Original article

Underutilization of warfarin for stroke prophylaxis in patients with atrial fibrillation or atrial flutter in Korea

Iyn-Hyang Lee (PhD)[a], Hyunah Kim (PharmD)[b], Nam Kyung Je (PharmD)[c,*]

[a] College of Pharmacy, Yeungnam University, Gyeongsan, Republic of Korea
[b] College of Pharmacy, Sookmyung Women's University, Seoul, Republic of Korea
[c] College of Pharmacy, Pusan National University, Busan, Republic of Korea

A B S T R A C T

Objective: Anticoagulation therapy with warfarin is recommended for stroke prevention in patients with atrial fibrillation (AF) or atrial flutter (AFL) whose risks for stroke are high. However, previous studies suggest that warfarin is markedly underused. This study aims to investigate the incidence and risk factors of warfarin underutilization in patients with high risk of stroke in Korea.
Methods: This was a cross-sectional study using the data of 2009 from National Patients Sample compiled by the Health Insurance Review and Assessment Service. Patients with high risk of thromboembolism were identified with congestive heart failure, hypertension, age $\geq$75 years, diabetes, and prior stroke (CHADS2) score $\geq$2. High-risk patients of bleeding were excluded using Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score >4. Warfarin and antithrombotic therapy underutilization were defined and estimated in high-risk patients. Any demographic and clinical factors associated with warfarin and antithrombotic therapy underutilization were explored using a logistic regression model.
Results: Of the national patient sample, 15,885 patients were identified with AF or AFL. Among them, a total of 8475 patients who had an admission history, CHADS2 $\geq$2, and ATRIA score $\leq$4 were included in the analysis. From the study sample, warfarin underutilization and antithrombotic therapy underutilization were estimated to be 64.0% and 20.4%, respectively. Predictors of warfarin underutilization include female sex, age $\geq$80 years, lower CHADS2 score, and insurance type (Medical Aid program).
Conclusions: A high portion of AF/AFL patients with CHADS2 score $\geq$2 were undertreated with warfarin. As ischemic stroke is one of the leading causes of death in Korea, a more aggressive approach to prevent stroke in patients with AF/AFL is required.

© 2015 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Atrial fibrillation (AF) or atrial flutter (AFL) is a common type of supraventricular arrhythmia, characterized by irregular and rapid heartbeat [1]. It was estimated that between 2.7 million and 6.1 million US citizens had AF in 2010, and the prevalence is expected to rise to between 5.6 and 12 million in 2050 [2]. It was projected that by 2050 there would be over 1 million patients with AF in Japan if limited to persistent and permanent type and around

2 million patients with AF if paroxysmal type was included [3]. In South Korea, the prevalence of AF was estimated to be 0.7% in the population of older than 40 years and 2.1% in those older than 65 years [4].

The most serious complication of AF/AFL is ischemic stroke, which can occur at any point in time during the clinical course of AF/AFL. AF/AFL patients have five times the risk of stroke occurrence than non-AF/AFL patients [5]. Therefore, all patients with any form of AF/AFL should be on antithrombotic therapy to prevent stroke if there were no compelling contraindications [6]. Either oral anticoagulation or antiplatelet therapy is recommended for this purpose in accordance to the patient's risk for stroke. There are several risk stratification systems. Among them congestive heart failure, hypertension, age $\geq$75 years, diabetes, previous stroke (CHADS2) system is one of the most utilized

systems because it is simple and well validated [7]. The CHADS2 system assigns 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and 2 points for prior stroke, transient ischemic attack (TIA), or thromboembolism [7]. The CHADS2 system can have a number ranging from 0 to 6, with higher risk of thromboembolism represented by a higher number. The relationship between the CHADS2 score and thromboembolic rate was investigated in a cohort study. The thromboembolic rate was estimated at 0.49, 1.52, 2.50, 5.27, 6.02, and 6.88 per 100 person-years for patients with CHADS2 score of 0, 1, 2, 3, 4, and 5/6, respectively [8]. The American Heart Association/ American Stroke Association (AHA/ASA) guideline recommends anticoagulation therapy with warfarin for patients with AF of CHADS2 score ≥2, and either anticoagulation or antiplatelet therapy for patients with AF of CHADS2 score equal to 1 [6]. Aspirin or no treatment is recommended for patients at very low risk (CHADS2 score = 0). The stroke prevention guideline in Korea also recommends warfarin for stroke prevention if patients belong to a high-risk group [9].

Despite the strong evidence of benefits, a number of studies have shown that warfarin has been underused among patients who appear to be appropriate candidates for it [10–25]. A systematic review was conducted with nine studies that utilized CHADS2 ≥2 to identify high-risk patients for stroke. These studies reported warfarin treatment levels ranging from 39% to 70%. Seven out of nine studies reported a treatment level of below 70% [24].

In Korea, stroke is the second leading cause of death after cancer, and the first leading cause of death if organ-based mortality is considered [26]. Compliance with evidence-based guidelines has not been widely studied among patients with AF/AFL in the Korean healthcare setting. This study aims to investigate warfarin underutilization (WU) in patients with high risks of stroke in Korea and its contributing factors.

