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ORIGINAL ARTICLE

Outcomes of direct oral anticoagulants with aspirin vs warfarin with aspirin: a registry-based cohort study

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Abstract

Background: For patients anticoagulated with direct oral anticoagulants (DOACs) or warfarin and on aspirin (ASA) for nonvalvular atrial fibrillation and/or venous thromboembolism, it is unclear if bleeding outcomes differ.

Objectives: To assess bleeding rates for ASA with DOACs vs warfarin and one another.

Methods: Registry-based cohort study of patients followed by a 6-center quality improvement collaborative in Michigan using data from 2009 to 2022. The study included adults on ASA with warfarin or DOACs for atrial fibrillation and/or venous thromboembolism without a recent myocardial infarction or heart valve replacement.

Results: After propensity matching by anticoagulant class, we compared 2 groups of 1467 patients followed for a median of 18.0 months. Any bleeding and nonmajor bleeding was increased with DOACs + ASA compared with warfarin + ASA (32.2 vs 27.8 and 27.1 vs 22.9 events/100 patient-years; relative risks [RRs], 1.1 and 1.2; 95% CIs, 1.1-1.2 and 1.1-1.3, respectively). After matching by drug, patients on apixaban + ASA vs warfarin + ASA had more bleeding (31.2 vs 27.8 events/100 patient-years; RR, 1.1; 95% CI, 1.0-1.2) and nonmajor bleeding but less major bleeding (3.8 vs 4.7 events/100 patient-years; RR, 0.8; 95% CI, 0.6-1.0) and emergency room visits for bleeding. Patients on rivaroxaban + ASA vs warfarin + ASA had more bleeding (39.3 vs 26.3 events/100 patient-years, RR, 1.5; 95% CI, 1.3-1.6), nonmajor bleeding, and thrombosis. Patients on apixaban + ASA vs rivaroxaban + ASA had significantly less bleeding (22.5 vs 39.3/100 patient-years; RR, 0.6; 95% CI, 0.5-0.7), nonmajor bleeding, major bleeding (2.1 vs 5.5 events/100 patient-years; RR, 0.4; 95% CI, 0.2-0.6), emergency room visits for bleeding, and thrombotic events.

Conclusion: Patients on DOAC + ASA without a recent myocardial infarction or heart valve replacement had more nonmajor bleeding but otherwise similar outcomes compared with warfarin + ASA. Patients treated with rivaroxaban + ASA experienced more adverse clinical events compared with warfarin + ASA or apixaban + ASA.

KEYWORDS
aspirin, factor Xa inhibitors, hemorrhage, outcome assessment, warfarin

Essentials

- Aspirin (ASA) is sometimes combined with oral anticoagulation, but this is not always indicated.
- We assessed outcomes of oral anticoagulation + ASA for venous thromboembolism and atrial fibrillation.
- Direct oral anticoagulants led to more nonmajor bleeding but similar outcomes to warfarin.
- Major bleeding was least with apixaban + ASA, followed by warfarin + ASA, and highest with rivaroxaban + ASA.

1 | INTRODUCTION

The antiplatelet agent aspirin (ASA) is used for a variety of indications, including the primary and secondary prevention of atherosclerotic cardiovascular disease [1–7]. ASA is appropriately combined with warfarin or therapeutically dosed direct oral anticoagulants (DOACs) for select patients with atrial fibrillation (AF) and/or venous thromboembolism (VTE) after acute coronary syndromes or percutaneous coronary interventions [8–11]. Warfarin and ASA may also be appropriate in combination for patients with valvular heart disease [12]. For most other patients, evidence suggests that combination therapy does more harm than good by increasing bleeding events without a clear reduction in thrombotic outcomes [10,13–18]. Despite this evidence, combination therapy is common in clinical practice [14,19].

Combination therapy with warfarin + ASA is estimated to result in a 1.5- to 2.0-fold increased risk of major bleeding compared with warfarin alone [18]. DOACs as a class have been associated with a lower rate of bleeding compared with warfarin [20–24]. However, it is not clear how outcomes with DOACs + ASA compare with warfarin + ASA, especially in patients with VTE. Existing data suggest that DOACs + ASA may be safer than warfarin + ASA, at least for patients with AF [25]. ASA use in landmark clinical trials of DOACs was not randomly assigned and did not routinely report ASA indication or adherence [25–27]. While 21% to 35% of patients in AF trials were on combination therapy [26], only 6% to 14% of anticoagulated patients were on combination therapy in the VTE studies [27]. Accordingly, it remains unclear if DOACs + ASA have a better safety profile than warfarin + ASA.

We sought to determine if bleeding outcomes were similar for adult patients on ASA with a DOAC compared with patients on ASA with warfarin among patients that may not have a more definitive indication for concomitant ASA, such as a recent myocardial infarction (within 6 months). We hypothesized that DOACs + ASA may have less bleeding compared with warfarin + ASA. Given that apixaban and rivaroxaban are the most used DOACs, we sought to compare apixaban + ASA, rivaroxaban + ASA, and warfarin + ASA outcomes.

2 | METHODS

2.1 | Study design and participants

We used data from the Michigan Anticoagulation Quality Improvement Initiative (MAQI [2]), a collaborative of 6 diverse outpatient anticoagulation clinics throughout the state of Michigan that includes both academic and community practices [28]. MAQI [2] includes both rural and urban practices, with patient censuses ranging from the hundreds to thousands. Since 2009, it has maintained a robust registry of patients on oral anticoagulation and includes patients with all types of health insurance. The 6 sites contribute data for patients treated with warfarin, and 4 sites also contribute data for patients on DOACs. For the current study, we used registry and follow-up data from January 2009 to June 2022.

2.2 | Eligibility criteria

We included adult patients (aged ≥18 years) starting or transitioning to warfarin or a DOAC for the indications of AF and/or VTE from January 2009 through June 2022 who were also on concomitant ASA therapy at the time of anticoagulant initiation. Patients were excluded if they had less than 3 months of follow-up data, a recent myocardial infarction, or a history of heart valve replacement.

2.3 | Data collection and outcome measures

Data were abstracted from the time of anticoagulant initiation through the earliest of anticoagulant discontinuation, transition to an anticoagulant other than warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban, loss to follow-up, the end of the study period, or patient death. Patients could contribute to both the warfarin and DOAC groups if they had been on both drug classes. Data collection was performed using trained data abstractors and standardized data collection forms. Exposures and outcomes were verified through routine random chart audits that were performed by the coordinating

center (University of Michigan) to ensure abstracted data matched the information contained in the primary electronic medical record. This study was approved by the institutional review board at each participating center with a waiver of informed consent.

