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Evaluation of anticoagulation status for atrial fibrillation on early stroke outcomes

Running title: AF and stroke outcomes

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ABSTRACT

Objective: We evaluated AF and anticoagulation status in relation to early outcomes in 1656 men (mean age:73.1yr±SD=13.2) and 1653 women (79.3yr±13.0) admitted with acute stroke to hyperacute stroke units (HASUs) in Surrey between 2014-2016.

Methods: Association between AF anticoagulation status with severe stroke on arrival (National Institutes of Health Stroke Scale score≥16), prolonged HASU stay (>3wks), urinary tract infection (UTI) and pneumonia within 7days of admission, severe disability on discharge (modified Rankin Scale score≥4), and inpatient mortality was assessed by logistic regression, adjusted for age, sex, hypertension, congestive cardiac failure, diabetes, previous stroke, and stroke subtype.

Results: Compared with stroke patients free from AF, those with AF without anticoagulation had an increased adjusted risk of having more severe stroke: OR=2.3 (95%CI:1.5-3.4;*p*<0.001), prolonged HASU stay: OR=1.4 (1.0-1.9;*p*=0.027) equating to 4.6days (1.6-7.6;*p*=0.002) longer, pneumonia: OR=2.0 (1.4-2.9;*p*<0.001), more severe disability: OR=1.5 (1.2-2.0;*p*=0.004) and mortality: OR=1.8 (1.3-2.4;*p*=0.001), and AF patients with anticoagulation also had greater risk for having UTI: OR=1.8 (1.2-2.7;*p*=0.004), pneumonia: OR=1.8 (1.3-2.5;*p*=0.001), more severe disability: OR=1.5 (1.2-2.0;*p*=0.003) and mortality: OR=2.4 (1.8-3.2;*p*<0.001) which was partly explained by an increased haemorrhagic stroke (23.3 *v.s.* 6.5%). Severe stroke was associated with greater adjusted risk of UTI by 2.7-fold (1.8-3.9;*p*<0.001), pneumonia 4.3-fold (1.7-6.0;*p*<0.001), more severe disability by 10.5-fold (7.4-15.0;*p*<0.001), mortality 10.0-fold (7.3-13.6;*p*<0.001) and prolonged HASU stay 6.6-fold (4.1-10.6;*p*<0.001). These relationships persisted after excluding haemorrhagic stroke from analysis.

Conclusions: Patients with AF, particularly those without anticoagulation, are at increased risk of severe stroke; associated with prolonged HASU stay and increased risk of early infection, disability, and mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strengths of the present study include its large homogenous cohort of patients derived from one of the largest NHS regions in England.
- The analysis was robustly weighted for age and sex, as well as major chronic conditions known to associate with stroke including hypertension, CCF, diabetes, previous stroke and in particular stroke subtype.
- The data were collected by healthcare providers for the patients using national SSNAP protocol.
- Although data are derived only from Surrey it is likely to be representative of the rest of the UK as stroke prevalence is similar to that of the UK.
- The study did not collect information on the length of anticoagulation treatment for individual patients but it is likely that it is closely related to their age.

INTRODUCTION

Each year, about 6.7 million people die of stroke worldwide, accounting for 11.9% of all deaths.[1] Stroke results in adverse health consequences including physical disability and cognitive impairment [2-4] which imposes enormous burdens on patients, their carers as well as social and healthcare systems.[5,6]

Patients with existing co-morbidities such as diabetes and cardiovascular diseases including coronary heart disease, poorly controlled hypertension or congestive heart failure (CCF) have an increased risk of stroke, but atrial fibrillation (AF) remains the biggest risk factor.[7,8] Although outcomes for stroke patients have improved significantly in the UK since the introduction of organised HASU care provided by multidisciplinary teams,[9,10] the elderly and those who have chronic health conditions continue to have increased risk of mortality and disability, as well as time to recovery requiring longer stay in hospital after a stroke.[11-13]

The present study aimed to evaluate the relationship of patients with AF and their anticoagulation status on the severity of stroke on admission, length of stay in hyperacute stroke unit (HASU), early disability on discharge and inpatient mortality.

METHODS

Patients and setting

A total of 3309 patients from Surrey, a relatively stable and homogenous population, were admitted to four HASUs within the county (one of the largest National Health Service regions in the England). The hospitals, Ashford and St Peter's (n = 1038), Frimley Park (n = 1010) and Royal Surrey County (n = 612) and Epsom (n = 649)

were surveyed between January 2014 and February 2016 for Sentinel Stroke National Audit Programme (SSNAP).[12] Twenty-two patients were admitted twice and two patients three times. For the purpose of analysis, data from the first admission for these 24 patients who were admitted multiple times were used.

Socio-demographic factors and medical history

All four study centres participated in SSNAP using identical protocols (available on request). Data were collected for socio-demographic factors including age at arrival, sex and ethnicity, as well as past medical history including AF, hypertension, CCF, diabetes mellitus, previous stroke and drug history including anticoagulants. In addition, details of new onset AF cases as well as urinary tract infection (UTI) and pneumonia acquired in hospital within seven days of admission were documented by the stroke team comprising consultants and stroke nurse specialists, including anticoagulation treatment from the point of admission to discharge.

Diagnosis of stroke and severity

Stroke was diagnosed based on clinical presentation and brain CT scan as guided by the National Institute for Health and Care Excellence (NICE).[14] The severity of stroke symptoms was assessed by the National Institutes of Health for Stroke Scale (NIHSS) with score range from no symptoms to severe stroke symptoms (NIHSS score: 0 to 42).

Disability and mortality

Degree of disability or dependence in daily activities were assessed by a modified Rankin Scale (mRS), ranging from no symptoms to severe symptoms (mRS score: 0 to 5) and mortality (mRS score: 6).

Categorisation of variables

Dichotomisation was applied for hypertension, CCF and diabetes according to the presence of history of the condition or not while age was dichotomised at the median value (<79 and ≥79 years). AF and anticoagulation status were categorised into four groups: free from AF; AF with anticoagulation; AF without anticoagulation; and AF unsuitable for anticoagulation. Severity of stroke and disability were dichotomised into two groups: no symptoms to moderate symptoms (NIHSS score <16 and mRS score <4) and moderately-severe to severe (NIHSS score ≥16 and mRS score ≥4). Prolonged stay in HASU was defined as patients who stayed in a HASU >3 weeks (upper fourth quartile of length of stay).

Statistical analysis

The frequency of patients with AF using anticoagulation before developing an ischaemic or haemorrhagic stroke was assessed by cross tabulation and chi-squared tests. Most variables had no missing data, except for information on type of stroke (1%), which were handled in analysis using a 'listwise deletion of missing data' approach.[15] Independent *t*-tests were performed to compare differences between two groups and analysis of variance (ANOVA) between three or more groups, with *post-hoc* analysis where applicable. Multivariable logistic regression was performed to assess the risk of moderately-severe to severe stroke on arrival

and disability on discharge, inpatient mortality after stroke and prolonged stay in HASU (dependent variables) from co-morbidities including AF, hypertension, CCF, diabetes and previous stroke (independent variables). Two logistic regression models were conducted, the first model was adjusted for age, sex, co-morbidities and stroke subtype (ischaemic and haemorrhagic) and the second model was a repeat of the first but haemorrhagic stroke cases were excluded, *i.e.* only ischaemic stroke patients were analysed (without stroke subtype as a confounding factor). Analyses were performed using SPSS V.22.0 (SPSS Inc, Chicago, Illinois, USA). The null hypothesis was rejected when p <0.05.

RESULTS

Admissions for stroke were equally distributed between men and women, with the onset of the first stroke 6.1 years (95% CI: 5.2, 7.0, p <0.001) earlier in men (**Table 1**). There were 76.9% of patients presented with first stroke and 23.1% with recurrent stroke: 83.3% with ischaemic stroke, 15.7% haemorrhagic stroke and 1% unspecified. Most patients were white Caucasians (92.1%) with the remaining 6.8% comprises mixed race, Black, Asian and other ethnic populations, and 1.2% not stated. On arrival, 666 (20.1%) patients had a history of AF, in whom 45.3% were treated in the community with an anticoagulant whilst 54.7% were untreated although 12.8% had been considered for anticoagulation and deemed unsuitable by their healthcare providers. Also on arrival, 7.7% of patients had moderate to severe stroke symptoms (NIHSS score 16-20) and 6.9% had severe symptoms (NIHSS 21-42). The remainder had no symptoms (13.4%, NIHSS 0); minor (38.2%, NIHSS 1-4) or moderate (33.8%, NIHSS 5-15) symptoms: a more detailed analysis of NIHSS scores is shown in **Figure 1**. The median length of stay in a HASU was 6.9 days

(interquartile range 2.7, 21.0) with a quarter of patients stayed >3 weeks (prolonged stay). On discharge 11.2% and 4.9% of the original patients respectively had moderately severe (mRS score: 4) or severe (mRS score: 5) symptoms. The rate of inpatient mortality was 15.1%. (**Table 1**).

Patients free from AF had significantly less severe stroke on admission as reflected by a lower NIHSS score (F = 19.2, p <0.001) and disability on discharge as indicated by a lower mRS score (F = 25.7, p <0.001) than patients with AF of any anticoagulation status (with anticoagulation, without anticoagulation or unsuitable for anticoagulation in the community) (**Figure 2**). ANOVA with *post-hoc* analysis by least significant difference tests showed that NIHSS score on arrival (**Figure 2a**) and mRS on discharge **(Figure 2b**) were significantly lower (p <0.001) for those free from AF compared with any of the other three groups of patients with AF (with anticoagulation, without anticoagulation or unsuitable for anticoagulation). The NIHSS score for those with AF who were treated with anticoagulant was also lower (p = 0.049) than that of those with AF without anticoagulation.

Table 2 shows that compared with stroke patients free of AF, those with AF but not anticoagulated had an increased adjusted risk of having more severe stroke (NIHSS score ≥16): OR = 2.3 (95%CI: 1.5-3.4, p<0.001), prolonged stay in HASU (>3 weeks): OR = 1.4 (1.0-1.9, p = 0.027) equating to 4.6 (1.6-7.6) days longer (p = 0.002), pneumonia: OR = 2.0 (1.4-2.9; p<0.001), more severe disability: OR = 1.5 (1.2-2.0; p=0.004) and mortality: OR = 1.8 (1.3-2.4; p=0.001). Patients with AF with anticoagulation also had greater risk than those free of AF for having UTI: OR = 1.8 (1.2-2.7; p=0.004), pneumonia: OR = 1.8 (1.3-2.5; p=0.001), more severe disability:

OR = 1.5 (1.2-2.0; *p*=0.003) and mortality: OR = 2.4 (1.8-3.2; *p*<0.001) which was partly explained by an increased haemorrhagic stroke (23.3 *v.s.* 6.5%). After the exclusion of haemorrhagic stroke cases, these ORs diminished to 1.2-fold (0.9-1.7, *p* = 0.198) for disability and 1.9-fold (1.4-2.8, *p* <0.001) for mortality. Significant relationships between AF patients without anticoagulation and the remaining outcomes continued to persist after excluding haemorrhagic stroke patients from analysis (**Model 2, Table 2**).

