Stroke events in a randomised controlled trial of intravenous iron strategies in patients treated with HD: a report from PIVOTAL

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ABSTRACT (300 words)

Background and objectives. People with kidney failure treated with hemodialysis (HD) have an increased risk of stroke. The increased risk is unlikely to only be due to a high prevalence of risk factors. One concern is that aggressive hemoglobin correction might increase stroke risk in chronic kidney disease. We studied risk factors for stroke in secondary analyses of a randomizsed controlled trial of intravenous iron strategies in HD.

Design, setting, participants, and measurements We analysed data from the Proactive IV Iron Therapy in haemodialysis Patients (PIVOTAL) trial focusing on variables associated with risk of stroke. The trial randomized 2,141 adults, having started hemodialysis <12 months earlier and receiving an erythropoiesis-stimulating agent (ESA), to receive 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 median 2.1 years follow up, 69 (3.2%) patients experienced a first stroke. 57 (82.6%) were ischemic strokes and 12 (17.4%) hemorrhagic strokes. Patients who had a stroke were more likely to be women and have diabetes and a history of stroke, as well as higher body mass index and systolic blood pressure than those who didn't experience a stroke. There were 34 first post randomization strokes in the proactive arm and 34 in the reactive arm (hazard ratio (95% confidence interval): 0.90 (0.56, 1.44), p=0.66). In multivariable models, female gender, history of stroke and diabetes, higher baseline systolic blood pressure, lower serum albumin and higher C-reactive protein were independently associated with

stroke. Hemoglobin, total iron or ESA dose were not associated with risk of stroke. 58% of patients with a stroke event died during follow up.

Conclusions In hemodialysis patients, stroke risk is primary associated with conventional vascular risk factors.. Proactive intravenous iron does not increase stroke risk.

INTRODUCTION

People with kidney failure requiring treatment with hemodialysis (HD) are at increased risk of stroke compared to people of a similar age without kidney failure. The estimated increased risk of stroke in patients treated with HD is approximately five times higher than that the risk in patients with normal kidney function[1, 2]. The prevalence of 'conventional' vascular risk factors, that are associated with increased stroke risk such as hypertension, diabetes, older age, prior cardiovascular disease and atrial fibrillation is high in patients treated with HD, but this seems unlikely to explain the magnitude of increased risk in patients requiring HD[3, 4].

Randomized clinical trials (RCTs) assessed the effect of correction of anemia with erythropoiesis stimulating agents (ESA) in patients with chronic kidney disease (CKD), requiring HD or in patients with heart failure. The overall effect of anemia correction on stroke risk has been variable with some studies demonstrating no excess stroke risk in the ESA treatment or higher hemoglobin group[5-7]. However, in two of the largest placebo-controlled RCTs of anemia correction with the ESA darbepoetin[8, 9], stroke risk was elevated in the higher hemoglobin arm of the trial, with this observation being statistically significant in the TREAT trial in patients with diabetes and CKD[8], suggesting that anemia correction with ESA may be associated with increased risk of stroke in patients at high vascular risk irrespective of other risk factors for stroke[10]. However, the effect of anemia correction driven by differing iron-based strategies to minimize ESA use on future stroke risk in patients treated with HD requiring is largely unknown.

The PIVOTAL trial was a randomized clinical trial (RCT) of proactive versus reactive intravenous iron therapy in patients requiring HD already treated with an ESA. The methods, baseline characteristics of the participants and main results of

the trial have been reported elsewhere[11, 12]. Briefly, the high-dose proactive intravenous iron regimen resulted in lower doses of erythropoiesis-stimulating agent being administered compared to the low-dose iron regimen with fewer cardiovascular events in the proactive arm of the trial. In this pre-specified analysis, we analyzed which factors were associated with risk of stroke in an RCT of different iron replacement strategies in patients requiring HD. We hypothesized that proactive iron (and the consequent rise in hemoglobin) would not be increased with increased stroke risk compared to reactive low dose iron.

