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Atrial fibrillation patients categorised as 'not for anticoagulation' with the 2014 Canadian Cardiovascular Society algorithm are not 'low risk'

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Abstract

Background Oral anticoagulation(OAC) is highly effective for stroke prevention in non-valvular atrial fibrillation(AF). We explored rates of stroke/thromboembolism/transient ischemic attack(TIA) amongst the 'OAC not recommended' patient group as defined by the 2014 Canadian Cardiovascular Society(CCS) algorithm (based on $CHADS_2$ score) but would have been offered OAC using the ESC guidelines approach (based on CHA_2DS_2-VASc score).

Methods We identified 22582 non-anticoagulated patients age <65 with a $CHADS_2$=0 who were stratified according to the CHA_2DS_2-VASc score, except female sex, which would be an indication for OAC according to the ESC guidelines. Event rates for each risk strata were compared by Cox proportional hazard ratios.

Results The overall rate of the combined endpoint of ischemic stroke/SE/TIA was 4.32 per 100 person-years(95%CI 3.26-5.74) at 1 year, amongst the patients who would have had an indication for OAC therapy according to ESC guidelines and 'OAC not recommended' according to CCS algorithm. This corresponded to an adjusted hazard ratio of 3.08(95%CI 2.21-4.29) relative to the subgroup with no indication for OAC by the ESC guidelines.

A subgroup of patients with prior vascular disease and $CHADS_2$ score=0 (i.e. only recommended aspirin treatment according to CCS algorithm) had an event rate of 4.84(95%CI 3.53-6.62) per 100-person-years at one-year follow-up.

Conclusion Based on the 2014 CCS algorithm, the 'OAC not recommended' subgroup can have a high 1 year stroke rate overall, showing that such patients are not 'low risk'. Use of the ESC guideline approach (based on CHA_2DS_2-VASc) offers refinement of stroke risk stratification in such patients.

Key words atrial fibrillation, stroke, risk stratification

Brief summary

We explored the rates of stroke/thromboembolism/transient ischemic attack amongst 'OAC not recommended' patients as defined by the 2014 Canadian Cardiovascular Society(CCS) algorithm (based on $CHADS_2$ score) but would have been offered OAC using the European Society of Cardiology guidelines approach (based on CHA_2DS_2-VASc score). Using the 2014 CCS algorithm, the 'OAC not recommended' subgroup can have a high 1 year stroke rate of 4.32 per 100 person-years, suggesting that such patients are not 'low risk'.

Introduction

Patients with atrial fibrillation (AF) have a five-fold increase in stroke risk, but this risk is not homogeneous, and depends on the presence of various stroke risk factors[1]. These risk factors have been used to derive stroke risk stratification schemes, such as the $CHADS_2$ [congestive heart failure, hypertension, age>75 years, diabetes mellitus, stroke (2 points)] score[1]. When the only available oral anticoagulant was the Vitamin K Antagonist class of drugs (VKA, e.g. warfarin), these schemes were used to identify 'high risk' patients, who could be targeted for warfarin therapy.

With the availability of NOACs and better management of VKAs, the focus of many guidelines (European Society of Cardiology (ESC), National Institute for Health and Care Excellence (NICE)) now is to initially identify 'low risk' patients who do not need any antithrombotic therapy[2 3]. Subsequent to this step, patients with ≥1 additional stroke risk factors can be offered effective stroke prevention, which is a NOAC or well-managed VKA (with time in therapeutic range >65-70%). The CHA_2DS_2-VASc [congestive heart failure or left ventricular dysfunction, hypertension, age>75 years (2 points), diabetes mellitus, stroke (2 points), vascular disease, age 65–75 years, and female sex)] score was introduced as a simple clinical risk score that reliably identifies those at 'low risk' (ie. CHA_2DS_2-VASc score=0 (male) or 1 (female)) of stroke and thromboembolism[4].

In 2014, the Canadian Cardiovascular Society (CCS) published its focused update guideline offering a simplified algorithm-based approach to stroke risk stratification[5]. The first step in the algorithm was to identify those 'age ≥65' who should be offered OAC. The second step is to identify those age<65 with $CHADS_2$ risk factors (heart failure, hypertension, diabetes or stroke/TIA), who should have OAC. Next, those age<65 who are '$CHADS_2$ score=0 with 'arterial disease i.e. coronary, aortic or peripheral' are recommended aspirin alone (and not OAC). Finally, those patients age<65 with no $CHADS_2$ risk factors nor vascular disease are recommended 'no

antithrombotic therapy'[5]. The 2014 CCS guideline text states that 'We do not consider female sex or vascular disease alone as sufficient reasons to prescribe OAC therapy.'

