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ORIGINAL RESEARCH

# Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients With Active Cancer

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## ABSTRACT

**BACKGROUND** Patients with cancer are more likely to develop nonvalvular atrial fibrillation (NVAF). Currently there are no definitive clinical trials or treatment guidelines for NVAF patients with concurrent cancer.

**OBJECTIVES** This subgroup analysis of the ARISTOPHANES study compared the risk of stroke/systemic embolism (stroke/SE) and major bleeding (MB) among NVAF patients with active cancer who were prescribed non–vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

**METHODS** A retrospective observational study was conducted in NVAF patients with active cancer who newly initiated apixaban, dabigatran, rivaroxaban, or warfarin from January 1, 2013, through September 30, 2015, with the use of Medicare and 4 U.S. commercial claims databases. Cox models were used to estimate the risk of stroke/SE and MB in the pooled propensity score–matched cohorts.

**RESULTS** A total of 40,271 patients were included, with main cancer types of prostate (29%), female breast (17%), genitourinary (14%), and lung (13%). Compared with warfarin, apixaban was associated with a lower risk of stroke/SE (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.45-0.78) and MB (HR: 0.58; 95% CI: 0.50-0.68); dabigatran and rivaroxaban had similar risks of stroke/SE (dabigatran: HR: 0.88 [95% CI: 0.54-1.41]; rivaroxaban: HR: 0.82 [95% CI: 0.62-1.08]) and MB (dabigatran: HR: 0.76 [95% CI: 0.57-1.01]; rivaroxaban: HR: 0.95 [95% CI: 0.85-1.06]). Risks of stroke/SE and MB varied among NOAC-NOAC comparisons, while consistent treatment effects were seen for all treatment comparisons across key cancer types.

**CONCLUSIONS** Among this cohort of NVAF patients with active cancer, the risk of stroke/SE and MB varied among oral anticoagulants and were consistent across cancer types. (J Am Coll Cardiol CardioOnc 2021;3:411–424) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**GI** = gastrointestinal

**GU** = genitourinary

**ICH** = intracranial hemorrhage

**MB** = major bleeding

**NOAC** = non-vitamin K antagonist oral anticoagulant

**NVAF** = nonvalvular atrial fibrillation

**PSM** = propensity score matching

**SE** = systemic embolism

**VTE** = venous thromboembolism

Atrial fibrillation (AF) is a heart rhythm condition that may lead to substantial morbidity and mortality, specifically in aging populations (1). In the U.S., 2.3 million individuals are considered to have AF, with an expected increase to 5.6 million by 2050 (1,2). AF occurs with many coexisting health conditions, including hypertension, coronary heart disease, chronic kidney disease, and diabetes mellitus (3). In addition, there is accumulated evidence suggesting an association between the incidence of AF and cancer (4,5).

A recent systematic review and meta-analysis of the association between cancer and AF revealed that patients with solid cancer were at a higher risk of developing AF compared with noncancer patients (4). Similarly, in the REGARDS (Reasons for Geographic and Racial Differences in Stroke Study), cancer patients were more likely to have prevalent AF than those without cancer (5). In addition, gastric, ovarian and cervical cancer patients have been associated with a higher risk of ischemic stroke compared to non-cancer patients (6-8), and it has been reported that major bleeding (MB) occurs in ~10% of all cancer patients (9).

Traditionally AF has been managed with the use of oral anticoagulants (OACs), such as vitamin K antagonists, but non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly being used. However, there are no specific clinical trials or guidelines for AF treatment in cancer patients (10). Post hoc analyses of clinical trials such as the ROCKET AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation; NCT00403767) and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; NCT00412984) trials have shown that the relative efficacy and safety of NOACs do not statistically differ from warfarin in patients with and without a history of cancer for the prevention of stroke/systemic embolism (SE) and the occurrence of MB (11,12). There was, however, a greater benefit seen in the composite of thrombotic events (stroke/SE, myocardial infarction, and death) among apixaban users with active cancer versus no cancer when compared to warfarin users in the ARISTOTLE trial (12).

Real-world studies, though limited, have also shown largely consistent results with the clinical trials regarding the generally uniform benefits seen among NOAC users regardless of cancer status (13-16). Increased risk of cardiac complications, such as stroke and MB, among AF patients with cancer (4-9) necessitates a comprehensive evaluation of available treatment strategies for this population. This subgroup analysis of ARISTOPHANES (Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients; NCT03087487), through the use of several data sources, aimed to respectively compare the risk of stroke/SE and MB among the nonvalvular AF (NVAF) population with active cancer newly prescribed to apixaban, dabigatran, rivaroxaban, or warfarin.

## METHODS

**DATA SOURCES AND PATIENT SELECTION.** NVAF patients with active cancer who were newly treated with apixaban, dabigatran, rivaroxaban, edoxaban, or warfarin were selected (17). Data were pooled from the U.S. Centers for Medicare and Medicaid Services (CMS) database and 4 U.S. commercial claims databases: the IBM MarketScan Commercial Claims and Encounter Database, the IQVIA PharMetrics Plus Database, the Optum Clinformatics Data Mart, and the Humana Research Database. Patients prescribed edoxaban were not included in this study given an insufficient sample size. Detailed data description and pooling processes can be found in previously published ARISTOPHANES reports (17,18).

From the ARISTOPHANES study population, NVAF patients with active cancer were selected if they had at least 1 OAC pharmacy claim from January 1, 2013, to September 30, 2015 (identification period). Active cancer was identified in patients who had at least 2 claims for cancer diagnosis or 1 claim for cancer diagnosis plus at least 1 claim for cancer treatment (eg, chemotherapy, radiation, cancer-related surgery) within 6 months before OAC treatment initiation (Supplemental Table 1). The first NOAC pharmacy claim during the identification period was designated as the index date for patients with any NOAC claim; the first warfarin prescription date was designated as the index date for those without a NOAC claim (19). Patients were required to have an AF diagnosis before or on the index date and needed continuous medical and pharmacy health plan enrollment for ≥12 months before the index date (baseline period). Patients were not required to be newly diagnosed with AF or cancer, but patients with OAC use during the baseline period were excluded. Detailed exclusion criteria are listed in **Figure 1**.

**OUTCOME MEASURES.** The primary outcomes were time to first stroke/SE and time to first MB. Hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis were used as the primary outcome measures. The primary effectiveness

outcome of stroke/SE was further stratified by ischemic stroke, hemorrhagic stroke, and SE. The primary safety outcome of MB was further stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and MB in other key sites (17,20,21). Patients were followed from the day after the index date to the earliest of 30 days after the date of discontinuation, switch, end of continuous medical and pharmacy enrollment, death (all-cause deaths from Medicare and hospitalization deaths from commercial datasets), or end of study period (September 30, 2015). Discontinuation was defined as no evidence of index OAC prescription for 30 days from the last day of the last filled prescription days' supply.

**STATISTICAL ANALYSIS.** All variables were stratified by cohort and analyzed descriptively. Mean ± SD were provided for continuous variables. Frequencies and percentages were provided for categoric variables. One-to-one propensity score matching (PSM) was conducted in each database for all comparisons before the datasets were pooled: NOAC versus warfarin (apixaban vs warfarin, dabigatran vs warfarin, and rivaroxaban vs warfarin) and NOAC versus NOAC (apixaban vs dabigatran, apixaban vs rivaroxaban, and dabigatran vs rivaroxaban) (17,18). Propensity scores were generated by logistic regression with the use of the following variables: demographics, Deyo-Charlson comorbidity index (CCI), comorbidities, baseline medications, cancer metastasis, and cancer-related treatment (variables are listed in **Tables 1, 2, 3, and 4**). Patients were matched by nearest neighbor matching without replacement (with a caliper of 0.01). The PSM-adjusted baseline variables were compared based on standardized differences, with a threshold of 10% for balance (22).

Kaplan-Meier curves were used to illustrate cumulative incidence rates, and log-rank tests were used to compare the curves across cohorts. Cox proportional hazard models were used to evaluate the risk of stroke/SE and MB with robust sandwich estimates to account for correlation within the matched populations (23). All matched confounders were balanced after PSM; therefore, only OAC treatment was included as an independent variable in the Cox models. Hazard ratios (HRs) are expressed with 95% confidence intervals (CIs). P values of $<0.05$ were considered as statistically significant. Data analysis was performed with the use of SAS statistical software version 9.4 (SAS Institute).

**SUBGROUP ANALYSIS.** Subgroup analysis was conducted for the following key cancer types across the OAC cohorts: breast cancer, lung cancer, hematologic cancer, genitourinary (GU) cancer, and upper/lower GI cancer. Patients in the dabigatran cohort and those with other cancer types were not included for the subgroup analysis owing to limited sample size. The PSM cohorts were stratified by the included cancer type, and interactions between treatment comparisons and cancer types on stroke/SE and MB were evaluated. P values of $<0.10$ were considered as statistically significant for the interaction analysis.

**ETHICAL APPROVAL.** Because this study did not involve the collection, use, or transmittal of individually identifiable data, it was exempt from institutional review board review. Both the datasets and the security of the offices where analysis was completed (and where the datasets are kept) meet the requirements of the Health Insurance Portability and Accountability Act of 1996.

