Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients with High Risk of Gastrointestinal Bleeding

Lip, Gregory Y.H.; Keshishian, Allison V.; Zhang, Yan; Kang, Amiee; Dhamane, Amol D.; Luo, Xuemei; Klem, Christian; Ferri, Mauricio; Jiang, Jenny; Yuce, Huseyin; Deitelzweig, Steven

Published in:
JAMA Network Open

DOI (link to publication from Publisher):
10.1001/jamanetworkopen.2021.20064

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

JAMA Network Open

Original Investigation | Cardiology

Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients With High Risk of Gastrointestinal Bleeding

Gregory Y. H. Lip, MD; Allison V. Keshishian, MPH; Yan Zhang, PhD; Amiee Kang, MPH; Amol D. Dhamane, MS; Xuemei Luo, PhD; Christian Klem, PharmD; Mauricio Ferri, MD; Jenny Jiang, MS; Huseyin Yuce, PhD; Steven Deitelzweig, MD

Abstract

IMPORTANCE Many patients with nonvalvular atrial fibrillation (NVAF) are at a high risk of gastrointestinal (GI) bleeding due to conditions including older age; stage III to V chronic kidney disease (CKD); HAS-BLED (hypertension, kidney or liver disease, stroke history, prior bleeding, unstable international normalized ratio, age >65, drug or alcohol use) score of 3 or greater; corticosteroid, antiplatelet or nonsteroidal anti-inflammatory drug (NSAID) use; or GI conditions.

OBJECTIVE To compare the risk of stroke and/or systemic embolism (SE) and major bleeding (MB) among patients with NVAF and high risk of GI bleeding who received non–vitamin K antagonist oral anticoagulants (NOACs) vs those who received warfarin.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included patients with NVAF who were 75 years and older; had stage III to V CKD; had an HAS-BLED score of 3 or greater; used corticosteroids, antiplatelets, or NSAIDs; or had GI conditions. Data were collected from the Centers for Medicare & Medicaid Services and 4 commercial insurance databases between January 1, 2012, and September 30, 2015. Data analysis was conducted from April to August 2020.

EXPOSURES New prescription for apixaban, dabigatran, rivaroxaban, or warfarin between January 1, 2013, and September 30, 2015 (identification period).

MAIN OUTCOMES AND MEASURES Six propensity score–matched cohorts were created to compare between study drugs. For the primary objective, Cox models were used to estimate stroke and/or SE and MB hazard ratios (HRs).

RESULTS A total of 381 054 patients (187 489 [49.2%] women) with NVAF and at least 1 high-risk GI bleeding factor were identified (HAS-BLED score ≥3: 284 527 [74.7%]; aged ≥75 years: 252 835 [66.4%]; corticosteroid, antiplatelet, or NSAID therapy: 107 675 [28.3%]; prior GI bleeding conditions: 74 818 [19.6%]; and stage III-V CKD: 56 892 [14.9%]). All NOACs were associated with a lower risk of stroke and/or SE vs warfarin (apixaban: HR, 0.60; 95% CI, 0.52-0.68; dabigatran: HR, 0.75; 95% CI, 0.64-0.88; rivaroxaban: HR, 0.79; 95% CI, 0.73-0.86). Compared with warfarin, apixaban and dabigatran were associated with a lower risk of MB (apixaban: HR, 0.59; 95% CI, 0.56-0.63; dabigatran: HR, 0.78; 95% CI, 0.70-0.86), while rivaroxaban was associated with a higher risk (HR, 1.11; 95% CI, 1.05-1.16).

CONCLUSIONS AND RELEVANCE In this study of patients with NVAF and high risk of GI bleed, NOACs were associated with lower rates of stroke and/or SE, but NOACs had varying risks of MB compared with warfarin. These results may help inform treatment options in this patient population.

Key Points

Question How does the risk of stroke and/or systemic embolism (SE) and major bleeding among patients with nonvalvular atrial fibrillation and high risk of gastrointestinal bleeding compare when prescribed non–vitamin K antagonist oral anticoagulants (NOACs) vs warfarin?

Findings In this cohort study of 381 054 patients, NOACs were associated with lower risk of stroke and/or SE but varying risks of major bleeding compared with warfarin.

Meaning These results may help inform decision-making regarding OACs in this high-risk patient population.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

JAMA Network Open. 2021;4(8):e2120064.
Corrected on September 15, 2021. doi:10.1001/jamanetworkopen.2021.20064

Introduction

Stroke prevention is the cornerstone of management in atrial fibrillation (AF), and oral anticoagulants (OACs) are recommended to reduce the risk of stroke; however, there is an increased risk of bleeding.[1-4] Non–vitamin K antagonists OACs (NOACs) have been proven to be at least as effective in stroke prevention compared with vitamin K antagonists in clinical trials and in real-world settings.[5-8] However, the risk of major and gastrointestinal (GI) bleeding could affect the safety of patients after treatment with NOACs.[1]

In clinical trials, apixaban, dabigatran, and edoxaban were associated with a lower MB risk compared with warfarin[7,8] and had varied risk of GI bleed: standard doses of dabigatran (150 mg, twice a day) and edoxaban (60 mg, once a day) were associated with a higher risk, while apixaban was associated with a lower risk. 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) study showed rivaroxaban was associated with a similar risk of MB compared with warfarin[9] and a higher rate of GI bleeds. As such, the 2020 European Society of Cardiology (ESC) guidelines indicate that apixaban or low-dose dabigatran (110 mg, twice a day; not licensed in the US for AF) should be considered for patients with a recent bleeding event.[10]

Compared with warfarin, real-world studies found a decreased risk of GI bleed with apixaban, a decreased-to-similar risk with dabigatran, and a similar-to-increased risk with rivaroxaban.[3,11,12] These previous studies assessed general populations of patients with nonvalvular AF (NVAF) and suggest that the risk of GI bleeding can differ. A number of factors, such as older patient age; patient use of nonsteroid anti-inflammatory drugs (NSAIDs); higher dose of NOAC medication; comorbid conditions, such as kidney impairment, congestive heart failure, or chronic liver disease; and patient history of GI bleeds, have been found to be associated with the risk of major GI bleeding in patients with NVAF.[3,5,12] It is important to identify patients with NVAF and high risk of GI bleeds based on these risk factors for further analyses, as variable patient characteristics must be taken into account to assist in choosing the appropriate OAC.[3,5] This analysis of patients at high risk of GI bleeding in the Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients (ARISTOPHANES; NCT03087487)[13] study aimed to provide complementary evidence by comparing the rates of stroke and/or systemic embolism (SE) and major bleeding (MB) among patients with NVAF and high risk of GI bleeding who were newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin.

Methods

This study was conducted among patients with NVAF and a high risk of GI bleeding who were newly treated with apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin—a subgroup analysis of the ARISTOPHANES study.[13] ARISTOPHANES was a retrospective cohort study that used data from the Centers for Medicare & Medicaid Services (CMS) Medicare database and 4 US commercial claims databases.[14] Since this study did not involve the collection, use, or transmittal of individually identifiable data, it was exempt from institutional review board review according to 45 CFR §46. Both the data sets and the security of the offices where analysis was completed (and where the data sets are kept) meet the requirements of the Health Insurance Portability and Accountability Act of 1996.

