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Potential missed opportunities to prevent ischaemic stroke: prospective multicentre cohort study of atrial fibrillation-associated ischaemic stroke and TIA

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ABSTRACT

Objective We report on: (1) the proportion of patients with known atrial fibrillation (AF); and (2) demographic, clinical or radiological differences between patients with known AF (and not treated) and patients with newly diagnosed AF, in a cohort of patients who presented with ischaemic stroke or transient ischaemic attack (TIA) not previously treated with anticoagulation.

Design We reviewed cross-sectional baseline demographic and clinical data from a prospective observational cohort study, (CROMIS-2).

Setting Patients were recruited from 79 hospital stroke centres throughout the UK and one centre in the Netherlands.

Participants Patients were eligible if they were adults who presented with ischaemic stroke or TIA and AF and had not been previously treated with oral anticoagulation.

Main outcome measures Proportion of patients with known AF before index ischaemic stroke or TIA from a cohort of patients who have not been previously treated with oral anticoagulation. Secondary analysis includes the comparison of CHA_2DS_2-VASc and HAS-BLED scores and other demographics and risk factors between those with newly diagnosed AF and those with previously known AF.

Results Of 1470 patients included in the analysis (mean age 76 years (SD 10)), 622 (42%) were female; 999 (68%) patients had newly diagnosed AF and 471 (32%) patients had known AF. Of the 471 patients with known AF, 68% had a strong indication for anticoagulation and 89% should have been considered for anticoagulation based upon CHA_2DS_2-VASc score. Patients with known AF were more likely to have a prior history of dementia (4% vs 2%, p=0.02) and had higher HAS-BLED scores (median 3 vs 2). CHA_2DS_2-VASc, other risk factors and demographics were similar.

Conclusions About 1/3 of patients who present with stroke and have AF who have not been treated with oral anticoagulation have previously known AF. Of these patients, at least 68% were not adequately treated with oral anticoagulation.

Trial registration number NCT02513316.

Strengths and limitations of this study

► CROMIS-2 atrial fibrillation (AF) was a prospective multicentre observational study with a richly phenotyped patient population, allowing us to explore multiple demographic and clinical variables.
► We recruited from multiple centres and the results therefore reflect a range of clinical practices throughout the UK.
► The sample size is large and to our knowledge, is the first and only study to look at structural imaging markers of small vessel disease when investigating this clinical question.
► CROMIS-2 did not collect information on patient preference not to be anticoagulated, the burden or paroxysms in those with paroxysmal AF, or the reason the general practitioner/cardiologist/physician decided the patient was not to be anticoagulated, such as assessment of frailty.
► Our sample included patients who underwent MRI and provided informed personal or consultee consent, and excluded patients previously treated with anticoagulation so might not represent the complete population of patients with ischaemic stroke and AF.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is a major cause of ischaemic stroke.[1] Current clinical guidelines recommend anticoagulation to reduce ischaemic complications in AF whereas antiplatelets are less effective and therefore no longer recommended.[2] Despite a wealth of evidence supporting the use of anticoagulation for primary prevention of ischaemic stroke in people with AF—and the creation of ischaemic (CHA_2DS_2-VASc) and bleeding (HAS-BLED) risk scores to aid clinicians[3 4]—anticoagulant underuse is well documented,

with little recent improvement over the last decade.[5][6] Moreover, the reasons for non-treatment with oral anticoagulation in those at risk of ischaemic stroke remain uncertain.

Using the dataset of a multicentre, prospective observational inception cohort study of patients with AF and ischaemic stroke without oral anticoagulants before their index stroke, we sought to determine: (1) the proportion of patients with known AF compared with patients newly diagnosed with AF and (2) report on any demographic, clinical or radiological differences between patients with known AF (and not treated) and patients with newly diagnosed AF from a cohort of patient not previously treated with anticoagulation.

METHODS

This cross-sectional analysis is from the CROMIS-2 AF study,[7] a prospective multicentre inception cohort study recruiting from 79 hospital stroke centres in the UK and one centre in the Netherlands between August 2011 and July 2015. In CROMIS-2 AF, patients were eligible if they were adults (aged over 18 years) presenting with ischaemic stroke or TIA and had AF (known or new onset) for which anticoagulation was to be commenced. Patients were excluded from CROMIS-2 AF if they had previously been treated with anticoagulation.

Patient and public involvement

The CROMIS-2 protocol was reviewed by a stroke patient panel. The results of CROMIS-2 have been presented at major conferences and are open access.

Data collection of baseline characteristics, CHA_2DS_2-VASc and HAS-BLED score

The following baseline characteristics were prospectively collected by trained stroke research practitioners: age, sex, baseline, stroke severity using the National Institutes of Health Stroke Scale (NIHSS) at index event, prior use of antiplatelet agents before the index stroke, presence (or absence) of the following risk factors: AF diagnosed before stroke or TIA, hypertension, diabetes mellitus, hyperlipidaemia, history of ischaemic stroke (other than index stroke), history of intracerebral haemorrhage, history of cognitive impairment or dementia, current smoker and alcohol use (defined as ≥8 units per week)

We calculated composite CHA_2DS_2-VASc[8] and HAS-BLED[4] scores before the index stroke for each patient. When calculating CHA_2DS_2-VASc and HAS-BLED score, we defined hypertension if the patient had a history of hypertension or was on antihypertensive medication. We did not included time in therapeutic range when calculating HAS-BLED as no patients were on previous anticoagulation.

Imaging analysis

A PhD (clinical neurology) student (DW) trained in rating structural markers of cerebral small vessel disease

rated cerebral microbleeds, white matter hyperintensities and cortical superficial siderosis using validated or widely accepted scoring systems in accordance with STRIVE (Standards for reporting vascular changes on neuroimaging) consensus guidelines.[9–11] We considered white matter hyperintensities severe if they were confluent (score 2 or above in either the periventricular or deep white matter)

Outcome measures and statistical analysis

The primary outcome measure was the proportion of patients with AF known before the index stroke. In a secondary analysis, we compared (1) CHA_2DS_2-VASc scores (using two thresholds: CHA_2DS_2-VASc score reaching evidence for recommended oral anticoagulation (class 1, level A evidence) and CHA_2DS_2-VASc score reaching evidence for consideration of oral anticoagulation (class 2a level b evidence) (2) HAS-BLED scores and (3) demographic and baseline characteristics between patients with known AF before study entry and those with newly diagnosed AF at study entry.

We performed group comparison using the χ^2 test for categorical variables and the Mann-Whitney U-test for continuous variables. All tests were two-tailed, and statistical significance was determined at α-level of 0.05. We performed statistical analyses using STATA V.13.

RESULTS

Of the 1490 patients, 1470 (99%) enrolled in CROMIS-2 had information on whether their AF was newly diagnosed at study entry or previously known. The mean age of the cohort was 76 years (SD 10) and 622 (42%) were female. Median NIHSS (available in 928 patients) at stroke onset was 4 (IQR 2 to 9). 1234 patients (84%) presented with a stroke, 236 (16%) with a TIA.

Of the 1470 patients, 999 (68%) patients had newly diagnosed AF at study entry and 471 (32%) had known AF prior to the occurrence of ischaemic stroke or TIA. CHA_2DS_2-VASc scores (median 3 for both, IQR 2–4) (figure 1) did not differ significantly between both groups. In line with current European guidelines, of the patients with known AF prior to their qualifying stroke 304/447 (68%) had a strong indication for anticoagulation (male
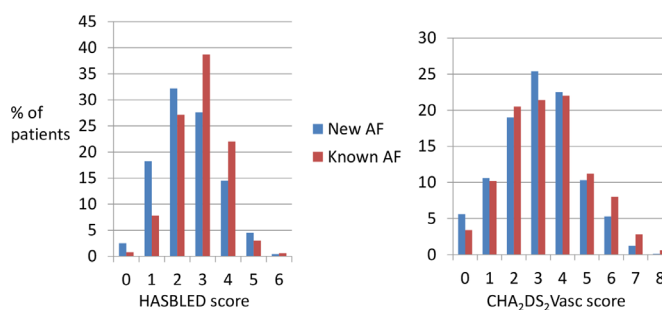

Figure 1 Distribution of HAS-BLED and CHA_2DS_2-VASc scores between patients with known AF versus those with newly diagnosed AF. AF, atrial fibrillation.