## RESULTS

After applying the selection criteria, a total of 40,271 NVAF patients in the pooled datasets were identified as also having active cancer, accounting for 9% of the total ARISTOPHANES NVAF patient population (N = 466,991) (**Figure 1**). Among the NVAF patients with active cancer, the index users of warfarin, apixaban, dabigatran, and rivaroxaban numbered 15,371 (38%), 9,517 (24%), 2,742 (7%), and 12,641 (31%), respectively.

Before PSM, the majority of patients included in the analysis had solid nonhematologic tumors (92%), with prostate cancer being the most common cancer site (29%), followed by female breast cancer (17%), GU cancer (14%), lung cancer (13%), and GI cancer (13%). More than one-half of the patients in each cohort reported receiving a cancer-related treatment 6 months before or on the index date (Supplemental Table 2). Furthermore, the majority of apixaban, dabigatran, and rivaroxaban users (73%, 81%, and 69%, respectively) were on standard doses of each medication. Before PSM, the incidence rates (per 100 person-years) for sroke/SE and MB, respectively, were as follows: warfarin: 2.64 and 10.56; apixaban: 1.45 and 6.01; dabigatran: 1.92 and 5.38; and rivaroxaban: 1.72 and 8.01.

After 1:1 PSM, the following NOAC-warfarin comparison cohorts were formed: apixaban-warfarin with 8,236 pairs, dabigatran-warfarin with 2,470 pairs, and rivaroxaban-warfarin with 9,988 pairs (**Table 1 and 2**). The NOAC-NOAC comparison cohorts were formed as apixaban-dabigatran with 2,413 pairs, apixaban-rivaroxaban with 8,608 pairs, and dabigatran-rivaroxaban with 2,553 pairs (**Table 3 and 4**). The mean follow-up time for the 6 matched cohorts ranged

**TABLE 1 Post-PSM Baseline Characteristics of NOAC-Warfarin Cohorts**

| | Apixaban vs Warfarin | | | | Dabigatran vs Warfarin | | | | Rivaroxaban vs Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Warfarin | | Dabigatran | | Warfarin | | Rivaroxaban | | Warfarin | |
| | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD |
| Sample size | 8,236 | 100% | 8,236 | 100% | 2,470 | 100% | 2,470 | 100% | 9,988 | 100% | 9,988 | 100% |
| Age, y[a] | 78.00 | 7.60 | 77.90 | 7.51 | 76.67 | 7.41 | 76.78 | 7.61 | 77.41 | 7.45 | 77.40 | 7.55 |
| 18-54 | 24 | 0.29% | 25 | 0.30% | 12 | 0.49% | 14 | 0.57% | 24 | 0.24% | 34 | 0.34% |
| 55-64 | 174 | 2.11% | 160 | 1.94% | 67 | 2.71% | 76 | 3.08% | 258 | 2.58% | 252 | 2.52% |
| 65-74 | 2,617 | 31.78% | 2,633 | 31.97% | 905 | 36.64% | 888 | 35.95% | 3,358 | 33.62% | 3,341 | 33.45% |
| ≥75 | 5,421 | 65.82% | 5,418 | 65.78% | 1,486 | 60.16% | 1,492 | 60.40% | 6,348 | 63.56% | 6,361 | 63.69% |
| Sex[a] | | | | | | | | | | | | |
| Male | 4,945 | 60.04% | 4,961 | 60.24% | 1,503 | 60.85% | 1,523 | 61.66% | 6,023 | 60.30% | 6,016 | 60.23% |
| Female | 3,291 | 39.96% | 3,275 | 39.76% | 967 | 39.15% | 947 | 38.34% | 3,965 | 39.70% | 3,972 | 39.77% |
| U.S. geographic region[a] | | | | | | | | | | | | |
| Northeast | 1,636 | 19.86% | 1,620 | 19.67% | 541 | 21.90% | 528 | 21.38% | 2,093 | 20.96% | 2,052 | 20.54% |
| Midwest | 1,838 | 22.32% | 1,865 | 22.64% | 559 | 22.63% | 593 | 24.01% | 2,510 | 25.13% | 2,536 | 25.39% |
| South | 3,353 | 40.71% | 3,331 | 40.44% | 896 | 36.28% | 872 | 35.30% | 3,662 | 36.66% | 3,684 | 36.88% |
| West | 1,394 | 16.93% | 1,406 | 17.07% | 472 | 19.11% | 476 | 19.27% | 1,703 | 17.05% | 1,697 | 16.99% |
| Other | 15 | 0.18% | 14 | 0.17% | NR | NR | NR | NR | 20 | 0.20% | 19 | 0.19% |
| Baseline comorbidity | | | | | | | | | | | | |
| Deyo-Charlson comorbidity index[a] | 4.64 | 3.56 | 4.62 | 3.55 | 4.12 | 3.42 | 4.08 | 3.35 | 4.61 | 3.55 | 4.62 | 3.58 |
| $CHA_2DS_2$-VASc score | 4.12 | 1.48 | 4.13 | 1.46 | 3.92 | 1.50 | 3.92 | 1.45 | 4.06 | 1.48 | 4.07 | 1.46 |
| 0 | 25 | 0.30% | 21 | 0.25% | 19 | 0.77% | 13 | 0.53% | 37 | 0.37% | 48 | 0.48% |
| 1 | 133 | 1.61% | 138 | 1.68% | 61 | 2.47% | 58 | 2.35% | 212 | 2.12% | 196 | 1.96% |
| 2 | 833 | 10.11% | 750 | 9.11% | 305 | 12.35% | 290 | 11.74% | 1,040 | 10.41% | 945 | 9.46% |
| 3 | 1,981 | 24.05% | 2,019 | 24.51% | 645 | 26.11% | 656 | 26.56% | 2,491 | 24.94% | 2,460 | 24.63% |
| ≥4 | 5,264 | 63.91% | 5,308 | 64.45% | 1,440 | 58.30% | 1,453 | 58.83% | 6,208 | 62.15% | 6,339 | 63.47% |
| HAS-BLED score | 3.58 | 1.29 | 3.57 | 1.28 | 3.37 | 1.26 | 3.32 | 1.24 | 3.53 | 1.26 | 3.52 | 1.28 |
| 0 | 17.00 | 0.21% | 15 | 0.18% | 15 | 0.61% | 10 | 0.40% | 28 | 0.28% | 31 | 0.31% |
| 1 | 274 | 3.33% | 281 | 3.41% | 108 | 4.37% | 114 | 4.62% | 356 | 3.56% | 361 | 3.61% |
| 2 | 1,500 | 18.21% | 1,507 | 18.30% | 521 | 21.09% | 547 | 22.15% | 1,785 | 17.87% | 1,883 | 18.85% |
| ≥3 | 6,445 | 78.25% | 6,433 | 78.11% | 1,826 | 73.93% | 1,799 | 72.83% | 7,819 | 78.28% | 7,713 | 77.22% |
| Bleeding history[a] | 2,889 | 35.08% | 2,904 | 35.26% | 812 | 32.87% | 782 | 31.66% | 3,569 | 35.73% | 3,564 | 35.68% |
| Heart failure[a] | 2,666 | 32.37% | 2,661 | 32.31% | 716 | 28.99% | 729 | 29.51% | 3,114 | 31.18% | 3,123 | 31.27% |
| Diabetes mellitus[a] | 3,129 | 37.99% | 3,085 | 37.46% | 938 | 37.98% | 938 | 37.98% | 3,894 | 38.99% | 3,863 | 38.68% |
| Hypertension[a] | 7,514 | 91.23% | 7,503 | 91.10% | 2,197 | 88.95% | 2,185 | 88.46% | 9,068 | 90.79% | 9,031 | 90.42% |
| Renal disease[a] | 2,656 | 32.25% | 2,614 | 31.74% | 567 | 22.96% | 559 | 22.63% | 2,881 | 28.84% | 2,889 | 28.92% |
| Liver disease[a] | 799 | 9.70% | 776 | 9.42% | 207 | 8.38% | 187 | 7.57% | 1,062 | 10.63% | 1,078 | 10.79% |
| Myocardial infarction[a] | 861 | 10.45% | 898 | 10.90% | 204 | 8.26% | 222 | 8.99% | 1,019 | 10.20% | 1,047 | 10.48% |
| Dyspepsia or stomach discomfort[a] | 2,367 | 28.74% | 2,340 | 28.41% | 654 | 26.48% | 637 | 25.79% | 2,808 | 28.11% | 2,807 | 28.10% |
| Non-stroke/SE peripheral vascular disease[a] | 4,952 | 60.13% | 4,956 | 60.17% | 1,408 | 57.00% | 1,402 | 56.76% | 5,914 | 59.21% | 5,906 | 59.13% |
| Stroke/SE[a] | 1,121 | 13.61% | 1,158 | 14.06% | 283 | 11.46% | 298 | 12.06% | 1,243 | 12.44% | 1,277 | 12.79% |
| Transient ischemic attack[a] | 673 | 8.17% | 712 | 8.64% | 183 | 7.41% | 168 | 6.80% | 766 | 7.67% | 777 | 7.78% |
| Anemia and coagulation defects[a] | 3,680 | 44.68% | 3,648 | 44.29% | 997 | 40.36% | 958 | 38.79% | 4,358 | 43.63% | 4,379 | 43.84% |
| Alcoholism[a] | 179 | 2.17% | 168 | 2.04% | 60 | 2.43% | 51 | 2.06% | 229 | 2.29% | 239 | 2.39% |
| Peripheral artery disease | 2,121 | 25.75% | 2,130 | 25.86% | 597 | 24.17% | 582 | 23.56% | 2,505 | 25.08% | 2,575 | 25.78% |
| Coronary artery disease | 4,252 | 51.63% | 4,295 | 52.15% | 1,169 | 47.33% | 1,205 | 48.79% | 5,074 | 50.80% | 5,046 | 50.52% |
| Dose of the index prescription | | | | | | | | | | | | |
| Standard dose[b] | 5,920 | 71.88% | NA | NA | 1,973 | 79.88% | NA | NA | 6,619 | 66.27% | NA | NA |
| Low dose[c] | 2,316 | 28.12% | NA | NA | 497 | 20.12% | NA | NA | 3,369 | 33.73% | NA | NA |

