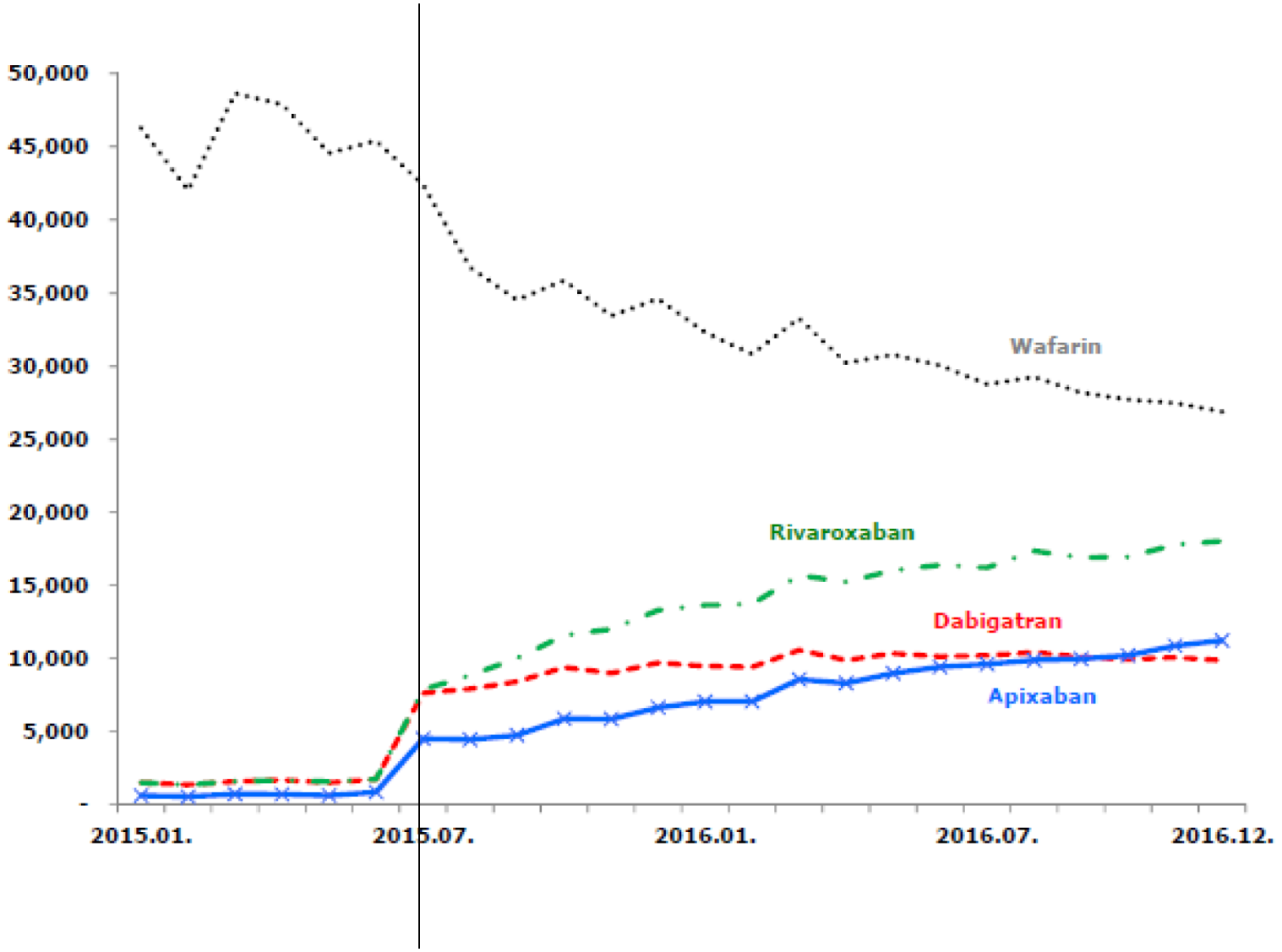
Real world data of NOACs in Korea

Min Soo Cho
Asan Medical Center
University of Ulan, College of Medicine

The Korean Heart Rhythm Society
COI Disclosure

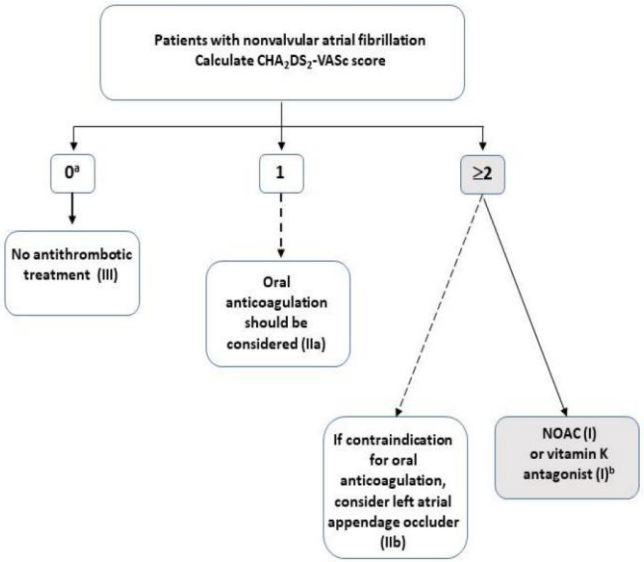
Name of First Author*: Min Soo Cho*

The author have no financial conflicts of interest to disclose concerning the presentation



Full reimbursement

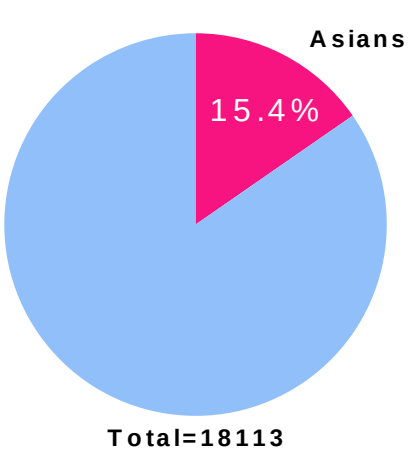
KHRS guideline on SPAF



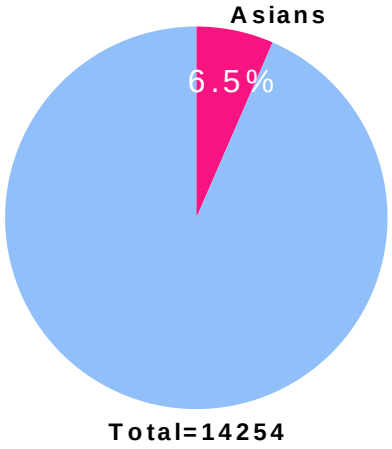
	Dose reduction criteria	Dose
Dabigatran	Creatinine clearance 30-50 mL/min P-glycoprotein inhibitors[a] Clopidogrel, aspirin, NSAIDs Increased bleeding risk[b] Age 75 years or more	110 mg bid
Rivaroxaban	Age 80 years or more Creatinine clearance 15-50 mL/min[c]	15 mg qd
Apixaban	At least two: 1) age 80 years or more, 2) body weight 60 kg or less, 3) creatinine ≥ 1.5 mg/dL	2.5 mg bid
Edoxaban	P-glycoprotein inhibitors[a] Body weight 60 kg or less Creatinine clearance 15-50 mL/min[c]	30 mg qd

NOAC, non-vitamin K antagonist oral anticoagulant; bid, bis in die (twice a day); qd, quaque die (once a day).
[a]P-glycoprotein inhibitors: amiodarone, verapamil, dronedarone, etc.
[b]Increased bleeding risk: coagulopathy, thrombocytopenia, platelet dysfunction, recent major trauma or biopsy, infective endocarditis
[c]Should be used with caution in patients with significant renal impairment (creatinine clearance 15-29 mL/min).

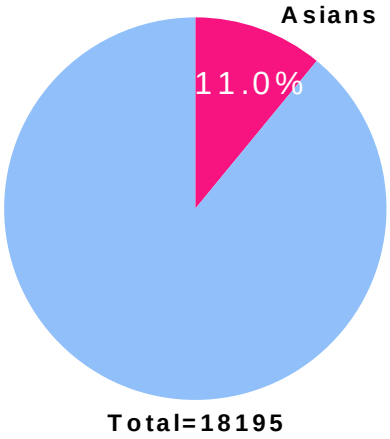
Asians in pivotal RCTs



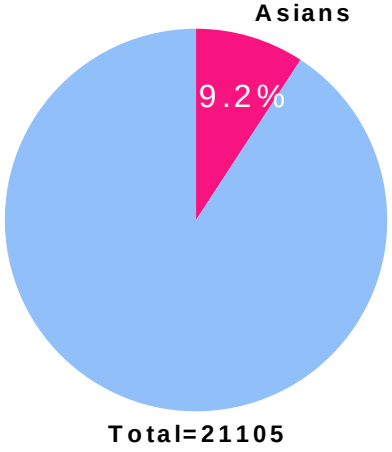
RE-LY



ROCKET



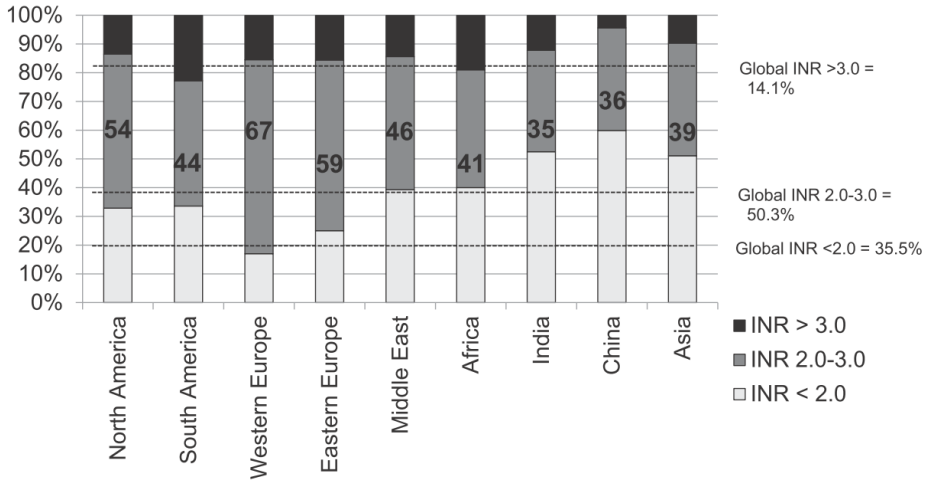
ARISTOTLE



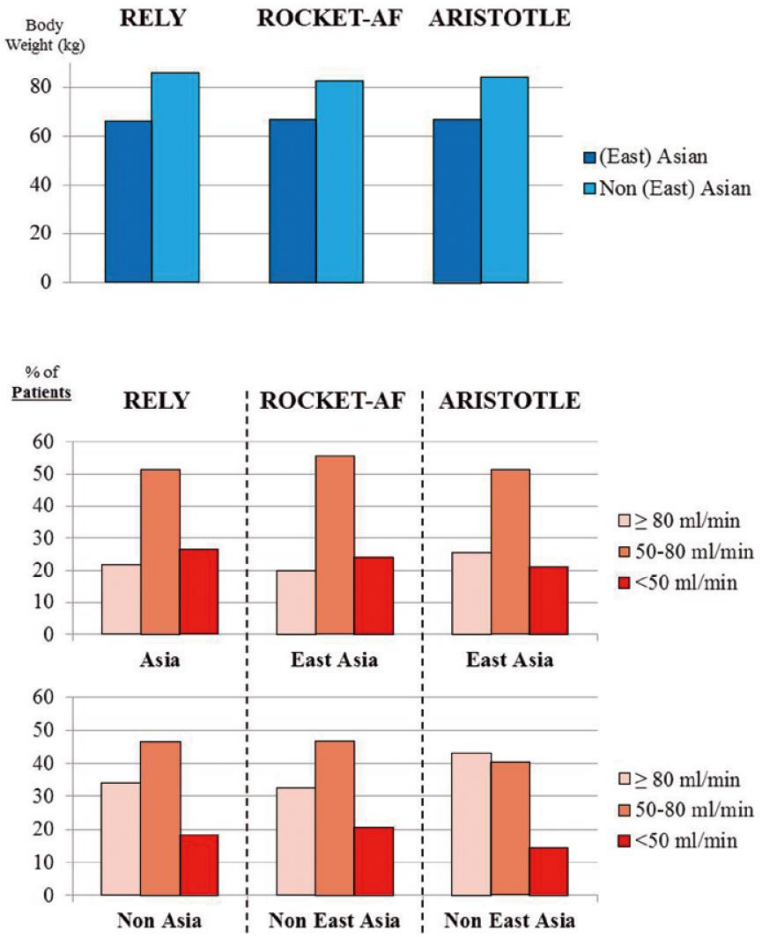
ENGAGE

- Asian patients comprised only 10% to 15% of the study population in pivotal RCTs