Logistic regression with adjustment of age, sex, co-morbidities including AF status and stroke subtype showed that patient with severe stroke on arrival were at greater risk of UTI by 2.7-fold (1.8-3.9;*p*<0.001), pneumonia 4.3-fold (1.7-6.0;*p*<0.001), more severe disability by 10.5-fold (7.4-15.0;*p*<0.001), mortality 10.0-fold (7.3-13.6;*p*<0.001) and prolonged HASU stay 6.6-fold (4.1-10.6;*p*<0.001) (**Model 1, Table 3**). Excluding haemorrhagic stroke cases from analysis resulted in minor changes to these ORs (**Model 2, Table 3**).

Longer stay in HASU was found in stroke patients with AF without anticoagulant than those free from AF by 4.6 days (1.6-7.6, *p* = 0.002) while anticoagulation in patients with AF reduced the length of stay in HASU to the same level of that observed in patients free from AF (*i.e.* no significant differences in length of stay between these two groups). Compared with the less severe stroke (NIHSS score <16) group of patients, those with more severe stroke (NIHSSS score ≥16) stayed in HASU longer by 20.2 days (15.6-24.7, *p* <0.001) (**Table 4**). Similar results were observed for length of hospital stay (results not shown).

DISCUSSION

We show that compared to patients without a history of AF, those with AF without anticoagulation had a greater risk of severe stroke (NIHSS score ≥16), prolonged stay in HASU (>3 weeks), risk of early pneumonia, more severe disability on discharge (mRS score ≥4) and inpatient mortality by 1.4- to 2.4-fold. It is notable that AF patients who were anticoagulated reduced their risk of severe stroke and length of stay in a HASU to the same level as those who were free from AF. In turn, compared with patients with less severe stroke, those with severe stroke had an increased risk of prolonged stay in HASU by 6.5-fold, early hospital acquired infections by 3- to 4-fold, having more severe disability on discharge by 10.5-fold and mortality by 10-fold. The increased risk of severe stroke on arrival, prolonged stay in HASU, more severe disability on discharge and inpatient mortality in patients with AF without anticoagulation was independent of age, sex, hypertension, CCF, diabetes, previous stroke and haemorrhagic stroke.

Given the growing ageing population,[16] disability from stroke will continue to impose massive burdens on healthcare systems in the foreseeable future worldwide, including the UK. There is therefore a need for early identification of AF, the biggest treatable risk factor of stroke, through systematic screening of at-risk patients in the community and intensive treatment for those diagnosed with AF.[17] However, there is evidence of under-treatment of AF in the community indicated in our recent study of this cohort of patients. We found a high proportion (95%) of AF patients who were not on anticoagulation in the community were anticoagulated on discharge after admission for acute stroke (**Han et al, 2017 unpublished**). Similar findings were observed in other studies including that of Perez et al who found that only 50% of

patients with AF who were eligible for anticoagulation were given this treatment,[18] while Waldo et al studied 945 patients and found that of the 86% of patients who were at high risk of stroke, only 55% received warfarin.[19] Greater collaboration between primary care and specialist cardiology services is necessary to improve stroke prevention through appropriate treatment of AF, particularly weighing up benefit: risk ratio for patients who pose as a treatment dilemma for anticoagulation, such as those with a history of bleeding. Other preventable risk factors such as obesity, hypertension, dyslipidaemia and hyperglycaemia/insulin resistance [17,20,21] should also be managed intensively.

A number of important findings emerge from the present study. All patients with AF, whether treated or untreated with an anticoagulant, have increased risks of early hospital acquired infections, disability and mortality. This suggests the inherent risk of AF that may be associated with other causes of cardiovascular disease leads to worse outcomes of stroke.[22] The increased risk of mortality in patients with AF who were treated with anticoagulation is partly due to the greater occurrence of haemorrhagic stroke associated with anticoagulation as shown in our study, and is a well-recognised adverse effect of anticoagulation.[23,24] In the present study, we conducted two models of logistic regression to minimise the confounding effect of haemorrhagic stroke on the outcomes. When haemorrhagic stroke cases were excluded from analysis (15.7% of the sample), the risk for severe disability on discharge and mortality observed in stroke patients with AF who were treated with anticoagulant was reduced substantially (in the case of disability, to non-significant level). In addition, we observed that there was no greater risk for having more severe stroke or prolonged stay in HASU among stroke patients with AF who were

anticoagulated than that of those who were free of AF; this evidence reinforces the value of intensive treatment of AF with anticoagulants.[25]

The strengths of the present study include its large homogenous cohort of patients derived from one of the largest NHS regions in England. The analysis was robustly weighted for age and sex, as well as major chronic conditions known to associate with stroke including hypertension, CCF, diabetes, previous stroke and in particular stroke subtype. The data were collected by healthcare providers for the patients using national SSNAP protocol. Our study focused on early disability on discharge and inpatient mortality. It would be of interest to assess the impact of AF anticoagulation status on these outcomes in longer term. Although data are derived only from Surrey it is likely to be representative of the rest of the UK as stroke prevalence is similar to that of the UK.[12] The study did not collect information on the length of anticoagulation treatment for individual patients but it is likely that it is closely related to their age. We chose cutoff point for NIHSS score at 16 based on previous studies showing that a baseline score of ≥16 (moderately-severe to severe stroke) was a strong predictor of mortality or severe disability,[26] while cutoff point for mRS score at 4 indicates that beyond this point, functional disability begins to worsen due to increasing severity of stroke.[27] “Prolonged stay” has variably been described.[28] In the present study, we defined prolonged stay for those who stayed in HASU >3 weeks as this point reflects the upper quartile of length of stay in HASU. It should be emphasised that these cutoff points tend to be arbitrary and the higher the level, the more severe is the condition. We have explored various other levels including cutoff points for NIHSS score at 12, mRS score at 3 and length of stay in

HASU at 1 week (50th centile) all showing similar patterns of, but weaker, association with AF treatment status.

In conclusion, patients with AF, particularly those without anticoagulation, are at increased risk of severe stroke; associated with prolonged HASU stay and increased risk of early infection, disability, and mortality.

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Contributorship: TSH and PS reviewed the topic related literature. BA, GG, CB, PK and TP performed the study coordination and data collection. TSH and PS performed the study concept and analysis design. TSH wrote the first draft, analysed and interpreted the data and revised the manuscript. CHF and PS edited the manuscript. All authors checked, interpreted results and approved the final version. TSH and PS are the guarantors for the study.

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LEGENDS

Figure 1. Distribution of patients against severity of stroke on admission based on NIHSS score.

Figure 2. Box plots showing AF and anticoagulation status in relation to stroke severity on arrival indicated by NIHSS score (a) and severity of disability on discharge indicated by mRS score (b). ANOVA showed significant group differences (p <0.001) therefore *post hoc* least significant difference tests were performed to compare NIHSS score between those †free from AF (No AF) and other three AF groups of different anticoagulation status, and between *AF with anticoagulation (AF-treated) and AF without anticoagulation (AF-untreated) groups. Box plots representing median and interquartile ranges; whiskers represent the 5th and 95th percentiles.

Table 1. Distribution of 3309 patients, 1656 men (mean age: 73.1 years ±SD 13.2) and 1653 women (79.3 years ±13.0), admitted with acute stroke to hospitals in Surrey between January 2014 and February 2016.

	n	Proportion (%)
Men: women	1650: 1653	50.0: 50.0
Caucasian: mixed race: not stated	3046: 95: 129	92.1: 2.9: 3.9
First stroke/TIA: Recurrent stroke/TIA	2543: 766	76.9: 23.1
Ischaemic stroke: haemorrhagic stroke	2758: 518	83.3: 15.7
Atrial fibrillation	666	20.1
AF with anticoagulation	302	45.3
AF without anticoagulation	279	41.9
AF not suitable for anticoagulation	85	12.8
Hypertension	1729	52.3
CCF	194	5.9
Diabetes	531	16.0
Stroke severity on arrival		
No stroke symptoms (NIHSS score: 0)	444	13.4
Minor stroke (NIHSS score: 1-4)	1263	38.2
Moderate stroke (NIHSS score: 5-15)	1120	33.8
Moderate to severe stroke (NIHSS score: 16-20)	255	7.7
Severe stroke (NIHSS score: 21-42)	227	6.9
Modified Rankin Scale on discharge (n = 3174)		
No symptoms (mRS score: 0)	760	23.9
No significant disability (mRS: 1)	553	17.4
Slight disability (mRS score: 2)	448	14.1
Moderate disability (mRS score: 3)	424	13.4
Moderately severe disability (mRS score: 4)	355	11.2
Severe disability (mRS score: 5)	154	4.9
Dead (mRS score: 6)	480	15.1

Table 2. Chi-squared test and logistic regression to assess the association of AF and anticoagulation status with moderately-severe to severe stroke (NIHSS score ≥16), UTI and pneumonia within seven days of admission, prolonged stay in HASU, moderately-severe to severe disability (mRS score ≥4) on discharge and mortality.