Methods

Study data

For this study, we analyzed the National Patients Sample data collected by Korean Health Insurance Review and Assessment Service from 2009 (HIRA-NPS-2009-0114). The data were extracted with stratified and systematic sampling methods, considering sex and age group among all patients who used medical services in 2009. HIRA-NPS-2009 contains 13% of patients who had admission history to health institutions (designated as inpatients; $n = 711,457$) and 1% of patients who had no history of admission (designated as outpatients; $n = 404,583$) [27]. The representativeness of HIRA-NPS-2009 was verified by the HIRA and five other medical associations in Korea [27]. The following data are available in HIRA-NPS: diagnosis, age, sex, insurance type, institution, medical expenses, operation name, and prescriptions.

Study subjects

We identified AF/AFL patients in HIRA-NPS-2009 using KCD-5 (Korean version of ICD-10) [28], which is I48. Patients with any admission history were included in this study ($n = 14,695$). We calculated each patient's CHADS2 score based on patient's age and clinical status including congestive heart failure (KCD-5 code: I50, I110), hypertension (I10, I11, I12, I13), diabetes mellitus (E10, E11, E12, E13, E14), previous stroke, TIA, or thromboembolism (I63, I74, G458, G459) using the diagnosis code. Then, we stratified patients into three groups according to the risk of thromboembolism: low-risk group (CHADS2 score = 0); intermediate-risk group (CHADS2 score = 1 point); and high-risk group (CHADS2 score = 2–6 points) (Fig. 1). For the purpose of reviewing warfarin utilization, we extracted only the high-risk group. We also calculated each patient's Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score to estimate bleeding risk on warfarin [29,30]. ATRIA score is simpler than other bleeding risk assessing tools such as HAS-BLED and HEMORR2HAGES scores [31–33]. To calculate ATRIA score, laboratory data such as hemoglobin and creatinine clearance are needed. We used KCD-5 to find patients with anemia or severe renal disease instead of using laboratory values (i.e. anemia is defined as hemoglobin <13 g/dL in males or <12 g/dL in females). In this tool, anemia (KCD-5 code: D46, D50-53, D55-61, D63-64), severe renal disease (I12.0, I13.1, I13.2, N03-05, N18-19, P96.0, T82.4, Y84.1, Z99.2), age ≥75 years, prior hemorrhage (I60-62, K25.0, K25.2, K25.4, K25.6, K92.2), and hypertension (I10–13) were identified as risk factors and 3 points for the first two factors
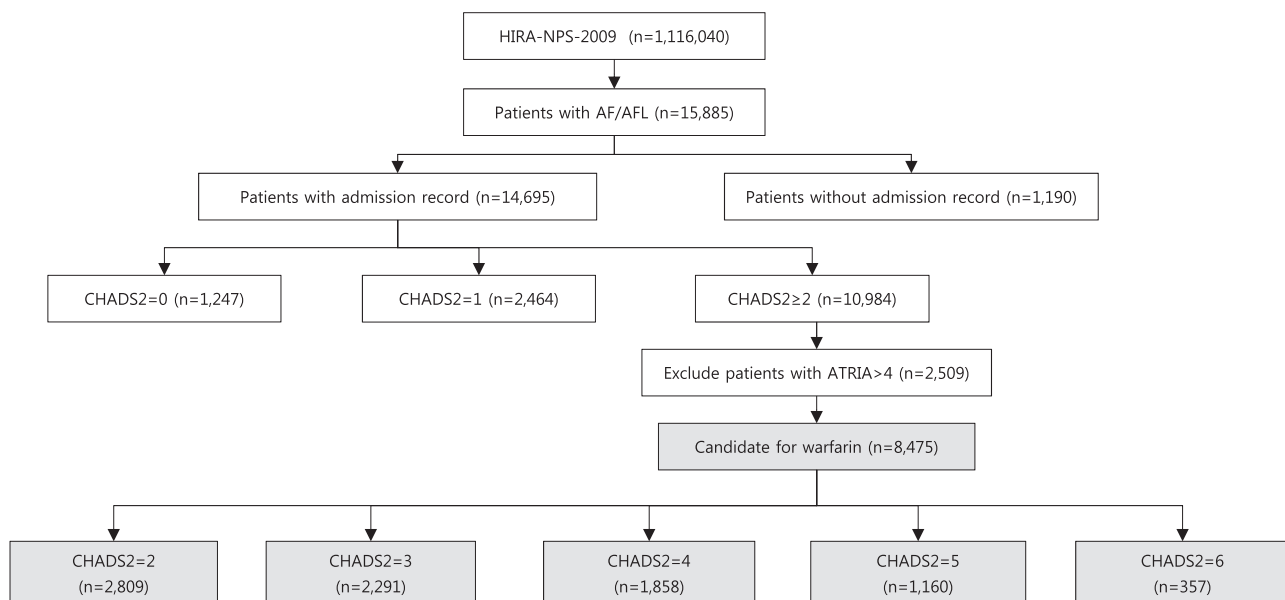

Fig. 1. Case extraction diagram. HIRA, Health Insurance Review and Assessment Service; NPS, National Patients Sample; AF, atrial fibrillation; AFL, atrial flutter; CHADS2, congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation.