Comparative clinical outcomes between direct oral anticoagulants and warfarin among elderly patients with non-valvular atrial fibrillation in the CMS medicare population

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Abstract
Atrial fibrillation (AF) prevalence increases with age; > 80% of US adults with AF are aged ≥ 65 years. Compare the risk of stroke/systemic embolism (SE), major bleeding (MB), net clinical outcome (NCO), and major adverse cardiac events (MACE) among elderly non-valvular AF (NVAF) Medicare patients prescribed direct oral anticoagulants (DOACs) vs warfarin. NVAF patients aged ≥ 65 years who initiated DOACs (apixaban, dabigatran, and rivaroxaban) or warfarin were selected from 01JAN2013-31DEC2015 in CMS Medicare data. Propensity score matching was used to balance DOAC and warfarin cohorts. Cox proportional hazards models estimated the risk of stroke/SE, MB, NCO, and MACE. 37,525 apixaban–warfarin, 18,131 dabigatran–warfarin, and 55,359 rivaroxaban–warfarin pairs were included. Compared to warfarin, apixaban (HR: 0.69; 95% CI 0.59–0.81) and rivaroxaban (HR: 0.82; 95% CI 0.73–0.91) had lower risk of stroke/SE, and dabigatran (HR: 0.88; 95% CI 0.72–1.07) had similar risk of stroke/SE. Apixaban (MB: HR: 0.61; 95% CI 0.57–0.67; NCO: HR: 0.64; 95% CI 0.60–0.69) and dabigatran (MB: HR: 0.79; 95% CI 0.71–0.89; NCO: HR: 0.84; 95% CI 0.76–0.93) had lower risk of MB and NCO, and rivaroxaban had higher risk of MB (HR: 1.08; 95% CI 1.02–1.14) and similar risk of NCO (HR: 1.04; 95% CI 0.99–1.09). Compared to warfarin, apixaban had a lower risk for stroke/SE, MB, and NCO; dabigatran had a lower risk of MB and NCO; and rivaroxaban had a lower risk of stroke/SE but higher risk of MB. All DOACs had lower risk of MACE compared to warfarin.

Keywords Apixaban · Dabigatran · Rivaroxaban · Warfarin · Non-valvular atrial fibrillation · Medicare

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• The prevalence of NVAF and risk of stroke increase with age.
• Few studies have compared DOACs to warfarin among elderly NVAF patients regarding such outcomes.
• This study showed that compared to warfarin, all DOACs were associated with lower risk of MACE, and there were varying rates of stroke/SE, MB, and NCO between the individual DOACs and warfarin.
• The findings warrant more studies to better understand effectiveness and safety profiles in the elderly NVAF population.
Introduction

The 2010 Global Burden of Disease Study estimated the worldwide age-adjusted prevalence of atrial fibrillation (AF) at 596 per 100,000 men and 373 per 100,000 women, equating to 33.5 million individuals (20.9 and 12.6 million men and women, respectively) [1]. In the United States, the estimated prevalence of AF is 3–5 million [2, 3]. The proportion of AF patients was found to increase sharply with age, especially in people aged ≥ 65 years, who account for three-quarters of the AF population [3].

Patients with AF diagnoses are at a nearly fivefold greater risk of stroke [4]. Moreover, the AF-attributable risk for ischemic stroke is age-dependent and increases from 4.6 to 7.9% to > 10% among patients aged 50–59, 60–69, and ≥ 70 years, respectively [4]. Hence, the stroke risk stratification schema CHA2DS2-VASc score considers older age (65–74 and ≥ 75 years) as a risk factor for stroke and thromboembolism in AF patients [5].

Oral anticoagulants (OACs) prevent stroke and systemic embolism (SE) among AF patients; they are recommended by the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines for patients with non-valvular AF (NVAF) and prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score ≥ 2 [6]. Warfarin, a vitamin K antagonist (VKA), has been used for stroke prevention among AF patients for decades. However, the narrow therapeutic window and increased risk of bleeding have hindered use, especially among the elderly [6].

