Dabigatran, Rivaroxaban, and Warfarin in the Oldest Adults with Atrial Fibrillation in Taiwan

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OBJECTIVES: To compare the effectiveness and safety of reduced-dose dabigatran, reduced-dose rivaroxaban, and warfarin in individuals aged 85 and older with atrial fibrillation (AF).
DESIGN: Retrospective cohort study.
SETTING: Taiwan National Health Insurance claims database, 2011∼2015.
PARTICIPANTS: Individuals with AF aged 85 and older (mean 88.6) with incident use of oral anticoagulants between June 1, 2012 and May 31, 2015 (N=4,722; dabigatran 110 mg, n=1,489; rivaroxaban 15 mg/10 mg, n=1,736; warfarin, n=1,497).
MEASUREMENTS: Clinical outcomes included all-cause death, cardiovascular death, ischemic stroke, acute myocardial infarction, arterial embolism or thrombosis, intracranial hemorrhage, and gastrointestinal hemorrhage needing transfusion. Propensity score–matched analysis was performed, and the marginal proportional hazards model was used to estimate the relative risk of various clinical outcomes in a matched dabigatran-warfarin cohort (n=1,180 in each group) and a rivaroxaban-warfarin cohort (n=1,207 in each group)
RESULTS: Mean follow-up was 6.6 months for the overall population. Dabigatran group participants had lower risks of all-cause death (hazard ratio (HR)=0.59, 95% confidence interval (CI)=0.45–0.77) and cardiovascular death (HR=0.45, 95% CI=0.30–0.68) than warfarin group participants. Rivaroxaban users also had lower risks of all-cause death (HR=0.61, 95% CI=0.47–0.79) and cardiovascular death (HR=0.52, 95% CI=0.35–0.75) than warfarin users. Dabigatran users also had a lower risk of intracranial hemorrhage than warfarin users (HR=0.31, 95% CI=0.10–0.97).
CONCLUSION: Individuals with AF aged 85 and older who used reduced-dose dabigatran or reduced-dose rivaroxaban had statistically significantly lower all-cause mortality and cardiovascular mortality than those who used warfarin. Reduced-dose dabigatran was also associated with lower risk of intracranial hemorrhage than warfarin. **J Am Geriatr Soc 66:1567–1574, 2018.**

Key words: dabigatran; rivaroxaban; warfarin; effectiveness; safety; octogenarian

The risk of ischemic stroke is 5 times as high in individuals with atrial fibrillation (AF) than in those without.[1] Warfarin, the classic vitamin K antagonist, can reduce the risk of ischemic stroke by approximately 60%,[2] but the narrow therapeutic window and risk of bleeding complications associated with warfarin therapy have led to its being underused.[1] Direct oral anticoagulants (DOACs) such as dabigatran and rivaroxaban are approved for prevention of ischemic stroke and systemic embolism in individuals with nonvalvular AF, and their clinical efficacy and safety have been established in large-scale clinical trials.[3,4] Several investigations,[5–9] including one report from Taiwan,[10] using real-world databases have also supported that DOACs are more effectiveness and safer than warfarin, but most participants in those studies were aged 65 to 80, with a mean age of 70 to 75, with the landmark study enrolling individuals with AF aged 75 and older or 65 to 74 plus major cardiovascular comorbidities.[3] Thus, individuals aged 80 and older have been underrepresented in clinical studies.

The aim of this study was to provide real-world data to compare the effectiveness and safety of dabigatran, rivaroxaban, and warfarin in individuals aged 85 and older using a retrospective cohort study design based on claims data from the National Health Insurance (NHI) program in Taiwan.