*Continued on the next page*

from 6 to 8 months. All baseline variables included in the PSM logistic model were balanced with a standardized difference of <10%, resulting in well balanced demographic and clinical characteristics between pairs. The Kaplan-Meier curves for cumulative incidence rates of stroke/SE and MB in the matched populations can be seen in Supplemental Figures 1 to 12.

**NOAC-WARFARIN COMPARISONS.** Among the NOAC cohorts, apixaban patients had a lower risk for stroke/

**TABLE 1 Continued**

| | Apixaban vs Warfarin | | | | Dabigatran vs Warfarin | | | | Rivaroxaban vs Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Warfarin | | Dabigatran | | Warfarin | | Rivaroxaban | | Warfarin | |
| | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD |
| Follow-up time, days | 181.10 | 165.61 | 228.54 | 214.08 | 222.27 | 223.36 | 229.25 | 214.07 | 214.88 | 207.85 | 227.94 | 212.57 |
| Median | 120 | | 145 | | 121 | | 147 | | 129 | | 145 | |
| Reasons for censoring | | | | | | | | | | | | |
| Discontinuation | 3,183 | 38.65% | 4,835 | 58.71% | 1,442 | 58.38% | 1,460 | 59.11% | 5,206 | 52.12% | 5,952 | 59.59% |
| Switch | 320 | 3.89% | NA | NA | 269 | 10.89% | NA | NA | 677 | 6.78% | NA | NA |
| Death | 461 | 5.60% | 801 | 9.73% | 160 | 6.48% | 208 | 8.42% | 711 | 7.12% | 962 | 9.63% |
| End of continuous medical/pharmacy enrollment | 98 | 1.19% | 168 | 2.04% | 40 | 1.62% | 61 | 2.47% | 230 | 2.30% | 222 | 2.22% |
| End of study period | 4,174 | 50.68% | 2,432 | 29.53% | 559 | 22.63% | 741 | 30.00% | 3,164 | 31.68% | 2,852 | 28.55% |

Cells with n < 11 are not reported (NR). [a]Variable used in propensity score matching. [b]5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. [c]2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 560 and 2,809 patients received 10 mg and 15 mg rivaroxaban, respectively, in the rivaroxaban-warfarin matched cohort.

$CHA_2DS_2$-Vasc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; PSM = propensity score matching; SD = standard deviation; SE = systemic embolism.

SE compared with those prescribed warfarin (HR: 0.59; 95% CI: 0.45-0.78) (**Central Illustration**). Dabigatran and rivaroxaban patients had a similar risk for stroke/SE compared with warfarin patients (dabigatran: HR: 0.88 [95% CI: 0.54-1.41]; rivaroxaban: HR: 0.82 [95% CI: 0.62-1.08]). Ischemic stroke was the most common embolic event, with a lower risk in apixaban patients (HR: 0.72; 95% CI: 0.52-0.99) and similar risks in dabigatran (HR: 0.95; 95% CI: 0.54-1.66) and rivaroxaban (HR: 1.02; 95% CI: 0.76-1.37) patients compared with warfarin patients.

The apixaban cohort was the only cohort that had a significantly lower risk for MB compared with the warfarin cohort (HR: 0.58; 95% CI: 0.50-0.68). Dabigatran and rivaroxaban patients had a similar risk of MB compared with warfarin patients (dabigatran: HR: 0.76 [95% CI: 0.57-1.01]; rivaroxaban: HR: 0.95 [95% CI: 0.85-1.06]).

Apixaban patients experienced a lower risk for all 3 types of MB compared with warfarin patients. Dabigatran patients had a lower risk for other MB compared with warfarin patients (HR: 0.65; 95% CI: 0.44-0.95), and rivaroxaban patients had a reduced risk for ICH compared with warfarin patients (HR: 0.49; 95% CI: 0.35-0.69).

**NOAC-NOAC COMPARISONS.** Apixaban patients had a lower risk for stroke/SE compared with dabigatran patients (HR: 0.41; 95% CI: 0.22-0.77) (**Figure 2**). Similar risks for stroke/SE were seen in the apixaban-rivaroxaban comparison (HR: 0.81; 95% CI: 0.60-1.08) and the dabigatran-rivaroxaban comparison (HR: 0.90; 95% CI: 0.50-1.63).

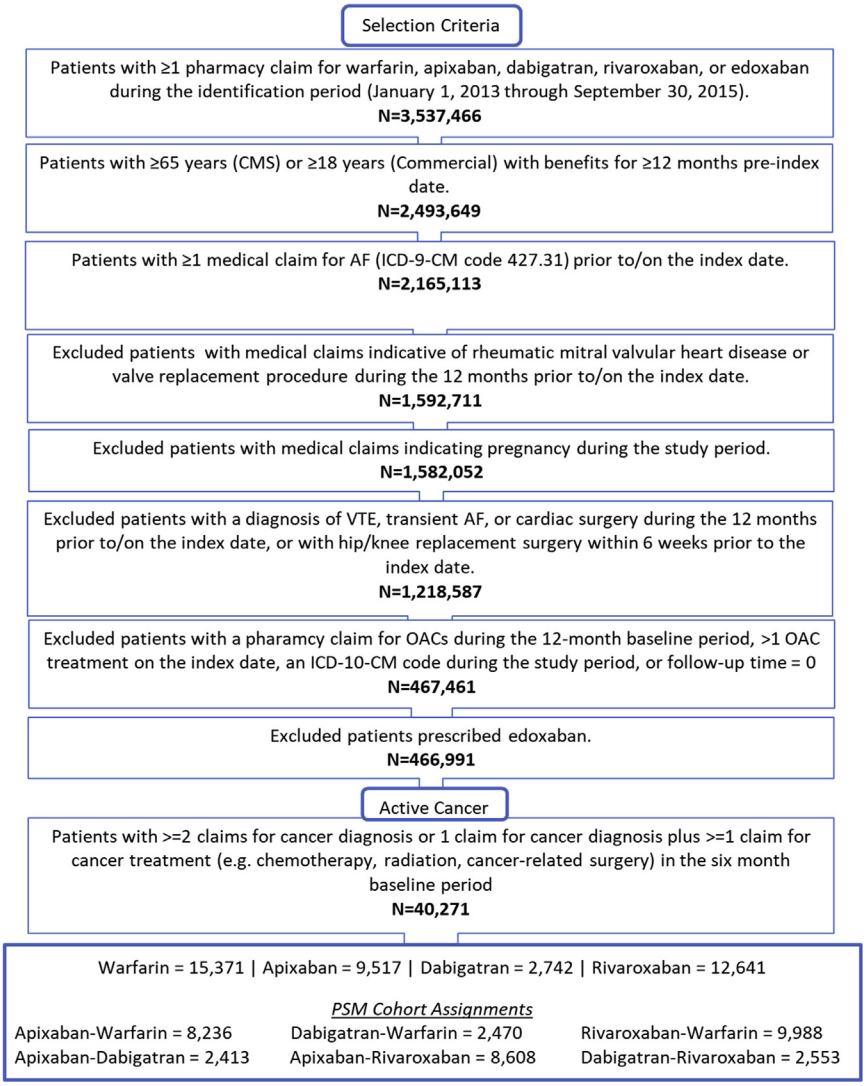
When evaluating MB, apixaban patients had a lower risk compared with rivaroxaban patients (HR: 0.66; 95% CI: 0.54-0.80) and a similar risk compared with dabigatran patients (HR: 0.83; 95% CI: 0.58-1.19). Dabigatran patients also experienced a lower risk for MB compared with those prescribed rivaroxaban (HR: 0.71; 95% CI: 0.52-0.95). The apixaban cohort continued to show a lower risk for MB compared with the rivaroxaban cohort in terms of GI bleeding (HR: 0.56; 95% CI: 0.45-0.69) and bleeding in other major sites (HR: 0.70; 95% CI: 0.54-0.91). The other NOAC-NOAC comparisons for the MB components all yielded similar risks to one another.

