity, primary kidney disease, body mass index, weight, systolic blood pressure (BP), diastolic BP, heart rate, duration of dialysis treatment, diabetes, previous diagnosis of hypertension, atrial fibrillation, myocardial infarction, peripheral vascular disease, heart failure, stroke, smoking status, hemoglobin, ferritin, TSAT, platelet count, standardized monthly ESA dose, C-reactive protein (CRP), albumin, dialysis vascular access in use, and randomized treatment arm. The following medications prescribed at baseline were also recorded and available for analysis: angiotensin-converting enzyme inhibitors, ARB, mineralocorticoid receptor antagonists, digoxin, calcium channel blockers, beta-blockers, diuretics, anticoagulants, and antiplatelets. These were all subject to univariate tests for association with VAT, with comparisons made using χ^2 tests or 2-sample t tests as appropriate.

Time-dependent covariates available for analysis included the monthly measurements of hemoglobin, ferritin, TSAT, platelet count, albumin, and vascular access in use, including quarterly measurements of CRP.

Cox proportional hazards models were constructed to investigate predictors of VAT. Owing to the limited number of end points relative to the potential number of predictor variables, the analysis was undertaken in 3 steps.

The first step was to fit models that included only those baseline variables that associated with VAT on univariate testing, in addition to variables of interest that included age, sex, BP (systolic BP, diastolic BP,

Table 1. Baseline characteristics and univariate analyses of those who experienced a vascular access thrombotic event compared with those who did not

Variable	Vascular access thrombosis (n = 480)	No vascular access thrombosis (n = 1661)	P value
Age (yr)	63.1 (14.8)	62.7 (15.1)	0.64
Males, n (%)	289 (60.2)	1109 (66.8)	0.01
Ethnicity, n (%)			
White	379 (79.0)	1319 (79.4)	0.62
Black	48 (10.0)	142 (8.6)	
Asian	41 (8.5)	144 (8.7)	
Other	12 (2.5)	56 (3.4)	
Standardized monthly ESA dose	36,988 (23,416)	37,246 (24,657)	0.84
BMI (kg/m^2)	29.2 (7.0)	28.6 (6.9)	0.09
Weight (kg)	82.6 (21.0)	81.9 (20.9)	0.55
SBP (mm Hg)	145.9 (23.6)	144.4 (23.7)	0.21
DBP (mm Hg)	73.5 (14.2)	73.7 (14.9)	0.85
Duration of dialysis treatment (mo)	5.1 (3.0–8.5)	4.8 (2.8–8.2)	0.24
Diabetes, n (%)	249 (51.9)	701 (42.2)	<0.001
Hypertension, n (%)	368 (76.7)	1189 (71.6)	0.03
AF, n (%)	36 (7.5)	128 (7.7)	0.88
MI, n (%)	47 (9.8)	137 (8.3)	0.23
PVD, n (%)	45 (9.4)	142 (8.6)	0.57
Heart failure, n (%)	21 (4.4)	65 (3.9)	0.65
Stroke, n (%)	38 (7.9)	138 (8.3)	0.78
Vascular access, n (%)			
Nontunneled dialysis catheter	17 (3.5)	60 (3.6)	0.007
Tunneled dialysis catheter	177 (36.9)	623 (37.5)	
Arteriovenous fistula	263 (54.8)	946 (57.0)	
Arteriovenous graft	23 (4.8)	32 (1.9)	
Primary cause of kidney disease, n (%)			
Hypertension	43 (9.0)	192 (11.6)	0.001
Diabetic nephropathy	201 (41.9)	511 (30.8)	
Glomerular disease	71 (14.8)	323 (19.5)	
Tubulointerstitial disease	45 (9.4)	156 (9.4)	
Renovascular disease	33 (6.9)	114 (6.9)	
Polycystic kidney disease	20 (4.2)	97 (5.8)	
Other	27 (5.6)	102 (6.1)	
Unknown	40 (8.3)	166 (10.0)	
Smoking status, n (%)			
Current	72 (15.0)	177 (10.7)	0.02
Former	124 (25.8)	421 (25.4)	
Never	284 (59.2)	1063 (64.0)	
Hemoglobin (g/l)	105.0 (14.3)	105.7 (13.6)	0.30
Ferritin (μg/l)[a]	223.5 (128.5–305.0)	214 (124.0–303.0)	0.97
TSAT (%)[a]	20.0 (16.0–24.0)	20 (16.0–24.0)	0.26
CRP (mg/l)[a]	6.0 (3.3–13.8)	6 (3.8–14.0)	0.43
Albumin (g/l)	35.6 (5.0)	35.8 (5.2)	0.55
ACE inhibitor, n (%)	89 (18.5)	278 (16.7)	0.36
Angiotensin receptor blocker, n (%)	41 (8.5)	206 (12.4)	0.02
Diuretic, n (%)	235 (49.0)	692 (41.7)	0.004
Mineralocorticoid receptor antagonist, n (%)	6 (1.3)	27 (1.6)	0.56
Digoxin, n (%)	14 (2.9)	23 (1.4)	0.02
Anticoagulant, n (%)	122 (25.4)	368 (22.2)	0.13
Antiplatelet, n (%)	232 (48.3)	740 (44.6)	0.14
Vitamin D supplement, n (%)	317 (66.0)	1079 (65.0)	0.66
Phosphate binder, n (%)	170 (35.4)	652 (39.3)	0.13
Proactive randomized treatment, n (%)	262 (54.6)	831 (50.0)	0.08

