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Original Article

Association of warfarin with congestive heart failure and peripheral artery occlusive disease in hemodialysis patients with atrial fibrillation

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Abstract

Background: The effect of warfarin on the risk of cardiovascular (CV) disease is unknown among chronic hemodialysis patients with atrial fibrillation (HD-AF).
Methods: Population-based propensity score and prescription time-distribution matched cohort study including 6719 HD-AF patients with CHA_2DS_2-VASc score ≥ 2 were divided into warfarin users and nonusers and followed-up for CV events and death.
Results: Warfarin treatment in HD-AF patients with AF preceding HD was associated with higher risks of developing congestive heart failure [hazard ratio (HR) = 1.82, 95% confidence interval (CI) = 1.29–2.58, $p < 0.01$], peripheral artery occlusive disease (HR = 3.42, 95% CI = 1.86–6.31, $p < 0.01$), and aortic valve stenosis (HR = 3.20, 95% CI = 1.02–9.98, $p < 0.05$). Warfarin users were not associated with risks of ischemic or hemorrhagic stroke and all-cause mortality as compared to nonusers.
Conclusion: Warfarin may be associated with vascular calcification, increasing the risks of congestive heart failure and peripheral artery occlusive disease among HD-AF patients.

Keywords: atrial fibrillation; hemodialysis; warfarin

1. Introduction

Patients with end-stage renal disease (ESRD) have an extremely high risk of developing cardiovascular (CV) diseases. Atrial fibrillation (AF) is the most common cardiac dysrhythmia in hemodialysis (HD) patients, with a prevalence rate of around 10%.[1] In the general population, clinical trial data supported the use of anticoagulants for stroke prevention in patients with a CHA2DS2-VASC score > 2.[2,3] However, due to the paucity of prospective trials in dialysis patients, the treatment strategy for this group was based on data obtained from retrospective observations. Although some studies have suggested that warfarin is beneficial for stroke prevention in HD patients with atrial fibrillation (HD-AF),[4] other studies have indicated that warfarin may actually increase the risk of stroke.[5,6] Furthermore, the risk of bleeding associated with

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warfarin treatment has been reported to be increased in patients with chronic kidney disease (CKD).[4] Consistent with the clinical uncertainty regarding the benefits of stroke prevention with warfarin, the most recent Kidney Disease Improving Global Outcomes recommendations neither supported nor rejected the use of warfarin therapy in HD patients.[7]

Apart from the potential effect on stroke, only a few studies have assessed the risks and benefits of warfarin on CV outcomes among chronic HD patients. Some preclinical studies have shown that warfarin inhibits vitamin K-dependent γ-carboxylase of matrix Gla protein (MGP) in arterial smooth muscle cells and is thus involved in the process of vascular calcification.[8–10] AF *per se* has been shown to impair cardiac performance,[11] and in combination with the potential negative effects of warfarin upon vascular health, the administration of warfarin in HD-AF patients may aggravate the severity of arterial stiffness, thereby increasing the risk of congestive heart failure (CHF) and electric instability of the heart leading to sudden cardiac death, which are the main causes of CV death in HD patients. Nevertheless, no large trials have yet analyzed the effect of warfarin on CHF and peripheral artery occlusive disease (PAOD) in HD-AF patients. Therefore, we used national registry data to investigate the effect of warfarin on the major CV outcomes among HD-AF patients.

2. Methods

2.1. Data source

The data used in this study were derived from the Taiwanese National Health Insurance (NHI) Research Database (NHIRD). Taiwan's NHI program, launched in 1995, currently covers 99.9% of the population of 23 million people. The de-identified information kept in the NHIRD includes date of birth, sex, residential area, diagnostic codes, drug prescriptions, and medical procedures. We used codes from the International Classification of Diseases, ninth revision (ICD-9) to define diseases. This study was approved by the Institutional Research Board of Taipei Veterans General Hospital (2015-08-003BC), and informed consent was waived due to the de-identified personal information in the NHIRD. We excerpted data from a specially ordered dataset that included all claims information from patients under the registry of catastrophic illnesses from January 2000 to December 2010. In Taiwan, patients with ESRD who need long-term dialysis can apply for catastrophic illness registration cards from the NHI Administration so that co-payments for medical services are exempted.

2.2. Design and study participants

This study was a propensity score and prescription time-distribution matched cohort study. We selected individuals who had chronic HD > 90 days and AF from January 1, 2000 through June 30, 2009. We excluded patients younger than 20 years, patients older than 90 years, and patients with a CHA2DS2-VASC score < 2. These high-risk HD-AF patients were then divided into warfarin users ($n = 744$) and nonusers ($n = 5975$). The number of days from AF diagnosis to first warfarin prescription was assessed for users. The date of first warfarin prescription was defined as the index date for users. To avoid the imbalance of the prescription time distribution between the two groups, an index date was randomly selected from this diagnosis-treatment distribution set for nonusers.[12] We presumed that a stable anticoagulation effect would be achieved 30 days after the first warfarin treatment, thus patients with major CV events that occurred within 30 days of warfarin initiation were considered to be nonusers. Patients with a follow-up of < 30 days were also excluded. A 1:3 (user vs. nonuser) propensity scored and prescription time-distribution matched cohort was followed to major CV events, death, or December 31, 2010, whichever occurred first. The primary outcomes were defined as death, major adverse cardiovascular events [(a composite outcome of hospitalization for ischemic stroke (ICD-9 code 433-434, 436-437) and acute myocardial infarction (AMI; ICD-9 code 410-414))], hospitalization for hemorrhagic stroke (ICD-9 code 430-432), CHF (ICD-9 code 428), PAOD (ICD-9 code 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 444.9, 447.8, 447.9), and aortic valve stenosis (ICD-9 code 424.1). Fig. 1 illustrates the patient selection flow chart.

2.3. Statistical analysis

Baseline characteristics were compared by two-sided *t* tests or Chi-square tests. In multivariate Cox proportional hazards regression models, the effect of warfarin was further adjusted for age, sex, Charlson comorbidity index, AMI, CHF, cerebrovascular accident, transient ischemic attack, bleeding history, and use of aspirin and clopidogrel. Results were expressed as hazard ratios (HRs) compared with the warfarin nonusers. The proportional hazards assumption, the constant HR over time, was evaluated by comparing estimated log-log survival curves for all time-independent covariates. All the assessed log-log survival plots graphically showed two parallel lines, indicating no violation of the assumption. Adjusted HRs for major CV outcomes associated with warfarin use were analyzed among two subgroups based on the occurrence of AF before and after HD. All p values were two-sided, and the significance level was set at 0.05. All analyses were performed using the commercially available software, SAS (version 9.3 SAS Institute Inc., Cary, North Carolina) and Stata SE (version 13.0; StataCorp., College Station, Texas, USA).

3. Results

In total, 7208 HD-AF patients were identified from the NHIRD database. Compared to warfarin nonusers, the warfarin users were younger, had a higher proportion of heart failure, and took more antiplatelet drugs (all $p < 0.05$). After propensity matching, 589 HD-AF warfarin users with high CHA2DS2-VASC scores and 1767 warfarin nonusers were selected. The baseline demographic data and drug exposure were comparable after matching (Table 1).

With a mean follow-up of 2 years, the average warfarin dosage was 2 mg/d in the warfarin user group, and the drug