**SUBGROUP ANALYSIS.** No significant interactions were seen between treatment comparisons and the included cancer types for stroke/SE and MB. Treatment effects were consistent across different cancer types (**Figures 3 and 4**). Owing to the small sample size of patients with the included cancer types, the subgroup analysis was not evaluated for the dabigatran cohorts.

## DISCUSSION

As far as we are aware, this is the largest contemporary cohort of NVAF patients with active cancer treated with NOACs and warfarin. Our principal findings in this subgroup analysis of the ARISTOPHANES study of NVAF patients with active cancer are that compared with warfarin, apixaban was associated with a lower risk of stroke/SE and MB and dabigatran and rivaroxaban had similar risks of stroke/SE and MB. Second, risks of stroke/SE and MB varied among NOAC-NOAC comparisons: apixaban patients had a lower risk of stroke/SE compared with dabigatran users, and a lower risk of MB compared with rivaroxaban users; and dabigatran patients experienced a lower risk in MB compared with those prescribed rivaroxaban. Third, when evaluating

**FIGURE 1 Selection Criteria**




The inclusion and exclusion criteria of this study yielded over 466,000 patients with nonvalvular atrial fibrillation, of which 40,271 had active cancer. These patients were matched into NOAC-warfarin and NOAC-NOAC cohorts via propensity score matching. AF = atrial fibrillation; CMS = U.S. Centers for Medicare and Medicaid Services; ICD-9/10-CM = International Classification of Diseases-9th/-10th Revision, Clinical Modification; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PSM = propensity score matching; VTE = venous thromboembolism.

patients according to major cancer types, consistent treatment effects on stroke/SE or MB were seen for the NOAC-warfarin and NOAC-NOAC comparisons across the different cancer types. As an ad hoc analysis of the ARISTOPHANES study focusing on patients with active cancer, the results of this analysis were generally consistent with the findings of the main ARISTOPHANES analysis on the whole patient population regardless of active cancer status (17). Both analyses showed that NOACs were associated with better or similar safety and effectiveness compared with warfarin. In addition, the present analysis showed consistent treatment effects across key cancer types.

Active cancer patients are more susceptible to developing not only cardiac disturbances such as NVAF, but also other thromboembolic and bleeding complications, such as ischemic stroke and MB,

**TABLE 2 Post-PSM Cancer-Related Baseline Characteristics of NOAC-Warfarin Cohorts**

| | Apixaban vs Warfarin | | | | Dabigatran vs Warfarin | | | | Rivaroxaban vs Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Warfarin | | Dabigatran | | Warfarin | | Rivaroxaban | | Warfarin | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Sample size | 8,236 | 100 | 8,236 | 100 | 2,470 | 100 | 2,470 | 100 | 9,988 | 100 | 9,988 | 100 |
| Cancer site | | | | | | | | | | | | |
| Prostate | 2,483 | 30.15 | 2,343 | 28.45 | 745 | 30.16 | 740 | 29.96 | 2,938 | 29.42 | 2,780 | 27.83 |
| Female breast | 1,497 | 18.18 | 1,398 | 16.97 | 468 | 18.95 | 430 | 17.41 | 1,757 | 17.59 | 1,704 | 17.06 |
| Gastrointestinal(GI)[a] | 1,004 | 12.19 | 1,100 | 13.36 | 288 | 11.66 | 312 | 12.63 | 1,338 | 13.40 | 1,403 | 14.05 |
| Lung | 946 | 11.49 | 1,156 | 14.04 | 269 | 10.89 | 357 | 14.45 | 1,228 | 12.29 | 1,448 | 14.50 |
| Lymphoma | 935 | 11.35 | 895 | 10.87 | 285 | 11.54 | 266 | 10.77 | 1,160 | 11.61 | 1,094 | 10.95 |
| Lower GI[b] | 751 | 9.12 | 792 | 9.62 | 200 | 8.10 | 219 | 8.87 | 972 | 9.73 | 1,000 | 10.01 |
| Bladder | 669 | 8.12 | 703 | 8.54 | 204 | 8.26 | 171 | 6.92 | 789 | 7.90 | 792 | 7.93 |
| Leukemia | 479 | 5.82 | 480 | 5.83 | 144 | 5.83 | 132 | 5.34 | 559 | 5.60 | 561 | 5.62 |
| Renal cell carcinoma | 368 | 4.47 | 386 | 4.69 | 90 | 3.64 | 99 | 4.01 | 408 | 4.08 | 453 | 4.54 |
| Gynecologic[c] | 256 | 3.11 | 255 | 3.10 | 80 | 3.24 | 79 | 3.20 | 350 | 3.50 | 326 | 3.26 |
| Multiple myeloma | 217 | 2.63 | 250 | 3.04 | 71 | 2.87 | 69 | 2.79 | 285 | 2.85 | 295 | 2.95 |
| Upper GI[d] | 133 | 1.61 | 169 | 2.05 | 37 | 1.50 | 52 | 2.11 | 193 | 1.93 | 209 | 2.09 |
| Pancreas | 79 | 0.96 | 106 | 1.29 | 31 | 1.26 | 31 | 1.26 | 120 | 1.20 | 128 | 1.28 |
| Stomach | 66 | 0.80 | 98 | 1.19 | 24 | 0.97 | 33 | 1.34 | 96 | 0.96 | 130 | 1.30 |
| Brain tumor | 67 | 0.81 | 73 | 0.89 | 28 | 1.13 | 20 | 0.81 | 87 | 0.87 | 96 | 0.96 |
| Testicular | 11 | 0.13 | NR | NR | NR | NR | NR | NR | 24 | 0.24 | 11 | 0.11 |
| Cancer metastasis[e] | 1,231 | 14.95 | 1,237 | 15.02 | 308 | 12.47 | 306 | 12.39 | 1,612 | 16.14 | 1,601 | 16.03 |
| Cancer type | | | | | | | | | | | | |
| Hematologic | 1,328 | 16.12 | 1,293 | 15.70 | 400 | 16.19 | 379 | 15.34 | 1,591 | 15.93 | 1,567 | 15.69 |
| Nonhematologic | 7,621 | 92.53 | 7,618 | 92.50 | 2,260 | 91.50 | 2,284 | 92.47 | 9,257 | 92.68 | 9,221 | 92.32 |
| Cancer-related treatment | 4,458 | 54.13 | 4,399 | 53.41 | 1,258 | 50.93 | 1,239 | 50.16 | 5,411 | 54.18 | 5,423 | 54.30 |
| Chemotherapy[e] | 3,793 | 46.05 | 3,753 | 45.57 | 1,033 | 41.82 | 1,018 | 41.21 | 4,583 | 45.89 | 4,572 | 45.77 |
| Hormone therapy[e] | 593 | 7.20 | 565 | 6.86 | 189 | 7.65 | 191 | 7.73 | 722 | 7.23 | 716 | 7.17 |
| Radiation[e] | 708 | 8.60 | 697 | 8.46 | 217 | 8.79 | 214 | 8.66 | 936 | 9.37 | 922 | 9.23 |
| Cancer-related surgery[e] | 245 | 2.97 | 224 | 2.72 | 66 | 2.67 | 63 | 2.55 | 323 | 3.23 | 313 | 3.13 |

Cells with n < 11 are not reported (NR). Immunotherapy was also assessed as a cancer-related treatment but had too few patients to report (n < 11). [a]GI cancer includes esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus cancers. [b]Lower GI cancer includes small intestine, large intestine, rectum, and anus cancers. [c]Gynecologic cancer includes uterus, cervix, placenta, ovary, and other female genital organ cancers. [d]Upper GI cancer includes esophagus and stomach cancers. [e]Variable used in propensity score matching.

Abbreviations as in Table 1.

compared with noncancer individuals (4-9). Owing to these increased risks, this patient population poses a unique challenge regarding anticoagulation management (24). However, current AF guidelines for cancer patients have yet to strongly recommend any specific treatment owing to the lack of evidence and research conducted within this at-risk patient population (25,26). This underscores the urgency in evaluating the potential risks and benefits of available treatment strategies for NVAF active cancer patients.

A recent systematic review and meta-analysis of post hoc analyses from the ROCKET AF, ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48), and ARISTOTLE trials, and 2 other cohort studies that compared NOACs with warfarin among AF patients with cancer showed results similar to those found in our analysis (25). The meta-analysis found that NOAC use was significantly associated with a reduced risk of stroke/SE (risk ratio [RR]: 0.52; 95% CI: 0.28-0.99) and a decreased risk of intracranial or GI bleeding (RR: 0.65; 95% CI: 0.42-0.98). In addition, NOAC use had a tendency toward significantly reducing the risk of MB (RR: 0.73; 95% CI: 0.53-1.00) in NVAF cancer patients.