Among patients included in the ARISTOPHANES study, patients with AF and an OAC pharmacy claim between January 1, 2013, and September 30, 2015 (ie, the identification period), were chosen; the first NOAC pharmacy claim during the identification period was designated as the index date for patients with any NOAC claim, and the first warfarin prescription date was designated as the index date for those without a NOAC claim. Patients prescribed edoxaban were not included in this study given the insufficient sample size. Patient exclusion criteria are listed in **Figure 1**. Based on the findings of previous studies, patients at high risk of GI bleed were identified as follows: (1) older age

(≥75 years)[3,12]; (2) impaired kidney function (chronic kidney disease [CKD], stage III, IV, or V or end-stage kidney disease)[3,14]; (3) a score of 3 or greater on the HAS-BLED (hypertension, kidney or liver disease, stroke history, prior bleeding, unstable international normalized ratio, age >65, drug or alcohol use)[3]; (4) concomitant use of NSAIDs, antiplatelet agents, or corticosteroids at index[3,14]; and (5) a past history of GI ulcers or bleeds.[3,4]

Outcome Measures

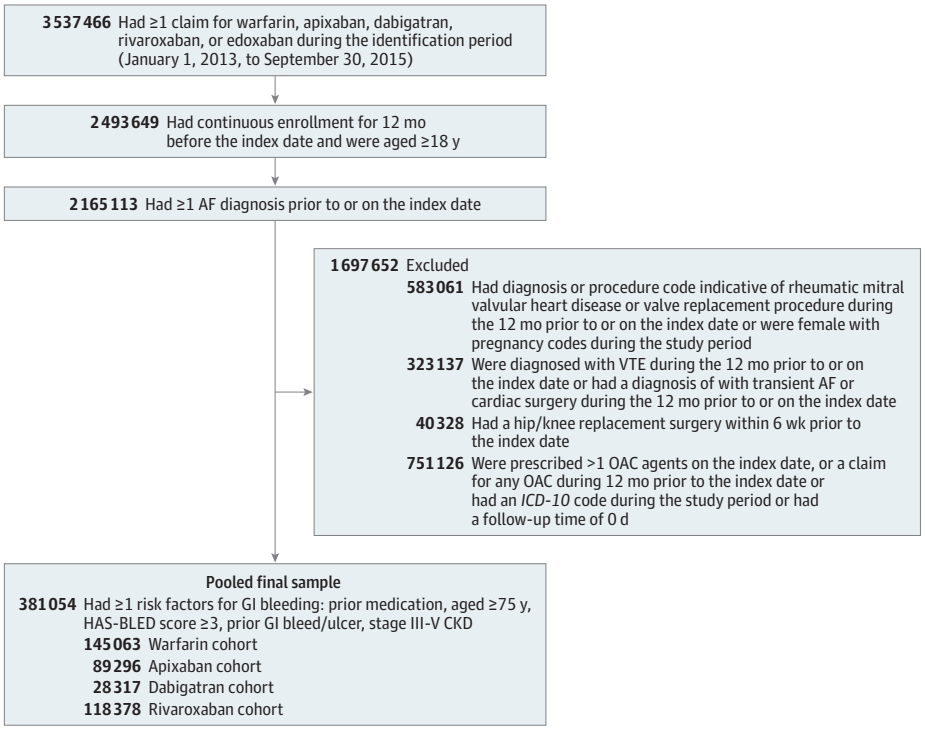
Primary effectiveness outcomes were stroke and/or SE, stratified by ischemic stroke, hemorrhagic stroke, and SE. Primary safety outcome was MB, stratified by GI bleeding, intracranial hemorrhage (ICH), and MB in other key sites (eTable 1 in the Supplement).[15,16] The primary outcomes were identified using inpatient claims with stroke and/or SE or MB as the principal (Medicare, MarketScan, and Optum) or first-listed (Humana and PharMetrics) diagnosis.

Outcomes were measured for the follow-up period, defined as the time from 1 day after the index date to the earliest of the following: 30 days after the discontinuation date, switch date, date of death (inpatient and all-cause death for commercial data and Medicare populations, respectively), end of continuous health plan enrollment, or study end (September 30, 2015).

Statistical Analysis

To control for different patient characteristics, propensity score matching (PSM) was used to compare NOAC vs warfarin (apixaban vs warfarin, dabigatran vs warfarin, and rivaroxaban vs warfarin) and NOAC vs NOAC (apixaban vs dabigatran, apixaban vs rivaroxaban, and dabigatran vs rivaroxaban). Patients were matched by type and number of risk factors for GI bleeding and then matched 1:1 by propensity scores generated using multivariable logistic regressions for baseline characteristics, including demographic and clinical characteristics. The complete covariate list appears in **Table 1** and **Table 2**. Further details on PSM methodology appear in prior publications.[13]

Figure 1. Patient Selection Criteria



The study population selected patients with nonvalvular atrial fibrillation (AF) with high risk for gastrointestinal bleed who initiated an oral anticoagulant (OAC) of interest, resulting in 6 PSM cohorts ranging from 22 282 to 76 500 matched patients. CKD indicates chronic kidney disease; HAS-BLED, hypertension, kidney or liver disease, stroke history, prior bleeding, unstable international normalized ratio, age 65 years or older, drug or alcohol use; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; GI, gastrointestinal; and VTE, venous thromboembolism.

Table 1. Baseline Characteristics of Patients Prescribed NOACs vs Warfarin After Propensity Score Matching

Characteristic	Patients, No. (%)					
	Apixaban vs warfarin		Dabigatran vs warfarin		Rivaroxaban vs warfarin	
	Apixaban cohort (n = 62 372)	Warfarin cohort (n = 62 372)	Dabigatran cohort (n = 23 003)	Warfarin cohort (n = 23 003)	Rivaroxaban cohort (n = 76 500)	Warfarin cohort (n = 76 500)
Age, y[a]						
Mean (SD)	79.4 (7.6)	79.4 (7.5)	77.8 (7.4)	78.4 (7.8)	78.7 (7.5)	79.1 (7.7)
<65	767 (1.2)	764 (1.2)	430 (1.9)	447 (1.9)	1273 (1.7)	1299 (1.7)
65-74	14 931 (23.9)	14 934 (23.9)	6863 (29.8)	6846 (29.8)	19 212 (25.1)	19 186 (25.1)
75-79	16 011 (25.7)	15 864 (25.4)	6526 (28.4)	5412 (23.5)	21 504 (28.1)	19 319 (25.3)
≥80	30 663 (49.2)	30 810 (49.4)	9184 (39.9)	10 298 (44.8)	34 511 (45.1)	36 696 (48.0)
Sex[a]						
Male	29 747 (47.7)	29 654 (47.5)	11 656 (50.7)	11 707 (50.9)	37 449 (49.0)	37 523 (49.0)
Female	32 625 (52.3)	32 718 (52.5)	11 347 (49.3)	11 296 (49.1)	39 051 (51.0)	38 977 (51.0)
Baseline Comorbidities						
Deyo-Charlson Comorbidity Index score, mean (SD)[a]	3.2 (2.7)	3.1 (2.7)	3.0 (2.6)	2.9 (2.5)	3.1 (2.6)	3.0 (2.6)
CHA_2DS_2-VASc score, mean (SD)						
Mean (SD)	4.3 (1.5)	4.3 (1.4)	4.2 (1.4)	4.1 (1.4)	4.2 (1.4)	4.2 (1.4)
0	82 (0.1)	74 (0.1)	46 (0.2)	52 (0.2)	155 (0.2)	150 (0.2)
1	497 (0.8)	443 (0.7)	282 (1.2)	265 (1.2)	811 (1.1)	748 (1.0)
2	4933 (7.9)	4604 (7.4)	2092 (9.1)	2002 (8.7)	6604 (8.6)	6186 (8.1)
3	13 251 (21.2)	13 484 (21.6)	5308 (23.1)	5412 (23.5)	17 083 (22.3)	17 262 (22.6)
≥4	43 609 (69.9)	43 767 (70.2)	15 275 (66.4)	15 272 (66.4)	51 847 (67.8)	52 154 (68.2)
HAS-BLED Score[b]						
Mean (SD)	3.3 (1.2)	3.3 (1.2)	3.3 (1.2)	3.2 (1.1)	3.3 (1.2)	3.3 (1.2)
0	35 (0.1)	30 (0.0)	17 (0.1)	24 (0.1)	76 (0.1)	67 (0.1)
1	3091 (5.0)	3168 (5.1)	1064 (4.6)	1104 (4.8)	4221 (5.5)	4237 (5.5)
2	12 042 (19.3)	11 970 (19.2)	4898 (21.3)	4851 (21.1)	15 695 (20.5)	15 688 (20.5)
≥3	47 204 (75.7)	47 204 (75.7)	17 024 (74.0)	17 024 (74.0)	56 508 (73.9)	56 508 (73.9)
Bleeding history[a]	13 191 (21.1)	13 220 (21.2)	4630 (20.1)	4647 (20.2)	15 998 (20.9)	16 198 (21.2)
Congestive heart failure[a]	19 478 (31.2)	19 289 (30.9)	6702 (29.1)	6624 (28.8)	22 585 (29.5)	22 465 (29.4)
Diabetes[a]	23 153 (37.1)	22 886 (36.7)	8781 (38.2)	8530 (37.1)	28 168 (36.8)	27 762 (36.3)
Hypertension[a]	55 907 (89.6)	56 205 (90.1)	20 661 (89.8)	20 736 (90.1)	68 002 (88.9)	68 226 (89.2)
Kidney disease[a]	16 204 (26.0)	15 686 (25.1)	4877 (21.2)	4651 (20.2)	17 482 (22.9)	16 469 (21.5)
Liver disease[a]	3171 (5.1)	3065 (4.9)	1147 (5.0)	1094 (4.8)	3934 (5.1)	3811 (5.0)
Myocardial infarction[a]	6140 (9.8)	5929 (9.5)	1917 (8.3)	1909 (8.3)	6985 (9.1)	6993 (9.1)
Dyspepsia or stomach discomfort[a]	12 318 (19.7)	12 141 (19.5)	4429 (19.3)	4291 (18.7)	14 763 (19.3)	14 778 (19.3)
Non-stroke or SE peripheral vascular disease[a]	34 697 (55.6)	34 340 (55.1)	12 439 (54.1)	12 360 (53.7)	41 320 (54.0)	41 190 (53.8)
Stroke and/or SE[a]	8914 (14.3)	9045 (14.5)	3068 (13.3)	3066 (13.3)	10 333 (13.5)	10 683 (14.0)
Transient ischemic attack[a]	5223 (8.4)	5257 (8.4)	1880 (8.2)	1846 (8.0)	6198 (8.1)	6247 (8.2)
Anemia and coagulation defects[a]	20 025 (32.1)	19 915 (31.9)	6794 (29.5)	6766 (29.4)	23 735 (31.0)	23 690 (31.0)
Alcohol use disorder[a]	1234 (2.0)	1237 (2.0)	538 (2.3)	512 (2.2)	1730 (2.3)	1757 (2.3)
Peripheral artery disease	13 915 (22.3)	14 284 (22.9)	4785 (20.8)	4906 (21.3)	16 733 (21.9)	16 857 (22.0)
Coronary artery disease	30 092 (48.2)	29 255 (46.9)	10 706 (46.5)	10 505 (45.7)	35 294 (46.1)	34 976 (45.7)
Baseline medication use[a]						
ACE and/or ARB	38 840 (62.3)	38 895 (62.4)	14 410 (62.6)	14 447 (62.8)	46 944 (61.4)	46 894 (61.3)
Amiodarone	7161 (11.5)	6900 (11.1)	2512 (10.9)	2397 (10.4)	8315 (10.9)	8055 (10.5)
β blockers	38 563 (61.8)	38 655 (62.0)	13 824 (60.1)	13 944 (60.6)	46 521 (60.8)	46 607 (60.9)
H2-receptor antagonists	4528 (7.3)	4320 (6.9)	1656 (7.2)	1539 (6.7)	5478 (7.2)	5433 (7.1)
Proton pump inhibitors	19 967 (32.0)	19 665 (31.5)	7104 (30.9)	6859 (29.8)	23 819 (31.1)	23 476 (30.7)
Statins	38 941 (62.4)	38 901 (62.4)	13 992 (60.8)	14 073 (61.2)	46 334 (60.6)	46 270 (60.5)
Antiplatelets	13 624 (21.8)	13 221 (21.2)	4783 (20.8)	4623 (20.1)	15 766 (20.6)	15 544 (20.3)
NSAIDs	15 039 (24.1)	15 277 (24.5)	6088 (26.5)	5998 (26.1)	18 771 (24.5)	18 960 (24.8)

