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ORIGINAL ARTICLE

Effectiveness and Safety of Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Diabetes Mellitus

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Abstract

Objective: To address gaps in the data comparing non–vitamin K antagonist oral anticoagulants (NOACs) and warfarin among patients with nonvalvular atrial fibrillation (NVAF) and diabetes.

Patients and Methods: A retrospective study was conducted on patients with NVAF and diabetes newly initiating apixaban, dabigatran, rivaroxaban, or warfarin from January 1, 2013, through September 30, 2015, with Medicare data from the US Centers for Medicare & Medicaid Services and 4 other US commercial claims databases. One-to-one propensity score matching was completed between NOACs and warfarin and between NOACs in each database, and the results were pooled. Cox proportional hazards models were used to evaluate the risk of stroke/systemic embolism (SE) and major bleeding (MB).

Results: A total of 154,324 patients were included in the 6 matched cohorts, with a mean follow-up time of 6 to 8 months. Compared with warfarin, apixaban (hazard ratio [HR], 0.67; 95% CI, 0.57-0.77) and rivaroxaban (HR, 0.79; 95% CI, 0.71-0.89) were associated with a lower risk of stroke/SE; dabigatran (HR, 0.84; 95% CI, 0.67-1.07) was associated with a similar risk of stroke/SE. Apixaban (HR, 0.60; 95% CI, 0.56-0.65) and dabigatran (HR, 0.78; 95% CI, 0.69-0.88) were associated with a lower risk of MB; rivaroxaban (HR, 1.02; 95% CI, 0.94-1.10) was associated with a similar risk of MB compared with warfarin. Compared with dabigatran and rivaroxaban, apixaban was associated with a lower risk of MB. Compared with rivaroxaban, dabigatran was associated with a lower risk of MB.

Conclusion: This study—the largest observational study to date of patients with NVAF and diabetes taking anticoagulants—found that NOACs were associated with variable rates of stroke/SE and MB compared with warfarin.

Trial Registration: clinicaltrials.gov Identifier: NCT03087487

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There have been important developments in the management of atrial fibrillation (AF), including the evolution of approaches to stroke prevention and bleeding risk minimization, specifically through the emergence of oral anticoagulants (OACs).[1] Vitamin K antagonists, such as warfarin, have previously dominated the therapeutic market of AF, and non–vitamin K oral anticoagulants (NOACs) have had increasing presence since their approval and inclusion in AF clinical guidelines in recent years. Warfarin is associated with a higher risk of major bleeding (MB) as compared with no antithrombotic treatment.[2] Moreover, required periodic monitoring of the

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international normalized ratio (INR) and the frequent need for dose adjustment make warfarin inconvenient and burdensome to the treatment of AF.[3] In randomized controlled trials comparing NOACs with warfarin, the 4 NOACs—apixaban, dabigatran, edoxaban, and rivaroxaban—have exhibited noninferiority for safety and efficacy.[4]

Concomitant comorbidities, such as diabetes, can complicate AF management. Diabetes increases the risk of developing AF and is one of the most common comorbidities in patients with AF.[5-8] The Framingham Heart Study reported that male and female diabetic patients were, respectively, 4 and 6 times more likely to develop AF than did nondiabetic patients.[9] In addition, increasing levels of hemoglobin A_{1c} and duration of diabetes have been reported to increase the risk of thromboembolism.[10,11] Diabetes is also an independent risk factor for stroke, and diabetic patients have more disabilities and an increased risk of mortality compared with nondiabetic patients.[12,13] Furthermore, other risk factors for stroke in patients with AF, such as renal failure and peripheral vascular disease, are more prevalent in patients with diabetes.[14,15] The CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes, stroke [previous], vascular disease, age 65-74 years, sex) score takes diabetes history into consideration (contributing 1 point to the final calculation), which emphasizes the importance of diabetes in AF management.[14] Diabetes is, therefore, an important risk factor for disease progression and adverse outcomes in patients with AF, making patients with diabetes a high-risk subgroup.[16-18]

Because of the increased risk of stroke/systemic embolism (SE) in patients with diabetes, OACs are recommended for patients with AF and concomitant diabetes.[19] A meta-analysis of the 4 NOAC trials found no significant interaction between treatment (NOACs vs warfarin) and diabetes status for stroke/SE or MB.[20,21] However, in a subgroup analysis of the ARISTOTLE (Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, diabetes and treatment had a significant interaction for the risk of MB, although there is no good mechanistic hypotheses to explain the interaction.[22] In the controlled trials, 23% to 40% of patients had diabetes, so it is an important high-risk subgroup study to evaluate.[22-24] There have been few observational studies comparing NOACs and warfarin in patients with NVAF and diabetes. To contribute real-world evidence from several data sources that may facilitate future research regarding this underrepresented population, this study analyzed the diabetes subgroup of the ARISTOPHANES (Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients; NCT03087487) study. The present study pooled NVAF patients with diabetes who were newly prescribed OACs and compared the risks of stroke/SE and MB associated with apixaban, dabigatran, rivaroxaban, and warfarin use.

PATIENTS AND METHODS

Data Sources

This study was a retrospective observational database analysis of a patient population of more than 180 million beneficiaries per year (~56% of the US population) using fee-for-service Medicare data from the US Centers for Medicare & Medicaid Services and 4 other US commercial claims databases: the Truven MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database, the IMS PharMetrics Plus database, the Optum Clinformatics Data Mart, and the Humana Research database.

The databases include patients with Medicare Fee-For-Service, Medicare Advantage, and commercial insurance. Database records include comprehensive demographic and clinical information and *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes, Healthcare Common Procedure Coding System codes, and National Drug Code.

Previously published articles include detailed descriptions of the data sets, the rationale for the pooling process, and the

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approaches to minimizing potential patient record duplicates across data sources.[25,26]

Patient Selection

Patients with NVAF were selected if they had 1 or more pharmacy claim for apixaban, dabigatran, rivaroxaban, or warfarin from January 1, 2013, through September 30, 2015 (identification period). Edoxaban was evaluated but excluded because of a small sample size due to its recent Food and Drug Administration approval. The first NOAC prescription date was designated as the index date if patients had a NOAC claim. The first warfarin prescription date was designated as the index date for patients without any NOAC claim. Patients were required to have an AF diagnosis before the index date and have continuous medical and pharmacy health plan enrollment for 12 months or more before the index date (baseline period) (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

To evaluate new initiators, patients treated with an OAC within 12 months before the index date were excluded. Patients were also excluded if they had claims indicating any of the following: valvular heart disease (defined by the presence of *International Classification of Diseases, Ninth Revision* codes 394.xx, 396.xx, 424.0, and 745.xx), venous thromboembolism, transient AF (pericarditis, hyperthyroidism, and thyrotoxicosis), or heart valve replacement/transplant during the baseline period; pregnancy during the study period; or hip or knee replacement surgery within 6 weeks before the index date. Detailed selection criteria are presented in Figure 1. Among the resulting patients with NVAF prescribed OACs, patients with type 1 and 2 diabetes (*ICD-9-CM* code 250.xx) during the baseline period were selected.

Outcome Measures

Outcome measures were time to first stroke/SE, including ischemic stroke, hemorrhagic stroke, and SE, and time to first MB, including gastrointestinal (GI) bleeding, intracranial hemorrhage, and bleeding at other key sites (Supplemental Table 1).[27,28] Outcomes were based on hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis. The follow-up period ranged from 1-day postindex date to 30 days after the discontinuation date, medication switch date, death (only inpatient death for the commercial databases and all-cause death for the Medicare database), end of continuous medical or pharmacy plan enrollment, or end of study (September 30, 2015), whichever occurred earliest.