	Proportion of cases and χ^2 test for group differences			Model 1: Adjusted for age, sex, co-morbidities† and stroke subtype in all patients			Model 2: Adjusted for age, sex, co-morbidities† in ischaemic stroke patients*		
Severe stroke on arrival (NIHSS ≥16) (n = 227)	**%**	**χ^2**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Free from AF	5.8			1	--	--	1	--	--
AF with anticoagulation	8.9			1.31	0.84-2.04	0.233	1.24	0.72-2.13	0.440
AF without anticoagulation	14.0	**29.8**	**<0.001**	**2.28**	**1.54-3.37**	**<0.001**	**2.42**	**1.60-3.64**	**<0.001**
AF not suitable for anticoagulation	9.4			1.41	0.663.03	0.373	1.31	0.55-3.14	0.539
Prolonged stay in HASU (>3 weeks) (n = 657)									
Free from AF	23.9			1	--	--	1	--	--
AF with anticoagulation	25.6			0.92	0.65-1.30	0.640	0.87	0.59-1.28	0.475
AF without anticoagulation	33.2	**10.6**	**0.014**	**1.42**	**1.04-1.94**	**0.027**	**1.42**	**1.03-1.97**	**0.034**
AF not suitable for anticoagulation	32.2			1.22	0.69-2.15	0.503	1.42	0.79-2.58	0.242
UTI within 7 days of admission (n = 243)									
Free from AF	6.2			1	--	--	1	--	--
AF with anticoagulation	13.4			**1.80**	**1.21-2.68**	**0.004**	**1.88**	**1.18-2.97**	**0.007**
AF without anticoagulation	10.5	**45.3**	**<0.001**	1.38	0.89-2.13	0.151	1.49	0.95-2.33	0.081
AF not suitable for anticoagulation	21.3			**3.26**	**1.81-5.85**	**<0.001**	**2.96**	**1.55-5.65**	**0.001**
Pneumonia within 7 days of admission (n = 358)									
Free from AF	9.0			1	--	--	1	--	--
AF with anticoagulation	19.0			**1.81**	**1.29-2.54**	**0.001**	**1.60**	**1.06-2.40**	**0.025**
AF without anticoagulation	19.3	**73.2**	**<0.001**	**2.03**	**1.44-2.87**	**<0.001**	**2.05**	**1.44-2.94**	**<0.001**
AF not suitable for anticoagulation	28.8			**3.18**	**1.89-5.36**	**<0.001**	**3.04**	**1.73-5.37**	**<0.001**
Moderately-severe to severe disability on discharge (mRS ≥4) (n = 181)									
Free from AF	26.8			1	--	--	1	--	--
AF with anticoagulation	43.7			**1.49**	**1.20-2.02**	**0.003**	1.20	0.90-1.66	0.198
AF without anticoagulation	40.5	**26.9**	**<0.001**	**1.50**	**1.14-1.96**	**0.004**	**1.56**	**1.18-2.06**	**0.002**
AF not suitable for anticoagulation	42.4			1.47	0.92-2.33	0.107	1.60	0.97-2.62	0.065
Inpatient mortality (n = 480)									

Free from AF	11.8	**88.5**	**<0.001**	1	--	--	1	--	--
AF with anticoagulation	29.8			**2.38**	**1.78-3.20**	**<0.001**	**1.94**	**1.35-2.78**	**<0.001**
AF without anticoagulation	21.1			**1.75**	**1.26-2.43**	**0.001**	**1.86**	**1.32-2.61**	**<0.001**
AF not suitable for anticoagulation	23.5			**1.82**	**1.06-3.13**	**0.030**	**1.83**	**1.01-3.30**	**0.046**

*Exclusion of 518 (15.7%) haemorrhagic stroke patients; †Co-morbidities: CCF, hypertension, diabetes and previous stroke.

Table 3. Chi-squared test and logistic regression to assess the association of stroke severity on arrival with UTI and pneumonia with seven days of admission, length of stay in HASU, disability on discharge and inpatient mortality.

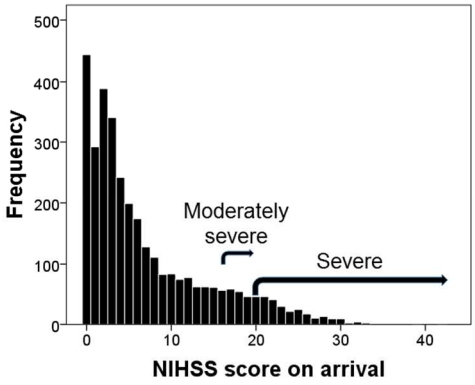
	Proportion of cases (%) and chi-squared test for group differences			Model 1: logistic regression adjusted for age, sex, co-morbidities† and stroke subtype in all patients			Model 2: logistic regression adjusted for age, sex, co-morbidities† in ischaemic stroke patients		
	%	χ^2	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Prolonged stay in HASU (>3 weeks)									
No symptoms to moderate stroke symptoms (NIHSS <16)	23.6	**80.4**	**<0.001**	1	--	**--**	1	--	**--**
Moderately-severe to severe stroke (NIHSS ≥16)	66.7			**6.57**	**4.09-10.55**	**<0.001**	**6.89**	**4.15-11.43**	**<0.001**
Urinary tract infection within 7 days of admission									
No symptoms to moderate stroke symptoms (NIHSS <16)	6.7	**56.1**	**<0.001**	1	--	**--**	1	--	**--**
Moderately-severe to severe stroke (NIHSS ≥16)	20.6			**2.67**	**1.83-3.89**	**<0.001**	**2.97**	**1.93-4.57**	**<0.001**
Pneumonia within 7 days of admission									
No symptoms to moderate stroke symptoms (NIHSS <16)	9.4	**142.1**	**<0.001**	1	--	**--**	1	--	**--**
Moderately-severe to severe stroke (NIHSS ≥16)	35.9			**4.34**	**1.72-5.97**	**<0.001**	**5.09**	**3.54-7.31**	**<0.001**
Moderately severe to severe disability on discharge (mRS ≥4)									
No symptoms to moderate stroke symptoms (NIHSS <16)	26.2	**299.3**	**<0.001**	1	--	**--**	1	--	**--**
Moderately-severe to severe stroke (NIHSS ≥16)	80.6			**10.54**	**7.39-15.03**	**<0.001**	**10.09**	**6.87-14.83**	**<0.001**
Inpatient mortality									
No symptoms to moderate stroke symptoms (NIHSS <16)	11.2	**389.6**	**<0.001**	1	--	**--**	1	--	**--**
Moderately-severe to severe stroke (NIHSS ≥16)	59.0			**9.99**	**7.34-13.58**	**<0.001**	**9.56**	**6.76-13.52**	**<0.001**

†Co-morbidities: atrial fibrillation, CCF, hypertension, diabetes and previous stroke.

Table 4. Analysis of variance to assess the length of stay in HASU for patients without AF and those with AF of different anticoagulation status, and independent t-tests to assess the length of stay in HASU for patients with different stroke severity on arrival.

	Mean (SD) length of stay (days)	Difference from referent group		
		Mean difference	95% CI	*p*
Free from AF (referent)†	15.6 (21.0)	--	--	--
AF with anticoagulation	16.3 (19.6)	0.8	-2.3 to 3.8	0.620
AF without anticoagulation	20.2 (22.9)	**4.6**	**1.6 to 7.6**	**0.002**
AF not suitable for anticoagulation	20.3 (24.8)	4.7	-0.7 to 10.2	0.090
No symptoms to moderate stroke (NIHSS <16) (referent)‡	15.4 (20.6)	--	--	--
Moderately severe to severe stroke (NIHSS ≥16)	35.6 (27.3)	**20.2**	**15.6 to 24.7**	**<0.001**

†ANOVA with *post-hoc* test by least significant difference: $F = 3.8$, $p = 0.009$; ‡independent t-test.



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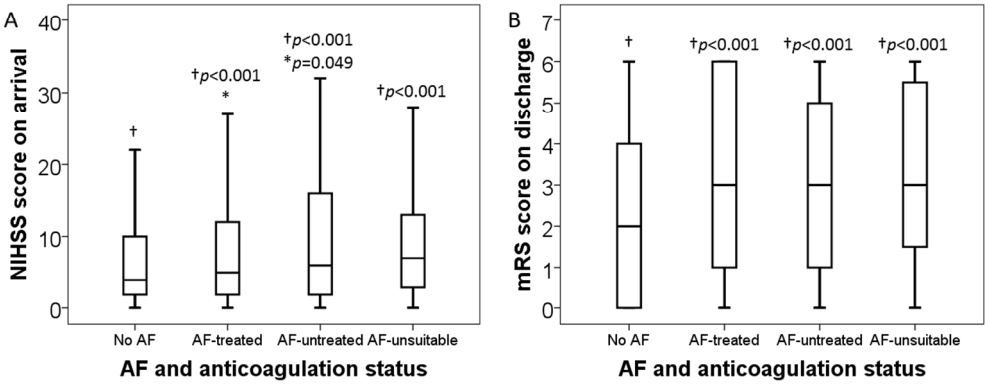

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Evaluation of anticoagulation status for atrial fibrillation on early ischaemic stroke outcomes: a registry-based, prospective cohort study of acute stroke care in Surrey, United Kingdom

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ABSTRACT

Objective: The relationship of anticoagulation therapies with stroke severity and outcomes have been well-documented in the literature. However, none of the previous research has reported the relationship of atrial fibrillation (AF)/anticoagulation therapies with urinary tract infection (UTI), pneumonia and length of stay in hyperacute stroke units (HASU). The present study aimed to evaluate AF and anticoagulation status in relation to early outcomes in 1387 men (median age=75yrs, IQR=65-83) and 1371 women (median age=83yrs, IQR=74-89) admitted with acute ischaemic stroke to HASUs in Surrey between 2014-2016.

Methods: We conducted this registry-based, prospective cohort study using data from the Sentinel Stroke National Audit Programme. Association between AF anticoagulation status with severe stroke on arrival (National Institutes of Health Stroke Scale score≥16), prolonged HASU stay (>3wks), UTI and pneumonia within 7days of admission, severe disability on discharge (modified Rankin Scale score=4 and 5), and inpatient mortality was assessed by logistic regression, adjusted for age, sex, hypertension, congestive heart failure, diabetes and previous stroke.

Results: Compared with stroke patients free from AF, those with AF without anticoagulation had an increased adjusted risk of having more severe stroke: 5.8% *v.s.* 14.0%, OR=2.4 (95%CI:1.6-3.6,p<0.001), prolonged HASU stay: 21.5% *v.s.* 32.0%, OR=1.4 (1.0-2.0,p=0.027), pneumonia: 8.2% *v.s.* 19.1%, OR=2.1 (1.4-2.9,p<0.001), more severe disability: 24.2 *v.s.* 40.4, OR=1.6 (1.2-2.1,p=0.004) and mortality: 9.3% *v.s.* 21.7%, OR=1.9 (1.4-2.8,p<0.001), and AF patients with anticoagulation also had greater risk for having UTI: 8.6% *v.s.* 12.3%, OR=1.9 (1.2-3.0,p=0.004), pneumonia: 8.2% *v.s.* 11.5%, OR=1.6 (1.1-2.4,p=0.025) and mortality: 9.7% *v.s.* 21.7%, OR=1.9 (1.4-2.8,p<0.001). The median HASU stay for stroke patients with AF without anticoagulation was 10.6days (IQR=2.8-26.4) compared with 5.8days (IQR=2.3-17.5) for those free from AF (p<0.001).