Characteristics of Asians



Circ 2014;129:1568



Circ J 2015;79:2098

Off-label Underdose Usage in Korea: CODE-AF

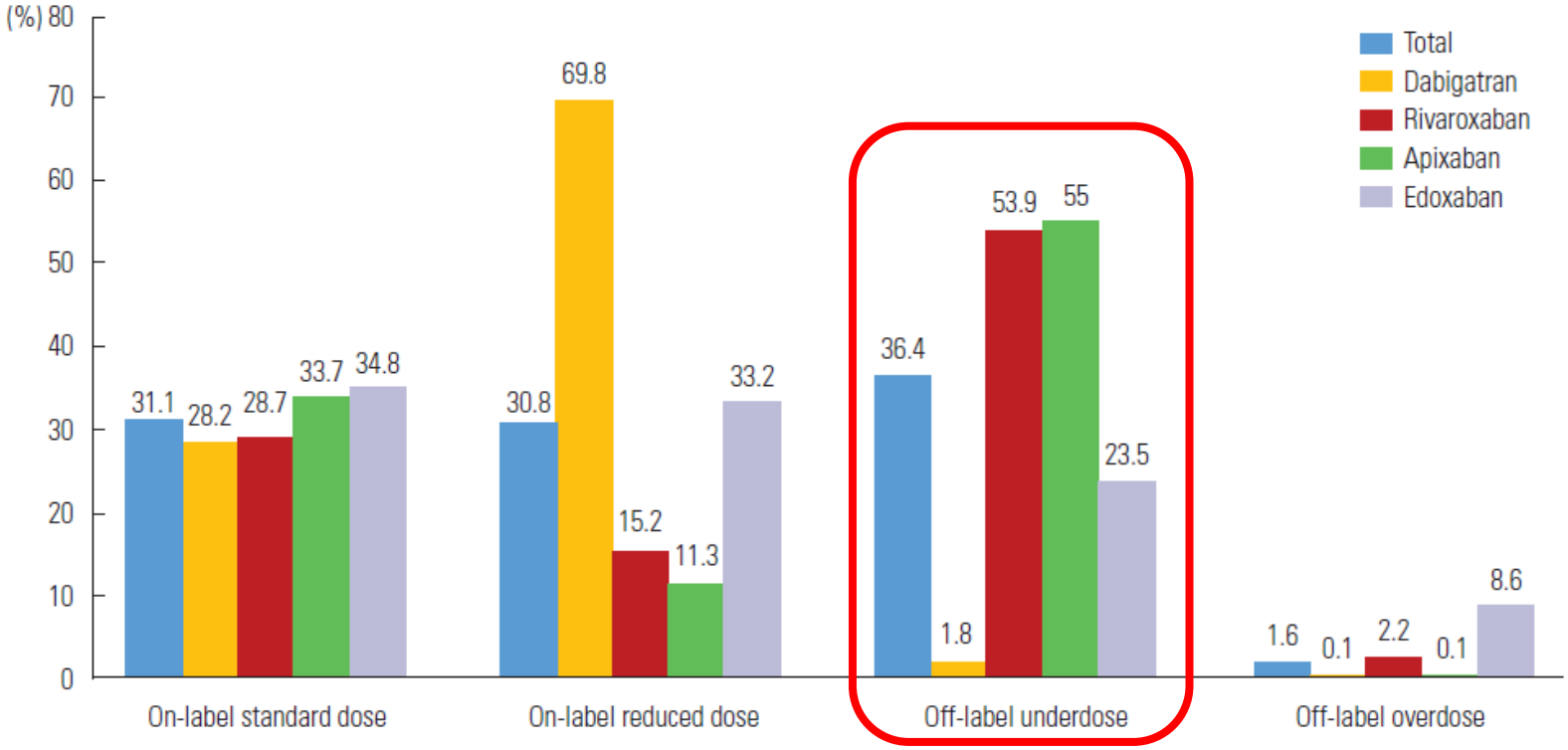


Fig. 1. Differences in drug-specific dose reduction recommendations for each NOAC and discrepancies in NOAC dosing. NOAC, non-vitamin K antagonist oral anticoagulant.

- Off-label underdosing was used in about half of the Korean patients

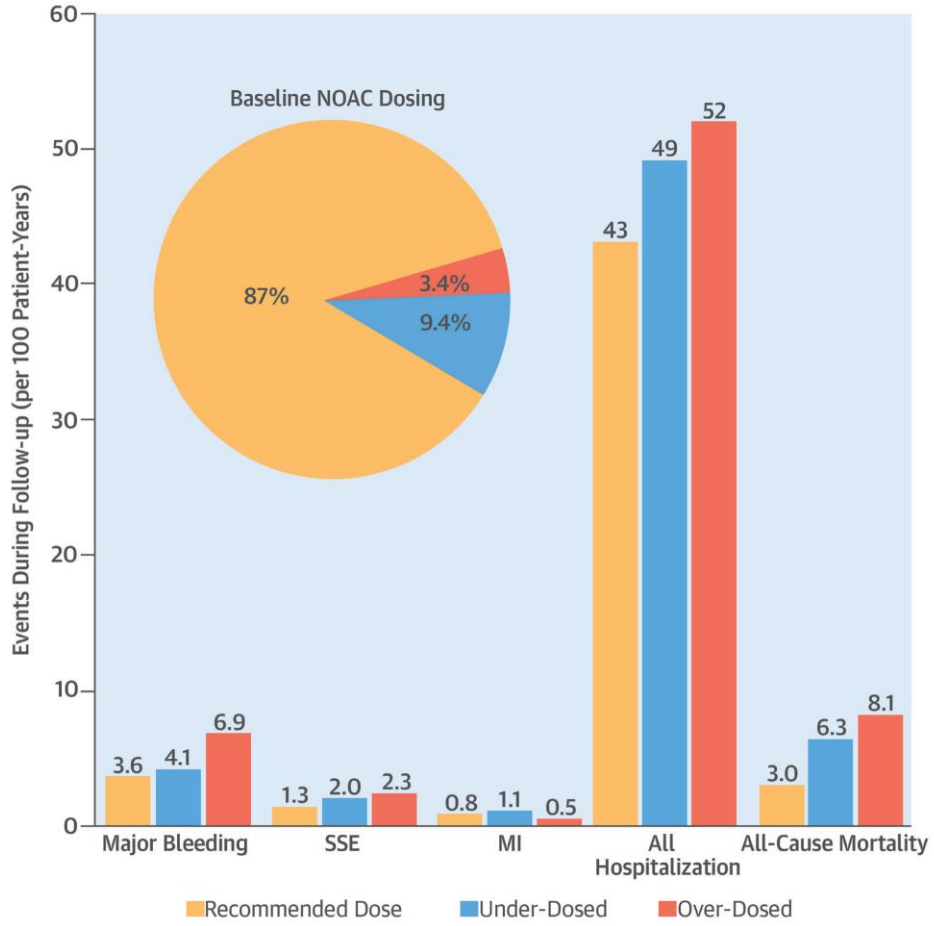
CODE-AF = COmparison study of Drugs for symptom control and complication prEvention of AF

Lee SR, et al. Yonsei Med J. 2019 Mar;60(3):277-284.

서울아산병원 Asan Medical Center

울산대학교

Impact of off-label underdosing



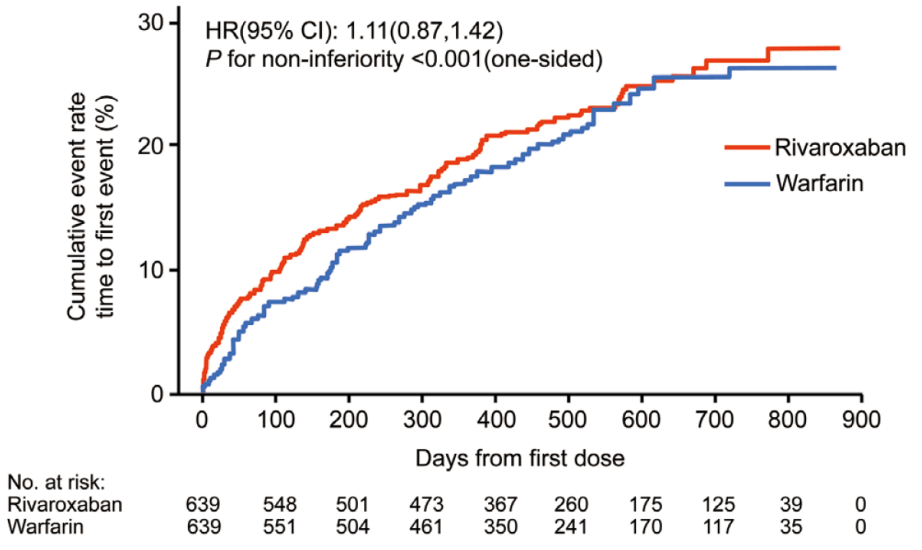
Steinberg, B.A. et al. J Am Coll Cardiol. 2016;68(24):2597-604.

- Inappropriate under or dosing associated with higher rate of clinical adverse events

JACC 2016;68:2597

Low dose NOACs are sufficient for Asians?

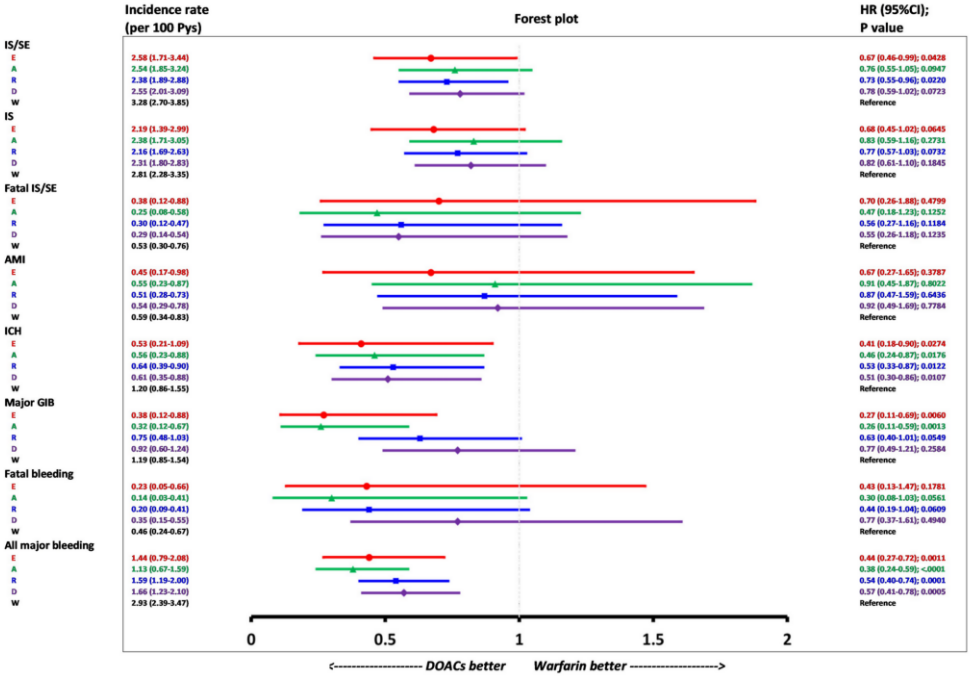
J-Rocket Study



Circ J 2012;76:2104

Taiwan cohort data

Reduced dose NOACs



Chest 2019, in press

- Real-world evidence of Korean population is important for its optimal use in our practice

서울아산병원
Asan Medical Center

울산대학교

Considerations for Optimal NOAC use

- Type of NOAC
- Chronic kidney disease or Creatinine clearance
- Age
- Body weight
- Comorbidities

Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asian Patients With Atrial Fibrillation

Myung-Jin Cha, MD; Eue-Keun Choi, MD, PhD; Kyung-Do Han, MD, PhD; So-Ryoung Lee, MD, PhD; Woo-Hyun Lim, MD; Seil Oh, MD, PhD; Gregory Y.H. Lip, MD

Background and Purpose—There are limited real-world data comparing the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in Asians with nonvalvular atrial fibrillation. We aimed to compare the effectiveness and safety between NOACs and warfarin users in the Korean atrial fibrillation population, with particular focus on high-risk patients.

Methods—Using the Korean National Health Insurance Service database, we analyzed the risk of ischemic stroke, intracranial hemorrhage (ICH) events, and all-cause death in NOAC users (n=11 611 total, n=5681 taking rivaroxaban, n=3741 taking dabigatran, and n=2189 taking apixaban) compared with propensity score-matched warfarin users (n=23 222) among patients with high-risk atrial fibrillation (CHA_2DS_2-VASc score ≥2) between 2014 and 2015.

Results—NOAC treatment was associated with similar risk of ischemic stroke and lower risk of ICH and all-cause mortality compared with warfarin. All 3 NOACs were associated with a similar risk of ischemic stroke and a lower risk of ICH compared with warfarin. Dabigatran and apixaban were associated with a lower risk of total mortality and the composite net clinical outcome (ischemic stroke, ICH, and all-cause death) compared with warfarin, whereas this was nonsignificant for rivaroxaban. Among previously oral anticoagulant–naive patients (n=23 262), dabigatran and apixaban were superior to warfarin for ICH prevention, whereas rivaroxaban and warfarin were associated with similar risk of ICH.

Conclusions—In real-world practice among a high-risk Asian atrial fibrillation population, all 3 NOACs demonstrated similar risk of ischemic stroke and lower risk of ICH compared with warfarin. All-cause mortality was significantly lower only with dabigatran and apixaban. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.018773.)**

Key Words: anticoagulants ■ Asian continental ancestry group ■ atrial fibrillation ■ intracranial hemorrhages ■ stroke ■ warfarin

