Does prior antithrombotic therapy influence recurrence and bleeding risk in stroke patients with atrial fibrillation or atrial flutter?

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Abstract

Background: Whilst antithrombotic therapy is recommended in people with atrial fibrillation (AF), little is known about the survival benefits of antithrombotic treatment in those with both high ischemic and bleeding risk scores. We aim to describe the distribution of these risk scores in those with a prior diagnosis of AF who have suffered stroke and to determine the net clinical benefit of antithrombotic treatment.

Methods: We used regional stroke register data in the UK. Patients with a prior diagnosis of AF and ischemic or hemorrhagic stroke patients were selected and their CHA_2DS_2-VAS_c and $HEMORR_2HAGES$ scores retrospectively calculated. Logistic regression and Cox-proportional hazards models were constructed to determine the association between antithrombotic therapy prior to stroke and in hospital and long term mortality.

Results: 1928 stroke patients (mean age 81.3 years (SD 8.5), 56.8 % women) with prior AF were included. Of these, 1761 (91.3%) suffered ischemic stroke. The most common phenotype (64%) was those with both high CHA_2DS_2-VAS_c (≥2) and high $HEMORR_2HAGES$ score (≥4). In our fully adjusted model, patients on antithrombotic treatment with both high ischemic and bleeding risk had a significant reduction in odds of 31% for in hospital mortality (OR 0.69;95%CI 0.48,1.00: p=0.049)) and 17% relative risk reduction for long term mortality (HR 0.83;95%CI 0.71,0.97: p=0.02)).

Conclusions: Our study suggests that antithrombotic treatment has a prognostic benefit following incident stroke in those with both high ischemic risk and high bleeding risk. This should be considered when choosing treatment options in this group of patients.

Key words: Stroke, atrial fibrillation, thromboprophylaxis, antithrombotic treatment

Introduction

Management of modifiable risk factors is one of the key preventative strategies in stroke. Atrial fibrillation (AF) is one of the most common clinically significant arrhythmias with a prevalence of 1.48% in the UK (1). It is associated with a 5 fold increase in the risk of stroke (2) and is responsible for up to 16% of ischemic strokes (3). Antithrombotic therapy can be initiated to reduce the risk of thrombotic events in people with AF but also carries the risk of hemorrhage. This includes antiplatelet and anticoagulant medication.

Risk stratification scores have been developed for estimation of future ischemic and hemorrhagic events and include CHA_2DS_2-VAS_c score for ischemic stroke and $HEMORR_2HAGES$, ATRIA, and HAS-BLED scores for bleeding risk (4). These scores form the basis of international guidelines for the management of patients with AF (5), (6).

Whether guideline-based decision making leads to complete and appropriate antithrombotic coverage of AF patients and how best to guide decision making in those with both high ischemic and bleeding risk scores remains unclear. Prior studies have quantified the reduction in risk of ischemic stroke in those receiving antithrombotic treatment for AF (7) as well as a reduction in the severity of stroke and stroke mortality (8). However, little is known about the distribution of ischemic and haemorrhagic risk in patients that have suffered a cerebrovascular event, or the relationship of these scores and clinical outcomes in such patients, particularly how the balance between ischemic and haemorrhagic risk may impact on clinical outcomes.

Using a regional prospective stroke registry from England, UK, we retrospectively calculated ischemic and bleeding risk scores in a disease cohort of stroke patients with prior AF and aimed to determine the distribution of ischemic and haemorrhagic risk, antithrombotic coverage and in hospital and long term stroke mortality for those with both high ischemic and high bleeding risk scores.

Methods

Population

This was a disease cohort of patients consecutively admitted with stroke drawn from Norfolk and Norwich Stroke Register (NNSTR). The NNSTR is a prospective UK hospital-based register which included consecutive stroke patients and has a catchment of approximately 750,000 people. Data collection and the development of this database have been published previously (9). The disease cohort was followed up long term through record linkage. Record linkage with the UK NHS system ensures a robust ascertainment of co-morbidities and almost complete follow up data for vital status. Index stroke type was based on evidence clinical examination and neuroimaging (typically computerized tomography or magnetic resonance imaging). Patients admitted with confirmed stroke between January 2003 and June 2013 were included in this study. In total 9835 patients were admitted between January 2003 and June 2013.