Statistical Methods

Propensity score matching (PSM) was conducted between NOAC and warfarin cohorts (apixaban vs warfarin, dabigatran vs warfarin, and rivaroxaban vs warfarin) and between NOAC cohorts (apixaban vs dabigatran, apixaban vs rivaroxaban, and dabigatran vs rivaroxaban) within each data set. The variables used for PSM are related to key patient characteristics, including demographic characteristics, Charlson Comorbidity Index scores,[29] common comorbidities, diabetes complications, and comedications. (A complete list of PSM model covariates is given in Tables 1 and 2.) In each database, patients were matched using 1:1 nearest neighbor matching without replacement (with a caliper of 0.01). The covariate balance was checked using standardized differences, with a threshold of 10%.[30] After ensuring that the cohorts were balanced in each database, study patients from the 5 data sets were pooled for the analysis.

The risk of stroke/SE and MB was evaluated using Cox proportional hazards models, with robust sandwich estimates.[31] Oral anticoagulant treatment was included as the independent variable; as the cohorts were balanced, no other covariates were included in the model. $P<.05$ was considered statistically significant. No adjustments for multiple comparisons were made.

Subgroup Analyses

Propensity score matching was conducted again in subgroup patients on the basis of the index dose of the NOAC. Patients prescribed standard-dose (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg) and

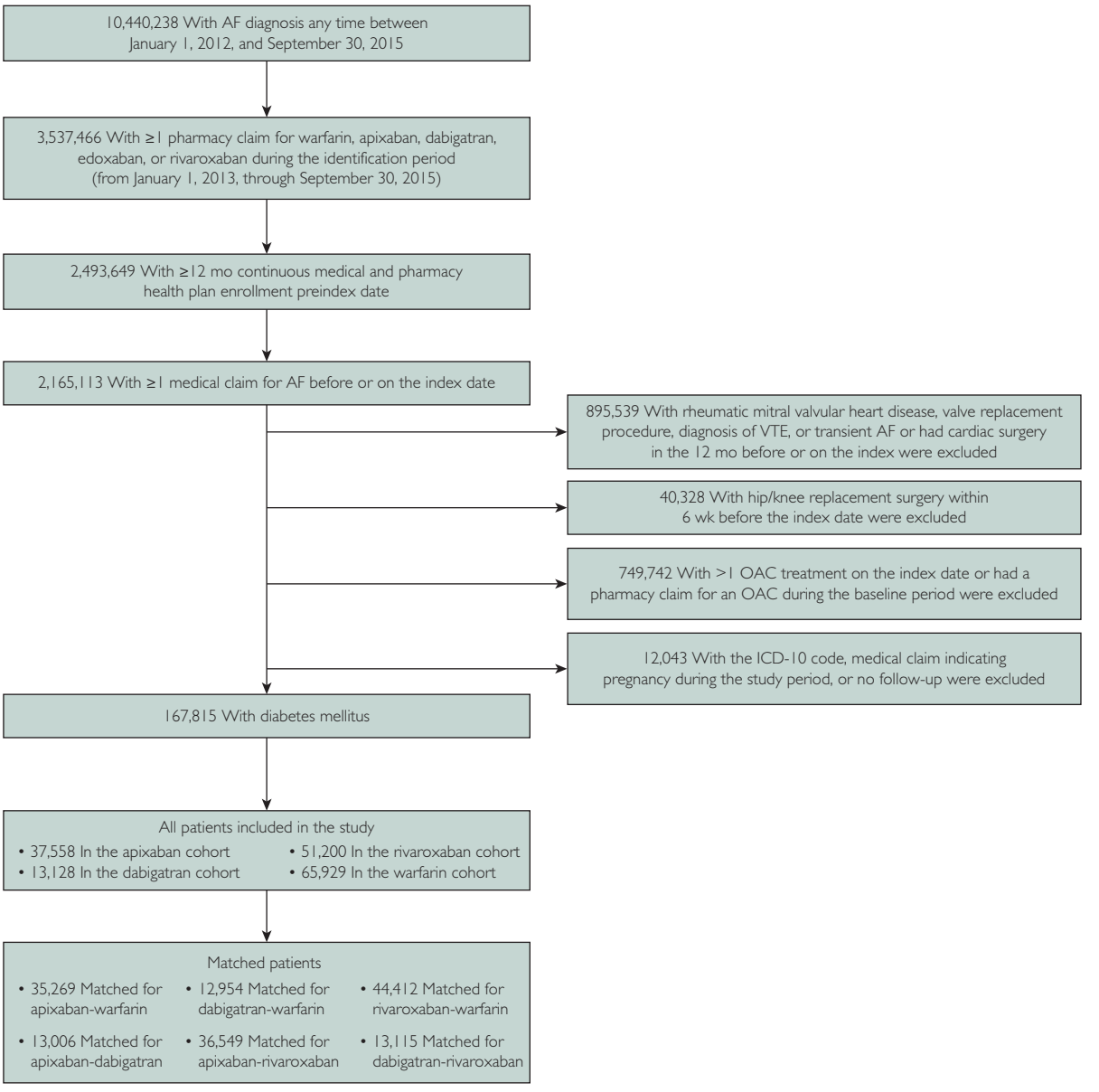

FIGURE 1. Selection criteria. Application of the selection criteria yielded more than 100,000 patients with nonvalvular atrial fibrillation and diabetes mellitus. These patients were matched in cohorts by propensity scores. AF = atrial fibrillation; *ICD-10 = International Classification of Diseases, Tenth Revision*; OAC = oral anticoagulant; VTE = venous thromboembolism.

lower-dose (apixaban 2.5 mg, dabigatran 75 mg, and rivaroxaban 15 mg/10 mg) NOACs were matched on the basis of their index dose. Furthermore, Cox proportional hazards models were completed for the standard-dose and lower-dose subgroups separately.

Institutional review board approval was not required because the study did not involve the collection, use, or transmittal of individual identifiable data. Both the data sets and the security of the offices in which the analysis was completed (and in which the data sets are kept) met the requirements

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TABLE 1. Baseline Characteristics of NOACs vs Warfarin After PSM[a,b]