(continued)

Table 1. Baseline Characteristics of Patients Prescribed NOACs vs Warfarin After Propensity Score Matching (continued)

Characteristic	Patients, No. (%)					
	Apixaban vs warfarin		Dabigatran vs warfarin		Rivaroxaban vs warfarin	
	Apixaban cohort (n = 62 372)	Warfarin cohort (n = 62 372)	Dabigatran cohort (n = 23 003)	Warfarin cohort (n = 23 003)	Rivaroxaban cohort (n = 76 500)	Warfarin cohort (n = 76 500)
Dose of the index prescription						
Standard dose[c]	43 266 (69.4)	NA	18 045 (78.4)	NA	50 134 (65.5)	NA
Lower dose[d]	19 106 (30.6)	NA	4958 (21.6)	NA	26 366 (34.5)	NA
Follow-up time, mean (SD), d						
Mean (SD)	190.8 (170.8)	249.8 (225.0)	237.6 (234.3)	253.5 (225.9)	236.4 (221.2)	251.6 (225.4)
Median (IQR)	130 (60-262)	165 (83-349)	133 (60-336)	169 (86-356)	149 (60-342)	167 (84-352)
Risk factors for GI bleeding						
Age ≥75 y	46 674 (74.8)	46 674 (74.8)	15 710 (68.3)	15 710 (68.3)	56 015 (73.2)	56 015 (73.2)
HAS-BLED score ≥3	47 204 (75.7)	47 204 (75.7)	17 024 (74.0)	17 024 (74.0)	56 508 (73.9)	56 508 (73.9)
Prior medications						
Any	14 686 (23.5)	14 686 (23.5)	5684 (24.7)	5684 (24.7)	18 303 (23.9)	18 303 (23.9)
Antiplatelets	7241 (11.6)	7519 (12.1)	2519 (11.0)	2740 (11.9)	8689 (11.4)	8990 (11.8)
NSAIDs	3966 (6.4)	3925 (6.3)	1788 (7.8)	1628 (7.1)	5115 (6.7)	5129 (6.7)
Corticosteroids	4963 (8.0)	4827 (7.7)	1994 (8.7)	1907 (8.3)	6434 (8.4)	6182 (8.1)
Prior GI conditions						
Any	8885 (14.2)	8885 (14.2)	3368 (14.6)	3368 (14.6)	10 821 (14.1)	10 821 (14.1)
Peptic ulcer	1009 (1.6)	1070 (1.7)	349 (1.5)	372 (1.6)	1173 (1.5)	1266 (1.7)
Prior GI bleeding	2914 (4.7)	3069 (4.9)	1098 (4.8)	1079 (4.7)	3398 (4.4)	3669 (4.8)
Helicobacter pylori	245 (0.4)	251 (0.4)	83 (0.4)	95 (0.4)	293 (0.4)	300 (0.4)
Diverticulosis	5612 (9.0)	5560 (8.9)	2162 (9.4)	2171 (9.4)	6908 (9.0)	6803 (8.9)
Angiodysplasias	166 (0.3)	171 (0.3)	60 (0.3)	65 (0.3)	177 (0.2)	193 (0.3)
GI cancer (ie, stomach, colon, esophageal, and rectal cancer)	796 (1.3)	885 (1.4)	276 (1.2)	311 (1.4)	1013 (1.3)	1064 (1.4)
Other GI lesions	590 (0.9)	378 (0.6)	161 (0.7)	154 (0.7)	594 (0.8)	496 (0.6)
Stage III-V CKD	8037 (12.9)	8037 (12.9)	2209 (9.6)	2209 (9.6)	7828 (10.2)	7828 (10.2)
Risk factors, No.						
1	20 856 (33.4)	20 856 (33.4)	8784 (38.2)	8784 (38.2)	27 435 (35.9)	27 435 (35.9)
2	23 352 (37.4)	23 352 (37.4)	8527 (37.1)	8527 (37.1)	28 681 (37.5)	28 681 (37.5)
3	14 917 (23.9)	14 917 (23.9)	4688 (20.4)	4688 (20.4)	17 042 (22.3)	17 042 (22.3)
4	3060 (4.9)	3060 (4.9)	927 (4.0)	927 (4.0)	3158 (4.1)	3158 (4.1)
5	187 (0.3)	187 (0.3)	77 (0.3)	77 (0.3)	184 (0.2)	184 (0.2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category; CKD, chronic kidney disease; GI, gastrointestinal; HAS-BLED, hypertension, kidney or liver disease, stroke history, prior bleeding, unstable international normalized ratio, age 65 years or older, drug or alcohol use; IQR, interquartile range; NA, not applicable; NOACs, non–vitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SE, systemic embolism.

[a] Variables controlled for in propensity score matching.

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

[c] Standard doses are as follows: apixaban, 5 mg; dabigatran, 150 mg; and rivaroxaban, 20 mg.

[d] Lower doses are as follows: apixaban, 2.5 mg; dabigatran, 75 mg; rivaroxaban, 10 or 15 mg. A total of 4569 patients received 10 mg rivaroxaban in the rivaroxaban-warfarin cohort.