METHODS

The design, baseline characteristics and main results of PIVOTAL are published[11, 12]. In summary, 2141 adults who had started HD within the previous year, who had a ferritin concentration <400 µg per litre and a transferrin saturation <30%, and who were receiving an ESA were enrolled. Patients were randomized in a 1:1 ratio, 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 litre 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 litre and transferrin saturation ≥20%, in line with current guidelines. The protocol required the use of an ESA in a dose sufficient to maintain a hemoglobin of 100 to 120 g per litre, but otherwise patients were treated according to usual practice. 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, analysed as time-to-first event. Stroke was a pre-specified secondary outcome. For this manuscript, the outcomes of time-to-first stroke are reported. In addition to time-to-first stroke, we also analysed recurrent stroke events, to account for the cumulative burden of events over time. We also 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. For the diagnosis of stroke, the following four criteria were required: 1) rapid onset of a focal/global neurological deficit, 2) duration of a focal/global neurological deficit ≥ 24 hours (<24 hours was permissible in the case of therapeutic intervention e.g. thrombolysis or brain imaging available clearly documenting a new hemorrhage or infarct or the neurological deficit results in death), 3) no other identifiable non-stroke cause for the presentation and 4) confirmation of the diagnosis by at least one of the following: neurology specialist, brain imaging (at least one of the following):(i) CT scan.(ii) MRI scan (iii) cerebral vessel angiography. c) lumbar puncture.

Focal/global neurological deficit was defined as change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia/aphasia, hemianopia, complete/partial loss of vision of one eye or other new neurological sign(s)/symptom(s) consistent with stroke.

If a stroke was reported by a local investigator but evidence of confirmation of the diagnosis by the methods outlined above was absent, the event could be adjudicated as a stroke if the adjudication committee was satisfied that the clinical presentation was convincing with no plausible non-stroke cause for the presentation. Fatal stroke refers to death after a documented stroke (verified by the diagnostic criteria or by typical post-mortem findings) that is a direct consequence of the stroke or a complication of the stroke with no evidence of another cause of death. In cases of early death where confirmation of the diagnosis cannot be obtained, the endpoint committee could adjudicate based on clinical presentation alone. Transient ischaemic attacks, subdural and extradural haemorrhage were not included as stroke endpoints.

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 Kaplan–Meier method was used to estimate mortality rates and cumulative incidence functions correcting for the competing risk of deaths not included in the outcome of interest, for stroke as a time to first event. Recurrent events were analysed using the proportional-means model of Lin et al[13]. 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 and those who did not

The PIVOTAL trial randomised 2141 patients of which 1093 patients were allocated to the high-dose group and 1048 to the low-dose group. During a median 2.1 years of follow up, 69 (3.2%) patients experienced a first strokepost 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 show Table 1. Patients who had a stroke were older, more likely to have diabetes and prior stroke, and had a higher BMI and systolic blood pressure (SBP) than those who did not. Those experiencing stroke had a lower serum albumin (NEED VALUES FOR THIS) and hemoglobin and a higher C-reactive protein (CRP) at baseline that those who did not.

Factors associated with stroke during follow up

There were 34 first strokes in the proactive arm and 34 in the reactive arm (hazard ratio (95% confidence interval): 0.90 (0.56, 1.44), p=0.66), Fig 1. Including second and subsequent strokes, there was a total of 46 strokes in the proactive arm with 49 in the reactive arm (rate ratio (95% confidence interval): 0.88 (0.53, 1.45), p=0.61), Table 2.

In a multivariable Cox regression model for the time to first fatal or non-fatal stroke, fitting only potential baseline risk factors omitting laboratory variables. From this model four baseline variables were identified that were significantly associated

with stroke: diabetes, SBP, gender and history of stroke (Table 3). These four variables remained independent predictors when laboratory variables and ESA dose were added to further multivariable models (Table 4). In these additional models serum albumin and $\log_e$CRP were also independent predictors of stroke. Finally, iron dose, ESA dose and time-updated hemoglobin did not predict risk of stroke or meaningfully influence the strength of the other predictive variables in the models(Table 5).