The MAQI [2] registry is designed to require entry to key data elements, including demographic data, anticoagulant dosing, and details regarding adverse events (eg, location and severity of a bleeding event) using an electronic data entry form with defined elements. Data collected at study enrollment included ASA dose, patient demographics, indication for anticoagulation, comorbidities, bleeding and thrombosis risk factors, histories of bleeding or thrombosis, laboratory tests, and concomitant medications (including antiplatelet therapies other than ASA). The Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly, Drugs/alcohol concomitantly (HAS-BLED) score [29], and a congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category (CHA_2DS_2-VASc) score [30] was calculated for each patient at the time of study enrollment, with the HAS-BLED score modified to exclude labile INR for all patients.

After study enrollment, data were abstracted at approximately 3- to 6-month intervals. Our primary outcome was the rate of any bleeding events, which included any documented bleeding event, regardless of severity. This includes major bleeding, nonmajor bleeding, and, rarely, documented bleeding events where it was unconfirmed if the event met criteria for nonmajor or major bleeding. Secondary outcomes included thrombotic outcomes (ischemic stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolism, intracardiac thrombus, or other or unknown clot; myocardial infarction was captured in other clots), major bleeding as defined by the International Society of Thrombosis and Haemostasis [31], and nonmajor bleeding (defined as any bleeding that did not meet the definition of major bleeding). We also assessed rates of emergency department visits and admissions related to bleeding and overall mortality. Patients could experience multiple events for the study outcomes if they continued to meet the study inclusion criteria.

2.4 | Statistical analysis

We compared 2 ASA-treated groups that were similar at the time of anticoagulant initiation aside from anticoagulant class or drug through propensity matching. Based on the clinical and demographic factors assessed at study enrollment (Supplementary Figures S1–S4), propensity scores were generated as a probability of receiving DOAC + ASA or warfarin + ASA through a logistic regression model. The first propensity score was used to match DOAC + ASA and warfarin + ASA groups using an optimal matching method (1:1) [32]. Initial review of the outcomes between DOACs + ASA and warfarin + ASA showed that outcomes differed based on specific anticoagulant drugs. Accordingly, we conducted a post hoc secondary analysis of apixaban + ASA, rivaroxaban + ASA, and warfarin + ASA. Dabigatran and edoxaban were excluded from this analysis, given that the other DOACs represented were used by over 93% of the initial study population (Table 1).

To complete this secondary analysis, additional propensity scores were generated to compare apixaban + ASA, warfarin + ASA, and rivaroxaban + ASA with variable matching ratios depending on the size of the baseline groups (1:1-4:1). Variable matching ratios were used to optimize power. The optimal matching method we used selects all matches simultaneously and without replacement to minimize the total absolute difference in propensity score across all matches. A standardized difference of less than 0.1 was used to indicate a negligible difference in the covariates between the groups. Covariates that maintained residual differences between the groups were included in subsequent Poisson models.

After the matched cohorts were created (Table 1), we compared event rates between the various outcome groups using Poisson regression to assess each of the various study outcomes (Figures 1–4, Tables 2–4). A 2-sided $P < .05$ was considered significant for all comparisons. All statistical analyses were carried out using SAS version 9.4 (SAS Institute) and R Statistical Software (v3.4.1; R Core Team 2017).

3 | RESULTS

Between January 2009 and June 2022, 4663 warfarin + ASA (2747 [58.9%] men; mean [SD] age, 69.3 ± 13.1 years) and 1501 DOAC + ASA (846 [56.4%] men; mean [SD] age, 71.9 ± 11.1 years) treated patients were identified who met the inclusion criteria. Full-dose DOACs were used for 1180 (78.9%) patients, and ASA doses were ≤100 mg for 5411 patients (87.8%). Most patients were anticoagulated for AF (4345 [70.5%]), with the remaining patients anticoagulated for VTE or both AF and VTE (Table 1).

3.1 | Outcomes for DOAC + ASA compared with warfarin + ASA

Two propensity-matched groups of 1467 patients on DOAC + ASA and warfarin + ASA were identified (Table 2, Supplementary Figure S1). After matching, the 2 groups were similar in terms of patient demographics, indications for anticoagulation, comorbidities, and history of bleeding or thrombosis (Table 2). Residual differences after propensity matching included Charlson comorbidity index, CHA_2DS_2-VASc, and modified HAS-BLED scores (Supplementary Figure S1), but these were not included in subsequent models because of inclusion of the individual components. Patients were followed for a median of 18.0 months (IQR, 42). Patients on DOAC + ASA compared with warfarin + ASA experienced more bleeding and the bleeding subset of nonmajor bleeding (32.2 vs 27.8 and 27.1 vs 22.9 events/100 patient-years respectively; relative risk [RR] of bleeding, 1.1; 95% CI, 1.1-1.2). Outcomes between the 2 groups in terms of major bleeding, thrombotic events, health care utilization, and mortality were otherwise similar (Table 2, Figure 1).

TABLE 1 Patient characteristics by class before propensity matching.[a]

