Stroke in hemodialysis patients randomized to different intravenous iron strategies: a prespecified analysis from the PIVOTAL trial

Running title: Stroke in the PIVOTAL trial

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Word count: Main text 2995

Abstract: 286

KEY POINTS

- In a prespecified analysis of the PIVOTAL randomized control trial, proactive intravenous iron dosing was not associated with increased stroke risk in patients requiring hemodialysis
- Risk factors for stroke during the trial were consistent with known risk factors for vascular events in this patient group including diabetes, history of prior stroke, higher baseline systolic blood pressure, lower serum albumin, higher C-reactive protein as well as female gender

ABSTRACT

Background People with kidney failure treated with hemodialysis (HD) are at increased risk of stroke compared to 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 **P**roactive **IV** Ir**O**n **T**herapy in Haemodi**AL**ysis Patients (PIVOTAL) trial focusing on variables associated with risk of stroke. The trial randomized 2,141 adults, who had started hemodialysis <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 follow-up, 69 (3.2%) patients experienced a first post randomization stroke. 57 (82.6%) were ischemic strokes and 12 (17.4%) hemorrhagic strokes. There were 34 post randomization strokes in the proactive arm and 35 in the reactive arm (hazard ratio (95% confidence interval): 0.90 (0.56, 1.44), p=0.66). In multivariable models, female gender, diabetes, history of prior stroke at baseline, higher baseline systolic blood pressure, lower serum albumin and higher C-reactive protein were independently associated with stroke events during follow up. Hemoglobin, total iron or ESA dose were not associated with risk of stroke. 58% of patients with a stroke event died during follow-up, compared to 23% without a stroke.

Conclusions In hemodialysis patients, 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.

INTRODUCTION

The estimated increased risk of stroke in patients treated with hemodialysis (HD) is approximately two to ten times higher than that 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 is high in patients treated with HD[5]. Other factors specific to HD treatment such as variation in blood pressure 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 (ESA) on both surrogate parameters, such as left ventricular hypertrophy, and clinical outcomes such as cardiovascular events or need for dialysis in patients in patients with chronic kidney disease (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 and 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 PIVOTAL trial was a RCT of proactive versus reactive intravenous iron therapy in patients requiring HD already treated with an ESA. The methods, baseline characteristics of the participants[14] and main trial results[15] have been reported elsewhere. Briefly, a high-dose proactive intravenous iron regimen resulted in lower doses of erythropoiesis-stimulating agent being administered when compared with a low-dose iron regimen, with fewer cardiovascular events occurring in the proactive arm of the trial. In this pre-specified 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 to reactive low-dose iron.

MATERIALS AND METHODS

The design, baseline characteristics[11] and main results of PIVOTAL are published[14, 15]. In summary, 2141 adults who had started HD within the previous year, who had a ferritin concentration <400 µg per liter and a transferrin saturation <30%, and who were receiving an ESA were enrolled. The PIVOTAL trial was being 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 and registered at EU Clinical Trials register (EudraCT Number: 2013-002267-25). All patients provided written informed consent.

Patients were randomized 1:1 to receive high-dose IV iron administered proactively or low-dose IV iron administered reactively. Ferritin concentration and transferrin saturation were measured monthly, and the results used to determine the monthly dose of iron sucrose. In the high-dose group, 400 mg of iron sucrose was prescribed, with safety cut-off limits (ferritin >700 µg per liter or transferrin saturation

>40%) above which further iron was withheld until the next blood test one month later. Patients in the low-dose group received 0 mg to 400 mg of iron sucrose monthly to maintain ferritin ≥200 µg per liter 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 per liter, but otherwise patients were treated according to usual practice. Blood pressure was recorded at the dialysis unit taken by the dialysis unit nursing staff. Investigators were asked to report cardiovascular comorbidities at baseline on an electronic case-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 pre-specified 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) non-fatal stroke.