In this analysis of non-anticoagulated patients from the Danish nationwide cohort study, we explored the rates of stroke/thromboembolism/TIA amongst the 'OAC not recommended' patient group as defined by the 2014 CCS algorithm (based on the $CHADS_2$ score) stratified according to OAC recommendation using the ESC guidelines (based on the CHA_2DS_2-VASc score). We tested the hypothesis that the 'OAC not recommended' patient group using the 2014 CCS algorithm could have further refinement of stroke risk stratification by using the ESC guidelines approach.

Methods

The detailed methods of the Danish registries have been previously described[6]. In brief, based on the Danish National Patient Register and the Danish National Prescription Registry we identified all incident hospital or ambulatory diagnoses of nonvalvular AF in the study period from 1999 to 2012. Nonvalvular AF was defined as presence of atrial fibrillation (ICD10: I48), and baseline absence of mitral stenosis or mechanical heart valves (ICD10: I05 or Z952-Z954). All patients were without VKA prescription at least one year prior to AF diagnose. As a measure of 'non-treatment with VKA', we used person-time off VKA treatment. Patients only contributed with person-time until a prescription of VKA was claimed (if any). The $CHADS_2$ and CHA_2DS_2-VASc scores were ascertained from the Danish registries as previously described[6]. The $CHADS_2$ score was ascertained by including diagnosis on congestive heart failure, hypertension, age, diabetes mellitus and presence of previous stroke/transient ischemic attack. The CHA_2DS_2-VASc score was calculated by including diagnosis on congestive heart failure/left ventricular dysfunction, hypertension, age, diabetes mellitus, female sex, vascular disease and presence of previous stroke/thromboembolism/transient ischemic attack; the detailed outline of the utilised ICD-10 diagnosis and concomitant medication is provided in supplementary Table 1. Thus, the CHA_2DS_2-VASc would include congestive heart failure (like $CHADS_2$, but also specifying recent decompensated heart failure, with reduced or preserved ejection fraction) and moderate-severe LV dysfunction on cardiac imaging (even if asymptomatic)[2].

As our focus was the 'OAC not recommended' patient group as defined by the 2014 CCS algorithm[5] in relation to the ESC guidelines (based on the CHA_2DS_2-VASc score), we restricted the study population to *patients with age below 65 years and with a $CHADS_2$ score of zero.* The main

outcome was stroke/thromboembolism and defined as a combined end point of ischemic stroke, systemic embolism (SE), and transient ischemic attack (TIA) (ICD-10: I63; I64, G45; I74). Person-time was censored if patients died, if a prescription of a VKA was claimed during follow-up, at emigration or end of follow-up, whichever came first. Secondary analyses investigated the outcomes of (extra cranial) major bleeding (ICD-10: D62; J942; H113; H356; H431; N02; N95; R04; R31; R58) and intracranial haemorrhage (ICD-10: I60; I61; I62), to indicate the bleeding risk of this cohort, as ultimately decisions on antithrombotic therapy would be based on the balance between stroke and serious bleeding risks. Two sensitivity analyses were performed, as follows: (i) we confined our primary endpoint analysis to ischemic stroke/SE, and (ii) we investigated a combined endpoint of ischemic stroke/haemorrhagic stroke/SE to ascertain if the benefit from stroke prophylaxis could offset by the risk of intracranial haemorrhage.

Event rates of stroke/thromboembolism per 100 person-years were calculated for the patient groups defined by whether there was an indication for OAC therapy according to ESC guidelines, i.e. a CHA_2DS_2-VASc score ≥1 (males) or ≥2 (females). A Cox proportional hazard analysis was constructed to inspect the risk related to treatment indication to ascertain if patients with a CHA_2DS_2-VASc score ≥1 (males) or ≥2 (females) were at greater risk of stroke/thromboembolism compared to those not indicated for treatment (i.e. CHA_2DS_2-VASc score =0 (males) or 1 (females), based on ESC guidelines). We performed both unadjusted and adjusted analyses (adjusted for baseline ASA use and year of inclusion, in a categorical manner). All analyses were reported for a 1-year follow-up.

Results

The study population comprised 22582 AF patients age <65 with a $CHADS_2$ score of zero; 1731 patients had indication for OAC treatment according to the ESC guidelines, see Table 1. A breakdown of what factors in the CHA_2DS_2-VASc score that led to their classification as 'anticoagulation indicated' (n=1731) consisted of n=54 with systemic embolism (35% females; 28% aspirin use), n=1149 with vascular disease (26% female; 38% aspirin use) and n=695 with left ventricular dysfunction (22% female; 11% aspirin use).