American Heart Association | American Stroke Association

서울아산병원 Asan Medical Center

울산대학교

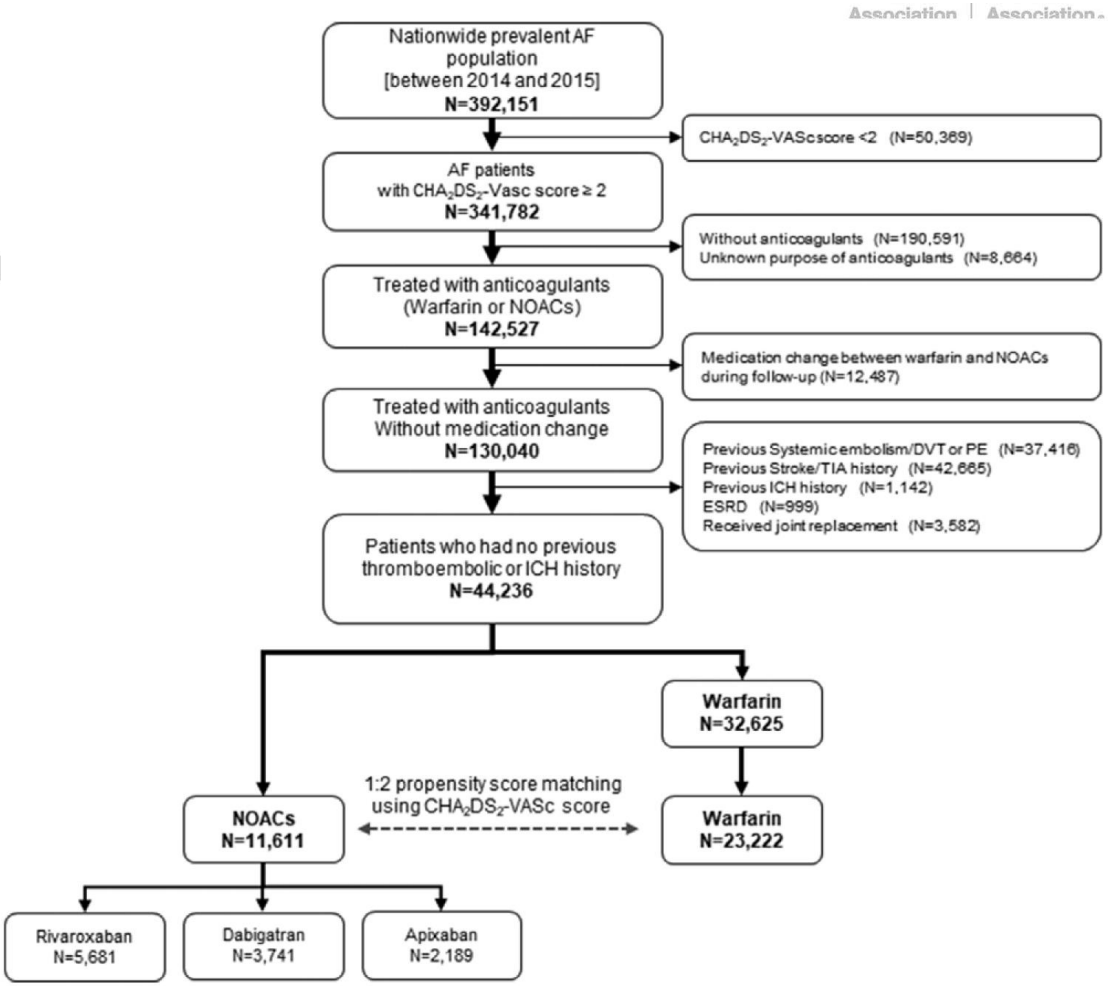
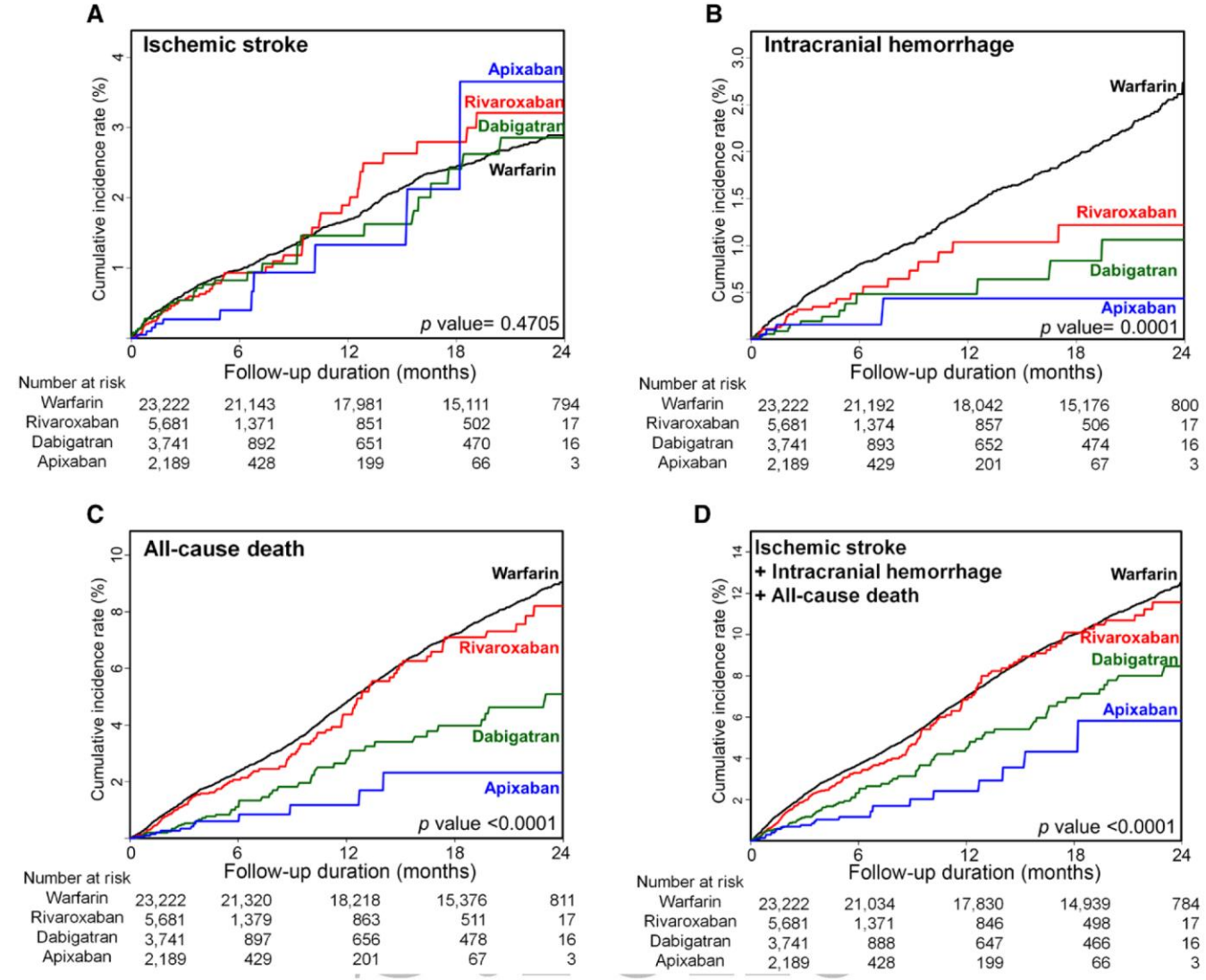

Nationwide prevalent AF population [between 2014 and 2015] N=392,151
CHA2DS2-VASc score <2 (N=50,369)
AF patients with CHA2DS2-Vasc score ≥ 2 N=341,782
Without anticoagulants (N=190,591)
Unknown purpose of anticoagulants (N=8,664)
Treated with anticoagulants (Warfarin or NOACs) N=142,527
Medication change between warfarin and NOACs during follow-up (N=12,487)
Treated with anticoagulants Without medication change N=130,040
Previous Systemic embolism/DVT or PE (N=37,416)
Previous Stroke/TIA history (N=42,665)
Previous ICH history (N=1,142)
ESRD (N=999)
Received joint replacement (N=3,582)
Patients who had no previous thromboembolic or ICH history N=44,236
Warfarin N=32,625
1:2 propensity score matching using CHA2DS2-VASc score
NOACs N=11,611
Warfarin N=23,222
Rivaroxaban N=5,681
Dabigatran N=3,741
Apixaban N=2,189

Table 1. Baseline Characteristics According to Treatment

Characteristics	Total	NOAC				Warfarin
		Rivaroxaban	Dabigatran	Apixaban	All	
No. in group	34 833	5681	3741	2189	11 611	23 222
Women	15 289 (43.9%)	2686 (47.3%)	1570 (42.0%)	998 (45.6%)	5254 (45.3%)	10 035 (43.1%)
Age, y	69.26±10.76	70.5±9.9	69.3±10.0	70.3±10.0	70.1±9.9	68.82±11.1
≥65	25 166 (72.3%)	4418 (77.8%)	2732 (73.0%)	1671 (76.3%)	8821 (76.0%)	16 345 (70.4%)
≥75	11 873 (34.1%)	2029 (35.7%)	1215 (32.5%)	801 (36.6%)	4045 (34.8%)	7828 (33.7%)
CHA_2DS_2-VASc score	3.57±1.31	3.60±1.32	3.51±1.28	3.57±1.29	3.57±1.31	3.57±1.31
2	8775 (25.2%)	1394 (24.5%)	993 (26.5%)	538 (24.6%)	2925 (25.2%)	5850 (25.2%)
3	9684 (27.8%)	1556 (27.4%)	1060 (28.3%)	612 (28.0%)	3228 (27.8%)	6456 (27.8%)
4	8061 (23.1%)	1310 (23.1%)	854 (22.8%)	523 (23.9%)	2687 (23.1%)	5374 (23.1%)
≥5	8313 (23.9%)	1421 (25.0%)	834 (22.3%)	516 (23.6%)	2771 (23.9%)	5542 (23.9%)
Hypertension	26 712 (76.7%)	4298 (75.7%)	2872 (76.8%)	1683 (76.9%)	8853 (76.3%)	17 859 (76.9%)
Diabetes mellitus	8914 (25.6%)	1353 (23.8%)	990 (26.5%)	517 (23.6%)	2860 (24.6%)	6054 (26.1%)
Dyslipidemia	14 690 (42.2%)	2456 (43.2%)	1719 (46.0%)	993 (45.4%)	5168 (44.5%)	9522 (41.0%)
Heart failure	17 052 (49.0%)	2519 (44.3%)	1682 (45.0%)	942 (43.0%)	5143 (44.3%)	11 909 (51.3%)
Myocardial infarction	1715 (4.9%)	243 (4.3%)	161 (4.3%)	115 (5.3%)	519 (4.5%)	1196 (5.2%)
Chronic obstructive pulmonary disease	7306 (21.0%)	1228 (21.6%)	751 (20.1%)	473 (21.6%)	2452 (21.1%)	4854 (20.9%)
Peripheral artery disease	5009 (14.4%)	945 (16.6%)	650 (17.4%)	335 (15.3%)	1930 (16.6%)	3079 (13.3%)
Follow-up, y	1.17±0.72	0.50±0.51	0.55±0.57	0.40±0.39	0.50±0.51	1.51±0.56

NOAC indicates non-vitamin K antagonist oral anticoagulants.



- First nation-wide cohort study evaluation outcomes after NOACs
- All 3 NOACs were at similar efficacy but lower risk of ICH

ESC European Society of Cardiology

Europace (2017) **19**, iv1–iv9
doi:10.1093/europace/eux247

CLINICAL RESEARCH

Optimal dose of dabigatran for the prevention of thromboembolism with minimal bleeding risk in Korean patients with atrial fibrillation

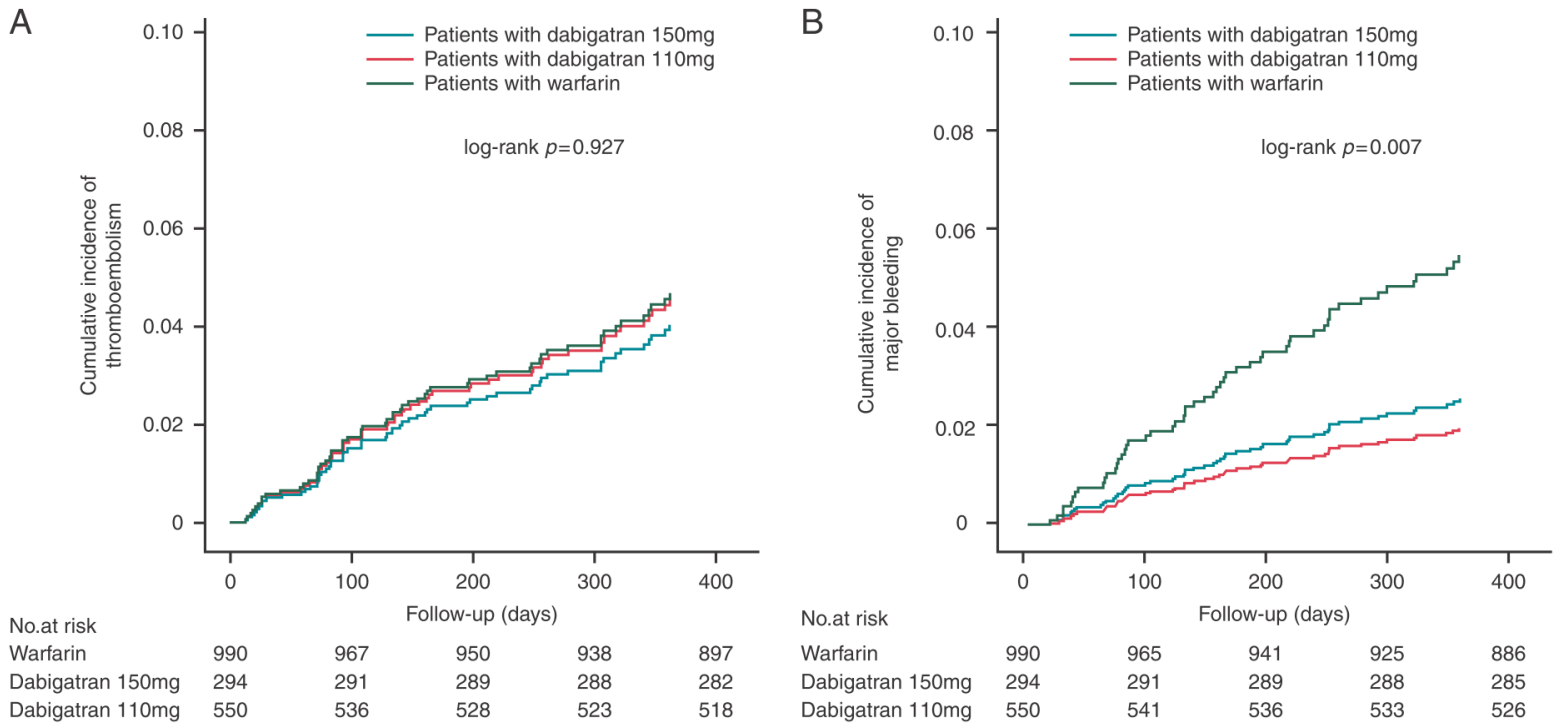
Ki Hong Lee, Hyung Wook Park*, Nuri Lee, Dae Young Hyun, Jumin Won, Sung Sik Oh, Hyuk Jin Park, Yongcheol Kim, Jae Yeong Cho, Min Chul Kim, Doo Sun Sim, Hyun Joo Yoon, Nam Sik Yoon, Kye Hun Kim, Young Joon Hong, Ju Han Kim, Youngkeun Ahn, Myung Ho Jeong, Jong Chun Park, and Jeong Gwan Cho

Cardiovascular Medicine, Chonnam National University Hospital, 42 Jaebong-ro, Dong-gu, Gwangju 61469, South Korea

Received 4 April 2017; editorial decision 29 June 2017; accepted 5 July 2017

서울아산병원 Asan Medical Center

울산대학교



- Standard (150mg) and even low (110mg) NOACs displayed similar efficacy and superior safety.
- Initial report regarding optimal NOAC dosing issue in Korean population

Outcomes After Use of Standard- and Low-Dose Non–Vitamin K Oral Anticoagulants in Asian Patients With Atrial Fibrillation

Min Soo Cho, MD, PhD*; Ji Eun Yun, PhD*; Ji Jeong Park, MPH; Yun Jung Kim, MPH; Jessie Lee, MPH; Hyungmin Kim, MPH; Duk-Woo Park, MD, PhD; Gi-Byoung Nam, MD, PhD

Background and Purpose—Limited data are available describing the relative effectiveness, safety, and optimal dosing of non–vitamin K antagonist oral anticoagulants (NOACs) for treatment of nonvalvular atrial fibrillation in East Asian patients. We tried to compare effectiveness and safety outcomes of standard- and low-dose NOACs and warfarin in this population.