Table 1 Difference in demographics and risk factors between patients with known AF and newly diagnosed AF

Variable	All patients (n=1470)	Newly diagnosed AF (n=999)	Known AF (n=471)	P value
Age, (SD)	76 (10)	75 (10)	77 (11)	0.04
Age (SD) in those with only one risk factor other than sex	68 (8)	67 (8)	66 (7)	0.501
Sex, female, n (%)	622 (42)	404 (40)	218 (46)	0.034
Known hypertension,n (%)	915 (63)	594/983 (60)	321/465 (69)	0.002
Known diabetes mellitus, n (%)	243/1469 (17)	164/998 (16)	79 (17)	0.87
Known hyperlipidaemia, n (%)	649/1449 (45)	421/986 (43)	228/463 (49)	0.019
Current smoker, n(%)	165/1425 (12)	114/968 (12)	51/461 (11)	0.674
Excessive alcohol, n(%)	110/1365 (8)	79/929 (9)	31/436 (7)	0.378
Prestroke mRS, median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 1)	0.002
Dependant living n (%)	97/1435 (7)	58/974 (6)	39/461 (8)	0.076
Previous ischaemic stroke n(%)	141/1445 (10)	94/977 (10)	47/468 (10)	0.801
Previous ICH n(%)	8/1450 (0.5)	5/981 (0.5)	3/469 (0.6)	0.719
Ischaemic heart disease n(%)	241 (16)	137 (14)	104 (22)	<0.001
Known dementia/cognitive impairment n(%)	37/1463 (3)	18/996 (2)	19/467 (4)	0.010
Known peripheral vascular disease n (%)	31/1445 (2)	19/990 (2)	12/464 (3)	0.412
Antiplatelets on admission, n (%)	765/1455 (53)	423/986 (43)	342/469 (73)	<0.001
Cerebral microbleeds, presence, n (%)	308 (21)	207 (21)	101 (21)	0.751
Confluent white matter hyperintensities, presence, n (%)	428 (29)	281 (28)	147 (31)	0.225
Cortical superficial siderosis, presence, n (%)	5 (0.3)	5 (0.5)	0 (0.0)	0.183
Prestroke CHA_2DS_2-VASc, median, (IQR) (available in 1374 patients)	3 (2 to 4)	3 (2 to 4)	3 (2 to 4)	0.001
CHA_2DS_2-VASc score≥1 n (%)	1306/1374 (95)	877/927 (95)	429/447(96)	0.274
CHA_2DS_2-VASc score reaching evidence for recommended oral anticoagulation (class 1a evidence), n (%)	895/1374 (65)	591/927 (64)	304/447 (68)	0.121
CHA_2DS_2-VASc score reaching evidence for consideration of oral anticoagulation (class 2b evidence) n (%)	1182/1374 (86)	786/927 (85)	396/447 (89)	0.057
Prestroke HAS-BLED median (IQR) (available in 1280 patients)	3 (2 to 3)	2 (2 to 3)	3 (2 to 3)	0.010

AF, atrial fibrillation; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale.

patient with a CHA_2DS_2-VASc score of two or more or female patient with a CHA_2DS_2-VASc score of three or more) and 396/447 (89%) ought to have been considered for anticoagulation (male patients with a CHA_2DS_2-VASc score of one or more, female patients with a CHA_2DS_2-VASc score of 2 or more).[2] Patients with known AF before their ischaemic stroke or TIA had higher HAS-BLED scores compared with those with newly diagnosed with AF (median 3 (IQR 2–3) vs 2, (IQR 2–3) p=0.010) (figure 1). Significantly more patients with known AF were on antiplatelet agents before the index stroke compared with patients with newly diagnosed AF (73% vs 43%, p<0.001). Patients with known AF were more likely to have a prior history of dementia or cognitive impairment (4% vs 2%, p=0.010), more likely to have hypertension (69% vs 61%, p=0.002) and hyperlipdaemia (49% vs 42%, p=0.019) and more likely to have ischaemic heart disease (22% vs 14%, p<0.001). Other variables in patients with known AF and those with newly diagnosed AF did not differ significantly

including the presence of small vessel disease structural imaging markers. (table 1)

