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Original Investigation

Warfarin Initiation, Atrial Fibrillation, and Kidney Function: Comparative Effectiveness and Safety of Warfarin in Older Adults With Newly Diagnosed Atrial Fibrillation

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Background: The effectiveness and safety of warfarin use among patients with atrial fibrillation (AF) and reduced kidney function are uncertain.

Study Design: Community-based retrospective cohort study (May 1, 2003, to March 31, 2012) using province-wide laboratory and administrative data in Alberta, Canada.

Setting & Participants: 14,892 adults 66 years or older with new AF and a measurement of kidney function. Long-term dialysis patients or kidney transplant recipients were excluded.

Predictor: Propensity scores were used to construct a matched-pairs cohort of patients with AF who did and did not have a warfarin prescription within a 60-day period surrounding their AF diagnosis.

Outcomes: Within 1 year of initiating warfarin therapy (or the matched date for nonusers): (1) the composite of all-cause death, ischemic stroke, or transient ischemic attack (also assessed as separate end points) and (2) first hospitalization or emergency department visit for a major bleeding episode defined as an intracranial, upper or lower gastrointestinal, or other bleeding.

Measurements: Baseline glomerular filtration rate (GFR) was estimated using the CKD-EPI creatinine equation. Patients were matched within estimated GFR (eGFR) categories: ≥90, 60 to 89, 45 to 59, 30 to 44, and <30 mL/min/1.73 m^2. Information for baseline characteristics (sociodemographics, comorbid conditions, and prescription drug use) was obtained.

Results: Across eGFR categories, warfarin therapy initiation was associated with lower risk for the composite outcome compared to nonuse (adjusted HRs [95% CI] for eGFR categories ≥ 90, 60-89, 45-59, 30-44, and <30 mL/min/1.73 m^2: 0.59 [0.35-1.01], 0.61 [0.54-0.70], 0.55 [0.47-0.65], 0.54 [0.44-0.67], and 0.64 [0.47-0.87] mL/min/1.73 m^2, respectively). Compared to nonuse, warfarin therapy was not associated with higher risk for major bleeding except for those with eGFRs of 60 to 89 mL/min/1.73 m^2 (HR, 1.36; 95% CI, 1.13-1.64).

Limitations: Selection bias.

Conclusions: Among older adults with AF, warfarin therapy initiation was associated with a significantly lower 1-year risk for the composite outcome across all strata of kidney function. The risk for major bleeding associated with warfarin use was increased only among those with eGFRs of 60 to 89 mL/min/1.73 m^2.

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INDEX WORDS: Atrial fibrillation (AF); chronic kidney disease (CKD); warfarin; stroke; death; major bleeding; estimated glomerular filtration rate (eGFR); antithrombotic therapy; cardiovascular disease; kidney function; ischemic stroke; transient ischemic attack (TIA); bleeding event.

Chronic kidney disease (CKD), defined primarily as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², affects 10% to 15% of adults worldwide.[1-3] Among patients with CKD, cardiovascular disease is the leading cause of death and the risk for stroke is 4 to 10 times greater than in the general population.[4,5] The incidence and prevalence of atrial fibrillation (AF), a major risk factor for stroke, also increase as kidney function declines,[6,7] emphasizing the potential importance of antithrombotic therapy in this high-risk group. Warfarin is highly effective in reducing embolic stroke risk in the broader AF population[8]; however, patients with CKD have an increased risk for bleeding with warfarin use[9-12] that may substantially alter the risk-benefit ratio of warfarin.[5]

Randomized trial evidence regarding the efficacy of warfarin in CKD is scarce because trials have typically excluded patients with CKD.[13] Large observational studies have reported conflicting evidence, with recent studies suggesting substantially better stroke and survival outcomes for warfarin users irrespective of kidney function,[14-16] but others reporting equivalent[17,18] or even worse outcomes associated with warfarin therapy among patients treated with dialysis.[9,19] Furthermore, recent observational studies have limitations, including limited generalizability due to the assessment of warfarin therapy in specific settings, such as after myocardial infarction[14] or among patients with CKD stage 5 on dialysis therapy,[9,16-19] and the use of administrative codes to define a single category of CKD.[15,20]

We used a population-based propensity score–matched cohort of older adults with AF to determine whether the comparative effectiveness of warfarin therapy and safety differed across categories of kidney function.