Ethics:

The register received ethical approval from the Newcastle and Tyneside National Health Service (NHS) and Research Ethics Committee (12/NE/0170) as a research database. The protocol was approved by the Steering Committee of the Register. The study was conducted in accordance with the principles of the Declaration of Helsinki (1964) and later amendments.

Measurement methods:

Data collection methods of the register have been reported previously (9). In brief, patient characteristic data on age, sex, stroke type (ischemic / hemorrhagic), Oxfordshire Community Stroke Project (OCSP) classification were retrieved from the hospital's patient administration database. Relevant biochemical and hematological measurements taken on hospital admission were collected by electronic record linkage. Information on pre-existing co-morbidities were identified from ICD-10 codes based on clinical findings and retrieved from the hospital's administration database (diabetes (ICD E10-E14), heart failure (I50), atrial fibrillation (I48), coronary heart disease (I20-I25), chronic kidney disease (N18), hypertension (I10-I15), dyslipidemia (E78), peripheral vascular disease (I73.9), cancer (C00-C99), and MI (I21)). Co-morbidities diagnosed during and after hospital admission were identified in the same manner. Dead or alive status at discharge was recorded to capture in-hospital mortality. Date of death was recorded to capture

long term mortality. Additional checks and linkage were performed against the hospital's administration database to further validate the sample. Atrial fibrillation and atrial flutter were diagnosed on the basis of a 12 lead Electrocardiogram (ECG) and grouped together as both have an associated risk of stroke. There was no minimal follow up period and follow up for mortality was obtained by electronic record linkage. Patients were censored at 30/June/2013 and deaths updated until 12/12/2013.

Statistical analysis

Statistical analysis was performed using SPSS v. 24 (SPSS Inc., Chicago, IL, USA). For the sampled disease cohort of patients consecutively admitted with stroke the CHA_2DS_2-VAS_c scores (low risk <2, high risk ≥2) and $HEMORR_2HAGES$ scores (low risk <4, high risk ≥4) were retrospectively calculated from recorded clinical data, excluding stroke. $HEMORR_2HAGES$ score was chosen as the bleeding risk score due to data availability. $HEMORR_2HAGES$ scores were based on recorded age, sex, relevant co-morbidities, anemia, alcohol use and antiplatelet use. Prior bleeding events and genetic factors were not collected and not used in the score calculation. CHA_2DS_2-VAS_c scores were based on age, sex and relevant co-morbidities. The sample was divided into those with a prior diagnosis of AF or atrial flutter that had ischemic stroke or hemorrhagic stroke at presentation. These groups were sub-divided into antithrombotic treatment or no treatment groups and groups based on their CHA_2DS_2-VAS_c and $HEMORR_2HAGES$ score. Antithrombotic treatment was defined as any anticoagulant or antiplatelet use before the index stroke, as described previously (10).

Descriptive statistics were presented for the overall sample and by stroke subtype and compared using one-way analysis of variance for means and Pearson's Chi-squared test for categorical measures. A scatter plot of CHA_2DS_2-VAS_c (high risk ≥2) and $HEMORR_2HAGES$ scores were derived and an R^2 value calculated to show correlation between the two. Logistic and Cox-proportional hazards models were constructed to determine the association between antithrombotic therapy and in-hospital and long term mortality, respectively, in those with both high CHA_2DS_2-VAS_c (high risk ≥2) and $HEMORR_2HAGES$ score (high risk ≥4). Adjusted analyses were undertaken to account for potential confounding factors such as age, sex, co-morbidities, stroke risk factors, stroke subtype and Oxford Community Stroke Project (OCSP) stroke classification. A variety of adjusted models were used to assess the effects of these potential confounding factors in a group sequential fashion. Model A adjusted for age and sex. Model B adjusted for variables in model A plus co-

morbidities diabetes, heart failure, coronary heart disease, chronic kidney disease, hypertension, MI and cancer. Model C adjusted for variables in model B plus stroke subtype and Oxford Community Stroke Project (OCSP) stroke classification.

This was a registry study with retrospective analysis of prospectively collected data. A power calculation was not performed.

Results

Between 2003 – 2013, a total of 2582 patients with confirmed stroke and a previous diagnosis of AF were identified, and of these 654 (25.3%) were excluded due to missing data needed to calculate their ischemic and bleeding risk scores leaving 1928 patients (mean age 81.3 years (SD 8.5), 56.8 % women, 91.3% ischemic stroke). There was no minimal follow up period and follow up for mortality was obtained by electronic record linkage. The mean follow up (SD) was 2.06 (2.49) years, median 1.06 years, total person years 3963.3. As shown in Table 4, the post exclusion sample was representative of the initial sample. The mean age, female predominance, stroke characteristics and co-morbidity proportions were similar before and after exclusion.