METHODS

Data sources

Taiwan has provided compulsory, universal insurance coverage for all citizens since 1995. Identification number,

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sex, birthdate, dates of outpatient clinic visits, dates of hospital admissions and discharges, diagnoses, procedures administered, dates of pharmacy dispensing, and drugs dispensed are available in the NHI claims database. Diagnoses are coded according to the *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification* (ICD-9-CM) system. Validation studies of diagnosis codes for diabetes mellitus,[11] ischemic stroke,[12,13] and acute myocardial infarction[14] in Taiwan NHI claims database have been reported. An individual's record can be linked to the Taiwan National Death Registry to obtain the exact date of death and the officially speculated main cause of death coded according to the ICD-10 system. The NHI has reimbursed for dabigatran for stroke prevention in individuals with AF with an estimated glomerular filtration rate (eGFR) of 30 mL/min per 1.73 m^2 or higher since June 1 2012, and for rivaroxaban since February 1, 2013.

Ethical approval

To comply with Taiwanese privacy regulations, all personal identifiers were encrypted, and all data were analyzed anonymously. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of the National Taiwan University Hospital Hsin-Chu Branch (104–009-E), which waived requirement for informed consent.

Study design and cohort definition

We used the NHI claims database from 2011 to 2015. The study design was a retrospective cohort study. All adult beneficiaries aged 85 and older with a diagnosis of AF and flutter at initiation of study medications during the June 1, 2012, to May 31, 2015, enrollment period were identified. The date of the first prescription of dabigatran, rivaroxaban, or warfarin was operationally defined as the index date. Subjects with unknown sex; a diagnosis of deep vein thrombosis, pulmonary embolism, mitral stenosis, or renal failure; or having any procedure including valvular replacement, mitral commissurotomy, heart transplantation, or extracorporeal circulatory support within 6 months before the index date were excluded (Supplementary Table S1). We also excluded individuals receiving two different kinds of study medications on the index date, those receiving concomitant antiplatelet therapy, those whose DOAC dosage could not be clarified, and those who had been exposed to warfarin between January 1, 2011, and May 31, 2012. Because less than 4% (171/4893) of our study population received a standard dose of dabigatran (150 mg) or rivaroxaban (20 mg), only those receiving reduced-dose dabigatran (110 mg), reduced-dose rivaroxaban (15 or 10 mg), or warfarin were retained for analysis (Figure 1).

Clinical outcomes

Clinical outcomes included all-cause death, cardiovascular death, ischemic stroke, acute myocardial infarction, arterial embolism or thrombosis, intracranial hemorrhage, and gastrointestinal hemorrhage needing transfusion.[15] We also included osteoporotic fracture as the falsification analysis[9] to explore the possible residual confounding effect (Supplementary Table S1).

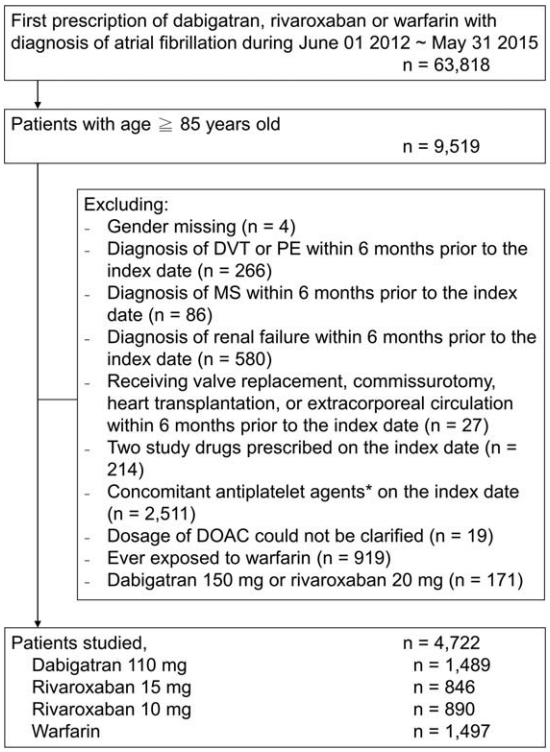

Figure 1. Participant flow diagram. *Antiplatelet agents included aspirin, clopidogrel, ticlopidine, ticagrelor, dipyridamole, and cilostazol. DOAC=direct oral anticoagulant; DVT=deep vein thrombosis; MS=mitral stenosis; PE=pulmonary embolism.