Adjudication of stroke events and outcomes:

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

Statistical analysis: 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 non-fatal stroke, fitting only potential baseline risk factors omitting laboratory variables. From this model we identified the four factors (diabetes, SBP, gender and history of stroke) that had evidence of association with outcome ($p<0.05$). The four baseline non-lab risk factors were carried forward for inclusion in models with lab variables (loge (CRP), albumin, Hb) and ESA dose. A further model was fitted with the subset of variable 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 based on chi-squared tests/Fishers 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 to the reactive low-dose group. The main trial results have been presented elsewhere – to summarize, 320 patients (29.3%) in the high-dose group had a primary end-point event, compared with 338 (32.3%) in the low-dose group (hazard ratio, 0.85; 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 post randomization. Of these, 57 (82.6%) were ischemic strokes and 12 (17.4%) 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, BMI, and systolic blood pressure (SBP), and C-reactive protein (CRP) at baseline were greater, whilst baseline albumin and hemoglobin were lower in those that had a stroke compared to those who did not. Supplementary Table 1 notes the day of the week when the baseline blood pressure was recorded.

Effect of treatment group on stroke incidence

There were 34 first strokes in the proactive arm and 35 in the reactive arm (hazard ratio (95% confidence interval): 0.90 (0.56, 1.44), p=0.66), Figure 1. In a recurrent event analysis considering the 10 patients with two stroke events and 1 patient with three stroke events (total 46 stroke events) in the in the proactive arm and the 10 patients with two stroke events and 2 patients with three stroke events (total 49 events) in the reactive arm, there was no significant difference in stroke incidence

between treatment groups (rate ratio (95% confidence interval): 0.88 (0.53, 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 non-fatal stroke, fitting only potential baseline risk factors, diabetes, SBP, female gender 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, female gender and history of prior stroke, low serum albumin and elevated $\log_e$CRP were independent predictors of stroke (Supplementary Table 2).

In a multivariable analysis taking account of baseline risk factors, with albumin, $\log_e$CRP, 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, female gender, low serum albumin and elevated $\log_e$CRP (Table 4).

Outcomes following stroke

A total of 40 patients (58%) who had a stroke post randomization subsequently died during follow up. This compares to 475 deaths (23%) in the remaining 2072 patients who did not have a stroke. Of the 40 patients with a first stroke, 3 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 non-stroke deaths (none within 7 days of the stroke and 1 within 30 days) and 22 were stroke deaths (5 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 Supplementary Figure 1.

DISCUSSION

In the PIVOTAL trial, first stroke events occurred in 69 patients (3.2% of the entire cohort), compared to 180 fatal or non-fatal myocardial infarction events (8.4%) and 121 (5.7%) hospitalizations for heart failure[15]. In this large RCTof two different strategies for iron replacement in HD patients requiring an ESA as treatment for renal anemia, the major independent baseline risk factors for stroke were female gender, history of diabetes mellitus or prior stroke, and baseline higher systolic blood pressure. 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 post randomization stroke had lower hemoglobin than those who did not, although this observation was not statistically significant on time to event analyses (Tables 4 and S1). We found no association between iron treatment allocation, hemoglobin level, total intravenous iron dose or erythropoiesis-stimulating agent dose and stroke risk. This is irrespective of hemoglobin rising faster initially (supplementary data of the primary results paper) 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 supports the observation that lower hemoglobin is associated with increased risk of stroke in hemodialysis, 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 requiring dialysis. In a RCT in incident hemodialysis patients, like those studied in PIVOTAL, 'full' correction of anemia with epoetin alfa to a hemoglobin target of 135-145 g/L compared to a target of 95-115 g/L was associated with a significantly higher incidence of stroke (4% vs 1%, p=0.045) over 94 weeks follow-up[24]. In both the placebo-controlled TREAT trial of 4038 patients with diabetes and a GFR of 20-60ml/min/1.73m^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 (HR for stroke in the darbepoetin group in TREAT was 1.9; 95% confidence interval, 1.4 –2.7, HR for stroke in CKD patients in RED-HF was 2.07, 95% CI 0.98–4.38[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 hemodialysis, nor the CHOIR and CREATE studies in patients with non-dialysis CKD, all of which used ESA 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 requiring dialysis.

