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The Value of the European Society of Cardiology Guidelines for Refining Stroke Risk Stratification in Patients With Atrial Fibrillation Categorized as Low Risk Using the Anticoagulation and Risk Factors in Atrial Fibrillation Stroke Score

A Nationwide Cohort Study

Gregory Y. H. Lip, MD; Peter Brønnum Nielsen, PhD; Flemming Skjøth, PhD; Deirdre A. Lane, PhD; Lars Hvilsted Rasmussen, MD, PhD; and Torben Bjerregaard Larsen, MD, PhD

BACKGROUND: Our objective was to determine stroke and thromboembolism event rates in patients with atrial fibrillation (AF) classified as "low risk" using the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score and to ascertain event rates in this group in relation to the stroke risk assessment advocated in the 2012 European Society of Cardiology (ESC) guidelines (based on the CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category] score). We tested the hypothesis that the stroke risk assessment scheme advocated in the ESC guidelines would be able to further refine stroke risk stratification in the low-risk category defined by the ATRIA score.

METHODS: In our cohort of 207,543 incident patients with AF from 1999 to 2012, we identified 72,452 subjects who had an ATRIA score of 0 to 5 (low risk).

RESULTS: Even among these patients categorized as low risk using the ATRIA score, the 1-year stroke/thromboembolic event rate ranged from 1.13 to 36.94 per 100 person-years, when subdivided by CHA_2DS_2-VASc scores. In patients with an ATRIA score 0 to 5, C statistics at 1 year follow-up in the Cox regression model were significantly improved from 0.626 (95% CI, 0.612-0.640) to 0.665 (95% CI, 0.651-0.679) when the CHA_2DS_2-VASc score was used for categorizing stroke risk instead of the ATRIA score ($P < .001$).

CONCLUSIONS: Patients categorized as low risk using an ATRIA score 0 to 5 are not necessarily low risk, with 1-year event rates as high as 36.94 per 100 person-years. Thus, the stroke risk stratification scheme recommended in the ESC guidelines (based on the CHA_2DS_2-VASc score) would be best at identifying the "truly low risk" subjects with AF who do not need any antithrombotic therapy.

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ABBREVIATIONS: AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; ESRD = end-stage renal disease; ICD-10 = *International Classification of Diseases, 10th edition;* NOAC = non-vitamin K antagonist; OAC = oral anticoagulation; R_2CHADS_2 = renal dysfunction, congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke; ROCKET-AF = The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKA = vitamin K antagonist

Atrial fibrillation (AF) confers an increased risk of stroke, and the use of oral anticoagulation (OAC) with the vitamin K antagonists (VKAs) (eg, warfarin) reduces stroke by 64% and all-cause mortality by 26% compared with placebo/control.[1] Although antithrombotic therapy reduces stroke, the downside is an increase in bleeding, particularly intracranial hemorrhage.

The risk of stroke is not homogeneous. Various stroke risk factors have been identified and clustered into stroke risk stratification schemes, which have been particularly developed to identify high-risk patients who could be targeted for OAC treatment, especially with an "inconvenient" drug, warfarin, which also conferred a risk of serious bleeding.[2,3] Nonetheless, stroke risk in AF is a continuum, with the division into low-, moderate-, and high-risk strata being artificial; despite the intended focus on the definition of high-risk patients, numerous studies have shown that these high-risk patients are undertreated with OAC.[4] In 2010, the European Society of Cardiology (ESC) guidelines deemphasized the artificial low/moderate/high-risk categorization and recommended a risk factor-based approach, given that any stroke risk factor confers a risk, and if AF is present, the patient could be at risk for a fatal or disabling stroke.[5]

In addition, the availability of the non-VKAs (NOACs) (previously referred to as new or novel oral anticoagulants) has changed the landscape of stroke prevention in AF, given that these drugs offered efficacy, safety, and convenience compared with VKAs.[6,7] Indeed, Eckman et al[8] proposed that the threshold for treatment using a NOAC could be a stroke rate of 0.9%/y compared with the threshold for warfarin, which was 1.7%/y. In 2012, the focused update of the ESC guidelines strongly advocated a clinical practice shift so that the initial decision step was the identification of truly low-risk patients with AF, who did not need any antithrombotic therapy. Subsequent to this initial step, patients with AF and one or more stroke risk factors can be offered effective stroke prevention, which is OAC—whether given as well-controlled VKA or one of the NOACs.[9] The 2012 focused update recommended use of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score,[10] which was good at identification of low-risk patients, and was as good as—and possibly better than—older scores, such as the $CHADS_2$ (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, previous stroke) score, in identifying the high-risk patients who subsequently developed stroke and thromboembolism.[11]

In 2013, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) investigators developed the ATRIA stroke risk score,[12] which performed better than the existing $CHADS_2$ and CHA_2DS_2-VASc stroke risk scores, showing improvement in predicting events (with a positive net reclassification improvement), although the C indexes were only marginally different. It was noted that the ATRIA score was based on the $CHADS_2$ risk factors and additionally included female sex, proteinuria, and low estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD), with different weighting for primary and secondary prevention cohorts (Table 1). This score categorized patients into low (0-5 points), moderate (6 points), and high (7-15 points) risk strata, and in the original validation paper classified a similar proportion into the low-risk strata as the $CHADS_2$ score (0). However, a $CHADS_2$ score = 0 has been shown to be poor at identifying low-risk patients, and in one study stroke/thromboembolism rates in patients with a $CHADS_2$ score = 0 range between 0.8% to 3.2% (with the upper boundary of the 95% CI as high as 6.4%) per year when substratified by the CHA_2DS_2-VASc score.[13-15]

Our objective was to determine stroke and thromboembolism event rates in real-world patients with AF classified as low risk using the ATRIA score and to ascertain event rates in these groups in relation to the stroke risk assessment advocated in the 2012 ESC guidelines (which is based on the CHA_2DS_2-VASc score). Given the current emphasis to initially identify low-risk patients as the first management step for stroke prevention in AF, we tested the hypothesis that the stroke risk assessment scheme advocated in the ESC guidelines would be able to further refine stroke risk stratification in the low-risk category defined by the ATRIA score. We tested this hypothesis in a large nationwide cohort study from Denmark.

AFFILIATIONS: From the University of Birmingham Centre for Cardiovascular Sciences (Drs Lip and Lane), City Hospital, Birmingham, England; the Aalborg Thrombosis Research Unit (Drs Lip, Nielsen, Skjøth, Rasmussen, and Larsen), Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark; and the Department of Cardiology (Drs Skjøth, Rasmussen, and Larsen), Aalborg AF Study Group, Aalborg University Hospital, Aalborg, Denmark.

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CORRESPONDENCE TO: Gregory Y. H. Lip, MD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, B18 7QH, England; e-mail: g.y.h.lip@bham.ac.uk

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