Characteristic	Apixaban cohort	Warfarin cohort	Dabigatran cohort	Warfarin cohort	Rivaroxaban cohort	Warfarin cohort
Sample size	35,269	35,269	12,954	12,954	44,412	44,412
Age (y)	75.8±9.0	75.8±8.9	73.7±9.1	73.9±9.3	75.2±8.9	75.3±8.9
18-54	635 (1.8)	641 (1.8)	388 (3.0)	393 (3.0)	827 (1.9)	831 (1.9)
55-64	2468 (7.0)	2447 (6.9)	1362 (10.5)	1341 (10.4)	3371 (7.6)	3362 (7.6)
65-74	12,388 (35.1)	12,306 (34.9)	5129 (39.6)	5100 (39.4)	16,542 (37.2)	16,467 (37.1)
≥75	19,778 (56.1)	19,875 (56.4)	6075 (46.9)	6120 (47.2)	23,672 (53.3)	23,752 (53.5)
Sex						
Male	18,963 (53.8)	18,936 (53.7)	7460 (57.6)	7484 (57.8)	24,511 (55.2)	24,491 (55.1)
Female	16,306 (46.2)	16,333 (46.3)	5494 (42.4)	5470 (42.2)	19,901 (44.8)	19,921 (44.9)
US geographic region						
Northeast	6402 (18.2)	6362 (18.0)	2613 (20.2)	2676 (20.7)	8488 (19.1)	8373 (18.9)
Midwest	7756 (22.0)	7869 (22.3)	2772 (21.4)	2761 (21.3)	10,653 (24.0)	10,686 (24.1)
South	15,884 (45.0)	15,863 (45.0)	5339 (41.2)	5258 (40.6)	17,883 (40.3)	17,892 (40.3)
West	5139 (14.6)	5087 (14.4)	2174 (16.8)	2209 (17.1)	7225 (16.3)	7310 (16.5)
Other	88 (0.2)	88 (0.2)	56 (0.4)	50 (0.4)	163 (0.4)	151 (0.3)
Baseline comorbidity						
Deyo-Charlson Comorbidity Index score	4.7±2.7	4.7±2.8	4.1±2.6	4.1±2.6	4.5±2.7	4.5±2.7
CHA_2DS_2-VASc score	4.8±1.5	4.8±1.5	4.5±1.5	4.5±1.5	4.7±1.5	4.7±1.5
1	157 (0.5)	142 (0.4)	124 (1.0)	105 (0.8)	250 (0.6)	235 (0.5)
2	1515 (4.3)	1486 (4.2)	938 (7.2)	921 (7.1)	2080 (4.7)	2005 (4.5)
3	5092 (14.4)	4893 (13.9)	2430 (18.8)	2316 (17.9)	7066 (15.9)	6820 (15.4)
≥4	28,505 (80.8)	28,748 (81.5)	9462 (73.0)	9612 (74.2)	35,016 (78.8)	35,352 (79.6)
HAS-BLED score[c]	3.5±1.3	3.5±1.3	3.2±1.3	3.2±1.3	3.4±1.3	3.4±1.3
0	134 (0.4)	159 (0.5)	101 (0.8)	120 (0.9)	229 (0.5)	253 (0.6)
1	1424 (4.0)	1490 (4.2)	855 (6.6)	837 (6.5)	2095 (4.7)	2148 (4.8)
2	6879 (19.5)	6940 (19.7)	3171 (24.5)	3132 (24.2)	9339 (21.0)	9637 (21.7)
≥3	26,832 (76.1)	26,680 (75.6)	8827 (68.1)	8865 (68.4)	32,749 (73.7)	32,374 (72.9)
Bleeding history	7836 (22.2)	7811 (22.1)	2517 (19.4)	2529 (19.5)	9819 (22.1)	9802 (22.1)
Congestive heart failure	13,516 (38.3)	13,603 (38.6)	4197 (32.4)	4275 (33.0)	16,320 (36.7)	16,352 (36.8)
Type 1 diabetes[d]	5146 (14.6)	5322 (15.1)	1920 (14.8)	1786 (13.8)	6474 (14.6)	6477 (14.6)
Type 2 diabetes[d]	35,019 (99.3)	35,048 (99.4)	12,873 (99.4)	12,871 (99.4)	44,064 (99.2)	44,132 (99.4)
Hypertension	33,642 (95.4)	33,652 (95.4)	12,220 (94.3)	12,237 (94.5)	41,984 (94.5)	41,986 (94.5)
Renal disease	12,557 (35.6)	12,639 (35.8)	3337 (25.8)	3365 (26.0)	13,869 (31.2)	13,726 (30.9)
Liver disease	2234 (6.3)	2205 (6.3)	753 (5.8)	788 (6.1)	2888 (6.5)	2814 (6.3)
Myocrdial infarction	4372 (12.4)	4385 (12.4)	1276 (9.9)	1294 (10.0)	5365 (12.1)	5395 (12.1)
Dyspepsia or stomach discomfort	8238 (23.4)	8287 (23.5)	2654 (20.5)	2593 (20.0)	10,187 (22.9)	10,042 (22.6)
Nonstroke/ SE peripheral vascular disease	22,511 (63.8)	22,479 (63.7)	7574 (58.5)	7553 (58.3)	27,328 (61.5)	27,382 (61.7)
Stroke/SE	5110 (14.5)	5036 (14.3)	1608 (12.4)	1657 (12.8)	6124 (13.8)	6190 (13.9)
Transient ischemic attack	2816 (8.0)	2861 (8.1)	891 (6.9)	897 (6.9)	3350 (7.5)	3365 (7.6)
Anemia and coagulation defects	12,969 (36.8)	12,928 (36.7)	3893 (30.1)	3960 (30.6)	15,663 (35.3)	15,534 (35.0)
Alcoholism	612 (1.7)	605 (1.7)	265 (2.0)	250 (1.9)	918 (2.1)	922 (2.1)
Peripheral artery disease	9366 (26.6)	9687 (27.5)	2943 (22.7)	3089 (23.8)	11,557 (26.0)	11,599 (26.1)
Coronary artery disease	20,088 (57.0)	19,903 (56.4)	6709 (51.8)	6630 (51.2)	24,174 (54.4)	24,144 (54.4)
Obesity	10,725 (30.4)	10,692 (30.3)	3779 (29.2)	3750 (28.9)	13,041 (29.4)	13,002 (29.3)
Hypoglycemia	909 (2.6)	990 (2.8)	312 (2.4)	283 (2.2)	1178 (2.7)	1156 (2.6)
Dyslipidemia	30,820 (87.4)	30,793 (87.3)	11,132 (85.9)	11,132 (85.9)	38,222 (86.1)	38,099 (85.8)
Diabetic nephropathy	4004 (11.4)	4032 (11.4)	1073 (8.3)	1079 (8.3)	4221 (9.5)	4140 (9.3)
Diabetic neuropathy	7375 (20.9)	7348 (20.8)	2438 (18.8)	2439 (18.8)	8759 (19.7)	8892 (20.0)
Diabetic retinopathy	4262 (12.1)	4278 (12.1)	1458 (11.3)	1510 (11.7)	5022 (11.3)	5072 (11.4)

Continued on next page

TABLE 1. Continued

Characteristic	Apixaban cohort	Warfarin cohort	Dabigatran cohort	Warfarin cohort	Rivaroxaban cohort	Warfarin cohort
Baseline medication use						
ACEi/ARB	25,712 (72.9)	25,790 (73.1)	9519 (73.5)	9533 (73.6)	32,172 (72.4)	32,362 (72.9)
Amiodarone	4548 (12.9)	4542 (12.9)	1523 (11.8)	1535 (11.8)	5350 (12.0)	5424 (12.2)
β-blockers	21,646 (61.4)	21,569 (61.2)	7751 (59.8)	7744 (59.8)	27,087 (61.0)	27,059 (60.9)
H2-receptor antagonists	2889 (8.2)	2881 (8.2)	956 (7.4)	925 (7.1)	3598 (8.1)	3585 (8.1)
Proton pump inhibitors	12,554 (35.6)	12,621 (35.8)	4195 (32.4)	4203 (32.4)	15,252 (34.3)	15,229 (34.3)
Statins	25,459 (72.2)	25,409 (72.0)	8966 (69.2)	8978 (69.3)	31,263 (70.4)	31,310 (70.5)
Anti-platelets	9206 (26.1)	9132 (25.9)	2860 (22.1)	2852 (22.0)	10,741 (24.2)	10,692 (24.1)
NSAIDS	8940 (25.3)	8888 (25.2)	3445 (26.6)	3456 (26.7)	11,210 (25.2)	11,158 (25.1)
Diuretics	22,484 (63.8)	22,506 (63.8)	7972 (61.5)	8002 (61.8)	27,610 (62.2)	27,674 (62.3)
Calcium channel blockers	16,540 (46.9)	16,584 (47.0)	5921 (45.7)	5932 (45.8)	20,465 (46.1)	20,501 (46.2)
Baseline diabetes medications						
Biguanides	14,764 (41.9)	14,818 (42.0)	6000 (46.3)	6027 (46.5)	18,927 (42.6)	19,071 (42.9)
Sulphonylureas	9199 (26.1)	9269 (26.3)	3513 (27.1)	3602 (27.8)	11,702 (26.3)	11,789 (26.5)
Meglitinide	405 (1.1)	396 (1.1)	147 (1.1)	141 (1.1)	529 (1.2)	520 (1.2)
Thiazolidinediones	1540 (4.4)	1583 (4.5)	641 (4.9)	608 (4.7)	1934 (4.4)	1930 (4.3)
DPP-4 inhibitors	3875 (11.0)	3892 (11.0)	1461 (11.3)	1474 (11.4)	4664 (10.5)	4600 (10.4)
Insulin	8199 (23.2)	8180 (23.2)	2886 (22.3)	2855 (22.0)	10,109 (22.8)	10,211 (23.0)
α-glucosidase inhibitors	166 (0.5)	156 (0.4)	58 (0.4)	64 (0.5)	195 (0.4)	178 (0.4)
SGLT-2 inhibitors	170 (0.5)	165 (0.5)	67 (0.5)	62 (0.5)	180 (0.4)	182 (0.4)
GLP-1 agonists	788 (2.2)	797 (2.3)	320 (2.5)	299 (2.3)	896 (2.0)	899 (2.0)
Dose of the index prescription						
Standard dose[e]	26,383 (74.8)		10,493 (81.0)		30,215 (68.0)	
Lower dose[f]	8886 (25.2)		2461 (19.0)		14,197 (32.0)	
Follow-up time (d)						
Mean	183.3±166.7	240.5±218.0	224.5±223.5	244.6±220.8	225.4±213.7	244.0±220.0
Median	121	158	122	161	142	162