Real-world studies that have investigated the impact of NOAC treatments in NVAF patients with active cancer are limited (13-16). In a Korean retrospective study, NVAF active cancer patients using NOACs (apixaban, dabigatran, and rivaroxaban) experienced lower stroke/SE, MB, and all-cause death incidence rates than those in the PSM warfarin cohort (13). A U.S. study using the MarketScan claims database identified 16,096 AF patients who were actively treated for cancer during the time of anticoagulation initiation (15). In that MarketScan study, patients initiating apixaban had significantly lower rates of severe bleeding (HR: 0.37; 95% CI:

**TABLE 3 Post-PSM Baseline Characteristics of NOAC-NOAC Cohorts**

| | Apixaban vs Dabigatran | | | | Apixaban vs Rivaroxaban | | | | Dabigatran vs Rivaroxaban | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Dabigatran | | Apixaban | | Rivaroxaban | | Dabigatran | | Rivaroxaban | |
| | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD |
| Sample size | 2,413 | 100% | 2,413 | 100% | 8,608 | 100% | 8,608 | 100% | 2,553 | 100% | 2,553 | 100% |
| Age, y[a] | 76.95 | 7.51 | 76.58 | 7.49 | 77.43 | 7.80 | 77.39 | 7.68 | 76.13 | 7.73 | 76.17 | 7.70 |
| 18-54 | NR | NR | NR | NR | 47 | 0.55% | 42 | 0.49% | 11 | 0.43% | 19 | 0.74% |
| 55-64 | 71 | 2.94% | 71 | 2.94% | 273 | 3.17% | 258 | 3.00% | 125 | 4.90% | 114 | 4.47% |
| 65-74 | 893 | 37.01% | 897 | 37.17% | 2,840 | 32.99% | 2,836 | 32.95% | 947 | 37.09% | 957 | 37.49% |
| ≥75 | 1,442 | 59.76% | 1,435 | 59.47% | 5,448 | 63.29% | 5,472 | 63.57% | 1,470 | 57.58% | 1,463 | 57.31% |
| Sex[a] | | | | | | | | | | | | |
| Male | 1,498 | 62.08% | 1,457 | 60.38% | 5,209 | 60.51% | 5,191 | 60.30% | 1,558 | 61.03% | 1,581 | 61.93% |
| Female | 915 | 37.92% | 956 | 39.62% | 3,399 | 39.49% | 3,417 | 39.70% | 995 | 38.97% | 972 | 38.07% |
| U.S. geographic region[a] | | | | | | | | | | | | |
| Northeast | 513 | 21.26% | 514 | 21.30% | 1,629 | 18.92% | 1,671 | 19.41% | 549 | 21.50% | 550 | 21.54% |
| Midwest | 518 | 21.47% | 539 | 22.34% | 1,817 | 21.11% | 1,825 | 21.20% | 576 | 22.56% | 600 | 23.50% |
| South | 932 | 38.62% | 927 | 38.42% | 3,756 | 43.63% | 3,733 | 43.37% | 958 | 37.52% | 960 | 37.60% |
| West | 449 | 18.61% | 431 | 17.86% | 1,390 | 16.15% | 1,365 | 15.86% | 467 | 18.29% | 441 | 17.27% |
| Other | NR | NR | NR | NR | 16 | 0.19% | 14 | 0.16% | NR | NR | NR | NR |
| Baseline comorbidity | | | | | | | | | | | | |
| Deyo-Charlson comorbidity index[a] | 4.06 | 3.40 | 4.00 | 3.38 | 4.42 | 3.53 | 4.42 | 3.52 | 3.94 | 3.37 | 3.99 | 3.27 |
| $CHA_2DS_2$-VASc score | 3.90 | 1.47 | 3.91 | 1.50 | 4.02 | 1.49 | 4.02 | 1.51 | 3.83 | 1.53 | 3.84 | 1.51 |
| 0 | 11 | 0.46% | 13 | 0.54% | 42 | 0.49% | 53 | 0.62% | 29 | 1.14% | 18 | 0.71% |
| 1 | 63 | 2.61% | 67 | 2.78% | 188 | 2.18% | 205 | 2.38% | 85 | 3.33% | 93 | 3.64% |
| 2 | 294 | 12.18% | 305 | 12.64% | 974 | 11.32% | 961 | 11.16% | 344 | 13.47% | 356 | 13.94% |
| 3 | 650 | 26.94% | 639 | 26.48% | 2,127 | 24.71% | 2,139 | 24.85% | 672 | 26.32% | 642 | 25.15% |
| ≥4 | 1,395 | 57.81% | 1,389 | 57.56% | 5,277 | 61.30% | 5,250 | 60.99% | 1,423 | 55.74% | 1,444 | 56.56% |
| HAS-BLED score | 3.40 | 1.26 | 3.38 | 1.26 | 3.50 | 1.28 | 3.50 | 1.27 | 3.32 | 1.29 | 3.31 | 1.25 |
| 0 | 9 | 0.37% | 15 | 0.62% | 26 | 0.30% | 33 | 0.38% | 23 | 0.90% | 12 | 0.47% |
| 1 | 101 | 4.19% | 103 | 4.27% | 348 | 4.04% | 349 | 4.05% | 138 | 5.41% | 133 | 5.21% |
| 2 | 508 | 21.05% | 505 | 20.93% | 1,646 | 19.12% | 1,559 | 18.11% | 552 | 21.62% | 556 | 21.78% |
| ≥3 | 1,795 | 74.39% | 1,790 | 74.18% | 6,588 | 76.53% | 6,667 | 77.45% | 1,840 | 72.07% | 1,852 | 72.54% |
| Bleeding history[a] | 782 | 32.41% | 780 | 32.32% | 2,878 | 33.43% | 2,844 | 33.04% | 811 | 31.77% | 780 | 30.55% |
| Heart failure[a] | 698 | 28.93% | 696 | 28.84% | 2,613 | 30.36% | 2,609 | 30.31% | 712 | 27.89% | 722 | 28.28% |
| Diabetes mellitus[a] | 893 | 37.01% | 893 | 37.01% | 3,145 | 36.54% | 3,169 | 36.81% | 933 | 36.55% | 957 | 37.49% |
| Hypertension[a] | 2,152 | 89.18% | 2,153 | 89.23% | 7,813 | 90.76% | 7,805 | 90.67% | 2,262 | 88.60% | 2,277 | 89.19% |
| Renal disease[a] | 555 | 23.00% | 542 | 22.46% | 2,455 | 28.52% | 2,449 | 28.45% | 551 | 21.58% | 563 | 22.05% |
| Liver disease[a] | 225 | 9.32% | 199 | 8.25% | 803 | 9.33% | 800 | 9.29% | 205 | 8.03% | 190 | 7.44% |
| Myocardial infarction[a] | 219 | 9.08% | 199 | 8.25% | 838 | 9.74% | 852 | 9.90% | 202 | 7.91% | 213 | 8.34% |
| Dyspepsia or stomach discomfort[a] | 658 | 27.27% | 636 | 26.36% | 2,402 | 27.90% | 2,410 | 28.00% | 653 | 25.58% | 665 | 26.05% |
| Non-stroke/SE peripheral vascular disease[a] | 1,342 | 55.62% | 1,363 | 56.49% | 5,081 | 59.03% | 5,109 | 59.35% | 1,421 | 55.66% | 1,429 | 55.97% |
| Stroke/SE[a] | 270 | 11.19% | 272 | 11.27% | 1,087 | 12.63% | 1,088 | 12.64% | 281 | 11.01% | 282 | 11.05% |
| Transient ischemic attack[a] | 159 | 6.59% | 179 | 7.42% | 714 | 8.29% | 703 | 8.17% | 186 | 7.29% | 179 | 7.01% |
| Anemia and coagulation defects[a] | 972 | 40.28% | 965 | 39.99% | 3,602 | 41.84% | 3,631 | 42.18% | 1,001 | 39.21% | 967 | 37.88% |
| Alcoholism[a] | 63 | 2.61% | 57 | 2.36% | 180 | 2.09% | 172 | 2.00% | 66 | 2.59% | 68 | 2.66% |
| Peripheral artery disease | 552 | 22.88% | 580 | 24.04% | 2,130 | 24.74% | 2,145 | 24.92% | 604 | 23.66% | 609 | 23.85% |
| Coronary artery disease | 1,160 | 48.07% | 1,139 | 47.20% | 4,355 | 50.59% | 4,396 | 51.07% | 1,179 | 46.18% | 1,209 | 47.36% |
| Dose of the index prescription | | | | | | | | | | | | |
| Standard dose[b] | 1,862 | 77.17% | 1,940 | 80.40% | 6,346 | 73.72% | 5,728 | 66.54% | 2,058 | 80.61% | 1,793 | 70.23% |
| Low dose[c] | 551 | 22.83% | 473 | 19.60% | 2,262 | 26.28% | 2,880 | 33.46% | 495 | 19.39% | 760 | 29.77% |

*Continued on the next page*

0.17-0.79) and had similar rates of ischemic stroke and other bleeding compared with warfarin users. Dabigatran and rivaroxaban had similar rates of ischemic stroke and severe bleeding compared with warfarin users. These MarketScan results are generally consistent with those of our study; however, our analysis included significantly more patients and additional comparisons.