Outcomes following stroke

A total of 40 patients who had a first stroke during the trial subsequently died during follow up. Of these, 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 Figure 2.

DISCUSSION

In a large randomized controlled trial of two different strategies for iron replacement in HD patients requiring an ESA as treatment for renal anemia, the major independent baseline risk factors for experiencing a stroke were female gender, history of diabetes mellitus or stroke, and baseline systolic blood pressure. On laboratory testing, inflammation (indicated by elevated CRP) and malnutrition (indicated by low serum albumin) were associated with increased risk of stroke. Therefore, in keeping with previous observational data in this population, the major risk factors for stroke in PIVOTAL were similar to 'conventional' cardiovascular risk factors for stroke observed in the general population[14, 15]. Inflammation and malnutrition have been associated with either stroke, atherosclerosis or cardiovascular events in several observational studies in patients with CKD[16, 17].

By reporting observations from a prospective RCT, we are able to provide further insights on the effects of a proactive iron strategy for addressing renal anemia on stroke risk. We found no association between iron treatment arm, hemoglobin level, or either total intravenous iron dose or erythropoiesis stimulating agent dose administered over the duration of the trial and stroke risk. This is in spite of hemoglobin rising faster initially in the proactive treatment arm and fewer blood transfusions being given in the proactive arm, presumably as a result of higher hemoglobins earlier in the trial[12]. It is worth contrasting this observation with the TREAT trial in which patients randomized to darbepoetin to achieve a higher hemoglobin target was associated with significantly higher stroke risk[8]. By comparison, in other large trials of anemia correction using ESA, stroke risk was not significantly greater in the higher hemoglobin group of the Normalized Haematocrit, CHOIR or CREATE in patients with CKD or RED-HF in patients with systolic heart

failure[5-7, 9]. Nevertheless, our results provide further reassurance to the headline data of the main findings of PIVOTAL, that proactive iron does not specifically increase risk of stroke events in addition to being overall superior to a low dose iron regime for both cardiovascular outcomes and lower ESA requirements[12]. We speculate that the lower ESA requirement may have offset any increased stroke risk associated with rising hemoglobin in the proactive arm.

The PIVOTAL trial was not designed to detect differences in stroke outcomes between the groups. Stroke has been a challenging outcome to study in RCTs of patients on dialysis. In the 4D study, a signal was observed with increased stroke risk in patients treated with atorvastatin[18]. This led to the primary end point of the AURORA trial being revised during the trial to take account of the likely neutral effect of lipid lowering on stroke risk compared to any potential cardiovascular benefit of the statin intervention on the other aggregated vascular end points in the trial[19]. Therefore, it is important to perform detailed analysis of prospective randomized data to better understand stroke risk and inform trial design in this population.

The survival after stroke for the dialysis patients in this trial was poor. This is consistent with findings of other studies[20-22]. 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 and hence poor outcome may be inevitable[20, 23]. Perhaps, these patients are less likely to receive interventions which may improve outcome such as thrombolysis, acute stroke unit care or antiplatelet therapy[20, 24]. There is a limited evidence base for treatment of stroke in patients requiring dialysis and it is unlikely many patients with dialysis dependent kidney

failure were studied in previous interventional studies in acute stroke[25]. The adverse outcome following stroke in PIVOTAL emphasises the need to continue to address this and in particular identify if poor outcomes are driven by inequalities of care offered (e.g., limited access to rehabilitation due to the need for attending time consuming dialysis sessions) or an absence of evidence-based therapies for acute stroke in this population[4, 20, 25].