Table 1 demonstrates sample characteristics by stroke subtype. There were significant differences (p=<0.05) between the groups in age, sex, OCSP classification (lacunar infarct (LACI), total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI)), CKD, antithrombotic therapy, CHA_2DS_2-VAS_c and $HEMORR_2HAGES$ Scores. Other co-morbidities were similar between the groups.

Figure 1 shows the proportion of those with high and low ischaemic event and bleeding risk scores subdivided into treatment groups and stroke subtypes. A higher proportion of those on antithrombotic treatment who had an ischaemic stroke, had a high bleeding risk score (74.5%) compared to those not on antithrombotic treatment (43.6%). This was echoed in those who had suffered hemorrhagic stroke (65.4% vs 38.4%).

Table 2 and Figure 1 show the proportion of ischemic stroke and hemorrhagic stroke patients who received treatment subdivided by their CHA_2DS_2-VAS_c and $HEMORR_2HAGES$ score. In the ischemic stroke group, 1091 (62.0%) of patients had a high CHA_2DS_2-VAS_c and a high $HEMORR_2HAGES$ Scores. Of these, 779 (71.4%) received antithrombotic treatment. A total of 627(35.6%) had a high CHA_2DS_2-VAS_c and a low $HEMORR_2HAGES$ Scores, 248 (39.6%) were on antithrombotic treatment. There were no patients that had a low CHA_2DS_2-VAS_c and a high $HEMORR_2HAGES$ Score. A total of 43 had a low CHA_2DS_2-VAS_c score and a low $HEMORR_2HAGES$ Score, of these 18 (41.9%) were on antithrombotic treatment. In the hemorrhagic stroke group, 145 patients had a high CHA_2DS_2-VAS_c and a high $HEMORR_2HAGES$ Score. Of these, 117 (80.7%) received antithrombotic treatment.

A total of 100 had a high CHA_2DS_2-VAS_c and a low $HEMORR_2HAGES$ Score, of these 56 (56%) were on antithrombotic treatment. There were no patients that had low CHA_2DS_2-VAS_c score and a high $HEMORR_2HAGES$ Score. A total of 7 had a both low scores, of these 6 (85.7%) were on antithrombotic treatment.

Table 3 shows logistic regression odds ratios (OR (95%CI)) for in hospital mortality and Cox regression hazard ratios (HR (95%CI)) for long term mortality for patients (n=1173) with both high CHA_2DS_2-VAS_c score and $HEMORR_2HAGES$ score on antithrombotic therapy compared to those not on antithrombotic therapy. In our fully adjusted model, patients on antithrombotic treatment with both high ischemic and bleeding risk had a significant reduction in odds of 31% for in hospital mortality (OR 0.69 (95%CI 0.48,1.00: p=0.049)) and a 17% relative risk reduction for long term mortality (95%CI 0.71, 0.97:p=0.02)).

There is a positive correlation between CHA_2DS_2-VAS_c score and $HEMORR_2HAGES$ scores for all 1928 men and women of the Norfolk and Norwich University Hospital Stroke Register with an R^2 value of 0.453.

Discussion

Our study has described the distribution of ischaemic stroke and bleeding risk within a large disease cohort of patients consecutively admitted with stroke who have suffered ischaemic or hemorrhagic stroke. Interestingly the most common phenotype (64%) described is those with both high ischaemic stroke and bleeding risk scores, which is perhaps not surprising given the overlap of risk factors within the scores. This clearly presents a challenge to clinicians weighing up the risks and benefits of antithrombotic treatment in this high-risk group of patients.

Paradoxically, as shown in table 2, we observed that a larger proportion of patients with both a high ischaemic stroke and bleeding risk scores were treated with antithrombotic therapy than those with a high ischaemic stroke and low bleeding risk scores (71.4% vs 39.6%). This suggests a mismatch between clinical guidelines and clinical practice when considering antithrombotic treatment in a high risk group of patients. This may lead to an increased incidence of preventable stroke and greater morbidity and cost to healthcare systems globally.