[a]ACEi/ARB = angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; CHA_2DS_2-VASc = congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65-74 years, sex category; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide; HAS-BLED = hypertension, abnormal (renal/liver function), stroke, bleeding, labile (international normalized ratio), elderly, drug/alcohol/medication (usage history); NOAC = non-vitamin K oral anticoagulant; NSAIDs = non-steroidal anti-inflammatory drugs; PSM = propensity score matching; SE = systemic embolism; SGLT-2 = sodium-glucose co-transporter 2.

[b]Data are presented as mean ± SD or as No. (percentage).

[c]As the international normalized ratio value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.

[d]Diabetes type was defined by the presence of International Classification of Disease, Ninth Revision, Clinical Modification diagnosis codes only and was not further validated.

[e]Standard dose: 5mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban.

[f]Lower dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 2,460 patients treated with rivaroxaban were prescribed 10 mg rivaroxaban.

of the Health Insurance Portability and Accountability Act of 1996.

RESULTS

After applying the selection criteria, a total of 167,815 patients with NVAF and concomitant diabetes mellitus (35.9% of patients with NVAF [466,991]) were identified, including 37,558 patients prescribed apixaban, 13,128 dabigatran, 51,200 rivaroxaban, and 65,929 warfarin (Figure 1). Before PSM, patients prescribed warfarin were the oldest and had the highest CHA_2DS_2-VASc and hypertension, abnormal (renal/liver function), stroke, bleeding, labile (international normalized ratio), elderly, drug/alcohol/medication (usage history) (HAS-BLED) scores, followed by those prescribed apixaban, rivaroxaban, and dabigatran. The number of patients who were prescribed the lower dose in each cohort was 9180 (24%) of those prescribed apixaban (2.5 mg), 2467 (19%) of those prescribed

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TABLE 2. Baseline Characteristics of NOACs vs NOACs After PSM[a,b]

Characteristic	Apixaban cohort	Dabigatran cohort	Apixaban cohort	Rivaroxaban cohort	Dabigatran cohort	Rivaroxaban cohort
Sample size	13,006	13,006	36,549	36,549	13,115	13,115
Age (y)	73.8±9.4	73.6±9.2	75.3±9.3	75.2±9.2	73.5±9.2	73.5±9.4
18-54	426 (3.3)	430 (3.3)	881 (2.4)	869 (2.4)	444 (3.4)	441 (3.4)
55-64	1373 (10.6)	1402 (10.8)	3014 (8.2)	2995 (8.2)	1432 (10.9)	1421 (10.8)
65-74	5100 (39.2)	5107 (39.3)	12,866 (35.2)	12,860 (35.2)	5160 (39.3)	5175 (39.5)
≥75	6107 (47.0)	6067 (46.6)	19,788 (54.1)	19,825 (54.2)	6079 (46.4)	6078 (46.3)
Sex						
Male	7526 (57.9)	7499 (57.7)	19,761 (54.1)	19,688 (53.9)	7596 (57.9)	7656 (58.4)
Female	5480 (42.1)	5507 (42.3)	16,788 (45.9)	16,861 (46.1)	5519 (42.1)	5459 (41.6)
US geographic region						
Northeast	2560 (19.7)	2604 (20.0)	6423 (17.6)	6427 (17.6)	2645 (20.2)	2674 (20.4)
Midwest	2758 (21.2)	2766 (21.3)	7737 (21.2)	7682 (21.0)	2779 (21.2)	2750 (21.0)
South	5496 (42.3)	5441 (41.8)	17,130 (46.9)	17,200 (47.1)	5450 (41.6)	5503 (42.0)
West	2142 (16.5)	2142 (16.5)	5174 (14.2)	5160 (14.1)	2181 (16.6)	2133 (16.3)
Other	50 (0.4)	53 (0.4)	85 (0.2)	80 (0.2)	60 (0.5)	55 (0.4)
Baseline comorbidity						
Deyo-Charlson Comorbidity Index score	4.1±2.6	4.1±2.6	4.5±2.7	4.5±2.7	4.1±2.6	4.1±2.6
CHA_2DS_2-VASc score	4.5±1.5	4.4±1.5	4.7±1.5	4.7±1.5	4.4±1.5	4.4±1.5
1	104 (0.8)	121 (0.9)	192 (0.5)	193 (0.5)	130 (1.0)	127 (1.0)
2	967 (7.4)	1007 (7.7)	1941 (5.3)	1950 (5.3)	1040 (7.9)	1072 (8.2)
3	2445 (18.8)	2432 (18.7)	5588 (15.3)	5515 (15.1)	2470 (18.8)	2383 (18.2)
≥4	9490 (73.0)	9446 (72.6)	28,828 (78.9)	28,891 (79.0)	9475 (72.2)	9533 (72.7)
HAS-BLED score[c]	3.2±1.3	3.2±1.3	3.4±1.3	3.4±1.3	3.2±1.3	3.2±1.3
0	89 (0.7)	102 (0.8)	167 (0.5)	157 (0.4)	106 (0.8)	110 (0.8)
1	849 (6.5)	890 (6.8)	1722 (4.7)	1786 (4.9)	916 (7.0)	892 (6.8)
2	3131 (24.1)	3191 (24.5)	7428 (20.3)	7301 (20.0)	3229 (24.6)	3176 (24.2)
≥3	8937 (68.7)	8823 (67.8)	27,232 (74.5)	27,305 (74.7)	8864 (67.6)	8937 (68.1)
Bleeding history	2529 (19.4)	2508 (19.3)	7798 (21.3)	7869 (21.5)	2521 (19.2)	2544 (19.4)
Congestive heart failure	4229 (32.5)	4182 (32.2)	13,362 (36.6)	13,373 (36.6)	4202 (32.0)	4308 (32.8)
Type 1 diabetes[d]	1802 (13.9)	1926 (14.8)	5151 (14.1)	5397 (14.8)	1938 (14.8)	1874 (14.3)
Type 2 diabetes[d]	12,903 (99.2)	12,924 (99.4)	36,295 (99.3)	36,290 (99.3)	13,030 (99.4)	13,006 (99.2)
Hypertension	12,288 (94.5)	12,282 (94.4)	34,855 (95.4)	34,837 (95.3)	12,374 (94.3)	12,385 (94.4)
Renal disease	3336 (25.6)	3331 (25.6)	12,030 (32.9)	12,108 (33.1)	3338 (25.5)	3314 (25.3)
Liver disease	766 (5.9)	754 (5.8)	2337 (6.4)	2358 (6.5)	758 (5.8)	732 (5.6)
Myocardial infarction	1297 (10.0)	1274 (9.8)	4332 (11.9)	4330 (11.8)	1277 (9.7)	1288 (9.8)
Dyspepsia or stomach discomfort	2665 (20.5)	2650 (20.4)	8479 (23.2)	8570 (23.4)	2666 (20.3)	2693 (20.5)
Nonstroke/SE peripheral vascular disease	7548 (58.0)	7572 (58.2)	22,962 (62.8)	23,016 (63.0)	7619 (58.1)	7543 (57.5)
Stroke/SE	1642 (12.6)	1607 (12.4)	5046 (13.8)	5069 (13.9)	1606 (12.2)	1628 (12.4)
Transient ischemic attack	875 (6.7)	895 (6.9)	2866 (7.8)	2903 (7.9)	894 (6.8)	893 (6.8)
Anemia and coagulation defects	3864 (29.7)	3876 (29.8)	12,768 (34.9)	12,830 (35.1)	3894 (29.7)	3890 (29.7)
Alcoholism	287 (2.2)	261 (2.0)	638 (1.7)	652 (1.8)	269 (2.1)	278 (2.1)
Peripheral artery disease	2979 (22.9)	2938 (22.6)	9342 (25.6)	9780 (26.8)	2952 (22.5)	3002 (22.9)
Coronary artery disease	6672 (51.3)	6711 (51.6)	20,503 (56.1)	20,347 (55.7)	6754 (51.5)	6632 (50.6)
Obesity	3849 (29.6)	3827 (29.4)	11,272 (30.8)	11,355 (31.1)	3835 (29.2)	3821 (29.1)
Hypoglycemia	295 (2.3)	310 (2.4)	912 (2.5)	976 (2.7)	313 (2.4)	304 (2.3)
Dyslipidemia	11,157 (85.8)	11,183 (86.0)	32,023 (87.6)	32,092 (87.8)	11,268 (85.9)	11,286 (86.1)
Diabetic nephropathy	1089 (8.4)	1073 (8.3)	3685 (10.1)	3681 (10.1)	1076 (8.2)	1023 (7.8)
Diabetic neuropathy	2479 (19.1)	2440 (18.8)	7357 (20.1)	7340 (20.1)	2455 (18.7)	2466 (18.8)
Diabetic retinopathy	1486 (11.4)	1459 (11.2)	4248 (11.6)	4297 (11.8)	1474 (11.2)	1472 (11.2)