Exposures and follow-up

According to our analysis, individuals receiving rivaroxaban 15 mg or 10 mg had comparable risks of various clinical outcomes (Supplementary Table S2, Supplementary Figure S1), so rivaroxaban 15 and 10 mg were pooled into one group in this study. Thus, we defined study groups as reduced-dose dabigatran (110 mg), reduced-dose rivaroxaban (15 or 10 mg), and warfarin according to initial prescription of study medications. All clinical outcomes were evaluated from inpatient records in the NHI claims database. All individuals were followed from their index date until death, a switch to another oral anticoagulant, discontinuation of study medication (30-day treatment gap), or end of follow-up at December 31, 2015, whichever came first.

Baseline characteristics

Age was ascertained at index date. The Taiwan NHI premium for each subject was used as a proxy of socioeconomic status, and quartiles of the insurance premium in the overall study population were used as cut-offs for categorization. We assessed comorbidities as appearance of

specific diagnosis codes twice in outpatient records or once in inpatient records during the 6-month period before the index date and coded as binary variables. Comorbidities were evaluated using the Elixhauser Comorbidity Index,[16] except for ischemic stroke, intracranial hemorrhage, myocardial infarction, and vascular disease (Supplementary Table S1). Only comorbidities with a prevalence of greater than 1.0% were retained in the analysis. Information on nasogastric intubation, medications ever used, total number of physician visits, and number of hospitalizations was extracted from the NHI claims database from the 6 months before the index date. Finally, $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75, diabetes, stroke) score[17] and CHA_2DS_2-VASc score (congestive heart failure; hypertension; aged $\geq$75; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism; vascular disease; aged 65–74; sex category)[18] were calculated according to baseline characteristics.

Statistical analysis

Two propensity score (PS)-matched cohorts were created: dabigatran versus warfarin (D-W cohort) and rivaroxaban versus warfarin (R-W cohort). The PS was derived using logistic regression[19] to model the probability of receipt of DOACs instead of warfarin as a function of all potential confounders listed in Supplementary Tables S3 and S4 except age, which was assumed to be homogeneous in this extreme elderly population. Based on PS, DOAC users were matched to warfarin users according to caliper measurements of less than 0.2 standard deviations of the logit of the PS at a 1:1 ratio to create specific PS-matched cohorts. We used standardized difference to measure covariate balance between study groups in the overall population and the PS-matched cohorts, whereby an absolute standardized difference of greater than 0.10 represented meaningful imbalance.[20]

Incidence rates of various clinical outcomes are presented as cases per 100 person-years in the overall population and the PS-matched population. The cumulative incidences for various clinical outcomes according to study group in the overall population were plotted using Fine and Gray's subdistribution method to estimate cumulative incidence function.[21]

To account for the correlated nature of the survival data within the PS-matched cohorts, the marginal proportional hazards model[22] was applied for estimation of the relative risks (hazard ratios (HRs)) of various clinical outcomes between study groups in the PS-matched cohorts as the primary analysis. Switching to other oral anticoagulants, discontinuation of study medications, and end of follow-up were treated as censoring. When exploring the relative risks of clinical outcomes other than all-cause death, death was treated as a competing risk rather than censoring.[21] To examine the robustness of the results of the primary analysis, the proportional hazards model with adjustment of PS quintiles in the overall population was used for the secondary analysis.[15]

Because rivaroxaban 10 mg is not licensed for stroke prevention in individuals with AF except in Japan, we further compared the rivaroxaban 15 mg group with the warfarin group to explore the effectiveness and safety of label-adherent dosing in rivaroxaban users.

All analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of study subjects in the overall population

Four thousand seven hundred twenty-two individuals met our inclusion criteria: 1,489 dabigatran users, 1,736 rivaroxaban users (846 rivaroxaban 15 mg, 890 rivaroxaban 10 mg), and 1,497 warfarin users (Figure 1). The mean age was 88.6, and the mean follow-up was 6.6 months. The 3 study groups differed significantly in baseline characteristics, but we found no difference in $CHADS_2$ (2.2–2.3) and CHA_2DS_2-VASc (3.8) scores between the 3 study groups (Supplementary Table S3).