**STUDY LIMITATIONS.** To the best of our knowledge, this study represents the largest cohort of NVAF

**TABLE 3 Continued**

| | Apixaban vs Dabigatran | | | | Apixaban vs Rivaroxaban | | | | Dabigatran vs Rivaroxaban | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Dabigatran | | Apixaban | | Rivaroxaban | | Dabigatran | | Rivaroxaban | |
| | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD | n or Mean | % or SD |
| Follow-up time, days | 186.88 | 169.89 | 224.31 | 224.61 | 182.10 | 166.01 | 217.29 | 209.18 | 224.44 | 225.79 | 220.97 | 210.09 |
| Median | 122 | | 122 | | 121 | | 132 | | 120 | | 139 | |
| Reasons for censoring | | | | | | | | | | | | |
| Discontinuation | 930 | 38.54% | 1,407 | 58.31% | 3,344 | 38.85% | 4,531 | 52.64% | 1,495 | 58.56% | 1,327 | 51.98% |
| Switch | 87 | 3.61% | 255 | 10.57% | 337 | 3.91% | 557 | 6.47% | 274 | 10.73% | 197 | 7.72% |
| Death | 96 | 3.98% | 158 | 6.55% | 453 | 5.26% | 599 | 6.96% | 157 | 6.15% | 137 | 5.37% |
| End of continuous medical/pharmacy enrollment | 27 | 1.12% | 35 | 1.45% | 125 | 1.45% | 201 | 2.34% | 49 | 1.92% | 69 | 2.70% |
| End of study period | 1,273 | 52.76% | 558 | 23.12% | 4,349 | 50.52% | 2,720 | 31.60% | 578 | 22.64% | 823 | 32.24% |

Cells with n < 11 are not reported (NR). [a]Variable used in propensity score matching. [b]5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. [c]2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban. 507 and 2,373 patients received 10 mg and 15 mg rivaroxaban, respectively, in the apixaban-rivaroxaban matched cohort and 133 and 627 patients received 10 mg and 15 mg rivaroxaban, respectively, in the dabigatran-rivaroxaban matched cohort.

Abbreviations as in Table 1.

**TABLE 4 Post-PSM Cancer Related Baseline Characteristics of NOAC-NOAC Cohorts**

| | Apixaban vs Dabigatran | | | | Apixaban vs Rivaroxaban | | | | Dabigatran vs Rivaroxaban | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | | Dabigatran | | Apixaban | | Rivaroxaban | | Dabigatran | | Rivaroxaban | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Sample size | 2,413 | 100 | 2,413 | 100 | 8,608 | 100 | 8,608 | 100 | 2,553 | 100 | 2,553 | 100 |
| Cancer site | | | | | | | | | | | | |
| Prostate | 762 | 31.58 | 738 | 30.58 | 2,650 | 30.79 | 2,573 | 29.89 | 782 | 30.63 | 760 | 29.77 |
| Female breast | 446 | 18.48 | 467 | 19.35 | 1,593 | 18.51 | 1,536 | 17.84 | 485 | 19.00 | 451 | 17.67 |
| Gastrointestinal(GI)[a] | 286 | 11.85 | 286 | 11.85 | 1,015 | 11.79 | 1,120 | 13.01 | 300 | 11.75 | 280 | 10.97 |
| Lung | 268 | 11.11 | 263 | 10.90 | 962 | 11.18 | 997 | 11.58 | 282 | 11.05 | 298 | 11.67 |
| Lymphoma | 276 | 11.44 | 253 | 10.48 | 991 | 11.51 | 1,032 | 11.99 | 267 | 10.46 | 320 | 12.53 |
| Lower GI[b] | 218 | 9.03 | 204 | 8.45 | 756 | 8.78 | 830 | 9.64 | 214 | 8.38 | 215 | 8.42 |
| Bladder | 188 | 7.79 | 194 | 8.04 | 671 | 7.80 | 682 | 7.92 | 210 | 8.23 | 193 | 7.56 |
| Leukemia | 139 | 5.76 | 138 | 5.72 | 480 | 5.58 | 466 | 5.41 | 145 | 5.68 | 170 | 6.66 |
| Renal cell carcinoma | 98 | 4.06 | 89 | 3.69 | 372 | 4.32 | 341 | 3.96 | 89 | 3.49 | 108 | 4.23 |
| Gynecologic[c] | 75 | 3.11 | 79 | 3.27 | 265 | 3.08 | 289 | 3.36 | 81 | 3.17 | 73 | 2.86 |
| Multiple myeloma | 57 | 2.36 | 67 | 2.78 | 218 | 2.53 | 238 | 2.76 | 69 | 2.70 | 71 | 2.78 |
| Upper GI[d] | 40 | 1.66 | 34 | 1.41 | 140 | 1.63 | 178 | 2.07 | 36 | 1.41 | 23 | 0.90 |
| Pancreas | 19 | 0.79 | 29 | 1.20 | 82 | 0.95 | 88 | 1.02 | 31 | 1.21 | 32 | 1.25 |
| Stomach | 15 | 0.62 | 28 | 1.16 | 68 | 0.79 | 70 | 0.81 | 30 | 1.18 | 19 | 0.74 |
| Brain tumor | 18 | 0.75 | 22 | 0.91 | 72 | 0.84 | 89 | 1.03 | 23 | 0.90 | 13 | 0.51 |
| Testicular | NR | NR | NR | NR | 14 | 0.16 | 19 | 0.22 | NR | NR | NR | NR |
| Cancer metastasis[e] | 296 | 12.27 | 283 | 11.73 | 1,242 | 14.43 | 1,233 | 14.32 | 297 | 11.63 | 299 | 11.71 |
| Cancer type | | | | | | | | | | | | |
| Hematologic | 384 | 15.91 | 373 | 15.46 | 1,357 | 15.76 | 1,363 | 15.83 | 399 | 15.63 | 431 | 16.88 |
| Nonhematologic | 2,243 | 92.95 | 2,222 | 92.08 | 7,975 | 92.65 | 7,971 | 92.60 | 2,341 | 91.70 | 2,334 | 91.42 |
| Cancer-related treatment | 1,228 | 50.89 | 1,230 | 50.97 | 4,608 | 53.53 | 4,629 | 53.78 | 1,297 | 50.80 | 1,294 | 50.69 |
| Chemotherapy[e] | 1,017 | 42.15 | 1,003 | 41.57 | 3,883 | 45.11 | 3,896 | 45.26 | 1,052 | 41.21 | 1,049 | 41.09 |
| Hormone therapy[e] | 165 | 6.84 | 187 | 7.75 | 656 | 7.62 | 641 | 7.45 | 195 | 7.64 | 183 | 7.17 |
| Radiation[e] | 231 | 9.57 | 213 | 8.83 | 762 | 8.85 | 764 | 8.88 | 238 | 9.32 | 255 | 9.99 |
| Cancer-related surgery[e] | 66 | 2.74 | 70 | 2.90 | 257 | 2.99 | 265 | 3.08 | 68 | 2.66 | 77 | 3.02 |

Cells with n < 11 are not reported (NR). Immunotherapy was also assessed as a cancer-related treatment but had too few patients to report (n < 11). [a]GI cancer includes esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus cancers. [b]Lower GI cancer includes small intestine, large intestine, rectum, and anus cancers. [c]Gynecologic cancer includes uterus, cervix, placenta, ovary, and other female genital organ cancers. [d]Upper GI cancer includes esophagus and stomach cancers. [e]Variable used in propensity score matching.

Abbreviations as in Table 1.

**CENTRAL ILLUSTRATION** **NOAC Versus Warfarin: PSM Incidence Rates and Hazard Ratios of Stroke/SE and MB**

## ARISTOPHANES Substudy

### Active Cancer

Patients with ≥ 2 claims for cancer diagnosis or 1 claim for cancer diagnosis plus ≥ 1 claim for cancer treatment (e.g. chemotherapy, radiation, cancer-related surgery) in the six month baseline period

N=40,271

Warfarin=15,371 / Apixaban=9,517 / Dabigatran=2,742 / Rivaroxaban=12,641

### Propensity Score Matched Cohort Assignments

Apixaban-Warfarin=8,236 Dabigatran-Warfarin=2,470 Rivaroxaban-Warfarin=9,988
Apixaban-Dabigatran=2,413 Apixaban-Rivaroxaban=8,608 Dabigatran-Rivaroxaban=2,553