Several qualifications limit the inferences which may be made from our data. Despite performing a RCT in over 2,000 patients, we observed a small number of strokes, and even fewer confirmed ischemic strokes. The small number permits only a small number of variables to be tested as being statistically associated with stroke. Despite 164 patients (7.6%) having AF at baseline, we captured only 4 strokes in patients with AF and therefore cannot comment further on AF as a risk factor for stroke in dialysis. This prevalence of AF was lower than reported in other HD cohorts where it is approximately 10-20% of patients, so our findings may simply reflect the lower prevalence of patients with AF being recruited to the trial[21, 26, 27]. As a trial performed in patients during the first year of dialysis, these patients may be marginally 'healthier' than those on long term maintenance dialysis. The overall incidence of stroke at 2.22 per 100 patient years is similar to other reports in the UK[28], but half that seen in some other observational studies in longer term dialysis patients[2, 29]. Additionally, stroke risk particularly tends to rise over the first 90 days after commencement of dialysis and then falls over the next year, prior to rising again, so interpreting stroke risk over the first year after commencing dialysis can be challenging[30]. The trial was performed in the United Kingdom and whilst representative of the dialysis population in the UK, <10% of participants were of

Black ethnicity. This contrasts with the higher incidence of stroke observed in patients of Black or Hispanic ethnicity in US data[29].

In conclusion, in a RCT performed in a population at high risk of vascular events, we observe no association with high dose iron and stroke risk despite a relatively more rapid initial rise in hemoglobin in the proactive iron group. This contrasts with the association with higher hemoglobin and vascular risk seen in at least one of the anemia correction RCTs performed using ESA to drive higher hemoglobin. These observations should provide further reassurance around the benefits of using proactive iron in treatment of renal anemia in patients requiring dialysis who require ESA therapy.

Disclosures

Acknowledgments

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 range as appropriate. Tests of significance are t-test, Mann-Whitney U, Chi-squared and Fisher's exact test as appropriate. Abbreviations CVD – cardiovascular disease, PVD- peripheral vascular disease, AV- arteriovenous, SBP_ - systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index,

Table 2 Comparison of first and recurrent stroke events for fatal and non-fatal stroke between the proactive and reactive iron groups

Table 3: Baseline predictors of stroke excluding lab data and ESA

Table 4: Baseline predictors of stroke including lab data and ESA

Table 5: Baseline and time varying lab, ESA dose and IV iron dose predictors of stroke

Figure 1 Cumulative incidence of stroke in the proactive (blue) and reactive (red) treatment groups.

Figure 2 Cumulative mortality following a first stroke event

	No Stroke		Stroke		Ischemic		Hemorrhagic		$P_{1 vs 2}$
	(1)		(2)		(3)		(4)		
n	2072	%	69	%	57	%	12	%	
Gender (male)	1366	65.9	32	46.4	24	42.1	8	66.6	0.001
Ethnicity (white)	1641	79.2	57	82.61	48	84.2	9	75.0	0.49
Age (years)	62.7	15.1	65.7	13.4	61.2	14.2	66.6	13.2	0.074
SBP (mmHg)	144.3	23.5	156.1	25.7	152.0	15.0	157.0	27.4	<0.001
DBP (mmHg)	73.6	14.8	74.4	16.1	76.3	18.5	74.0	15.7	0.68
BMI	28.7	6.9	30.8	7.9	28.2	5.7	31.3	8.3	0.033
Dialysis vintage	5.8	3.7	5.0	3.5	5.2	3.9	5.0	3.4	0.086
Smoking: current	240	11.6	9	13.0	6	10.5	3	25.0	0.53
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	38	66.7	8	66.7	<0.001
Stroke baseline	165	8.0	11	15.9	10	17.5	1	8.3	0.018
Myocardial infarction	175	8.5	9	13.0	8	14.0	1	8.3	0.18
Heart Failure	84	4.1	2	2.9	1	1.7	1	8.3	0.63
Atrial fibrillation	160	7.7	4	5.8	3	5.3	1	8.3	0.55
PAD	182	8.8	5	7.3	4	7.0	1	8.3	0.66
Previous CVD	590	28.5	28	40.6	24	42.1	4	33.3	0.29
AV fistula/graft	1222	59.0	35	50.7	32	56.1	3	25.0	0.17
Primary renal disease									
Hypertension	228	11.0	7	10.1	5	8.8	2	16.7	0.016
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	
Other	126	6.1	3	4.4	2	3.5	1	8.3	
Polycystic kidney disease	117	5.7	0	0	0	0	0	0	
Unknown	201	9.7	5	7.3	5	8.8	0	0	
Hemoglobin (g/L)	105.7	13.7	100.9	12.8	103.3	13.6	100.4	12.7	0.003
Albumin (g/L)									
$\log_e$CRP (mg/L)	1.86	1.08	2.30	0.98	2.08	0.91	2.34	1.00	0.001
ESA dose (IU/week)	8589	5636	8561	5500	4917	2314	9328	5678	0.97

