Risk factors of ischemic stroke and subsequent outcome in hemodialysis patients

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Key words: Stroke, hemodialysis, end-stage renal disease, ESRD

Subject Codes: [8] Epidemiology [13] Cerebrovascular disease/stroke [66] Risk Factors for Stroke

Word Count: 4,136 **Figures:** 2 **Tables:** 2

Abstract

Background and purpose:

End stage renal disease (ESRD) requiring hemodialysis (HD) carries up to a 10-fold greater risk of stroke than normal renal function. Knowledge concerning risk factors and management strategies derived from the general population may not be applicable to those with ESRD. We studied a large ESRD population to identify risk factors and outcomes for stroke.

Methods:

All adult patients receiving HD for ESRD from 01/01/2007 to 31/12/2012 were extracted from the electronic patient record. Variables associated with stroke were identified by survival analysis; demographic, clinical, imaging and dialysis related variables were assessed and case-fatality determined. Follow-up was until 31/12/2013.

Results

1382 patients were identified (mean age 60.5 years, 58.5% male). The prevalence of AF was 21.2% and 59.4% were incident HD patients. 160 (11.6%) experienced a stroke during 3471 patient-years of follow-up (95% ischemic). Stroke incidence was 41.5/1000 patient-years in prevalent and 50.1/1000 patient-years in incident HD patients. Factors associated with stroke on regression analysis were prior stroke, diabetes and age at starting renal replacement therapy. AF was not significantly associated with stroke and warfarin did not affect stroke risk in warfarin treated patients. Fatality was 18.8% at 7, 26.9% at 28 and 56.3% 365 days after stroke.

Conclusions

Incidence of stroke is high in patients with ESRD on HD with high case-fatality. Incident HD patients had the highest stroke incidence. Many, but not all, important risk factors commonly

associated with stroke in the general population were not associated with stroke in patients receiving HD.

Introduction

The risk of stroke is 5-10 times greater in those with end stage renal disease(ESRD) on hemodialysis (HD) compared to patients with normal renal function[1]. However, risk factors for stroke in ESRD may differ compared to the general population. Atrial fibrillation(AF), for example, is associated with adverse outcomes in the ESRD population[2–5] but its influence on stroke risk is less clear. Moreover, warfarin use may not protect against stroke in patients with ESRD and AF[6]. Further, there is a temporary rise in stroke incidence following commencement of HD[7] suggesting that either commencement of dialysis itself or specific dialysis related variables increase stroke risk. For instance, in the general population it is recognised that diuretic induced potassium depletion is associated with stroke[8]. Finally, most data on stroke risk in ESRD originates from large US registry studies, or relatively small single centre studies with low absolute number of stroke events.

We performed a contemporary study in a large dialysis centre in a population with a high background prevalence of vascular disease, to identify risk factors for stroke in HD. We hypothesised that 1) stroke risk would be high, with high case-fatality in patients treated with HD, 2) that some common traditional risk factors for stroke would not be associated with stroke risk (with a particular focus on AF and the effect of warfarin) and 3) that dialysis specific variables would be associated with stroke risk.

Methods

All adult HD patients attending Glasgow Renal and Transplant Unit for hospital HD between 1st January 2007 and 31st December 2012 were identified using the electronic patient record (EPR), (Strathclyde Electronic Renal Patient Record, Vitalpulse, UK). Cohort entry was recorded as 1st January 2007 in patients already receiving HD (prevalent HD patients) or from date of commencing HD as their first renal replacement therapy (RRT) modality for ESRD

(incident HD patients). Patients treated with HD for acute kidney injury were excluded. Clinical and demographic details at cohort entry were recorded including primary renal diagnosis, presence of diabetes, cardiovascular disease, cerebrovascular disease, AF and antithrombotic drug use. We also extracted pre and post-dialysis blood pressure, ultrafiltration volume, pre-dialysis serum albumin, adjusted calcium, phosphate, blood hemoglobin, pre and post-dialysis serum potassium and urea reduction ratio at 90 days. The value from 90-days post cohort entry was used. The EPR links to all radiology departments in the West of Scotland so we were able to review all reports of brain imaging (computed tomography or magnetic resonance imaging).