Characteristics of study subjects in the PS-matched population

After using the PS-matching procedure, 1,180 dabigatran users were matched to 1,180 warfarin users in the D-W cohort, and 1,207 rivaroxaban users were matched to 1,207 warfarin users in the R-W cohort. The PS-matching procedure improved balance of the observed characteristics between matched study groups (Supplementary Table S4).

Incidence rates of clinical outcomes

In the overall population, the incidence rate of all-cause death was 24.27/100 person-years in the warfarin group, 11.34/100 person-years in the dabigatran group, and 15.88/100 person-years in the rivaroxaban group. The incidence rate of cardiovascular death was 13.48/100 person-years in the warfarin group, 4.45/100 person-years in the dabigatran group, and 7.24/100 person-years in the rivaroxaban group. The incidence rate of intracranial hemorrhage was 1.68/100 person-years in the warfarin group, 0.67/100 person-years in the dabigatran group, and 1.3/100 person-years in the rivaroxaban group in the overall population (Table 1).

The cumulative incidences of various clinical outcomes according to study group in the overall population are shown in Figure 2.

Primary analysis

In the D-W cohort, the risks of all-cause death and cardiovascular death in the dabigatran group were significantly lower than in the warfarin group (HR=0.59, 95% confidence interval (CI)=0.45–0.77 for all-cause death; HR=0.45, 95% CI=0.30–0.68 for cardiovascular death). The rivaroxaban group was also at lower risk of all-cause death (HR=0.61, 95% CI=0.47–0.79) and cardiovascular death (HR=0.52, 95% CI=0.35–0.75) than the warfarin group in the R-W cohort. The dabigatran group was also at lower risk of intracranial hemorrhage than the warfarin group (HR=0.31, 95% CI=0.10–0.97) in the R-W cohort.

Table 1. Incidence Rates of Various Clinical Outcomes in Overall and Propensity Score (PS)-Matched Population

	n (Incidence Rate Per 100 Person-Years)						
	Overall Population			PS-Matched Population			
				Dabigatran Versus Warfarin Cohort		Rivaroxaban Versus Warfarin Cohort	
Outcome	Warfarin, n = 1,497	Dabigatran, n = 1,489	Rivaroxaban, n = 1,736	Warfarin, n = 1,180	Dabigatran, n = 1,180	Warfarin, n = 1,207	Rivaroxaban, n = 1,207
All-cause death	189 (24.27)	102 (11.34)	147 (15.88)	129 (20.53)	84 (12.11)	147 (23.02)	94 (14.59)
Cardiovascular death	105 (13.48)	40 (4.45)	67 (7.24)	69 (10.98)	34 (4.9)	76 (11.9)	41 (6.37)
Ischemic stroke	34 (4.43)	37 (4.19)	43 (4.71)	25 (4.04)	33 (4.86)	28 (4.43)	29 (4.58)
Acute myocardial infarction	10 (1.29)	8 (0.89)	7 (0.76)	6 (0.96)	8 (1.16)	9 (1.41)	6 (0.94)
Arterial embolism or thrombosis	16 (2.07)	10 (1.12)	11 (1.19)	12 (1.93)	9 (1.3)	11 (1.74)	7 (1.09)
Intracranial hemorrhage	13 (1.68)	6 (0.67)	12 (1.3)	12 (1.92)	4 (0.58)	12 (1.89)	6 (0.93)
Gastrointestinal hemorrhage	41 (5.36)	52 (5.85)	34 (3.7)	32 (5.18)	41 (5.97)	29 (4.62)	24 (3.76)
Osteoporotic fracture	26 (3.41)	20 (2.25)	24 (2.64)	23 (3.74)	13 (1.89)	20 (3.21)	18 (2.85)

All other comparisons regarding risk of various clinical outcomes were not statistically significant in the matched D-W and R-W cohorts (Figure 3).

Secondary analysis

The main findings of the primary analysis did not change substantially in the secondary analysis (Figure 3).