Variable	All (n =2141)	Proactive (n =1093)	Reactive (n =1048)
Events per patient			
0	2072 (96.78%)	1059 (96.89%)	1013 (96.66%)
1	46 (2.15%)	23 (2.10%)	23 (2.19%)
2	20 (0.93%)	10 (0.91%)	10 (0.95%)
3	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
Method	Rate Ratio	95% Confidence Interval	P-value
Lin, Wei, Ying & Yang	0.88	(0.53, 1.45)	0.61

Table 2. Recurrent events analysis for fatal and non-fatal stroke

Variable	HR (95% CI)	p	HR (95% CI)	p
Dialysis Vintage (per month)	0.87 (0.54,1.41)	0.58		
Age (per 5 years)	1.08 (0.98, 1.19)	0.10		
SBP (per 10 mmHg)	1.18 (1.07, 1.30)	0.0012	1.18 (1.07, 1.30)	0.00090
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
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		
Gender (female/male)	2.11 (1.31, 3.40)	0.0022	2.15 (1.34, 3.45)	0.0016

Table 3: Baseline predictors of stroke excluding laboratory data and ESA dose in univariable (left) and multivariable models (right)

Variable	HR (95% CI)	p	HR (95% CI)	p
SBP (per 10 mmHg)	1.18 (1.07, 1.30)	0.0010	1.18 (1.07, 1.30)	0.00085
Diabetes (Yes/No)	2.03 (1.22, 3.38)	0.0066	2.00 (1.20, 3.34)	0.0075
Stroke (Yes/No)	1.93 (1.01, 3.68)	0.047	1.91 (1.00, 3.65)	0.050
Gender (female/male)	2.02 (1.25, 3.26)	0.0042	2.09 (1.30, 3.37)	0.0024
Loge(CRP) (per 1 unit)	1.47 (1.14, 1.91)	0.0035	1.47 (1.14, 1.90)	0.0032
Albumin (per 10 units)	0.61 (0.38, 0.97)	0.037	0.57 (0.36, 0.89)	0.014
Hemoglobin (per 10 units)	0.89 (0.74, 1.06)	0.19		
ESA (per 100 units)	1.00 (0.998, 1.001)	0.31		

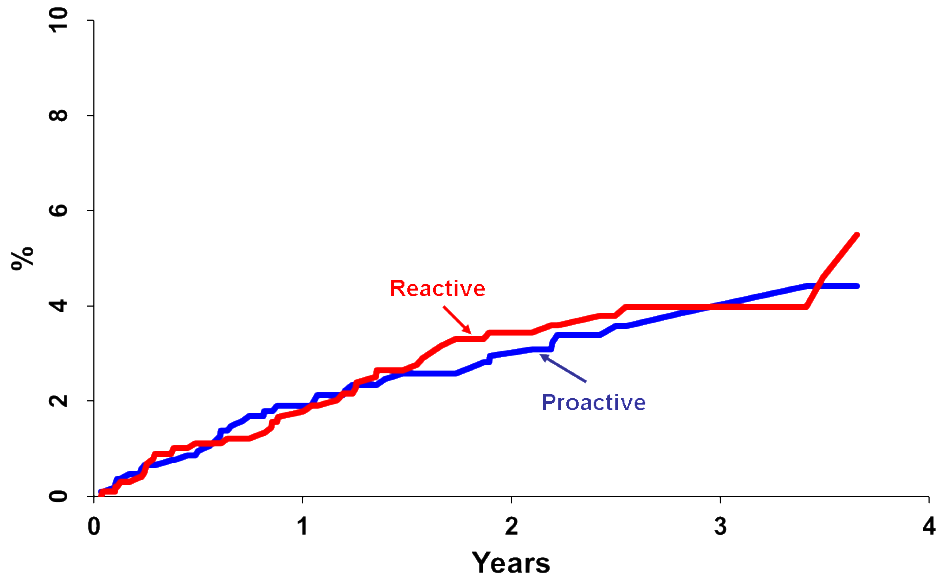
Table 4: Baseline predictors of stroke including laboratory data and ESA dose in univariable (left) and multivariable models (right)

Variable	HR (95% CI)	p	HR (95% CI)	p
SBP (per 10 mmHg)	1.19 (1.08, 1.31)	0.00060	1.18 (1.08, 1.31)	0.00046
Diabetes (Yes/No)	1.96 (1.18, 3.26)	0.0097	1.96 (1.18, 3.26)	0.0093
Stroke (Yes/No)	1.98 (1.03, 3.76)	0.040	1.98 (1.04, 3.78)	0.038
Gender (female/male)	2.14 (1.33, 3.45)	0.0018	2.15 (1.34, 3.47)	0.0016
**Log_eCRP (per 1 unit)	1.40 (1.13, 1.73)	0.0014	1.42 (1.15, 1.75)	0.0013
**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		

**Time varying covariate = most recent previous level

*Time varying covariate = average of previous levels

Table 5: Baseline and time varying laboratory, ESA dose and IV iron dose predictors of stroke dose in univariable (left) and multivariable models (right)



Numbers at risk:

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

Figure 1 Cumulative incidence of stroke in the proactive (blue) and reactive (red) treatment groups.

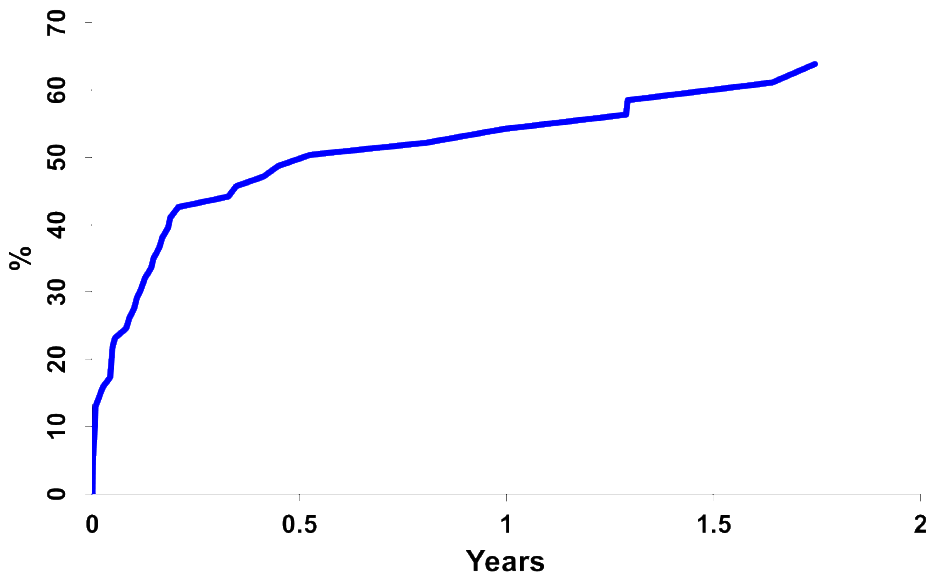


Figure 2 Cumulative mortality following a first stroke event

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