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Original Investigation

Outcomes After Warfarin Initiation in a Cohort of Hemodialysis Patients With Newly Diagnosed Atrial Fibrillation

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Background: Although warfarin is indicated to prevent ischemic strokes in most patients with atrial fibrillation (AF), evidence supporting its use in hemodialysis patients is limited. Our aim was to examine outcomes after warfarin therapy initiation, relative to no warfarin use, following incident AF in a large cohort of hemodialysis patients who had comprehensive prescription drug coverage through Medicare Part D.

Study Design: Retrospective observational cohort study.

Setting & Participants: Patients in the US Renal Data System undergoing maintenance hemodialysis who had AF newly diagnosed in 2007 to 2011, with Medicare Part D coverage, who had no recorded history of warfarin use.

Predictor: Warfarin therapy initiation, identified by a filled prescription within 30 days of the AF event.

Outcomes: Death, ischemic stroke, hemorrhagic stroke, severe gastrointestinal bleeding, and composite outcomes.

Measurements: HRs estimated by applying Cox regression to an inverse probability of treatment and censoring-weighted cohort.

Results: Of 12,284 patients with newly diagnosed AF, 1,838 (15%) initiated warfarin therapy within 30 days; however, ~70% discontinued its use within 1 year. In intention-to-treat analyses, warfarin use was marginally associated with a reduced risk of ischemic stroke (HR, 0.68; 95% CI, 0.47-0.99), but not with the other outcomes. In as-treated analyses, warfarin use was associated with reduced mortality (HR, 0.84; 95% CI, 0.73-0.97).

Limitations: Short observation period, limited number of nonfatal events, limited generalizability of results to more affluent patients.

Conclusions: In hemodialysis patients with incident AF, warfarin use was marginally associated with reduced risk of ischemic stroke, and there was a signal toward reduced mortality in as-treated analyses. These results support clinical equipoise regarding the use of warfarin in hemodialysis patients and underscore the need for randomized trials to fill this evidence gap.

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INDEX WORDS: Dialysis; end-stage renal disease (ESRD); hemodialysis; atrial fibrillation (AF); cardiac arrhythmia; warfarin; oral anticoagulation; drug safety; ischemic stroke; hemorrhagic stroke; bleeding; prevention; mortality.

Atrial fibrillation (AF), the most common cardiac arrhythmia, is estimated to affect more than 2.7 million Americans.[1] Lower estimated glomerular filtration rate (eGFR) and higher albuminuria, key measures of kidney function, are strong independent risk factors for incident AF.[2] In older patients with end-stage renal disease (ESRD) initiating hemodialysis therapy at 67 years or older, the incidence of AF has been estimated at 148 events/1,000 person-years[3] compared with 28 events/1,000 person-years in the general Medicare population.[4]

One of the most dreaded consequences of AF is ischemic stroke. Based on clear evidence from randomized trials, international guidelines recommend the use of oral anticoagulation in most patients with AF.[5] However, patients with advanced kidney disease, including those with ESRD, were systematically excluded from these trials. In the absence of randomized

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trials, there is considerable uncertainty about whether the benefits of oral anticoagulation in AF extend to patients with ESRD. Several observational studies examining the effectiveness and safety of oral anticoagulation in ESRD have yielded conflicting results,[6-9] leading the KDIGO (Kidney Disease: Improving Global Outcomes) expert panel to no longer universally recommend anticoagulation for primary and secondary stroke prevention in ESRD.[10]

We conducted the following study to examine outcomes after warfarin therapy initiation relative to no warfarin use following newly diagnosed AF in a large cohort of hemodialysis patients who had comprehensive prescription drug coverage through Medicare Part D.

METHODS

Study Population

From the US Renal Data System (USRDS), we identified all hemodialysis patients who had a new diagnosis of AF in July 2007 to December 2011 based on 1 inpatient or 2 outpatient diagnosis codes within 30 days of each other indicating AF or atrial flutter (*International Classification of Diseases, Ninth Revision* codes 427.3x; Fig 1). We excluded those with a history of valvular disease associated with AF (Table S1, available as online supplementary material).[11] For patients with AF diagnosed from an inpatient code, we excluded patients whose hospitalization exceeded 30 days (including transfers to a skilled nursing facility) or who died within 30 days of discharge. For patients with AF diagnosed from 2 outpatient codes, patients were required to survive 30 days from the first diagnosis.

