CLINICAL RESEARCH STUDY

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CHA_2DS_2-VASc Score Is Directly Associated with the Risk of Pulmonary Embolism in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND: The risk stratification score, which includes Congestive heart failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled]- Vascular disease, Age 65-74, and Sex category [female] (CHA_2DS_2-VASc), is used to predict stroke in atrial fibrillation. However, whether high CHA_2DS_2-VASc score carries a higher risk of pulmonary embolism remains unknown. We aimed to investigate the association between the severity of CHA_2DS_2-VASc score and the incidence of pulmonary embolism.

METHODS: A total of 73,541 adults with atrial fibrillation diagnosed before January 1, 2012, and no history of pulmonary embolism, were retrospectively identified from the computerized database of the Clalit Health Services, which is the largest not-for-profit health maintenance organization in Israel. The CHA_2DS_2-VASc score was calculated for each subject at study entry. The cohort was followed for the first occurrence of pulmonary embolism until December 31, 2012 (70,210 person-years).

RESULTS: Pulmonary embolism developed in 158 subjects, representing an incidence of 225.0 per 100,000 person-years. The incidence of pulmonary embolism increased with increasing CHA_2DS_2-VASc score ($P <$ .001). On Cox proportional analysis, CHA_2DS_2-VASc score was significantly associated with pulmonary embolism (hazard ratio, 1.22; 95% confidence interval [CI], 1.13-1.32) for a 1-point increase in CHA_2DS_2-VASc score. The results were similar after adjusting for anticoagulants and antiplatelet use (hazard ratio, 1.24; 95% CI, 1.14-1.34), and remained unchanged after further adjustment for active malignancy. The predictive values for pulmonary embolism were similar for CHA_2DS_2-VASc score and the classic risk stratification score which includes Congestive heart failure, Hypertension, Age >75 years, Diabetes, and Stroke [doubled] ($CHADS_2$); the areas under the receiver operating characteristic curves were 0.619 (95% CI, 0.579-0.660) and 0.616 (95% CI, 0.575-0.656), respectively.

CONCLUSIONS: CHA_2DS_2-VASc score is directly associated with the incidence of pulmonary embolism in atrial fibrillation.

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Subjects with atrial fibrillation have a higher tendency to form thrombus in the left atrium, particularly in the appendages, predisposing them to increased risk of stroke.[1] The risk stratification score, which includes Congestive heart failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] — Vascular disease, Age 65-74, and Sex category [female] (CHA_2DS_2-VASc), is a well-validated risk stratification score for stroke prediction in patients with atrial fibrillation and serves to determine the need for anticoagulants.[2,3]

Although a cause—effect relationship has not been firmly established, available data suggest that most components of the CHA_2DS_2-VASc score also are potential risk factors for venous thromboembolism.[4-14] Congestive heart failure, hypertension, and age are well-established risk factors for venous thromboembolism.[4-8] The risk of venous

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thromboembolism also was found to be higher in diabetic patients.[8-10] An association between venous thromboembolism and atherosclerosis also was reported.[11-14] Although the 2 entities may share common risk factors, it has been suggested that atherosclerosis has the potential to promote the development of venous thromboembolism by activation of both platelets and blood coagulation and increase in fibrin turnover.[14]

Moreover, several studies suggest that atrial fibrillation could be associated with an increased risk of pulmonary embolism.[4,15] Although still under major debate, clot formation in the right atrium, which seems to occur more frequently in patients with atrial fibrillation,[16-19] was proposed as a potential mechanism for the increased risk of pulmonary embolism in patients with atrial fibrillation.[17,20]

Thus, the hypothesis that CHA_2DS_2-VASc score may be associated with an increased risk of pulmonary embolism in patients with atrial fibrillation seems plausible. Although the CHA_2DS_2-VASc score is recommended by the European Society of Cardiology as a risk stratification for stroke prevention, it has been derived using any thromboembolism event, including pulmonary embolism.[3] However, the association between the severity of CHA_2DS_2-VASc score and the risk of pulmonary embolism in patients with atrial fibrillation was not previously studied separately from stroke. We presumed that the Clalit Health Services (CHS) database, which is a population-based database, may provide a suitable platform that may help clarify this issue.

CLINICAL SIGNIFICANCE

- CHA_2DS_2-VASc score is directly associated with the incidence of pulmonary embolism in patients with atrial fibrillation.
- CHA_2DS_2-VASc and $CHADS_2$ score have similar and modest predictive value for pulmonary embolism in patients with atrial fibrillation.
- Anticoagulant use is associated with decreased risk of pulmonary embolism in patients with atrial fibrillation.

MATERIALS AND METHODS

Study Population and Data Source

We used data from the CHS database,[21,22] which is a not-for-profit health maintenance organization covering more than half of the Israeli population. The centralized electronic databases of the CHS includes data from multiple sources: primary care physician, specialty clinic in the community, hospitalizations, laboratories, and pharmacies. A chronic disease registry is compiled from these data sources. Diagnoses are captured in the registry by diagnosis-specific algorithms, using both code reading (eg, International Classification of Diseases, Ninth Revision and International Classification of Primary Care) and text reading. A record is kept of the sources and dates used to establish the diagnosis, with the earliest recorded date being considered the starting date.

The CHS computerized database was searched retrospectively for all members in whom atrial fibrillation was diagnosed before January 1, 2012, and who were alive at that date. We included only subjects aged ≥18 years. For the purpose of this study, we considered only first-time pulmonary embolism; therefore, subjects who had a history of pulmonary embolism before January 1, 2012, were excluded (a total of 73,541 subjects with atrial fibrillation were included in the study).

Follow-up

The cohort of subjects with atrial fibrillation was followed retrospectively for the first event of pulmonary embolism from January 1, 2012, to December 31, 2012. Subjects without the event of interest and those who died during the study period were censored at the date of their death. Mortality was established by matching our data with the National Death Index using a distinct identification number that each resident of Israel holds.

Study Variables and Definition of Terms

Variables that were retrieved from the CHS computerized database were demographic and clinical variables that are components of the CHA_2DS_2-VASc score. The CHA_2DS_2-VASc score is a risk stratification score that ranges from 0 to 9 depending on the number and weight of the score risk components and is calculated as follows: congestive heart failure (1 point), hypertension (1 point), age 65 to 74.9 years (1 point), age ≥75 years (2 points), diabetes mellitus (1 points), stroke (2 point), vascular disease (1 point), and female gender (1 point).[2,3] The CHA_2DS_2-VASc score was calculated at the study entry for each participant.

Antithrombotic therapy with oral anticoagulation and antiplatelets was established by searching the pharmacy database for any prescription filled during the 4 months before enrollment into the study. Anticoagulants that were considered included those that were in use in Israel for stroke prevention at the time of the study: vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, and antiplatelet agents, which included aspirin and clopidogrel. Antithrombotic therapy was classified into 3 groups: (1) antiplatelets (if antiplatelets were the only antithrombotic therapy used), (2) anticoagulants (if anticoagulants were the only antithrombotic therapy used), and (3) combination therapy (when both anticoagulants and antiplatelets were used).

Statistical Methods

Continuous variables that are normally distributed are summarized with mean ± standard deviation, and skewed variables are summarized with median and interquartile range. Categoric variables are presented as proportions. We