Given the significant difference in HAS-BLED scores between patients with known AF and those with newly diagnosed AF, we evaluated this further by exploring the individual components of the score. This revealed a significant difference in medications predisposing to bleeding between the two groups (73% vs 46%, p<0.001). Of the medications predisposing to bleeding, 95% were taking antiplatelets and 5% were taking non-steroidal anti-inflammatory drugs. The probable indications for antiplatelets were also different between the groups; the known AF patients had a significantly higher prevalence of ischaemic heart disease 22% vs 14%.

DISCUSSION
In this cohort of patients with ischaemic stroke or TIA and AF, we found that 396/447 (89%) of patients with

known AF had a CHA_2DS_2-VASc score indicating anticoagulation should be considered yet were not anticoagulated at the time of their qualifying stroke representing a potential missed opportunity to prevent their ischaemic stroke or TIA.

In our cohort of patients with stroke and known AF, 68% were at high risk of ischaemic stroke with a strong indication for anticoagulation.[2] Although not a true denominator group (which would require patients from the same population with known AF who did not have strokes), the patients who presented with stroke and newly diagnosed AF do serve as a comparator to generate hypotheses regarding why patients with known AF are not being appropriately anticoagulated. In comparison with the patients with newly diagnosed AF, patients with known AF had a higher prevalence of cognitive impairment or dementia, higher prevalence of hypertension and hyperlipidaemia and higher HAS-BLED scores. The HAS-BLED scores were higher, mainly due to the use of antiplatelet agents before their index stroke. There was no difference between structural imaging markers of the cerebral small vessel diseases that cause over 80% of spontaneous (nontraumatic) intracerebral haemorrhage. We found no difference in the neuroimaging features associated with so-called 'bleeding prone arteriopathies' (namely cerebral microbleeds and cortical superficial siderosis, features of cerebral amyloid angiopathy) on brain imaging between those with known AF compared with those with newly diagnosed AF.

Our finding that a large proportion of patients who present with stroke and have AF and have not been previously treated with oral anticoagulation, have previously known AF is consistent with previous studies, although most of these were retrospective. For example, a large retrospective Finnish registry study involving 3404 patients with AF investigating ischaemic stroke events showed that only 55% of patients at high risk of ischaemic stroke ($CHADS_2$ ≥2) were anticoagulated.[5] The most common reason for withholding anticoagulation in this cohort were infrequent paroxysms of AF (14%), previous bleeding (13%) and patient choice (9%), although no clear reason was documented in the majority of cases (35%). The percentage of patients with a $CHADS_2$ ≥2 who were anticoagulated increased over the study period between 2003 and 2012 (from 49% to 65%, p<0.001). A large Swedish retrospective cross-sectional cohort of patients with AF spanning 2004 to 2010 found that only 48% of patients with AF were treated with oral anticoagulants, and of those that were not, 75% did not have a documented reason for withholding.[6] Similarly, data from a New Zealand registry from 2010 to 2014 including 10 406 patients with AF and a CHA_2DS_2-VASc≥2 found that only 6298 (61%) were using anticoagulation.[12] Data from a large North American cohort of just under 95 000 patients from the 'get with the guidelines' programme showed that only 16% of patients with known AF were receiving anticoagulation.[13] By contrast with these studies, a prospective registry[14] of consecutive patients

from European centres reported that patients with known AF and CHA_2DS_2-VASc≥2 had a higher rate of anticoagulant use (86%; 5600 of 7493 patients) than we observed. However, patients were recruited from hospital-based centres, so might not reflect practice in primary care. Of note, CROMIS-2 AF has the advantage of being a prospective inception cohort with excellent phenotyping, so does not rely on discharge and general practice codes to identify diagnosis and risk factors, which can be inaccurate. Of note, most of our patients (68%) had newly diagnosed AF at the time of their qualifying stroke. A proportion of these patients might have had undiagnosed AF for some time before the stroke. With accessible technology (such as heart monitors in watches) becoming more prevalent, it is possible that the proportion of patients with known AF will increase, presenting a further opportunity to prevent ischaemic stroke in the future.