In recent years, randomized clinical trials have demonstrated that compared to warfarin, direct OACs (DOACs)—including apixaban, dabigatran, edoxaban, and rivaroxaban—were all associated with similar to lower risk of stroke/SE and major bleeding (MB) among elderly patients [7–9]. Introduced in 2008, the Fit-for-The-Aged (FORTA) classification is the first system with both negative (harmful or critical drugs: D and C labels) and positive (beneficial drugs: A and B labels) labelling at the individual drug and drug group levels. Based on FORTA and the Delphi process, warfarin, dabigatran, edoxaban, and rivaroxaban were labelled B (beneficial; safely and effectively treat AF), and apixaban was labelled A (absolutely; most beneficial risk–benefit ratio) for the treatment of AF patients aged > 65 years [10].

Using the largest US claims database of elderly patients, we evaluated real-world comparative risks of stroke/SE, MB, net clinical outcomes (stroke/SE or MB [NCO]), and major adverse cardiac events (MACE) among NVAF patients who initiated either DOACs (apixaban, dabigatran, and rivaroxaban) or warfarin. This study added more recent data and additional outcome measures to our previous study, which provides comprehensive and current evidence to help prevent stroke among the elderly NVAF population [11]. The results also supplement clinical trials and add key information to real-world literature.

Methods

Data source

This retrospective observational study used the fee-for-service (FFS) US Centers for Medicare & Medicaid Services (CMS) data from 01JAN2012-31DEC2015. This dataset is composed of adults aged ≥ 65 years, certain young people with disabilities, and people with end-stage renal disease. As of 2015, > 38 million beneficiaries were enrolled in this insurance [12]. The data include institutional (inpatient, skilled nursing facility, home health, hospice, and hospital outpatient) and non-institutional (physician/supplier–carrier and durable medical equipment) claims and Part D prescription claims, coded using International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM) diagnosis and procedure codes, the Health Care Common Procedure Coding System, Current Procedural Terminology codes, and National Drug Codes [13].

Patient selection

AF (ICD-9-CM: 427.31 or ICD-10-CM: I48.0-I48.2, I48.91) patients aged ≥ 65 years with ≥ 1 pharmacy claim for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin between 01JAN2013-31DEC2015 (identification period) were selected. The first DOAC claim date during the identification period was designated as the index date for patients with any DOAC claim; the first warfarin prescription date was designated as the index date for those without a DOAC claim [14]. Patients were also required to have continuous health plan enrollment with both medical and pharmacy benefits for the 12-month pre-index (baseline) period.

To select OAC treatment-naïve patients, those with any OAC claim during the baseline period were excluded. Patients with evidence of valvular heart disease or transient AF during the baseline period were also excluded. To omit OAC use for the treatment or prophylaxis of venous thromboembolism (VTE), patients with VTE in the baseline period or who had hip or knee replacement surgery within 6 weeks prior to the index date were excluded. Detailed selection criteria appear in Fig. 1.

Outcome measures

The primary outcomes were the occurrence of stroke/SE and MB, identified by hospitalizations with stroke/SE or MB as
the principal diagnosis. Stroke/SE was further categorized by ischemic stroke, hemorrhagic stroke, and SE; MB was categorized by gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and MB at other key sites [15, 16].

The secondary outcomes were NCO (a composite of stroke/SE and MB) and MACE, comprised of stroke (hemorrhagic and ischemic stroke), myocardial infarction (MI), and all-cause death. Claims databases cannot evaluate cardiovascular-related death, so the MACE definition included all-cause death.

Patients were censored at the earliest of the discontinuation date of the index treatment (no evidence of a prescription for 30 days from the last day of the index medication days’ of supply), date of switch from the index drug to another OAC (a prescription for an OAC other than the index drug within 30 days before or after the discontinuation date), date of death, end of continuous enrollment, or end of study.

Statistical methods

One-to-one propensity score matching (PSM) was conducted between DOACs and warfarin (apixaban versus warfarin, dabigatran versus warfarin, and rivaroxaban versus warfarin) to control for potential confounders such as baseline demographics and clinical characteristics.

Using established methodology, propensity scores were generated by logistic regression. Age, sex, US geographic region, Charlson comorbidity index (CCI) [17], CHA₂DS₂-VASc, and HAS-BLED scores, prior bleeding and stroke, comorbidities, baseline co-medications, and baseline inpatient visits were included in the models as covariates. The nearest neighbor without replacement method and a caliper of 0.01 were implemented in the PSM [18]. After PSM, the balance of covariates was checked based on standardized differences, with a threshold of 10% [19].

