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Stroke in Hemodialysis Patients Randomized to Different Intravenous Iron Strategies: A Prespecified Analysis from the PIVOTAL Trial

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Key Points

- In analysis of the PIVOTAL trial, proactive intravenous iron dosing was not associated with increased stroke risk in patients on hemodialysis.
- Risk factors for stroke included diabetes, prior stroke, higher BP, lower serum albumin, inflammation, and women.
- Mortality of stroke was high; 58% of patients with a stroke event died during follow-up compared with 23% without a stroke.

Abstract

Background

People with kidney failure treated with hemodialysis (HD) are at increased risk of stroke compared with similarly aged people with normal kidney function. One concern is that treatment of renal anemia might increase stroke risk. We studied risk factors for stroke in a prespecified secondary analysis of a randomized, controlled trial of intravenous iron treatment strategies in HD.

Methods

We analyzed data from the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial, focusing on variables associated with risk of stroke. The trial randomized 2141 adults who had started HD <12 months earlier and who were receiving an erythropoiesis-stimulating agent (ESA) to high-dose IV iron administered proactively or low-dose IV iron administered reactively in a 1:1 ratio. Possible stroke events were independently adjudicated. We performed analyses to identify variables associated with stroke during follow-up and assessed survival following stroke.

Results

During a median 2.1 years of follow-up, 69 (3.2%) patients experienced a first postrandomization stroke. Fifty-seven (82.6%) were ischemic strokes, and 12 (17.4%) were hemorrhagic strokes. There were 34 postrandomization strokes in the proactive arm and 35 postrandomization strokes in the reactive arm (hazard ratio, 0.90; 95% confidence interval, 0.56 to 1.44; $P=0.66$). In multivariable models, women, diabetes, history of prior stroke at baseline, higher baseline systolic BP, lower serum albumin, and higher C-reactive protein were independently associated with stroke events during follow-up. Hemoglobin, total iron, and ESA dose were not associated with risk of stroke. Fifty-eight percent of patients with a stroke event died during follow-up compared with 23% without a stroke.

Conclusions

In patients on HD, stroke risk is broadly associated with risk factors previously described to increase cardiovascular risk in this population. Proactive intravenous iron does not increase stroke risk.

Clinical Trial registry name and registration number: Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL), 2013-002267-25

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Introduction

The estimated increased risk of stroke in patients treated with hemodialysis (HD) is approximately two to ten times higher than the risk of otherwise similarly age-matched patients from the general population, with greatest excess risk in younger people (1–4). The prevalence of "conventional" risk factors associated with increased stroke risk, such as hypertension, diabetes, older age, prior cardiovascular disease, and atrial fibrillation (AF), is high in patients treated with HD (5). Other factors specific to HD treatment, such as variation in BP and altered cerebral blood flow during dialysis, may increase stroke risk (6).

Several randomized, controlled trials (RCTs) have assessed the effect of correction of anemia with erythropoiesis-stimulating agents (ESAs) on both surrogate parameters, such as left ventricular hypertrophy, and clinical outcomes, such as cardiovascular events or need for dialysis, in patients with CKD or heart failure (7–10). The overall effect of anemia correction on stroke risk in subjects with CKD has been variable, with some trials demonstrating no excess stroke risk in the ESA treatment or higher hemoglobin group (8,9,11). However, in two of the largest placebo-controlled RCTs of anemia correction in patients with CKD with the ESA darbepoetin (7,12,13), stroke risk was elevated in the group randomized to darbepoetin to target a higher hemoglobin. This observation was statistically significant in the TREAT trial in patients with diabetes and CKD and in the subgroup of patients with CKD in the RED-HF trial, suggesting that anemia correction with ESA is associated with increased risk of stroke in patients at high vascular risk with CKD irrespective of other risk factors for stroke (7,13). However, the effect of anemia correction using high iron dosing strategies (to minimize ESA use) on future stroke risk in patients treated with HD is unknown.

The Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial was an RCT of proactive versus reactive intravenous iron therapy in patients requiring HD already treated with an ESA. The methods, the baseline characteristics of the participants (14), and the main trial results (15) have been reported elsewhere. Briefly, a high-dose proactive intravenous iron regimen resulted in lower doses of ESA being administered when compared with a low-dose iron regimen, with fewer cardiovascular events occurring in the proactive arm of the trial. In this prespecified analysis, we analyzed which factors were associated with risk of stroke. We hypothesized that proactive high-dose iron would not be associated with increased stroke risk compared with reactive low-dose iron.

Materials and Methods

The design, baseline characteristics (11), and main results of PIVOTAL have been published (14,15). In summary, 2141 adults who had started HD within the previous year, who had a ferritin concentration <400 μg/L and a transferrin saturation <30%, and who were receiving an ESA were enrolled. The PIVOTAL trial was conducted in compliance with the principles of the Declaration of Helsinki (1996). The study protocol was approved by the South East Coast–Brighton and Sussex Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency. All patients provided written informed consent.

Patients were randomized 1:1 to receive high-dose intravenous iron administered proactively or low-dose intravenous iron administered reactively. Ferritin concentration and transferrin saturation were measured monthly, and the results were used to determine the monthly dose of iron sucrose. In the high-dose group, 400 mg of iron sucrose was prescribed, with safety cutoff limits (ferritin >700 μg/L or transferrin saturation >40%) above which further iron was withheld until the next blood test 1 month later. Patients in the low-dose group received 0–400 mg of iron sucrose monthly to maintain ferritin ≥200 μg/L and transferrin saturation ≥20%, in line with current guidelines. The protocol required the use of an ESA in a dose sufficient to maintain hemoglobin between 100 and 120 g/L, but otherwise, patients were treated according to usual practice. BP was taken by the dialysis unit nursing staff at the dialysis unit and recorded. Investigators were asked to report cardiovascular comorbidities at baseline on an electronic patient report form.

Clinical Outcomes

The primary outcome of the trial was the composite of myocardial infarction, stroke, hospitalization for heart failure, or death from any cause analyzed as time to first event. Stroke was a prespecified secondary outcome. For this manuscript, the outcomes of time to first stroke are reported. We also analyzed recurrent stroke events to account for the cumulative burden of events over time. Finally, we examined mortality related to (initially) nonfatal stroke.

Adjudication of Stroke Events and Outcomes

All potential end points and all deaths were adjudicated by an independent committee, blinded to treatment allocation. Stroke was defined as an acute episode of neurologic dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury. Full details of the adjudication criteria for stroke are listed in Supplemental Material.

Statistical Analyses

The time to first event analyses were performed in the intention-to-treat population using Cox proportional hazards regression. All analyses by treatment group allocation were adjusted for the stratification variables of vascular access, diabetes, and time on dialysis. The strategy adopted was to fit a multivariable Cox regression model for the time to first event of fatal or nonfatal stroke, fitting only potential baseline risk factors omitting laboratory variables. From this model, we identified the four factors (diabetes, systolic BP [SBP], sex, and history of stroke) that had evidence of association with outcome ($P=0.05$). The four baseline nonlaboratory risk factors were carried forward for inclusion in models with laboratory variables [$\log_e$(C-reactive protein [CRP]), albumin, and hemoglobin] and ESA dose. A further model was fitted with the subset of variables showing evidence of association with outcome ($P=0.05$).

The Kaplan–Meier method was used to estimate mortality rates and cumulative incidence functions for stroke as a time to first event, correcting for the competing risk of deaths not included in the outcome of interest. Deaths

following a stroke are analyzed descriptively. Recurrent events were analyzed using the proportional means model of Lin *et al.* (16). Baseline characteristics were summary counts and percentages. *P* values for between-group differences on the basis of chi-squared tests/Fisher exact tests, as appropriate, are provided. Analyses were performed using SAS software version 9.4 (SAS Institute) and R version 3.6.0.