Outcomes and definition of stroke

The time to first stroke in patients receiving HD occurring after study inception was recorded. Stroke was defined from the EPR as either 1) a new clinical diagnosis of stroke recorded in the diagnostic timeline, 2) the presence of ischemic or hemorrhagic stroke on brain imaging associated with a clinical history of new neurological deficit or stroke, or 3) any of cerebrovascular disease, cerebrovascular accident, cerebral infarct, subarachnoid hemorrhage or intracerebral hemorrhage listed on death certificate as a primary or major contributory factor to a patient death. All events were reviewed by 2 independent clinicians (M.D.F., P.B.M.) with cases adjudicated by a third observer (P.C.T.) where disagreement arose. Subdural and extradural hemorrhage were excluded. The West of Scotland Ethics Committee officer waived the need for ethical committee review on the basis that this was analysis of routine clinical data.

Statistical analysis

Follow up data were available to December 31st 2013. Patient follow up was censored at renal transplantation. Baseline demographics were compared using Student's t-test, Mann-Whitney U test, Chi-square test or one-way ANOVA as appropriate. Kaplan-Meier survival analysis was performed for time to first stroke and for mortality in all patients. A multivariable Cox survival analysis was performed to identify significant independent risk factors for stroke. A backward stepwise regression model was applied to identify significantly influential variables as defined at a $p < 0.05$ and those were re-entered into a multivariable cox regression analysis. Data were analysed using SPSS version 21 (IBM, Armonk, New York) and StataSE 13 (Statacorp, College Station, Texas).

Results

A total of 1382 patients receiving HD were included. Of these, 59.4% were incident HD patients. The median RRT vintage was 1206 days (IQR 2222) in the prevalent patients. The mean age was 60.5 years, 58.5% were male and 21.2% had AF. 245 (17.7%) patients received a kidney transplant during follow up. Censoring for death or transplantation, median follow-up for the cohort was 2.1 (IQR 2.9) years.

160 patients (11.6%) experienced a stroke event over 3471 patient-years of follow up (table 1). 149 patients (93.1%) had brain imaging performed as part of diagnostic assessment, with the rest considered to have a clinical diagnosis of stroke based on the death certification or at post mortem examination. The majority (95%) of events were ischemic. Stroke incidence was 41.5/1000 patient-years in prevalent HD patients and 50.1/1000 patient-years in patients incident to HD during the follow up period. Age-adjusted stroke rates (WHO world standard) are available online (supplemental tables I&II). There were baseline differences between patients who suffered stroke and patients who did not (table 1).

Atrial fibrillation, warfarin, antiplatelet therapy and risk of stroke, intracerebral hemorrhage or death

There was no increased in rate of stroke in patient with AF compared to no AF on survival analysis (Figure 1). AF was more common in patients who died (26.2% vs 14.2%, p<0.001 supplementary figure I). The rate of stroke did not differ in AF patients treated with warfarin compared to AF patients who were not (14.4% vs. 11.4%, p=0.45, Figure 2).

Survival analyses of variables associated with risk of stroke

Multivariable regression analyses revealed that age at starting RRT, previous cerebrovascular disease, presence of diabetes and post dialysis serum potassium were significantly associated with the risk of stroke. Backward stepwise regression was applied to identify significant variables (p<0.05) for use in the final cox regression model. This revealed a significant independent association for age, prior cerebrovascular disease and diabetes with stroke (model 1). Removing all cases with a prior history of cerebrovascular disease from the analyses revealed that age at starting RRT and diabetes were still associated with stroke (model 2).

Outcome in patients following stroke

Case fatality (death within 7 days) for all stroke was 18.8% (n=30) and 126 of 160 (78.8%) died during follow-up. Fatality was 26.9% at 28 days and 56.3% at 1 year. Fatality was higher in patients with hemorrhagic compared to ischemic stroke with 7, 28 and 365 day fatality of 62.5%, 87.5% and 100% for hemorrhage compared to 16.4, 23.7 and 53.9% for ischemia. Fatality rates were higher when those with prior cerebrovascular disease were removed with 7, 28 and 365 day fatality of 24, 34 and 72%.

Discussion

In the general population stroke is common and a leading cause of disability[9] with firmly established risk factors. Although incidence, outcomes and risk factors are described in the ESRD population, most published data originate from the US or Japan and are not necessarily representative of the UK or European populations. Amongst a large cohort of incident and prevalent HD patients in the west of Scotland we have described a high incidence of stroke events alongside stroke variables and fatality rates. Of note, we report a higher incidence of stroke in the incident dialysis population compared to the prevalent patients and, interestingly, no association between AF or warfarin use and stroke events.