We further required the following additional conditions: uninterrupted Medicare Part A and B coverage for at least 1 year prior to the first AF diagnosis code and at least 6 months of uninterrupted Medicare Part D coverage with a low-income subsidy prior to the AF diagnosis with at least one prescription filled as an indication of active use of the prescription drug benefit. We excluded patients with any filled prescription for warfarin during this time. The index date for all analyses was day 30 after hospital discharge or day 30 after the first outpatient AF diagnosis (Fig 2). All patients had to have continuous Medicare Part A plus B plus D (low-income subsidy) coverage until the index date.

From the 12,684 patients on hemodialysis therapy, 400 (3.2%) were missing the medical evidence form or information for race or census division. Three percent were warfarin nonusers and 3.9% were users. Given the small percentage of observations missing, we performed a complete case analysis with the 12,284 patients with complete information available.

Outcomes

We examined death from any cause, cardiovascular death, and stroke-specific death. Nonfatal outcomes of interest were ischemic stroke, hemorrhagic stroke, and severe gastrointestinal bleeding (events requiring hospitalization or with gastrointestinal bleeding as reported cause of death). These were ascertained from validated claims-based algorithms (Table S2). In addition to individual outcomes, we also studied a composite end point of death, hemorrhagic or ischemic stroke, or gastrointestinal bleeding. For the outcomes of death from any cause and cardiovascular death, patients were censored at end of study, January 1, 2012. For all other outcomes, patients were censored at end of study or loss of Medicare Part A and B coverage.

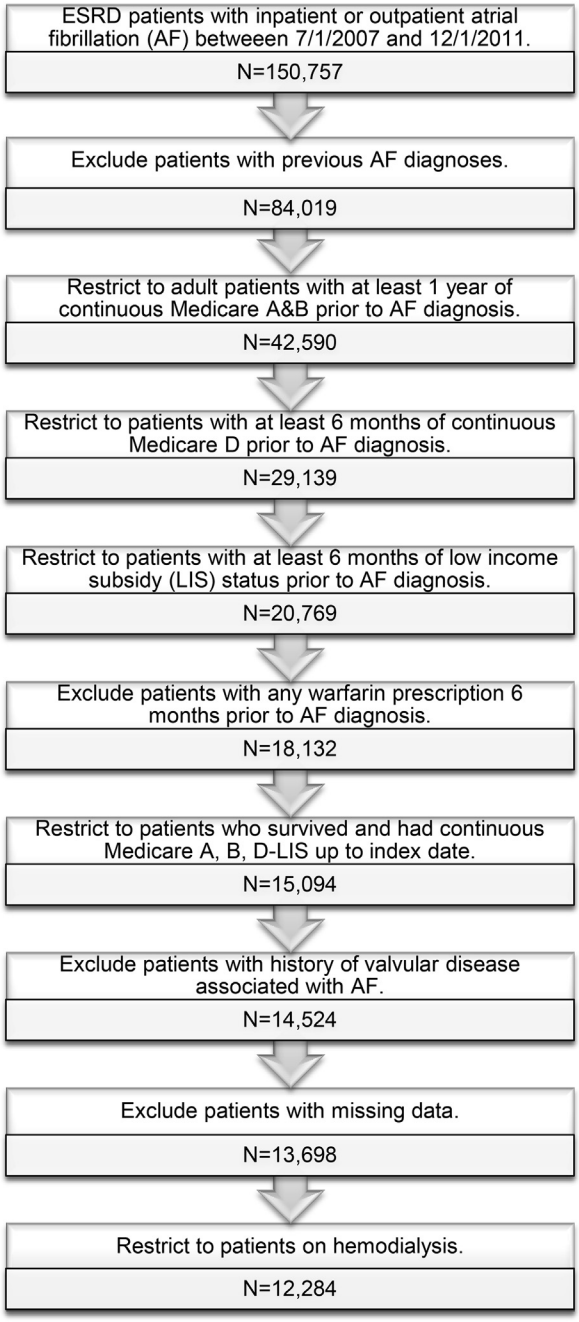

Figure 1. Study population selection from the US Renal Data System. We identified a cohort of adult patients on hemodialysis therapy who had atrial fibrillation (AF) newly diagnosed in 2007 to 2011 and participated in a low-income subsidy (LIS) program of Medicare Part D. Index date indicates day 30 after discharge from the first hospitalization with an AF diagnosis or day 30 after a first outpatient AF diagnosis. Abbreviation: ESRD, end-stage renal disease.

Warfarin Use

The exposure of interest was initiation of warfarin therapy within 30 days after discharge from the hospital or the first outpatient encounter during which AF was diagnosed (Fig 2). The number of days of warfarin supplied was ascertained from Medicare Part D claims. For analyses using an approach that