Conclusions: Patients with AF, particularly those without anticoagulation, are at increased risk of severe stroke, associated with prolonged HASU stay and increased risk of early infection, disability, and mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strengths of the present study include its large homogenous cohort of patients derived from one of the largest NHS regions in England.
- The analysis was robustly adjusted for age and sex, as well as major chronic conditions known to associate with stroke including hypertension, congestive heart failure (CHF), diabetes and previous stroke.
- The data were collected by healthcare providers for the patients using national SSNAP protocol.
- Although data are derived only from Surrey it is likely to be representative of the rest of the UK as stroke prevalence is similar to that of the UK.
- The study did not collect information on types of oral anticoagulants, international normalised ratio (INR). Information on the duration of anticoagulation treatment for individual patients was also not available but it is likely to be closely related to their age.

INTRODUCTION

Each year, about 6.7 million people die of stroke worldwide, accounting for 11.9% of all deaths.[1] Stroke results in adverse health consequences including physical disability and cognitive impairment [2-4] which imposes enormous burdens on patients, their carers as well as social and healthcare systems.[5, 6]

Patients with existing co-morbidities such as diabetes and cardiovascular diseases including coronary heart disease, poorly controlled hypertension or CHF have an increased risk of stroke, but atrial fibrillation (AF) remains the biggest risk factor.[7, 8] Although outcomes for stroke patients have improved significantly in the UK since the introduction of organised hyperacute stroke unit (HASU) care provided by multidisciplinary teams,[9, 10] the elderly and those who have chronic health conditions continue to have increased risk of mortality and disability, as well as time to recovery requiring longer stay in hospital after a stroke.[11-13] The relationship of anticoagulation therapies with stroke severity and outcomes have been well-documented in the literature.[14-16] However, none of the previous research has reported the relationship of AF/anticoagulation therapies with urinary tract infection (UTI), pneumonia and length of stay in HASU.

The present study aimed to evaluate the relationship of patients with AF and their anticoagulation status on the severity of stroke on admission, length of stay in HASU, UTI and pneumonia within the first week in hospital, early disability on discharge and inpatient mortality.

METHODS

Study design, patients and setting

We conducted this registry-based, prospective cohort study using data from the Sentinel Stroke National Audit Programme (SSNAP) which is the national register of stroke care in England and Wales. Data were collected prospectively from the time of admission up to six months after stroke and validated by Stroke teams and entered into the SSNAP database via a secure web interface. These data comprise clinical characteristics and care quality of patients admitted to all acute care hospitals in England and Wales with acute ischaemic stroke or primary intracerebral haemorrhage.[12] We used an anonymised extract of a total of 3309 patients from Surrey, a relatively stable and homogenous population, who were admitted to four HASUs within the county (one of the largest National Health Service regions in the England). The hospitals, Ashford and St Peter's (n = 1038), Frimley Park (n = 1010), Royal Surrey County (n = 612) and Epsom (n = 649) were surveyed between January 2014 and February 2016. Twenty-two patients were admitted twice and two patients three times. For the purpose of analysis, data from the first admission for these 24 patients who were admitted multiple times were used.

SSNAP has approval from the Confidentiality Advisory Group of the Health Research Authority to collect patient data under section 251 of the National Health Service Act 2006. No additional ethical approval was sought.

Socio-demographic factors and medical history

Data were collected for socio-demographic factors including age at arrival, sex and ethnicity, as well as past medical history including AF, hypertension, CHF, diabetes

mellitus, previous stroke and drug history. In addition, details of new onset AF cases as well as UTI and pneumonia acquired in hospital within seven days of admission were documented by the stroke team comprising consultants and stroke nurse specialists, including anticoagulation treatment from the point of admission to discharge.

Diagnosis of stroke and severity

Stroke was diagnosed based on clinical presentation and brain CT scan as guided by the National Institute for Health and Care Excellence (NICE).[17] The severity of stroke symptoms was assessed by the National Institutes of Health for Stroke Scale (NIHSS) with score range from no symptoms to severe stroke symptoms (NIHSS score = 0 to 42).

Disability and mortality

Degree of disability or dependence in daily activities were assessed by a modified Rankin Scale (mRS), ranging from no symptoms to severe symptoms (mRS score = 0 to 5) and mortality (mRS score = 6).

Categorisation of variables

Dichotomisation was applied for hypertension, CHF and diabetes according to the presence of history of the condition or not while age was dichotomised at the median value (<79 and ≥79 years). AF and anticoagulation status were categorised into four groups: free from AF; AF with anticoagulation; AF without anticoagulation; and AF unsuitable for anticoagulation. Severity of stroke and disability were dichotomised into two groups: no symptoms to moderate symptoms (NIHSS score <16 and mRS

score <4) and moderately-severe to severe (NIHSS score ≥16 and mRS score = 4 and 5). Prolonged stay in HASU was defined as patients who stayed in a HASU >3 weeks (upper fourth quartile of length of stay).

Statistical analysis

Of the 3309 patients collected in the database, we analysed 2758 (83.3%) patients presented with ischaemic stroke and the remaining 518 (15.7%) patients with haemorrhagic stroke and 33 (1.0%) who were unspecified were excluded. The frequency of patients with AF using anticoagulation before developing an ischaemic stroke was assessed by cross tabulation and chi-squared tests. Most variables had no missing data, which were handled in analysis using a 'listwise deletion of missing data' approach.[18] Independent *t*-tests were performed to compare differences between two groups and analysis of variance (ANOVA) between three or more groups, with *post-hoc* analysis where applicable. Multivariable logistic regression was performed to assess the risk of moderately-severe to severe stroke on arrival and disability on discharge, inpatient mortality after stroke and prolonged stay in HASU (dependent variables) from co-morbidities including AF, hypertension, CHF, diabetes and previous stroke (independent variables). Two logistic regression models were conducted, the first model was unadjusted and the second adjusted for age, sex and co-morbidities. Analyses were performed using SPSS V.22.0 (SPSS Inc, Chicago, Illinois, USA). The null hypothesis was rejected when p <0.05.

RESULTS

Admissions for stroke were almost equally distributed between men (50.3%) and women (49.7%), with the onset of the first stroke 6.5 years (95% CI: 5.5, 7.5, p

<0.001) earlier in men. **Table 1** shows that there were 77.0% of patients presented with first stroke and 23.0% with recurrent stroke. Most patients were white Caucasians (92.2%) with the remaining 6.6% comprises mixed race, Black, Asian and other ethnic populations, and 1.2% not stated. On arrival, 546 (20.4%) patients had a history of AF, in whom 40.8% were treated in the community with an anticoagulant whilst 46.1% were untreated although 13.1% had been considered for anticoagulation and deemed unsuitable by their healthcare providers. Also on arrival, 7.1% of patients had moderate to severe stroke symptoms (NIHSS score = 16-20) and 6.3% had severe symptoms (NIHSS = 21-42). The remainder had no symptoms (13.3%, NIHSS = 0); minor (39.6%, NIHSS = 1-4) or moderate (33.7%, NIHSS = 5-15) symptoms: a more detailed analysis of NIHSS scores is shown in **Figure 1**. On discharge 10.3% and 4.7% of the original patients respectively had moderately severe (mRS score = 4) or severe (mRS score = 5) symptoms. The rate of inpatient mortality was 12.1% (**Table 1**).

Baseline characteristics of patients in different categories of AF and anticoagulation status are shown in **Table 2**. The median age of patients without AF were 77 years old while those with AF were between 83 and 84 years old. Hypertension, CHF and moderate to severe stroke were more commonly observed among patients with AF than those free of AF.

Patients free from AF had significantly less severe stroke on admission as reflected by a lower NIHSS score (F = 21.8, p <0.001) and disability on discharge as indicated by a lower mRS score (F = 20.9, p <0.001) than patients with AF of any anticoagulation status (with anticoagulation, without anticoagulation or unsuitable for

anticoagulation in the community) (**Figure 2**). ANOVA with *post hoc* analysis by least significant difference tests showed that NIHSS score on arrival (**Figure 2a**) and mRS on discharge **(Figure 2b**) were significantly lower (p <0.01) for those free from AF compared with any of the other three groups of patients with AF (with anticoagulation, without anticoagulation or unsuitable for anticoagulation). The NIHSS score for those with AF who were treated with anticoagulant was also lower than that of those with AF who were not treated with (p = 0.011) or considered unsuitable for anticoagulation (p = 0.023).

Table 3 shows that compared with stroke patients free of AF, those with AF but not anticoagulated had an increased adjusted risk of having more severe stroke (NIHSS score ≥16): 5.8% *v.s.* 14.0%, OR = 2.4 (95%CI:1.6-3.6, p <0.001), prolonged HASU stay: OR = 21.5% *v.s.* 32.0%, 1.4 (1.0-2.0, p = 0.027), pneumonia: 8.2% *v.s.* 19.1%, OR = 2.1 (1.4-2.9; p <0.001), more severe disability: 24.2 *v.s.* 40.4, OR =1.6 (1.2-2.1, p = 0.004) and mortality: OR = 9.3% *v.s.* 21.7%, 1.9 (1.4-2.8, p <0.001). Patients with AF with anticoagulation also had greater risk than those free of AF for having UTI: OR = 8.6% *v.s.* 12.3%, 1.9 (1.2-3.0, p = 0.004), pneumonia: 8.2% *v.s.* 11.5%, OR = 1.6 (1.1-2.4, p = 0.025) and mortality: OR = 9.7% *v.s.* 21.7%, 1.9 (1.4-2.8, p <0.001).

The median length of stay in HASU of 5.8 days (IQR = 2.3-17.5 days) for stroke patients free of AF. In comparison, the corresponding values were 10.6 days (IQR = 2.8-26.4 days) for stroke patients with AF without anticoagulant (p <0.001) and 9.8 days (IQR = 4.0-30.0 days) for stroke patients who were deemed unsuitable for anticoagulation (p = 0.010), while anticoagulation in patients with AF reduced the

median length of stay in HASU to 7.1 days (IQR = 3.1-19.3 days) which is not significantly different from stroke patients free of AF (p = 0.062).

Among patients with AF who were not anticoagulated or deemed unsuitable for anticoagulation on admission, 91.8% and 75.0% of these patients respectively were treated with an anticoagulant on discharge (χ^2 = 16.2, p <0.001).