The PSM-adjusted baseline variables were compared based on standardized differences, with a threshold of 10%.[17]

The incidence rates of stroke and/or SE and MB in the matched population were calculated using the number of events divided by total person-years at risk and multiplied by 100, with Kaplan-Meier curves to illustrate cumulative rates. Cox proportional hazard models with robust sandwich estimates were also applied to the PSM population to evaluate the comparative risks.[18] OAC treatment was included as the independent variable in the Cox models because all the matched confounders were balanced after PSM between the 2 comparative cohorts. Statistical significance was set at $P < .05$, and all tests were 2-tailed. For the NOAC cohorts, standard-dose (apixaban: 5 mg,

Table 2. Baseline Characteristics of Patients Prescribed NOACs vs NOACs After Propensity Score Matching

Characteristic	Patients, No. (%)					
	Apixaban vs dabigatran		Apixaban vs rivaroxaban		Dabigatran vs rivaroxaban	
	Apixaban cohort (n = 22 282)	Dabigatran cohort (n = 22 282)	Apixaban cohort (n = 70 093)	Rivaroxaban cohort (n = 70 093)	Dabigatran cohort (n = 25 123)	Rivaroxaban cohort (n = 25 123)
Age, y[a]						
Mean (SD)	78.3 (8.1)	77.7 (7.7)	78.6 (8.1)	78.2 (7.9)	76.9 (8.2)	77.1 (8.4)
<65	624 (2.8)	621 (2.8)	2072 (3.0)	2089 (3.0)	1257 (5.0)	1284 (5.1)
65-74	6551 (29.4)	6554 (29.4)	18 670 (26.6)	18 653 (26.6)	7806 (31.1)	7779 (31.0)
75-79	5312 (23.8)	6252 (28.1)	17 215 (24.6)	18 972 (27.1)	6710 (26.7)	6338 (25.2)
≥80	9795 (44.0)	8855 (39.7)	32 136 (45.8)	30 379 (43.3)	9350 (37.2)	9722 (38.7)
Sex[a]						
Male	11 161 (50.1)	11 149 (50.0)	33 780 (48.2)	33 832 (48.3)	12 989 (51.7)	12 994 (51.7)
Female	11 121 (49.9)	11 133 (50.0)	36 313 (51.8)	36 261 (51.7)	12 134 (48.3)	12 129 (48.3)
Baseline comorbidities						
Deyo-Charlson Comorbidity Index score, mean (SD)[a]	2.8 (2.5)	2.9 (2.5)	3.0 (2.6)	3.0 (2.6)	2.9 (2.5)	2.9 (2.5)
CHA_2DS_2-VASc Score, mean (SD)						
Mean (SD)	4.1 (1.4)	4.1 (1.5)	4.2 (1.5)	4.2 (1.5)	4.0 (1.5)	4.0 (1.5)
0	65 (0.3)	78 (0.4)	255 (0.4)	222 (0.3)	165 (0.7)	159 (0.6)
1	326 (1.5)	344 (1.5)	958 (1.4)	1038 (1.5)	598 (2.4)	609 (2.4)
2	2290 (10.3)	2110 (9.5)	6517 (9.3)	6529 (9.3)	2645 (10.5)	2695 (10.7)
3	5220 (23.4)	5179 (23.2)	15 596 (22.3)	15 497 (22.1)	5921 (23.6)	5895 (23.5)
≥4	14 381 (64.5)	14 571 (65.4)	46 767 (66.7)	46 807 (66.8)	15 794 (62.9)	15 765 (62.8)
HAS-BLED Score[b]						
Mean (SD)	3.2 (1.1)	3.2 (1.1)	3.3 (1.2)	3.3 (1.2)	3.2 (1.2)	3.2 (1.2)
0	26 (0.1)	35 (0.2)	88 (0.1)	92 (0.1)	71 (0.3)	70 (0.3)
1	1111 (5.0)	1065 (4.8)	3495 (5.0)	3557 (5.1)	1300 (5.2)	1391 (5.5)
2	4717 (21.2)	4754 (21.3)	13 825 (19.7)	13 759 (19.6)	5448 (21.7)	5358 (21.3)
≥3	16 428 (73.7)	16 428 (73.7)	52 685 (75.2)	52 685 (75.2)	18 304 (72.9)	18 304 (72.9)
Bleeding history[a]	4277 (19.2)	4415 (19.8)	14 449 (20.6)	14 632 (20.9)	4994 (19.9)	4904 (19.5)
Congestive heart failure[a]	5957 (26.7)	6222 (27.9)	19 968 (28.5)	20 014 (28.6)	6882 (27.4)	6835 (27.2)
Diabetes[a]	7971 (35.8)	8199 (36.8)	24 972 (35.6)	25 304 (36.1)	9312 (37.1)	9364 (37.3)
Hypertension[a]	20 097 (90.2)	19 999 (89.8)	62 854 (89.7)	62 791 (89.6)	22 484 (89.5)	22 437 (89.3)
Kidney disease[a]	4272 (19.2)	4426 (19.9)	15 226 (21.7)	15 723 (22.4)	4954 (19.7)	4972 (19.8)
Liver disease[a]	1057 (4.7)	1084 (4.9)	3640 (5.2)	3703 (5.3)	1248 (5.0)	1233 (4.9)
Myocardial infarction[a]	1767 (7.9)	1812 (8.1)	6415 (9.2)	6544 (9.3)	2027 (8.1)	2039 (8.1)
Dyspepsia or stomach discomfort[a]	4106 (18.4)	4341 (19.5)	14 296 (20.4)	14 313 (20.4)	4946 (19.7)	4924 (19.6)
Non-stroke and/or SE peripheral vascular disease[a]	11 896 (53.4)	12 002 (53.9)	38 507 (54.9)	38 618 (55.1)	13 327 (53.0)	13 372 (53.2)
Stroke and/or SE[a]	2801 (12.6)	2902 (13.0)	9132 (13.0)	9121 (13.0)	3129 (12.5)	3088 (12.3)
Transient ischemic attack[a]	1810 (8.1)	1860 (8.3)	5762 (8.2)	5740 (8.2)	1998 (8.0)	1961 (7.8)
Anemia and coagulation defects[a]	6249 (28.0)	6361 (28.5)	20 890 (29.8)	21 328 (30.4)	6985 (27.8)	6952 (27.7)
Alcohol use disorder[a]	414 (1.9)	466 (2.1)	1270 (1.8)	1287 (1.8)	647 (2.6)	635 (2.5)
Peripheral artery disease	4567 (20.5)	4558 (20.5)	14 907 (21.3)	15 349 (21.9)	5003 (19.9)	5229 (20.8)
Coronary artery disease	10 223 (45.9)	10 354 (46.5)	33 424 (47.7)	33 206 (47.4)	11 505 (45.8)	11 349 (45.2)
Baseline medication use[a]						
ACE and/or ARB	14 165 (63.6)	14 101 (63.3)	43 893 (62.6)	43 905 (62.6)	15 851 (63.1)	15 913 (63.3)
Amiodarone	2437 (10.9)	2518 (11.3)	8097 (11.6)	8075 (11.5)	2826 (11.2)	2868 (11.4)
β blockers	13 560 (60.9)	13 601 (61.0)	43 401 (61.9)	43 327 (61.8)	15 158 (60.3)	15 119 (60.2)
H2-receptor antagonists	1431 (6.4)	1518 (6.8)	5071 (7.2)	4952 (7.1)	1737 (6.9)	1790 (7.1)
Proton pump inhibitors	6847 (30.7)	7049 (31.6)	23 013 (32.8)	23 006 (32.8)	7871 (31.3)	7822 (31.1)
Statins	13 687 (61.4)	13 708 (61.5)	43 907 (62.6)	43 768 (62.4)	15 235 (60.6)	15 199 (60.5)
Antiplatelets	4682 (21.0)	4720 (21.2)	16 166 (23.1)	15 797 (22.5)	5277 (21.0)	5217 (20.8)
NSAIDs	6140 (27.6)	6214 (27.9)	19 207 (27.4)	19 133 (27.3)	7259 (28.9)	7191 (28.6)

(continued)

Table 2. Baseline Characteristics of Patients Prescribed NOACs vs NOACs After Propensity Score Matching (continued)