Methods—Using nationwide administrative claims-based datasets from the Korean National Health Insurance Service Database (July 1, 2015, to December 31, 2016), this study comprised 56 504 anticoagulation-naive nonvalvular atrial fibrillation patients with high thromboembolic risk (CHA_2DS_2-VASc score, ≥2) treated with oral anticoagulants. Main study outcomes included thromboembolic events (ischemic stroke or systemic embolism), major bleeding, and mortality.

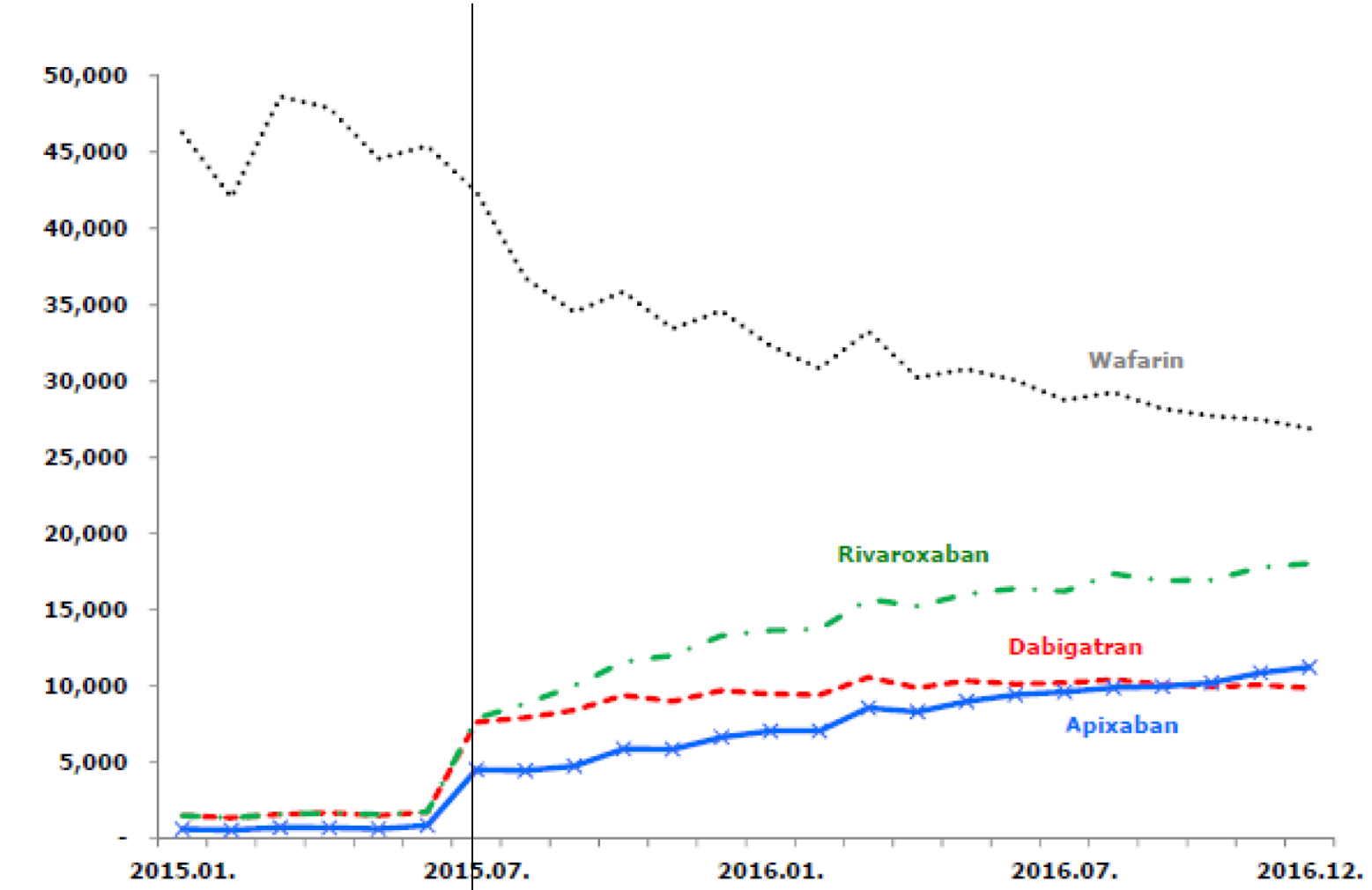
Results—Among the study patients, 10 409 (18.4%) received warfarin and 46 095 (81.6%) were treated with NOACs: dabigatran (n=12 593; 22.3%), rivaroxaban (n=21 000; 37.2%), and apixaban (n=12 502; 22.1%). Low-dose NOAC (75.1% dabigatran, 59.7% rivaroxaban, and 62.7% apixaban) was more frequently used than standard-dose NOAC. During median follow-up of 15.0 months, each NOAC was associated with significantly lower risk of thromboembolic events (hazard ratio [HR], 0.76; 95% CI, 0.75–0.81 for dabigatran; HR, 0.74; 95% CI, 0.65–0.83 for rivaroxaban; and HR, 0.68; 95% CI, 0.59–0.78 for apixaban). Regarding safety outcomes, dabigatran (HR, 0.81; CI, 0.69–0.95) and apixaban (HR, 0.67; CI, 0.56–0.79) were associated with lower risk of major bleeding but not with rivaroxaban (HR, 0.96; CI, 0.84–1.11). Among adults <75 years of age without chronic kidney disease, use of low-dose apixaban did not demonstrate clinical benefit over warfarin with respect to thromboembolic events (HR, 0.99; CI, 0.76–1.28) and mortality (HR, 0.85; CI, 0.62–1.16).

Conclusions—In this cohort of East Asian patients with nonvalvular atrial fibrillation, NOACs were associated with better effectiveness and safety outcomes versus warfarin. Lower NOAC doses were more often used, but an unjustified underdosing of apixaban seems to result in lower clinical benefit. **(*Stroke*. 2019;50:110-118. DOI: 10.1161/STROKEAHA.118.023093.)**

Key Words: adult ■ anticoagulants ■ atrial fibrillation ■ brain ischemia ■ hemorrhage

서울아산병원 Asan Medical Center

울산대학교



SNU data

AMC+NECA

서울아산병원
Asan Medical Center

울산대학교

Study population

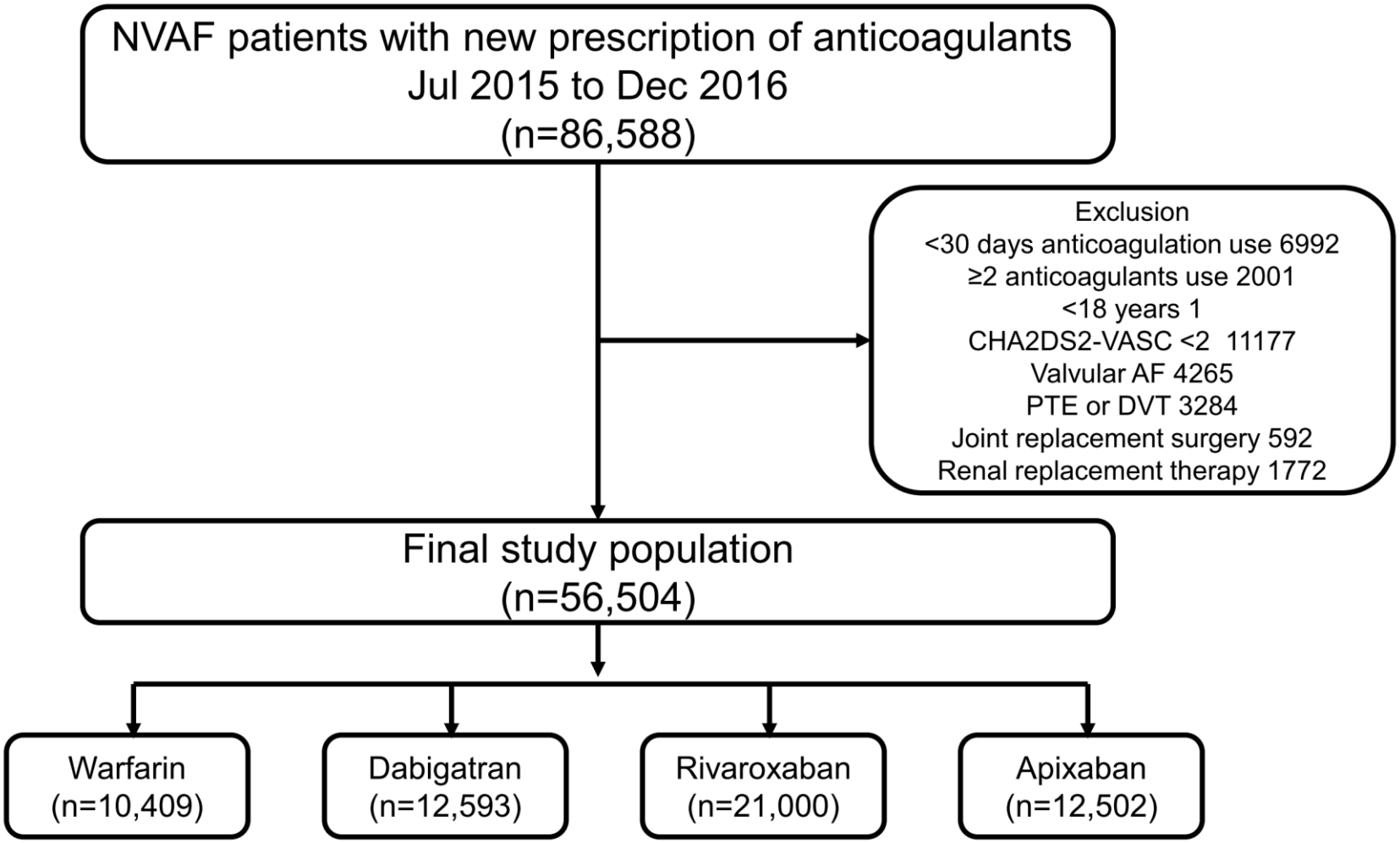


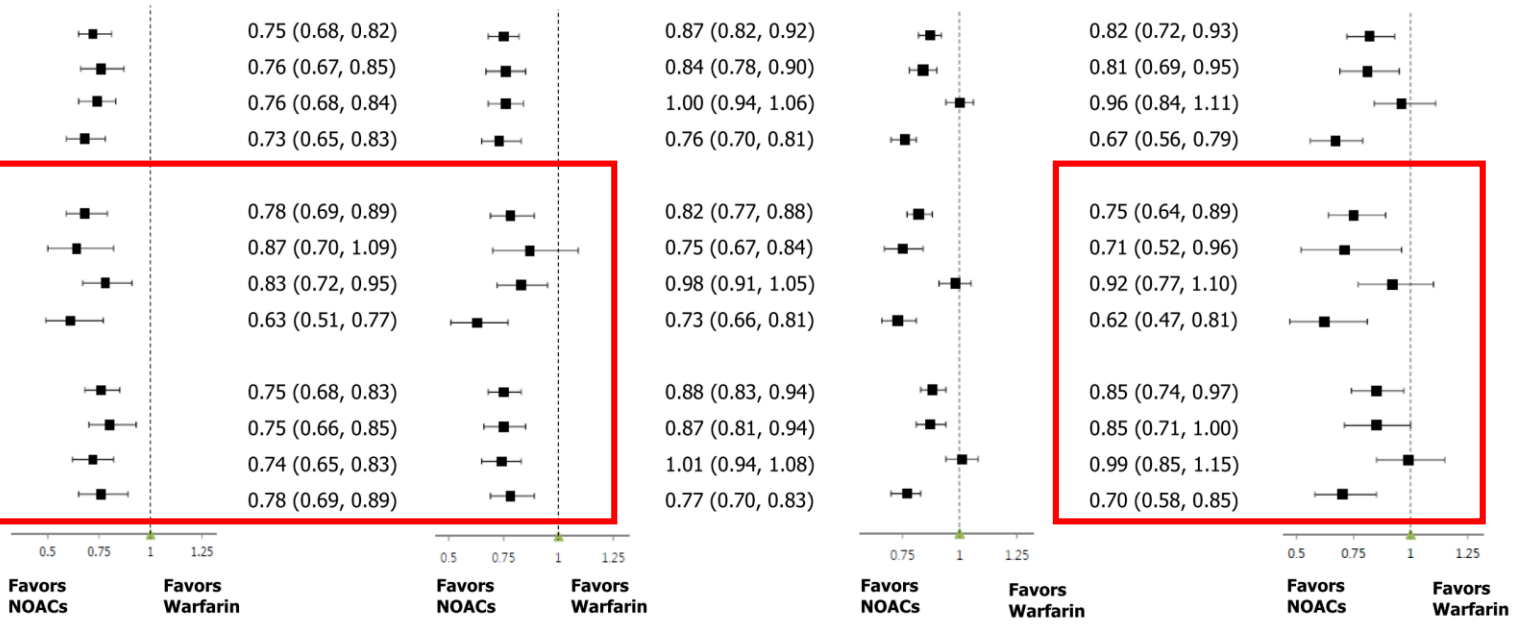
Table 1. Baseline Characteristics of Patients With Atrial Fibrillation According to the Type of Anticoagulant