Continued on next page

TABLE 2. Continued

Characteristic	Apixaban cohort	Dabigatran cohort	Apixaban cohort	Rivaroxaban cohort	Dabigatran cohort	Rivaroxaban cohort
Baseline medication use						
ACEi/ARB	9571 (73.6)	9576 (73.6)	26,897 (73.6)	26,855 (73.5)	9656 (73.6)	9669 (73.7)
Amiodarone	1498 (11.5)	1528 (11.7)	4679 (12.8)	4710 (12.9)	1536 (11.7)	1580 (12.0)
β-blockers	7743 (59.5)	7792 (59.9)	22,538 (61.7)	22,578 (61.8)	7842 (59.8)	7772 (59.3)
H2-receptor antagonists	954 (7.3)	949 (7.3)	2935 (8.0)	2974 (8.1)	956 (7.3)	1008 (7.7)
Proton pump inhibitors	4332 (33.3)	4219 (32.4)	13,034 (35.7)	13,084 (35.8)	4231 (32.3)	4309 (32.9)
Statins	9035 (69.5)	8995 (69.2)	26,354 (72.1)	26,379 (72.2)	9057 (69.1)	9023 (68.8)
Anti-platelets	2868 (22.1)	2864 (22.0)	9514 (26.0)	9587 (26.2)	2878 (21.9)	2921 (22.3)
NSAIDs	3557 (27.3)	3499 (26.9)	9731 (26.6)	9714 (26.6)	3533 (26.9)	3527 (26.9)
Diuretics	8041 (61.8)	7998 (61.5)	23,044 (63.0)	23,067 (63.1)	8057 (61.4)	8095 (61.7)
Calcium channel blockers	5988 (46.0)	5966 (45.9)	17,188 (47.0)	17,183 (47.0)	6006 (45.8)	5962 (45.5)
Baseline diabetes medications						
Biguanides	6091 (46.8)	6066 (46.6)	15,989 (43.7)	15,921 (43.6)	6130 (46.7)	6089 (46.4)
Sulphonylureas	3565 (27.4)	3505 (26.9)	9416 (25.8)	9378 (25.7)	3550 (27.1)	3574 (27.3)
Meglitinide	157 (1.2)	151 (1.2)	427 (1.2)	438 (1.2)	151 (1.2)	150 (1.1)
Thiazolidinediones	674 (5.2)	672 (5.2)	1702 (4.7)	1689 (4.6)	681 (5.2)	708 (5.4)
DPP-4 inhibitors	1537 (11.8)	1503 (11.6)	4321 (11.8)	4282 (11.7)	1519 (11.6)	1559 (11.9)
Insulin	2875 (22.1)	2890 (22.2)	8252 (22.6)	8244 (22.6)	2919 (22.3)	2949 (22.5)
α-glucosidase inhibitors	56 (0.4)	57 (0.4)	168 (0.5)	168 (0.5)	56 (0.4)	60 (0.5)
SGLT-2 inhibitors	72 (0.6)	78 (0.6)	364 (1.0)	357 (1.0)	81 (0.6)	83 (0.6)
GLP-1 agonists	402 (3.1)	355 (2.7)	1016 (2.8)	1001 (2.7)	356 (2.7)	357 (2.7)
Dose of the index prescription						
Standard dose[e]	10,545 (81.1)	10,543 (81.1)	27,852 (76.2)	24,605 (67.3)	10,648 (81.2)	9509 (72.5)
Lower dose[f]	2461 (18.9)	2463 (18.9)	8697 (23.8)	11,944 (32.7)	2467 (18.8)	3606 (27.5)
Follow-up time (d)						
Mean	187.6±171.0	225.0±223.5	183.7±167.0	225.5±213.7	224.6±223.3	230.0±216.9
Median	124	123	122	142	123	147

[a]ACEi/ARB = angiotensin converting enzyme inhibitors/angiotensin-receptor blocker; CHA_2DS_2-VASc = congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65-74 years, sex category; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide; HAS-BLED = hypertension, abnormal (renal/liver function), stroke, bleeding, labile (international normalized ratio), elderly, drug/alcohol/medication (usage history); NOAC = non-vitamin K oral anticoagulant; NSAIDs = non-steroidal anti-inflammatory drugs; PSM = propensity score matching; SE = systemic embolism; SGLT-2 = sodium-glucose co-transporter 2.

[b]Data are presented as mean ± SD or as No. (percentage).

[c]As the international normalized ratio value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.

[d]Diabetes type was defined by the presence of International Classification of Disease, Ninth Revision, Clinical Modification diagnosis codes only and was not further validated.

[e]Standard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban.

