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Letter to the Editor

Using the CHA_2DS_2-VASc score for stroke prevention in atrial fibrillation: A focus on vascular disease, females and simple practical application

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We recently provided evidence that using the new risk stratification algorithm approach from the Canadian Cardiovascular Society (CCS) Guidelines could leave patients with a high 1-year stroke rate (4.86 per 100 person-years)[1]; hence, patients with such high stroke rates are not 'low risk', as acknowledged by Cairns et al. in their accompanying Editorial[2].

In the 2014 focused guidelines update, the CCS recommends use of the $CHADS_2$ schema referring to the original Gage et al publication[3] (and thus implying use of a similar definition). Thus, patients with some risk factors already included within the CHA_2DS_2-VASc score would not have been included in the 2014 CCS guidelines. Indeed, it is very important to strictly define the precise criteria for providing points related to each component in risk stratification scoring systems, and we welcome a clarifying update from the CCS committee on this matter.

Notwithstanding this inconsistency/misinterpretation on definitions, Cairn et al. raises the concern that previous publications using the Danish nationwide registries showed different event rates relative to those we presented. However, the devil is in the detail. Different populations and inclusion criteria, study settings, definitions on outcomes and time frames may account for the variation in event rates seen in various studies (see Online Supplement for full details).

In an attempt to specify and fully describe our event rates challenged by Cairns et al., we are pleased to provide a stratified analysis of 987 patients with prior vascular disease. We defined the 'VASc' component as follows: prior myocardial infarction, prior peripheral artery disease, or aortic plaque, as we have done previously[4]. It is evident that all subgroups of prior vascular diseases carry a high one-year thromboembolic event rate, see Table 1. Contrasting low risk CHA_2DS_2-VASc (that is, score 0 (male) or 1 (female)) as a reference population vs those with $\geq$1 additional stroke risk factors (ie. CHA_2DS_2-VASc score =1 (male) or =2 (females)) to express the hazard attributable to vascular disease resulted in a crude HR of 2.7 (95%CI 1.7-4.2).

To investigate the subgroup of AF patients with a $CHADS_2$=0 and concomitant MI, we excluded those with prior peripheral artery disease and aortic plaque. Contrasting CHA_2DS_2-VASc=0 (male) or 1 (female) as reference population vs CHA_2DS_2-VASc score =1 (male) or =2 (females) resulted in a crude HR of 2.2 (95%CI 1.2-3.8) and1.6 (95%CI 1.0-2.4), for one and five years follow-up, respectively. Thus, there is still a relative risk increase in ischemic stroke/SE/TIA in the AF group with prior MI.

Although long follow-up times (i.e. 10 or 12 years) may provide interesting insights into very long-term outcomes in AF patients, caution is warranted as baseline assumptions (on comorbidity and medication use) can be violated

To conclude, we could perhaps suggest a very simplified risk stratification and thromboprophylaxis algorithm based on the approach recommended by the ESC and NICE guidelines (see Online Figure S1). By assessing the CHA_2DS_2-VASc score it is possible to identify the truly low risk patients (0 (male) or 1 (female)), who do not need any antithrombotic therapy.

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Table 1: Event rates (per 100 person-years) of ischemic stroke/SE/TIA in 980 AF patients ($CHADS_2$=0) with prior vascular disease stratified according to type for 1 and 5 years of follow-up*.

		1 year of follow-up		5 years of follow-up	
Type of vascular disease	Number of patients	Number of events /person-time	Event rate (95% CI)	Number of events /person-time	Event rate (95% CI)
MI	651	12/490	2.5 (1.4-4.3)	23/1,783	1.3 (0.9-1.9)
Peripheral artery disease	294	6/201	3.0 (1.3-6.7)	13/669	1.9 (1.1-3.4)
Both MI and peripheral artery disease	35	3/20	15.0 (4.8-46.4)	5/57	8.7 (3.6-21.0)

*Groups comprising ≤5 patients (e.g. aortic plaque and MI) have been omitted from the table (n=7 patients)

Online Supplement

Using the CHA_2DS_2-VASc score for stroke prevention in atrial fibrillation: A focus on vascular disease, females and simple practical application

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We recently provided the evidence that using the new risk stratification algorithm approach from the Canadian Cardiovascular Society (CCS) Guidelines could leave patients with a high 1-year stroke rate (4.86 per 100 person-years)[1]; hence, patients with such high stroke rates are not 'low risk', as acknowledged by Cairns et al. in their accompanying Editorial[2].

In the 2012 CCS guidelines (as in the 2010) it was recommended to use the $CHADS_2$ scoring system for risk stratification[3]; however, the components were defined similarly to those of the CHA_2DS_2-VASc score. The 'VASc' component was in combination with female sex triggering a recommendation for anticoagulant treatment, but not vascular disease (nor female sex) alone. In the 2014 focused update, the CCS recommends use of the $CHADS_2$ schema referring to the original Gage et al publication[4] (and thus implying use of a similar definition). Thus, patients with some risk factors already included within the CHA_2DS_2-VASc score would not have been included in the 2014 CCS guidelines. Indeed, it is very important to strictly define the precise criteria for providing points related to each component in risk stratification scoring systems, and we welcome a clarifying update from the CCS committee on this matter.

Notwithstanding this inconsistency/misinterpretation on definitions, we would like to specifically provide the evidence for a high stroke rate of 4.85 per 100 person-years in AF patients with vascular disease as a single risk factor. This corresponds to CHA_2DS_2-VASc=1 for males and a CHA_2DS_2-VASc=2 for females, where our paper reported rates of 4.53 and 5.69, respectively. We defined the 'VASc' component as follows: prior myocardial infarction, prior peripheral artery disease, or aortic plaque, as we have done previously[5–8].