Characteristic	Patients, No. (%)					
	Apixaban vs dabigatran		Apixaban vs rivaroxaban		Dabigatran vs rivaroxaban	
	Apixaban cohort (n = 22 282)	Dabigatran cohort (n = 22 282)	Apixaban cohort (n = 70 093)	Rivaroxaban cohort (n = 70 093)	Dabigatran cohort (n = 25 123)	Rivaroxaban cohort (n = 25 123)
Dose of the index prescription						
Standard dose[c]	16 404 (73.6)	17 533 (78.7)	50 383 (71.9)	46 253 (66.0)	19 995 (79.6)	17 238 (68.6)
Lower dose[d]	5878 (26.4)	4749 (21.3)	19 710 (28.1)	23 840 (34.0)	5128 (20.4)	7885 (31.4)
Follow-up time, mean (SD), d						
Mean (SD)	194.1 (172.6)	238.3 (234.7)	191.4 (171.6)	236.2 (221.0)	236.5 (233.5)	235.7 (220.7)
Median (IQR)	134 (60-268)	134 (60-338)	130 (60-264)	149 (60-339)	133 (60-333)	150 (60-338)
Risk factors for GI bleeding						
Age ≥75 y	15 107 (67.8)	15 107 (67.8)	49 351 (70.4)	49 351 (70.4)	16 060 (63.9)	16 060 (63.9)
HAS-BLED score ≥3	16 428 (73.7)	16 428 (73.7)	52 685 (75.2)	52 685 (75.2)	18 304 (72.9)	18 304 (72.9)
Prior medications						
Any	5531 (24.8)	5531 (24.8)	17 929 (25.6)	17 929 (25.6)	6672 (26.6)	6672 (26.6)
Antiplatelets	2581 (11.6)	2518 (11.3)	8690 (12.4)	8741 (12.5)	2874 (11.4)	2972 (11.8)
NSAIDs	1649 (7.4)	1776 (8.0)	5205 (7.4)	5197 (7.4)	2219 (8.8)	2122 (8.4)
Corticosteroids	1849 (8.3)	1837 (8.2)	5908 (8.4)	5987 (8.5)	2287 (9.1)	2312 (9.2)
Prior GI conditions						
Any	3314 (14.9)	3314 (14.9)	11 331 (16.2)	11 331 (16.2)	4164 (16.6)	4164 (16.6)
Peptic ulcer	345 (1.5)	349 (1.6)	1211 (1.7)	1196 (1.7)	417 (1.7)	456 (1.8)
Prior GI bleeding	957 (4.3)	1045 (4.7)	3422 (4.9)	3376 (4.8)	1267 (5.0)	1152 (4.6)
Helicobacter pylori	91 (0.4)	88 (0.4)	297 (0.4)	329 (0.5)	109 (0.4)	110 (0.4)
Diverticulosis	2154 (9.7)	2150 (9.6)	7243 (10.3)	7321 (10.4)	2718 (10.8)	2707 (10.8)
Angiodysplasias	48 (0.2)	48 (0.2)	204 (0.3)	179 (0.3)	60 (0.2)	65 (0.3)
GI cancer (ie, stomach, colon, esophageal, and rectal cancer)	265 (1.2)	258 (1.2)	958 (1.4)	1017 (1.5)	305 (1.2)	356 (1.4)
Other GI lesions	242 (1.1)	166 (0.7)	826 (1.2)	647 (0.9)	219 (0.9)	268 (1.1)
Stage III-V CKD	1944 (8.7)	1944 (8.7)	7282 (10.4)	7282 (10.4)	2136 (8.5)	2136 (8.5)
Risk factors, No.						
1	8670 (38.9)	8670 (38.9)	24 543 (35.0)	24 543 (35.0)	10 007 (39.8)	10 007 (39.8)
2	8183 (36.7)	8183 (36.7)	26 221 (37.4)	26 221 (37.4)	9152 (36.4)	9152 (36.4)
3	4487 (20.1)	4487 (20.1)	15 929 (22.7)	15 929 (22.7)	4912 (19.6)	4912 (19.6)
4	883 (4.0)	883 (4.0)	3194 (4.6)	3194 (4.6)	971 (3.9)	971 (3.9)
5	59 (0.3)	59 (0.3)	206 (0.3)	206 (0.3)	81 (0.3)	81 (0.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category; CKD, chronic kidney disease; GI, gastrointestinal; HAS-BLED, hypertension, kidney or liver disease, stroke history, prior bleeding, unstable international normalized ratio, age 65 years or older, drug or alcohol use; IQR, interquartile range; NOACs, non–vitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SE, systemic embolism.

[a] Variables controlled for in the propensity score matching.

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

[c] Standard doses are as follows: apixaban, 5 mg; dabigatran, 150 mg; and rivaroxaban, 20mg.

[d] Lower doses are as follows: apixaban, 2.5 mg; dabigatran, 75 mg; rivaroxaban, 10 or 15 mg. A total of 4114 and 1443 patients received 10mg rivaroxaban in the apixaban-rivaroxaban and dabigatran-rivaroxaban cohorts, respectively.

twice a day; dabigatran: 150 mg, twice a day; rivaroxaban: 20 mg, once a day) and lower-dose (apixaban: 2.5 mg, twice a day; dabigatran: 75 mg, twice a day; rivaroxaban: 15 mg or 10 mg once a day) cohorts were examined separately based on index prescription dosage. Patients in the warfarin cohort were matched to patients in the NOAC cohorts with either dosage. The statistical methods of the main analysis were used, wherein 1:1 PSM patients in each data set were pooled and compared.

Outcomes for each of the 5 risk factors for GI bleeding were examined separately. The statistical methods of the main analysis were used, wherein Cox proportional hazards models were conducted. Data analysis was performed using statistical software SAS version 9.4 (SAS Institute Inc).

Results

After applying the selection criteria, a total of 381 054 patients with NVAF and high risk of GI bleed were identified (representing 81.6% of the total ARISTOPHANES population of 466 991 patients), including 89 296 (23.4%) prescribed apixaban; 28 317 (7.4%), dabigatran; 118 378 (31.1%), rivaroxaban; and 145 063 (38.1%), warfarin (Figure 1). Among patients at high risk of GI bleeding, the mean (SD) age for those receiving apixaban, dabigatran, rivaroxaban, and warfarin was 77.9 (8.7) years, 76.3 (8.7) years, 76.7 (8.9) years, and 78.4 (8.4) years, respectively; 187 489 patients (49.2%) were women. Across the cohorts, the mean CCI ranged from 3.0 to 3.6, and the mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category) score ranged from 4.0 to 4.3. Additional baseline characteristics for each treatment cohort can be found in eTable 2 in the Supplement. Among these identified high-risk patients, 284 527 (74.7%) had a HAS-BLED score of 3 or greater; 252 835 (66.4%) were aged 75 years or older; 107 675 (28.3%) used corticosteroid, antiplatelet, or NSAID therapy at index; 74 818 (19.6%) had a prior GI bleeding condition; and 56 892 (14.9%) had stage III to V CKD. Most patients (355 673 [93.3%]) had 3 or fewer risk factors concurrently during the baseline period; the largest risk factor combinations were patients aged 75 years or older with a HAS-BLED score of 3 or greater (76 723 [20.1%]), patients aged ≥75 years (61 907 [16.2%]), and patients with a HAS-BLED score ≥3 (46 414 [12.2%]). A full distribution of risk factor groups is shown in eFigure 1 in the Supplement.

The unadjusted incidence rate of stroke and/or SE (including ischemic stroke, hemorrhagic stroke, and SE) was 1.5 per 100 person-years for apixaban, 1.7 per 100 person-years for dabigatran, 1.6 per 100 person-years for rivaroxaban, and 2.3 per 100 person-years for warfarin. The unadjusted incidence rate of MB (including GI bleeding, ICH, and other MB) was 4.1 per 100 person-years for apixaban, 4.3 per 100 person-years for dabigatran, 6.4 per 100 person-years for rivaroxaban, and 7.0 per 100 person-years for warfarin. For patients receiving apixaban, dabigatran, and rivaroxaban, 25 165 (28.2%), 5704 (20.1%), and 37 543 (31.7%) had lower dosage regimens, respectively (eTable 2 in the Supplement).

After 1:1 PSM, a total of 62 372 apixaban-warfarin, 23 003 dabigatran-warfarin, 76 500 rivaroxaban-warfarin, 22 282 apixaban-dabigatran, 70 093 apixaban-rivaroxaban, and 25 123 dabigatran-rivaroxaban PSM pairs were evaluated. All baseline variables included in the PSM logistic models were balanced with standardized differences of less than 10% (Table 1 and Table 2).