Supplementary analysis

Comparisons between the rivaroxaban 15 mg and warfarin groups were essentially the same as the comparisons between the pooled rivaroxaban 15 mg/10 mg and warfarin groups. The rivaroxaban 15 mg group had a lower risk of arterial embolism or thrombosis than warfarin group in the matched analysis (Supplementary Table S5, Supplementary Figure S2).

DISCUSSION

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, 18,113 individuals with AF with a mean age of 71 and a $CHADS_2$ score of 2.1 were randomly assigned to receive dabigatran or warfarin. After a median follow-up of 2.0 years, the risks of stroke and systemic embolism were lower in the dabigatran 150 mg group than in the warfarin group. The dabigatran 110 mg and 150 mg groups had lower risks of hemorrhagic stroke than the warfarin group.[3] The investigators also performed several subgroup analyses stratified according to variables such as previous history of medication exposure, sex, body mass index, ethnic group, renal function, heart failure, hypertension, diabetes, stroke, and $CHADS_2$ score, but the efficacy of dabigatran in different age groups, especially the oldest adults, was not reported.[3]

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) enrolled 14,264 individuals with nonvalvular AF with a median age of 73 and a mean $CHADS_2$ score of 3.5. Participants were randomly assigned to receive fixed-dose rivaroxaban (20 or 15 mg/d in individuals with a creatinine clearance of 30 to 49 mL/min) or adjusted-dose warfarin. After a median follow-up of 707 days, rivaroxaban was shown to be noninferior to warfarin with regard to prevention of stroke or systemic embolism. The risk of intracranial hemorrhage was significantly lower in the rivaroxaban group.[4] The investigators further conducted a subgroup analysis to compare the efficacy and safety of rivaroxaban with that of warfarin in individuals of different ages ($<$ vs $\geq$ 75 at entry).[23] Although higher incidences of primary efficacy end point (stroke or systemic embolism) and primary safety endpoint (major or intracranial bleeding) in individuals aged 85 and older were noted in the report, the efficacy and safety of rivaroxaban relative to that of warfarin in these individuals could not be clarified because of small sample size (n=663).[23]

Anticoagulation therapy for very old adults is an important clinical concern with regard to the frailty of elderly adults and their greater bleeding risk.[23] An Italian

