JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 10, 2019

PUBLISHED BY ELSEVIER

Outcomes of Direct Oral Anticoagulants in Patients With Mitral Stenosis

Ju Youn Kim, MD,[a] Sung-Hwan Kim, MD,[b] Jun-Pyo Myong, MD,[c] Yoo Ri Kim, MD,[d] Tae-Seok Kim, MD,[e] Ji-Hoon Kim, MD,[f] Sung-Won Jang, MD,[g] Yong-Seog Oh, MD,[b] Man Young Lee, MD,[h] Tai-Ho Rho, MD[g]

ABSTRACT

BACKGROUND Patients with mitral stenosis and atrial fibrillation (AF) require anticoagulation for stroke prevention. Thus far, all studies on direct oral anticoagulants (DOACs) have excluded patients with moderate to severe mitral stenosis.

OBJECTIVES The aim of this study was to validate the efficacy of DOACs in patients with mitral stenosis.

METHODS The study population was enrolled from the Health Insurance Review and Assessment Service (HIRA) database in the Republic of Korea, and it included patients who were diagnosed with mitral stenosis and AF and either were prescribed DOACs for off-label use or received conventional treatment with warfarin. The primary efficacy endpoint was ischemic strokes or systemic embolisms, and the safety outcome was intracranial hemorrhage.

RESULTS A total of 2,230 patients (mean age 69.7 ± 10.5 years; 682 [30.6%] males) were included in the present study. Thromboembolic events occurred at a rate of 2.22%/year in the DOAC group, and 4.19%/year in the warfarin group (adjusted hazard ratio for DOAC: 0.28; 95% confidence interval: 0.18 to 0.45). Intracranial hemorrhage occurred in 0.49% of the DOAC group and 0.93% of the warfarin group (adjusted hazard ratio for DOAC: 0.53; 95% confidence interval: 0.22 to 1.26).

CONCLUSIONS In patients with AF accompanied with mitral stenosis, DOAC use is promising and hypothesis generating in preventing thromboembolism. Our results need to be replicated in a randomized trial.
(J Am Coll Cardiol 2019;73:1123–31) © 2019 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is associated with an increased risk of thromboembolic events. Direct oral anticoagulants (DOACs) are effective in preventing thromboembolisms among patients with AF (1). However, patients with moderate to severe mitral stenosis and mechanical prosthetic heart valves have been excluded from all pivotal trials (2–6). Warfarin remains the only oral anticoagulant approved for patients with AF and mechanical prosthetic heart valves or moderate to severe mitral stenosis. AF combined with valvular heart disease is common and more often requires mandatory long-term anticoagulation compared with patients without valvular heart disease (7,8). Mitral stenosis combined with AF increases the risk of a stroke >20 times, and is related to blood stasis in the left atrium (9). Strokes or systemic embolisms can be the first manifestation of mitral stenosis, and they can occur in patients

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Division of Cardiology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, South Korea; [b]Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [c]Department of Occupational & Environmental Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [d]Division of Cardiology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, South Korea; [e]Division of Cardiology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, South Korea; [f]Division of Cardiology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, South Korea; [g]Division of Cardiology, Department of Internal Medicine, St. Paul's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; and the [h]Division of Cardiology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea. The authors have received financial support from the Catholic Medical Center Research Foundation given in the program year of 2015.

Manuscript received November 27, 2018; accepted December 6, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.12.047

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DOAC = direct oral anticoagulant

HIRA = Health Insurance Review and Assessment Service

HR = hazard ratio

NHIS = National Health Insurance Service

with mild mitral stenosis even before the development of other symptoms (10,11). Furthermore, the thrombi present in mitral stenosis, even in the absence of AF, are much more often "giant" and can cause disastrous embolisms (12,13). The efficacy of warfarin in the prevention of thromboembolisms in mitral stenosis and atrial fibrillation can be hampered by the poor quality of the anticoagulation therapy, which is more pronounced in developing countries (14–16). Based on these considerations, it is desirable to determine the efficacy of DOACs in patients with mitral stenosis and AF. Many physicians are unclear of the definition of "nonvalvular AF," and some of them try off-label use of DOACs in patients with mitral stenosis, especially in the case of adverse events with warfarin (17). The medical records of these patients were reviewed from the national health insurance database, the Health Insurance Review and Assessment Service (HIRA) of the Republic of Korea, and their outcomes were compared with patients who received conventional warfarin treatment.