DISCUSSION

We show that compared to patients without a history of AF, those with AF without anticoagulation had a greater risk of severe stroke (NIHSS score ≥16), prolonged stay in HASU (>3 weeks), risk of early pneumonia, more severe disability on discharge (mRS score = 4 and 5) and inpatient mortality by 1.4- to 2.4-fold. Our study of the association of AF/anticoagulation therapies with pneumonia, UTI and length of stay in HASU is novel. It is notable that AF patients who were anticoagulated reduced their risk of severe stroke and length of stay in a HASU to the same level as those who were free from AF. The increased risk of severe stroke on arrival, prolonged stay in HASU, more severe disability on discharge and inpatient mortality in patients with AF without anticoagulation was independent of age, sex, hypertension, CHF, diabetes and previous stroke.

Given the growing ageing population,[19] disability from stroke will continue to impose massive burdens on healthcare systems in the foreseeable future worldwide, including the UK. There is therefore a need for early identification of AF, the biggest treatable risk factor of stroke, through systematic screening of at-risk patients in the community and intensive treatment for those diagnosed with AF.[20] However, there is evidence of under-treatment of AF in the community. In the present study, we

observed 46.1% of patients with AF who were not on anticoagulation on admission. This figure is consistent with findings from Passand *et al* [21] who observed that 36.9% of AF patients with CHA2DS2-VASc ≥2 were not on anticoagulant therapy at inclusion and from Perez et al who found that only 50% of patients with AF who were eligible for anticoagulation were given this treatment.[22] Similarly Waldo et al studied 945 patients and found that of the 86% of patients who were at high risk of stroke, only 55% received warfarin.[23] Data from our study revealed that most patients with AF who were not treated or deemed unsuitable for treatment with an anticoagulant on admission were subsequently treated on discharge. This suggests that the number of patients who are actually contraindicated to anticoagulation is small, with most being simply untreated.

Greater collaboration between primary care and specialist cardiology services is necessary to improve stroke prevention through appropriate treatment of AF. The roles of experts such as cardiologists, neurologists and haematologists are vital in providing specialist advice on anticoagulation therapy for patients who pose as a treatment dilemma for anticoagulation, such as those with a history of bleeding. Other preventable risk factors such as obesity, hypertension, dyslipidaemia and hyperglycaemia/insulin resistance [20, 24, 25] should also be managed intensively.

A number of important findings emerge from the present study. All patients with AF, whether treated or untreated with an anticoagulant, have increased risks of early hospital acquired infections, disability and mortality. This suggests the inherent risk of AF that may be associated with other causes of cardiovascular disease leads to worse outcomes of stroke.[26] In the present study, we observed that there was no

greater risk for having more severe stroke or prolonged stay in HASU among stroke patients with AF who were anticoagulated than that of those who were free of AF; this evidence reinforces the value of intensive treatment of AF with anticoagulants.[14]

The strengths of the present study include its large homogenous cohort of patients derived from one of the largest NHS regions in England. The analysis was robustly adjusted for age and sex, as well as major chronic conditions known to associate with stroke including hypertension, CHF, diabetes, previous stroke and in particular stroke subtype. The data were collected by healthcare providers for the patients using national SSNAP protocol. Our study focused on early disability on discharge and inpatient mortality. It would be of interest to assess the impact of AF anticoagulation status on these outcomes in longer term. Although data are derived only from Surrey it is likely to be representative of the rest of the UK as stroke prevalence is similar to that of the UK.[12] Our study did not collect information on types of oral anticoagulants or INR which could have some bearing on the outcomes. This information is beyond the scope of our study. The length of anticoagulation treatment for individual patients was not available but it is likely that it is closely related to their age. We chose cut-off point for NIHSS score at 16 based on previous studies showing that a baseline score of ≥16 (moderately-severe to severe stroke) was a strong predictor of mortality or severe disability,[27] while cut-off point for mRS score at 4 indicates that beyond this point, functional disability begins to worsen due to increasing severity of stroke.[28] “Prolonged stay” has variably been described.[29] In the present study, we defined prolonged stay for those who stayed in HASU >3 weeks as this point reflects the upper quartile of length of stay in HASU.

It should be emphasised that these cut-off points tend to be arbitrary and the higher the level, the more severe is the condition. We have explored various other levels including cut-off points for NIHSS score at 12, mRS score at 3 and length of stay in HASU at 1 week (50th centile) all showing similar patterns of, but weaker, association with AF treatment status.

In conclusion, patients with AF, particularly those without anticoagulation, are at increased risk of severe stroke; associated with prolonged HASU stay and increased risk of early infection, disability and mortality.

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Contributorship: TSH and PS reviewed the topic related literature. BA, GG, CB, PK and TP performed the study coordination and data collection. TSH and PS performed the study concept and analysis design. TSH wrote the first draft, analysed and interpreted the data and revised the manuscript. CHF, DF, SS and PS edited the manuscript. All authors checked, interpreted results and approved the final version. TSH and PS are the guarantors for the study.

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LEGENDS

Figure 1. Distribution of patients against severity of stroke on admission based on NIHSS score.

Figure 2. Box plots showing AF and anticoagulation status in relation to stroke severity on arrival indicated by NIHSS score (a) and severity of disability on discharge indicated by mRS score (b). ANOVA showed significant group differences (p <0.001) therefore *post hoc* least significant difference tests were performed to compare NIHSS score between those †free from AF (No AF) and other three AF groups of different anticoagulation status, and between *AF with anticoagulation (AF-treated) and AF without anticoagulation (AF-untreated) groups. Box plots representing median and interquartile ranges; whiskers represent the 5th and 95th percentiles.

Table 1. Distribution of 2758 patients admitted with acute ischaemic stroke to hospitals in Surrey between January 2014 and February 2016.

	Median	IQR
Age of men (years)	75.0	65.0-83.0
Age of women (years)	83.0	74.0-89.0
	n	**Proportion (%)**
Men: women	1387: 1371	50.3: 49.7
Caucasian: mixed race, Black, Asian and other ethnic populations: not stated	2544: 180: 34	93.4: 6.6: 1.2
First stroke/TIA: Recurrent stroke/TIA	2123: 635	77.0: 23.0
Atrial fibrillation	564	20.4[†]
AF with anticoagulation	230	40.8[‡]
AF without anticoagulation	260	46.1[‡]
AF not suitable for anticoagulation	74	13.1[‡]
Hypertension	1446	52.4
CHF	171	6.2
Diabetes	463	16.8
Stroke severity on arrival		
No stroke symptoms (NIHSS score: 0)	368	13.3
Minor stroke (NIHSS score: 1-4)	1092	39.6
Moderate stroke (NIHSS score: 5-15)	930	33.7
Moderate to severe stroke (NIHSS score: 16-20)	195	7.1
Severe stroke (NIHSS score: 21-42)	173	6.3
Modified Rankin Scale on discharge		
No symptoms (mRS score: 0)	682	24.7
No significant disability (mRS: 1)	489	17.7
Slight disability (mRS score: 2)	377	13.7
Moderate disability (mRS score: 3)	362	13.1
Moderately severe disability (mRS score: 4)	284	10.3
Severe disability (mRS score: 5)	130	4.7
Dead (mRS score: 6)	333	12.1

[†]Proportion relative to the total number of all patients in the present study (n = 2758);
[‡]Proportion relative to the number of patients with AF (n = 546).

Table 2. Baseline characteristics of patients admitted with ischaemic stroke according the AF and anticoagulation status.

	Non-AF (n = 2194)		AF with anticoagulation (n = 230)		AF without anticoagulation (n = 260)		AF not suitable for anticoagulation (n = 74)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age (years)	77.0	66.0-85.0	83.0	77.0-88.0	84.0	77.0-90.0	84.0	78.8-88.2
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Men: women	1133: 1061	51.6: 48.4	111:119	48.3: 51.7	106:154	40.8: 59.2	37: 37	50.0: 50.0
Hypertension	1093	49.8	142	61.7	160	61.5	51	68.9
CHF	105	4.8	28	12.2	10	13.5	171	6.2
Diabetes	364	16.6	44	19.1	41	15.8	14	18.9
Moderate to severe stroke on arrival (NIHSS score: ≥16)	114	5.2	17	7.4	36	13.8	6	8.1

Table 3. Chi-squared test and logistic regression to assess the association of AF and anticoagulation status with moderately-severe to severe stroke (NIHSS score ≥16), UTI and pneumonia within seven days of admission, prolonged stay in HASU, moderately-severe to severe disability (mRS score = 4 and 5) on discharge and mortality.

	Chi-squared test				Logistic regression analysis					
	Event rates (%) between study groups				Unadjusted			Adjusted for age, sex, co-morbidities†		
Severe stroke on arrival (NIHSS ≥16)	**Event rates**	**%**	**χ^2**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Free from AF	114/2194	5.8			1	--	--	1	--	--
AF with anticoagulation	17/230	8.9			1.46	0.86-2.47	0.164	1.24	0.72-2.13	0.440
AF without anticoagulation	36/260	14.0	**30.6**	**<0.001**	**2.93**	**1.97-4.37**	**<0.001**	**2.42**	**1.60-3.64**	**<0.001**
AF not suitable for anticoagulation	6/74	9.4			1.61	0.68-3.79	0.275	1.31	0.55-3.14	0.539
Prolonged stay in HASU (>3 weeks)										
Free from AF	339/1852	21.5			1	--	--	1	--	--
AF with anticoagulation	38/169	22.5			1.06	0.72-1.54	0.776	0.87	0.59-1.28	0.475
AF without anticoagulation	64/200	32.0	**15.0**	**0.002**	**1.71**	**1.25-1.35**	**0.001**	**1.42**	**1.03-1.97**	**0.034**
AF not suitable for anticoagulation	18/53	34.0			**1.87**	**1.05-3.34**	**0.034**	1.42	0.79-2.58	0.242
UTI within 7 days of admission										
Free from AF	119/2116	5.6			1	--	--	1	--	--
AF with anticoagulation	27/219	12.3			**2.36**	**1.52-3.68**	**<0.001**	**1.88**	**1.18-2.97**	**0.007**
AF without anticoagulation	28/257	10.9	**39.5**	**<0.001**	2.05	1.33-3.17	0.081	1.49	0.95-2.33	0.081
AF not suitable for anticoagulation	14/70	20.0			**4.20**	**2.27-7.75**	**<0.001**	**2.96**	**1.55-5.65**	**0.001**
Pneumonia within 7 days of admission										
Free from AF	173/2116	8.2			1	--	--	1	--	--
AF with anticoagulation	34/219	11.5			**2.06**	**1.39-3.07**	**<0.001**	**1.60**	**1.06-2.40**	**0.025**
AF without anticoagulation	49/257	19.1	**59.5**	**<0.001**	**2.45**	**1.87-3.75**	**<0.001**	**2.05**	**1.44-2.94**	**<0.001**
AF not suitable for anticoagulation	19/70	21.7			**4.18**	**2.42-5.25**	**<0.001**	**3.04**	**1.73-5.37**	**<0.001**
Moderately-severe to severe disability on discharge (mRS = 4 and 5)										
Free from AF	530/2194	24.2			1	--	--	1	--	--
AF with anticoagulation	81/230	35.2			**1.71**	**1.28-2.28**	**<0.001**	1.20	0.90-1.66	0.198
AF without anticoagulation	105/260	40.4	**48.7**	**<0.001**	**2.13**	**1.63-2.78**	**<0.001**	**1.56**	**1.18-2.06**	**0.002**
AF not suitable for anticoagulation	31/74	41.9			**2.26**	**1.41-3.63**	**0.001**	1.60	0.97-2.62	0.065
Inpatient mortality										