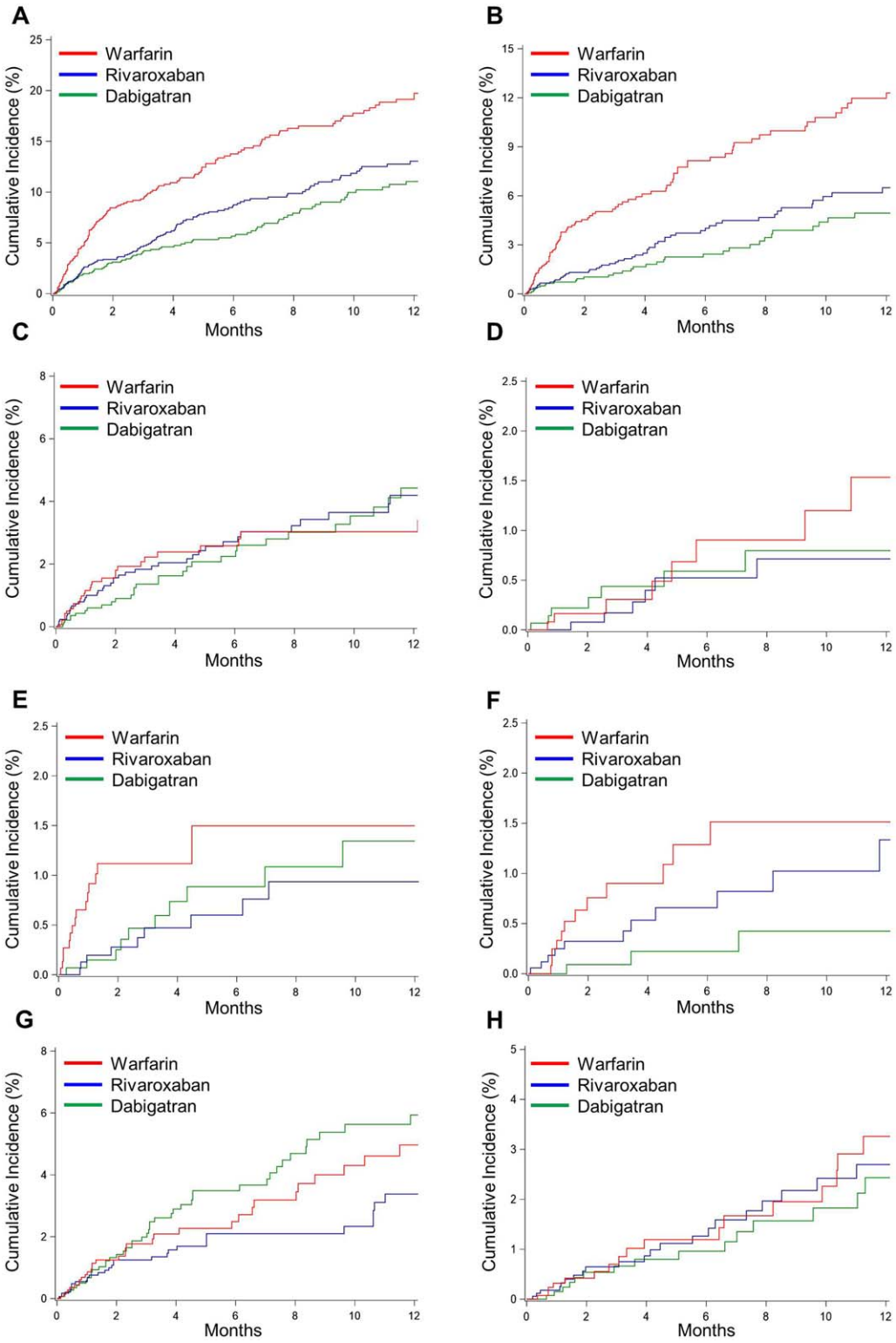

Figure 2. Cumulative incidence of various clinical outcomes according to study group in the overall population: (A) all-cause death, (B) cardiovascular death, (C) ischemic stroke, (D) acute myocardial infarction, (E) arterial embolism or thrombosis, (F) intracranial hemorrhage, (G) gastrointestinal hemorrhage needing transfusion, (H) osteoporotic fracture.

study showed the safety of warfarin therapy in individuals aged 80 and older, but the study revealed a higher rate of bleeding in individuals aged 85 and older than in those aged 80 to 85.[24] The major finding of a real-world observational study using a database from the United States to explore the relative risk of major bleeding in individuals initiating different DOACs or warfarin therapy[7] was that initiation with rivaroxaban or warfarin was associated with a significantly greater risk of major bleeding than initiation of apixaban. The study showed that individuals