Patient characteristic	DOAC + ASA N = 1501	Warfarin + ASA N = 4663
Anticoagulant		
Apixaban	1007 (67.1)	N/A
Dabigatran	83 (5.5)	N/A
Edoxaban	2 (0.1)	N/A
Rivaroxaban	409 (27.3)	N/A
Warfarin	N/A	4663
DOAC dose[b]		
Low dose	278 (18.5)	N/A
High dose	1180 (78.9)	N/A
Demographics		
Age, y (mean ± SD)	71.9 ± 11.1	69.3 ± 13.1
Sex (% male)	846 (56.4)	2747 (58.9)
Race (% White)	1195 (79.6)	3695 (79.2)
BMI > 30 kg/m^2	757 (50.4)	2019 (43.3)
Alcohol or drug use	104 (6.9)	239 (5.1)
Former tobacco use	649 (43.2)	1730 (37.1)
Current tobacco use	113 (7.5)	333 (7.1)
Indication[c]		
AF/Aflutter	1122 (74.8)	3223 (69.1)
DVT/PE	409 (27.3)	1498 (32.1)
Both	30 (2.0)	58 (1.2)
Comorbidities		
CAD	670 (44.6)	2000 (42.9)
Cancer	386 (25.7)	976 (20.9)
CHF	395 (26.3)	1218 (26.1)
Chronic liver disease	65 (4.3)	109 (2.3)
CKD	362 (24.1)	1686 (36.2)
Diabetes mellitus	510 (34.0)	1453 (31.2)
History of falls	134 (8.9)	199 (4.3)
Hypercoagulable state	17 (1.1)	108 (2.3)
HTN	992 (66.1)	3524 (75.6)
PAD	140 (9.3)	446 (9.6)
Prior PCI/CABG	326 (21.7)	940 (20.2)
History of bleeding or thrombosis		
Bleeding (≤30 d)[d]	60 (4.0)	132 (2.8)
Bleeding (>30 d)[d]	83 (5.5)	160 (3.4)
History of embolism (not DVT/PE)	32 (2.1)	62 (1.3)
Prior CVA/TIA	245 (16.3)	723 (15.5)
Prior DVT/PE	140 (9.3)	664 (14.2)
Prior GIB	97 (6.5)	263 (5.6)
Remote MI (>6 mo)	179 (11.9)	554 (11.9)
Medications		
Aspirin ≤ 100 mg[e]	1377 (91.7)	4034 (86.5)
Aspirin > 100 mg[e]	127 (8.5)	636 (13.6)
Estrogen/progesterone	12 (0.8)	28 (0.6)
Non-ASA antiplatelet	52 (3.5)	386 (8.3)
NSAID	44 (2.9)	195 (4.2)
PPI/H2RA	570 (38.0)	1849 (39.7)
Other, (mean ± SD)		
Mo of follow-up, median (IQR)	18 (42.0)	9.2 (30.2)
Modified HAS-BLED[f]	3.5 ± 1.1	3.5 ± 1.2
CCI	5.1 ± 1.9	5.1 ± 2.3

AF, atrial fibrillation; Aflutter, atrial flutter; ASA, acetylsalicylic acid or aspirin; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCI, Charlson comorbidity Index; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; GIB, gastrointestinal bleed; H2RA, H2 receptor antagonists; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; HTN, hypertension; MI, myocardial infarction; N/A, not available; NSAID, nonsteroidal antiinflammatory drug; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PPI, proton pump inhibitor; TIA, transient ischemic attack.

[a]Values are *n* (%) unless otherwise noted. If not otherwise specified, the denominator is equal to *N* at the top of the column.

[b]Low dose defined as a total daily dose of dabigatran < 300 mg, apixaban < 10 mg, rivaroxaban < 20 mg, and edoxaban < 60 mg. High dose is considered a total daily dose of dabigatrain ≥ 300 mg, apixaban ≥ 10 mg, rivaroxaban ≥ 20 mg, and edoxaban ≥ 60 mg. DOAC dose was unknown at enrollment for a small number of patients.

[c]Patients with both indications for anticoagulation were included in both the AF/Aflutter and DVT/PE groups.

[d]Indicates bleeding history as assessed at the time of anticoagulant initiation.

[e]ASA dose was uncertain for a small number of patients that were counted in both the low (≤100 mg) and high (>100 mg) dose ASA groups.

[f]HAS-BLED score modified to exclude labile INR.

3.2 | Outcomes for apixaban + ASA compared with warfarin + ASA

A total of 987 patients in the initial study cohort were on apixaban + ASA. After a 1:2 propensity match, 987 apixaban + ASA-treated patients were compared with 1974 patients on warfarin + ASA. The propensity-matched groups were well balanced (Supplementary Figure S2) and followed for a median of 17.1 months (IQR, 38.4). Residual differences after propensity matching included modified HAS-BLED and Charlson comorbidity index scores (Supplementary

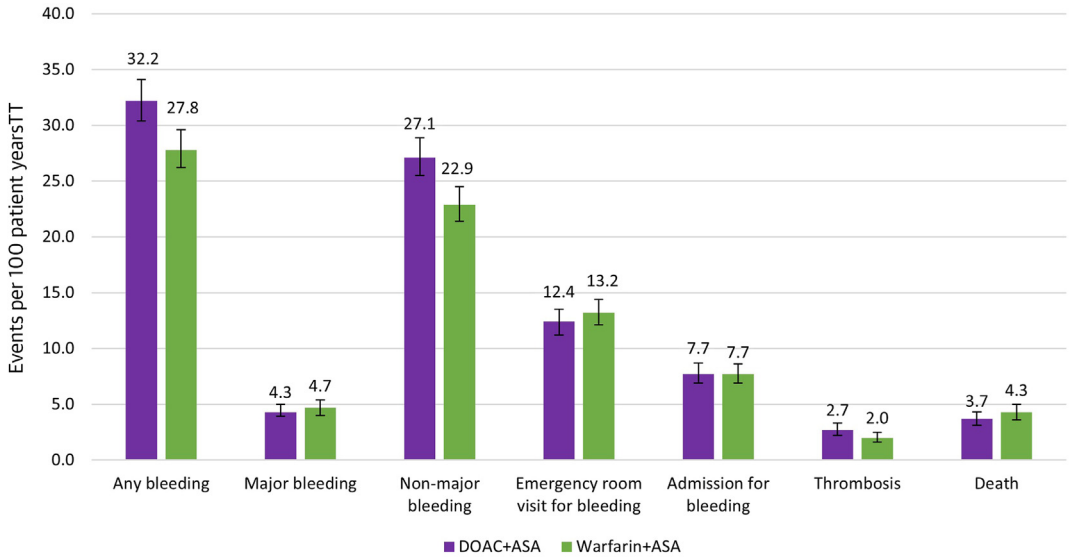

FIGURE 1 Bar graph comparing outcomes of direct oral anticoagulants (DOACs) + acetylsalicylic acid or aspirin (ASA) with warfarin + ASA. Events per 100 patient-years. ASA, acetylsalicylic acid or aspirin.

Figure S2), but this was not included in subsequent models because of inclusion of the individual components. Patients on apixaban + ASA had significantly more bleeding (31.2 vs 27.8 events/100 patient-years; RR, 1.1; 95% CI, 1.0-1.2) and nonmajor bleeding (26.5 vs 22.8 events/100 patient-years; RR, 1.1; 95% CI, 1.0-1.3). Patients on apixaban + ASA had significantly fewer major bleeding events (3.8 vs 4.7 events/100 patient-years; RR, 0.8; 95% CI, 0.6-1.0) and emergency room visits for bleeding (12.3 vs 13.8 events/100 patient-years; RR, 0.9; 95% CI, 0.7-1.0) compared with warfarin + ASA. Outcomes for admissions for bleeding, thrombosis, and death were similar between treatment groups (Figure 2, Table 3).