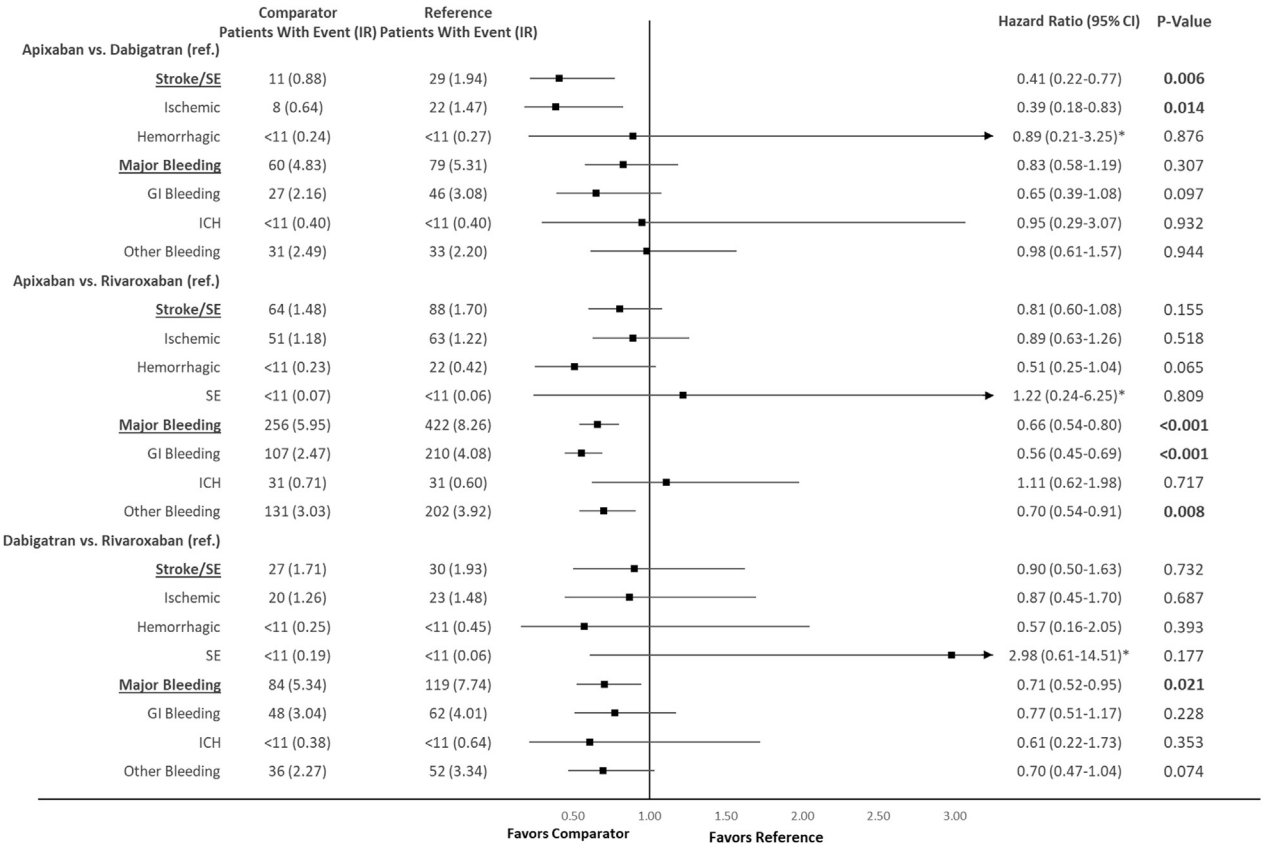
### Risk of Stroke/Systemic Embolism (SE) or Major Bleeding

| | NOAC Patients with Event (IR) | Warfarin (ref.) Patients with Event (IR) | Hazard Ratio | P-Value |
|---|---|---|---|---|
| **Apixaban vs. Warfarin** | | | | |
| ***Stroke/SE*** | 62 (1.50) | 124 (2.39) | 0.59 | <0.001 |
| Ischemic | 48 (1.16) | 79 (1.52) | 0.72 | 0.042 |
| Hemorrhagic | 11 (0.27) | 36 (0.69) | 0.36 | 0.006 |
| SE | <11 (0.07) | <11 (0.17) | 0.42 | 0.212 |
| ***Major Bleeding*** | 245 (5.98) | 477 (9.35) | 0.58 | <0.001 |
| GI Bleeding | 103 (2.50) | 203 (3.93) | 0.58 | <0.001 |
| ICH | 27 (0.65) | 64 (1.23) | 0.51 | 0.002 |
| Other Bleeding | 128 (3.11) | 235 (4.55) | 0.62 | <0.001 |
| **Dabigatran vs. Warfarin** | | | | |
| ***Stroke/SE*** | 29 (1.91) | 34 (2.17) | 0.88 | 0.590 |
| Ischemic | 23 (1.52) | 25 (1.60) | 0.95 | 0.852 |
| Hemorrhagic | <11 (0.26) | <11 (0.57) | 0.45 | 0.188 |
| ***Major Bleeding*** | 84 (5.57) | 114 (7.40) | 0.76 | 0.058 |
| GI Bleeding | 47 (3.11) | 47 (3.01) | 1.04 | 0.864 |
| ICH | <11 (0.39) | 13 (0.83) | 0.47 | 0.132 |
| Other Bleeding | 37 (2.44) | 59 (3.80) | 0.65 | 0.028 |
| **Rivaroxaban vs. Warfarin** | | | | |
| ***Stroke/SE*** | 105 (1.77) | 134 (2.14) | 0.82 | 0.157 |
| Ischemic | 76 (1.28) | 78 (1.24) | 1.02 | 0.907 |
| Hemorrhagic | 28 (0.47) | 47 (0.74) | 0.62 | 0.049* |
| SE | <11 (0.05) | <11 (0.14) | 0.35 | 0.115 |
| ***Major Bleeding*** | 505 (8.64) | 556 (8.99) | 0.95 | 0.366 |
| GI Bleeding | 231 (3.91) | 231 (3.69) | 1.04 | 0.623 |
| ICH | 41 (0.69) | 88 (1.39) | 0.49 | <0.001 |
| Other bleeding | 259 (4.39) | 270 (4.32) | 1.00 | 0.973 |


**Deitelzweig, S. et al. J Am Coll Cardiol CardioOnc. 2021;3(3):411–424.**

Incidence rates [IR] (per 100 person-years) and hazard ratios (with 95% confidence intervals [CIs]) of non-vitamin K oral anticoagulants (NOACs) vs warfarin. Apixaban was associated with a lower risk for stroke/systemic embolism (SE) and major bleeding (MB) compared with warfarin, and dabigatran and rivaroxaban were associated with similar risks for stroke/SE and MB compared with warfarin. Risk of SE is not reported for dabigatran versus warfarin comparison owing to small sample size. **P* value is considered to be significant because the upper limit of the 95% CI was rounded from 0.997 to 1.00. GI = gastrointestinal; ICH = intracranial hemorrhage.

**FIGURE 2** **NOAC Versus NOAC: PSM Incidence Rates and Hazard Ratios of Stroke/SE and MB**



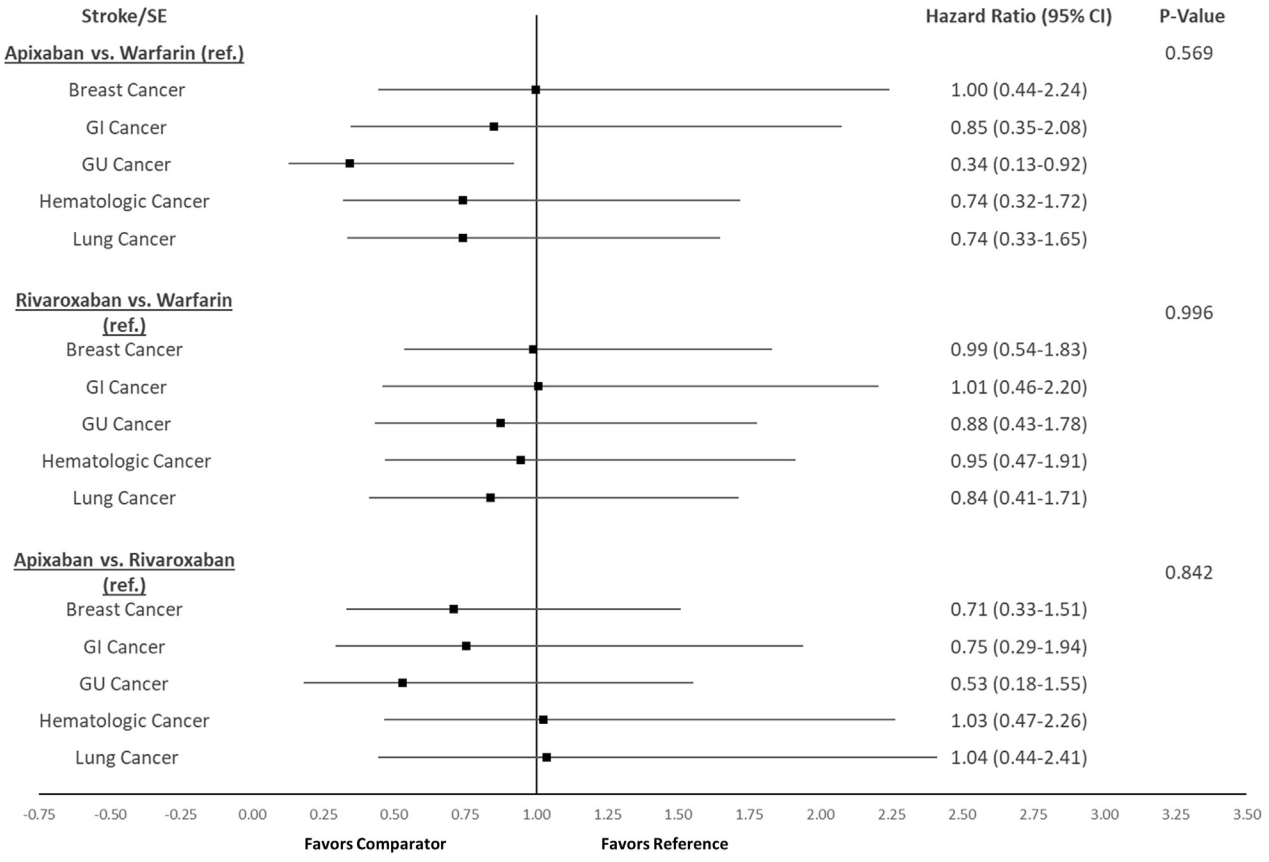

Incidence rates (IRs) (per 100 person-years) and hazard ratios (HRs) (with 95% confidence intervals [CIs]) of NOACs vs NOACs. Apixaban was associated with a lower risk of stroke/SE compared with dabigatran users, and a lower risk of MB compared with rivaroxaban. Dabigatran was associated with a lower risk in MB compared with rivaroxaban. Risk of SE is not reported for apixaban vs dabigatran comparisons owing to small sample size. *Upper limit of 95% CI extends beyond chart.
GI = gastrointestinal; ICH = intracranial hemorrhage; MB = major bleeding; SE = systemic embolism; other abbreviations as in Figure 1.