The overall rate of the combined endpoint of ischemic stroke/SE/TIA was 4.32 per 100 person-years (95%CI 3.26-5.74) at 1 year, amongst patients who would have had indication for OAC therapy according to ESC guidelines [Table 2]. In contrast, the subjects with no indication for OAC according to the ESC guideline criteria had an ischemic stroke/SE/TIA event rate of 1.13 per 100 person-years.

When compared to those with no indication for OAC by the ESC guidelines, an unadjusted and adjusted analysis (adjusting for baseline aspirin use and year of inclusion) showed hazard ratios of 3.60 (95%CI 2.62-4.94) and 3.08 (95%CI 2.21-4.29), respectively for ischemic stroke/SE/TIA in patients who by ESC guidelines had an indication for treatment.

Sensitivity analyses

A sensitivity analysis confining our combined endpoint to 'ischemic stroke/SE' did not change our conclusions, with event rates of 3.96 per 100 person-years (95%CI 2.95-5.32) for patients with indication for OAC treatment and 0.94 (95%CI 0.80-1.10) for patients with no indication for OAC treatment, according to the ESC guideline criteria.

Investigating the combined endpoint of 'both ischemic and haemorrhagic stroke, and SE' showed consistent result of event rates being higher in the group with indication for OAC treatment (according to the ESC guideline criteria) compared to those no indication for OAC, that is, 4.14 (95%CI 3.10-5.53) vs 1.15 (95%CI 1.00-1.33) per 100 person-years, respectively.

Subgroup and secondary analyses

Analysing the subgroup of patients with vascular disease (n=1149) who by CCS guidelines would not require OAC treatment (i.e. presence of vascular disease and $CHADS_2$ score=0), the stroke/SE/TIA rate was 4.84 (95%CI 3.53-6.62) for one year follow-up.

In this subgroup of AF patients with vascular disease, the event rates per 100 person-years for males and females were 4.53 (95%CI 3.11-6.61; 27 events) and 5.69 (95%CI 3.23-10.01; 12 events), respectively; also, the adjusted hazard ratio for sex for the full follow-up period showed an increase in hazard ratio for female sex, 1.74 (95%CI 1.06-2.86).

Secondary analyses on major bleeding (extra cranial) and intracranial haemorrhage events showed low event rates in the group with an indication for OAC therapy according to ESC guidelines, of 1.26 (95%CI 0.74-2.12) and 0.25 (95%CI 0.13-0.95), respectively.

Discussion

In this analysis we show that based on the 2014 CCS algorithm, the 'OAC not recommended' subgroup can have a 1-year stroke rate overall of 4.32 per 100-patient years, showing that such patients are not 'low risk'. Indeed, vascular disease and female sex should not be ignored when undertaking stroke risk stratification of AF patients. Thus, the 'OAC not recommended' patient group based on the 2014 CCS guidelines could have further refinement of stroke risk stratification by using the ESC guidelines approach.

Decisions on thromboprophylaxis require a balance between stroke and bleeding risks, and in patients with >1 additional stroke risk factors, the net clinical benefit balancing stroke, mortality and serious bleeding is usually in favour of OAC use.[7, 8] With the availability of NOACs that offer relative efficacy, safety and convenience compared to the VKAs, Eckman et al[9] have even estimated that the 'tipping point' threshold for OAC treatment may be a stroke rate of ≥0.9%/year. Indeed, secondary analyses shows that our patient group was also at low risk of major bleeding or ICH[10]. Thus, our data support the approach in the ESC and NICE guidelines that advocates a clinical practice shift towards the initial step of identifying 'truly low risk' patients (who do not need any antithrombotic therapy), using the CHA_2DS_2-VASc score. Subsequent to that step, effective stroke prevention (which is OAC, whether a NOAC or well-controlled warfarin) can then be offered to those with ≥1 additional stroke risk factors[11].

Vascular disease is also an independent predictor of stroke risk. In a recent systematic review, vascular disease was clearly contributory to an increased stroke risk[12]. This may be particularly evident in Asians, where 1.8 fold increase in stroke risk was seen on multivariable analysis[13] compared to Europeans, where (for example) a 1.22 fold increase was reported in the Swedish AF cohort study (with similar adjusted relative hazard to hypertension and diabetes mellitus)[14] and 1.12

fold in the Danish cohort[15]. Thus, vascular disease should be included when undertaking stroke risk stratification of AF patients.