[f]Lower dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 2,005 and 672 patients were prescribed 10 mg of rivaroxaban in the apixaban-rivaroxaban and dabigatran-rivaroxaban cohorts, respectively.

dabigatran (75 mg), and 12,477 (24%) of those prescribed rivaroxaban (15 mg). In addition, 5% of patients treated with rivaroxaban were prescribed 10 mg of rivaroxaban (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

The unadjusted incidence rates of stroke/SE in the warfarin, apixaban, dabigatran, and rivaroxaban cohorts were 2.5, 1.7, 1.8, and 1.7 events per 100 person-years, respectively. The unadjusted incidence rates of MB in the warfarin, apixaban, dabigatran, and rivaroxaban cohorts were 8.2, 4.8, 4.8, and 6.9 events per 100 person-years, respectively (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

After PSM, a total of 154,324 unique patients were included. PSM produced 35,269, 12,954, and 44,412 patient pairs for the apixaban-warfarin, dabigatran-warfarin, and rivaroxaban-warfarin cohorts, respectively.

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PSM for NOAC comparisons included 13,006, 36,549, and 13,115 patient pairs for the apixaban-dabigatran, apixaban-rivaroxaban, and dabigatran-rivaroxaban cohorts, respectively (Figure 1). The baseline characteristics of the matched populations are listed in Tables 1 and 2. After matching, all demographic and clinical characteristics were well balanced. Across the matched cohorts during the baseline period, 22% to 23%, 42% to 47%, and 26% to 28% were prescribed insulin, biguanides, and sulfonylureas, respectively. The mean follow-up ranged between 6 and 8 months in all matched cohorts.

The baseline characteristics of patients with NVAF prescribed standard- and lower-dosed NOACs are summarized in Supplemental Tables 4, 5, 6, and 7 (available online at http://www.mayoclinicproceedings.org).

Non–Vitamin K Oral Anticoagulant and Warfarin Comparisons

Compared with warfarin, apixaban (hazard ratio [HR], 0.67; 95% CI, 0.57-0.77) and rivaroxaban (HR, 0.79; 95% CI, 0.71-0.89) were associated with a lower risk of stroke/SE. There was no significant difference in the risk of stroke/SE (HR, 0.84; 95% CI, 0.67-1.07) between dabigatran and warfarin. Compared with those prescribed warfarin, patients prescribed apixaban had a 26% lower risk of ischemic stroke (HR, 0.74; 95% CI, 0.65-0.85) whereas those prescribed rivaroxaban had a 14% lower risk of ischemic stroke (HR, 0.86; 95% CI, 0.77-0.97) (Figure 2A). In addition, patients prescribed apixaban (HR, 0.48; 95% CI, 0.30-0.77), dabigatran (HR, 0.36; 95% CI, 0.21-0.60) and rivaroxaban (HR, 0.56; 95% CI, 0.45-0.69) had a lower risk of hemorrhagic stroke than did patients prescribed warfarin.

Compared with warfarin, apixaban (HR, 0.60; 95% CI, 0.56-0.65) and dabigatran (HR, 0.78; 95% CI, 0.69-0.88) were associated with a lower risk of MB. Compared with warfarin, rivaroxaban was associated with a similar risk of MB (HR, 1.02; 95% CI, 0.94-1.10).

Compared with those prescribed warfarin, patients prescribed apixaban had a lower risk of GI bleeding (HR, 0.58; 95% CI, 0.53-0.65), patients prescribed rivaroxaban had a higher risk of GI bleeding (HR, 1.19; 95% CI, 1.09-1.30), and patients prescribed dabigatran had a similar risk of GI bleeding (HR, 0.99; 95% CI, 0.84-1.17). All NOACs were associated with a lower risk of intracranial hemorrhage compared with warfarin (Figure 2A).

Non–Vitamin K Oral Anticoagulant and NOAC Comparisons

Apixaban was associated with a lower risk of stroke/SE compared with dabigatran (HR, 0.78; 95% CI, 0.64-0.94) and rivaroxaban (HR, 0.87; 95% CI, 0.75-1.00). Similarly, apixaban was associated with a lower risk of MB compared with dabigatran (HR, 0.73; 95% CI, 0.63-0.84) and rivaroxaban (HR, 0.59; 95% CI, 0.54-0.65), both driven by GI bleeding. Dabigatran was associated with a similar risk of stroke/SE (HR, 1.11; 95%, 0.85-1.46) and lower risk of MB (HR, 0.76; 95% CI, 0.66-0.86) compared with rivaroxaban (Figure 2B).

The Kaplan-Meier curves for the cumulative incidence rates of stroke/SE and MB in the matched populations are shown in Supplemental Figure 1A and B (available online at http://www.mayoclinicproceedings.org).

The results of the standard- and low-dose subgroup analysis were generally consistent with the main analysis (Figure 3).

DISCUSSION

This ARISTOPHANES analysis of a high-risk subgroup of diabetic patients is the largest retrospective observational study to date that examines the risk of stroke/SE and MB patients with NVAF and diabetes who have initiated OAC treatment. The relevance of evaluating diabetic patients as a high-risk subgroup is paramount, as diabetes is one of the most common concomitant comorbid conditions in patients with AF.[6,7] With pooled data of US Centers for Medicare & Medicaid Services Medicare and 4 large US national claims databases, this study found that apixaban and rivaroxaban were associated with lower rates of stroke/SE compared with warfarin. In addition, apixaban and