Stroke Incidence in hemodialysis

We found a high unadjusted incidence of stroke in patients with ESRD (46.1/1000 patient-years) in keeping with previous reports where it ranges from 17.3 – 49/1000 patient-years[1,10–13] but higher than a recent report from a UK study (46.1 vs 17.3/1000 patient-years)[12]. This could be explained by the differences in study methodology (they excluded stroke within the first 90 days of commencing dialysis and required neuroimaging to diagnose all stroke events) and geographical variation (Scotland has the higher prevalence of cardiovascular disease in the UK[14,15]). Incidence of stroke was higher in the incident compared to the prevalent HD patients (50.1 vs 41.5/1000 patient-years). The increase in stroke risk associated with dialysis initiation[7] has previously been described, however we are the first to describe a difference in stroke rate between incident and prevalent HD groups within the same population. We report fewer cases of hemorrhage than in previous reports – a finding which is not unexpected for a predominantly (92.6%) Caucasian population[16].

Case fatality following stroke was high, with a markedly higher rate in hemorrhagic stroke, and higher in those who experience their first ever stroke. As expected, fatality in our dialysis

population is higher than the reported background fatality rates for stroke in Scotland (26.9% vs 15.9% at 28 days)[15] but in keeping with reported rates in ESRD (30d fatality of 17.9% in ischemic stroke and 53.4% for hemorrhagic stroke)[17].

Risk Factors for stroke

Risk factors for stroke in the general population include increasing age, prior cardiovascular disease, diabetes, hypertension and AF[18]. We found older age, presence of diabetes, previous cerebrovascular disease, a lower diastolic blood pressure and higher post dialysis potassium were significantly associated with stroke in patients receiving HD. This effect of potassium contrasts with the general population where higher potassium levels are associated with a lower blood pressure and stroke risk[8,19] although the mechanism is unclear. As it was of clinical interest we looked at the association of post dialysis potassium on risk of stroke using a univariable cox proportional hazards model. In the absence of other covariates, post HD potassium was significantly associated with stroke, HR 1.4 (95% CI 1.03, 1.9). However, when other covariates identified by stepwise regression were added into the model post HD potassium was no longer associated with stroke (table 2). A higher serum potassium following dialysis is likely to represent underlying comorbidity. In our study the mitigation of potassium's effect on stroke risk is likely to reflect an association with presence of diabetes Interestingly, whilst presence of AF at baseline was associated with a higher mortality, we found no association between the presence of AF or warfarin use and stroke. In our group, the presence of AF represents a marker of comorbidity and advanced age rather than a cause of mortality. HD favours the initiation of AF through rapid shifts in fluid and electrolytes (potassium) and episodes of AF are common during HD [20] Whilst HD induced AF may contribute to the increase in stroke risk observed in those initiating dialysis it must be acknowledged that patients are anti-coagulated during their dialysis sessions. Therefore, it is

possible that HD-related AF may carry a lower risk of stroke than AF in the general population.

Anticoagulation in ESRD

Use of dose adjusted warfarin is accepted as an effective treatment in reducing the risk of ischemic stroke[21] in non-valvular AF. However, we did not detect an effect of warfarin on stroke risk in our study. In recent years data has emerged suggesting that warfarin use is either not protective against ischemic stroke[22], associated with an increase in hemorrhagic and ischemic stroke[4,13,23] or is associated with harm through bleeding in the haemodialysis population[6,22]. Guidelines reflect this uncertainty and either do not mention patients with ESRD or make no recommendation[24–26]. There is unease about using vitamin K antagonists in ESRD not only due to the increased risk of bleeding but also the association with vascular calcification inducing cardiovascular disease or calciphylaxis[27,28]. Unfortunately, no suitable alternative currently exists. Although recently developed new oral anti-coagulants (NOACS) have been shown to be non-inferior or superior to warfarin in patients with non-valvular AF[25,29]in the general population, patients with ESRD are excluded from such stroke prophylaxis trials. Presently, NOACS are not recommended in those with a GFR <30ml/min[25].

Limitations

We report a single centre study and have described the clinical behaviour of stroke disease in 1382 HD patients over 3471 years of patient follow-up. This is one of the largest single centre studies ever reported. We do however, recognised the following limitations. Due to the observational nature of our cohort we can only describe associations and not causation. Despite the size of this study the relatively low numbers of stroke events limit our ability to

detect risk factors associated with death within the stroke group. We acknowledge that as no association between ischaemic stroke and AF was described, we would not expect warfarin to be protective. However, the absence of any influence of warfarin on stroke risk remains notable. Specifically, warfarin use did not increase hemorrhagic stroke risk. Finally, important data were not available from this study which could support our lack of findings regarding atrial fibrillation. For example the absence of echocardiography prevents reporting of structural abnormalities which may be relevant and absence of INR reporting prevents comment about the time in therapeutic range.