SEE PAGE 1132

METHODS

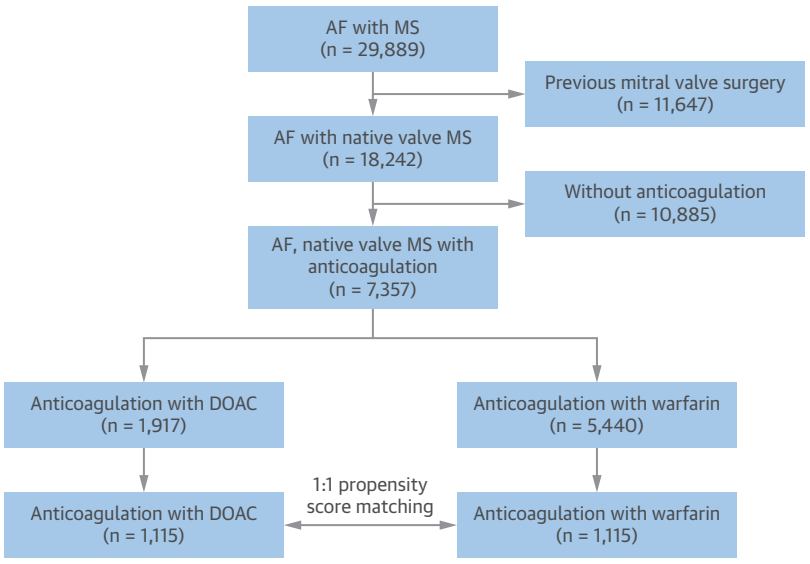
More than 98% of the Korean population belong to the mandatory National Health Insurance Service (NHIS) program, and the remaining 2% receive medical benefits for the lowest income population (18). This study used the HIRA database in South Korea. The HIRA is a national organization that reviews and assesses medical costs and health care service quality, and it is mandatory that all health care providers join the program. This cohort dataset contained an encoded version of the patient's original identification number, as well as age, sex, prescription drugs, and diagnoses. This study was approved by the local Institutional Review Board of the Catholic Medical Center, South Korea (KC15EISI0450).

STUDY POPULATION. Patients with AF and any degree of mitral stenosis who were prescribed oral anticoagulation for at least >3 weeks between February 2008 and January 2017 were included in this study. Mitral stenosis was defined using codes I342, I050, and I052 in the International Classification of Diseases-10th Revision. A diagnosis of AF was established if code I48 was recorded at least once in the database at hospital discharge or more than twice in the outpatient department. A case-control analysis was performed where patients were assigned to 1 of 2 groups based on the anticoagulation therapy used. Patients with off-label use of DOACs and those with propensity score matched warfarin use were included at a 1:1 ratio. We excluded all patients who had a history of mitral valve surgery.

DATA COLLECTION AND STUDY OUTCOMES. The basic demographic data of each subject was acquired from the HIRA database, and the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) was calculated using the patient's age, sex, and history of congestive heart failure, hypertension, diabetes mellitus, vascular disease, and thromboembolisms. The primary outcome was defined as the first hospitalization with a principal diagnosis of an ischemic stroke or systemic embolism after 3 weeks of DOAC use. Ischemic strokes were defined as codes I63, I64, and I67. Systemic embolisms, including renal infarctions, splenic infarctions, SMA thromboses, and other arterial thromboembolisms, were defined as codes N28, D735, K55, and I74. To extract diagnostic codes as naïve events, ischemic strokes and systemic embolisms were defined as patients who did not have the preceding codes recorded for >1 year, and new recorded codes were displayed consecutively at least twice at the time of the hospital discharge diagnosis. The safety endpoint was the occurrence of an intracranial hemorrhage, which was defined as code I61, and the extraction method was the same as that for ischemic strokes. A detailed definition of the variables is given in Online Table 1.