Characteristics	Warfarin (n=10 409)	Dabigatran (n=12 593)	Rivaroxaban (n=21 000)	Apixaban (n=12 502)	*P* Value
Age, y	70.8±11.0	72.9±8.9	73.8±8.8	74.3±8.9	<0.0001
Men	5617 (54.0)	6755 (53.6)	10 695 (50.9)	5967 (47.7)	<0.0001
BMI, kg/m^2	24.4±2.8	24.7±2.8	24.6±2.9	24.4±2.8	<0.0001
Current smoker	864 (8.3)	895 (7.1)	1364 (6.5)	722 (5.8)	<0.0001
Baseline comorbidities					
Hypertension	9022 (86.7)	10 950 (87.0)	18 447 (87.8)	10 739 (85.9)	<0.0001
Diabetes mellitus	5034 (48.4)	5728 (45.5)	9547 (45.5)	5657 (45.3)	<0.0001
Stroke/TIA/TE	2842 (27.3)	3056 (24.3)	4440 (21.1)	2998 (24.0)	<0.0001
Intracranial hemorrhage	124 (1.2)	159 (1.3)	235 (1.1)	210 (1.7)	<0.0001
Congestive heart failure	2371 (22.8)	2269 (18.0)	4295 (20.5)	2576 (20.6)	<0.0001
Vascular disease	1337 (12.8)	1491 (11.8)	2420 (11.5)	1474 (11.8)	0.0078
CKD	782 (7.5)	381 (3.0)	767 (3.7)	636 (5.1)	<0.0001
Prior coronary stenting	139 (1.3)	165 (1.3)	249 (1.2)	149 (1.2)	0.5689
Prior bypass surgery	14 (0.1)	15 (0.1)	32 (0.2)	15 (0.1)	0.8211
Charlson comorbidity index	1.3±0.6	1.2±0.6	1.2±0.6	1.2±0.6	<0.0001
CHA_2DS_2-VASc score	3.5±1.2	3.5±1.2	3.6±1.2	3.7±1.2	<0.0001
Modified HAS-BLED score	2.6±1.0	2.5±0.9	2.5±0.9	2.5±0.9	0.0002
Concurrent medications					
Aspirin	1819 (17.5)	1193 (9.5)	1943 (9.3)	1153 (9.2)	<0.0001
ADP-2 inhibitor	976 (9.4)	64 (5.1)	1047 (5.0)	780 (6.2)	<0.0001
β-Blocker	5073 (48.7)	6158 (48.9)	10 161 (48.4)	6542 (52.3)	<0.0001
Calcium-channel blocker	4021 (38.6)	4966 (39.4)	8131 (38.7)	5191 (41.5)	<0.0001
ACE inhibitors or ARB	5362 (51.5)	6695 (53.2)	11 457 (54.6)	6466 (51.7)	<0.0001
Statin	4817 (46.3)	6361 (50.5)	9759 (46.5)	6168 (49.3)	<0.0001
Digoxin	2249 (21.6)	2270 (18.0)	4091 (19.5)	2032 (16.3)	<0.0001
Dose of NOAC					
Standard dose		3138 (24.9)	8601 (41.0)	4661 (37.3)	
Low dose		9455 (75.1)	12 399 (59.0)	7841 (62.7)	

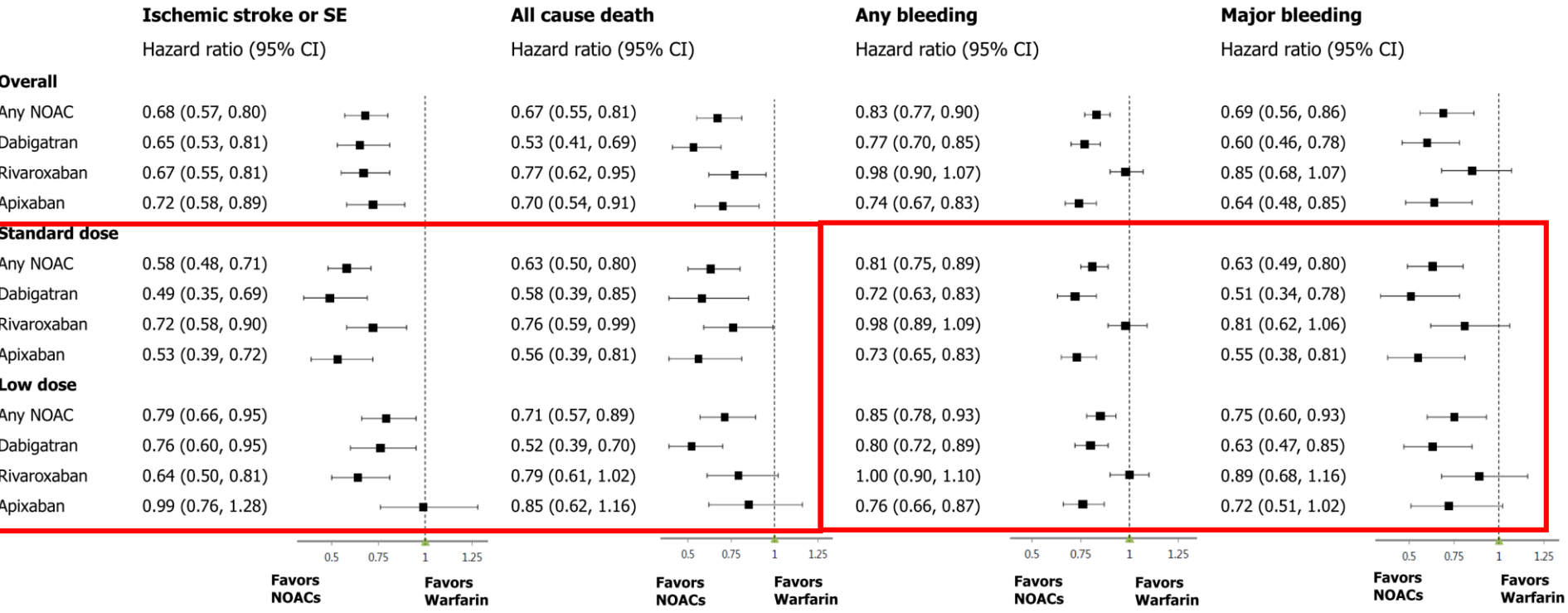
Data are presented as mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; NOAC, non–vitamin K antagonist oral anticoagulant; TE, thromboembolism; and TIA, transient ischemic attack.

Overall population

	Ischemic stroke or SE Hazard ratio (95% CI)	All cause death Hazard ratio (95% CI)	Any bleeding Hazard ratio (95% CI)	Major bleeding Hazard ratio (95% CI)
Overall				
Any NOAC	0.72 (0.65, 0.81)	0.75 (0.68, 0.82)	0.87 (0.82, 0.92)	0.82 (0.72, 0.93)
Dabigatran	0.76 (0.66, 0.87)	0.76 (0.67, 0.85)	0.84 (0.78, 0.90)	0.81 (0.69, 0.95)
Rivaroxaban	0.74 (0.65, 0.83)	0.76 (0.68, 0.84)	1.00 (0.94, 1.06)	0.96 (0.84, 1.11)
Apixaban	0.68 (0.59, 0.78)	0.73 (0.65, 0.83)	0.76 (0.70, 0.81)	0.67 (0.56, 0.79)
Standard dose				
Any NOAC	0.68 (0.59, 0.79)	0.78 (0.69, 0.89)	0.82 (0.77, 0.88)	0.75 (0.64, 0.89)
Dabigatran	0.64 (0.50, 0.82)	0.87 (0.70, 1.09)	0.75 (0.67, 0.84)	0.71 (0.52, 0.96)
Rivaroxaban	0.78 (0.67, 0.91)	0.83 (0.72, 0.95)	0.98 (0.91, 1.05)	0.92 (0.77, 1.10)
Apixaban	0.61 (0.49, 0.77)	0.63 (0.51, 0.77)	0.73 (0.66, 0.81)	0.62 (0.47, 0.81)
Low dose				
Any NOAC	0.76 (0.68, 0.85)	0.75 (0.68, 0.83)	0.88 (0.83, 0.94)	0.85 (0.74, 0.97)
Dabigatran	0.80 (0.70, 0.93)	0.75 (0.66, 0.85)	0.87 (0.81, 0.94)	0.85 (0.71, 1.00)
Rivaroxaban	0.72 (0.62, 0.82)	0.74 (0.65, 0.83)	1.01 (0.94, 1.08)	0.99 (0.85, 1.15)
Apixaban	0.76 (0.65, 0.89)	0.78 (0.69, 0.89)	0.77 (0.70, 0.83)	0.70 (0.58, 0.85)



<75 years without CKD



서울아산병원
Asan Medical Center

울산대학교

Conclusion

- All three types of NOACs were superior to warfarin with regard to thromboembolic events and mortality
- NOACs were generally safer than warfarin, whereas rivaroxaban showed a similar risk of bleeding
- There was a dose-dependent trend toward less effectiveness with lower doses of NOACs
- Lower-dose apixaban did not achieve a beneficial effect over warfarin among relatively young patients without CKD

Edoxaban in Asian Patients With Atrial Fibrillation

Effectiveness and Safety

So-Ryoung Lee, MD,[a] Eue-Keun Choi, MD, PhD,[b] Kyung-Do Han, PhD,[c] Jin-Hyung Jung, BSc,[c] Seil Oh, MD, PhD,[b] Gregory Y.H. Lip, MD[d,e,f]

ABSTRACT

BACKGROUND It is unclear whether edoxaban shows better risk reduction of ischemic stroke, bleeding, and all-cause mortality than warfarin in Asian patients with nonvalvular atrial fibrillation (AF).

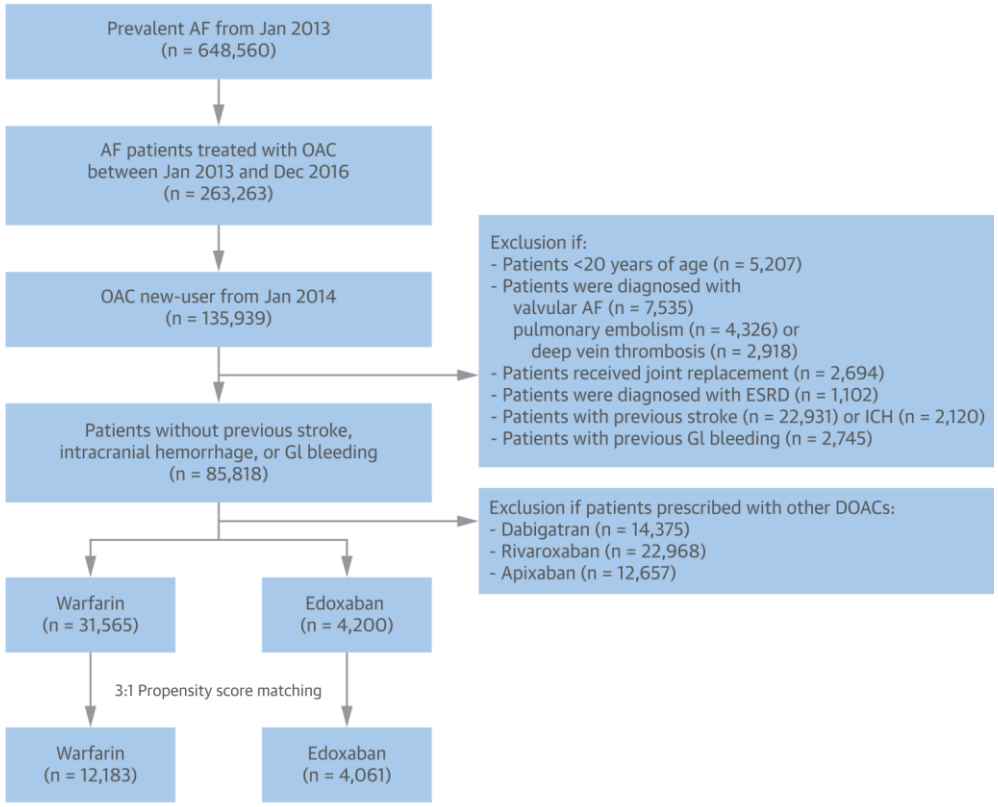
OBJECTIVES This study compared the effectiveness and safety of edoxaban with those of warfarin in a Korean population with AF.

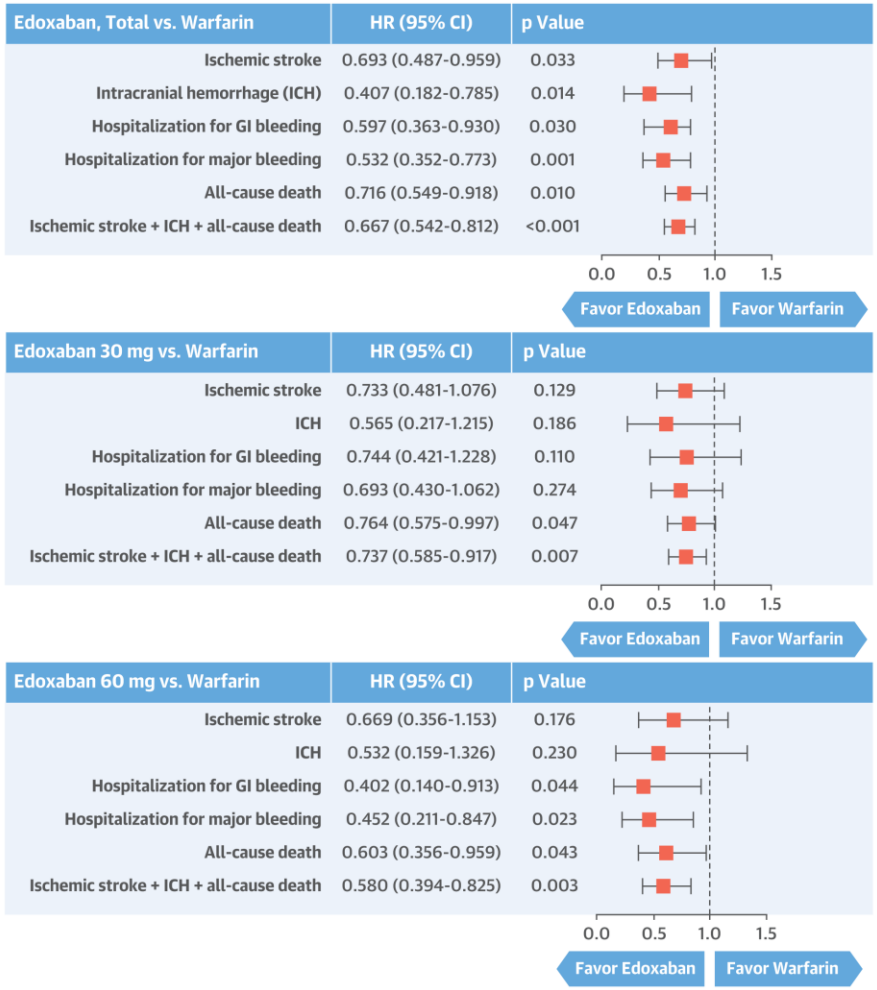
METHODS Using the Korean National Health Insurance Service database, we included new users of edoxaban and warfarin in patients with AF from January 2014 to December 2016 (n = 4,200 on edoxaban, and n = 31,565 on warfarin) and analyzed the risk of ischemic stroke, intracranial hemorrhage (ICH), hospitalization for gastrointestinal (GI) bleeding, hospitalization for major bleeding, and all-cause death. The propensity score matching method was used to balance covariates across edoxaban and warfarin users.