Although our study highlights the ongoing underuse of anticoagulants in patients with known AF, we were unable to draw firm conclusions for several reasons: most importantly, we excluded patients who were on or previously exposed to anticoagulation, thus we do not know how many patients had ischaemic strokes despite anticoagulation. While we found a higher prevalence of dementia and cognitive impairment in the patients with known AF, this only accounted for 19 patients (4%). As 96% of patients in CROMIS-2 AF were subsequently anticoagulated,[7] it seems unlikely that a strong and persistent contraindication to anticoagulation would explain our results. Although we acknowledge that the strength of the indication for anticoagulation could change after having a TIA or stroke, we did not observe a difference in previous ischaemic or haemorrhagic stroke when comparing those with known and new AF. Secular changes in guidelines are also unlikely to have influenced results as our recruitment started in 2012 and finished in 2015. The European Society of Cardiology guidelines on AF were updated in 2012 and then not again until 2016, so all treatment of patients within the CROMIS-2 AF cohort should have followed the 2012 guidance (which recommends anticoagulation for CHA_2DS_2-VASc≥1). Ambiguity regarding ischaemic stroke risk in patients with low CHA_2DS_2VASc scores might be another potential reason for the low anticoagulation rates in our cohort. A recent study revealed a wide variation in reported rates of stroke across cohorts, especially those with low CHA2DS2-VASc scores (0–1),[15] where the low rate of subsequent stroke does not indicate a clear expected net benefit with anticoagulation. This is reflected in the 2016 European Society of Cardiology guidelines which recommend anticoagulation for males with a CHA_2DS_2-VASc≥1 and females with a CHA_2DS_2-VASc≥2. The higher HAS-BLED score in those with known AF was largely being driven by a higher use of antiplatelets. Nevertheless, we do not know the definite indication for antiplatelets in this patient group and whether antiplatelets were being used as an oral anticoagulant replacement, although the higher percentage of ischaemic heart disease in the known AF group may

partially explain this difference; a clear indication for antiplatelet agents may dissuade the use of anticoagulants, in particular, if dual antiplatelet agents are used, but this does not fully account for the cohort. A higher HAS-BLED score should not exclude anticoagulation per se; HAS-BLED scores≥3 should identify patients at higher risk of bleeding, leading to closer monitoring and reduction in modifiable risk factors,[2] rather than a reason to not anticoagulate. Indeed, studies have shown that patients with higher HAS-BLED score benefit the most from anticoagulation.[16 17] Furthermore, the higher predisposition to major bleeding should not discourage clinicians from starting anticogulants as the bleeding risk on aspirin is comparable to the bleeding risk on warfarin.[18]

Our study has strengths; CROMIS-2 AF was a prospective multicentre observational study with a richly phenotyped patient population, allowing us to explore multiple demographic and clinical variables. It recruited from multiple centres and the results therefore reflect a range of clinical practice. The sample size is large and to our knowledge, is the first and only study to look at structural imaging markers of small vessel disease when exploring this clinial question. Since intention to anticoagulate was an inclusion criterion we were able to investigate a cohort without clear contraindications to treatment. The main weakness of our study with regard to the current paper is that CROMIS-2 was not designed to answer this research question; rather, this post-hoc analysis was designed to determine the extent of ongoing underuse of anticoagulation in primary stroke prevention in patients with AF and generate hypotheses to explain the findings. CROMIS-2 did not collect information on: patient preference not to be anticoagulated; the burden or paroxysms in those with paroxysmal AF; reasons for antiplatelet therapy; or reasons that the treating physician or GP decided against anticoagulation, for example, the assessment of frailty. We also acknowledge some strokes may have not been related to AF, although expect this to have been similar across the two groups.

Nevertheless, our findings show patients with AF who are at risk of ischaemic stroke are not being treated adequately, with little progress has been made over the last quarter-century.[19] Further improvements in education to both primary and secondary care physicians as well as patients are required. Bleeding risk scores also need to be interpreted as they were designed: to identify patients for closer monitoring and treatment of modifiable risk factors, and not as a tool to avoid starting anticoagulation.[20] Healthcare policies should focus on closing this persistent translational gap.

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