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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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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 CHA_2DS_2-VASc score, which provides 1 point each for **C**ongestive heart failure, **H**ypertension, **D**iabetes, **Va**scular disease (1 point each if present; 0 if absent) and **S**ex **c**ategory (1 if female, 0 if male); 2 points for prior **S**troke/transient ischemic attack (TIA)/embolic event; 1 point for **A**ge 65-74 and 2 points for age≥75.[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 $CHADS_2$ risk factors (congestive heart failure, hypertension, diabetes and stroke/TIA/embolism) or for age≥65.[3] This system was introduced in 2014[4] and 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 occurs 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 (ESC) 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≥65 and any of the $CHADS_2$ factors, but not for vascular disease alone (CHADS-65; essentially CHA_2DS_2 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, comparing 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 van Willebrand's factor (vWF) and plasminogen-activator inhibitor-1 (PAI-1). K_s is a measure of fibrin clot structure. Lower values reflect more compact fibrin clots, and are associated with increased risk of both major bleeding and stroke/TIA.[10] CLT quantifies the resistance of clots to breakdown 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 find an increased thrombogenic profile in patients with a single non-sex CHA_2DS_2-VASc score risk factor (i.e. score of 1 in men or 2 in women) - they have smaller values of K_s and larger values of CLT and ETP, as well as increases in the thrombotic biomarkers

vWF and PAI-1, compared to those with lower CHA_2DS_2-VASc scores. They then go 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 was a significant determinant of all thrombotic indices: 65-74-year olds displayed 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 versus without vascular disease, or for males versus females.

These findings suggest that patients with CHA_2DS_2-VASc score of 1 in men or 2 in women have increased values of all thrombotic indices compared to 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. On the other hand, 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. 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 based on hard clinical outcome data that require large clinical trials and database analyses, not on thrombogenic indices (even though these have been well studied in AF).[13] Nevertheless, the associations between the thrombotic

measures data in the Glowicki study and the components of stroke-risk prediction algorithms are striking. A recent study analyzing extensive results from clinical trials suggested that biomarker 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 Glowicki report 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.

Current stroke risk stratification schemes do not include all stroke risk factors and are meant to be reductionist, aiding 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] Both CHA_2DS_2-VASc and CHADS-65 are useful in this regard. The Glowicki study 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 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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