NOAC-Warfarin Comparisons

Apixaban (hazard ratio [HR], 0.60, 95% CI, 0.52-0.68), dabigatran (HR, 0.75; 95% CI, 0.64-0.88), and rivaroxaban (HR, 0.79; 95% CI, 0.73-0.86) use were associated with a lower risk of stroke/SE compared with warfarin (**Figure 2**). Regarding MB, apixaban (HR, 0.59; 95% CI, 0.56-0.63) and dabigatran (HR, 0.78; 95% CI, 0.70-0.86) were associated with a lower risk compared with warfarin. Rivaroxaban (HR, 1.11; 95% CI, 1.05-1.16) was associated with a higher risk of MB vs warfarin. Likewise, apixaban was associated with a lower risk of GI bleeding (HR, 0.59; 95% CI, 0.54-0.64), and rivaroxaban was associated with a higher risk (HR, 1.29; 95% CI, 1.20-1.38) vs warfarin. Dabigatran was associated with a similar risk of GI bleeding vs warfarin (HR, 1.04; 95% CI, 0.91-1.19) (Figure 2).

NOAC-NOAC Comparisons

Patients taking apixaban had a lower risk of stroke and/or SE compared with those taking dabigatran (HR, 0.75; 95% CI, 0.62-0.91) and rivaroxaban (HR, 0.74; 95% CI, 0.67-0.83), and patients taking dabigatran were associated with a similar risk of stroke and/or SE compared with those taking rivaroxaban (HR, 1.12; 95% CI, 0.95-1.33) (**Figure 3**). Compared with dabigatran and rivaroxaban, apixaban was associated with a lower risk of MB (dabigatran: HR, 0.74; 95% CI, 0.62-0.88; rivaroxaban: HR, 0.55; 95% CI, 0.52-0.58) and lower risk of GI bleeding (dabigatran: HR, 0.64; 95% CI, 0.50-0.81; rivaroxaban: HR, 0.47; 95% CI, 0.43-0.51). Compared with rivaroxaban, dabigatran

was associated with a lower risk of MB and GI bleeding (MB: HR, 0.73; 95% CI, 0.66-0.80; GI bleeding: HR, 0.77; 95% CI, 0.67-0.87) (Figure 3). The Kaplan-Meier curves for cumulative incidence of stroke and/or SE and MB in the matched populations appear in eFigure 2 and eFigure 3 in the Supplement.

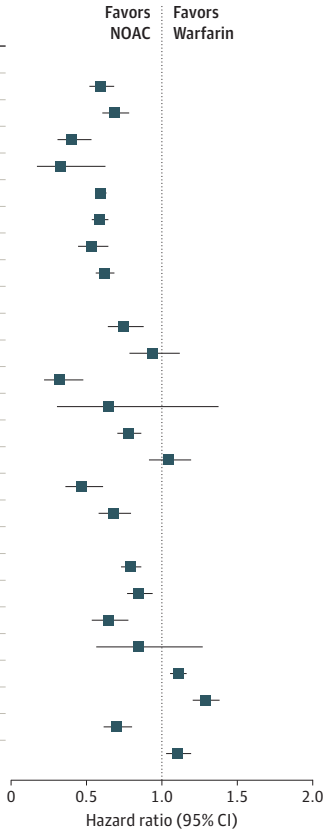
Subgroup Analyses

Results of the standard-dose and low-dose subgroup analysis were generally consistent with the main analysis for stroke and/or SE and MB in both NOAC-warfarin comparisons and NOAC-NOAC comparisons (eTable 3 and eTable 4 in the Supplement). There was no significant difference between low-dose dabigatran and warfarin for stroke and/or SE or MB or between standard-dose apixaban and dabigatran for stroke and/or SE.

When each risk factor was evaluated separately, the comparative risks of stroke and/or SE and MB were generally consistent to the main analysis for NOAC-warfarin and NOAC-NOAC comparisons, with a few exceptions. In patients with prior corticosteroid, antiplatelet, or NSAID use, the risk of stroke and/or SE was similar in dabigatran compared with warfarin, and the risk of stroke and/or SE was significantly higher in dabigatran compared with rivaroxaban. In patients with stage III to V CKD, risk of stroke and/or SE and MB was similar in dabigatran compared with warfarin; the risk of MB was similar in dabigatran compared with rivaroxaban. In addition, among patients with stage III to V CKD or prior corticosteroid, antiplatelet, or NSAID use, the risk of MB was similar in patients taking rivaroxaban compared with those taking warfarin. In patients with prior GI conditions, risk of stroke and/or SE was similar among those taking dabigatran compared with those taking warfarin, and the risk of MB was similar in patients receiving rivaroxaban compared with those receiving warfarin. The

Figure 2. Propensity Score–Matched Incidence Rates and Hazard Ratios of Stroke and/or Systemic Embolism (SE) and Major Bleeding for Non–Vitamin K Antagonist Oral Anticoagulant (NOAC) vs Warfarin

Source	No. of events (incidence per 100 person-years) NOAC	Warfarin	Hazard ratio (95% CI)	*P* value
Apixaban vs warfarin				
Stroke/SE	466 (1.41)	933 (2.16)	0.60 (0.52-0.68)	<.001
Ischemic	374 (1.13)	641 (1.48)	0.69 (0.61-0.78)	<.001
Hemorrhagic	84 (0.25)	256 (0.59)	0.41 (0.31-0.53)	<.001
SE	11 (0.03)	41 (0.09)	0.33 (0.17-0.63)	<.001
Major bleeding	1275 (3.88)	2559 (6.00)	0.59 (0.56-0.63)	<.001
GI bleeding	620 (1.88)	1249 (2.90)	0.59 (0.54-0.64)	<.001
ICH	184 (0.55)	431 (0.99)	0.54 (0.44-0.65)	<.001
Other bleeding	545 (1.65)	1044 (2.42)	0.62 (0.56-0.68)	<.001
Dabigatran vs warfarin				
Stroke/SE	232 (1.53)	326 (2.02)	0.75 (0.64-0.88)	<.001
Ischemic	193 (1.27)	217 (1.34)	0.94 (0.78-1.12)	.47
Hemorrhagic	28 (0.18)	92 (0.56)	0.32 (0.22-0.48)	<.001
SE	11 (0.07)	18 (0.11)	0.65 (0.30-1.37)	.26
Major bleeding	657 (4.36)	890 (5.57)	0.78 (0.70-0.86)	<.001
GI bleeding	403 (2.67)	419 (2.60)	1.04 (0.91-1.19)	.53
ICH	69 (0.45)	156 (0.96)	0.47 (0.36-0.61)	<.001
Other bleeding	237 (1.56)	370 (2.30)	0.68 (0.58-0.79)	<.001
Rivaroxaban vs warfarin				
Stroke/SE	809 (1.61)	1071 (2.01)	0.79 (0.73-0.86)	<.001
Ischemic	588 (1.17)	726 (1.36)	0.85 (0.77-0.94)	.001
Hemorrhagic	185 (0.36)	303 (0.56)	0.65 (0.54-0.78)	<.001
SE	39 (0.07)	48 (0.08)	0.85 (0.56-1.27)	.42
Major bleeding	3144 (6.34)	2985 (5.66)	1.11(1.05-1.16)	<.001
GI bleeding	1766 (3.54)	1437 (2.70)	1.29 (1.20-1.38)	<.001
ICH	336 (0.66)	507 (0.94)	0.70 (0.61-0.80)	<.001
Other bleeding	1293 (2.58)	1227 (2.31)	1.11 (1.03-1.19)	.007



Cox proportional hazard models with robust sandwich estimates were used to evaluate the risk of stroke and/or SE and major bleeding. GI indicates gastrointestinal; ICH, intracranial hemorrhage.

hazard ratios for stroke and/or SE, MB, and GI bleeding in the risk factor cohorts appear in eFigure 4 and eFigure 5 in the Supplement.