RESULTS We compared a 1:3 propensity score–matched cohort of patients with AF who were new users of edoxaban and warfarin (n = 4,061 and n = 12,183, respectively). Baseline characteristics were balanced between the 2 groups (median age 72 years; median CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female)] score 3). Edoxaban users had a significantly lower risk of ischemic stroke (hazard ratio [HR]: 0.693; 95% confidence interval [CI]: 0.487 to 0.959), ICH (HR: 0.407; 95% CI: 0.182 to 0.785), hospitalization for GI bleeding (HR: 0.597; 95% CI: 0.363 to 0.930), hospitalization for major bleeding (HR: 0.532; 95% CI: 0.352 to 0.773), and all-cause death (HR: 0.716; 95% CI: 0.549 to 0.918) than warfarin users. All subgroups (age, sex, CHA_2DS_2-VASc score, renal function, edoxaban dose) showed better clinical outcomes with edoxaban than with warfarin.

CONCLUSIONS In this real-world Asian population with AF, edoxaban might be associated with reduced risk of ischemic stroke, major bleeding, and all-cause death compared with warfarin. These benefits were consistent across various high-risk subgroups. (J Am Coll Cardiol 2018;72:838–53) © 2018 by the American College of Cardiology Foundation.

서울아산병원 Asan Medical Center
울산대학교





Lee, S.-R. et al. J Am Coll Cardiol. 2018;72(8):838-53.

- Edoxaban associated with reduced risk of ischemic stroke, major bleeding, and all-cause death
- First real-world evidence on the outcomes after Edoxaban use

서울아산병원
Asan Medical Center

울산대학교

Impact of Renal Function on Outcomes With Edoxaban in Real-World Patients With Atrial Fibrillation

A Nationwide Cohort Study

Hee Tae Yu, MD, PhD*; Pil-Sung Yang, MD*; Tae-Hoon Kim, MD; Eunsun Jang, MS; Daehoon Kim, MD; Jae-Sun Uhm, MD, PhD; Jong-Youn Kim, MD, PhD; Hui-Nam Pak, MD, PhD; Moon-Hyoung Lee, MD, PhD; Gregory Y.H. Lip, MD†; Boyoung Joung, MD, PhD†

Background and Purpose—Edoxaban is a direct oral factor Xa inhibitor with proven efficacy and safety among patients with atrial fibrillation. Concerns have been raised about an excess of stroke among patients with creatinine clearance (CrCl) >95 mg/mL treated with edoxaban. We assessed the real-world effectiveness and safety of edoxaban in atrial fibrillation patients in relation to CrCl.

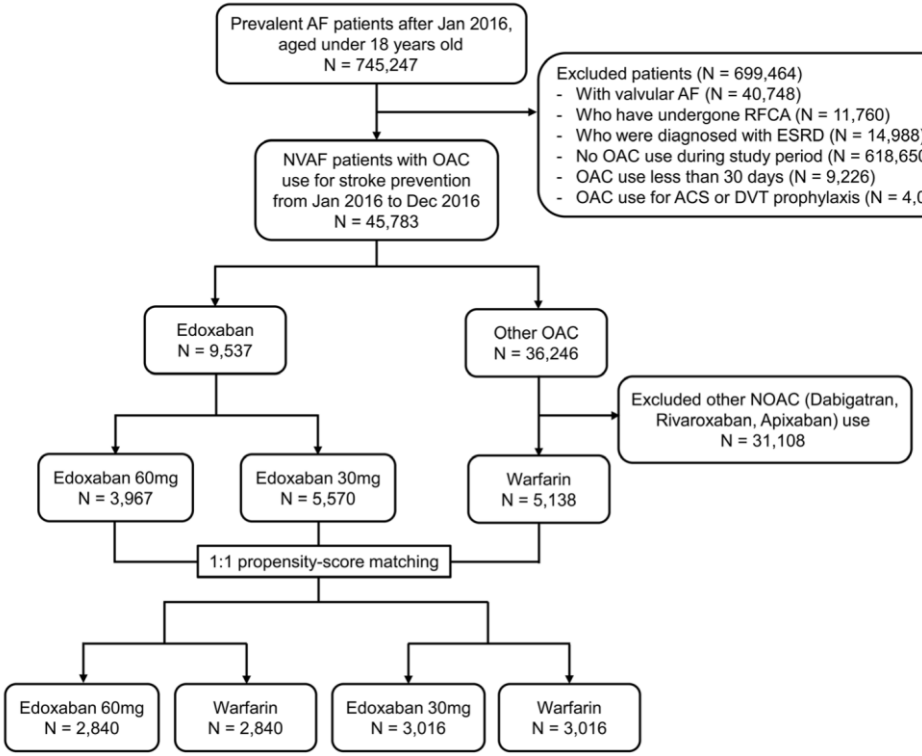
Methods—In the Korean National Health Insurance Service data during the period from January to December 2016, we identified 9537 edoxaban-treated patients. Effectiveness and safety outcomes were compared between high-dose edoxaban regimen (HDER, 60 mg daily, n=2840) and a propensity score–matched warfarin group (n=2840) and between low-dose edoxaban regimen (LDER, 30 mg daily, n=3016) and matched warfarin group (n=3016).

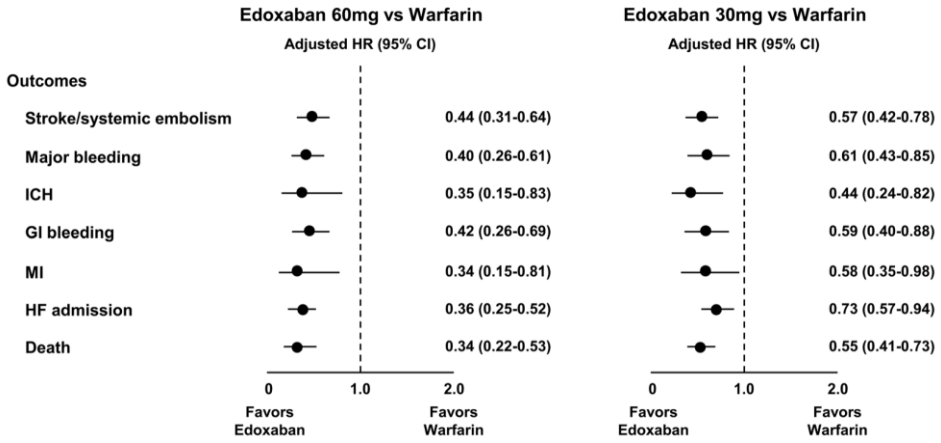
Results—The median follow-up period was 5.0 months (interquartile range, 2–7 months). The mean age was 68 years, and 63% were men in HDER group, and the mean age was 73 years, and 52% were men in LDER group. Compared with warfarin, both HDER and LDER significantly decreased the risk for ischemic stroke or systemic embolism (S/SE; HDER: adjusted hazard ratio [aHR], 0.44; 95% CI, 0.31–0.64; LDER: aHR, 0.57; 95% CI, 0.42–0.78), major bleeding (HDER: aHR, 0.40; 95% CI, 0.26–0.61; LDER: aHR, 0.61; 95% CI, 0.43–0.85), and mortality (HDER: aHR, 0.34; 95% CI, 0.22–0.53; LDER: aHR, 0.55; 95% CI, 0.41–0.73). In patients with CrCl >95 mL/min, the incidence of S/SE was higher with LDER than warfarin and comparable between HDER and warfarin group. There was lower effectiveness for the prevention of S/SE with LDER compared with warfarin at higher CrCl levels (*P* for interaction=0.023).

Conclusions—In real-world practice, both doses of edoxaban were associated with reduced risks for S/SE, major bleeding, and mortality compared with warfarin. LDER had lower effectiveness for the prevention of S/SE compared with warfarin at higher levels of CrCl (>95 mL/min). **(*Stroke*. 2018;49:2421-2429. DOI: 10.1161/STROKEAHA.118.021387.)**

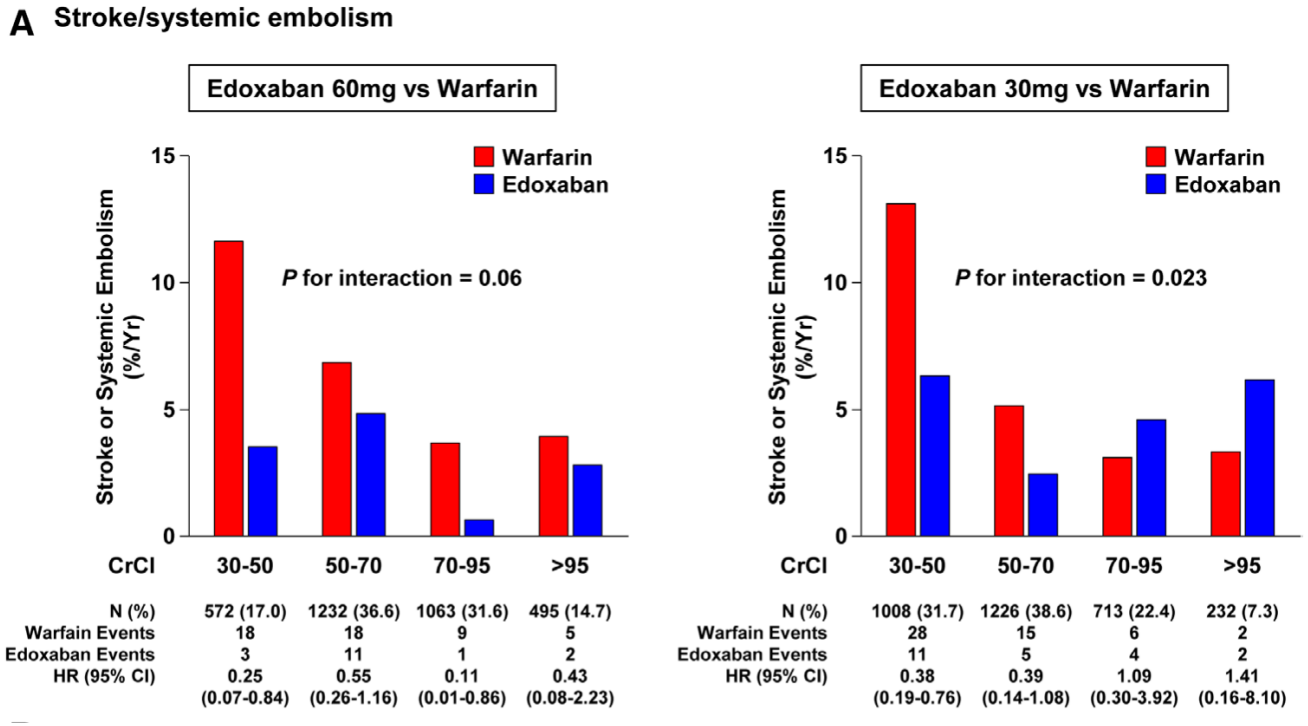
Key Words: atrial fibrillation ■ edoxaban ■ heart failure ■ myocardial infarction ■ stroke ■ warfarin

Study flow and clinical outcomes





Subgroup analysis



- Decreased efficacy when low dose edoxaban is inappropriately used in patient with normal - supernormal creatinine clearance
- Plausible hypothesis for explaining decreased NOAC effectiveness in supernormal creatinine clearance

Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight

So-Ryoung Lee, MD,[a] Eue-Keun Choi, MD, PhD,[b] Chan Soon Park, MD,[c] Kyung-Do Han, PhD,[d] Jin-Hyung Jung, BSc,[d] Seil Oh, MD, PhD,[b] Gregory Y.H. Lip, MD[e,f]

ABSTRACT

BACKGROUND It is unclear whether the overall effectiveness and safety of direct oral anticoagulants (DOACs) are consistent in patients with nonvalvular atrial fibrillation (AF) and extremely low body weight (<50 kg).

OBJECTIVES This study compared DOACs with warfarin in AF patients with low body weight.

METHODS Using data from the Korean National Health Insurance Service database from January 2014 to December 2016, AF patients with body weight ≤60 kg and who were treated with oral anticoagulants (n = 14,013 taking DOACs and n = 7,576 taking warfarin) were included and examined for ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal bleeding, major bleeding, all-cause death, and composite outcome. The propensity score weighting was used to balance the 2 groups.

RESULTS Baseline characteristics were well balanced between the 2 groups (mean age 73 years, mean CHA_2DS_2-VASc score 4, and 28% of patients weighed <50 kg). DOACs were associated with lower risks of ischemic stroke (hazard ratio [HR]: 0.591; 95% confidence interval [CI]: 0.510 to 0.686) and major bleeding (HR: 0.705; 95%: CI 0.601 to 0.825), which were caused by a reduction in ICH (HR: 0.554; 95% CI: 0.429 to 0.713) compared with warfarin. DOAC improved the net clinical benefit compared with warfarin (HR for composite outcome: 0.660; 95% CI: 0.606 to 0.717), and this was consistent in patients who weighed <50 kg (HR for composite outcome: 0.665; 95% CI: 0.581 to 0.762).