STATISTICAL ANALYSIS. The baseline characteristics are presented as the mean ± SD for continuous variables and as frequencies with percentages for categorical variables. Continuous variables were compared using the unpaired Student's *t*-test and categorical variables were compared using either the chi-square test or Fisher exact test as appropriate. To reduce the effect of selection bias, we performed adjustments using propensity score matching with SAS software version 9.3 (SAS Institute, Cary, North Carolina), as described elsewhere (19). The propensity scores were generated with adjusted covariates, including 10 variables (age class, sex, previous history of hypertension, diabetes, stroke, congestive heart failure, vascular disease, dyslipidemia, chronic kidney disease, and chronic obstructive pulmonary disease) (Online Figure 1). The DOAC- and warfarin-treated groups were matched at a 1:1 ratio. An absolute difference (caliber) between the propensity scores of 0.001 was applied and a closest option was used to optimize the model. The replacement for the missing value was not applied. More detailed scripts

FIGURE 1 Flow Chart of Atrial Fibrillation With Mitral Stenosis Patients



The study population was divided according to the type of oral anticoagulant. A total of 1,917 patients received DOAC therapy and 5,440 were treated with warfarin. After 1:1 propensity score matching, the data from a total of 2,230 patients were analyzed. AF = atrial fibrillation; DOAC = direct oral anticoagulant; MS = mitral stenosis.

and explanation are described elsewhere (19). Event rate curves were obtained using a Kaplan-Meier analysis and compared using the log-rank test. The risk of thromboembolisms was assessed using a Cox proportional hazards model, and is presented as a hazard ratio (HR). All p values <0.05 were considered statistically significant. All statistical analysis was performed using SAS software, version 9.3.

RESULTS

CLINICAL CHARACTERISTICS. A total of 29,889 patients who had mitral stenosis with AF between 2008 and 2017 were included in the present study. The 11,647 patients who had mitral valve surgery were excluded. Among the included patients, 10,885 did not receive any oral anticoagulation therapy, leaving 7,357 remaining. The study population was divided into 2 groups: 1,917 (26.1%) patients who received DOAC therapy and 5,440 (73.9%) treated with warfarin. After 1:1 propensity score matching, the data from a total of 2,230 patients was analyzed (Figure 1). The mean age was 69.7 ± 10.5 years, and 682 (30.6%) patients were men. The mean CHA_2DS_2-VASc score was 5.2 ± 1.7. Among the patients who received DOAC, 367 (32.9%) were treated with dabigatran, 472 (42.3%) with rivaroxaban, 192 (17.2%) with apixaban, and 84 (7.5%) with edoxaban. The baseline characteristics of the patients according to the type of anticoagulation therapy after propensity score matching are summarized in Table 1.

OUTCOME. The mean follow-up duration was 27 months. Strokes or systemic embolisms occurred in 30 patients in the DOAC group (2.22%/year; adjusted HR: 0.28; 95% confidence interval [CI]: 0.18 to 0.45) compared with 146 patients in the warfarin group

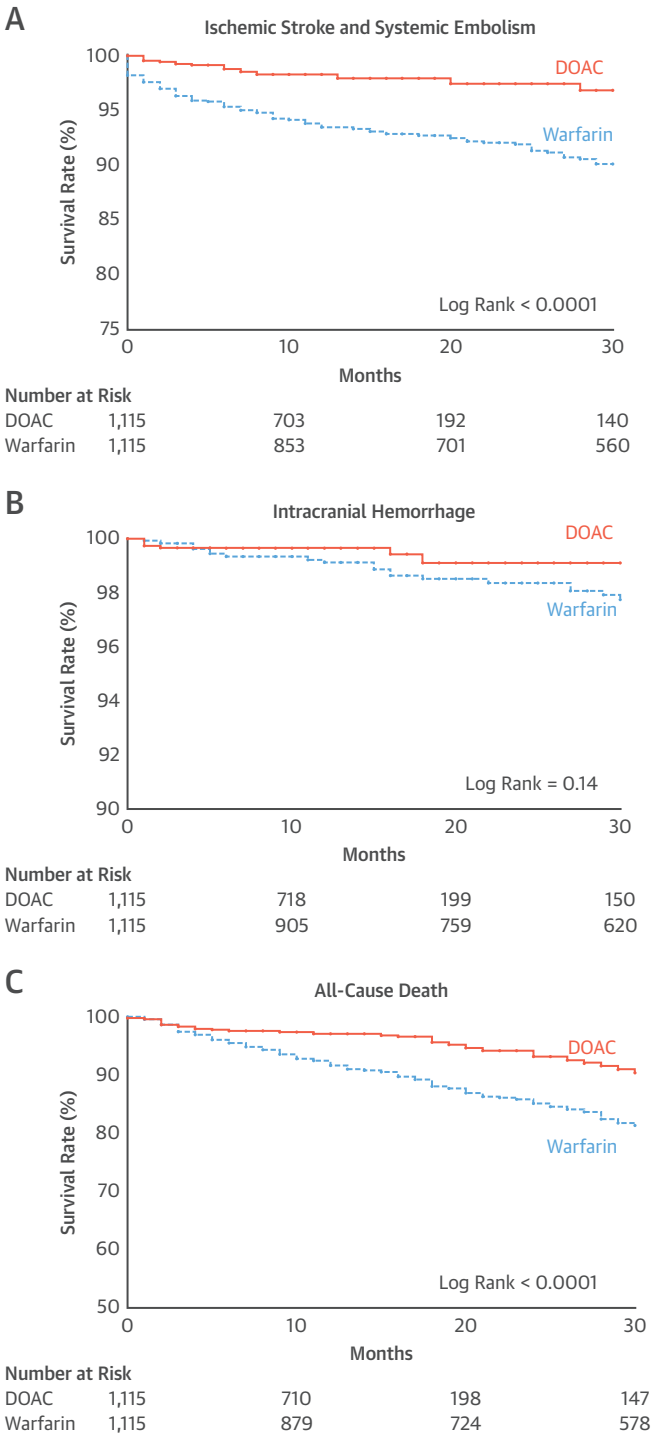
TABLE 1 Baseline Characteristics According to the Type of Oral Anticoagulant

