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Efficacy of Warfarin Anticoagulation and Incident Dementia in a Community-Based Cohort of Atrial Fibrillation

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Abstract

Objective: To study the association between time in therapeutic range (TTR) during warfarin therapy and risk of dementia in a population-based cohort of incident atrial fibrillation (AF).

Patients and Methods: We conducted an observational population-based study of 2800 nondemented patients with incident AF from January 1, 2000, through December 31, 2010. The association of incident dementia with warfarin therapy and TTR was examined using Cox proportional hazards regression models.

Results: Mean patient age was 71.2 years; 53% were men (n=1495), and warfarin was prescribed to 50.5% (n=1414) within 90 days of AF diagnosis. Incident dementia diagnosis occurred in 357 patients (12.8%) over a mean ± SD follow-up of 5.0±3.7 years. After adjusting for confounders, warfarin therapy was associated with a reduced incidence of dementia (hazard ratio [HR], 0.80; 95% CI, 0.64-0.99). However, only those in the 2 highest quartiles of TTR were associated with lower risk of dementia. A 10% increase in TTR with a 10% reduction in time spent in the subtherapeutic (HR, 0.71; 95% CI, 0.64-0.79) and supratherapeutic (HR, 0.67; 95% CI, 0.57-0.79) ranges were associated with decreased risk of dementia.

Conclusion: In the community, warfarin therapy for AF is associated with a 20% reduction in risk of dementia. Increasing TTR on warfarin is associated with reduced risk of dementia. The risk of dementia was reduced with a reduction in time spent in subtherapeutic and supratherapeutic international normalized ratio range. Effective anticoagulation may prevent cognitive impairment in patients with AF.

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Atrial fibrillation (AF) is the most common arrhythmia of clinical significance in adults and is expected to afflict 5.6 million adults in the United States by 2050.[1,2] The prevalence of AF increases with age, and 45% of affected individuals are older than 75 years.[1] Atrial fibrillation is associated with a 40% increased risk of dementia independent of the occurrence of clinical stroke.[3,4] Dementia, in turn, is an important cause of morbidity and mortality in the elderly and an enormous public health problem with a major impact from personal and socioeconomic standpoints.[5]

Atrial fibrillation is associated with cerebral thromboembolism, a proposed mechanism by which AF may increase the risk of dementia.[6-8] Oral anticoagulation with warfarin is effective in preventing thromboembolism in AF, but its effect on risk of dementia is unknown. The efficacy of warfarin in preventing thromboembolism also depends on the intensity of anticoagulation as measured by the international normalized ratio (INR). Although subtherapeutic INR levels can increase the risk of cerebral thromboembolism, supratherapeutic INR levels can predispose to intracranial hemorrhage, both of which may increase the risk of cognitive decline.[9-11] The time in therapeutic range (TTR) is a measure of the efficacy of warfarin anticoagulation. The aim of this study was to assess the impact of warfarin

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anticoagulation and the TTR on the risk of dementia in a community-based cohort of incident AF.

METHODS

Study Population

This study was conducted in Olmsted County, Minnesota, where most health care is provided by Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals. All health care—related data were retrieved through the records linkage system of the Rochester Epidemiology Project.[12-14] This study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

The study design and data retrieval are detailed previously.[15] Briefly, adults (aged ≥18 years) with AF or atrial flutter from January 1, 2000, through December 31, 2010, were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 427.31 and 427.32 or diagnosis of AF or atrial flutter on an electrocardiogram obtained at Mayo Clinic. Those with AF or atrial flutter diagnosed before 2000 were classified as having prevalent AF and were excluded. The medical records of the remaining patients were manually reviewed to validate incident AF if electrocardiographic evidence or a physician diagnosis was present. Patients with the only event of AF documented within 30 days of cardiothoracic surgery without any subsequent recurrence were considered to have postsurgical AF and were excluded.

Ascertainment of Clinical Data

Clinical data on comorbid conditions were obtained using *ICD-9* codes from inpatient and outpatient encounters. We required at least 2 occurrences of a code (either the same code or different codes in the code set) in the 5 years before incident AF to validate the diagnosis. The list of diagnosis codes used to define each comorbidity can be found in the Supplemental Table (available online at http://www.mayoclinicproceedings.org). Stroke risk was assessed by calculating the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score.[16] Smoking status, height, and weight were manually abstracted from the medical record at the time of incident AF. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Diagnosis of Dementia

We used *ICD-9* codes 290, 294.1, 294.8, 331.0-331.2, 331.7, and 331.82 to identify study participants diagnosed as having dementia based on previously validated codes.[17] If the diagnosis of dementia was first established before or within 6 months of diagnosis of AF, it was considered prevalent dementia and the individual was excluded.

Time in Therapeutic Range

International normalized ratio measurements were obtained to determine patients who were prescribed warfarin and to calculate the TTR for warfarin. All patients in the county had their INR measured at 1 of 2 hospitals, providing a complete record of their INRs. Most patients in the county are managed at anticoagulation clinics that use a standard protocol for warfarin dose adjustment, although the site of anticoagulation management for individual patients in the cohort is not available. Patients with all INRs less than 1.5 were considered to have never been taking warfarin. When a gap of more than 90 days between consecutive INR measurements was observed, we assumed that warfarin was discontinued. When warfarin was initiated (or reinitiated after a gap), INRs obtained within the first 7 days were excluded. When multiple INRs were measured on the same day, the mean value was used for that day. An INR was calculated for each day during follow-up using linear interpolation for the days between INR measurements.[18]

Statistical Analyses

Characteristics of the patients at the time of AF diagnosis are described as mean ± SD for normally distributed continuous variables, median (25th-75th percentile) for nonnormally distributed continuous variables, and number (percentage) for categorical variables. Logistic regression was used to test for differences in patient characteristics for those who initiated warfarin therapy within the first 90 days of follow-up and those not taking warfarin in the first 90 days. Cox proportional hazards