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Editorial

Guideline Implications of Prothrombotic State Assessment in Low-Risk Atrial Fibrillation Patients: Consistency With CHA_2DS_2-VASc and Support for CHADS-65

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See article by Głowicki et al., pages 634–643 of this issue.

One of the most important objectives in the treatment of atrial fibrillation (AF) is the safe and effective prevention of thromboembolic stroke. All major society AF guidelines expend substantial energy on the provision of clear recommendations for the use of oral anticoagulants in stroke prevention.[1] Because oral anticoagulants increase bleeding risk, their use is generally not recommended for patients at the lowest risk for stroke, with the logical (but not really proven) assumption that the potential risks outweigh the gains in such individuals. By far the most widely used system for estimating stroke risk in AF is the **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex Category (Female) (CHA_2DS_2-VASc) score, which provides 1 point each for congestive heart failure, hypertension, diabetes, vascular disease (1 point each if present; 0 if absent) and sex category (1 if female, 0 if male); 2 points for previous stroke/transient ischemic attack (TIA)/embolic event; 1 point for age 65-74 years and 2 points for age $\geq$ 75 years.[2] The Canadian Cardiovascular Society (CCS) uses a similar but somewhat different system, often called "CHADS-65," with anticoagulation recommended for any of the classical **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) risk factors (congestive heart failure, hypertension, diabetes and stroke/TIA/embolism) or for age $\geq$ 65 years.[3] This system was introduced in 2014[4] and was first referred to as "CHADS-65" in the 2016 CCS AF guidelines update.[5]

For the lowest-risk patients, none of the major societies recommend oral anticoagulation. For high-risk patients, there is similar congruity among all societies in recommending oral anticoagulation. The greatest differences among guidelines occur for patients with low but not lowest risk. For patients with one CHA_2DS_2-VASc factor (besides sex category, which is now accepted to constitute a risk modifier, rather than a risk factor per se),[6] the European Society of Cardiology and the 2019 focused update of the American Heart Association/American College of Cardiology/Heart Rhythm Society 2019 guidelines recommend that oral anticoagulation may be considered.[7,8] The CCS recommends anticoagulation for age $\geq$ 65 years and any of the $CHADS_2$ factors, but not for vascular disease or female sex alone (CHADS-65; essentially the CHA_2DS_2-VASc without vascular disease or female sex).[3-5]

In this issue of the *Canadian Journal of Cardiology*, Glowicki et al. report the results of a systematic approach to examining the thromboembolic risk profile in patients with one additional CHA_2DS_2-VASc risk factor (beyond sex).[9] They systematically measured important prothrombotic indices in AF patients, and compared the results in 52 patients with a CHA_2DS_2-VASc score of 0 in men or 1 in women with those in 118 individuals with a CHA_2DS_2-VASc score of 1 in men or 2 in women. The measures that they examined include plasma clot permeability (K_s), clot lysis time (CLT), and endogenous thrombin potential (ETP), along with a range of plasma biomarkers including von Willebrand factor and plasminogen-activator inhibitor-1. K_s is a measure of fibrin clot structure. Lower values reflect more compact fibrin clots, and are associated with increased risk of major bleeding and stroke/TIA.[10] CLT quantifies the resistance of clots to break down in the blood, with longer CLT being associated with cardiovascular disease and risk factors.[11] ETP is an index of the thrombin-generating ability resulting from the balance between coagulation-promoting and -inhibiting factors in the blood.[12] Thus, greater thrombotic risk is associated with lower values of K_s and higher values of CLT and ETP.

Glowicki et al. reported an increased thrombogenic profile in patients with a single non-sex CHA_2DS_2-VASc score risk factor (ie, score of 1 in men or 2 in women)—they have

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smaller values of K_s and larger values of CLT and ETP, as well as increases in the thrombotic biomarkers von Willebrand factor and plasminogen-activator inhibitor-1, compared with those with lower CHA_2DS_2-VASc scores. They went on to examine individual CHA_2DS_2-VaSc risk factors to determine their specific relationship with thrombotic risk. Of the CHA_2DS_2-VASc factors, in the optimized multivariate model only age 65-74 years was a significant determinant of all thrombotic indices: 65- to 74-year-old patients had smaller K_s and larger CLT and ETP values than younger individuals. Of the other risk factors, hypertension and heart failure patients had lower K_s and higher CLT values than those without; neither were significantly associated with ETP. Vascular disease, diabetes, and sex were not significant determinants of any of the thrombotic indices in the multivariate model. When each factor was considered alone, patients with diabetes had lower K_s values than those without, but there were no differences in any of the variables for those with vs without vascular disease, or for male vs female patients.

These findings suggest that patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women have increased values of all thrombotic indices compared with those at low risk, consistent with the notion that the CHA_2DS_2-VASc score is a good measure of thrombogenic potential in AF patients. However, they do not suggest a significant prothrombotic predisposition in patients with vascular disease or female sex, while emphasizing the important thrombotic risk associated with age 65-74 years. These results evoke the CHADS-65 approach of the CCS, including age 65-74 years as a key determinant of thrombotic risk while de-emphasizing sex and vascular disease.

Stroke risk estimation algorithms and guidelines must be established on the basis of hard clinical outcome data that require large clinical trials and database analyses, not on thrombogenic indices (although these have been well studied in AF).[13] Nevertheless, the associations between the thrombotic measures data in the study by Glowicki et al.[9] and the components of stroke risk prediction algorithms are striking. In a recent study in which extensive results from clinical trials were analyzed, the authors suggested that biomarkers data have the potential to improve stroke risk prediction,[14] although the added value of considering biomarkers is less clear for "real-world data."[15] The results of the study by Glowicki et al. raise the interesting possibility that direct measures of prothrombotic indices might be useful in further refining and defining the risk of thromboembolic events in AF patients.[9]

Current stroke risk stratification schemes do not include all stroke risk factors and are meant to be reductionist, to aid clinical and practical decision-making on whether or not oral anticoagulation is indicated. Thus, the default position is to offer stroke prevention unless patients are at truly low risk, and the recent 2018 CHEST guidelines recommend initial focus on identifying "low risk" patients first rather than our current obsession with identifying high-risk patients, whether clinically or with biomarkers.[16] The CHA_2DS_2-VASc and the CHADS-65 are useful in this regard. The study by Glowicki et al.[9] provides results for meaningful thrombotic indices in a substantial (albeit moderate) number of patients that are consistent with the higher-risk identification of individuals with a single non-sex CHA_2DS_2-VASc score risk factor. Their findings point to the dominant role of age 65-74 years in this characterization and fail to identify a contribution of vascular disease or sex to prothrombotic profile, thus providing support to the approach of CHADS-65.

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