Survival after stroke for the dialysis patients 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 outcome may be inevitable[26, 29]. Perhaps these patients are less likely to receive interventions which may improve outcome 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 post *hoc* analyses of ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) comparing two thrombolysis regimes, every 10 mL/min/1.73 m^2 lower estimated glomerular filtration rate 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 dialysis receive thrombolysis with no specific restrictions compared to those with normal kidney function[33]. Combined National Stroke and Renal Registry data from Scotland show people treated with dialysis are less likely to be managed on an acute stroke unit following a stroke than the wider stroke population (67.4% vs. 79.6%; $p < 0.001$). Survival after stroke in the same report was significantly shorter in those on dialysis (median survival 0.8 years on dialysis compared to 3.1 years in the non-ESRD stroke population ($P < 0.0001$))[26]. The adverse outcomes following stroke in PIVOTAL emphasizes 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 dialysis patients which have not been addressed by the PIVOTAL trial. Despite performing a RCT in over 2,000 patients, we observed a small number of strokes, although the stoke incidence was similar to other cohort studies[34, 35]. This limits the number of variables that could be tested in multivariable analysis. The PIVOTAL trial was not designed to detect differences in stroke outcomes between groups. Whilst stroke incidence is relatively high in patients treated with dialysis, a RCT specifically targeting stroke as an efficacy end point would be challenging. Despite 164 patients (7.6%) having AF at baseline, we captured only 4 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 hemodialysis, 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 per 100 patient years is similar to some reports[34], but half that in other observational studies in longer term HD patients[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 preparations 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 dialysis patients of

Black or Hispanic ethnicity in the US[38]. We only collected baseline blood pressure and do not have pre- and post-dialysis blood pressure. Cerebral perfusion drops during dialysis which may increase risk of stroke[6].

In conclusion, in a RCT performed in a population at high risk of vascular events, we observed no association with 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 proactive iron treatment regimen in renal anemia in hemodialysis patients requiring ESA therapy.

Disclosures

PBM reports personal fees and non-financial support from Vifor, personal fees from Astrazeneca, Astellas, Novartis and Janssen grants from Boehringer Ingelheim, personal fees and non-financial support from Pharmacosmos, personal fees and non-financial support from Napp, outside the submitted work. PSJ reports speakers and advisory board fees from AstraZeneca. Speakers and advisory board fees from Novartis and advisory board fees and grants from Boehringer Ingelheim. MCP reported receiving lecture fees from AstraZeneca and Eli Lilly during the conduct of the study and personal fees from Novo Nordisk, AstraZeneca, NAPP Pharmaceuticals, Takeda. AP reports personal fees from Vifor Fresenius Renal Pharma, personal fees from Bayer GmBH outside the submitted work. CW is an employee of Pfizer. SA reports grants and personal fees from Vifor Int, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Novartis, personal fees from Servier, grants and personal fees from Abbott Vascular, personal fees from Impulse Dynamics, and personal fees from SJM outside the submitted work. 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. PAK reports grants and personal fees from Vifor during the conduct of the study as well as grants and personal fees from Vifor, personal fees from Pharmacosmos, grants and personal fees from Astellas, personal fees from Bayer, personal fees from MundiPharma, personal fees from Napp, personal fees from AstraZeneca, grants from BergenBio, personal fees from Boehringer Ingelheim, and personal fees from Novonordisk outside the submitted work. JJVM's employer the University of Glasgow has been remunerated by Astrazeneca, Cardiorentis, Amgen,

Oxford University/Bayer, Theracos, Abbvie, Novartis, Glaxo Smith Kline, Vifor-Fresenius, Kidney Research UK, and Novartis, Bayer, DalCor, Pfizer, Merck, Bristol Myers, and Squibb. ICM reports personal fees from Vifor Pharma and GlaxoSmithKline. All remaining authors have nothing to disclose.