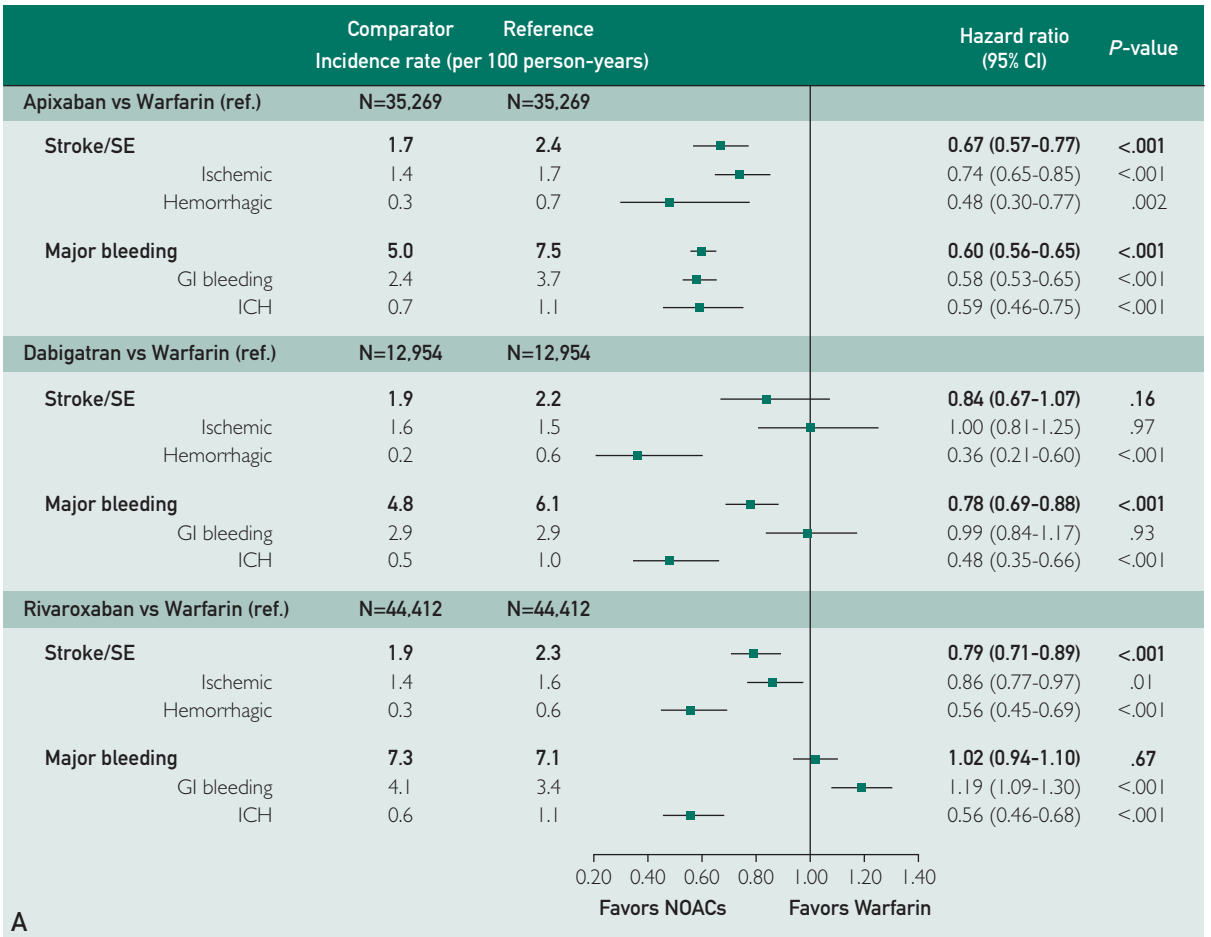

FIGURE 2. Incidence and hazard ratios of (A) NOACs vs warfarin and (B) NOACs vs NOACs. Incidence rates were measured per 100 person-years for matched NOAC cohorts. Hazard ratios were measured along with 95% CIs. [a]Upper limit of 95% was rounded from 0.997 to 1.00. GI = gastrointestinal; ICH = intracranial hemorrhage; NOAC = non–vitamin K oral anticoagulant; ref. = reference; SE = systemic embolism.

dabigatran were associated with lower rates of MB compared with warfarin. As a hypothesis-generating analysis, NOAC and NOAC comparisons suggested that there was a significantly lower risk of stroke/SE with apixaban compared to dabigatran and rivaroxaban. Apixaban was associated with a lower risk of MB compared with dabigatran and rivaroxaban and dabigatran was associated with a lower risk of MB compared with rivaroxaban.

Subgroup analyses of the ARISTOTLE, Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) and 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) trials have revealed that apixaban, dabigatran, and rivaroxaban have no significant interaction with diabetes status for the reduction of stroke/SE.[22-24] However, in the diabetes subgroup analysis of the ARISTOTLE trial, apixaban was associated with a reduction in MB in patients without diabetes (HR, 0.60; 95% CI, 0.51-0.72) but a similar risk of MB in patients with diabetes (HR, 0.96; 95% CI, 0.74-1.25; $P_{\text{interaction}}$=.003) compared with warfarin.[22] The significant interaction may have been due to chance. There was no significant interaction for

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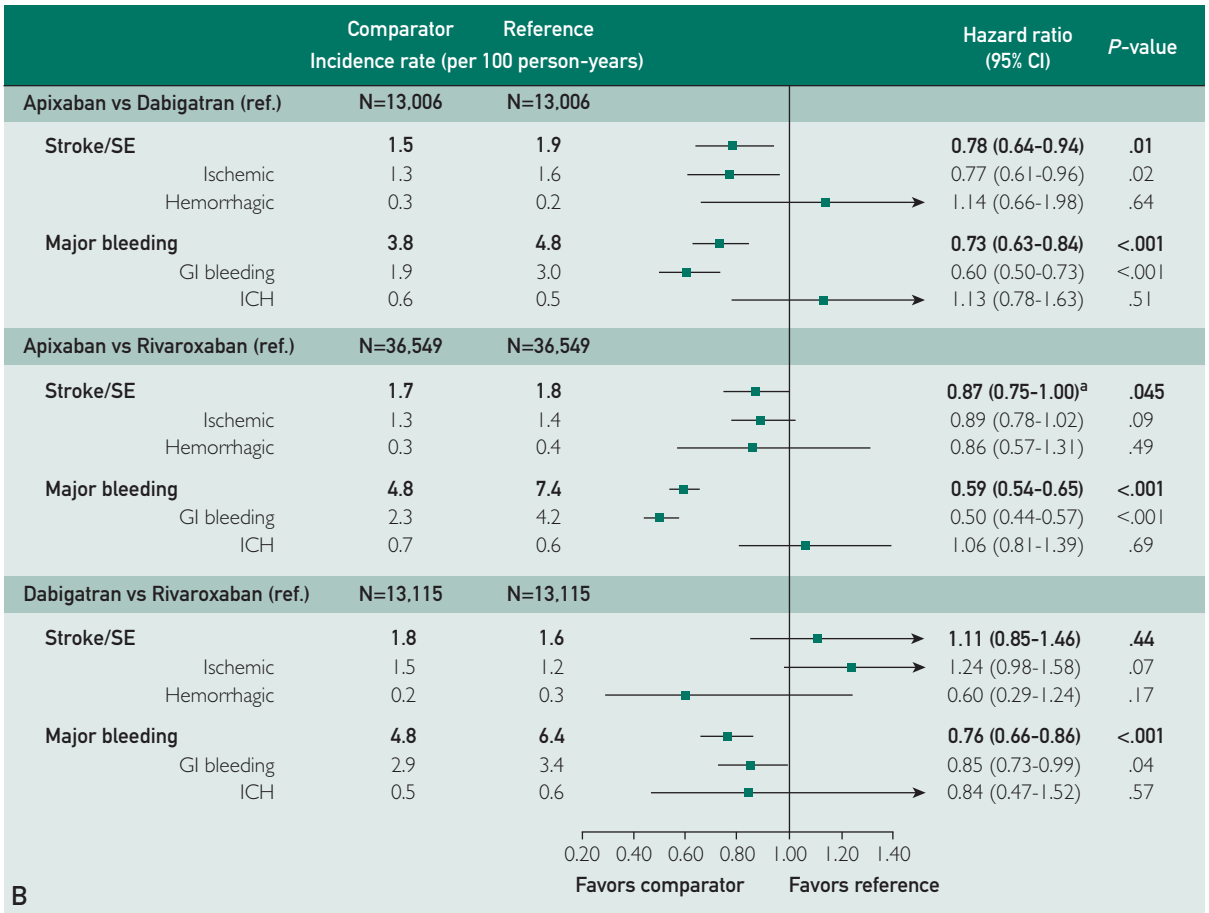

FIGURE 2. (*continued*).

intracranial hemorrhage; apixaban was associated with reduced intracranial hemorrhage compared with warfarin in patients with and without diabetes. The ROCKET-AF and the RE-LY trials reported that the incidence of MB for dabigatran (150 mg) or rivaroxaban was similar to that for warfarin, regardless of diabetes status.[23,24] Meta-analyses of randomized controlled trials (including ARISTOTLE, RE-LY, ROCKET-AF, and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation [ENGAGE-AF]) have revealed that diabetes status has no differential effect on the safety or effectiveness of all NOACs combined vs warfarin. Non–vitamin K oral anticoagulants were found to reduce the risk of stroke/SE and MB compared with warfarin in both diabetic and nondiabetic patients.[20,21]

Few retrospective observational studies have evaluated clinical outcomes in patients with NVAF and diabetes prescribed NOACs. One retrospective study using US commercial claims, leveraging data from the Truven MarketScan database, found no significant difference in the risk of stroke/SE and MB between rivaroxaban and warfarin therapy in diabetic patients with NVAF.[32] A study of US Department of Defense records found that rivaroxaban was associated with a higher incidence of MB in diabetic patients than in nondiabetic patients (3.7 events per 100 person-years vs 2.5 events per 100 person-years).[33] A study in Taiwan in diabetic patients with NVAF found that compared with those prescribed warfarin, patients prescribed dabigatran had a lower risk of all-cause mortality and GI bleeding whereas