Conclusions

In summary we have shown that in a high risk population of ESRD patients on HD the incidence of stroke is high with associated poor outcomes. Presence of AF is associated with mortality but we did not detect an association between AF and stroke in this cohort. Neither stroke risk nor mortality are altered by warfarin use in this study. We have described a higher incidence of new onset stroke in the incident HD population compared to the prevalent

Sources of Funding

MF is currently funded by a Kidney Research UK Training Fellowship and supported by a grant from Darlinda's Charity for Renal Research.

Disclosures

None

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Legend

Figure 1

Kaplan Meier survival curve of time to stroke in all period-prevalent HD patients with and without AF

Figure 2

Kaplan Meier survival curve of time to stroke in all period-prevalent HD patients with AF comparing warfarin or no warfarin users

Table 1

Stroke vs no stroke, ischemic stroke and hemorrhagic stroke during follow-up

Table 2

Stepwise regression of Cox PH model with and without prior cerebrovascular disease

Variable	No stroke follow up	Stroke during follow up	p	IS	HS	p (IS vs. no stroke)
	1222(88.4)	160(11.6)	-	152(11.0)	8(0.6)	
Male(%)	726(59.4)	83(51.9)	0.069	77(50.7)	6(75)	0.04
Age at starting RRT(years)	59.9±16.7	65.7±14.3	<0.001	66.3±14.2	54.4±14	<0.001
Race(%)						
White	1125 (92.0)	155(96.9)	0.151	148(97.4)	7(87.5)	0.12
Black	6(0.5)	0(0)		0(0)	0(0)	
South Asian	79(6.5)	5(3.1)		4(2.6)	1(12.5)	
Other	12(1.0)	0(0)		0(0)	0(0)	
Incident patients(%)	731(59.8)	90(56.3)	0.387	88(57.9)	2(25)	0.65
Dialysis vintage* (median days and IQR)	1248(2344)	1080(1286)	0.075	1046(1286)	1268(1330)	0.08
Diabetes(%)	331(27.1)	57(35.6)	0.024	56(36.8)	1(12.5)	0.01
AF(%)	256(20.9)	37(23.1)	0.527	36(23.7)	1(12.5)	0.44
Previous CVD(%)	284(23.2)	43(26.9)	0.309	42(27.6)	1(12.5)	0.23
Previous CeVD(%)	30(2.5)	21(13.1)	<0.001	21(13.8)	0(0)	<0.001
Warfarin(%)	203(16.6)	36(22.5)	0.064	35(23.0)	1(12.5)	0.05
Antiplatelet(%)	958(78.4)	133(83.1)	0.168	128(84.2)	5(62.5)	0.10
Hemoglobin(g/dL)	11.1±1.6	11.0±1.7	0.804	11.0±1.6	10.4±1.9	0.99
Albumin(g/L)	33±6	33±5.0	0.69	33±5	33±7	0.68
Urea reduction ratio	72±8	72±8	0.863	72±8	74±7	0.99
Post dialysis K(mmol/L)	3.5±0.5	3.6±0.5	0.041	3.6±0.5	3.4±0.5	0.03
Pre-dialysis PO4(mmol/L)	1.64±0.57	1.65±0.47	0.856	1.65±0.47	1.75±0.52	0.95
Pre-dialysis SBP(mmHg)	143±26	145±29	0.282	146±30	135±24	0.21
Pre-dialysis DBP(mmHg)	74±15	70±16	0.007	70±16	71±18	0.01