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent; MI, myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; TSAT, transferrin saturation.
[a]Variables where median and interquartile range are presented.
For categorical variables, number and percentage are reported. For continuous variables, mean and SD are reported.

history of hypertension), the natural logarithm of CRP protein, TSAT, ferritin, albumin, platelets, hemoglobin, and randomized treatment arm.

The second step used the significant predictors from step 1 in a model that also included baseline concomitant medications. The third step used the significant baseline predictors from step 2 in a model where hemoglobin, platelet count, TSAT, ferritin, the natural logarithm of CRP protein, albumin, and vascular access status (catheter access—either nontunneled or tunneled, fistula or graft) were incorporated as time-varying covariates.

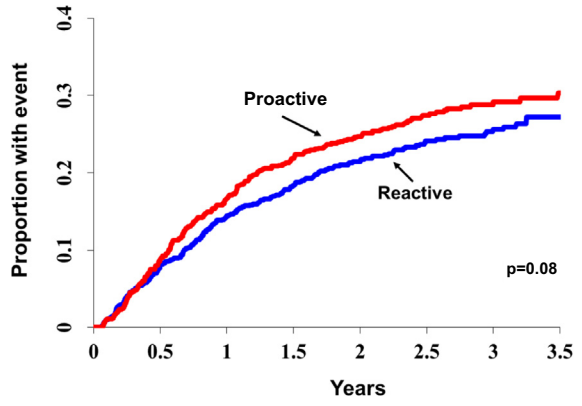
Analyses were performed using SAS software, version 9.4 (SAS Institute) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 2141 patients randomized, 1209 (56.5%) were using an AVF, 877 (41.0%) a CVC, and 55 (2.6%) an AVG at baseline. Overall, 480 patients (22.4%) experienced at least one VAT during follow-up. The number of patients experiencing at least one episode of VAT was 194 of 877 (22.1%) for those using CVC, Furthermore, it is 263 of 1209 (21.8%) for AVF and 23 of 55 (41.8%) in those using AVG.