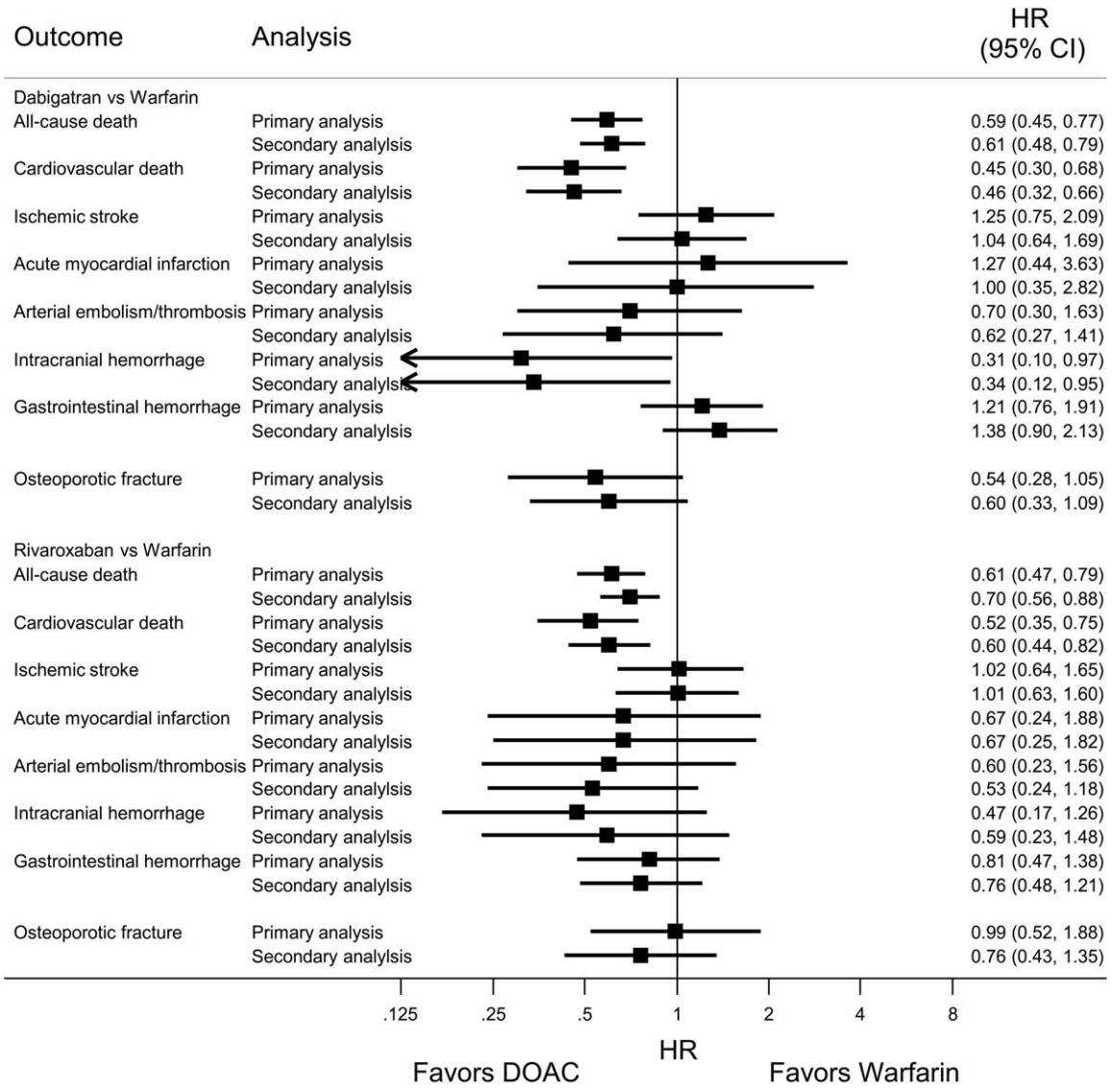

Figure 3. Summary of relative risks of various clinical outcomes between study groups. CI=confidence interval; DOAC=direct oral anticoagulant; HR=hazard ratio.

aged 50 to 79 had a lower risk of major bleeding requiring hospitalization than those aged 80 and older in the overall study population.[7] Even though several observational studies have compared the clinical effectiveness and safety of dabigatran and rivaroxaban therapy with that of warfarin in a real-world setting,[5,6,8–10] no report had focused on the oldest adults.

Most elderly individuals with AF in Taiwan received reduced dosages of DOACs (e.g., dabigatran 110 mg, rivaroxaban 15 or 10 mg). In the Japan ROCKET-AF (J-ROCKET-AF) study, 15 mg once-daily rivaroxaban (10 mg daily in individuals with creatinine clearance 30–49 mL/min) was shown to be noninferior to warfarin in individuals with nonvalvular AF.[25] The lower dosage of DOACs used in Taiwan reflects the influence of the J-ROCKET AF study on Asian populations. Underdosing of DOAC therapy is not infrequent even in the United States.[26] Our study results provide a good reference for the comparative effectiveness and safety of DOACs and warfarin in oldest adults who are usually underrepresented in clinical trials.