3.3 | Outcomes for rivaroxaban + ASA compared with warfarin + ASA

A total of 409 patients in the initial study cohort were on rivaroxaban + ASA. After a 1:4 propensity match, 401 rivaroxaban + ASA-treated patients were compared with 1604 patients on warfarin + ASA. The propensity-matched groups were well balanced (Supplementary Figure S3) and followed for a median of 12.0 months (IQR, 41.3). Residual differences after propensity matching included the modified HAS-BLED and CHA_2DS_2-VASc scores (Supplementary Figure S3), but these were not included in subsequent models because of inclusion of

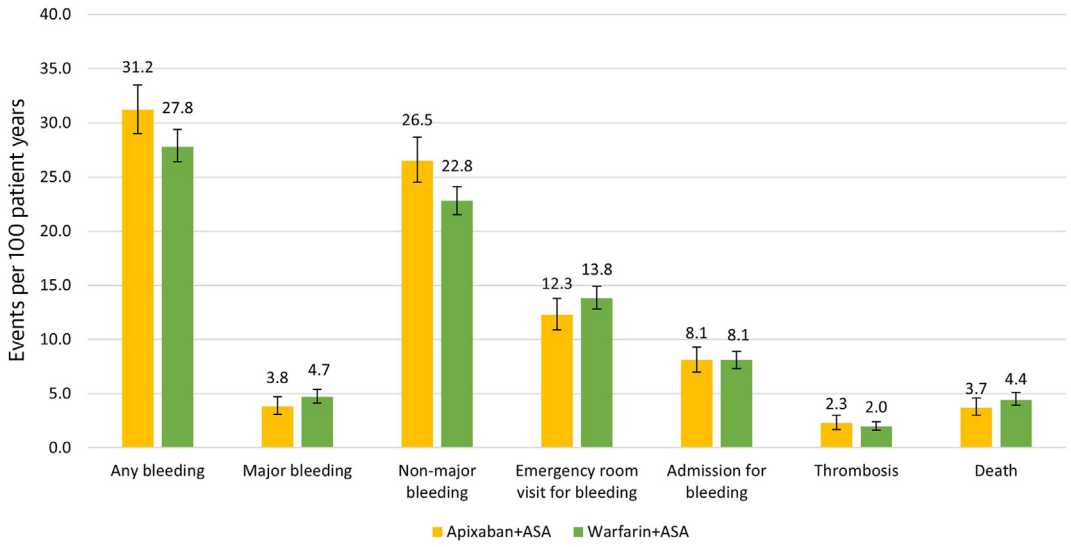

FIGURE 2 Bar graph comparing outcomes of apixaban + acetylsalicylic acid or aspirin (ASA) with warfarin + ASA. Events per 100 patient-years.

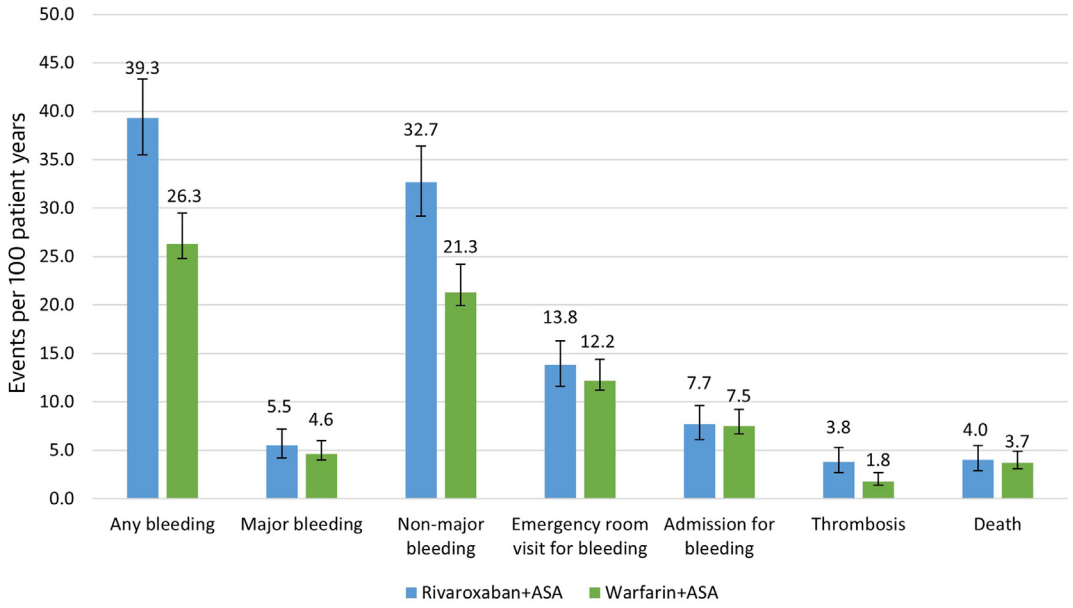

FIGURE 3 Bar graph comparing outcomes of rivaroxaban + acetylsalicylic acid or aspirin (ASA) with warfarin + ASA. Events per 100 patient-years.

the individual components. There were more patients with both AF and VTE in the rivaroxaban + ASA group compared with warfarin + ASA; accordingly, this was included in the subsequent Poisson models. Patients on rivaroxaban + ASA had significantly higher rates of any bleeding (39.3 vs 26.3 events/100 patient-years; RR, 1.5; 95% CI, 1.3-1.6) and the bleeding subset of nonmajor bleeding (32.7 vs 21.3 events/100 patient-years, RR, 1.5; 95% CI, 1.3-1.7) with no difference in major bleeding (5.5 vs 4.6 events/100 patient-years, RR, 1.1; 95% CI, 0.8-1.5). Thrombotic events were higher with rivaroxaban + ASA (3.8 vs 1.8 events/100 patient-years; RR, 2.2; 95% CI, 1.5-3.2) compared with warfarin + ASA. Other outcomes of emergency room visits for bleeding, admissions for bleeding, and death were similar between treatment groups (Figure 3, Table 3).

3.4 | Outcomes for rivaroxaban + ASA compared with apixaban + ASA

After a 1:1 propensity match, 401 patients on rivaroxaban + ASA were compared with an equal group of patients on apixaban + ASA. The propensity-matched groups were well balanced (Supplementary Figure S4) and followed for a median of 18.0 months (IQR, 42.0).