Univariate Analysis

The baseline characteristics of those who experienced VAT, compared with those who did not, are summarized in Table 1, with the results of univariate testing for association with VAT detailed for each variable. Baseline variables significantly associated with VAT on univariate testing were female sex ($P = 0.01$), diabetes mellitus ($P < 0.001$), or hypertension ($P = 0.028$) at baseline, AVG as access for dialysis ($P = 0.01$), primary renal disease of diabetic nephropathy ($P = 0.001$), former or current smoker ($P = 0.02$), use of diuretic at baseline ($P = 0.004$), and use of digoxin at baseline ($P = 0.02$), whereas fewer VAT were found in those



Numbers at risk:

Proactive:	1093	698	445	142
Reactive:	1048	673	424	161

Figure 1. Cumulative incidence curves of vascular access thrombosis events within each of the randomized treatment arms of proactive and reactive iron dosing.

receiving an ARB at baseline ($P = 0.02$). Baseline diagnoses of atrial fibrillation, myocardial infarction, peripheral vascular disease, heart failure, and stroke were not significantly associated with VAT on univariate testing. Baseline hemoglobin, platelet count, ferritin, and TSAT were not significantly associated with VAT on univariate testing. The randomized treatment arm allocation did not significantly associate with outcome (Table 1) with 262 of 1093 (24.0%) events in patients randomized to proactive high-dose iron and 218 of 1048 (20.8%) events in patients randomized to reactive lower dose iron ($P = 0.08$). A cumulative incidence plot of events by randomized treatment arm allocation is provided in Figure 1. When considering the randomized treatment arm within baseline vascular access subgroups, univariate testing had a significant increase in VAT risk with proactive iron in the baseline AVF group (147 of 611 [24.0%] vs. 116 of 598 [19.4%], $P = 0.050$), but not in the baseline CVC group (100 of 449 [22.2%] vs. 94 of 428 [22.0%], $P = 0.912$), nor baseline AVG group (15 of 33 [45.4%] vs. 8 of 22 [36.4%], $P = 0.503$).

Multivariate Analysis

In the first multivariable model, age, systolic BP, diastolic BP, log CRP, TSAT, ferritin, albumin, platelets, hemoglobin, and randomized treatment arm were included alongside the significant univariates of sex, history of hypertension, diabetes as a cause of kidney failure, smoking status, and vascular access. In this model, diabetes as a cause of kidney failure (HR 1.49, $P < 0.001$), use of an AVG at baseline (HR 2.30, $P < 0.001$), female sex (HR 1.31, $P < 0.004$), and current smoking (HR 1.47, $P = 0.004$) were independent predictors of VAT (Table 2—model 1).

In the second multivariate model, significant variables from model 1 plus concomitant medications at baseline were analyzed. In this model, diabetes as a cause of kidney failure (HR 1.45, $P < 0.001$), AVG use (HR 2.29, $P < 0.001$), female sex (HR 1.33, $P < 0.002$), current smoking (HR 1.32, $P = 0.004$), digoxin use at baseline (HR 2.48, $P < 0.001$), and diuretic use at baseline (HR 1.25, $P < 0.001$) were independent predictors of VAT. ARB use at baseline was associated with a lower risk of VAT (HR 0.66, $P = 0.01$) (Table 2—model 2).

In the third multivariate model, significant variables from model 2 were included alongside the time-varying variables that were recorded each month in the trial, specifically hemoglobin, TSAT, ferritin, log CRP, albumin, platelet count, and dialysis access. In this model, ARB use (HR 0.66, $P = 0.01$), digoxin use (HR 2.58, $P < 0.001$), diuretic use (HR 1.27, $P = 0.01$), current smoking (HR 1.51, $P = 0.002$), diabetes as a cause of kidney failure (HR 1.44, $P < 0.001$), and female sex (HR 1.33, $P = 0.002$) were found to have independent association with VAT. Of the time-varying variables included in this model, only AVG use had independence of association with VAT (HR 3.00, $P < 0.001$). Time-updated hemoglobin level (per 10 U), TSAT (per 5 U), serum ferritin (per 50 U), serum albumin, platelet count, and Log_e CRP were not associated with risk of VAT (Table 3).