For post-PSM cohorts, the incidence of primary and secondary outcomes was calculated as the number of events per 100 person-years.

Cox proportional hazards models with robust sandwich estimates were used to evaluate the hazard ratios (HRs) of stroke/SE, MB, NCO, and MACE in each matched cohort [18]. After ensuring all the matched baseline covariates were balanced post-PSM, OAC treatment was included in the Cox models as the only independent variable.

Sensitivity analysis was conducted wherein patients were censored at 6 months of follow-up, creating more balance between cohorts.

Statistical analyses were performed using the Statistical Analysis System (SAS) Version 9.3 (Cary, NC).

Results

The study included eligible 198,171 patients; 81,410 (41.1%) were prescribed warfarin, 38,466 (19.4%) apixaban, 18,162 (9.2%) dabigatran, and 60,133 (30.3%) rivaroxaban (Fig. 1). Edoxaban was excluded due to small sample size (N = 150). Before PSM, patients who initiated warfarin were older with
a mean age of 79 years, followed by those who initiated apixaban (78 years), rivaroxaban (78 years), and dabigatran (77 years). In addition, warfarin patients also had higher CCI and CHA2 DS2 -VASc scores than DOAC patients (Table 1).

Through PSM, 37,525 apixaban, 18,131 dabigatran, and 55,359 rivaroxaban patients were separately matched to warfarin patients. Baseline characteristics were balanced after matching with mean standardized differences <10%. For the matched cohorts, the means were: age: 77–78 years, CHA2 DS2 -VASc scores: 4.4–4.6, and HAS-BLED scores: 3.2–3.4 (Table 2). Patient data were assessed for a mean duration of 8–10 months. 71%, 80%, and 66% of patients were prescribed the standard dose of DOAC (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg), respectively.

**Stroke/SE and MB**

Compared to warfarin, apixaban (HR: 0.69; 95% confidence interval [CI] 0.59–0.81, p < 0.001) and rivaroxaban (HR: 0.82; 95% CI 0.73–0.91, p < 0.001) were associated with a significantly lower risk of stroke/SE; dabigatran (HR: 0.88; 95% CI 0.72–1.07, p = 0.206) was associated with a non-significantly lower risk of stroke/SE (Fig. 2). All DOACs were associated with a lower risk of hemorrhagic stroke versus warfarin.

Compared to warfarin, apixaban (HR: 0.61; 95% CI 0.57–0.67, p < 0.001), and dabigatran (HR: 0.79; 95% CI 0.71–0.89, p < 0.001) were associated with a significantly lower risk of MB, and rivaroxaban (HR: 1.08; 95% CI 1.02–1.14, p = 0.006) was associated with a higher risk of MB, mainly due to GI bleeding (Fig. 2). All DOACs were associated with a lower risk of ICH versus warfarin.

**NCO and MACE**

As a composite of stroke/SE and MB, the risk of NCO was significantly lower than warfarin for apixaban (HR: 0.64; 95% CI 0.60–0.69, p < 0.001) and dabigatran, (HR: 0.84; 95% CI 0.76–0.93, p = 0.001) but similar for rivaroxaban (HR: 1.04; 95% CI 0.99–1.09, p = 0.169) (Fig. 3).

Compared to warfarin, all DOACs were associated with a lower risk of MACE (apixaban: HR: 0.70; 95% CI 0.67–0.74, p < 0.001; dabigatran: HR: 0.76; 95% CI 0.71–0.82, p < 0.001; rivaroxaban: HR: 0.83; 95% CI 0.80–0.86, p < 0.001; Fig. 3).

**Sensitivity analysis**

In the sensitivity analysis wherein the follow-up period was censored at 6 months, the results were consistent with the main analysis (Supplemental Table 1).

**Discussion**

Using Medicare FFS data from 2012 to 2015, this study showed that compared to warfarin among elderly patients with NVAF, apixaban was associated with significant lower risks of stroke/SE, MB, NCO, and MACE. Dabigatran was associated with significantly lower risks of MB, NCO, and MACE as well as a numerically lower risk of stroke/SE. Rivaroxaban was associated with lower risks of stroke/SE and MACE, but higher MB and numerically higher NCO risks compared to warfarin.