Strength of this study

We excluded individuals who had ever been exposed to warfarin before our enrollment period to conform the new users design.[27] Because advanced renal failure is a contraindication for DOACs, we excluded individuals with previous diagnosis of renal failure to ensure comparability between study groups. Because the risk of osteoporotic fracture was not statistically significant in all the comparisons of the DOAC groups and the warfarin group, a residual confounding effect was not a major concern according to the falsification analysis.[9]

Study limitations

Some study limitations must be acknowledged. First, the international normalized ratio (INR) and time in therapeutic range (TTR) could not be ascertained through this insurance claims database. The TTR was 64% in the warfarin group in RE-LY[3] and 55% in ROCKET-AF.[4] Suboptimal dosage control

of warfarin in Taiwanese had been inferred in one study,[28] and another study from southern Taiwan found a very low TTR of 24.3% in individuals with AF and acute ischemic stroke/transient ischemic attack.[29] The survival benefit in the dabigatran and rivaroxaban groups over that of the warfarin group in our study might result from the poor dosing of warfarin therapy and low TTR of INR in Taiwanese; nevertheless, our findings were practical and pragmatic in that stability of INR in individuals undergoing long-term warfarin therapy is difficult to maintain in real-world practice.[30]

Second, the HAS-BLED score (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly (≥65), drugs and alcohol) can be a practical tool to assess bleeding risk in individuals with AF.[31] Because labile INR and alcohol use could not be obtained from the NHI claims database, and individuals with renal failure were excluded from this study, we did not calculate the HAS-BLED score, although we included all the other components of the HAS-BLED score into our list of potential confounders during construction of the PS.

Third, mean follow-up in our cohort was only 6.6 months, in contrast with the long follow-up of up to 2 years in landmark clinical trials,[3,4] but short follow-up seemed inevitable under strict criteria for censoring in observational studies, with 1 observational study from the United States reporting an even shorter duration (108–111 days).[32]

Fourth, although the Taiwan NHI has reimbursed for apixaban since June 1, 2014, the sample size was too small to be included in our analysis (n=184 after applying the enrollment criteria).

Finally, this study was based on elderly ethnic Chinese with AF taking reduced-dosage DOACs. We recommend caution in extrapolating these findings to Western populations or individuals receiving standard-dose DOACs.

CONCLUSIONS

In this observational study focused on elderly ethnic Chinese with AF aged 85 and older in Taiwan, where lower dosages of DOACs were used ordinarily and poor dosing of warfarin was prevalent, we found that dabigatran and rivaroxaban were associated with significantly lower risks of all-cause and cardiovascular death than with warfarin therapy. Dabigatran was also associated with lower risk of intracranial hemorrhage than warfarin. The risks of ischemic stroke, acute myocardial infarction, arterial embolism or thrombosis, and gastrointestinal hemorrhage needing transfusion were similar with dabigatran, rivaroxaban, and warfarin. Our findings provide some reassurance of the effectiveness and safety of DOACs in the oldest adults.

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Conflict of Interest: Dr. Lai reports receiving lecture fees from AstraZeneca, Pfizer, Bayer, Novartis, Actelion, Boehringer Ingelheim, Excelsior, Sanofi-Aventis, MSD, Tanabe, Daiichi-Sankyo, and Abbott. The other authors report no relationships that could be construed as a conflict of interest.

Author Contributions: Lai: study design, interpretation of data, drafting of the manuscript, obtaining funding. Chen: study design, acquisition of data, statistical analysis, interpretation of data. Liao: study design, interpretation of data, obtaining funding, administrative support. Lin: study design, interpretation of data, revision of the manuscript, administrative support.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site

Table S1. Diagnosis codes used in this study.

Table S2. Covariate distribution by different dosage rivaroxaban groups in the overall population and the propensity score-matched population.

Figure S1. Summary of relative risks of various clinical outcomes between different dosages of rivaroxaban with rivaroxaban 15 mg as the reference group.

Table S3. Covariate distribution by treatment groups in the overall population.

Table S4. Covariate distribution by treatment groups in the propensity score-matched population.

Table S5. Covariate distribution between rivaroxaban 15 mg group and warfarin group in the overall population and the propensity score-matched population.

Figure S2. Summary of relative risks of various clinical outcomes between rivaroxaban 15 mg group and warfarin group.

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