Free from AF	212/2194	9.7	**58.8**	**<0.001**	1	--	--	1	--	--
AF with anticoagulation	50/230	21.7			**2.60**	**1.84-3.66**	**<0.001**	**1.94**	**1.35-2.78**	**<0.001**
AF without anticoagulation	55/260	21.2			**2.51**	**1.80-3.49**	**<0.001**	**1.86**	**1.32-2.61**	**<0.001**
AF not suitable for anticoagulation	16/74	21.6			**2.58**	**1.46-4.57**	**0.001**	**1.83**	**1.01-3.30**	**0.046**

[†]Co-morbidities: CHF, hypertension, diabetes and previous stroke.

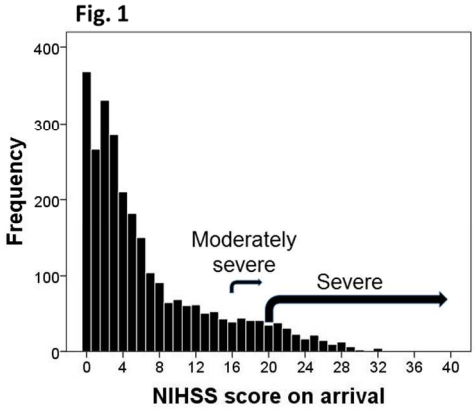

Figure 1

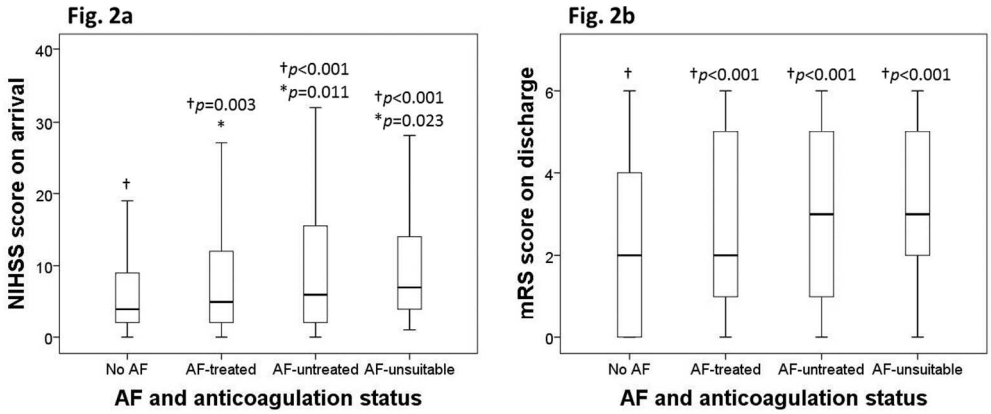

Figure 2 a & b

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	11-12
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-7
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5 & Tables 1 & 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 & 2
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2 & 3
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of anticoagulation status for atrial fibrillation on early ischaemic stroke outcomes: a registry-based, prospective cohort study of acute stroke care in Surrey, United Kingdom

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Evaluation of anticoagulation status for atrial fibrillation on early ischaemic stroke outcomes: a registry-based, prospective cohort study of acute stroke care in Surrey, United Kingdom

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ABSTRACT

Objective: The relationship of anticoagulation therapies with stroke severity and outcomes have been well-documented in the literature. However, none of the previous research has reported the relationship of atrial fibrillation (AF)/anticoagulation therapies with urinary tract infection (UTI), pneumonia and length of stay in hyperacute stroke units (HASU). The present study aimed to evaluate AF and anticoagulation status in relation to early outcomes in 1387 men (median age=75yrs, IQR=65-83) and 1371 women (median age=83yrs, IQR=74-89) admitted with acute ischaemic stroke to HASUs in Surrey between 2014-2016.

Methods: We conducted this registry-based, prospective cohort study using data from the Sentinel Stroke National Audit Programme. Association between AF anticoagulation status with severe stroke on arrival (National Institutes of Health Stroke Scale score≥16), prolonged HASU stay (>3wks), UTI and pneumonia within 7days of admission, severe disability on discharge (modified Rankin Scale score=4 and 5), and inpatient mortality was assessed by logistic regression, adjusted for age, sex, hypertension, congestive heart failure, diabetes and previous stroke.

Results: Compared with stroke patients free from AF, those with AF without anticoagulation had an increased adjusted risk of having more severe stroke: 5.8% *v.s.* 14.0%, OR=2.4 (95%CI:1.6-3.6,p<0.001), prolonged HASU stay: 21.5% *v.s.* 32.0%, OR=1.4 (1.0-2.0,p=0.027), pneumonia: 8.2% *v.s.* 19.1%, OR=2.1 (1.4-2.9,p<0.001), more severe disability: 24.2 *v.s.* 40.4, OR=1.6 (1.2-2.1,p=0.004) and mortality: 9.3% *v.s.* 21.7%, OR=1.9 (1.4-2.8,p<0.001), and AF patients with anticoagulation also had greater risk for having UTI: 8.6% *v.s.* 12.3%, OR=1.9 (1.2-3.0,p=0.004), pneumonia: 8.2% *v.s.* 11.5%, OR=1.6 (1.1-2.4,p=0.025) and mortality: 9.7% *v.s.* 21.7%, OR=1.9 (1.4-2.8,p<0.001). The median HASU stay for stroke patients with AF without anticoagulation was 10.6days (IQR=2.8-26.4) compared with 5.8days (IQR=2.3-17.5) for those free from AF (p<0.001).

Conclusions: Patients with AF, particularly those without anticoagulation, are at increased risk of severe stroke, associated with prolonged HASU stay and increased risk of early infection, disability, and mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strengths of the present study include its large homogenous cohort of patients derived from one of the largest NHS regions in England.
- The analysis was robustly adjusted for age and sex, as well as major chronic conditions known to associate with stroke including hypertension, congestive heart failure (CHF), diabetes and previous stroke.
- The data were collected by healthcare providers for the patients using national SSNAP protocol.
- Although data are derived only from Surrey it is likely to be representative of the rest of the UK as stroke prevalence is similar to that of the UK.
- The study did not collect information on types of oral anticoagulants, international normalised ratio (INR). Information on the duration of anticoagulation treatment for individual patients was also not available but it is likely to be closely related to their age.

INTRODUCTION

Each year, about 6.7 million people die of stroke worldwide, accounting for 11.9% of all deaths.[1] Stroke results in adverse health consequences including physical disability and cognitive impairment [2-4] which imposes enormous burdens on patients, their carers as well as social and healthcare systems.[5, 6]

Patients with existing co-morbidities such as diabetes and cardiovascular diseases including coronary heart disease, poorly controlled hypertension or CHF have an increased risk of stroke, but atrial fibrillation (AF) remains the biggest risk factor.[7, 8] Although outcomes for stroke patients have improved significantly in the UK since the introduction of organised hyperacute stroke unit (HASU) care provided by multidisciplinary teams,[9, 10] the elderly and those who have chronic health conditions continue to have increased risk of mortality and disability, as well as time to recovery requiring longer stay in hospital after a stroke.[11-13] The relationship of anticoagulation therapies with stroke severity and outcomes have been well-documented in the literature.[14-16] However, none of the previous research has reported the relationship of AF/anticoagulation therapies with urinary tract infection (UTI), pneumonia and length of stay in HASU.

The present study aimed to evaluate the relationship of patients with AF and their anticoagulation status on the severity of stroke on admission, length of stay in HASU, UTI and pneumonia within the first week in hospital, early disability on discharge and inpatient mortality.

METHODS

Study design, patients and setting

We conducted this registry-based, prospective cohort study using data from the Sentinel Stroke National Audit Programme (SSNAP) which is the national register of stroke care in England and Wales. Data were collected prospectively from the time of admission up to six months after stroke and validated by Stroke teams and entered into the SSNAP database via a secure web interface. These data comprise clinical characteristics and care quality of patients admitted to all acute care hospitals in England and Wales with acute ischaemic stroke or primary intracerebral haemorrhage.[12] We used an anonymised extract of a total of 3309 patients from Surrey, a relatively stable and homogenous population, who were admitted to four HASUs within the county (one of the largest National Health Service regions in the England). The hospitals, Ashford and St Peter's (n = 1038), Frimley Park (n = 1010), Royal Surrey County (n = 612) and Epsom (n = 649) were surveyed between January 2014 and February 2016. Twenty-two patients were admitted twice and two patients three times. For the purpose of analysis, data from the first admission for these 24 patients who were admitted multiple times were used.

SSNAP has approval from the Confidentiality Advisory Group of the Health Research Authority to collect patient data under section 251 of the National Health Service Act 2006. No additional ethical approval was sought.

Socio-demographic factors and medical history

Data were collected for socio-demographic factors including age at arrival, sex and ethnicity, as well as past medical history including AF, hypertension, CHF, diabetes

mellitus, previous stroke and drug history. In addition, details of new onset AF cases as well as UTI and pneumonia acquired in hospital within seven days of admission were documented by the stroke team comprising consultants and stroke nurse specialists, including anticoagulation treatment from the point of admission to discharge.