Tests of Interaction

Investigation for interaction between significant predictors of VAT and baseline vascular access type was undertaken. It was not possible to fit interactions between access type and digoxin or ARB usage due to relatively small numbers. There was no evidence of an interaction with sex or diabetes. However, there was evidence supporting an interaction between smoking and catheter use at baseline (current smoker vs. never, HR 2.1, $P = 0.0002$). The overall test for an interaction between smoking and access type however was not significant ($P = 0.15$). There was some evidence of an interaction between diuretic with AVF use at baseline (HR 1.50, $P = 0.001$) but not with the other access subgroups; the overall test of an interaction between diuretic and access type at baseline was statistically significant ($P = 0.033$).

Analysis by Baseline Vascular Access Subgroup

In the AVF at baseline subgroup, univariate testing found that those with a VAT were more likely to have diabetes (51.7% vs. 40.8%, $P = 0.002$), a history of hypertension (81.0% vs. 73.7%, $P = 0.014$), differing primary kidney disease profiles ($P = 0.010$), greater diuretic use at baseline (57.0% vs. 43.2%, $P < 0.001$),

Table 2. Multivariate modeling of baseline variables for association with vascular access thrombosis

Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1[a]				
Age (per 5 yr)	1.00 (0.96–1.03)	0.83		
Sex (male/female)	0.74 (0.61–0.89)	0.002	0.76 (0.63–0.92)	0.004
SBP (per 10 mm Hg)	0.98 (0.94–1.03)	0.46		
DBP (per 5 mm Hg)	1.01 (0.97–1.05)	0.57		
Log_e (CRP) (per 1 U)	1.01 (0.92–1.10)	0.85		
TSAT (per 5 U)	1.07 (0.99–1.16)	0.11		
Ferritin (per 20 U)	0.99 (0.97–1.01)	0.34		
Albumin (per 10 U)	0.99 (0.82–1.20)	0.92		
Platelets (per 10 U)	0.99 (0.98–1.01)	0.38		
Hemoglobin (per 10 U)	0.94 (0.88–1.01)	0.09		
Hypertension (yes/no)	1.15 (0.93–1.43)	0.20		
Diabetes as cause of kidney failure (yes/no)	1.50 (1.24–1.81)	<0.001	1.49 (1.24–1.78)	<0.001
Smoking				
Current (referent)	1.00			
Former	0.80 (0.60–1.08)	0.15	0.77 (0.58–1.03)	0.079
Never	0.70 (0.54–0.91)	0.008	0.68 (0.53–0.88)	0.004
Vascular access				
Catheter (referent)	1.00			
Fistula	0.95 (0.79–1.15)	0.60	0.96 (0.80–1.15)	0.65
Graft	2.30 (1.49–3.56)	<0.001	2.30 (1.49–3.54)	<0.001
Treatment arm (proactive/reactive)	1.13 (0.94–1.36)	0.18		
Model 2[b]				
Gender (male/female)	0.74 (0.62–0.89)	0.0018	0.75 (0.62–0.90)	0.002
Diabetes as cause of kidney failure (yes/no)	1.44 (1.19–1.74)	0.00015	1.45 (1.21–1.75)	<0.001
Smoking				
Current (referent)	1.00		1.00	
Former	0.76 (0.57–1.02)	0.067	0.76 (0.57–1.02)	0.07
Never	0.68 (0.53–0.89)	0.0041	0.68 (0.53–0.88)	0.004
Vascular access				
Catheter (referent)	1.00		1.00	
Fistula	0.95 (0.78–1.14)	0.56	0.94 (0.78–1.14)	0.55
Graft	2.37 (1.53–3.67)	0.00011	2.29 (1.49–3.54)	<0.001
Baseline meds (yes/no)				
ACE inhibitor	1.04 (0.83–1.32)	0.71		
Angiotensin receptor blocker	0.66 (0.48–0.92)	0.013	0.66 (0.48–0.91)	0.01
MRA	0.62 (0.27–1.40)	0.25		
Digoxin	2.35 (1.36–4.04)	0.0021	2.48 (1.45–4.23)	<0.001
Calcium channel blocker	1.01 (0.84–1.21)	0.91		
Beta blocker	1.13 (0.94–1.35)	0.20		
Diuretic	1.24 (1.03–1.50)	0.022	1.25 (1.04–1.50)	0.018
Anticoagulant	1.13 (0.92–1.40)	0.24		
Antiplatelet	1.01 (0.84–1.21)	0.92		