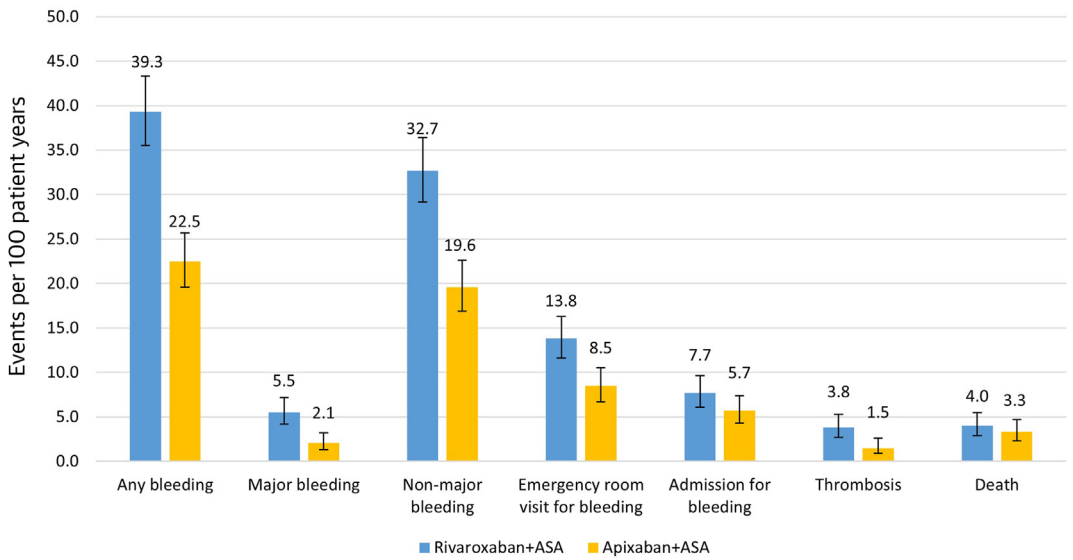

FIGURE 4 Bar graph comparing outcomes of apixaban + acetylsalicylic acid or aspirin (ASA) with rivaroxaban + ASA. Events per 100 patient-years.

TABLE 2 Characteristics and outcomes of propensity-matched cohorts of patients on direct oral anticoagulants and aspirin vs warfarin and aspirin.[a]

Patient characteristic	DOAC + ASA *N* = 1467	Warfarin + ASA *N* = 1467
Anticoagulant		
Apixaban	987 (67.3)	N/A
Dabigatran	77 (5.3)	N/A
Edoxaban	2 (0.1)	N/A
Rivaroxaban	401 (27.3)	N/A
Warfarin	N/A	4434
Warfarin %TTR (%SD)	N/A	59.0 (20.9)
DOAC dose[b]		
Low dose	273 (18.6)	N/A
High dose	1152 (78.5)	N/A
Demographics		
Age, y (mean ± SD)	71.9 ± 11.1	71.6 ± 11.8
Sex (% male)	828 (56.4)	828 (56.4)
BMI > 30 kg/m^2	757 (51.6)	782 (53.3)
Alcohol or drug use	102 (7.0)	95 (6.5)
Former tobacco use	637 (43.4)	630 (42.9)
Current tobacco use	112 (7.6)	115 (7.8)
Indication		
AF/Aflutter	1093 (74.5)	1069 (72.9)
DVT/PE	404 (27.5)	415 (28.3)
Both	30 (2.0)	17 (1.2)
Comorbidities		
CAD	653 (44.5)	627 (42.7)
Cancer	381 (26)	390 (26.6)
CHF	388 (26.5)	389 (26.5)
Chronic liver disease	64 (4.4)	63 (4.3)
CKD	356 (24.3)	355 (24.2)
Diabetes mellitus	505 (34.4)	495 (33.7)
History of falls	133 (9.1)	121 (8.3)
Hypercoagulable state	17 (1.2)	17 (1.2)
HTN	975 (66.5)	995 (67.8)
PAD	137 (9.3)	131 (8.9)
Prior PCI/CABG	316 (21.5)	298 (20.3)
History of bleeding or thrombosis		
Bleeding (≤30 d)[c]	60 (4.1)	67 (4.6)
Bleeding (>30 d)[c]	83 (5.7)	75 (5.1)
History of embolism (not DVT/PE)	32 (2.2)	27 (1.8)
Prior CVA/TIA	240 (16.4)	217 (14.8)
Prior DVT/PE	140 (9.5)	138 (9.4)

(Continues)

TABLE 2 (Continued)

Patient characteristic	DOAC + ASA N = 1467	Warfarin + ASA N = 1467
Prior GIB	97 (6.6)	94 (6.4)
Remote MI (>6 mo)	176 (12)	163 (11.1)
Medications		
Aspirin ≤ 100 mg	1348 (91.9)	1352 (92.2)
Aspirin > 100 mg	122 (8.3)	117 (8.0)
Estrogen/progesterone	12 (0.8)	14 (1.0)
Non-ASA antiplatelet	52 (3.5)	46 (3.1)
NSAID	44 (3.0)	59 (4.0)
PPI/H2 blockers	555 (37.8)	550 (37.5)
Other (mean ± SD)		
Mo of follow-up, median (IQR)	18 (42.0)	13.7 (43.6)
Modified HAS-BLED[d]	3.5 ± 1.1	3.3 ± 1.1
CCI	5.1 ± 1.9	5.3 ± 2.1
Outcomes		
Event rate (95% CI) No. of events/100 patient-y[e]	**DOAC + ASA N = 1467**	**Warfarin + ASA N = 1467**	**RR (95% CI)**
Any bleeding	32.2 (30.4, 34.1)	27.8 (26.2, 29.6)	1.1 (1.1, 1.2)
Major bleeding	4.3 (3.6, 5.0)	4.7 (4.0, 5.4)	0.9 (0.7, 1.1)
Nonmajor bleeding	27.1 (25.5, 28.9)	22.9 (21.4, 24.5)	1.2 (1.1, 1.3)
Fatal	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.8 (0.2, 2.8)
Life-threatening	1.2 (0.8, 1.6)	1.3 (0.9, 1.7)	0.9 (0.6, 1.4)
Intracranial or intraspinal	0.5 (0.3, 0.7)	0.8 (0.6, 1.1)	0.6 (0.3, 1.1)
Emergency room visit for bleeding	12.4 (11.2, 13.5)	13.2 (12.1, 14.4)	0.9 (0.8, 1.0)
Admission for bleeding	7.7 (6.9, 8.7)	7.7 (6.9, 8.6)	1.0 (0.8, 1.1)
Thrombosis	2.7 (2.2, 3.3)	2.0 (1.6, 2.5)	1.3 (1.0, 1.8)
Ischemic/embolic stroke	0.7 (0.5, 1.0)	0.7 (0.4, 1)	1.0 (0.6, 1.7)
PE	0.3 (0.1, 0.6)	0.2 (0.1, 0.3)	1.8 (0.7, 5.0)
DVT	0.5 (0.3, 0.8)	0.6 (0.4, 0.9)	0.8 (0.5, 1.6)
Death	3.7 (3.1, 4.3)	4.3 (3.6, 5.0)	0.9 (0.7, 1.1)