	DOAC (n = 1,115)	Warfarin (n = 1,115)	Standardized Difference	p Value
Age, yrs	69.2 ± 10.9	70.2 ± 10.2	0.0947	
<65	311 (27.9)	318 (28.5)	0.0192	0.90
65–74	401 (36.0)	404 (36.2)		
≥75	403 (36.1)	393 (35.3)		
Female	775 (69.5)	773 (69.3)	0.0039	0.93
Hypertension	1,076 (96.5)	1,080 (96.9)	0.0200	0.64
Diabetes mellitus	759 (68.1)	760 (68.2)	0.0019	0.96
Previous stroke	518 (46.5)	521 (46.7)	0.0054	0.90
Congestive heart failure	832 (74.6)	838 (75.2)	0.0124	0.77
Previous vascular disease	625 (56.1)	623 (55.9)	0.0036	0.93
Dyslipidemia	810 (72.7)	808 (72.5)	0.0040	0.92
COPD	265 (23.7)	267 (24.0)	0.0042	0.92
CKD	80 (3.59)	73 (6.55)	0.0248	0.56

Values are mean ± SD or n (%).

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulants.

FIGURE 2 Kaplan-Meier Curves of the Primary Efficacy and Safety Outcomes (Warfarin vs. DOAC)



The efficacy outcome **(A)** was freedom from ischemic strokes or systemic embolisms (adjusted hazard ratio [HR]: 0.28; 95% confidential interval [CI]: 0.18 to 0.45). The safety outcome was freedom from **(B)** intracranial hemorrhage (adjusted HR: 0.53; 95% CI: 0.22 to 1.26), and **(C)** all-cause death (adjusted HR: 0.41; 95% CI: 0.30 to 0.56). DOAC = direct oral anticoagulant.

TABLE 2 Outcomes

		Ischemic Stroke or Systemic Embolism		Intracranial Hemorrhage	
	Patients	Events	Event Rate, %/yr	Events	Event rate, %/yr
DOAC	1,115	30	2.22	7	0.49
Warfarin	1,115	146	4.19	36	0.93

Values are n unless otherwise indicated.
DOAC = direct oral anticoagulant.

(4.19%/year). The overall cumulative incidence curves showed a greater reduction in ischemic strokes or systemic embolisms in the DOAC group compared with the warfarin group (log-rank $p < 0.0001$) (Figure 2A).

The rate of the incidence of intracranial hemorrhages exhibited a nonsignificant difference between the DOAC group and warfarin group (DOAC group, 0.49%/year; warfarin group, 0.93%/year; adjusted HR: 0.53; 95% CI: 0.22 to 1.26) (Table 2). The Kaplan-Meier curves for the safety outcomes were similar for the DOAC and warfarin groups (log-rank $p = 0.14$) (Figure 2B).