ACE, angiotensin-converting enzyme; CRP, C-reactive protein; DBP, diastolic blood pressure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; TSAT, transferrin saturation; VAT, vascular access thrombosis.
[a]Testing of baseline variables excluding medications with refitting of the model including only significant predictors.
[b]Testing of baseline medication use and variables independently associated with VAT in model 1, with refitting of the model with significant predictors.

less ARB use at baseline (7.6% vs. 13.5%, $P = 0.009$), and more likely to be randomized to the proactive i.v. iron treatment arm of the study (55.9% vs. 49.0%, $P = 0.05$). A multivariable model was constructed using all significant variables from the previous models, with the randomized treatment group (proactive/reactive). In this model, the randomized treatment group did not reach significance (HR 1.22, $P = 0.11$).

In the CVC at baseline subgroup, those with VAT were more likely to be male (56.7% vs. 65.3%, $P = 0.028$), had smoking exposure previously or at the time of study entry ($P = 0.003$), and have differing primary kidney disease profiles ($P = 0.003$).

In the AVG at baseline subgroup, those with a subsequent vascular access thrombotic event had a higher baseline serum ferritin (312 μg/l vs. 237μg/l, $P = 0.034$) and CRP (8.0 vs. 5.0, $P = 0.035$).

DISCUSSION

This *post hoc* analysis of the PIVOTAL trial found that female sex, diabetic etiology, smoking, use of an AVG,

Table 3. Multivariate analysis of time-dependent variables and risk association with vascular access thrombosis, adjusting for baseline predictors previously found to be significant

Variables	HR (95% CI)	*P* value
Baseline variables		
Angiotensin receptor blocker (yes/no)	0.66 (0.48, 0.92)	0.01
Digoxin (yes/no)	2.58 (1.50,4.41)	<0.001
Diuretic (yes/no)	1.27 (1.06–1.53)	0.01
Smoking		
Current (referent)	1.00	
Former	0.76 (0.57–1.02)	0.06
Never	0.66 (0.51–0.86)	0.002
Diabetes as cause of kidney failure (yes/no)	1.44 (1.20–1.74)	<0.001
Gender (male/female)	0.75 (0.62–0.90)	0.002
Time-varying variables		
Hemoglobin (per 10 U)	0.96 (0.89–1.03)	0.25
TSAT (per 5 U)	0.99 (0.94–1.04)	0.60
Ferritin (per 50 U)	1.00 (0.98–1.01)	0.73
Log_e (CRP)	0.97 (0.91–1.04)	0.45
Albumin (per 10 U)	1.15 (0.96–1.38)	0.13
Platelets (per 10 U)	1.00 (0.98–1.01)	0.50
Vascular access Catheter (referent)		
Fistula	0.95 (0.77–1.19)	0.72
Graft	3.00 (2.10–4.28)	<0.001

CRP, C-reactive protein; HR, hazard ratio; TSAT, transferrin saturation.

and prescription of digoxin or a diuretic at baseline were independent predictors of VAT. Use of an ARB was associated independently with lower risk of VAT. When considering factors related to anemia, the baseline and time-dependent analyses suggested no independent association with VAT for hemoglobin, platelets, ferritin, or TSAT level. Within the confines of this study design, there was no evidence to suggest that the randomized treatment arm associated with VAT, and although patients with AVFs at baseline who were randomized to the proactive dosing schedule experienced significantly more VAT on univariate testing, this association was not found on multivariate testing.