Results

Baseline Characteristics of Patients Experiencing Stroke

The PIVOTAL trial randomized 2141 patients, of which 1093 patients were allocated to the proactive high-dose group and 1048 were allocated to the reactive low-dose group. The main trial results have been presented elsewhere. To summarize, 320 (29.3%) patients in the high-dose group had a primary end point event compared with 338 (32.3%) patients in the low-dose group (hazard ratio, 0.85; 95% confidence interval [95% CI], 0.73 to 1.00; $P<0.001$ for noninferiority; $P=0.04$ for superiority) (15). During a median 2.1 years of follow-up, 69 (3.2%) patients experienced a first stroke postrandomization. Of these, 57 (82.6%) were ischemic strokes, and 12 (17.4%) were hemorrhagic strokes. Baseline characteristics of patients experiencing stroke and those who did not are shown in Table 1. The prevalence of diabetes and prior stroke was higher in those who had a stroke during follow-up. The prevalence of atrial fibrillation was not higher in those who had a stroke. Age, body mass index, SBP, and CRP at baseline were greater, whereas baseline albumin and hemoglobin were lower in those who had a stroke compared within those who did not. Supplemental Table 1 notes the day of the week when the baseline BP was recorded.

Effect of Treatment Group on Stroke Incidence

There were 34 first strokes in the proactive arm and 35 first strokes in the reactive arm (hazard ratio, 0.90; 95% CI, 0.56 to 1.44; $P=0.66$) (Figure 1). In a recurrent event analysis considering the ten patients with two stroke events and one patient with three stroke events (total of 46 stroke events) in the proactive arm and the ten patients with two stroke events and two patients with three stroke events (total of 49 stroke events) in the reactive arm, there was no significant difference in stroke incidence between treatment groups (rate ratio, 0.88; 95% CI, 0.53 to 1.45; $P=0.61$) (Table 2).

Factors Associated with Risk of Stroke during the PIVOTAL Trial

In a multivariable Cox regression model analyzing the whole cohort for the time to first fatal or nonfatal stroke fitting only potential baseline risk factors, diabetes, SBP, women, and history of prior stroke were associated with stroke during follow-up (Table 3). In a further analysis including baseline laboratory variables and baseline ESA dose at the start of the trial, diabetes, SBP, women, and history of prior stroke, low serum albumin and elevated $\log_e$CRP were independent predictors of stroke (Supplemental Table 2).

In a multivariable analysis taking account of baseline risk factors with albumin, $\log_e$CRP, and hemoglobin prior to the stroke and the mean iron dose and ESA dose over the duration of the trial as time-dependent variables, the variables associated with stroke were SBP, diabetes, prior stroke, women, low serum albumin, and elevated $\log_e$CRP (Table 4).

Outcomes following Stroke

A total of 40 (58%) patients who had a stroke postrandomization subsequently died during follow-up. This compares with 475 deaths (23%) in the remaining 2072 patients who did not have a stroke. Of the 40 patients with a first stroke, three of the first strokes were fatal, and one patient died on the same day as the stroke, with cause of death given as infection. Of the remaining 36 deaths, 14 were nonstroke deaths (none within 7 days of the stroke and one within 30 days), and 22 were stroke deaths (five within 7 days of the stroke and 12 within 30 days). The Kaplan–Meier time to event curve for time to death after a stroke is given in Supplemental Figure 1.

Discussion

In the PIVOTAL trial, first stroke events occurred in 69 patients (3.2% of the entire cohort) compared with 180 fatal or nonfatal myocardial infarction events (8.4%) and 121 (5.7%) hospitalizations for heart failure (15). In this large RCT of two different strategies for iron replacement in patients on HD requiring an ESA as treatment for renal anemia, the major independent baseline risk factors for stroke were women, history of diabetes mellitus or prior stroke, and baseline higher SBP. On laboratory testing, inflammation (indicated by elevated CRP) and malnutrition (indicated by low serum albumin) were associated with increased stroke risk. Therefore, in keeping with previous observational data in this population, the major risk factors for stroke in PIVOTAL were conventional risk factors for stroke observed in the general population (17,18). Inflammation and malnutrition have been associated with stroke and reduced survival in several observational studies in patients with CKD (19–21). At baseline, patients who had a postrandomization stroke had lower hemoglobin than those who did not, although this observation was not statistically significant on time to event analyses (Table 4, Supplemental Table 2). We found no association between iron treatment allocation, hemoglobin level, total intravenous iron dose, or ESA dose and stroke risk. This is irrespective of hemoglobin rising faster initially (Supplemental Material) in the proactive treatment arm and patients in the proactive group being significantly less likely to receive blood transfusions, presumably because of the initially higher hemoglobin level over the first 12 months of the trial (15). Some observational registry data support the observation that lower hemoglobin is associated with increased risk of stroke in HD, but this has not been a consistent observation (1,22,23).