It is interesting to note that in our disease cohort who have suffered stroke those at high risk of both ischemic stroke and bleeding events who were treated with antithrombotic medication had a significant reduction in odds of in hospital mortality by 31% (OR 0.69 (95%CI 0.48 – 1.00 p=0.049)) and a relative risk reduction in long term mortality of 17% (HR 0.83 95%CI 0.71 – 0.97 p=0.02)). This suggests that even in those with a high bleeding risk antithrombotic treatment has a prognostic benefit following incident stroke and this should be taken into consideration when clinicians consider treatment in this group of patients. The treatment instituted after the specific stroke type is therefore assumed to be beneficial or will have similar impact on those who received the respective treatment. Therefore, they are not adjusted and regarded as process variable rather than a confounding factor in our study.

In our study, over 40% of patients were not on antithrombotic treatment demonstrating low antithrombotic coverage within our disease cohort of patients consecutively admitted with stroke. This is in line with previous studies, which showed that between 30–50% of patients were undertreated (11). In the UK alone, it is estimated that if all those with AF were appropriately treated up to 7000 strokes would be prevented and 2000 lives saved each year (12).

Net clinical benefit analysis has been previously carried out examining the risk and benefit of anticoagulation in AF patients. In general, these have shown that only those patients with a CHA_2DS_2-VAS_c score of 0 have a negative net clinical benefit and all other patients derive a positive benefit from antithrombotic treatment (13). In fact, those with a high bleeding risk score have been shown to derive a higher net clinical benefit from antithrombotic treatment as the risk reduction in ischemic stroke outweighs the relatively small increase in bleeding risk (14), (15).

Barriers to initiation of antithrombotic therapy have been cited to include the risk of falls and concomitant medications (16). Additional composite risk scores may be useful in such circumstances, taking into account variables such as pre-stroke morbidity, anticoagulant profiles and frailty, in order to better risk stratify these patients. However, recent studies designing and validating composite risk scores have shown inconsistent results or lack convincing validation (17), (18). The development of such scores needs further investigation and validation in future studies. Whilst it is established that antithrombotic treatment improves survival following stroke (19), little is known about whether this benefit continues in those with a high risk of both ischemic stroke and bleeding events calculated based on their co-morbidities. In our fully adjusted model, accounting for age, sex, co-morbidities and stroke characteristics we have demonstrated a significant reduction in odds of in hospital mortality by 31% (OR 0.69 (95%CI 0.48 – 1.00 p=0.049)) and a relative risk reduction in long term mortality of 17% (HR 0.83 95%CI 0.71 – 0.97 p=0.02)) in this high risk group.

Interestingly, the underutilization of antithrombotic medications in at risk populations has been demonstrated in a number of studies. A recent publication from a nationwide AF programme in Belgium (subjects screen between 2012 and 2014) showed sub-optimal antithrombotic therapy in those with CVD. Of those with prevalent CVD 1094 (72.3%) were not taking any antithrombotic medications. This shows a low use of antithrombotic in those with prior CVD, despite international guidelines recommending this as secondary prevention in these patients. Those with prevalent CVD and AF (n=137) were either under- and over- treated; 32.5% were not taking any antithrombotic medication, 65.1% were taking both antiplatelet and anticoagulant medication and only 1.7% took an anticoagulant alone. This study also reiterated the importance of AF as a risk factor for CVD (OR 3.28, 95CI 2.77 – 3.89, P <0.001) (20). In another study, of the 10,406 patients (81.9%) at high risk (CHA2DS2-VASc score ≥2) for thromboembolism in a large retrospective general practice derived cohort study in New Zealand (participants recruited in 2014), 60.5% were treated with anticoagulants, 24.1% received aspirin monotherapy and 15.4% were not treated with any

antithrombotic medication. It also showed that 31.5% of patients at low risk (CHA2DS2-VASc <2) were treated with oral anticoagulants (21). These studies, in line with our study, highlights the disparity in antithrombotic treatment globally and the need for improved provision of antithrombotic treatment and adherence to treatment guidelines in those with AF and stroke.

Our study has several strengths. We used a large disease cohort of patients consecutively admitted with stroke derived hospital based sample which consisted validated stroke events, which improves the generalisability of our findings. As a prospective study, with robust case ascertainment, we introduce less bias. We were able to control for a range of demographic, medical co-morbidities and stroke characteristics.