The incidence rates of all-cause death were 3.45%/year in the DOAC group compared with 8.08%/year in the warfarin group (adjusted HR: 0.41; 95% CI: 0.30 to 0.56). The overall survival curve demonstrated a reduction of all-cause death in the DOAC group compared with the warfarin group (log-rank $p < 0.0001$) (Figure 2C).

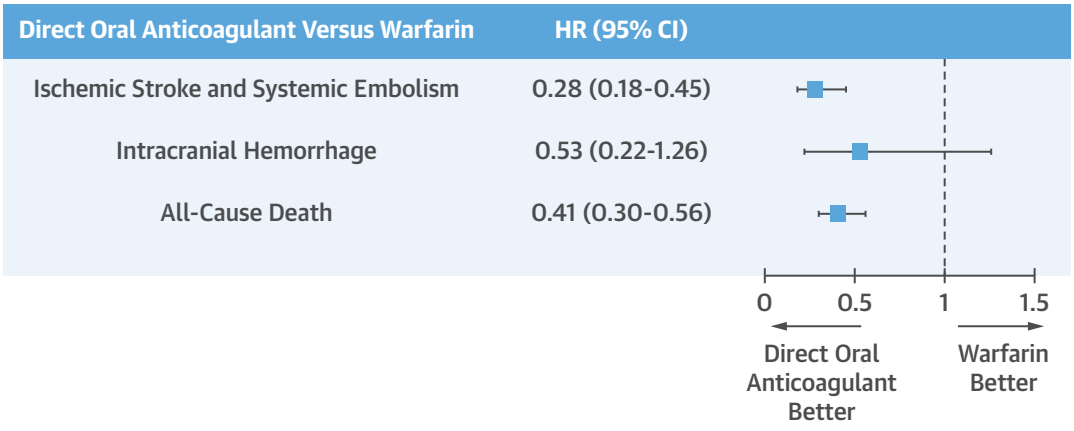
A sensitivity analysis using a trimmed propensity score was performed and eliminated those in the top 5% and bottom 5% of the score. It did not change the general results for strokes or systemic embolisms (adjusted HR: 0.27; 95% CI: 0.16 to 0.47) and intracranial hemorrhages (adjusted HR: 0.68; 95% CI: 0.28 to 1.67).

DISCUSSION

To the best of our knowledge, this study is the first investigation of the efficacy of DOACs in patients with mitral stenosis and AF. The main findings are as follows: first, DOACs were associated with lower rates of thromboembolism than warfarin; and second, DOACs were as effective as warfarin in preventing hemorrhagic strokes (Central Illustration).

THE EFFICACY OF DOACs IN PATIENTS WITH AF AND MITRAL STENOSIS. Oral anticoagulation therapy with a vitamin K antagonist is recommended in patients with mitral stenosis and AF or those in sinus rhythm with a prior embolic event or left atrial thrombus (20) because mitral stenosis itself is a

CENTRAL ILLUSTRATION **Mitral Stenosis and Atrial Fibrillation for Direct Oral Anticoagulant Versus Warfarin: Hazard Ratios**



Kim, J.Y. et al. J Am Coll Cardiol. 2019;73(10):1123–31.

Strokes or systemic embolisms and all-cause death rates were significantly lower in the direct oral anticoagulant group compared with the warfarin group. There was a nonsignificant difference in the rate of the incidence of intracranial hemorrhages between the direct oral anticoagulant group and the warfarin group. CI = confidence interval; HR = hazard ratio.

high-risk factor for thromboembolisms. Mitral stenosis has the highest risk of thromboembolism in the setting of AF with native valve condition, and patients with mitral stenosis who had a previous embolic event are also at higher risk for thromboembolism. The mechanisms of thromboses in mitral stenosis may have different features compared with other AF. Some reports suggest that the incidence and distribution of thrombus formation is different in mitral stenosis patients (21). Thrombi in mitral stenosis occur outside of the left atrial appendage and are frequently related to blood stasis.