Other RCTs have reported the effect of anemia treatment regimens using ESAs in patients with CKD and/or those requiring dialysis. In an RCT in patients on incident HD, like those studied in PIVOTAL, "full" correction of anemia with epoetin alfa to a hemoglobin target of 135–145 g/L compared with a target of 95–115 g/L was associated with a significantly higher incidence of stroke (4% versus 1%;

Table 1. Baseline characteristics of patients experiencing stroke and those who did not

Statistic	(1) No Stroke		(2) Stroke		*P* Value (1) versus (2)	(3) Ischemic		(4) Hemorrhagic		*P* Value (3) versus (4)
	Count/ Mean/ Median	%/SD/ (Lower Quartile, Upper Quartile)	Count/ Mean/ Median	%/SD/ (Lower Quartile, Upper Quartile)		Count/ Mean/ Median	%/SD/ (Lower Quartile, Upper Quartile)	Count/ Mean/ Median	%/SD/ (Lower Quartile, Upper Quartile)	
n	2072		69			57		12		
Randomized to proactive	1059	51.1	34	49.28	0.76	30	52.6	4	33.3	0.22
Sex, % men	1366	65.9	32	46.4	0.001	24	42.1	8	66.6	0.12
Ethnicity, % White	1641	79.2	57	82.61	0.49	48	84.2	9	75.0	0.44
Age, yr	62.7	±15.1	65.7	±13.4	0.07	61.2	±14.2	66.6	±13.2	0.24
SBP, mm Hg	144.3	±23.5	156.1	±25.7	<0.001	152.0	±15.0	157.0	±27.4	0.38
DBP, mm Hg	73.6	±14.8	74.4	±16.1	0.68	76.3	±18.5	74.0	±15.7	0.71
BMI, kg/m^2	28.7	±6.9	30.8	±7.9	0.03	28.2	±5.7	31.3	±8.3	0.12
Dialysis duration, mo	5.8	3.7	5.0	3.5	0.09	5.2	3.9	5.0	3.4	0.86
Smoking, %										
Current	240	11.6	9	13.0	0.53	6	10.5	3	25.0	0.33
Former	524	25.3	21	25.5		17	29.8	4	33.3	
Never	1308	63.1	39	62.9		34	59.7	5	41.7	
Diabetes, %	904	43.6	46	66.7	<0.001	38	66.7	8	66.7	>0.99
Stroke baseline, %	165	8.0	11	15.9	0.02	10	17.5	1	8.3	0.43
Myocardial infarction, %	175	8.5	9	13.0	0.18	8	14.0	1	8.3	0.59
Heart failure, %	84	4.1	2	2.9	0.63	1	1.7	1	8.3	na
Atrial fibrillation, %	160	7.7	4	5.8	0.55	3	5.3	1	8.3	na
PVD, %	182	8.8	5	7.3	0.66	4	7.0	1	8.3	na
AV fistula/graft, %	1222	59.0	35	50.7	0.17	32	56.1	3	25.0	0.05
Primary kidney disease					0.02					na
Hypertension, %	228	11.0	7	10.1		5	8.8	2	16.7	
Diabetic nephropathy, %	677	32.7	35	50.7		28	49.1	7	58.3	
Glomerular disease, %	386	18.6	8	11.6		7	12.3	1	8.3	
Tubulointerstitial disease, %	198	9.6	3	4.4		2	3.5	1	8.3	
Renovascular disease, %	139	6.7	8	11.6		8	14.0	0	0	
Polycystic kidney disease, %	117	5.7	0	0		0	0	0	0	
Other, %	126	6.1	3	4.4		2	3.5	1	8.3	
Unknown, %	201	9.7	5	7.3		5	8.8	0	0	
Hemoglobin, g/L	105.7	±13.7	100.9	±12.8	0.003	103.3	±13.6	100.4	±12.7	0.52
Albumin, g/L	35.8	±5.1	33.3	±5.3	<0.001	32.9	±5.4	35.3	±4.7	0.13
log$_e$CRP, mg/L	1.86	±1.08	2.30	±0.98	0.001	2.08	±0.91	2.34	±1.00	0.40
ESA dose, IU/wk	8589	5636	8561	5500	0.97	4917	2314	9328	5678	<0.001
Mean IV iron dose/mo, mg	183	125,257	180	132,232	0.56	133	181,235	171	110,221	0.72