There are some limitations worth discussing. Potential confounders were measured at baseline and it is possible that these may vary during the follow up period. While the HAS-BLED score performed best in predicting clinically relevant bleeding, with net reclassification improvement (10.3% compared with HEMORR(2)HAGES) and receiver-operating characteristic (ROC) analyses (c-indexes: 0.60 vs.0.55 for HAS-BLED compared to HEMORR(2)AGES), we used the latter due to data availability. Nevertheless, both predict bleeding risk and those with a high HEMORR2HAGES score will most likely have a high HAS-BLED score (4). Prior bleeding events and genetic factors were not collected and not used in the score calculation for patient HEMORR$_2$HAGES score. It is therefore possible that patient bleeding risk scores have been underestimated. As our disease cohort is comprised of those that survived stroke and did not die on transfer to hospital, there is a survival selection bias which may influence interpretation and generalisability of the survival benefits described. However they fit with other prognostic benefits described in the literature (19). It is clear that current practice has changed since data collection, in particular the advent of non-vitamin K antagonist oral anticoagulants, however this study aims to describe the risk scores in those with a prior diagnosis of AF who have suffered stroke and to determine the net clinical benefit of antithrombotic treatment in general terms to help guide future decision making. Events not requiring admission and certain non-medical general characteristics were not captured. However, the number of stokes occurring that do not lead to hospital admission will be low and therefore only likely to minimally attenuate the results. Whilst we were able to adjust for key potential confounders such as age, sex, co-morbidities and stroke risk factors, stroke subtype and OCSP

stroke classification, due to data availability we were unable to adjust for biological confounders such as arterial blood pressure and serum lipid levels. We were unable to control for unknown or known confounders which were not adjusted for. An important missing confounder is the use of statins before index stroke. This data was unavailable in our dataset. However, we have accounted for major co-morbidities and stroke risk factors.

Conclusion

It is clear there is a need for improved provision of antithrombotic treatment and adherence to treatment guidelines to reduce the global burden of stroke. We have described the distribution of bleeding and ischaemic stroke risk in those with a prior diagnosis of atrial fibrillation who have suffered as well as demonstrating the prognostic benefit of antithrombotic treatment in those with both high ischemic stroke risk and bleeding risk scores. Clinicians should take this into account when discussing treatment options with patients with both high ischemic and hemorrhagic risk scores in order to make evidence based decisions in stroke prevention.

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Disclosures and conflict of interest

No Disclosures from any authors

Contributorship

PKM is the PI of the NNUSTR. PKM & MAM conceived the study. DG, RB, SL, JBS and AC contributed to the design of the study. Data were analysed by DTG and RB under the supervision of all co-authors. DTG and PKM drafted the paper and all of the authors contributed in writing the paper.

Transparency statement

I, Phyo Kyaw Myint, lead author (the manuscript's guarantor) of the manuscript affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no

important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Tables and figures:

Table 1**:** Sample characteristics by stroke subtypes of 1928 men and women of the Norfolk and Norwich University Hospital Stroke Register.

Table 2: CHA_2DS_2-VAS_c and $HEMORR_2HAGES$ score groups sub divided into antithrombotic treatment groups for Ischemic and Hemorrhagic stroke groups.

Table 3: Logistic regression odds ratios (OR (95%CI)) and cox regression hazard ratios (HR (95%CI)) for in hospital and long term mortality for those with both high CHA_2DS_2-VAS_c score and $HEMORR_2HAGES$ score on antithrombotic therapy compared to those not on antithrombotic therapy.

Table 4: Sample characteristics before and after exclusion of men and women of the Norfolk and Norwich University Hospital Stroke Register.

Figure 1: Proportion of those with high and low ischemic stroke and bleeding risk scores on antithrombotic treatment subdivided into stroke type for all 1928 men and women of the Norfolk and Norwich University Hospital Stroke Register.

Figure 2**:** flow chart for criteria for selection of included sample

Table 1: Sample characteristics by stroke subtypes of 1928 men and women of the Norfolk and Norwich University Hospital Stroke Register.

	All (n= 1928)*	**Before eclusion**	**Ischemic stroke (n=1761) 91.34%**	**Hemorrhagic stroke (n=252)**	**P***
Age (SD)	81.3 (8.5)	81.54 (8.64)	81.4 (8.5)	80.1 (7.8)	0.029
Sex (%)					0.008
Men	832 (43.2)	910 (43.2)	746 (42.4)	131 (52.0)	
Women	1096 (56.8)	1192 ca Ischaemic stroke – 87.7	1015 (57.6)	121 (48.0)	
OCSP classification (%)					<0.001
LACS	320 (16.6)		316 (17.9)	16 (6.3)	
PACS	708 (36.7)		680 (38.6)	63 (25.0)	
POCS	263 (13.6)		217 (12.3)	64 (25.4)	
TACS	536 (27.8)		485 (27.5)	66 (26.2)	
Other	24 (1.2)		14 (0.8)	12 (4.8)	
Unknown	77 (4.0)		49 (2.8)	31 (12.3)	
Diabetes (%)	381 (19.8)	18.3	359 (20.4)	46 (18.3)	0.18

Heart failure (%)	599 (31.1)		549 (31.2)	70 (27.8)	0.25
Coronary heart disease (%)	814 (42.2)		749 (42.5)	104 (41.4)	0.32
Chronic kidney disease (%)	851 (44.1)		789 (44.8)	92 (36.5)	0.002
Hypertension (%)	1428 (74.1)		1310 (74.4)	188 (74.6)	0.67
MI (%)	215 (11.2)		201 (11.4)	23 (9.1)	0.72
Cancer (%)	373 (19.3)	16.1	347 (9.7)	46 (18.3)	0.22
Antithrombotic therapy (%)	1175 (60.9)		1045 (59.3)	179 (71.0)	<0.001
CHA_2DS_2-VAS_c score (SD)	4.6 (1.7)	3.7 (SD1.81)	4.6 (1.7)	4.7 (1.7)	0.041
$HEMORR_2HAGES$ score (SD)	4.0(1.6)	3.03 (SD 1.78)	4.0 (1.6)	3.9 (1.6)	0.035

*n=85 had both ischemic and hemorrhagic stroke

LACS = lacunar syndrome, PACS = Partial anterior circulation stroke, POCS = Posterior circulation syndrome, TACS = Total anterior circulation stroke

Table 2: CHA_2DS_2-VAS_c and $HEMORR_2HAGES$ score groups sub divided into antithrombotic treatment groups for Ischemic and Hemorrhagic stroke groups.

Ischemic stroke	Low CHA_2DS_2-VAS_c score (n=43)		High CHA_2DS_2-VAS_c score (n=1718)	
	Treatment (n=18)	No treatment (n=25)	Treatment (n=1027)	No treatment (n=691)
High $HEMORR_2HAGES$ score (n=1091)	0 (0%)	0 (0%)	779 (71.4%)	312 (28.6%)
Low $HEMORR_2HAGES$ score (n=670)	18 (41.9%)	25 (58.1%)	248 (39.6%)	379 (60.4%)
Hemorrhagic stroke	Low CHA_2DS_2-VAS_c score (n=7)		High CHA_2DS_2-VAS_c score (n=245)	
	Treatment (n=6)	No treatment (n=1)	Treatment (n=173)	No treatment (n=72)
High $HEMORR_2HAGES$ score (n=145)	0 (0%)	0 (0%)	117 (80.7%)	28 (19.3%)

Low HEMORR$_2$HAGES score (n=107)	6 (85.7%)	1 (14.3%)	56 (56%)	44 (44%)

Table 3: Logistic regression (OR (95%CI)) and cox regression hazard ratios (HR (95%CI)) for in hospital and long term mortality for those with both high CHA_2DS_2-VAS_c score and $HEMORR_2HAGES$ score on antithrombotic therapy compared to those not on antithrombotic therapy

Logistic regression odds ratios for in hospital mortality				
Models	**Events**	**OR**	**95% CI**	***p*-value**
A	312/1173	0.67	0.49 – 0.91	0.01
B	312/1173	0.67	0.49 – 0.92	0.013
C	312/1173	0.69	0.48 – 1.00	0.049
Cox regression hazard ratios for long term mortality				
Models	**Events**	**HR**	**95% CI**	***p*-value**
A	841/1173	0.81	0.69 – 0.95	0.007
B	841/1173	0.80	0.68 – 0.93	0.005
C	841/1173	0.83	0.71 – 0.97	0.02

Model A – adjusted for age and sex.

Model B – model A plus co-morbidities diabetes, heart failure, coronary heart disease, chronic kidney disease, hypertension, MI and cancer.

Model C – model B plus stroke subtype and Oxford Community Stroke Project (OCSP) classification

stroke classification.

