Trends in Cardiovascular Medicine 29 (2019) 150–152

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Stroke risk in female patients with atrial fibrillation: Relationship to current guideline recommendations☆

Peter Brønnum Nielsen, MSc, PhD[a,b,*], Tatjana S. Potpara, MD, PhD[c], Gregory Y.H. Lip, MD[a,c,d]

[a] Aalborg Thrombosis Research Unit, Faculty of Medicine, Aalborg University, Denmark
[b] Department of Cardiology, Aalborg University Hospital, Denmark
[c] Cardiology Clinic, Clinical Center of Serbia, School of Medicine, University of Belgrade, Serbia
[d] Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom

Introduction

Atrial fibrillation (AF) is a major cause of stroke and mortality, and optimal stroke risk stratification is essential to reduce the burden of stroke among AF patients [1]. The increase in AF prevalence has correspondingly increased the proportion of AF patients that should be considered for antithrombotic treatment. Preventing stroke with oral anticoagulant treatment (OAC) comes at the cost of an increased bleeding risk, but the net clinical benefit of treatment is often substantially higher than withholding treatment [2].

Risk stratification helps identify those AF patients who may or may not need thromboprophylaxis [3]. In general, the default should be the provision of stroke prevention by means of oral anticoagulation unless patients are low risk [4]. However, 'low risk' categorization is often arbitrary and has been subject for much debate. A source for this debate originates from the interpretation of estimated stroke risk on the basis of the risk factors, which are included in stroke risk stratification tools [5,6]. Here we briefly review the current AF guidelines recommendations on OAC treatment. Specific focus is given to the importance of concise interpretation of female sex as a risk factor for stroke in AF.

Guideline discrepancies

Contemporary European and North American AF guidelines recommend the use of CHA_2DS_2-VASc (**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus, previous **S**troke/transient ischemic attack, **V**ascular disease, **A**ge 65–74 years, **S**ex **c**ategory) score [3,7]. The maximum cumulative score is 9, where female sex contributes one point to reflect the overall increased risk of stroke among female AF patients. However, the threshold for recommendations are not aligned, where different recommendations of antithrombotic therapy varies across different risk categories, see Table 1. Currently, North American guidelines for managing AF patients suggest that patients with a CHA_2DS_2-VASc score of 1 may be considered for no antithrombotic therapy, aspirin, or oral anticoagulant [7]. In an observational cohort study including 49916 AF patients with a CHA_2DS_2-VASc score of 1 beyond sex, treatment with warfarin in comparison with no treatment or aspirin exhibited a positive net clinical benefit [2]. These data supported the 2012 European Society of Cardiology [8] (ESC) guidelines to recommend OAC treatment, and also showed that aspirin should not be considered as an effective stroke prevention strategy in these patients. However, the North American guidelines do not separate the risk factor of sex from other (clinical) stroke risk factors. Thus, female patients with no additional stroke risk factors may even be considered for antithrombotic therapy based on these recommendations. To our knowledge, there has not been evidence published to support the use of aspirin treatment to prevent stroke in female patients with AF with no additional stroke risk factors.

In Europe, the guideline recommendations differentiate between males and females by setting different point level thresholds for recommending OAC treatment initiation. In the contemporary ESC AF guidelines, the treating physician is required to make a choice based on the CHA_2DS_2-VASc score points and an individualized stroke risk assessment [3]. Specifically, for male patients with a single non-sex specific stroke risk factor, i.e. 1 point and females with 2 points, the guideline suggest to '*consider*' OAC treat-

☆ *Disclosures:* None related to this manuscript.
Others: All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr Nielsen has received speaking fees from Boehringer Ingelheim, consulting fees from Bayer; and grant support from BMS/Pfizer. Dr. Potpara is a speaker for Bayer. Dr Lip has received consulting fees from Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo.

* Corresponding author at: Aalborg Thrombosis Research Unit, Faculty of Medicine, Aalborg University, Søndre Skovvej 15, Aalborg 9000, Denmark.
E-mail address: pbn@rn.dk (P.B. Nielsen).

https://doi.org/10.1016/j.tcm.2018.07.003

Table 1
Contemporary guideline recommendations for initiating antithrombotic treatment in AF patients based on the CHA_2DS_2-VASc score.

	North American guideline recommendations		European guideline recommendations	
	Females	Males	Females	Males
CHA_2DS_2-VASc = 0	N/A[a]	No therapy	N/A[a]	No therapy
CHA_2DS_2-VASc = 1	OAC, aspirin, or no therapy		No therapy	Consider OAC
CHA_2DS_2-VASc = 2	Recommend OAC		Consider OAC	Recommend OAC
CHA_2DS_2-VASc ≥ 3	Recommend OAC			

[a] Females cannot score 0, as female sex triggers 1 point.

ment initiation. For two or more non-sex specific CHA_2DS_2-VASc score risk factors, i.e. male patients with ≥2 points and females with ≥3 points, there is a clear recommendation of OAC treatment (Table 1).

Withholding OAC treatment initiating in patients with a score of 2 (i.e. two risk factor components for males, and one risk factor for females) was investigated in a large cohort of AF patients who did not receive antithrombotic treatment [9]. The rate of thromboembolism per 100 person-years was 1.97 – for most clinicians, clearly high enough to warrant stroke prevention. Nevertheless, the approach of recommending treatment based on rates from cumulative score by including sex as a risk factor may be too simplistic.