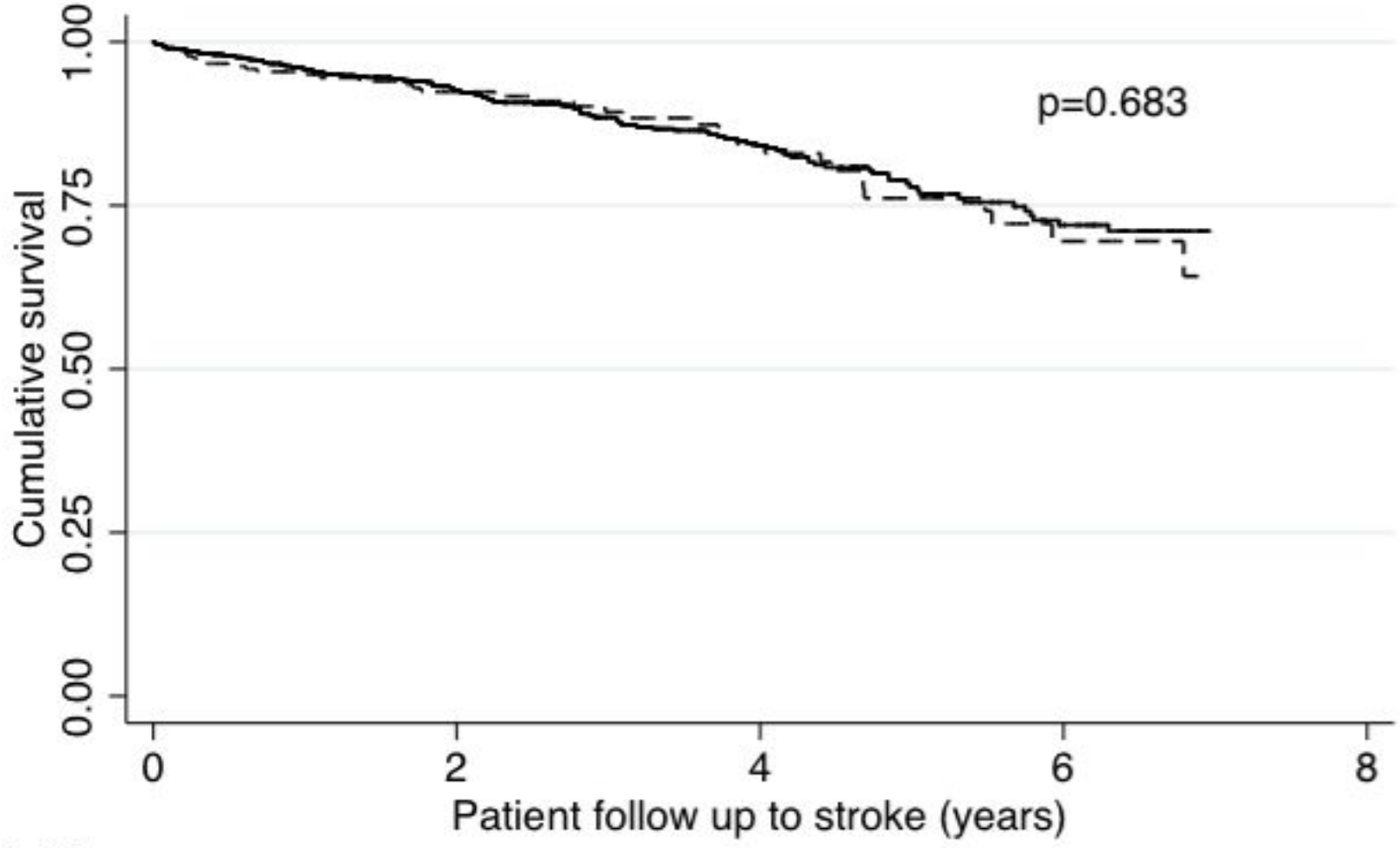
Table 1 Stroke vs no stroke. The following non-significant values have been removed: Pre – dialysis potassium, adjusted serum calcium, ultrafiltration volume, post-dialysis blood pressure. Abbreviations: IS = ischemic stroke, HS=hemorrhagic stroke, AF= atrial

fibrillation, RRT = renal replacement therapy, CVD=cardiovascular disease, CeVD=cerebrovascular disease, K= serum potassium, PO4=serum phosphate, SBP=systolic blood pressure, DBP=diastolic blood pressure. *Prevalent patients only

Model 1				
Variable	**HR**	**95% HR Confidence Limits**		**p-value**
Previous CeVD	4.5	2.7	7.3	<0.0001
Age at starting RRT(y)	1.0	1.0	1.1	<0.0001
Post dialysis K(mmol/L)	1.3	0.9	1.7	0.13
Diabetes	1.5	1.0	2.1	0.04
Model 2				
Variable	**HR**	**95% HR Confidence Limits**		**p-value**
Age at starting RRT(y)	1.0	1.0	1.05	<0.0001
Post dialysis K(mmol/L)	1.3	0.99	1.8	0.06
Diabetes	1.6	1.1	2.2	0.01