active cancer patients who have been treated with NOACs and warfarin. Using a pooled analysis of 5 U.S. claims databases, this study provides a significant sample size and sufficient statistical power. As a retrospective observational study, however, several limitations need to be noted for this analysis.

First, the results of this study can only be representative of statistical associations, not causal relationships, between the exposures of interest and study outcomes. Even with the use of PSM, the matched cohorts are subject to residual confounders, such as over-the-counter aspirin use or lack of laboratory values, which is especially important when interpreting NOAC-NOAC comparisons. These comparisons are primarily intended for hypothesis generation, given the lack of head-to-head clinical trials.

Second, claims database studies used only ICD-9-CM, CPT, and HCPCS codes to identify outcomes and clinical conditions. These codes lack crucial clinical information on pathology, and are prone to misclassification, which has been observed in cancer metastasis diagnosis (27,28). For example, detailed characteristics including cancer stage, progression, and primary versus secondary cancer diagnosis are lacking in our analysis, which may be pivotal in understanding potential variations in NVAF treatment outcomes as a result of severity of cancer status and/or type. The evaluation of label-adherent dosing for apixaban is also deterred because information on patient weight and renal function, which are needed to assess whether apixaban dose has been used appropriately or not, are not available in the claims data used in this study. Furthermore, because of the study period of this analysis, cancer treatment advancements that

**FIGURE 3** PSM HRs of Stroke/SE for Cancer Subgroups




HRs (95% CIs) of stroke/SE for NOACs vs warfarin and NOACs vs NOACs within cancer subgroups. *P* value represents statistically significant interaction between treatment and cancer type. No significant interactions were observed; treatment effect was consistent across cancer types. GU = genitourinary; other abbreviations as in Figures 1 and 2.

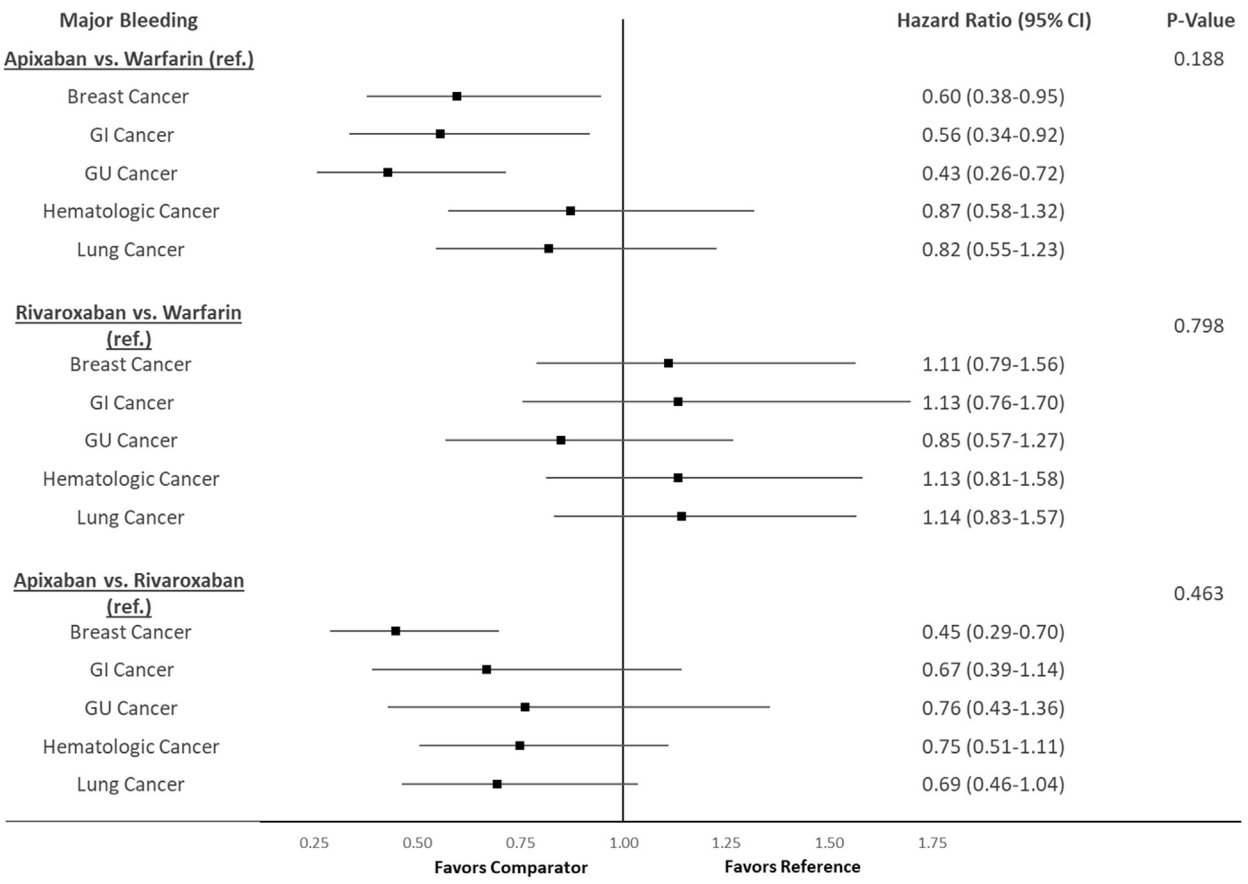
have led to improvements in major health outcomes (eg, MB in hematologic cancers) also are not considered. In addition, this analysis had a relatively short mean follow-up time of 6-8 months.

It should also be noted that unobserved heterogeneity may exist across the 5 datasets used in this analysis. The likelihood of duplicate observations is relatively low, researched to be 0.5%, and is not likely to have a significant impact on study results (29). Although this study represents the largest-to-date real-world retrospective claims study of NOAC versus warfarin and NOAC versus NOAC comparisons among active cancer patients with NVAF, it is not reflective of the overall active cancer NVAF population in the US. Uninsured patients and patients solely covered by other public health insurance plans were not included in this analysis. More studies are needed to better understand the effectiveness and safety of OACs in specific cancer populations. Owing to limited sample size, especially for dabigatran patients, dose was not assessed in separate subgroup analyses. In addition, future analyses with increased sample sizes of dabigatran patients would allow more confidence in the present findings for this patient cohort (large confidence intervals in the risk estimates for dabigatran vs other OACs were observed because of small sample size).

## CONCLUSIONS

Among NVAF patients with active cancer, apixaban was associated with a lower risk, and dabigatran and rivaroxaban with similar risks of stroke/SE and MB compared with warfarin. Apixaban users also had a

**FIGURE 4** PSM HRs of Major Bleeding for Cancer Subgroups




HRs (95% CIs) of MB for NOACs vs warfarin and NOACs vs NOACs within cancer subgroups. *P* value represents statistically significant interaction between treatment and cancer type. No significant interactions were observed; treatment effect was consistent across cancer types. Abbreviations as in Figures 1 to 3.

lower risk of stroke/SE compared with dabigatran users and a lower risk of MB compared with rivaroxaban users. Dabigatran was associated with a lower risk of MB compared with rivaroxaban. Treatment effects were consistent across several common cancer types for NOAC-warfarin and NOAC-NOAC comparisons. Subsequent real-world studies are warranted to further study the impact of NOAC treatment options in the NVAF cancer population, specifically addressing NOAC treatment outcomes within specific cancer subtypes.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In NVAF patients with active cancer, initiation of NOACs is associated with a similar or reduced risk in thromboembolic and bleeding complications compared with treatment with warfarin. These findings were consistent across several common cancer types.

**TRANSLATIONAL OUTLOOK:** Future studies are needed to further understand patient- and dosing-specific characteristics to enhance the safety and effectiveness of NOACs in the cancer population. A more detailed evaluation of NOAC treatment outcomes according to specific cancer types and disease severity is necessary.

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**KEY WORDS** active cancer, anticoagulants, bleeding, nonvalvular atrial fibrillation, stroke

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.