Values are numbers and percentages, means±SD, and medians and interquartile ranges as appropriate. Tests of significance are the *t*, the Mann–Whitney *U*, the chi-squared, and the Fisher exact tests as appropriate. SBP, systolic BP; DBP, diastolic BP; BMI, body mass index; na, not applicable; PVD, peripheral vascular disease; AV, arteriovenous; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; IU, international units; IV, intravenous.

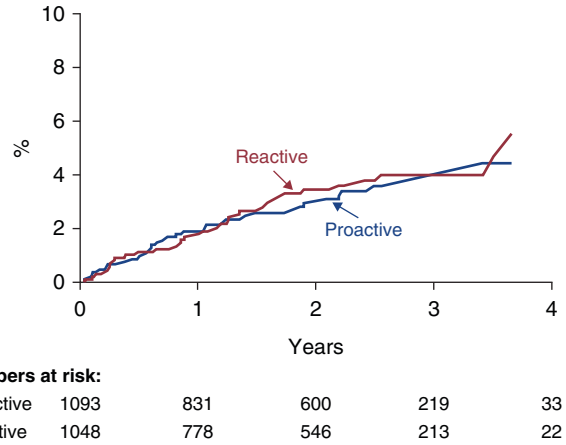

Figure 1. | Cumulative incidence of stroke in the proactive (blue) and reactive (red) treatment groups accounting for the competing risk of nonstroke deaths. Between-group hazard ratio, 0.90; 95% confidence interval, 0.56 to 1.44; $P=0.66$.

$P=0.05$) over 94 weeks of follow-up (24). Both in the placebo-controlled TREAT trial of 4038 patients with diabetes and GFR of 20–60 ml/min per 1.73 m^2 randomized to darbepoetin to achieve a hemoglobin of 130g/L or placebo and in the subgroup of 816 patients with diabetes and CKD in the RED-HF trial in patients with systolic heart failure using a similar placebo-controlled intervention, the higher hemoglobin arm was associated with a significantly higher stroke risk (hazard ratio for stroke in the darbepoetin group in TREAT, 1.9; 95% CI, 1.4 to 2.7; hazard ratio for stroke in patients with CKD in RED-HF, 2.07; 95% CI, 0.98 to 4.38) (7,13). However, in all subjects in the TREAT trial irrespective of treatment allocation, the stroke risk was significantly increased with a lower hemoglobin (7,25). By comparison, stroke risk was not significantly greater in the higher hemoglobin arm of the Normal Hematocrit study in HD or the CHOIR and CREATE studies in patients with nondialysis CKD, all of which used ESAs to target a higher hemoglobin but with no placebo in the "control" group (8,9,11).

In summary, our results provide further reassurance to the headline data of the main findings of PIVOTAL that proactive iron had a neutral effect on stroke events in addition to being overall superior to a low-dose iron regime for cardiovascular outcomes and lower ESA requirements (15). We did not see a relationship between ESA dosing in PIVOTAL and risk of stroke. Cumulatively, our results, combined with these other data from RCTs, demonstrate that overall a low hemoglobin is associated with higher stroke risk in patients with CKD and/or those requiring dialysis.