	Standard dose			Lower dose		
	Incidence (per 100 person-years)	Hazard ratio (95% CI)	*P*-value	Incidence (per 100 person-years)	Hazard ratio (95% CI)	*P*-value
Apixaban (com.) vs Warfarin (ref.)						
Stroke/SE	1.5 vs 2.1	0.66 (0.56-0.78)	**<.001**	2.4 vs 3.5	0.64 (0.50-0.83)	**<.001**
Major bleeding	4.6 vs 6.5	0.65 (0.60-0.71)	**<.001**	6.0 vs 10.4	0.54 (0.47-0.61)	**<.001**
Dabigatran (com.) vs Warfarin (ref.)						
Stroke/SE	1.6 vs 1.7	0.97 (0.70-1.34)	.83	2.8 vs 3.1	0.89 (0.61-1.29)	.52
Major bleeding	4.2 vs 5.5	0.75 (0.65-0.87)	**<.001**	7.5 vs 10.7	0.70 (0.55-0.89)	**.004**
Rivaroxaban (com.) vs Warfarin (ref.)						
Stroke/SE	1.6 vs 2.0	0.81 (0.71-0.92)	**.001**	2.3 vs 3.0	0.75 (0.64-0.88)	**<.001**
Major bleeding	6.4 vs 5.9	1.07 (0.97-1.19)	.19	9.4 vs 9.2	0.99 (0.90-1.08)	.77
Apixaban (com.) vs Dabigatran (ref.)						
Stroke/SE	1.3 vs 1.6	0.76 (0.61-0.95)	**0.02**	2.3 vs 2.8	0.74 (0.49-1.11)	.15
Major bleeding	3.9 vs 4.2	0.87 (0.73-1.03)	.11	5.0 vs 7.6	0.58 (0.42-0.79)	**.001**
Apixaban (com.) vs Rivaroxaban (ref.)						
Stroke/SE	1.4 vs 1.6	0.84 (0.70-1.00)[a]	**.049**	2.4 vs 2.5	0.87 (0.68-1.13)	.29
Major bleeding	4.2 vs 6.5	0.59 (0.54-0.65)	**<.001**	6.0 vs 10.4	0.55 (0.48-0.63)	**<.001**
Dabigatran (com.) vs Rivaroxaban (ref.)						
Stroke/SE	1.6 vs 1.4	1.16 (0.86-1.58)	.33	2.8 vs 1.7	1.65 (1.01-2.68)	**.045**
Major bleeding	4.2 vs 5.9	0.72 (0.60-0.85)	**<.001**	7.6 vs 9.6	0.82 (0.65-1.03)	.09

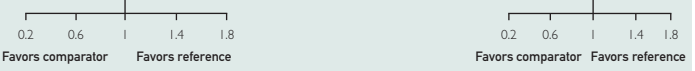

FIGURE 3. Incidence and hazard ratios for dose subgroup analysis. Incidence rates were measured per 100 person-years for matched non–vitamin K oral anticoagulant cohorts. Hazard ratios were measured along with 95% CIs. comp. = comparator; ref. = reference; SE = systemic embolism. [a]Upper limit of 95% was rounded from 0.999 to 1.00.

those prescribed rivaroxaban had a similar risk of mortality, stroke, and bleeding. Also, compared with those prescribed rivaroxaban, patients prescribed dabigatran had significantly lower rates of all-cause mortality.[34] An analysis of patients with and without diabetes from a retrospective observational study, leveraging data from US HealthCore claims, revealed that patients prescribed rivaroxaban had MB event rates similar to those of patients prescribed warfarin; however, compared with those prescribed warfarin, patients prescribed apixaban and dabigatran were associated with a reduction in MB events, regardless of diabetes status.[35] Both patients prescribed dabigatran and those prescribed apixaban had a lower risk of MB than did those prescribed rivaroxaban among patients with and without diabetes. Compared with those prescribed dabigatran, patients prescribed apixaban had a similar risk of MB irrespective of diabetes status.[35]

Compared with previous studies, the ARISTOPHANES study included a larger sample of patients with NVAF and concomitant diabetes, providing this analysis with higher statistical power. Consistent with earlier publications, the present study reported that in this high-risk diabetes subgroup, apixaban and dabigatran were associated with a lower risk of MB compared with warfarin and rivaroxaban.[26,35,36]

This retrospective observational study has several limitations. First, only statistical associations could be concluded, not causal relationships. Although cohorts were matched through PSM, there were potential residual confounders. This limitation is especially important for interpreting NOAC and NOAC comparison results, which are intended for hypothesis generation, given the lack of head-to-head trials. Second, because of the nature of claims studies, outcome measures could only be based on *ICD-9-CM* codes without further adjustment with precise clinical criteria. In addition, the dose of warfarin and laboratory values, such as INR measurements, are not available in the data set, so the time in therapeutic range for patients prescribed warfarin was indeterminable. Nonetheless, the inclusion of patients with potentially poorer quality control of warfarin therapy in everyday clinical practice may enable the study findings to better reflect real-world situations. In

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addition, a previous study found that PSM using claims-defined baseline characteristics was sufficient in balancing mean INR and INR categories across post-PSM warfarin cohorts matched to different NOACs (dabigatran, rivaroxaban, and apixaban).[37] Given our limited ability to clinically characterize diabetes type and severity (represented by diabetes medications and complications) because of our reliance on claims data, we could not further assess whether our findings would be different by type and severity of diabetes, such as duration of diabetes or hemoglobin A_{1c} levels.[10,11] Type 1 diabetes occurs at a younger age and type 2 diabetes occurs at an older age and has a higher prevalence of AF. Previous studies have found that stroke risk may be higher in type 1 diabetic patients, but a recent study of patients with NVAF did not find an association between type of diabetes and risk of thromboembolism.[38-40] We are not able to assess the effect of the type of diabetes in our study. Moreover, unobserved heterogeneity may exist across the 5 data sources. Although some of the data sets contain information from different insurance plans that do not overlap at the plan level, others are employer-based claims data sets that may contain duplicate patient records when pooled together. However, the number of such duplicates is likely to be low—on the basis of a published estimate of 0.5%—and therefore unlikely to have any significant effect on the results.[41] Finally, the results may not reflect the overall population with NVAF in the United States, because the study did not include uninsured patients and those solely covered by other public health insurance plans.

CONCLUSION

This study, the largest observational study of NVAF with concomitant diabetes, reports that NOACs were associated with variable rates of stroke/SE and MB compared with warfarin and compared with each other. These findings supplement the information from the NOAC randomized controlled trials and may support future studies on patients with NVAF and concomitant diabetes to provide clinicians with a better understanding of the real-world clinical outcomes of diabetic patients in routine clinical practice.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **ARISTOPHANES** = Anticoagulants for Reduction In STroke: Observational Pooled analysis on Health outcomes ANd Experience of patientS; **ARISTOTLE** = Apixaban for Reduction In STroke and Other ThromboembboLic Events in Atrial Fibrillation; **CHA_2DS_2-VASc** = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke (previous), vascular disease, age 65-74 years, sex; **ENGAGE-AF** = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; **GI** = gastrointestinal; **HAS-BLED** = hypertension, abnormal (renal/liver function), stroke, bleeding, labile (international normalized ratio), elderly, drug/alcohol/medication (usage history); **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **INR** = international normalized ratio; **MB** = major bleeding; **NOAC** = non—vitamin K oral anticoagulant; **OAC** = oral anticoagulant; **PSM** = propensity score matching; **RE-LY** = Randomized Evaluation of Long-term anticoagulant therapy; **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; **SE** = systemic embolism

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