The PIVOTAL trial was conducted in patients who had started regular hemodialysis within the previous 12 months. Activity to establish arteriovenous access is especially heightened during this period, for whom there remains a high rate of primary failure through access thrombosis.[17] These findings have clinical relevance for patients during this period, and this work provides a degree of reassurance that i.v. iron dosing and associated measures of anemia did not seem to incur an increased risk of VAT on multivariate testing.

Of the risk associates identified in this study, biological plausibility may be found behind the role of diabetes, exposure to diuretic, and digoxin use as a surrogate for low cardiac output states, when considering thrombosis in a dialysis circuit reliant on blood flow at a consistent level of sufficient arterial pressure, such as that revealed with AVG and AVF. These findings are consistent with the existing literature.[18] In this analysis, however, it is notable that several traditional risk factors for cardiovascular thrombosis, such as age, coronary artery disease, peripheral vascular disease, and obesity did not have any association with VAT.[19,20] One explanation may relate to the PIVOTAL cohort starting the trial after having commenced hemodialysis, and by definition having functional dialysis access. Therefore, many in the PIVOTAL trial will have cleared the initial hurdle of primary vascular access failure before randomization. The phase of primary and or secondary assisted patency failure may largely have been avoided in this trial, where traditional vascular risk factors for thrombosis may be expected to predominate.

The finding of reduced risk of VAT in patients taking an ARB is curious and has not been found in the literature to date. This finding was not found in those taking angiotensin-converting enzyme inhibitors at baseline in this study and would merit further consideration in future studies.

When considering the risk of VAT between different types of vascular access, this is inherently limited by the degree of crossover from one access type to another that occurs as part of routine care within hemodialysis populations. This was partially mitigated in our analysis of vascular access subtype as a time-varying covariate where the monthly prevalent vascular access data were included in the analysis. When regarded as such, AVG access remained a significant independent associate with increased risk of VAT at baseline and as a time-varying covariate when compared with AVFs and CVCs—a finding that is in keeping with the published literature.[11]

When considering iron exposure and risk of VAT within the individual subgroups of AVF, AVG and CVC the most striking finding occurred in the AVF group where a significant univariate association was found with proactive i.v. iron prescription and increased risk of VAT. When we analyzed this further by multivariate analysis, using the variables independently associated with VAT in our final model, proactive i.v. iron dosing no longer reached our threshold for statistical significance. This finding adds to the literature exploring the issue of anemia management and potential impact on VAT in hemodialysis patients. Data from other randomized controlled trials have suggested that higher VAT rates may be exhibited when higher hematocrit or hemoglobin levels are targeted.[12,21] Both these studies deployed ESAs to achieve the desired target, although in the normal as compared with low hematocrit study a greater exposure to i.v. iron was also found in the normal hematocrit group. In

PIVOTAL, the weekly ESA dose was the same in those who experienced VAT as compared with those who did not. It also seems that the randomized i.v. iron strategy did not clearly associate with VAT risk. Nonetheless, the question of whether proactive i.v. iron dosing may increase the risk of VAT in the subgroup of patients using AVFs may not have been answered definitively given the inherent limitations of undertaking subanalysis and the potential for only partial mitigation for the crossover between the differing vascular access types. Any concerns about the possibility of increased VAT with proactive iron prescribing in this subgroup should be tempered by the proven benefit on cardiovascular events found with proactive i.v. iron dosing revealed by PIVOTAL.