AF, atrial fibrillation; Aflutter, atrial flutter; ASA, acetylsalicylic acid or aspirin; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; GIB, gastrointestinal bleed; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; HTN, hypertension; MI, myocardial infarction; N/A, not available; NSAID, nonsteroidal antiinflammatory drug; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; RR, relative risk; TIA, transient ischemic attack; TTR, time in the therapeutic range.

[a]Values are *n* (%) unless otherwise noted. If not otherwise specified, the denominator is equal to *N* at the top of the column.

[b]High dose is considered a total daily dose of dabigatran ≥ 300 mg, apixaban ≥ 10 mg, rivaroxaban ≥ 20 mg, and edoxaban ≥ 60 mg. DOAC dose was unknown at enrollment for a small number of patients. Other doses are considered low doses.

[c]Indicates bleeding history as assessed at the time of anticoagulant initiation.

[d]HAS-BLED score modified to exclude labile INR.

[e]Adjusted for HAS-BLED score (bleeding) or CHA_2DS_2-VASc score (thrombosis), CCI, and follow-up time.

There were no residual differences after propensity matching. Patients on apixaban + ASA had significantly lower rates of any bleeding (22.5 vs 39.3 events/100 patient-years; RR, 0.6; 95% CI, 0.5-0.7), and the bleeding subsets of nonmajor bleeding (19.6 events vs 32.7 events/100 patient-years; RR, 0.6; 95% CI, 0.5-0.7), and major bleeding (2.1 vs 5.5 events/100 patient-years; RR, 0.4; 95% CI, 0.2-0.6). Patients on apixaban + ASA had significantly lower rates of emergency room visits for bleeding (8.5 vs 13.8 events/100 patient-

TABLE 3 Outcomes of apixaban and aspirin vs warfarin and aspirin and outcomes of rivaroxaban and aspirin vs warfarin and aspirin for propensity-matched patients.

Patient characteristics	Apixaban + ASA N = 987	Warfarin + ASA N = 1974	Rivaroxaban + ASA N = 401	Warfarin + ASA N = 1604
Age, y (mean ± SD)	72.9 ± 11.2	72.7 ± 11.1	69.8 ± 10.9	69.8 ± 12.0
Sex (% male)	544 (55.1)	1088 (55.1)	231 (57.6)	924 (57.6)
Aspirin ≤ 100 mg (%)	915 (92.7)	1833 (92.9)	362 (90.3)	1436 (89.5)
Aspirin > 100 mg (%)	74 (7.5)	145 (7.4)	40 (10.0)	172 (10.7)
CHA_2DS_2-VASc score (mean ± SD)	4.1 ± 1.7	4 ± 1.7	3.6 ± 1.7	3.4 ± 1.8
HAS-BLED score (mean ± SD)[a]	3.6 ± 1.1	3.5 ± 1.1	3.3 ± 1.1	3.1 ± 1.1
CCI (mean ± SD)	5.2 ± 1.9	5.5 ± 2.1	4.8 ± 1.9	4.9 ± 2.1
Indication (%)				
Atrial fibrillation	759 (76.9)	1509 (76.4)	258 (64.3)	1043 (65.0)
VTE	244 (24.7)	491 (24.9)	155 (38.7)	575 (35.9)
Both	16 (1.6)	26 (1.3)	12 (3.0)	14 (0.9)
Follow-up mo, median (IQR)	18 (36.0)	12.5 (41.0)	18 (42.0)	11.4 (43.4)
Follow-up, mean ± SD	28.9 ± 24.0	30.3 ± 36.8	30.3 ± 28.4	30.3 ± 37.8
Warfarin %TTR (%SD)	N/A	58.8 (21.1)	N/A	59.4 (20.8)
DOAC dose[b]				
Low dose	221 (22.3)	N/A	49 (12.2)	N/A
High dose	745 (75.5)	N/A	339 (84.5)	N/A

Event rate (95% CI) No. of events/100 patient-y[c]	Apixaban + ASA N = 987	Warfarin + ASA N = 1974	RR (95% CI)	Rivaroxaban + ASA N = 401	Warfarin + ASA N = 1604	RR (95% CI)
Any bleeding	31.2 (29.0, 33.5)	27.8 (26.4, 29.4)	1.1 (1, 1.2)	39.3 (35.5, 43.3)	26.3 (24.8, 28.0)	1.5 (1.3, 1.6)
Major bleeding	3.8 (3.1, 4.7)	4.7 (4.1, 5.4)	0.8 (0.6, 1)	5.5 (4.2, 7.2)	4.6 (4, 5.4)	1.1 (0.8, 1.5)
Nonmajor bleeding	26.5 (24.5, 28.7)	22.8 (21.5, 24.1)	1.1 (1, 1.3)	32.7 (29.2, 36.4)	21.3 (19.9, 22.8)	1.5 (1.3, 1.7)
Emergency room visit for bleeding	12.3 (10.9, 13.8)	13.8 (12.8, 14.9)	0.9 (0.7, 1)	13.8 (11.6, 16.3)	12.2 (11.2, 13.4)	1.1 (0.9, 1.3)
Admission for bleeding	8.1 (7.0, 9.3)	8.1 (7.3, 8.9)	1.0 (0.8, 1.1)	7.7 (6.1, 9.6)	7.5 (6.7, 8.4)	1.0 (0.7, 1.2)
Thrombosis	2.3 (1.7, 3.0)	2.0 (1.6, 2.4)	1.1 (0.8, 1.6)	3.8 (2.7, 5.3)	1.8 (1.4, 2.3)	2.2 (1.5, 3.2)
Ischemic /embolic stroke	0.5 (0.3, 0.9)	0.7 (0.5, 1.0)	0.7 (0.4, 1.4)	1.0 (0.5, 1.8)	0.5 (0.3, 0.8)	2.0 (0.9, 4.3)
PE	0.3 (0.1, 0.6)	0.1 (0.1, 0.3)	2.1 (0.7, 6.1)	0.4 (0.1, 1)	0.1 (0.04, 0.29)	3.3 (0.9, 12.1)
DVT	0.3 (0.1, 0.6)	0.6 (0.4, 0.9)	0.5 (0.2, 1.1)	0.9 (0.4, 1.7)	0.7 (0.5, 1.1)	1.2 (0.6, 2.6)
Death	3.7 (3.0, 4.6)	4.4 (3.9, 5.1)	0.8 (0.7, 1.1)	4.0 (2.9, 5.5)	3.7 (3.1, 4.3)	1.0 (0.7, 1.5)

ASA, acetylsalicylic acid or aspirin; CCI, Charlson comorbidity index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; N/A, not available; PE, pulmonary embolism; RR, relative risk; TTR, time in the therapeutic range; VTE, venous thromboembolism.