Cairn et al. raises the concern that previous publications using the Danish nationwide registries showed different event rates relative to those we presented. However, the devil is in the detail. The paper by Olesen et al.[9] used a combined primary endpoint of ischemic stroke (ICD10: I63; I64),

pulmonary embolism (PE) (ICD10: I26) and systemic embolism (SE) (ICD10: I74) or death from either of these events (using the Danish Register of Cause of Death [10]) and had a different time frame, over the period of 1997 to 2006. Different populations and inclusion criteria, study settings, definitions on outcomes and time frames may account for the variation in event rates seen in various studies. A recent systematic review shows the accentuated stroke and thromboembolism risk where AF is associated with atherosclerotic vascular disease[11].

In a different report, also by Olesen et al.[12], AF patients with prior vascular disease were studied. In this study peripheral artery disease was somewhat more strictly defined (i.e. leaving out atherosclerosis of the aorta (ICD10: I700)). Cairns et al. notes that the event rates, reported in a supplementary analysis, for vascular disease were 1.07 % at one year (total of 5 events) and 1.61% at 12 years of follow-up (total of 42 events) for patients with a CHA_2DS_2-VASc =1. However, analysing the main results provided in this publication reveals that the thromboembolic event rate of 2.31% at one year for patients with a $CHADS_2$=0 was primarily affected by patients with peripheral artery disease (5.71% and 2.57% for patients with both peripheral artery disease and MI), while patients with prior MI (and no peripheral artery disease) displayed a thromboembolic event rate of 1.79%. The supplementary analysis of patients with a CHA_2DS_2-VASc=1 (referred to by Cairns et al.) included zero events in this subgroup of patients with prior peripheral artery disease; thus the event rate of 1.07% for one year was based solely on patients with prior MI.

Rasmussen et al. [13] also studied the impact of vascular disease in predicting of stroke and death in an inception cohort of AF patients. After adjustments for risk factors within the $CHADS_2$ score, the adjusted hazard ratio (HR) at one year follow-up for the primary endpoint was 2.51 (95% confidence interval [CI] 1.91-3.29) contrasting AF patients with or without (latter being the reference population) prior vascular disease.

In an attempt to specify and fully describe our event rates challenged by Cairns et al., we are pleased to provide a stratified analysis of 987 patients with prior vascular disease (as defined in our CCS analysis[1] and excluding patients with prior SE or left ventricular dysfunction), see Table 1. It is evident that all subgroups of prior vascular diseases carry a high one-year thromboembolic event rate. Contrasting low risk CHA_2DS_2-VASc (that is, score 0 (male) or 1 (female)) as a reference population vs those with ≥1 additional stroke risk factors (ie. CHA_2DS_2-VASc score =1 (male) or =2 (females)) to express the hazard attributable to vascular disease resulted in a crude HR of 2.7 (95%CI 1.7-4.2).

Of note, the event rate for patients with MI was 1.3 per 100 person-years using 5 years of follow-up. To investigate this subgroup of AF patients with a $CHADS_2$=0 (defined in accordance with the CHA_2DS_2-VASc components (i.e. no prior SE, left ventricular dysfunction, and age<65 years) with prior MI (504 males and 147 females), we excluded those with prior peripheral artery disease and aortic plaque. Contrasting CHA_2DS_2-VASc=0 (male) or 1 (female) as reference population vs CHA_2DS_2-VASc score =1 (male) or =2 (females) resulted in a crude HR of 2.2 (95%CI 1.2-3.8) for one year of follow-up, and for five years of follow-up, HR 1.6 (95%CI 1.0-2.4). Thus, there is still a relative risk increase in ischemic stroke/SE/TIA in the AF group with prior MI compared to those without. Finally, the high stroke risk associated with females with AF has recently been systematically reviewed[14], and this accentuated thromboembolic risk would be further accentuated in the presence of ≥1 *additional* stroke risk factors.

Although long follow-up times (i.e. 10 or 12 years) may provide interesting insights into very long-term outcomes in AF patients, caution is warranted as baseline assumptions (on comorbidity and medication use) can be violated; specifically in this context, the requirement of a non-OAC treated cohort with a $CHADS_2$ score =0. As previously[1,7], we have attempted to account for this by censoring person-time if a prescription of an OAC drug was claimed. By design this will censor

some of the studied events, while patients actually treated with OAC will not count in the analysis and thereby introduce an unmeasurable bias. In relation to practical use of risk scoring systems for stratification on treatment decisions, extensive follow-up times seem less interesting.

To conclude, we could perhaps suggest a very simplified risk stratification and thromboprophylaxis algorithm [Figure S1] based on the approach recommended by the ESC and NICE guidelines where the initial step is to identify the low risk patients with CHA_2DS_2-VASc=0 (male) or 1 (female), who do not need any antithrombotic therapy [STEP 1]. Subsequently, we should offer effective stroke prevention (which is OAC) to those with ≥1 stroke risk factors [STEP 2]. In Step 2, OAC can be with well controlled Vitamin K Antagonist (VKA, with time in therapeutic range >70%) or Non-VKA oral anticoagulant (NOAC), and the decision to anticoagulate is already made, irrespective of CHA_2DS_2-VASc score.

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*Groups comprising ≤5 patients (e.g. aortic plaque and MI) have been omitted from the table (n=7 patients).

Figure S1: A simple practical algorithm for stroke risk stratification and decision making on thromboprophylaxis