Relatively few patients with kidney failure avoid regular hemodialysis and its inherent requirement for vascular access. Much published research on vascular access complications focuses on risk of infection[22]—it should be noted in PIVOTAL that there was no effect between iron treatment group and VA infection.[15,16,23] In PIVOTAL, VAT was regarded as an adverse event for spontaneous reporting during the trial. The threshold for defining such an event lay with the local investigator. We expect that all clinically significant vascular access thromboses were captured within the trial; however, it is possible that we did not account for partially or near-complete occlusive access thrombotic episodes that were addressed locally, for instance, by use of anticoagulants, thrombolytics, or reconfiguration of the hemodialysis prescription. Nonetheless, in PIVOTAL, 22% of trial participants were reported as having experienced at least 1 episode of VAT. The clinical implications of these events differ between the access types. What is common to this problem though is that across the hemodialysis population, VAT does seem to incur morbidity, hospitalization, and cost. Indeed, gaining a better understanding of the causes of VAT, prevention and treatment of VAT have been highlighted in the recent KDOQI vascular access guidelines.[24]

This study has provided an insight into clinically significant VAT events through the lens of a randomized controlled trial and has not revealed any clear independent association between the main laboratory indices that inform on renal anemia management. It has not revealed any clear independent association between proactive or reactive iron dosing strategies and VAT events, although the question of whether proactive i.v. iron dosing in those using AVFs is associated with VAT may not have been definitively resolved. Through this analysis, some areas have been identified, which would merit scrutiny when undertaking clinical studies of hemodialysis vascular access in the future, and only through continuing to explore this issue may methods of preventing VAT across all the vascular access types be developed.

APPENDIX

List of PIVOTAL Investigators and Committees

PIVOTAL Trial Sites and Investigators England Basildon and Thurrock Hospital, Basildon: Georgia Winnett; Bradford Teaching Hospital, Bradford: Habib Akbani; Churchill Hospital, Oxford: Christopher Winearls; City General Hospital, Stoke-on-Trent: Julie Wessels; Coventry University Hospital, Coventry: Waqar Ayub; Derriford Hospital, Plymouth: Andrew Connor; Freeman Hospital, Newcastle: Alison Brown; Gloucestershire Royal Hospital, Gloucestershire: Jim Moriarty; Guy's and St. Thomas' Hospital, London: Paramit Chowdury; Hammersmith Hospital, London: Megan Griffiths; Heartlands Hospital, Birmingham: Indranil Dasgupta; Hull Royal Infirmary, Hull: Sunil Bhandari; Kent and Canterbury Hospital, Canterbury: Timothy Doulton; King's College Hospital, London: Iain Macdougall; Leicester General Hospital, Leicester: Jonathan Barratt; Lister Hospital, Stevenage: Enric Vilar; Manchester Royal Infirmary, Manchester: Sandip Mitra; New Cross Hospital, Wolverhampton: Babu Ramakrishna, Johann Nicholas; Norfolk and Norwich Hospital, Norwich: Calum Ross; Northern General Hospital, Sheffield: Arif Khwaja; Nottingham City Hospital, Nottingham: Matt Hall; Queen Alexandra Hospital, Portsmouth: Adam Kirk; Queen Elizabeth Hospital, Birmingham: Stuart Smith, Mark Jesky, Clara Day; Royal Berkshire Hospital, Reading: Bassam Alchi; Royal Cornwall Hospital, Cornwall: Jon Stratton; Royal Devon and Exeter Hospital, Exeter: Helen Clarke; Royal Free Hospital, London: Stephen Walsh; Royal Liverpool Hospital, Liverpool: Rebecca Brown; Royal London Hospital, London: Kieran McCafferty; Royal Preston Hospital, Preston: Laurie Solomon; Royal Shrewsbury Hospital, Shrewsbury: Suresh Ramadoss, Babu Ramakrishna; Royal Sussex Hospital, Brighton: Kolitha Basanyake, Sarah Lawman; Salford Royal NHS Foundation Trust, Salford: Philip Kalra; Southend University Hospital, Southend: Gowrie Balasubramaniam; Southmead Hospital, Bristol: Albert Power; St. George's Hospital, London: Debasish Banerjee; St. Helier Hospital, Carlshalton: Pauline Swift; St. James' Hospital, Leeds: Matt Wellberry-Smith; University Hospital, Aintree: Christopher Goldsmith; Wirral University Teaching Hospital, Wirral: Thomas Ledson Wales Morriston Hospital, Swansea: Ashraf Mikhail; University Hospital, Cardiff: Ruth Benzimra Scotland Ninewells Hospital, Dundee: Samira Bell, Alison Severn; Royal Infirmary of Edinburgh, Edinburgh: John Neary; Victoria Hospital, Kirkcaldy: Arthur Doyle; Queen Elizabeth University Hospital,