Survival after stroke for the patients on dialysis in PIVOTAL was poor, and 23 subjects (33.3% of patients with a stroke) had a recurrent stroke event. This is consistent with findings of other studies (26–28). The overall number of patients with a stroke was too small to explore factors that contributed to the poor outcomes of these patients. We did not collect data on specific therapies offered to patients in the trial who had a stroke. Other observational studies suggest that patients requiring dialysis have high functional dependence prior to stroke, and hence, poor outcomes may be inevitable (26,29). Perhaps these patients are less likely to receive interventions that may improve outcomes, such as thrombolysis, acute stroke unit care, antiplatelet therapy, and associated rehabilitation therapies (26,30). There is a limited evidence base for treatment of stroke in patients requiring dialysis, with no data from RCTs specific to those on dialysis (5,31). Reduction in kidney function has been demonstrated to be associated with poor outcomes following stroke. In the *post hoc* analyses of the Enhanced Control of Hypertension and Thrombolysis Stroke study comparing two thrombolysis regimes, every 10–ml/min per 1.73 m^2 lower eGFR was associated with an adjusted 9% increased odds of death following acute ischemic stroke (32). Current thrombolysis guidelines suggest that patients with advanced CKD, including those on dialysis, receive thrombolysis, with no specific restrictions compared with those with normal kidney function (33). Combined National Stroke and Renal Registry data from Scotland show that people treated with dialysis are less likely to be managed in an acute stroke unit following a stroke than the wider stroke population (67.4% versus 79.6%; $P<0.001$). Survival after stroke in the same report was significantly shorter in those on dialysis (median survival was 0.8 years on dialysis compared with 3.1 years in the non-ESKD stroke population; $P<0.001$) (26). The adverse outcomes following stroke in PIVOTAL emphasize the need to identify if poor outcomes are driven by inequalities of care offered (26) or an absence of evidence-based therapies for acute stroke in this population (5,26,31).

There are several limitations to this analysis and further remaining questions regarding anemia management in patients on dialysis that have not been addressed by the

Table 2. Incidence of stroke events, including both first stroke and recurrent fatal and nonfatal stroke events

Variable	All, $n=2141$	Proactive, $n=1093$	Reactive, $n=1048$
Events per patient			
Patients with 0 events	2072 (96.78%)	1059 (96.89%)	1013 (96.66%)
Patients with only 1 event	46 (2.15%)	23 (2.10%)	23 (2.19%)
Patients with 2 events	20 (0.93%)	10 (0.91%)	10 (0.95%)
Patients with 3 events	3 (0.14%)	1 (0.09%)	2 (0.19%)
Total patients with at least 1 stroke	69	34	35
Patients with at least 1 stroke per 100 person-yr	1.62	1.54	1.70
Total (first and recurrent) strokes	95	46	49
Total no. of strokes per 100 person-yr	2.22	2.08	2.38

Table 3. Baseline clinical variables associated with stroke events during the trial in univariable (left) and multivariable models (right)

Variable	Hazard Ratio (95% Confidence Interval)	*P* Value	Hazard Ratio (95% Confidence Interval)	*P* Value
Sex, women/men	2.11 (1.31 to 3.40)	0.002	2.15 (1.34 to 3.45)	0.002
Diabetes, yes/no	2.09 (1.26 to 3.47)	0.004	2.08 (1.25 to 3.45)	0.005
Stroke, yes/no	1.98 (1.03 to 3.78)	0.04	2.02 (1.06 to 3.85)	0.03
SBP, per 10 mm Hg	1.18 (1.07 to 1.30)	0.001	1.18 (1.07 to 1.30)	<0.001
Dialysis vintage duration, per mo	0.87 (0.54 to 1.41)	0.58		
Age, per 5 yr	1.08 (0.98 to 1.19)	0.10		
AF, yes/no	0.78 (0.28 to 2.18)	0.63		
Vascular access, graft/fistula/catheter	0.78 (0.48 to 1.25)	0.30		
Treatment, proactive/reactive	0.89 (0.48 to 1.44)	0.64		

SBP, systolic BP; AF, atrial fibrillation.