Discussion

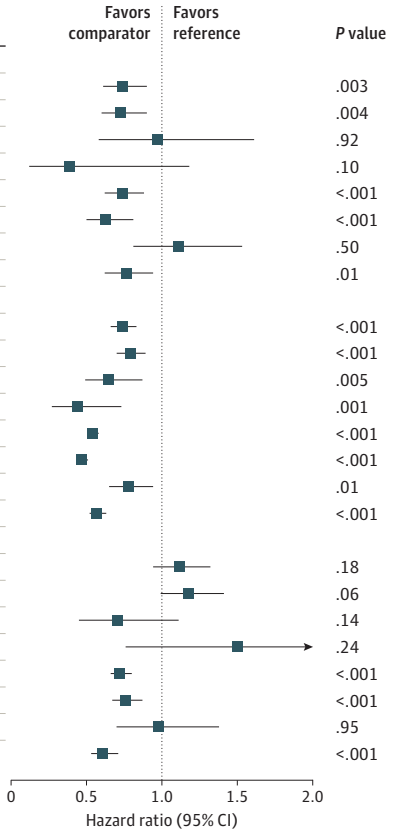
To our knowledge, this is the largest and one of the first real-world studies to compare NOACs with warfarin among patients with NVAF population and high risk of GI bleed. In this subgroup analysis of the ARISTOPHANES study, NOACs were associated with lower risk of stroke and/or SE compared with warfarin use among patients with NVAF and high risk of GI bleeding. Compared with warfarin, apixaban and dabigatran were associated with a lower risk of MB, and rivaroxaban was associated with a higher risk. Apixaban was associated with a lower risk of GI bleeding and rivaroxaban a higher risk compared with warfarin. Analyses in key subgroups, including NOAC low-dose and standard-dose populations and patients with each risk factor, showed generally consistent findings.

A notably high proportion of the ARISTOPHANES study cohort was at high risk, given that 82% of patients with NVAF had at least 1 risk factor for GI bleeding. The most common risk factors were having a HAS-BLED score of 3 or greater (74.7%) and being aged 75 years or older (66.4%); patients with both of these risk factors accounted for the most common combination of risk factors (20.1% of patients). Given that most patients in the ARISTOPHANES study were found to have high risk of GI bleeding, our findings provide additional evidence regarding treatment options for this high-risk subgroup.

In the ARISTOTLE trial, apixaban was shown to be superior to warfarin in reducing stroke and MB.[7] Consistent findings were found in this subgroup of patients with NVAF and high risk of GI

Figure 3. Propensity Score–Matched Incidence Rates and Hazard Ratios of Stroke and/or Systemic Embolism (SE) and Major Bleeding for Non–Vitamin K Antagonist Oral Anticoagulant (NOAC) Comparisons

Source	No. of events (incidence per 100 person-years)		Hazard ratio (95% CI)	*P* value
	Comparator	Reference		
Apixaban vs dabigatran				
Stroke/SE	159 (1.32)	234 (1.59)	0.75 (0.62-0.91)	.003
Ischemic	131 (1.09)	195 (1.32)	0.74 (0.60-0.91)	.004
Hemorrhagic	24 (0.19)	27 (0.18)	0.97 (0.59-1.62)	.92
SE	<11 (0.03)	12 (0.08)	0.39 (0.13-1.19)	.10
Major bleeding	392 (3.28)	599 (4.09)	0.74 (0.62-0.88)	<.001
GI bleeding	203 (1.69)	361 (2.46)	0.64 (0.50-0.81)	<.001
ICH	63 (0.52)	63 (0.42)	1.12 (0.81-1.53)	.50
Other bleeding	150 (1.25)	221 (1.50)	0.77 (0.63-0.95)	.01
Apixaban vs rivaroxaban				
Stroke/SE	489 (1.31)	755 (1.64)	0.74 (0.67-0.83)	<.001
Ischemic	382 (1.02)	551 (1.20)	0.79 (0.70-0.89)	<.001
Hemorrhagic	91 (0.24)	163 (0.35)	0.66 (0.49-0.88)	.005
SE	18 (0.04)	45 (0.09)	0.45 (0.28-0.73)	.001
Major bleeding	1393 (3.76)	2886 (6.36)	0.55 (0.52-0.58)	<.001
GI bleeding	680 (1.83)	1629 (3.57)	0.47 (0.43-0.51)	<.001
ICH	196 (0.52)	297 (0.64)	0.79 (0.65-0.95)	.01
Other bleeding	599 (1.61)	1191 (2.60)	0.57 (0.52-0.63)	<.001
Dabigatran vs rivaroxaban				
Stroke/SE	259 (1.57)	232 (1.41)	1.12 (0.95-1.33)	.18
Ischemic	214 (1.30)	182 (1.10)	1.18 (0.99-1.41)	.06
Hemorrhagic	30 (0.18)	42 (0.25)	0.72 (0.46-1.12)	.14
SE	15 (0.09)	<11 (0.06)	1.51 (0.76-2.97)	.24
Major bleeding	684 (4.18)	941 (5.79)	0.73 (0.66-0.80)	<.001
GI bleeding	413 (2.51)	542 (3.31)	0.77 (0.67-0.87)	<.001
ICH	74 (0.44)	75 (0.45)	0.99 (0.70-1.39)	.95
Other bleeding	250 (1.51)	409 (2.49)	0.61 (0.53-0.71)	<.001



Cox proportional hazard models with robust sandwich estimates were used to evaluate the risk of stroke and/or SE and major bleeding. GI indicates gastrointestinal; ICH, intracranial hemorrhage.

bleeding, as apixaban was shown to be associated with a lower risk of stroke and/or SE and MB compared with warfarin in the current analysis. However, the ARISTOTLE trial found a similar risk of GI bleeding among patients with NVAF, whereas we found apixaban to be associated with a significantly lower risk of GI bleeding in these patients (HR, 0.59; 95% CI, 0.54-0.64). The lower risk of GI bleeding associated with apixaban vs warfarin was also observed in the main analysis of ARISTOPHANES.[13]

Few studies have evaluated the effectiveness and safety of OACs among a large group of patients with multiple risk factors for GI bleeding. In a post hoc analysis of ARISTOTLE, baseline NSAIDs were not found to be associated with the risk of GI bleeding, and there was no significant interaction between NSAID use and OAC treatment (apixaban vs warfarin) for stroke and/or SE, MB, or GI bleeding.[19] In a retrospective commercial administrative claims analysis of OAC-naive patients with NVAF and stage III to V CKD (a risk factor for GI bleeding), apixaban was associated with a lower risk of MB compared with warfarin.[5] These results were generally consistent with the findings of our analysis.

In the RE-LY trial,[8] dabigatran was found to be noninferior to warfarin for stroke and MB. Our analysis of patients with high risk of GI bleeding showed consistent findings. Conversely, risk of GI bleeding was found to be significantly higher in dabigatran compared with warfarin in the RE-LY trial cohort, while our study of patients with high risk found the risk to be similar. In a retrospective commercial administrative claims analysis of OAC-naive patients with NVAF and stage III to V CKD, the rate of MB associated with dabigatran was similar to warfarin.[5] These results were similar to the findings of our analysis in patients with stage III to V CKD.

Rivaroxaban was found to be noninferior to warfarin for stroke and/or SE prevention in the ROCKET AF trial, and our analysis of the subgroup of patients with high risk of GI bleeding observed consistent findings. In ROCKET AF, the rate of all MB was found to be similar in patients treated with rivaroxaban compared with those treated with warfarin, while the rate of GI bleeding was higher in the rivaroxaban cohort compared with the warfarin cohort.[9] In this analysis of patients with high risk of GI bleeding, patients treated with rivaroxaban had a higher risk of MB and GI bleeding than patients treated with warfarin. The higher risk of GI bleeding associated with rivaroxaban vs warfarin was also observed in the main analysis of ARISTOPHANES.[13] In a recent retrospective cohort analysis of patients with NVAF and stage IV to V CKD, the risk of stroke and/or SE and MB was comparable in patients treated with rivaroxaban vs those with warfarin.[20] Our analyses of patients with stage III to V CKD support these results, also showing comparable risks of MB and GI bleeding in patients treated with rivaroxaban vs warfarin.

There are a limited number of real-world studies evaluating NOACs among patients with NVAF at risk of GI bleeds. Few studies previously mentioned examined this topic[5,20]; a limited number of GI risk factors were evaluated, and each subgroup was composed of a single risk factor. This study provides a more comprehensive analysis by considering a more complete list of GI risk factors based on the literature and evaluating risk factors in combination and individually. The latter also reemphasizes the need to mitigate modifiable bleeding risk factors and to use bleeding risk assessment appropriately to optimize AF care.[21]

Limitations

This study has several limitations. Given the nature of retrospective observational studies, no causal relationships can be examined. In addition, the data sets engender certain specific limitations. For example, potential residual confounders, such as over-the-counter aspirin use, and laboratory values (eg, serum creatinine and creatinine clearance) are unavailable, and the lack of this information may introduce bias. Further, given that *International Classification of Diseases, Ninth Revision, Clinical Modification*, *Current Procedural Terminology*, and the Healthcare Common Procedure Coding System codes were used to identify diagnoses and procedures, some variables in the data sets may lack clinical accuracy due to human data entry errors. Additionally, the lack of laboratory information (eg, lack of international normalized ratio to determine time in therapeutic range) precluded

evaluation of the quality of warfarin control. Nevertheless, by including patients with potentially poor quality of warfarin treatment, this study may reflect real-world clinical practice. Additionally, because claims were used to determine the risk factors for GI bleeding, risk factors such as stage III to V CKD or use of antiplatelets may sometimes be misclassified due to the lack of information about the creatinine clearance for patients with CKD and over-the-counter antiplatelets, such as aspirin.