METHODS

Identification of Study Cohort

Diagnosis of New-Onset AF and Warfarin Use

We conducted a retrospective propensity score–matched cohort study using data from Alberta, Canada. Albertans are eligible for prescription drug coverage at age 65 years; therefore, to allow for a 1-year baseline assessment period, the study population included Alberta residents 66 years or older who had a diagnosis of AF (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 427.31/2[21]; *ICD, Tenth Revision* [*ICD-10*] code I48; see Table S1, provided as online supplementary material), defined as having 2 or more diagnostic codes for AF within 1 year and 30 or more days apart between May 1, 2003, and March 31, 2012, from hospitalization, physician claims, and emergency department data sources. We excluded patients with a history of mitral aortic valvular disease (valvular AF), valve surgery, or previously documented AF in the preceding 5 years (Fig 1).

The index date was defined as the date of the first dispensed warfarin prescription during the period 30 days before and 30 days after the newly diagnosed AF event among those with no warfarin prescription in the prior year. This 60-day period spanning the AF diagnosis was used to account for potential delays in data recording. Patients with a dispensed warfarin prescription during this 60-day period (warfarin users) were matched to patients with no dispensed warfarin (nonusers) who were alive at the time of the first dispensed warfarin prescription of their matched counterparts based on propensity scores calculated at the time of the new AF diagnosis. To avoid immortal time bias, the index date for nonusers in the matched set corresponded to the date of their new AF diagnosis plus the time between their matched user's new AF diagnosis date and the warfarin prescription date (Fig 2).

Warfarin exposure was considered a time-fixed variable throughout study follow-up (intention to treat). For descriptive purposes, we sought to assess for durations of continuous warfarin exposure among patients who were identified as warfarin users based on a dispensed warfarin prescription during the 60-day period using a validated algorithm[22,23] involving warfarin prescriptions and international normalized ratio (INR) measurements. Continuous use was defined as 2 warfarin prescriptions dispensed within 120 days or intervening INR measurements occurring at least every 6 weeks for prescription lapses of longer than 120 days. Similarly, among nonusers, we determined the proportion of patients who had 1 or more dispensed prescription for warfarin after the 60-day warfarin exposure ascertainment period and during the 1-year study follow-up.

Assessment of Kidney Function

Eligible participants were those with 1 or more outpatient serum creatinine measurement within the 1 year prior to or 90 days after the AF diagnosis. We calculated eGFR using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation and grouped participants into the following eGFR categories[24]: ≥90, 60 to 89, 45 to 59, 30 to 44, and <30 mL/min/1.73 m². We excluded participants who had received long-term dialysis or a kidney transplant at any time prior to the new AF diagnosis.

Covariates

Information for demographic characteristics and comorbid conditions was obtained from the administrative data files of the provincial health ministry. Aboriginal race/ethnicity was determined from First Nations status in the registry file. Diabetes mellitus[25] and hypertension[26] were identified using validated algorithms. We used the hospital discharge records and physician claims to calculate the $CHADS_2$[27] (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack [TIA]) score (based on a previously validated algorithm[27]) and the modified HAS-BLED[28] (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, and drugs/alcohol concomitantly) score (modified for use with administrative data because our data sources did not contain information for alcohol use or INR measurements for the full study period). Albuminuria was measured as in our prior studies.[29]

Other comorbid conditions based on the Deyo classification of Charlson comorbid conditions were identified using validated *ICD-9* and *ICD-10* coding algorithms. We identified previous hospital admissions involving bleeding or a diagnosis of deep vein thrombosis or pulmonary embolism within the 3-year period prior to the date of the incident AF. Antiplatelet and nonsteroidal anti-inflammatory drug (NSAID) use, defined as 1 or more prescription within 120 days prior to the date of the incident AF, was obtained from prescription drug records. Median neighborhood household income quintile and location of residence were defined as in our prior studies.[30]