Table 4: Sample characteristics before and after exclusion of men and women of the Norfolk and Norwich University Hospital Stroke Register.

	Before exclusion (n=9828)	**After exclusion (n=7503)**	**P value**
Age (SD)	77.17 (11.99)	77.22 (11.77)	0.79
Sex (%)			
Men	4654 (47.4)	3571 (47.6)	0.75
Women	5174 (52.6)	3932 (52.4)	
*** OCSP classification (%)**			
LACS	2132 (21.7)	1728 (23.0)	0.04
PACS	3122 (31.8)	2435 (32.5)	0.34
POCS	1607 (16.4)	1275 (17.0)	0.26
TACS	1996 (20.3)	1556 (20.7)	0.49
Diabetes (%)	1534 (15.6)	1151 (15.3)	0.63
Heart failure (%)	1325 (13.5)	998 (13.3)	0.73
Coronary heart disease (%)	2602 (26.5)	1977 (26.4)	0.85
Hypertension (%)	5610 (57.1)	4252 (56.7)	0.59
MI (%)	675 (6.9)	512 (6.8)	0.91
Cancer (%)	1408 (14.3)	1046 (13.9)	0.47

*** LACS = lacunar syndrome, PACS = Partial anterior circulation stroke, POCS = Posterior circulation syndrome, TACS = Total anterior circulation stroke**

Figure 1: Proportion of those with high and low ischemic stroke and bleeding risk scores on antithrombotic treatment subdivided into stroke type for all 1928 men and women of the Norfolk and Norwich University Hospital Stroke Register.

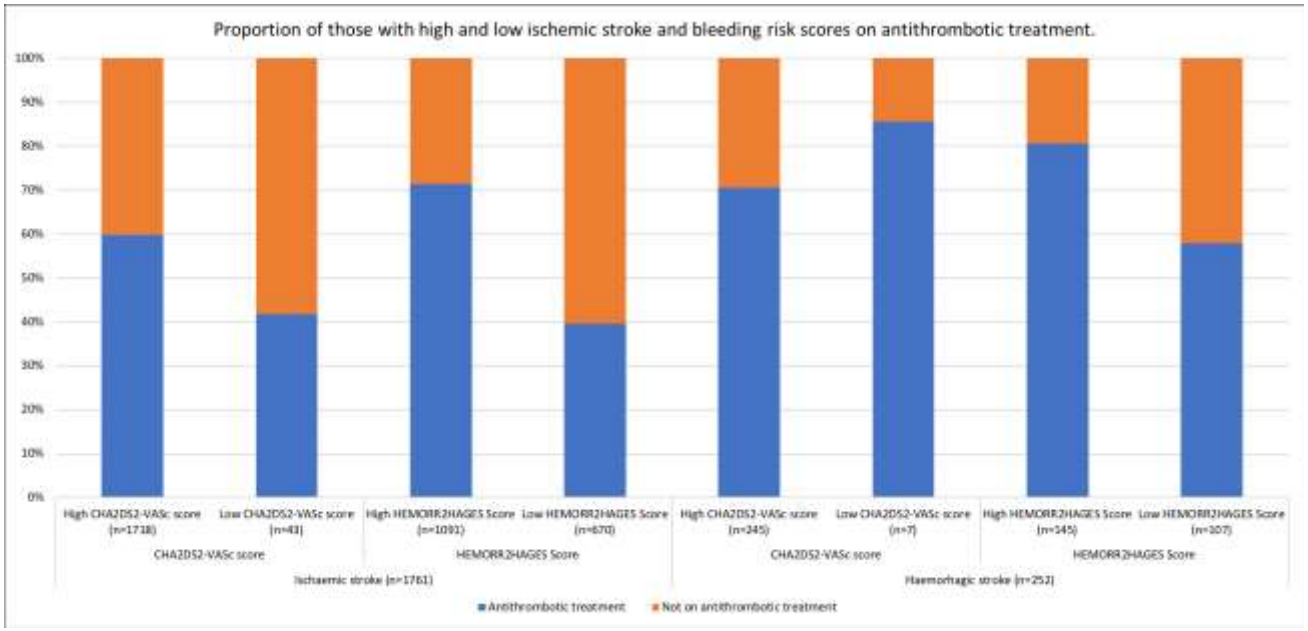

Figure 2: flow chart for criteria for selection of included sample