Glasgow: Peter Thomson Northern Ireland Altnagelvin Hospital, Derry: Girish Shivashankar; Antrim Area Hospital, Antrim: Stephanie Bolton, Michael Quinn; Belfast City Hospital, Belfast: Peter Maxwell; Daisy Hill Hospital, Newry: John Harty 3 PIVOTAL Committees and Coordinating Groups Steering Committee Iain Macdougall (chair), Ian Ford (biostatistician), Stefan Anker, Sunil Bhandari, Kenneth Farrington, Philip Kalra, John McMurray, Charles Tomson, David Wheeler, Christopher Winearls Endpoint Adjudication Committee (University of Glasgow) John McMurray (chair), Mark Petrie (co-chair), Eugene Connolly, Pardeep Jhund, Michael MacDonald, Patrick Mark, Matthew Walters Independent Data Monitoring Committee Alan Jardine (chair), Janet Peacock (biostatistician), Chris Isles, Donal Reddan Independent Data and Biostatistical Centre, Robertson Centre for Biostatistics, University of Glasgow Ian Ford (director), Jane Aziz, Sarah Boyle, Claire Burton, Ross Clarke, Eleanor Dinnett, Neil Hillen, Sharon Kean, Claire Kerr, Heather Murray, Amanda Reid, Kirsty Wetherall, Robbie Wilson Clinical Coordinating Centre, Kings College Hospital, London Iain Macdougall (chief investigator), Claire White (clinical trial manager), Sadiq Andani (clinical trial assistant).

DISCLOSURE

PCT reports receiving personal fees from W.L. Gore & Associates outside the submitted work. PBM reports receiving personal fees and nonfinancial support from Vifor, Pharmacosmos, and Napp; personal fees from AstraZeneca, Astellas, Novartis, and Janssen; and grants from Boehringer Ingelheim, outside the submitted work. PSJ reports receiving speaker and advisory board fees from AstraZeneca and Novartis and advisory board fees and grants from Boehringer Ingelheim. SA reports receiving grants and personal fees from Vifor Int and Abbott Vascular; and personal fees from Bayer, Boehringer Ingelheim, Novartis, Servier, Impulse Dynamics, and SJM, outside the submitted work. SB reports receiving personal fees from Pharmacosmos and Vifor Pharma. DCW has an ongoing consultancy contract with AstraZeneca and has received honoraria from Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Mundipharma, Napp, Tricida, and Vifor Fresenius. CW is an employee of Pfizer. PAK reports receiving grants and personal fees from Vifor during the conduct of the study; grants and personal fees from Vifor and Astellas; personal fees from Pharmacosmos, Bayer, MundiPharma, Napp, AstraZeneca, Boehringer Ingelheim, and Novonordisk, outside the submitted work; and grants from BergenBio. JJVM's employer the University of Glasgow has been remunerated by AstraZeneca, Cardiorentis, Amgen, Oxford University/Bayer, Theracos, AbbVie, Novartis, GlaxoSmithKline, Vifor-Fresenius, Kidney Research UK, Novartis, Bayer, DalCor, Pfizer, Merck, and Bristol Myers Squibb. ICM reports receiving personal fees from Vifor Pharma and GlaxoSmithKline. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

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