Acknowledgments The PIVOTAL trial was funded by Kidney Research UK which was supported by an unrestricted grant from Vifor Fresenius Medical Care Renal Pharma.

Author Contributions

PBM developed the first draft of the manuscript and contributed to the analysis plan. IF provided biostatistical support, analysed the data and critically revised the manuscript. MR provided biostatistical support and analysed the data. ICMcD conceived the study, lead the study design, contributed to the statistical analysis plan and critically revised the manuscript. All other authors contributed to the study design, analysis plan and critically reviewed and revised by the the manuscript.

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Legend

Table 1 Baseline characteristics of patients experiencing stroke and those who did not. Values are number and percentage, mean and standard deviation (±) and median and interquartile range as appropriate. Tests of significance are t-test, Mann-Whitney U, Chi-squared and Fisher's exact test as appropriate. Abbreviations, PVD- peripheral vascular disease, AV- arteriovenous, SBP - systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index

Table 2 Incidence of stroke events including both first stroke and recurrent fatal and non-fatal stroke events

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

Table 4: Association between baseline clinical variables, laboratory data and post randomization stroke events in univariable (left) and multivariable models. Hemoglobin, ESA and IV iron dose used for this analysis are time varying variables based on the **most recent previous level or * mean of previous levels over the post randomization values for each variable during the trial

Figure 1 Cumulative incidence of stroke in the proactive (blue) and reactive (red) treatment groups accounting for the competing risk of non-stroke deaths. Between group Hazard Ratio (95% confidence interval): 0.90 (0.56, 1.44), p=0.66)

	No Stroke		Stroke		$P_{1 vs 2}$	Ischemic		Hemorrhagic		$P_{3 vs 4}$
	(1)		(2)			(3)		(4)		
n	2072		69			57		12		
Statistic	Count/ mean/ med	%/SD/ (LQ,UQ)	Count/mean/med	%/SD/ (LQ,UQ)		Count/mean/med	%/SD/ (LQ,UQ)	Count/ mean/ med	%/SD/ (LQ,UQ)	
Randomised to Proactive	1059	51.1	34	49.28	0.76	30	52.6	4	33.3	0.22
Gender (% male)	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 (years)	62.7	±15.1	65.7	±13.4	0.074	61.2	±14.2	66.6	±13.2	0.24
SBP (mmHg)	144.3	±23.5	156.1	±25.7	<0.001	152.0	±15.0	157.0	±27.4	0.38
DBP (mmHg)	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	0.033	28.2	±5.7	31.3	±8.3	0.12
Dialysis duration (months)	5.8	3.7	5.0	3.5	0.086	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	1.00
Stroke baseline (%)	165	8.0	11	15.9	0.018	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 renal disease					0.016					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_eCRP (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/week)	8589	5636	8561	5500	0.97	4917	2314	9328	5678	<0.001
Mean IV iron dose/month (mg)	183	125,257	180	132,232	0.56	133	181,235	171	110,221	0.72

Table 1

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/100 person-years	1.62	1.54	1.70
Total (first and recurrent) strokes	95	46	49
Total number of strokes per 100 person-years	2.22	2.08	2.38

Table 2. Incidence of stroke events including both first stroke and recurrent fatal and non-fatal stroke events