[a]HAS-BLED score modified to exclude labile international normalized ratio.

[b]High dose is considered a total daily dose of apixaban ≥ 10 mg or rivaroxaban ≥ 20 mg. Other doses are considered low doses.

[c]Adjusted for HAS-BLED score (bleeding) or CHA_2DS_2-VASc score (thrombosis), CCI, indication for anticoagulation, and follow-up time.

years; RR, 0.6; 95% CI, 0.5-0.8) and rates of thrombosis (1.5 vs 3.8 vs 1.5 events/100 patient-years; RR, 0.4; 95% CI, 0.2-0.7) compared with rivaroxaban + ASA. Outcomes for admissions for bleeding and death were similar between treatment groups (Figure 4, Table 4).

4 | DISCUSSION

In this large, registry-based cohort study of patients on oral anticoagulation and ASA for AF and/or VTE, clinical outcomes were

TABLE 4 Outcomes of apixaban and aspirin vs rivaroxaban and aspirin for propensity-matched patients.

Patient characteristics	Apixaban + ASA *N* = 401	Rivaroxaban + ASA *N* = 401
Age, y (mean ± SD)	70.1 ± 12	69.8 ± 10.9
Sex (% male)	231 (57.6)	231 (57.6)
Aspirin ≤ 100 mg (%)	362 (90.3)	362 (90.3)
Aspirin > 100 mg (%)	41 (10.2)	40 (10.0)
CHA_2DS_2-VASc score (mean ± SD)	3.6 ± 1.8	3.6 ± 1.7
HAS-BLED score (mean ± SD)[a]	3.3 ± 1.1	3.3 ± 1.1
CCI (mean ± SD)	4.8 ± 1.8	4.8 ± 1.9
Indication (%)		
Atrial fibrillation	260 (64.8)	258 (64.3)
VTE	151 (37.7)	155 (38.7)
Both	10 (2.5)	12 (3.0)
Follow-up mo, median (IQR)	18 (42.0)	18 (42.0)
Follow-up mo, mean ± SD	29.0 ± 25.4	30.3 ± 28.4
DOAC dose[b]		
Low dose	98 (25.1)	49 (12.6)
High dose	293 (74.9)	339 (87.4)

Event rate (95% CI) No. of events/100 patient-y[c]	Apixaban + ASA *N* = 401	Rivaroxaban + ASA *N* = 401	RR (95% CI)
Any bleeding	22.5 (19.6, 25.7)	39.3 (35.5, 43.3)	0.6 (0.5, 0.7)
Major bleeding	2.1 (1.3, 3.2)	5.5 (4.2, 7.2)	0.4 (0.2, 0.6)
Nonmajor bleeding	19.6 (16.9, 22.6)	32.7 (29.2, 36.4)	0.6 (0.5, 0.7)
Fatal	0.1 (0.0, 0.6)	0.1 (0.0, 0.6)	1.0 (0.1, 16.7)
Life-threatening	0.6 (0.2, 1.3)	1.2 (0.6, 2.1)	0.5 (0.2, 1.4)
Intracranial or intraspinal	-	0.5 (0.2, 1.2)	-
Emergency room visit for bleeding	8.5 (6.7, 10.5)	13.8 (11.6, 16.3)	0.6 (0.5, 0.8)
Admission for bleeding	5.7 (4.3, 7.4)	7.7 (6.1, 9.6)	0.7 (0.5, 1.0)
Thrombosis	1.5 (0.9, 2.6)	3.8 (2.7, 5.3)	0.4 (0.2, 0.7)
Ischemic/embolic stroke	0.3 (0.1, 0.9)	1 (0.5, 1.8)	0.3 (0.1, 1.1)
PE	0.2 (0.0, 0.7)	0.4 (0.1, 1.0)	0.5 (0.1, 2.8)
DVT	0.4 (0.1, 1.1)	0.9 (0.4, 1.7)	0.5 (0.1, 1.5)
Death	3.3 (2.3, 4.7)	4.0 (2.9, 5.5)	0.8 (0.5, 1.3)

ASA, acetylsalicylic acid or aspirin; CCI, Charlson comorbidity index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.

[a]HAS-BLED score modified to exclude labile international normalized ratio.

[b]High dose is considered a total daily dose of apixaban ≥ 10 mg or rivaroxaban ≥ 20 mg. Other doses are considered low doses.

[c]Adjusted for follow-up time.

largely similar between warfarin + ASA and DOACs + ASA as a class. Any bleeding was increased among DOAC + ASA users, seemingly driven by differences in nonmajor bleeding that includes any patient-reported bleeding outcome such as bruising, epistaxis, minor gastrointestinal bleeding, and hematuria. Evaluating specific anticoagulants in combination with ASA, we observed that any bleeding was more common when ASA was combined with rivaroxaban than with warfarin or apixaban. Nonmajor bleeding was more common when

ASA was combined with rivaroxaban compared with warfarin. In contrast, apixaban combined with ASA was associated with lower rates of major bleeding and emergency room visits but increased nonmajor bleeding than when warfarin was combined with ASA. We observed significantly more thrombotic events with rivaroxaban + ASA compared with the other 2 anticoagulants with concomitant ASA, while thrombotic outcomes were similar between apixaban + ASA and warfarin + ASA. These results are similar to what has been observed for patients on anticoagulant monotherapy [33] and may have implications for individual anticoagulant selection.