In the 2014 American Heart Association guidelines, the term "nonvalvular AF" is defined as AF in the absence of rheumatic mitral stenosis, mechanical or bioprosthetic heart valves, or a mitral valve repair (22). On the other hand, the European guidelines state that no satisfactory or uniform definition of "valvular or non-valvular" exists (7). The term was eliminated in the 2016 ESC guidelines, and a novel classification has been suggested with a functional Evaluated Heartvalves, Rheumatic or Artificial (EHRA) categorization. EHRA Type 1 refers to AF patients with valvular heart disease needing therapy with a vitamin K antagonist, including moderate to severe mitral stenosis of a rheumatic origin and mechanical prosthetic valve replacement. EHRA Type 2 refers to valvular heart disease patients needing thromboembolic prevention therapy for AF with warfarin or a DOAC, including all other native valvular stenosis and insufficiencies as well as mitral valve repairs, bioprosthetic valve replacements, and transaortic valve intervention (23). However, both guidelines recommend that DOACs are one of the options to prevent thromboembolisms in nonvalvular AF. These confusing definitions of valvular AF may lead to problems determining when DOAC use is indicated. In each of the 4 pivotal clinical trials, patients with mechanical heart valves or hemodynamically significant mitral stenosis were excluded (1-4). Therefore, no published data have disclosed the effects of DOACs in patients with moderate to severe mitral stenosis thus far. Furthermore, the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) trial using dabigatran in patients with prosthetic heart valves demonstrated that dabigatran increased both embolic and bleeding events (24). In patients with a mechanical heart valve, thrombi formation can be related to artificial valve leaflets or the sewing ring (25). Exposure of these materials can activate the intrinsic coagulation cascade, and tissue damage may also lead to extrinsic pathway activation (26). The main mechanism of thrombi formation in patients with a mechanical heart valve is not blood stasis or endothelial dysfunction. In this regard, the main pathogenesis of thrombus formation in patients with mitral stenosis is different than for those with a prosthetic heart valve. Rheumatic mitral valve disease is a native valve

condition in which the mechanism of the thrombus formation is similar to other AF and is related to a low flow or stasis of the blood in the left atrial appendage. Our findings demonstrate that off-label DOAC use is effective in mitral stenosis patients.

VALVULAR HEART DISEASE ACCOMPANIED BY AF. Significant valvular disease, other than a mechanical prosthetic valve or moderate to severe mitral stenosis, typically includes bioprosthetic valves, surgical valve repairs, transcatheter valve replacements, and valvular disease requiring surgery (27,28). The pivotal DOAC trials had some variations in their inclusion and exclusion criteria. The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trials included other native valve disease or prior valvuloplasty, whereas the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial included native valve disease such as mitral regurgitation, tricuspid regurgitation, aortic regurgitation, aortic stenosis, and mild mitral stenosis (1–4). A post hoc analysis and meta-analysis of these patients with valvular heart disease demonstrated similar efficacy between DOACs and warfarin for stroke prevention. Furthermore, the rates of hemorrhagic strokes were significantly lower or similar in the DOAC group than in the warfarin group (29–33). All pivotal studies included mild mitral stenosis and the number of patients was limited (193 in RELY, 131 in ARISTOTLE, 254 in ENGAGE AF-TIMI 48, and not reported in the ROCKET-AF trial). Although we were not able to ascertain the severity of the mitral stenosis, we included 2,230 patients with mitral stenosis in our study. This was the largest study related to mitral stenosis patients.

Mitral stenosis is also a native valve disease that has a much higher risk than other native valve diseases for strokes, and these patients should receive strict anticoagulation therapy. However, the REMEDY (Global Rheumatic Heart Disease Registry) trial showed that only a quarter of the patients had an international normalized ratio (INR) in a therapeutic range (16). Meanwhile, DOACs have better compliance due to fewer drug and food interactions, no need for INR monitoring, and a lack of fluctuation (34). Therefore, more data are needed regarding the use of DOACs in patients with mitral stenosis with AF to achieve a more effective anticoagulation therapy.