Diagnosis of stroke and severity

Stroke was diagnosed based on clinical presentation and brain CT scan as guided by the National Institute for Health and Care Excellence (NICE).[17] The severity of stroke symptoms was assessed by the National Institutes of Health for Stroke Scale (NIHSS) with score range from no symptoms to severe stroke symptoms (NIHSS score = 0 to 42).

Disability and mortality

Degree of disability or dependence in daily activities were assessed by a modified Rankin Scale (mRS), ranging from no symptoms to severe symptoms (mRS score = 0 to 5) and mortality (mRS score = 6).

Categorisation of variables

Dichotomisation was applied for hypertension, CHF and diabetes according to the presence of history of the condition or not while age was dichotomised at the median value (<79 and ≥79 years). AF and anticoagulation status were categorised into four groups: free from AF; AF with anticoagulation; AF without anticoagulation; and AF unsuitable for anticoagulation. Severity of stroke and disability were dichotomised into two groups: no symptoms to moderate symptoms (NIHSS score <16 and mRS

score <4) and moderately-severe to severe (NIHSS score ≥16 and mRS score = 4 and 5). Prolonged stay in HASU was defined as patients who stayed in a HASU >3 weeks (upper fourth quartile of length of stay).

Statistical analysis

Of the 3309 patients collected in the database, we analysed 2758 (83.3%) patients presented with ischaemic stroke and the remaining 518 (15.7%) patients with haemorrhagic stroke and 33 (1.0%) who were unspecified were excluded. The frequency of patients with AF using anticoagulation before developing an ischaemic stroke was assessed by cross tabulation and chi-squared tests. Most variables had no missing data, which were handled in analysis using a 'listwise deletion of missing data' approach.[18] Independent *t*-tests were performed to compare differences between two groups and analysis of variance (ANOVA) between three or more groups, with *post-hoc* analysis where applicable. Multivariable logistic regression was performed to assess the risk of moderately-severe to severe stroke on arrival and disability on discharge, inpatient mortality after stroke and prolonged stay in HASU (dependent variables) from co-morbidities including AF, hypertension, CHF, diabetes and previous stroke (independent variables). Two logistic regression models were conducted, the first model was unadjusted and the second adjusted for age, sex and co-morbidities. Analyses were performed using SPSS V.22.0 (SPSS Inc, Chicago, Illinois, USA). The null hypothesis was rejected when p <0.05.

RESULTS

Admissions for stroke were almost equally distributed between men (50.3%) and women (49.7%), with the onset of the first stroke 6.5 years (95% CI: 5.5, 7.5, p

<0.001) earlier in men. **Table 1** shows that there were 77.0% of patients presented with first stroke and 23.0% with recurrent stroke. Most patients were white Caucasians (92.2%) with the remaining 6.6% comprises mixed race, Black, Asian and other ethnic populations, and 1.2% not stated. On arrival, 546 (20.4%) patients had a history of AF, in whom 40.8% were treated in the community with an anticoagulant whilst 46.1% were untreated although 13.1% had been considered for anticoagulation and deemed unsuitable by their healthcare providers. Also on arrival, 7.1% of patients had moderate to severe stroke symptoms (NIHSS score = 16-20) and 6.3% had severe symptoms (NIHSS = 21-42). The remainder had no symptoms (13.3%, NIHSS = 0); minor (39.6%, NIHSS = 1-4) or moderate (33.7%, NIHSS = 5-15) symptoms: a more detailed analysis of NIHSS scores is shown in **Figure 1**. On discharge 10.3% and 4.7% of the original patients respectively had moderately severe (mRS score = 4) or severe (mRS score = 5) symptoms. The rate of inpatient mortality was 12.1% (**Table 1**).

Baseline characteristics of patients in different categories of AF and anticoagulation status are shown in **Table 2**. The median age of patients without AF were 77 years old while those with AF were between 83 and 84 years old. Hypertension, CHF and moderate to severe stroke were more commonly observed among patients with AF than those free of AF.

Patients free from AF had significantly less severe stroke on admission as reflected by a lower NIHSS score (F = 21.8, p <0.001) and disability on discharge as indicated by a lower mRS score (F = 20.9, p <0.001) than patients with AF of any anticoagulation status (with anticoagulation, without anticoagulation or unsuitable for

anticoagulation in the community) (**Figure 2**). ANOVA with *post hoc* analysis by least significant difference tests showed that NIHSS score on arrival (**Figure 2a**) and mRS on discharge **(Figure 2b**) were significantly lower (p <0.01) for those free from AF compared with any of the other three groups of patients with AF (with anticoagulation, without anticoagulation or unsuitable for anticoagulation). The NIHSS score for those with AF who were treated with anticoagulant was also lower than that of those with AF who were not treated with (p = 0.011) or considered unsuitable for anticoagulation (p = 0.023).

Table 3 shows that compared with stroke patients free of AF, those with AF but not anticoagulated had an increased adjusted risk of having more severe stroke (NIHSS score ≥16): 5.8% *v.s.* 14.0%, OR = 2.4 (95%CI:1.6-3.6, p <0.001), prolonged HASU stay: OR = 21.5% *v.s.* 32.0%, 1.4 (1.0-2.0, p = 0.027), pneumonia: 8.2% *v.s.* 19.1%, OR = 2.1 (1.4-2.9; p <0.001), more severe disability: 24.2 *v.s.* 40.4, OR =1.6 (1.2-2.1, p = 0.004) and mortality: OR = 9.3% *v.s.* 21.7%, 1.9 (1.4-2.8, p <0.001). Patients with AF with anticoagulation also had greater risk than those free of AF for having UTI: OR = 8.6% *v.s.* 12.3%, 1.9 (1.2-3.0, p = 0.004), pneumonia: 8.2% *v.s.* 11.5%, OR = 1.6 (1.1-2.4, p = 0.025) and mortality: OR = 9.7% *v.s.* 21.7%, 1.9 (1.4-2.8, p <0.001).

The median length of stay in HASU of 5.8 days (IQR = 2.3-17.5 days) for stroke patients free of AF. In comparison, the corresponding values were 10.6 days (IQR = 2.8-26.4 days) for stroke patients with AF without anticoagulant (p <0.001) and 9.8 days (IQR = 4.0-30.0 days) for stroke patients who were deemed unsuitable for anticoagulation (p = 0.010), while anticoagulation in patients with AF reduced the

median length of stay in HASU to 7.1 days (IQR = 3.1-19.3 days) which is not significantly different from stroke patients free of AF (p = 0.062).

Among patients with AF who were not anticoagulated or deemed unsuitable for anticoagulation on admission, 91.8% and 75.0% of these patients respectively were treated with an anticoagulant on discharge (χ^2 = 16.2, p <0.001).

DISCUSSION

We show that compared to patients without a history of AF, those with AF without anticoagulation had a greater risk of severe stroke (NIHSS score ≥16), prolonged stay in HASU (>3 weeks), risk of early pneumonia, more severe disability on discharge (mRS score = 4 and 5) and inpatient mortality by 1.4- to 2.4-fold. Our study of the association of AF/anticoagulation therapies with pneumonia, UTI and length of stay in HASU is novel. It is notable that AF patients who were anticoagulated had a reduced risk of severe stroke and length of stay in a HASU to the same level as those who were free from AF. The increased risk of severe stroke on arrival, prolonged stay in HASU, more severe disability on discharge and inpatient mortality in patients with AF without anticoagulation was independent of age, sex, hypertension, CHF, diabetes and previous stroke.

Given the growing ageing population,[19] disability from stroke will continue to impose massive burdens on healthcare systems in the foreseeable future worldwide, including the UK. There is therefore a need for early identification of AF, the biggest treatable risk factor of stroke, through systematic screening of at-risk patients in the community and intensive treatment for those diagnosed with AF.[20] However, there is evidence of under-treatment of AF in the community. In the present study, we

observed 46.1% of patients with AF who were not on anticoagulation on admission. This figure is consistent with findings from Bassand *et al* [21] who observed that 36.9% of AF patients with CHA2DS2-VASc ≥2 were not on anticoagulant therapy at inclusion and from Perez et al who found that only 50% of patients with AF who were eligible for anticoagulation were given this treatment.[22] Similarly Waldo et al studied 945 patients and found that of the 86% of patients who were at high risk of stroke, only 55% received warfarin.[23] Data from our study revealed that most patients with AF who were not treated or deemed unsuitable for treatment with an anticoagulant on admission were subsequently treated on discharge. This suggests that the number of patients who are actually contraindicated to anticoagulation is small, with most being simply untreated.

Greater collaboration between primary care and specialist cardiology services is necessary to improve stroke prevention through appropriate treatment of AF. The roles of experts such as cardiologists, neurologists and haematologists are vital in providing specialist advice on anticoagulation therapy for patients who pose as a treatment dilemma for anticoagulation, such as those with a history of bleeding. Other preventable risk factors such as obesity, hypertension, dyslipidaemia and hyperglycaemia/insulin resistance [20, 24, 25] should also be managed intensively.

A number of important findings emerge from the present study. All patients with AF, whether treated or untreated with an anticoagulant, have increased risks of early hospital acquired infections, disability and mortality. This suggests the inherent risk of AF that may be associated with other causes of cardiovascular disease leads to worse outcomes of stroke.[26] In the present study, we observed that there was no

greater risk for having more severe stroke or prolonged stay in HASU among stroke patients with AF who were anticoagulated than that of those who were free of AF; this evidence reinforces the value of intensive treatment of AF with anticoagulants.[14]

The strengths of the present study include its large homogenous cohort of patients derived from one of the largest NHS regions in England. The analysis was robustly adjusted for age and sex, as well as major chronic conditions known to associate with stroke including hypertension, CHF, diabetes, previous stroke and in particular stroke subtype. The data were collected by healthcare providers for the patients using national SSNAP protocol. Our study focused on early disability on discharge and inpatient mortality. It would be of interest to assess the impact of AF anticoagulation status on these outcomes in longer term. Although data are derived only from Surrey it is likely to be representative of the rest of the UK as stroke prevalence is similar to that of the UK.[12] Our study did not collect information on types of oral anticoagulants or INR which could have some bearing on the outcomes. This information is beyond the scope of our study. The length of anticoagulation treatment for individual patients was not available but it is likely that it is closely related to their age. We chose cut-off point for NIHSS score at 16 based on previous studies showing that a baseline score of ≥16 (moderately-severe to severe stroke) was a strong predictor of mortality or severe disability,[27] while cut-off point for mRS score at 4 indicates that beyond this point, functional disability begins to worsen due to increasing severity of stroke.[28] “Prolonged stay” has variably been described.[29] In the present study, we defined prolonged stay for those who stayed in HASU >3 weeks as this point reflects the upper quartile of length of stay in HASU.

It should be emphasised that these cut-off points tend to be arbitrary and the higher the level, the more severe is the condition. We have explored various other levels including cut-off points for NIHSS score at 12, mRS score at 3 and length of stay in HASU at 1 week (50th centile) all showing similar patterns of, but weaker, association with AF treatment status.

In conclusion, patients with AF, particularly those without anticoagulation, are at increased risk of severe stroke; associated with prolonged HASU stay and increased risk of early infection, disability and mortality.

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Contributorship: TSH and PS reviewed the topic related literature. BA, GG, CB, PK and TP performed the study coordination and data collection. TSH and PS performed the study concept and analysis design. TSH wrote the first draft, analysed and interpreted the data and revised the manuscript. CHF, DF, SS and PS edited the manuscript. All authors checked, interpreted results and approved the final version. TSH and PS are the guarantors for the study.

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Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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LEGENDS

Figure 1. Distribution of patients against severity of stroke on admission based on NIHSS score.

Figure 2. Box plots showing AF and anticoagulation status in relation to stroke severity on arrival indicated by NIHSS score (a) and severity of disability on discharge indicated by mRS score (b). ANOVA showed significant group differences (p <0.001) therefore *post hoc* least significant difference tests were performed to compare NIHSS score between those †free from AF (No AF) and other three AF groups of different anticoagulation status, and between *AF with anticoagulation (AF-treated) and AF without anticoagulation (AF-untreated) groups. Box plots representing median and interquartile ranges; whiskers represent the 5th and 95th percentiles.

Table 1. Distribution of 2758 patients admitted with acute ischaemic stroke to hospitals in Surrey between January 2014 and February 2016.

	Median	IQR
Age of men (years)	75.0	65.0-83.0
Age of women (years)	83.0	74.0-89.0
	n	**Proportion (%)**
Men: women	1387: 1371	50.3: 49.7
Caucasian: mixed race, Black, Asian and other ethnic populations: not stated	2544: 180: 34	93.4: 6.6: 1.2
First stroke/TIA: Recurrent stroke/TIA	2123: 635	77.0: 23.0
Atrial fibrillation	564	20.4[†]
AF with anticoagulation	230	40.8[‡]
AF without anticoagulation	260	46.1[‡]
AF not suitable for anticoagulation	74	13.1[‡]
Hypertension	1446	52.4
CHF	171	6.2
Diabetes	463	16.8
Stroke severity on arrival		
No stroke symptoms (NIHSS score: 0)	368	13.3
Minor stroke (NIHSS score: 1-4)	1092	39.6
Moderate stroke (NIHSS score: 5-15)	930	33.7
Moderate to severe stroke (NIHSS score: 16-20)	195	7.1
Severe stroke (NIHSS score: 21-42)	173	6.3
Modified Rankin Scale on discharge		
No symptoms (mRS score: 0)	682	24.7
No significant disability (mRS: 1)	489	17.7
Slight disability (mRS score: 2)	377	13.7
Moderate disability (mRS score: 3)	362	13.1
Moderately severe disability (mRS score: 4)	284	10.3
Severe disability (mRS score: 5)	130	4.7
Dead (mRS score: 6)	333	12.1

[†]Proportion relative to the total number of all patients in the present study (n = 2758);
[‡]Proportion relative to the number of patients with AF (n = 546).

Table 2. Baseline characteristics of patients admitted with ischaemic stroke according the AF and anticoagulation status.

	Non-AF (n = 2194)		AF with anticoagulation (n = 230)		AF without anticoagulation (n = 260)		AF not suitable for anticoagulation (n = 74)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age (years)	77.0	66.0-85.0	83.0	77.0-88.0	84.0	77.0-90.0	84.0	78.8-88.2
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Men: women	1133: 1061	51.6: 48.4	111:119	48.3: 51.7	106:154	40.8: 59.2	37: 37	50.0: 50.0
Hypertension	1093	49.8	142	61.7	160	61.5	51	68.9
CHF	105	4.8	28	12.2	10	13.5	171	6.2
Diabetes	364	16.6	44	19.1	41	15.8	14	18.9
Moderate to severe stroke on arrival (NIHSS score: ≥16)	114	5.2	17	7.4	36	13.8	6	8.1

Table 3. Chi-squared test and logistic regression to assess the association of AF and anticoagulation status with moderately-severe to severe stroke (NIHSS score ≥16), UTI and pneumonia within seven days of admission, prolonged stay in HASU, moderately-severe to severe disability (mRS score = 4 and 5) on discharge and mortality.

	Chi-squared test				Logistic regression analysis					
	Event rates (%) between study groups				Unadjusted			Adjusted for age, sex, co-morbidities†		
Severe stroke on arrival (NIHSS ≥16)	**Event rates**	**%**	**χ^2**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Free from AF	114/2194	5.8			1	--	--	1	--	--
AF with anticoagulation	17/230	8.9			1.46	0.86-2.47	0.164	1.24	0.72-2.13	0.440
AF without anticoagulation	36/260	14.0	**30.6**	**<0.001**	**2.93**	**1.97-4.37**	**<0.001**	**2.42**	**1.60-3.64**	**<0.001**
AF not suitable for anticoagulation	6/74	9.4			1.61	0.68-3.79	0.275	1.31	0.55-3.14	0.539
Prolonged stay in HASU (>3 weeks)										
Free from AF	339/1852	21.5			1	--	--	1	--	--
AF with anticoagulation	38/169	22.5			1.06	0.72-1.54	0.776	0.87	0.59-1.28	0.475
AF without anticoagulation	64/200	32.0	**15.0**	**0.002**	**1.71**	**1.25-1.35**	**0.001**	**1.42**	**1.03-1.97**	**0.034**
AF not suitable for anticoagulation	18/53	34.0			**1.87**	**1.05-3.34**	**0.034**	1.42	0.79-2.58	0.242
UTI within 7 days of admission										
Free from AF	119/2116	5.6			1	--	--	1	--	--
AF with anticoagulation	27/219	12.3			**2.36**	**1.52-3.68**	**<0.001**	**1.88**	**1.18-2.97**	**0.007**
AF without anticoagulation	28/257	10.9	**39.5**	**<0.001**	2.05	1.33-3.17	0.081	1.49	0.95-2.33	0.081
AF not suitable for anticoagulation	14/70	20.0			**4.20**	**2.27-7.75**	**<0.001**	**2.96**	**1.55-5.65**	**0.001**
Pneumonia within 7 days of admission										
Free from AF	173/2116	8.2			1	--	--	1	--	--
AF with anticoagulation	34/219	11.5			**2.06**	**1.39-3.07**	**<0.001**	**1.60**	**1.06-2.40**	**0.025**
AF without anticoagulation	49/257	19.1	**59.5**	**<0.001**	**2.45**	**1.87-3.75**	**<0.001**	**2.05**	**1.44-2.94**	**<0.001**
AF not suitable for anticoagulation	19/70	21.7			**4.18**	**2.42-5.25**	**<0.001**	**3.04**	**1.73-5.37**	**<0.001**
Moderately-severe to severe disability on discharge (mRS = 4 and 5)										
Free from AF	530/2194	24.2			1	--	--	1	--	--
AF with anticoagulation	81/230	35.2			**1.71**	**1.28-2.28**	**<0.001**	1.20	0.90-1.66	0.198
AF without anticoagulation	105/260	40.4	**48.7**	**<0.001**	**2.13**	**1.63-2.78**	**<0.001**	**1.56**	**1.18-2.06**	**0.002**
AF not suitable for anticoagulation	31/74	41.9			**2.26**	**1.41-3.63**	**0.001**	1.60	0.97-2.62	0.065
Inpatient mortality										

Free from AF	212/2194	9.7	**58.8**	**<0.001**	1	--	--	1	--	--
AF with anticoagulation	50/230	21.7			**2.60**	**1.84-3.66**	**<0.001**	**1.94**	**1.35-2.78**	**<0.001**
AF without anticoagulation	55/260	21.2			**2.51**	**1.80-3.49**	**<0.001**	**1.86**	**1.32-2.61**	**<0.001**
AF not suitable for anticoagulation	16/74	21.6			**2.58**	**1.46-4.57**	**0.001**	**1.83**	**1.01-3.30**	**0.046**

[†]Co-morbidities: CHF, hypertension, diabetes and previous stroke.

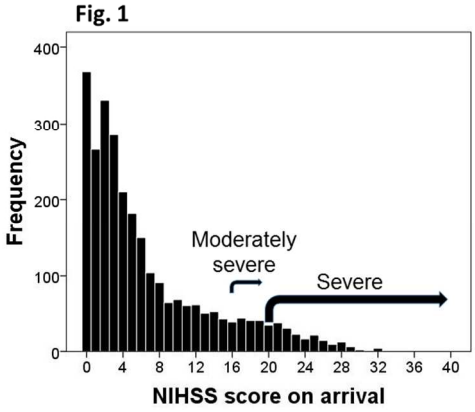

Figure 1

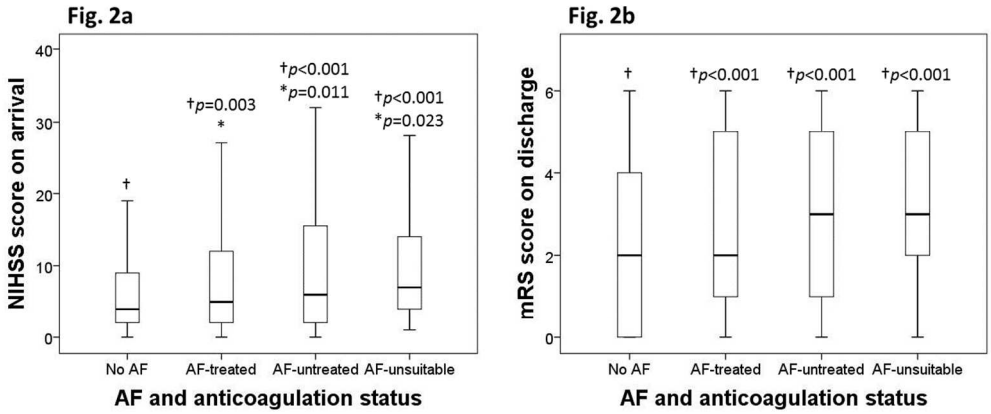

Figure 2 a & b

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	11-12
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-7
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5 & Tables 1 & 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 & 2
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2 & 3
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.