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Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND It is unclear whether the non-vitamin K antagonist oral anticoagulant agents rivaroxaban and dabigatran are superior to warfarin for efficacy and safety outcomes in Asians with nonvalvular atrial fibrillation (NVAF).

OBJECTIVES The aim of this study was to compare the risk for thromboembolic events, bleeding, and mortality associated with rivaroxaban and dabigatran versus warfarin in Asians with NVAF.

METHODS A nationwide retrospective cohort study was conducted of consecutive patients with NVAF taking rivaroxaban (n = 3,916), dabigatran (n = 5,921), or warfarin (n = 5,251) using data collected from the Taiwan National Health Insurance Research Database between February 1, 2013 and December 31, 2013. The propensity score weighting method was used to balance covariates across study groups. Patients were followed until the first occurrence of any study outcome or the study end date (December 31, 2013).

RESULTS A total of 3,425 (87%) and 5,301 (90%) patients were taking low-dose rivaroxaban (10 to 15 mg once daily) and dabigatran (110 mg twice daily), respectively. Compared with warfarin, both rivaroxaban and dabigatran significantly decreased the risk for ischemic stroke or systemic embolism ($p = 0.0004$ and $p = 0.0006$, respectively), intracranial hemorrhage ($p = 0.0007$ and $p = 0.0005$, respectively), and all-cause mortality ($p < 0.0001$ and $p < 0.0001$, respectively) during the short follow-up period. In comparing the 2 non-vitamin K antagonist oral anticoagulant agents with each other, no differences were found regarding risk for ischemic stroke or systemic embolism, intracranial hemorrhage, myocardial infarction, or mortality. Rivaroxaban carried a significantly higher risk for hospitalization for gastrointestinal bleeding than dabigatran ($p = 0.0416$), but on-treatment analysis showed that the risk for hospitalized gastrointestinal bleeding was similar between the 2 drugs ($p = 0.5783$).

CONCLUSIONS In real-world practice among Asians with NVAF, both rivaroxaban and dabigatran were associated with reduced risk for ischemic stroke or systemic embolism, intracranial hemorrhage, and all-cause mortality without significantly increased risk for acute myocardial infarction or hospitalization for gastrointestinal bleeding compared with warfarin. (J Am Coll Cardiol 2016;68:1389–401) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AMI = acute myocardial infarction

ASMD = absolute standardized mean difference

CI = confidence interval

CKD = chronic kidney disease

GI = gastrointestinal

HR = hazard ratio

ICH = intracranial hemorrhage

INR = international normalized ratio

NHIRD = National Health Insurance Research Database

NOAC = non-vitamin K antagonist oral anticoagulant agent

NVAF = nonvalvular atrial fibrillation

OAC = oral anticoagulant agent

VKA = vitamin K antagonist

Atrial fibrillation (AF) significantly increases the risk for thromboembolic events and death, affecting 2% to 3% of the global population (1,2). Oral anticoagulants (OACs) such as vitamin K antagonists (VKAs) (such as warfarin) effectively decrease the risk for thromboembolic events in patients with AF, while increasing the risk for intracranial hemorrhage (ICH) (3,4). The results of several large trials have suggested that non-VKA OACs (NOACs), such as dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, are convenient and safe alternatives to VKAs (5,6). NOACs have been shown to be noninferior or superior to VKAs in preventing thromboembolic events, depending strongly on choosing either standard-dose NOAC administration (i.e., 150 mg for dabigatran) or low-dose NOAC administration (i.e., 110 mg for dabigatran). Evaluation of NOAC safety has shown that both dabigatran and rivaroxaban reduced the risk for ICH, while unexpectedly increasing the risk for gastrointestinal (GI) bleeding compared with warfarin (7,8).

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Of particular note, Asians show a higher risk for ICH than non-Asians when taking VKAs (9), but limited data are available to determine whether NOACs are as effective and safe in an Asian population than in non-Asians (10,11). In our recent study of a large nationwide Asian cohort with nonvalvular AF (NVAF) (12), dabigatran administered mainly at a low dose of 110 mg twice daily was associated with reduced risk for ischemic stroke, ICH, and all-cause mortality compared with warfarin, and it did not increase the risk for major GI bleeding compared with warfarin. However, no published data are available to directly compare efficacy and safety outcomes in Asians with AF who are taking rivaroxaban versus dabigatran during the same period. The objective of this study was to evaluate the risk for thromboembolic events, bleeding events, and all-cause mortality associated with the NOACs dabigatran and rivaroxaban versus warfarin in a real-world population of Asians with NVAF.

METHODS

In this retrospective cohort study, all patient data were obtained from the Taiwan National Health Insurance Research Database (NHIRD). Taiwan has a mandatory universal health insurance program providing comprehensive medical care coverage to all Taiwanese, currently including >23 million enrollees. The NHIRD is a national billing administrative database of health care services covering >99% of the Taiwanese population in 2014 (13). Because patients' original NHIRD identification numbers are encrypted and deidentified to protect their privacy, informed consent was waived. The consistent data encrypting process made it feasible to link and continuously follow all claims belonging to the same patient within the NHIRD. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

STUDY DESIGN. We studied patients with NVAF treated with rivaroxaban, dabigatran, or warfarin (**Figure 1**). We identified a total of 304,252 patients with new AF using International Classification of Diseases, Ninth Revision, Clinical Modification code 427.31 from January 1, 1996, to December 31, 2013. Among the 304,252 patients, 80,365 patients had at least 1 prescription filled for rivaroxaban, dabigatran, or warfarin after AF was diagnosed. The approval dates of dabigatran and rivaroxaban in Taiwan were June 1, 2012, and February 1, 2013, respectively. We selected 3 study groups taking the first dose of rivaroxaban, dabigatran, or warfarin between February 1, 2013 and December 31, 2013—rivaroxaban (n = 3,916), dabigatran (n = 5,921), and warfarin (n = 5,251)—on the basis of each patient's final anticoagulant status. Some patients had experience with more than 1 of the drugs studied. Thus, the detailed profile of each treatment group was as follows: 1) the dabigatran group included only dabigatran users (n = 2,781), rivaroxaban-experienced dabigatran users (n = 45), and warfarin-experienced dabigatran users (n = 3,095); 2) the rivaroxaban group included only rivaroxaban users (n = 1,441), dabigatran-experienced rivaroxaban users (n = 375), and warfarin-experienced rivaroxaban users (n = 2,100); and 3) the warfarin group included only warfarin users (n = 5,251). Dabigatran- or rivaroxaban-experienced warfarin users (n = 327) were excluded from our analysis. The index date was defined as the date of first prescription of these 2 NOACs or warfarin after February 1, 2013, for each group. The follow-up period was defined as from the index date until the first occurrence of any study outcome or the end date of the study period (December 31, 2013), whichever came first.

STUDY OUTCOMES. Six outcomes were used in the present study to determine the efficacy and safety of NOACs and warfarin, including ischemic stroke or systemic embolism, ICH, hospitalization for GI