Table 2: Stepwise Cox proportional hazards regression looking at time to stroke, n=1121. The following non-significant (p>0.05) covariates were removed; prior cardiovascular disease, atrial fibrillation, use of warfarin or antiplatelet therapy, serum albumin, calcium, phosphate, blood haemoglobin, pre dialysis systolic blood pressure, ultrafiltration volume urea reduction ratio and incident haemodialysis status. Post HD potassium was retained as it was of clinical interest. Using these four variables generated model 1 where previous CeVD, age at starting RRT and diabetes are

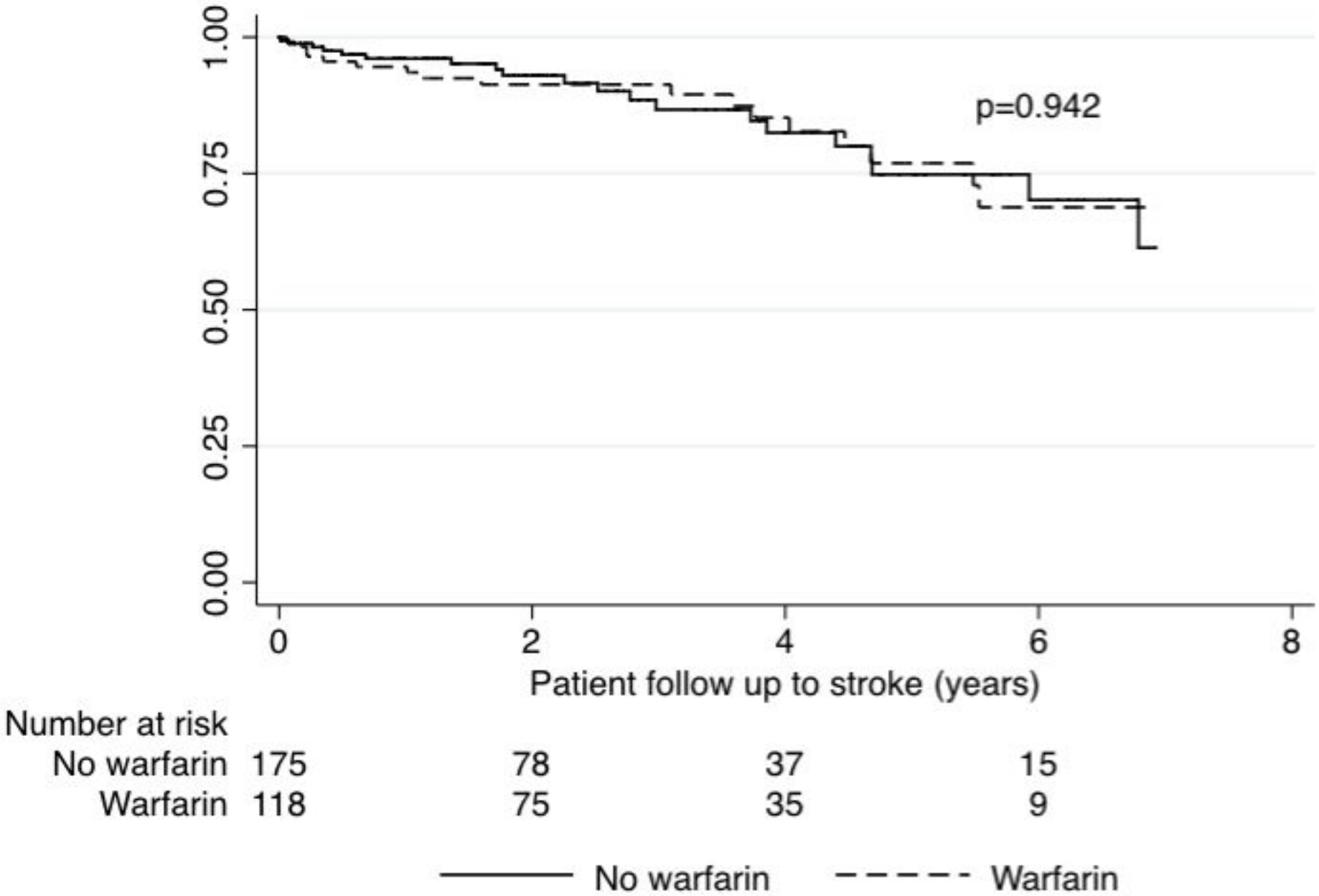
significant associations. Removing previous CeVD from the analysis (model 2) retains age and diabetes only.



Number at risk

No AF	1089	544	245	97
AF	293	153	72	24

No AF AF


1.00
0.75
0.50
0.25
0.00
p=0.942
0
2
4
6
8
Patient follow up to stroke (years)
Number at risk
No warfarin 175 78 37 15
Warfarin 118 75 35 9
No warfarin
Warfarin

SUPPLEMENTAL MATERIAL

	Population at risk		Age-specific Incidence rate per 100 000 (95% CI)					
			n	**All HD patients**	*n*	**Female**	*n*	**Male**
Age (y)	**Male**	**Female**		(n=1382)		(n = 573)		(n=809)
<25	14	11	0	0	0	0	0	0
25-34	20	17	2	2304.3 (585.6 – 9067.0)	2	5793.9 (1509.3 - 22241.8)	0	0
35-44	91	46	9	2209.1 (1157.8 - 4215.1)	2	1619.6 (409.7 - 6403.4)	7	2465.5 (1186.3 - 5124.4)
45-54	122	72	13	2375.2 (1388.2 – 4064.1)	7	3366.7 (1625.3 - 6973.8)	6	1767.8 (799.9 - 3907.1)
55-64	159	94	30	4476.0 (3155.0 – 6350.1)	10	3963.0 (2159.0 -7274.7)	20	4785.7 (3120.5 - 7339.6)
65-74	208	170	52	5139.9 (3944.4 – 6697.6)	22	4589.5 (3051.4 - 6902.9)	30	5635.3 (3980.7 - 7977.8)
75-84	169	143	45	7141.0 (5388.7 – 9463.2)	28	9305.1 (6539.2 - 13240.8)	17	5163.2 (3249.9 - 8202.9)
>85	26	20	9	11864.3 (6424.9 – 21908.5)	6	28662.0 (14581.4 - 56339.7)	3	5462.1 (1817.7 - 16413.2)
All ages	809	573	160	4595.0 (3949.6 – 5345.8)	77	5363.4 (4315.9 - 6665.1)	83	4055.8 (3285.2 - 5007.2)
Standardised rate				1816.8 (1535.3-2098.3)		2478.8 (1925.1 – 3032.4)		1387.5 (1089.0-1686.0)

(1) Table I) Incidence rates of stroke (first-ever and recurrent) of hemodialysis study population. Age standardisation with the WHO world standard population distribution, based on world average population between 2000-2025 (Ahmad et al, 2001) was performed by the direct method.

SUPPLEMENTAL MATERIAL

	Population at risk		Age-specific Incidence rate per 100 000 (95% CI)					
			n	**All HD patients**	*n*	**Female**	*n*	**Male**
Age (y)	**Male**	**Female**		(n=1331)		(n = 555)		(n=776)
<25	14	11	0	0	0	0	0	0
25-34	20	17	2	2304.3 (585.6 - 9067.0)	2	5793.9 (1509.3 - 22241.8)	2	0
35-44	90	45	7	1744.0 (836.8 - 3634.6)	1	816.7 (116.0 - 5751.5)	1	2151.1 (974.8 - 4746.9)
45-54	119	71	10	1883.8 (1019.5 - 3480.6)	6	2963.9 (1347.6 - 6518.9)	6	1218.0 (459.9 - 3225.8)
55-64	143	94	25	3935 (2679.7 - 5778.3)	10	3963.0 (2159.0 - 7274.7)	10	3916.5 (2384.9 - 6431.8)
65-74	200	162	47	4774.8 (3612.4 - 6311.3)	20	4285.0(2791.5 - 6580.5)	20	5215.5 (3612.5 - 7529.8)
75-84	165	136	40	6582.8 (4879.0 - 8881.6)	24	8479.6 (5783.0- 12433.6)	24	4928.9 (3056.8 - 7947.8)
>85	25	19	8	10967.2 (5703.4 - 21089.3)	5	25099.6(11754.8 - 53594.3)	5	5657.8(1885.0 - 16982.0)
All ages	776	555	139	4122.4 (3503.1- 4851.1)	68	4865.7 (3858.9 - 6135.2)	68	3596.1 (2861.9- 4518.8)
Standardised rate				1614 (1345.7 – 1882.3)		2264.3 (1726.1 – 2802.5)		1183.5 (908.2 -1458.8)

(2) Table II) Incidence rates of first –ever stroke in the study group. Age standardisation with the WHO world standard population distribution, based on world average population between 2000-2025 (Ahmad et al, 2001) was performed by the direct method.

1. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age Standardization of Rates: A New WHO Standard. Geneva, World Health Organisation, 2001. GPE Discussion Paper Series: No 31.

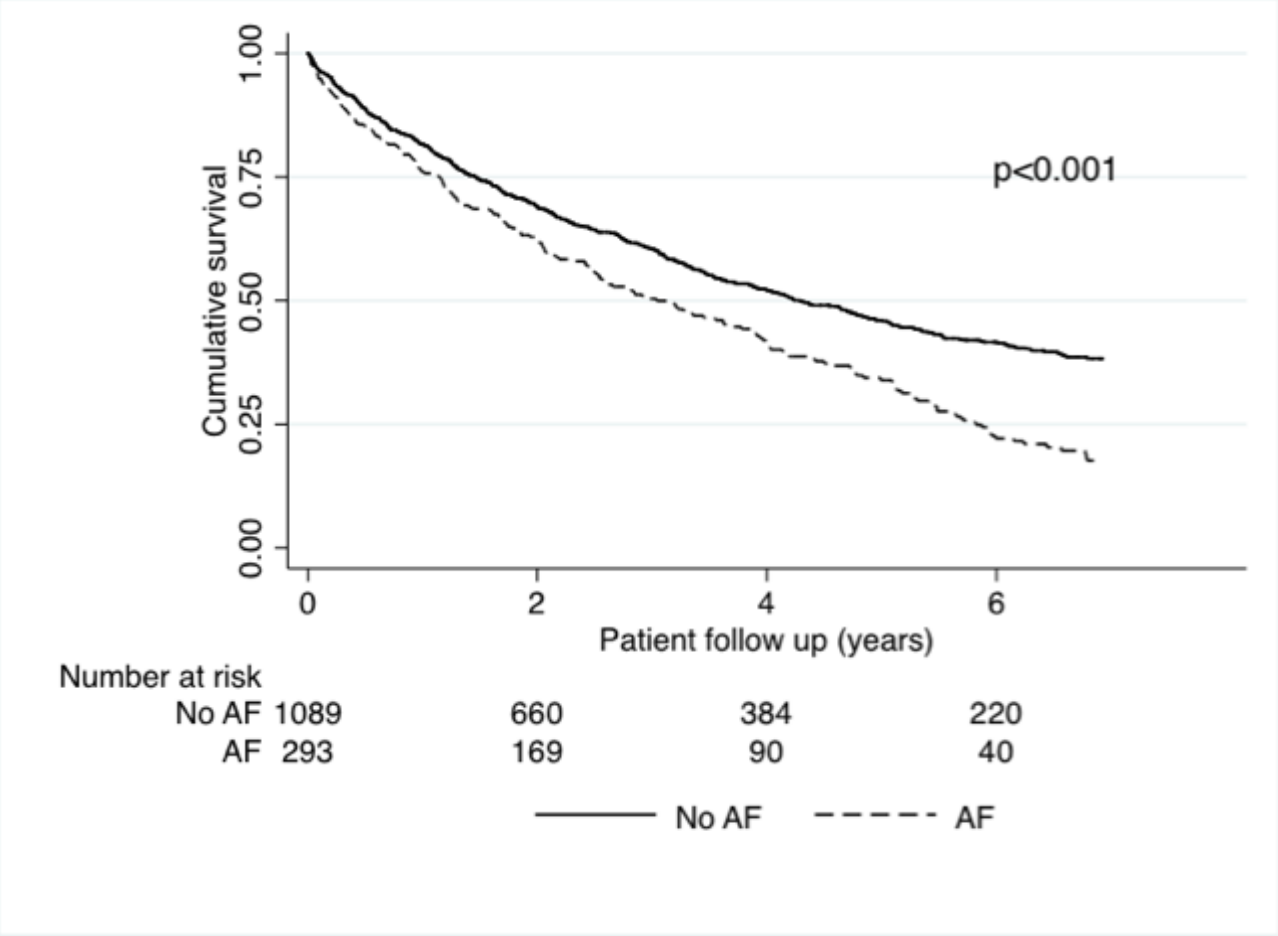


Figure I) Presence of atrial fibrillation and effect on survival, all hemodialysis patients.