CONCLUSIONS In this real-world Asian AF population with low body weight, DOACs showed better effectiveness and safety than warfarin. These results were consistent in patients with extremely low body weight. Regular dosages of DOACs showed comparable results as reduced dosages of DOACs in both effectiveness and safety.
(J Am Coll Cardiol 2019;73:919–31) © 2019 by the American College of Cardiology Foundation.

서울아산병원 Asan Medical Center

울산대학교

Study population

FIGURE 1 Study Population Enrollment Flow

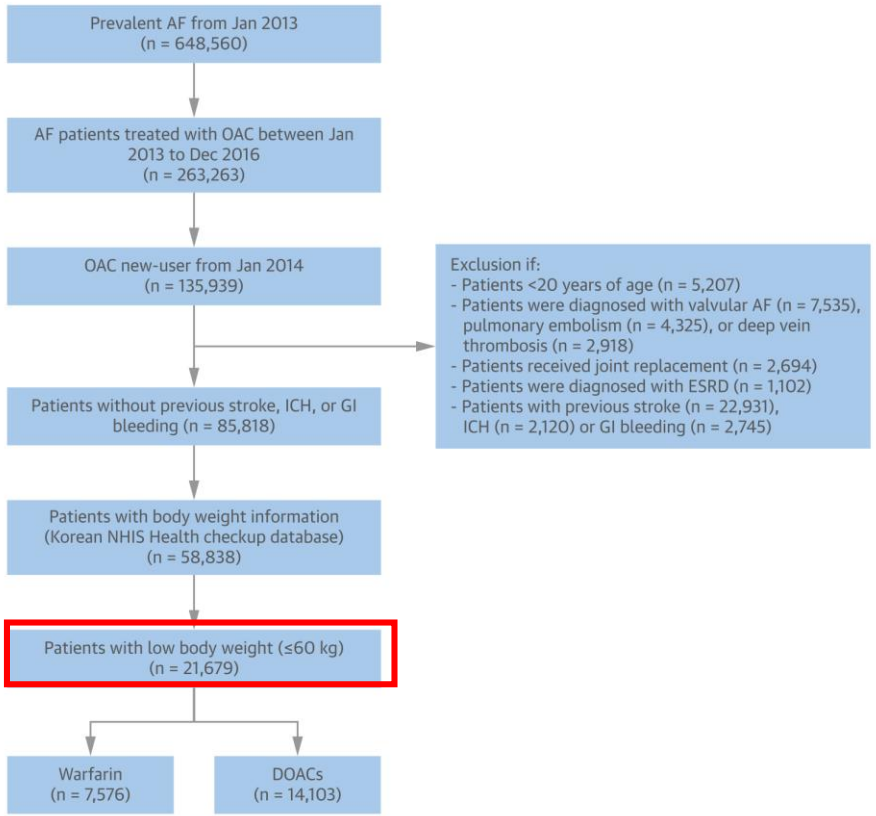
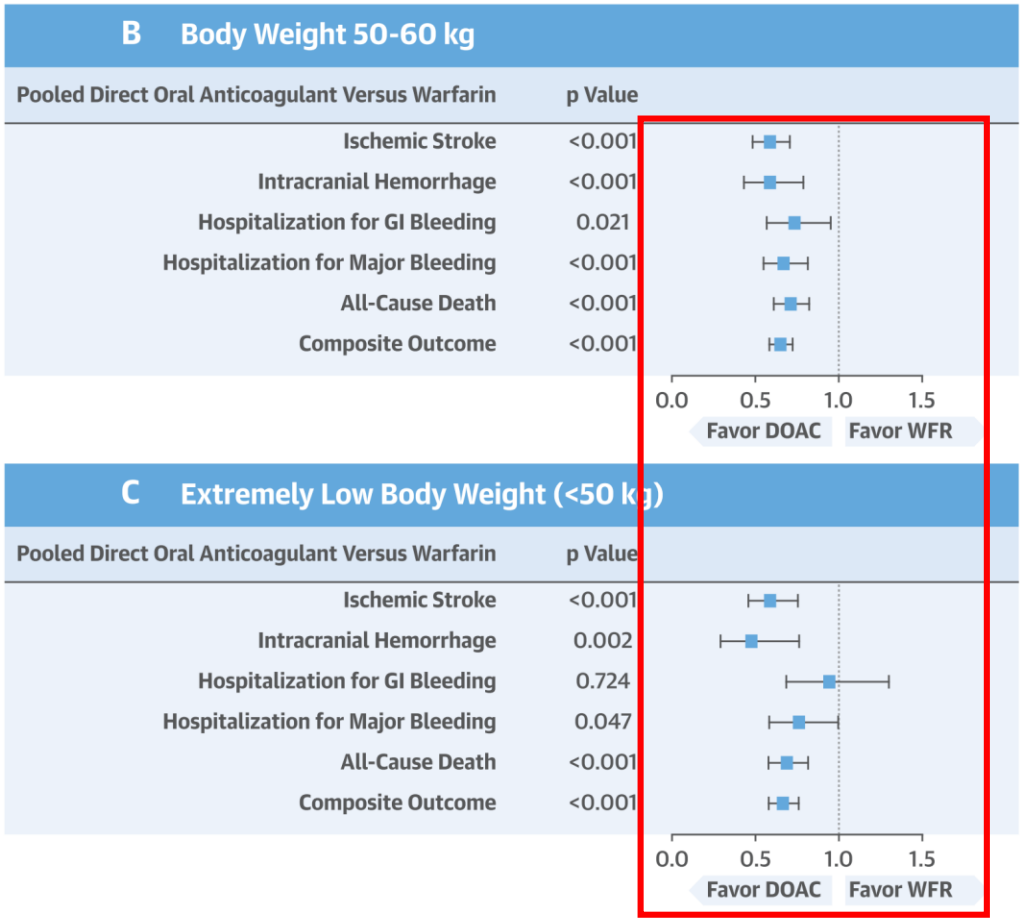


TABLE 1 Baseline Characteristics of Patients Using Warfarin Versus DOACs

	Propensity Score Weighting					
	Before			After (With 5% Trimming)		
	DOACs (n = 14,103)	Warfarin (n = 7,575)	ASD	DOACs (n = 12,810)	Warfarin (n = 6,692)	ASD
Age, yrs	73.4 ± 8.1	70.1 ± 10.8	0.348	72.6 ± 7.4	72.9 ± 8.5	0.043
<65	13	28		14	17	
65-74	39	33		43	36	
≥75	48	39		43	47	
Men	31	34	0.095	32	32	0.009
CHA_2DS_2-VASc score	3.91 ± 1.61	3.86 ± 1.87	0.031	3.92 ± 1.64	3.97 ± 1.83	0.032
0-1	5	11		6	9	
2-3	36	33		36	32	
≥4	59	56		58	59	
Body weight, kg	53.2 ± 5.5	53.3 ± 5.5	0.010	53.2 ± 5.5	53.2 ± 5.6	0.002
50-60	72	72		72	72	
<50	28	28		28	28	
Body mass index, kg/m^2	22.3 ± 2.5	22.1 ± 2.5	0.116	22.3 ± 2.5	22.3 ± 2.5	0.007
CrCl, ml/min	79.7 ± 35.1	80.1 ± 32.7	0.011	78.9 ± 22.7	78.6 ± 20.4	0.010
Hypertension	67	67	0.003	68	68	0.003
Diabetes mellitus	18	18	0.004	19	19	0.010
Dyslipidemia	38	36	0.048	38	39	0.013
Heart failure	32	43	0.223	36	36	0.013
Previous MI	3	5	0.088	3	4	0.025
PAD	19	17	0.045	18	18	0.007
COPD	21	24	0.065	22	23	0.012
DOAC dose						
Regular dose*	38	–	–	40	–	-
Reduced dose†	62	–	–	60	–	-

서울아산병원
Asan Medical Center

NOAC vs Warfarin in low body weight



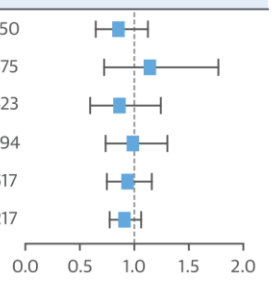
- NOAC is better than warfarin in patients with low body weight

Regular vs. reduced dose

B

Body Weight 50-60 kg

Regular Dose vs Reduced Dose	HR* (95% CI)	p Value
Ischemic Stroke	0.852 (0.644-1.119)	0.250
Intracranial Hemorrhage	1.136 (0.724-1.765)	0.575
Hospitalization for GI Bleeding	0.862 (0.595-1.236)	0.423
Hospitalization for Major Bleeding	0.981 (0.736-1.300)	0.894
All-Cause Death	0.932 (0.748-1.155)	0.517
Composite Outcome	0.907 (0.775-1.059)	0.217

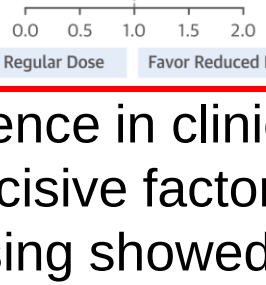


Favor Regular Dose | Favor Reduced Dose

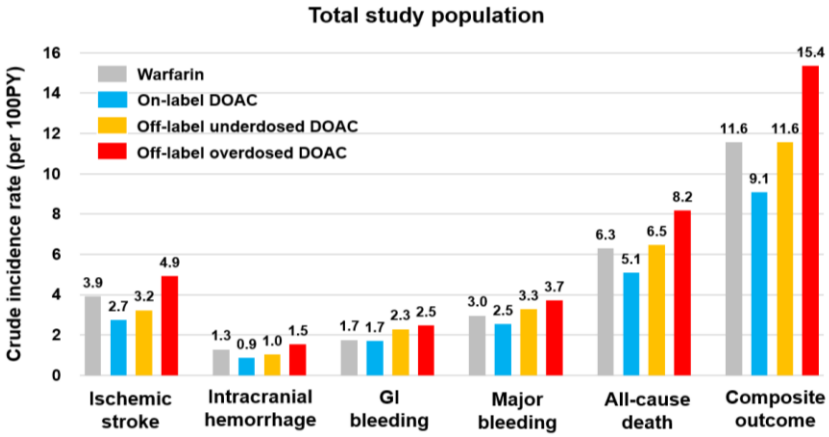
C

Extremely Low Body Weight (<50 kg)

Regular Dose vs Reduced Dose	HR* (95% CI)	p Value
Ischemic Stroke	0.961 (0.655-1.394)	0.836
Intracranial Hemorrhage	0.897 (0.378-2.004)	0.794
Hospitalization for GI Bleeding	0.998 (0.625-1.569)	0.991
Hospitalization for Major Bleeding	0.971 (0.642-1.451)	0.888
All-Cause Death	1.031 (0.775-1.365)	0.830
Composite Outcome	1.073 (0.866-1.324)	0.520



Favor Regular Dose | Favor Reduced Dose



- No significant difference in clinical outcomes between regular vs. reduced -> not a decisive factor
- On-label DOAC dosing showed a larger risk reduction in clinical outcomes than off-label underdosing and overdosing

서울아산병원 Asan Medical Center

울산대학교

Optimal Rivaroxaban Dose in Asian Patients With Atrial Fibrillation and Normal or Mildly Impaired Renal Function

So-Ryoung Lee, MD; Eue-Keun Choi, MD, PhD; Kyung-Do Han, PhD; Jin-Hyung Jung, BSc; Seil Oh, MD, PhD; Gregory Y.H. Lip, MD

Background and Purpose—Although rivaroxaban 15 mg (R15) was only given to patients with creatinine clearance (CrCl) ≤50 mL/min in the pivotal clinical trial, this dose has been commonly prescribed in Asian patients with nonvalvular atrial fibrillation regardless of renal function. There is a paucity of information on the clinical outcomes of R15 compared with rivaroxaban 20 mg (R20) in patients with CrCl ≥50 mL/min. This study aimed to examine the effectiveness and safety of 2 doses of rivaroxaban in Asian patients with atrial fibrillation and CrCl ≥50 mL/min.

Methods—Using the Korean National Health Insurance Service database, patients with atrial fibrillation and normal or mildly impaired renal function (CrCl ≥50 mL/min) and naive to rivaroxaban or warfarin were included from January 2014 to December 2016. Three separate 1:1 propensity score–matched cohorts were conducted: R20 versus warfarin (n=15 584), R15 versus warfarin (n=11 554), and R20 versus R15 (n=10 392). Hazard ratios for ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, major bleeding, all-cause death, and composite clinical outcome were analyzed.

