CLINICAL RESEARCH STUDY

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Does CHA_2DS_2-VASc Improve Stroke Risk Stratification in Postmenopausal Women with Atrial Fibrillation?

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ABSTRACT

BACKGROUND: Risk stratification of atrial fibrillation patients with a congestive heart failure (C), hypertension (H), age $\geq$ 75 (A), diabetes (D), stroke or transient ischemic attack (TIA) (S_2) ($CHADS_2$) score of $<$2 remains imprecise, particularly in women. Our objectives were to validate the $CHADS_2$ and congestive heart failure (C), hypertension (H), age $\geq$ 75 (A_2), diabetes (D), stroke, TIA or prior thromboembolic disease (S_2)- vascular disease (V), age 65-74 (A), female gender (S) (CHA_2DS_2-VASc) stroke risk scores in a healthy cohort of American women with atrial fibrillation and to determine whether CHA_2DS_2-VASc further risk-stratifies individuals with a $CHADS_2$ score of $<$2.

METHODS: We identified a cohort of 5981 women with atrial fibrillation not on warfarin at baseline (mean age 65.9 $\pm$ 7.2 years) enrolled in the Women's Health Initiative and followed for a median of 11.8 years. Univariate and multivariate proportional hazards analyses were used to examine these 2 risk scores, with main outcome measures being annualized event rates of ischemic stroke or transient ischemic attack stratified by risk score.

RESULTS: Annualized stroke/transient ischemic attack rates ranged from 0.36% to 2.43% with increasing $CHADS_2$ score (0-4+) (hazard ratio [HR] 1.57; 95% confidence interval [CI], 1.45-1.71 for each 1-point increase) and 0.20%-2.02% with increasing CHA_2DS_2-VASc score (1-6+) (HR 1.50; 95% CI, 1.41-1.60 for each 1-point increase). CHA_2DS_2-VASc had a higher *c* statistic than $CHADS_2$: 0.67 (95% CI, 0.65-0.69) versus 0.65 (95% CI, 0.62-0.67), P $<$.01. For $CHADS_2$ scores $<$2, stroke risk almost doubled with every additional CHA_2DS_2-VASc point.

CONCLUSIONS: Although both $CHADS_2$, and CHA_2DS_2-VASc are predictive of stroke risk in postmenopausal women with atrial fibrillation, CHA_2DS_2-VASc further risk-stratifies patients with a $CHADS_2$ score $<$2.

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Reported stroke rates in patients with atrial fibrillation not treated with anticoagulation range from $<$1% (low risk) to $>$18% (high risk) per year,[1-3] and studies show that women are at higher risk.[3-7] Although guidelines recommend treatment with anticoagulants in higher-risk and aspirin in lower-risk patients, the distinction between these 2 risk categories remains unclear.[8,9]

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Of the many scoring systems developed to predict stroke risk in atrial fibrillation, congestive heart failure (C), hypertension (H), age ≥ 75 (A), diabetes (D), stroke or transient ischemic attack (TIA) (S_2) ($CHADS_2$)[1] and congestive heart failure (C), hypertension (H), age ≥ 75 (A_2), diabetes (D), stroke, TIA or prior thromboembolic disease (S_2)- vascular disease (V), age 65-74 (A), female gender (S) (CHA_2DS_2-VASc)[6] are the most widely used. $CHADS_2$, developed from a combination of Atrial Fibrillation Investigators and Stroke Prevention in Atrial Fibrillation, was validated using the National Registry of Atrial Fibrillation comprising 1733 Medicare beneficiaries aged 65-95 years with nonrheumatic atrial fibrillation not on warfarin at hospital discharge.[1] In this score, whereas congestive heart failure (C), hypertension (H), age ≥75 years (A), and diabetes (D) receive 1 point each, stroke or transient ischemic attack (S_2) receives 2 points.

CLINICAL SIGNIFICANCE

- $CHADS_2$, and CHA_2DS_2-VASc, the most widely used stroke risk scores for patients with atrial fibrillation, guide decisions about anticoagulation.
- $CHADS_2$ classifies more than half of patients with atrial fibrillation as being at low or intermediate risk for stroke (score <2).
- CHA_2DS_2-VASc further risk-stratifies $CHADS_2$ <2 patients, which may help to guide clinical decisions about anticoagulation.

CHA_2DS_2-VASc, a modification of the 2006 Birmingham/National Institute for Health and Clinical Excellence scheme,[8] was validated in a cohort of 1084 hospitalized, ambulatory patients not anticoagulated at baseline from the Euro Heart Survey on atrial fibrillation.[6] CHA_2DS_2-VASc expands on $CHADS_2$ by 1) including a history of systemic thromboembolism (S_2) in the stroke category and 2) adding vascular disease (defined as prior myocardial infarction, peripheral arterial disease, or aortic plaque [V]), age (65-74 years [A]), and female sex (S) as risk factors. All risk factors receive 1 point, except age ≥75 years and history of prior stroke/transient ischemic attack/thromboembolism, which receive 2 points each.

As there are no validation studies comparing $CHADS_2$ and CHA_2DS_2-VASc in an ambulatory US population of women with atrial fibrillation, our objectives were to validate and compare the predictive power of these scores, determine the annualized rates of stroke, and clarify the discriminatory ability of CHA_2DS_2-VASc in such a population.

METHODS

Study Population

The study design has been described previously.[10,11] Study participants were members of the Women's Health Initiative (WHI) cohort: a prospective, multiarm clinical trial and observational study that focused on the causes and prevention of cardiovascular disease, cancer, and osteoporosis in women. Major exclusion criteria were predicted survival <3 years, alcohol or drug dependency, dementia, severe mental illness, and participation in another clinical trial. WHI comprised an observational study and 4 randomized clinical trials: 1) estrogen plus progestin versus placebo, 2) estrogen alone versus placebo in hysterectomized women, 3) dietary modification trial, and 4) calcium/vitamin D versus placebo trial.

Beginning in 1993, 161,809 postmenopausal women aged 50-79 years were prospectively enrolled in WHI. Events through September 2010 were used for this retrospective analysis. The initial study population consisted of women who reported a history of atrial fibrillation or had an electrocardiogram with documented atrial fibrillation at baseline (n = 7108). From this group, we excluded 291 with valvular heart disease or hyperthyroidism, 85 with missing values for either $CHADS_2$ or CHA_2DS_2-VASc, and 790 on warfarin at WHI randomization or enrollment. There were 1127 excluded, leaving a final sample of 5981, of whom 2390 were participants in one of the clinical trials and 3591 were enrolled in the observational study; 5901 women with atrial fibrillation were identified by self-report, 24 by electrocardiogram, and 56 had both.

Definition of Variables

Congestive heart failure, *diabetes mellitus*, and *prior stroke or transient ischemic attack* were defined by self-report at initial examination. *Hypertension* was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of any antihypertensive medication. *Vascular disease* was defined as self-report of any of the following: myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or peripheral vascular disease. Information on aortic plaque and systemic thromboembolism, although included among the CHA_2DS_2-VASc risk factors,[6] was not collected by WHI.

Follow-Up and End-Point Determination

Intensity of follow-up visits varied based on enrollment arm, ranging from every 6 months (clinical trials) to every 3 years (observational study). When a potential outcome was identified, medical records were obtained and stroke (including self-reports) and transient ischemic attack (only the first event) were centrally adjudicated.[12] No bleeding end points were collected. We lost 2.3% of our cohort to follow-up and 4.2% stopped follow-up early.

Statistical Analysis

We summarized baseline characteristics with means and SDs for continuous variables and frequencies and percentages for

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