WARFARIN TREATMENT IN KOREAN PATIENTS. Warfarin is the only oral anticoagulant approved for use in patients with moderate to severe mitral stenosis and AF thus far. Maintaining a proper therapeutic range is important for the efficacy and safety of warfarin. However, the real-world data show that the quality of warfarin therapy is inadequate in Koreans. A multicenter observational study of the quality of anticoagulation with warfarin in Korean patients showed that only 31% of patients were within the therapeutic range, and 41% had an INR <2.0 (35). This low INR control was influenced by the high intake of vitamin K rich foods and a high frequency of genetic polymorphisms in Asians. Also, physicians' concerns regarding the much higher incidence rate of intracranial hemorrhage with anticoagulation in the Asian population (HR: 4.06 vs. Caucasian) (36) may have caused them to make the INR target low or not prescribe an anticoagulant. A low prescription rate of anticoagulation in patients with atrial fibrillation has been reported in Western countries as well (37). A survey reported that only 25% patients with mitral stenosis and atrial fibrillation were adequately treated with warfarin. Unlike the CHA_2DS_2-VASc score system, the general cardiologists as well as primary physicians may not be familiar with the stroke risk of mitral stenosis and atrial fibrillation. Therefore, the portion of patients without anticoagulation in our data was not extraordinary. A nationwide population-based study on the trends in antithrombotic therapy in high-risk patients with AF showed that the proportion of patients who received anticoagulants was <40% prior to DOACs being approved (38). Our study was also a nationwide population-based study that contained primary health care service data. Treatment with warfarin and monitoring the INR is difficult in that setting.

The rate of thromboembolic events with DOAC therapy in patients with mitral stenosis and AF in our study was significantly lower than that in the warfarin group. This increased efficacy was notably higher compared to the previous DOAC studies. This may be due to the low therapeutic control of the INR in the warfarin group and the fact that most patients could not achieve the target therapeutic range under the clinical practice conditions. Furthermore, mitral stenosis is one of the highest risk factors for systemic embolisms. Therefore, the event rates were higher in this study population. The stroke and systemic embolism rate in this study was 2.22% in the DOAC group and 4.19% in the warfarin group; meanwhile, the

event rates in the other DOAC studies of patients with AF were <2% (1–4). These high event rates made a large impact on the statistical differences.

STUDY LIMITATIONS. Under the present guidelines, warfarin remains the drug of choice for patients with moderate to severe mitral stenosis with AF. Therefore, our study was conducted with data from off-label use, which resulted in difficulty in recruiting cases. There were several reasons why the patients received DOACs in this study: 1) developing thromboembolisms or bleeding events during warfarin use; 2) off-label use of DOACs before the evaluation of the presence of mitral stenosis; or 3) mild mitral stenosis.

Second, as this was a retrospective observational study using the HIRA database, we were not able to ascertain the severity of the mitral stenosis and particularly valvular pathologies in a significant number of patients. Also, these data do not contain the laboratory findings or clinical measurements. Therefore, there could be selection bias and residual confounding factors due to the unmeasured differences and an incomplete adjustment. To account for this limitation, we assessed a propensity score matching analysis. However, a randomized controlled trial is the gold standard for validating efficacy. Furthermore, the largest concern was that we could not rule out the possibility of a misclassification of patients with mitral stenosis. However, there are some reports in relation to the validity of the ICD codes in medical insurance claims in Korea. Park et al. (39) assessed the accuracy of the ICD codes for cerebrovascular diseases in medical insurance claims in Korea and found it was 83%. This was also confirmed in rare intractable diseases, and showed 98% sensitivity and 93% specificity (40). Although mitral stenosis is not a rare intractable disease, it is a rare disease, and it may be said that the diagnosis in the HIRA database had a relatively higher accuracy than in the other insurance data.

Third, we excluded patients who underwent mitral valve surgery in this study protocol. This meant that patient groups that had severe mitral stenosis and a higher risk for thromboembolic events were excluded. This might have caused the results to become exaggerated. Fourth, the reduced study population after propensity score matching should also be considered. To minimize the number of patients who were not matched, the matching ratio was set as 1:1. With an effort to maximize matching, a lot of information was not used; however, information bias might be reduced due to computerized propensity score matching without the author's intention. A well-designed prospective study should be undertaken as the next step to overcome this potential limitation. Last, the information regarding the INR and time in a therapeutic range was not available in all cases because this research was based on a national database. However, this reflected the general clinical practice conditions and inadequate INR control, which supports that DOAC use is essential for effective anticoagulation in these patients. Therefore, a prospective, randomized, large-scale trial is necessary to confirm these results (41).

CONCLUSIONS

This study revealed worthwhile exploratory data on the effectiveness of DOACs in patients with mitral stenosis and AF. Our observation supports that DOAC use appears reasonable in patients with mitral stenosis with AF. Based on this consideration, a clinical trial evaluation of the superiority of DOACs in moderate to severe mitral stenosis would be justified.