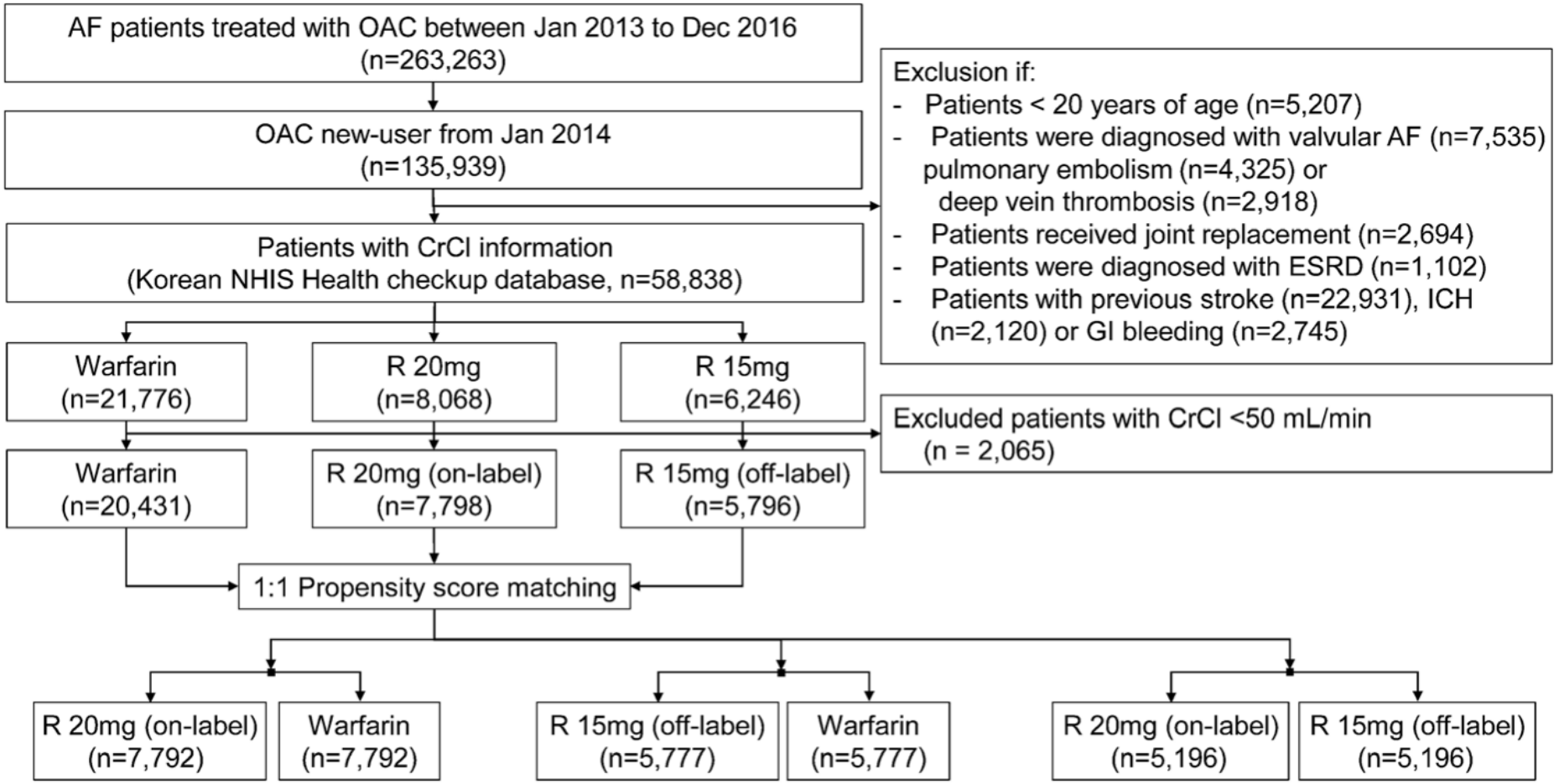
Results—Compared with warfarin, both R20 and R15 showed significantly lower risk for ischemic stroke, major bleeding (mainly through reduction of intracranial hemorrhage), and all-cause death. Compared with R15, R20 showed better results for the composite clinical outcome (hazard ratio, 0.852; 95% CI, 0.735–0.988). This benefit was consistently observed in patients aged ≥80 years and those <50 kg. R20 was associated with higher risk of major bleeding than R15 in patients with marginal CrCl (50–60 mL/min).

Conclusions—Among Asians with atrial fibrillation and CrCl ≥50 mL/min, both R20 and R15 were associated with reduced risk of ischemic stroke, intracranial hemorrhage, major bleeding, and all-cause death without significantly increased risk of gastrointestinal bleeding compared with warfarin. In patients with CrCl ≥50 mL/min, on-label R20 showed better results for the composite clinical outcome compared with off-label R15. **(*Stroke*. 2019;50:1140-1148. DOI: 10.1161/STROKEAHA.118.024210.)**

Key Words: anticoagulants ■ atrial fibrillation ■ creatinine ■ optimal dosage ■ rivaroxaban ■ warfarin

서울아산병원 Asan Medical Center

울산대학교

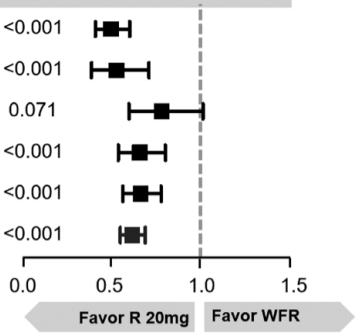

AF patients treated with OAC between Jan 2013 to Dec 2016 (n=263,263)
OAC new-user from Jan 2014 (n=135,939)
Patients with CrCl information (Korean NHIS Health checkup database, n=58,838)
Exclusion if:
- Patients < 20 years of age (n=5,207)
- Patients were diagnosed with valvular AF (n=7,535) pulmonary embolism (n=4,325) or deep vein thrombosis (n=2,918)
- Patients received joint replacement (n=2,694)
- Patients were diagnosed with ESRD (n=1,102)
- Patients with previous stroke (n=22,931), ICH (n=2,120) or GI bleeding (n=2,745)
Warfarin (n=21,776)
R 20mg (n=8,068)
R 15mg (n=6,246)
Excluded patients with CrCl <50 mL/min (n = 2,065)
Warfarin (n=20,431)
R 20mg (on-label) (n=7,798)
R 15mg (off-label) (n=5,796)
1:1 Propensity score matching
R 20mg (on-label) (n=7,792)
Warfarin (n=7,792)
R 15mg (off-label) (n=5,777)
Warfarin (n=5,777)
R 20mg (on-label) (n=5,196)
R 15mg (off-label) (n=5,196)

Clinical outcomes

A

*Warfarin served as the reference.

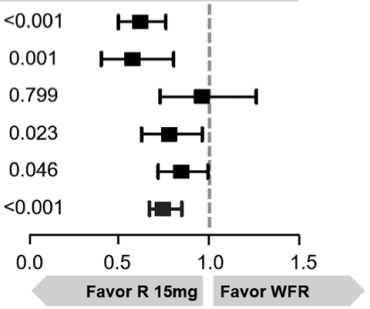
On-label R20 vs Warfarin	HR* (95% CI)	P-value
Ischemic stroke	0.497 (0.408-0.602)	<0.001
Intracranial hemorrhage	0.528 (0.386-0.713)	<0.001
Hospitalization for GI bleeding	0.784 (0.599-1.019)	0.071
Hospitalization for major bleeding	0.660 (0.538-0.806)	<0.001
All-cause death	0.665 (0.564-0.781)	<0.001
Composite clinical outcome	0.617 (0.550-0.691)	<0.001



B

*Warfarin served as the reference.

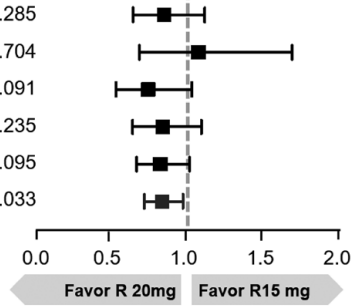
Off-label R15 vs Warfarin	HR* (95% CI)	P-value
Ischemic stroke	0.623 (0.503-0.766)	<0.001
Intracranial hemorrhage	0.579 (0.408-0.809)	0.001
Hospitalization for GI bleeding	0.965 (0.733-1.265)	0.799
Hospitalization for major bleeding	0.782 (0.631-0.966)	0.023
All-cause death	0.850 (0.723-0.997)	0.046
Composite clinical outcome	0.759 (0.675-0.853)	<0.001



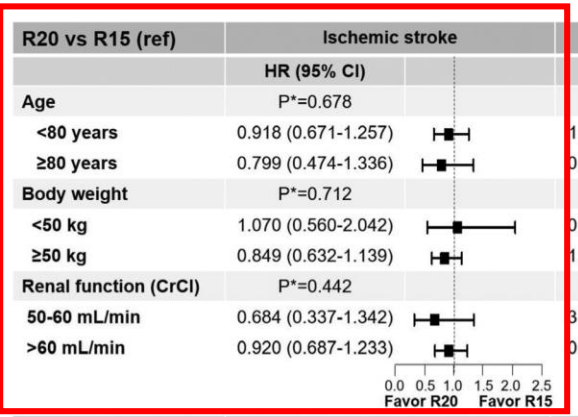
C

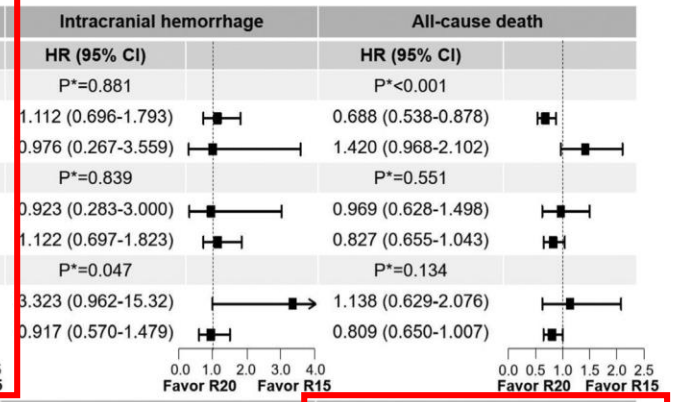
*R15 served as the reference.

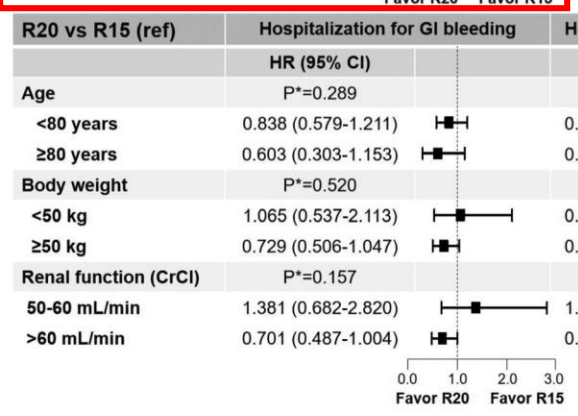
On-label R20 vs Off-label R15	HR* (95% CI)	P-value
Ischemic stroke	0.864 (0.662-1.129)	0.285
Intracranial hemorrhage	1.088 (0.703-1.699)	0.704
Hospitalization for GI bleeding	0.760 (0.551-1.045)	0.091
Hospitalization for major bleeding	0.855 (0.660-1.108)	0.235
All-cause death	0.840 (0.685-1.031)	0.095
Composite clinical outcome	0.852 (0.735-0.988)	0.033

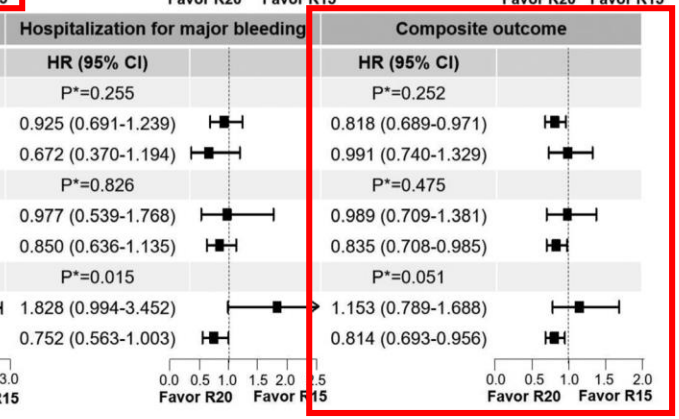


- Both R20 and R15 showed better clinical outcomes compared to warfarin
- Non significant trend toward lower risks of ischemic stroke in R20 compared to R15
- R20 showed better composite outcomes compared to R15 in patients with CrCl ≥50mL/min









- No significant difference in terms of SPAF between R20 and R15
- Trend of better composite outcomes in R20 than R15 in younger, normal weight, and normal CrCl

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

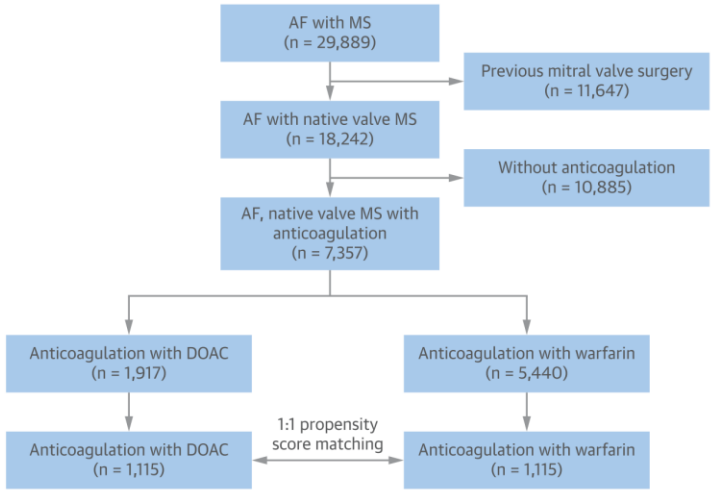
METHODS The study population was enrolled from the Health Insurance Review and Assessment Service (HIRA) database in the Republic of Korea, and it included patients who were diagnosed with mitral stenosis and AF and either were prescribed DOACs for off-label use or received conventional treatment with 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.

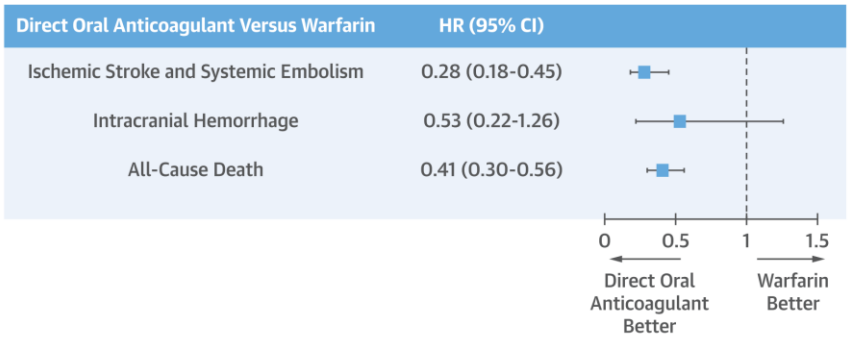
서울아산병원 Asan Medical Center
울산대학교

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.

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.

- NOAC use appears reasonable in patients with MS with AF
- Hypothesis generation on the NOAC use in previously contra-indicated population

Optimal NOAC use based on Korean RWE

- Type of drug
  - Strict label adherence is critical factor for Apixaban
  - It might be relatively liberal for Rivaroxaban
- Chronic kidney disease, Creatinine clearance
  - Label adherence is important
- Age
  - Standard Rivaroxaban dose is more appropriate for <80 years
- Body weight
  - Does not influence the 1) superiority of NOAC over warfarin 2) off-label underdosing
- Comorbidities
  - Need more data

Conclusion

- NOAC showed better effectiveness and safety than warfarin in Korean patients
- Label adherence is important for optimal clinical outcomes, especially for apixaban and edoxaban
- Valuable findings of Korean registry studies should be reaffirmed in future RCTs

Thank you for your attention!!!