When males and females with '$CHADS_2$=0 plus vascular disease' were compared, stroke rates were higher in the female patients, with a hazard ratio of 1.74. Thus, our data suggest that female AF patients age <65 with vascular disease represent a high stroke risk subgroup; however, the 2014 CCS algorithm does not recommend OAC in this population. Our data are consistent with a recent systematic review and meta-analysis showing female sex as a risk factor, regardless of OAC use [Risk Ratio (95%CI 1.29(1.09-1.52) and 1.49(1.17-1.90) in non-anticoagulated vs. anticoagulated/ mixed cohorts, respectively)[16]. Thus, female sex should not be ignored when undertaking stroke risk stratification of AF patients, but would only be relevant with ≥1 additional stroke risk factors. Indeed, females with a CHA_2DS_2-VASc score=1 by virtue of their sex alone are 'low risk'[17].

Limitations

The limitations of this nationwide cohort study are well recognized by us, especially its observational, non-randomised design where residual confounding may be evident[6]. Nonetheless, our data urge caution such that vascular disease should not be ignored when undertaking stroke risk stratification of AF patients, when considering patients for OAC. As reflected by the small decrease in the analysis adjusted for baseline aspirin treatment, aspirin is minimally effective for stroke prevention in AF, and not safe nor cost-effective[3].

In conclusion, based on the 2014 CCS algorithm, the 'OAC not recommended' subgroup can still have a high stroke rate overall. Such patients are not 'low risk', and should be considered for OAC. Use of the ESC guideline approach (based on the CHA_2DS_2-VASc score) would allow refinement of stroke risk stratification in such patients.

DISCLOSURES

Professor Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speaker's bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

Other authors – none relevant to this paper.

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Table 1: Baseline characteristics for non-anticoagulated atrial fibrillation patients age <65 with a $CHADS_2$ score of zero ('OAC not recommended' as defined by the 2014 CCS algorithm)

	No indication for OAC treatment	**Indication for OAC treatment based on the ESC guidelines**
N (%)	n=20,851 (92.3)	n=1,731 (7.7)
Age, mean (IQR)	55.5 (47.0 – 60.7)	58.9 (53.5 – 62.1)
Female sex	7,505 (36.0)	428 (24.7)
Previous systemic embolism	0	54 (3.1)
Prior vascular disease	0	1149 (66.4)
Prior left ventricular dysfunction	0	695 (40.2)
Aspirin	2,151 (10.3)	473 (27.3)
Clopidogrel	66 (0.3)	92 (5.3)
Dipyridamole	92 (0.4)	95 (5.5)
CHA_2DS_2VASc score		
Male=0 / female=1	20,851	0
1 (males)	0	1,179 (68.1)
2	0	479 (27.7)
3	0	51 (2.9)
4	0	20 (1.2)
5	0	2 (0.1)

CCS, Canadian Cardiovascular Society; ESC, European Society of Cardiology

$CHADS_2$ and CHA_2DS_2-VASc, see text

OAC, oral anticoagulation

Table 2: Event rates for ischemic stroke/SE/TIA stratified on indication for OAC treatment according to the ESC guidelines.

		One year follow-up				
	N	Person-years	Events	Event rate (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
No indication for treatment	20,851	16,278	184	1.13 (0.98-1.31)	Ref	Ref
Indication for OAC treatment	1,731	1,110	48	4.32 (3.26-5.74)	3.60 (2.61-4.94)	3.08 (2.21-4.29)

Ref=Reference

Supplementary Table 1

	International Classification of Diseases 10th revision (ICD-10) code	Anatomical Therapeutic Chemical (ATC) code
Condition		
Congestive heart failure	I11.0; I13.0; I13.2; I42.0; I50	CO3C
Left ventricular dysfunction	I50.1; I50.9	
Hypertension		See specified definition*
Diabetes mellitus	E10.0; E10.1; E10.9; E11.0; E11.1; E11.9	A10
Ischemic stroke	I63; I64	
Systemic embolism	I74	
Transient ischemic disease	G45	
Aortic plaque	I70.0	
Peripheral arterial disease	I70.2-I70.9; I71; I73.9; I74	
Myocardial infarction	I21-I23	
Nonvalvular atrial fibrillation	I48 and baseline absence of I05 and Z952, Z953, Z954	
Extra cranial major bleeding	D62 J942 H113 H356 H431 N02 N95 R04 R31 R58	

Intracranial bleeding	I60 I61 I62
Traumatic intracranial bleeding	S063C S064 S065 S066
Retinal bleeding	H356

Medication

Warfarin	B01AA03
Aspirin/Clopidogrel	B01AC06/B01AC04
Dipyridamole	B01AC07

* We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive Drugs:

I. Alpha adrenergic blockers (C02A, C02B, C02C)

II. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III. Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV. Beta blockers (C07)

V. Calcium channel blockers (C07F, C08, C09BB, C09DB)

VI. Renin-angiotensin system inhibitors (C09).