PIVOTAL trial. Despite performing an RCT in over 2000 patients, we observed a small number of strokes, although the stroke incidence was similar to other cohort studies (34,35). This limits the number of variables that could be tested in multivariable analyses. The PIVOTAL trial was not designed to detect differences in stroke outcomes between groups. Although stroke incidence is relatively high in patients treated with dialysis, an RCT specifically targeting stroke as an efficacy end point would be challenging. Despite 164 (7.6%) patients having AF at baseline, we captured only four strokes in these patients and cannot comment further on AF as a risk factor for stroke in HD. The prevalence of AF was lower than reported in other HD cohorts (10%–20%) (27,36,37). As the trial was performed in patients during their first year of HD, the results may not be extrapolated to patients with a longer dialysis history. Longer-term safety data on the effect of proactive iron on iron overload are required. The incidence of stroke at 2.22/100 patient-years is similar to some reports (34) but half that in other observational studies in longer-term patients on HD (2,38). Stroke risk rises over the first 90 days after HD commencement and then falls over the next year prior to rising again, so interpreting stroke risk over the first year after commencing HD is challenging (39). The intravenous iron used in PIVOTAL was iron sucrose. It is unknown if similar results would be replicated for a proactive iron dosing strategy if an alternative intravenous iron preparation was used. Less than 10% of participants were of Black ethnicity, making it challenging to extrapolate the results directly to all ethnic groups. This is important given the high incidence of stroke observed in patients on dialysis of Black or Hispanic ethnicity in the United States (38). We only collected baseline BP and do not have pre- and post-dialysis BP. Cerebral perfusion drops during dialysis, which may increase risk of stroke (6).

In conclusion, in an RCT performed in a population at high risk of vascular events, we observed no association between high-dose iron and stroke risk, despite a relatively sharper initial rise in hemoglobin in the proactive iron group (15). This contrasts with the association with higher hemoglobin and vascular risk seen in the placebo-controlled anemia correction RCTs in CKD using ESA to drive a higher hemoglobin (7,13). These observations should provide further reassurance to support the use of a

Table 4. Association between baseline clinical variables, laboratory data, and postrandomization stroke events in univariable (left) and multivariable models (right)

Variable	Hazard Ratio (95% Confidence Interval)	*P* Value	Hazard Ratio (95% Confidence Interval)	*P* Value
Sex, women/men	2.14 (1.33 to 3.45)	0.002	2.15 (1.34 to 3.47)	0.002
Stroke, yes/no	1.98 (1.03 to 3.76)	0.04	1.98 (1.04 to 3.78)	0.04
Diabetes, yes/no	1.96 (1.18 to 3.26)	0.01	1.96 (1.18 to 3.26)	0.009
Log_eCRP,[a] per 1 unit	1.40 (1.13 to 1.73)	0.001	1.42 (1.15 to 1.75)	0.001
SBP, per 10 mm Hg	1.19 (1.08 to 1.31)	0.001	1.18 (1.08 to 1.31)	0.001
Albumin,[a] per 10 units	0.62 (0.40 to 0.95)	0.03	0.59 (0.38 to 0.89)	0.01
Hemoglobin,[a] per 10 units	0.92 (0.77 to 1.10)	0.35		
ESA,[b] per 100 units	1.00 (1.00 to 1.00)	0.98		
IV iron dose,[b] per 100 units	0.97 (0.81 to 1.15)	0.71		

CRP, C-reactive protein; SBP, systolic BP; ESA, erythropoiesis-stimulating agent; IV, intravenous.
[a]Hemoglobin, ESA, and IV iron dose used for this analysis are time-varying variables on the basis of the most recent previous level over the postrandomization values for each variable during the trial.
[b]Hemoglobin, ESA, and IV iron dose used for this analysis are time-varying variables on the basis of the mean of previous levels over the postrandomization values for each variable during the trial.

proactive iron treatment regimen in renal anemia in patients on HD requiring ESA therapy.

Disclosures

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Author Contributions

I.C. Macdougall conceptualized the study; all authors were responsible for investigation; all authors were responsible for formal analysis; all authors were responsible for methodology; I. Ford and M. Robertson were responsible for project administration; I.C. Macdougall provided supervision; P.B. Mark wrote the original draft; and all authors reviewed and edited the manuscript.

Supplemental Material

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Supplemental Material. Adjudication of stroke events and outcomes.

Supplemental Figure 1. Cumulative mortality following a first stroke event.

Supplemental Table 1. (a) Table of mean (SD) for baseline SBP by day of the week with *P* value from ANOVA and (b) by days of the week grouped to take account of dialysis shift (*i.e.*, Monday/Tuesday as typically following the "long gap" between dialysis sessions) with *P* value from ANOVA.

Supplemental Table 2. Association between baseline clinical variables, laboratory data and post randomization stroke events in univariable (left) and multivariable models. In comparison with Table 4, hemoglobin here is the baseline value at randomization, with ESA dose similarly the dose at the time of randomization.

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