Stroke risk in female AF patients

Madsen and colleagues recently provided an update on the impact of conventional stroke risk factors on the occurrence of stroke in female individuals compared with males [10]. They accurately highlighted the consistently reported higher crude risk of ischemic stroke among female AF patients compared with males. However, significant interactions between female sex and age or other stroke risk factors have been repeatedly reported.

Indeed, in terms of stroke risk stratification, including female sex (the "Sc" component) as an independent stroke risk factor in AF may be too simplistic to appreciate the higher stroke risk observed among female AF patients, which has a dependency on age and other risk factors. In a recent analysis including nearly 240,000 newly diagnosed AF patients (48.7% females), we investigated the "Sc" component as a prognostic factor rather than a risk factor for stroke within the CHA_2DS_2-VASc score [11]. This investigation indicated that the excess female sex-related risk of stroke was evident only in the presence of other CHA_2DS_2-VASc risk factors, especially among female AF patients with ≥2 concomitant non-gender CHA_2DS_2-VASc risk factors. Indeed, when including female sex as an interaction term (and not an independent risk factor), we observed a 5-year risk ratio of stroke between 1.16 (95%CI, 1.02–1.30) and 1.43 (95%CI, 1.30–1.56), dependent on the number of concomitant sex-specific CHA_2DS_2-VASc risk factors.

These results highlighted that female sex could be considered a *risk modifier* rather than an independent *risk factor for* stroke among AF patients Hence, female AF patients without other CHA_2DS_2-VASc risk factors could be considered to be stratified into a 'low stroke risk' category, and thus potentially requiring no antithrombotic therapy. This would entail that the initial step in stroke risk stratification is the identification of low risk patients (CHA_2DS_2-VASc 0 in males, 1 in females) who do not need any antithrombotic therapy, following which stroke prevention (i.e. oral anticoagulation) should be offered to those with ≥1 stroke risk factors [4]. This has also been acknowledged in the recent European Heart Rhythm Association Consensus Document on sex differences in cardiac arrhythmias [14], which emphasized a consistent underrepresentation of female patients in AF trials and recommended consideration of OAC use in all female patients with one or more additional non-sex specific stroke risk factors (i.e., a CHA_2DS_2-VASc score of ≥2). Nevertheless, OAC treatment remains in general under-used among AF patients with low bleeding risk and high stroke risk, and clearly warrants more insight and efforts among prescribing physicians [12]. Yet, this pattern was consistent among males and females [13].

Importantly, regular clinical follow-up for the re-assessment of stroke risk factors is mandatory, since the risk is not static and may change over time [9]. Indeed, the dynamic changes in stroke or bleeding risk profile are the best predictors of adverse outcomes [9,10]. While it may seem appropriate to consider a change in the use of the CHA_2DS_2-VASc score to reflect that male and females have different stroke risk across different score levels, we do not recommend such change at this time. We fear this could even potentially confuse prescribing physicians, unintentionally indicating that women carry excess stroke risk relative to male peers [11]. Accurate stroke risk prediction in AF is important; however, the prediction accuracy should be balanced against the practicality and ease of use in a busy clinical setting. The clinical value of refining stroke risk stratification may therefore lie in improving the identification of patients at sufficiently low risk of stroke. Current data suggests that female AF patients with no additional stroke risk factors are such candidates, and we therefore question the current US guideline options that include aspirin treatment or OAC treatment for these patients.

References

[1] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.
[2] Lip GYH, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. Thromb Haemost 2015;114:826–34.
[3] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.
[4] Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost 2017;117:1230–9.
[5] Argulian E, Conen D, Messerli FH. Misconceptions and facts about atrial fibrillation. Am J Med 2015;128:938–42.
[6] Nielsen PB, Larsen TB, Lip GYH. Misconceptions on interpretation of risk prediction tools in atrial fibrillation. Am J Med 2016;129:e31.
[7] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 2014;64:e1–e76.
[8] Camm A, Lip G, De Caterina R, Savelieva I, Atar D, Hohnloser S, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Hear J 2012;33:2719–47.
[9] Nielsen PB, Larsen TB, Skjøth F, Overvad TF, Lip GYH. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. Sci Rep 2016;6:27410.
[10] Madsen TE, Howard VJ, Jiménez M, Rexrode KM, Acelajado MC, Kleindorfer D, et al. Impact of conventional stroke risk factors on stroke in women. Stroke 2018;49:536–42.

[11] Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc. Circulation 2018;137:832–840.
[12] Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand J-P, Berge E, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart 2017;103:307–14.
[13] Mazurek M, Huisman M V, Rothman KJ, Paquette M, Teutsch C, Diener H-C, et al. Gender differences in antithrombotic treatment for newly diagnosed atrial fibrillation: the GLORIA-AF registry program. Am J Med 2018.
[14] Linde C, et al. Sex differences in cardiac arrhythmia- a Consensus document of the European Heart Rhythm Association, Heart Rhythm Society, and Asia Pacific Heart Rhythm Society. Europace 2018 in press. doi:10.1093/europace/euy067.