Conclusions

In this study of patients with NVAF at high risk of GI bleed, apixaban, dabigatran, and rivaroxaban were associated with lower risk of stroke and/or SE vs warfarin; apixaban and dabigatran were associated with lower risk of MB vs warfarin. Additionally, apixaban was associated with a lower risk and rivaroxaban was associated with a higher risk of GI bleeding compared with warfarin. This is one of the first real-world studies to compare NOACs in the patients with NVAF and high risk of GI bleed; the results may help inform decision-making regarding OACs in this high-risk patient population.

ARTICLE INFORMATION

Accepted for Publication: May 22, 2021.

Published: August 16, 2021. doi:10.1001/jamanetworkopen.2021.20064

Correction: This article was corrected on September 15, 2021, to fix errors in Figure 2, Figure 3, and the Supplement.

Corresponding Author: Gregory Y. H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Centre for Cardiovascular Science, William Henry Duncan Bldg, Liverpool, Merseyside L7 8TX United Kingdom (gregory.lip@liverpool.ac.uk).

Author Affiliations: Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom (Lip); Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (Lip); Ochsner Clinic Foundation, Department of Hospital Medicine, New Orleans, Louisiana (Lip, Deitelzweig); The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, Louisiana (Lip, Deitelzweig); STATinMED Research, Ann Arbor, Michigan (Keshishian); New York City College of Technology, City University of New York (Keshishian, Yuce); Bristol Myers Squibb Company, Lawrenceville, New Jersey (Zhang, Kang, Dhamane, Klem, Ferri, Jiang); Pfizer, Inc., Groton, Connecticut (Luo).

Author Contributions: Drs Kang and Yuce had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Lip, Keshishian, Zhang, Kang, Dhamane, Luo, Klem, Ferri, Deitelzweig.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Lip, Keshishian, Deitelzweig.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Keshishian, Dhamane, Jiang, Yuce, Deitelzweig.

Obtained funding: Kang, Deitelzweig.

Administrative, technical, or material support: Keshishian, Zhang, Kang, Klem, Deitelzweig.

Supervision: Lip, Zhang, Kang, Luo, Klem, Ferri, Yuce, Deitelzweig.

Conflict of Interest Disclosures: Dr Lip reported serving as a consultant for Bayer/Janssen, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and being a speaker for Bayer, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo outside the submitted work. Ms Keshishian reporting being an employee of STATinMED Research, a paid consultant to Pfizer and Bristol Myers Squibb. Drs Zhang, Kang, Dhamane, Klem, Ferri, and Jiang reported being employees of Bristol Myers Squibb. Dr Kang, Klem, and Jiang reported holding stocks in Bristol Myers Squibb. Dr Luo reported being an employee of and holding stocks in Pfizer. Dr Deitelzweig reported consulting for Bristol Myers Squibb/Pfizer, Daiichi-Sankyo, Portola, and Boehringer Ingelheim; being on the speakers' bureau for Bristol Myers Squibb/Pfizer and Boehringer

Ingelheim; and receiving research support from Alexion outside the submitted work. No other disclosures reported.

Funding/Support: This study was funded by Bristol Myers Squibb and Pfizer.

Role of the Funder/Sponsor: Bristol Myers Squibb and Pfizer had a role in the design and conduct of the study; interpretation of the data; and preparation, review, or approval of the manuscript. Funders had no role in collection, management, analysis, or decision to submit the manuscript for publication.

Additional Contributions: The authors acknowledge Kate Lovett, MPH, with her permission, for data analyses and manuscript writing assistance, which was funded by BMS and Pfizer.

Additional Information: Data and materials are available from the corresponding author at reasonable request.

REFERENCES

1. Li G, Lip GYH, Holbrook A, et al. Direct comparative effectiveness and safety between non–vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. *Eur J Epidemiol*. 2019;34(2):173-190. doi:10.1007/s10654-018-0415-7

2. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future—comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;117(7):1230-1239. doi:10.1160/TH16-11-0876

3. Cheung KS, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: risk, prevention and management. *World J Gastroenterol*. 2017;23(11):1954-1963. doi:10.3748/wjg.v23.i11.1954

4. Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ*. 2015;350:h1857. doi:10.1136/bmj.h1857

5. Adeboyeje G, Sylwestrzak G, Barron JJ, et al. Major bleeding risk during anticoagulation with warfarin, dabigatran, apixaban, or rivaroxaban in patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm*. 2017;23(9):968-978. doi:10.18553/jmcp.2017.23.9.968

6. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5(6):e003725. doi:10.1161/JAHA.116.003725

7. Granger CB, Alexander JH, McMurray JJV, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

8. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561

9. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638

10. Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498. doi:10.1093/eurheartj/ehaa612

11. Anghel L, Sascău R, Trifan A, Zota IM, Stătescu C. Non–vitamin K antagonist oral anticoagulants and the gastrointestinal bleeding risk in real-world studies. *J Clin Med*. 2020;9(5):1398. doi:10.3390/jcm9051398

12. Chan YH, Yeh YH, Tu HT, et al. Bleeding risk with dabigatran, rivaroxaban, warfarin, and antiplatelet agent in Asians with non-valvular atrial fibrillation. *Oncotarget*. 2017;8(58):98898-98917. doi:10.18632/oncotarget.22026

13. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients. *Stroke*. 2018;49(12):2933-2944. doi:10.1161/STROKEAHA.118.020232

14. Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice: a propensity-matched analysis of 76,940 patients. *Thromb Haemost*. 2017;117(6):1072-1082. doi:10.1160/TH17-01-0068

15. Thigpen JL, Dillon C, Forster KB, et al. Validity of *International Classification of Disease* codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8(1):8-14. doi:10.1161/CIRCOUTCOMES.113.000371

16. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566. doi:10.1002/pds.2109

17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697

18. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33(7):1242-1258. doi:10.1002/sim.5984

19. Dalgaard F, Mulder H, Wojdyla DM, et al. Patients with atrial fibrillation taking nonsteroidal anti-inflammatory drugs and oral anticoagulants in the ARISTOTLE trial. *Circulation*. 2020;141(1):10-20. doi:10.1161/CIRCULATIONAHA.119.041296

20. Weir MR, Ashton V, Moore KT, Shrivastava S, Peterson ED, Ammann EM. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and stage IV-V chronic kidney disease. *Am Heart J*. 2020;223:3-11. doi:10.1016/j.ahj.2020.01.010

21. Guo Y, Lane DA, Chen Y, Lip GYH; mAF-App II Trial investigators. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the mAFA-II randomized trial. *Am J Med*. 2020;133(10):1195-1202.e2. doi:10.1016/j.amjmed.2020.03.019

SUPPLEMENT.

eTable 1. *ICD-9-CM* Codes for Stroke/SE and Major Bleeding
eTable 2. Baseline Characteristics and Outcomes for Prematched Apixaban, Dabigatran, Rivaroxaban, and Warfarin Patients
eTable 3. Hazard Ratios of Stroke/SE and Major Bleeding in the Low-Dose Population
eTable 4. Hazard Ratios of Stroke/SE and Major Bleeding in the Standard-Dose Population
eFigure 1. Patient Risk Factors for GI Bleeding
eFigure 2. Cumulative Incidence of Stroke/SE and Major Bleeding in NOAC-Warfarin Propensity Score Matched Cohorts
eFigure 3. Cumulative Incidence of Stroke/SE and Major Bleeding in NOAC-NOAC Propensity Score Matched Cohorts
eFigure 4. Propensity Score–Matched Incidence Rates and Hazard Ratios of Stroke/SE, Major Bleeding, and GI Bleeding for NOAC vs Warfarin Stratified by Risk Factor
eFigure 5. Propensity Score–Matched Incidence Rates and Hazard Ratios of Stroke/SE, Major Bleeding, and GI Bleeding for NOAC Comparisons Stratified by Risk Factor