ADDRESS FOR CORRESPONDENCE: Dr. Sung-Hwan Kim, Division of Cardiology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. E-mail: sunghwan@catholic.ac.kr. OR Dr. Jun-Pyo Myong, Department of Occupational and Environmental Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. E-mail: jpmyong@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Observational data suggest that DOACs may be effective for prevention of thromboembolism in patients with mitral stenosis and atrial fibrillation.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to confirm the safety and efficacy of DOACs relative to vitamin K antagonists in patients with mitral stenosis and atrial fibrillation.

REFERENCES

1. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

2. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

4. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

5. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493–503.

6. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125:2298–307.

7. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719–47.

8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

9. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.

10. Wood P. An appreciation of mitral stenosis. I. Clinical features. Br Med J 1954;1:1051–63.

11. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Br Heart J 1962;24:349–57.

12. Rider OJ, Malhotra A, Newton JD. Free floating left atrial ball thrombus: a rare cause of stroke. J Stroke Cerebrovasc Dis 2013;22:e238–9.

13. Santos PM, Lopez EB, Barrio EE, et al. Massive left atrium thrombus. Int J Cardiovasc Imaging 2014;30:67.

14. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029–37.

15. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975–83.

16. Zuhlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J 2015;36:1115–22a.

17. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. Europace 2014;16:1720–5.

18. Kim L, Kim JA, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. Epidemiol Health 2014;36:e2014008.

19. Murphy B, Fraeman K. A General SAS® macro to implement optimal N:1 propensity score matching within a maximum radius. SAS Global Forum 2017 Proceedings. Available at: http://support.sas.com/resources/papers/proceedings17/0812-2017.pdf. Accessed January 18, 2019.

20. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440–92.

21. Blustin JM, McBane RD, Ketha SS, Wysokinski WE. Distribution of thromboembolism in valvular versus non-valvular atrial fibrillation. Expert Rev Cardiovasc Ther 2014;12:1129–32.

22. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

23. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330–93.

24. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206–14.

25. Dewanjee MK, Gross DR, Zhai P, et al. Thrombogenicity of polyethylene oxide-bonded Dacron sewing ring in a mechanical heart valve. J Heart Valve Dis 1999;8:324–30.

26. Lip GYH, Collet JP, Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace 2017;19:1757–8.

27. Potpara TS, Lip GY, Larsen TB, et al. Stroke prevention strategies in patients with atrial fibrillation and heart valve abnormalities: perceptions of 'valvular' atrial fibrillation: results of the European Heart Rhythm Association Survey. Europace 2016;18:1593–8.

28. Carnicelli AP, O'Gara PT, Giugliano RP. Anticoagulation after heart valve replacement or transcatheter valve implantation. Am J Cardiol 2016;118:1419–26.

29. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with nonvalvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J 2014;35:3377–85.

30. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation 2015;132:624–32.

31. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation 2016;134:589–98.

32. De Caterina R, Renda G, Carnicelli AP, et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 Trial. J Am Coll Cardiol 2017;69:1372–82.

33. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Am Coll Cardiol 2017;69:1363–71.

34. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. J Am Heart Assoc 2016;5:e003074.

35. Hong KS, Kim YK, Bae HJ, et al. Quality of anticoagulation with warfarin in Korean patients with atrial fibrillation and prior stroke: a multicenter retrospective observational study. J Clin Neurol 2017;13:273–80.

36. Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol 2007;50:309–15.

37. Bath PM, Prasad A, Brown MM, MacGregor GA. Survey of use of anticoagulation in patients with atrial fibrillation. BMJ 1993;307:1045.

38. Lee SR, Choi EK. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. PLoS One 2017;12:e0189495.

39. Park JK, Kim KS, Kim CB, et al. The accuracy of ICD codes for cerebrovascular diseases in medical insurance claims. Korean J Prev Med 2000;33:76–82.

40. Kim HJ, Hann HJ, Hong SN, et al. Incidence and natural course of inflammatory bowel disease in Korea, 2006–2012: a nationwide population-based study. Inflamm Bowel Dis 2015;21:623–30.

41. De Caterina R, John Camm A. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial. Europace 2016;18:6–11.

KEY WORDS atrial fibrillation, intracranial hemorrhage, ischemic stroke, mitral stenosis, systemic embolism

APPENDIX For a supplemental table and figure, please see the online version of this paper.