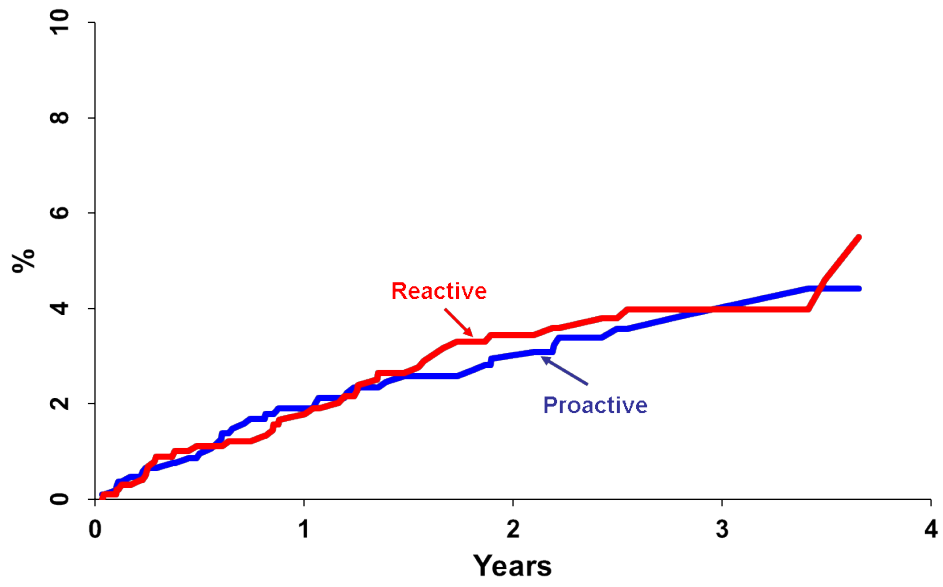
Table 3: Baseline clinical variables associated with stroke events during the trial in univariable (left) and multivariable models (right)

Variable	HR (95% CI)	p	HR (95% CI)	p
Gender (female/male)	2.11 (1.31, 3.40)	0.0022	2.15 (1.34, 3.45)	0.0016
Diabetes (Yes/No)	2.09 (1.26, 3.47)	0.0042	2.08 (1.25, 3.45)	0.0046
Stroke (Yes/No)	1.98 (1.03, 3.78)	0.039	2.02 (1.06, 3.85)	0.033
SBP (per 10 mmHg)	1.18 (1.07, 1.30)	0.0012	1.18 (1.07, 1.30)	0.00090
Dialysis Vintage duration (per month)	0.87 (0.54,1.41)	0.58		
Age (per 5 years)	1.08 (0.98, 1.19)	0.10		
AF (Yes/No)	0.78 (0.28, 2.18)	0.63		
Vascular access (Graft/Fistula/ Catheter)	0.78 (0.48, 1.25)	0.30		
Treatment (Proactive/Reactive)	0.89 (0.48, 1.44)	0.64		

Variable	HR (95% CI)	p	HR (95% CI)	p
Gender (female/male)	2.14 (1.33, 3.45)	0.0018	2.15 (1.34, 3.47)	0.0016
Stroke (Yes/No)	1.98 (1.03, 3.76)	0.040	1.98 (1.04, 3.78)	0.038
Diabetes (Yes/No)	1.96 (1.18, 3.26)	0.0097	1.96 (1.18, 3.26)	0.0093
**Log_eCRP (per 1 unit)	1.40 (1.13, 1.73)	0.0014	1.42 (1.15, 1.75)	0.0013
SBP (per 10 mmHg)	1.19 (1.08, 1.31)	0.00060	1.18 (1.08, 1.31)	0.00046
**Albumin (per 10 units)	0.62 (0.40, 0.95)	0.029	0.59 (0.38, 0.89)	0.013
**Hemoglobin (per 10 units)	0.92 (0.77, 1.10)	0.35		
*ESA (per 100 units)	1.00 (1.00, 1.00)	0.98		
*IV iron dose (per 100 units)	0.97 (0.81, 1.15)	0.71		

Table 4: Association between baseline clinical variables, laboratory data and post randomization stroke events in univariable (left) and multivariable models. Hemoglobin, ESA and IV iron dose used for this analysis are time varying variables based on the **most recent previous level or * mean of previous levels over the post randomization values for each variable during the trial

Figure 1



Numbers at risk:

Proactive	1093	831	600	219	33
Reactive	1048	778	546	213	22