While other studies [25] have shown reduced thrombotic outcomes and similar to improved safety with DOACs + ASA instead of warfarin + ASA for AF, we found largely similar event rates when analyzing outcomes by anticoagulant class. The study by Bennaghmouch et al. [25] was a meta-analysis of randomized trials that accordingly did not adjust for ASA indication, dose, or some factors that could potentially reflect thrombotic risk, thus potentially yielding different results from our real-world observational study. Despite this limitation, this study was large with over 20,000 patients and may have had greater power to detect subtle differences in event rates [25]. As the authors point out, DOACs were analyzed in aggregate assuming similar efficacy and safety which may not be the case; it is possible that the differences observed in this study were influenced by the inclusion of apixaban, dabigatran, edoxaban, and rivaroxaban [25]. Our study found different secondary outcomes comparing individual anticoagulants. Our study also differed by the inclusion of patients anticoagulated for VTE (n = 1907 of the original study population, 30.9%). An analysis of randomized clinical trials studying oral anticoagulants for VTE similarly found comparable outcomes between DOACs + ASA vs vitamin K antagonists and ASA [27].

Rivaroxaban and apixaban are both reversible inhibitors of activated factor Xa with generally similar pharmacokinetics. However, the once-daily administration of rivaroxaban results in greater variation between peak and trough concentrations compared with the twice-daily administration of apixaban [33]. It has been proposed that this may explain the results of comparative efficacy studies of patients with AF that show rivaroxaban to be associated with both increased episodes of stroke and bleeding compared with apixaban [33]. Similar findings have also been observed for patients anticoagulated for VTE, with rivaroxaban associated with increased rates of recurrent VTE and bleeding relative to apixaban. While differences in pharmacology may explain differences in clinical effectiveness, other factors, such as variations in bioavailability of rivaroxaban with food or some other unknown factor, may explain these observations [33,34]. Medication adherence was not assessed in this study. It has been reported that medication adherence might be better with rivaroxaban compared with apixaban [35]. It is unclear if this could contribute to increased bleeding with rivaroxaban that was observed.

While previous studies are intriguing, they have some limitations largely due to the use of insurance claims data and potentially a greater risk for unadjusted confounding. Our registry uses direct chart abstraction, with collected data elements focused on anticoagulation quality and outcomes. We have accurate data on a variety of patient clinical, demographic, and laboratory variables. We also closely track anticoagulant exposure, as anticoagulants are directly followed by our clinics. Studies using claims data may not be able to accurately assess anticoagulant use and clinical outcomes, such as recurrent VTE. Our study also adds to the literature given the diverse nature of our patient population, which is not restricted to a single type of health care insurance or age group, thus potentially increasing the generalizability. Finally, we compared both of our most commonly used anticoagulants (apixaban and rivaroxaban) not only with one another but also with warfarin, which provides greater insight into anticoagulant selection.

While DOACs are increasingly used for the management of nonvalvular AF and VTE, selecting among the DOACs is challenging with lack of randomized clinical trials comparing their effectiveness and safety. DOAC selection must consider a variety of factors, including dosing regimen, organ function, indication, medication access, bleeding risk, storage, side effects, and more [26,36]. The Comparison of Bleeding Risk Between Rivaroxaban and Apixaban for the Treatment of Acute Venous Thromboembolism (NCT 03266783) study is anticipated to be completed in December 2023, and the Comparison of Bleeding Risk Between Rivaroxaban and Apixaban in Patients with AF (NCT 04642430) is anticipated to be completed in December 2026. Until trial data are available, observational data such as this study may help guide anticoagulant selection. This is especially true for patients for whom an oral anticoagulant and ASA are felt to be necessary.

4.1 | Strengths and limitations

Strengths of our study include the large, robust data set from chart-abstracted, real-world data across multiple diverse centers. Patients underwent a robust propensity match, and we evaluated both bleeding and thrombotic outcomes. Despite the better safety profile of the DOACs relative to warfarin, our study did not find that adding ASA was less risky in this population. Surprisingly, the data suggests that more, generally, nonmajor bleeding events may be linked with such treatment. Ultimately, providers must work with patients to carefully consider the pros and cons of coadministering ASA therapy with oral anticoagulation, with careful review of available data exploring the comparative outcomes of individual anticoagulants. Randomized trials are needed to help guide selection among the individual DOACs.

Limitations include those inherent to a registry-based study design, including the potential for selection bias, missing data, or unadjusted confounding variables. While propensity matching was used to try to limit confounding, residual confounding remains very possible. However, our chart-abstracted data focusing specifically on anticoagulation may offer the best data available to answer this research question. Despite differences in patient characteristics at baseline, our propensity-matched comparisons were well balanced. Without randomization, it may not be possible to determine causation. Our DOAC-specific analyses were post hoc and likely underpowered for rare outcome types. While patients switching from warfarin to

DOACs were included in this study (26.1% of the matched study population), given the long duration of average follow-up of about 2 years, we do not think this influenced the results. Such patients may have a lower bleeding risk compared with patients newly initiating anticoagulation, but this is a low percentage of the overall population. Given that ASA is available without a prescription, all ASA use was per patient report. It is possible that patients self-adjusted their ASA use or used it inconsistently. Patients were all followed by experienced anticoagulation clinics that regularly engage in quality improvement projects that may limit generalizability. Specifically, efforts to reduce unnecessary ASA use were ongoing at the time of this study, especially among warfarin-treated patients. In addition, the study was geographically limited, only including patients in the state of Michigan. Data on myocardial infarction may not have been well captured as a study outcome. Patients receiving medical care for outcome events outside of our hospital network may not have been well captured if these events were not reported back to the managing anticoagulation clinic staff. Thrombosis and bleeding outcomes were not adjudicated independently. Finally, the overall event rates were low, potentially limiting our power to detect differences for some outcome measures.

5 | CONCLUSIONS

For patients on oral anticoagulation for VTE and/or AF with concomitant ASA, outcomes are generally similar, comparing DOACs as a class to warfarin. Any and nonmajor bleeding was increased among DOAC + ASA users. When analyzing outcomes by specific anticoagulant drugs, bleeding outcomes are worse for combination therapy with rivaroxaban followed by warfarin and then apixaban. Thrombotic outcomes are worse with rivaroxaban but similar between warfarin and apixaban. These findings should be confirmed in randomized trials given the potential implications for therapy.

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AUTHOR CONTRIBUTIONS

G.D.B., B.H., and J.K.S. conceived and designed the study. G.D.B. and J.K.S. drafted the manuscript. X.K. and J.E. analyzed the data. G.D.B. and J.B.F. obtained funding for the underlying quality improvement initiative. All authors were involved in data acquisition. All authors had full access to the data and participated in manuscript writing and revision.

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SUPPLEMENTARY MATERIAL

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