The study results supplement RCT findings for apixaban, dabigatran, and rivaroxaban compared to warfarin and their corresponding age subgroup analyses [20–25]. In the RE-LY trial, patients (overall and ≥ 75 years) with 150 mg dabigatran had lower rates of stroke/SE and similar rates of MB compared to warfarin [20, 23]. In this real-world study among NVAF patients aged ≥ 65 years, 150 mg and 75 mg dabigatran showed numerically lower stroke/SE and significantly lower MB risks versus warfarin. Although NCO was not studied in the RE-LY trial’s elderly group, overall dabigatran and warfarin patient analysis demonstrated that compared to warfarin, 150 mg twice-daily dabigatran was associated with a non-significantly lower risk of net clinical benefit (a composite of stroke/SE, pulmonary embolism, MI, death, and MB) [20]. In this study, elderly dabigatran patients were associated with significantly lower NCO and MACE risks than warfarin patients.

In the ARISTOTLE trial, apixaban was associated with lower rates of stroke/SE, MB, and net clinical events (stroke/SE, MB, and all-cause death) compared to warfarin among all patients and patients aged ≥ 65 years [22, 25]. This study found consistent trends. In the ROCKET AF trial, rivaroxaban was associated with a non-inferior rate of stroke/SE and similar rate of MB compared to warfarin [21]. Among patients aged ≥ 75 years, 20 and 15 mg daily rivaroxaban showed a numerically lower risk of stroke/SE but a higher risk of MB compared to warfarin [24]. This study found similar trends between rivaroxaban and warfarin among patients aged ≥ 65 years. To the best of our knowledge, no previous studies have compared net clinical benefits between rivaroxaban and warfarin.

Several real-world studies have focused on effectiveness and safety comparisons between DOACs and warfarin in an elderly NVAF population [11, 26–29]. Our previous study of the elderly Medicare population from 2012 to 2014 consistent results of stroke/SE and major bleeding were found for the comparisons between DOACs and warfarin [11]. This study provides more recent and comprehensive analysis with updated data and added NCO and MACE outcomes. Using Medicare data from 2010 to 2012, Graham et al. [26] demonstrated that...
### Table 1 Baseline descriptive table before PSM

|                      | Warfarin (N=81,410) | Apixaban (N=38,466) | Dabigatran (N=18,162) | Rivaroxaban (N=60,133) |
|----------------------|----------------------|----------------------|------------------------|------------------------|
| **Age**              |                      |                      |                        |                        |
| 65–74                | 7.5                  | 7.5                  | 7.0                    | 7.3                    |
| 75–84                | 32.0%                | 35.4%                | 41.2%                  | 38.7%                  |
| ≥ 85                 | 24.9%                | 23.0%                | 21.3%                  | 15.9%                  |
| **Sex**              |                      |                      |                        |                        |
| Male                 | 50.4%                | 48.3%                | 51.4%                  | 49.7%                  |
| Female               | 49.6%                | 51.7%                | 48.6%                  | 50.3%                  |
| **Race**             |                      |                      |                        |                        |
| White                | 90.5%                | 91.8%                | 89.8%                  | 90.9%                  |
| Black                | 5.2%                 | 3.7%                 | 4.3%                   | 3.9%                   |
| Hispanic             | 1.3%                 | 1.1%                 | 1.6%                   | 1.5%                   |
| Other                | 3.0%                 | 3.4%                 | 4.1%                   | 3.7%                   |
| **Geographic region**|                      |                      |                        |                        |
| Northeast            | 19.7%                | 16.9%                | 19.9%                  | 17.6%                  |
| North Central        | 30.8%                | 20.6%                | 23.6%                  | 23.0%                  |
| South                | 32.5%                | 44.8%                | 25.4%                  | 38.3%                  |
| West                 | 16.9%                | 17.7%                | 18.6%                  | 4.6                    |
| Other                | 0.1%                 | 0.1%                 | 0.2%                   | 0.2%                   |
| **Medicaid dual-eligibility** |        |                      |                        |                        |
|                      | 23.2%                | 19.5%                | 23.5%                  | 19.4%                  |
| **Part D low-income subsidy** |          |                      |                        |                        |
|                      | 26.3%                | 22.6%                | 26.5%                  | 22.7%                  |
| **Baseline comorbidity** |                    |                      |                        |                        |
| Deyo-Charlson comorbidity index | 3.1    | 2.8                  | 2.9                    | 2.6                    |
| CHADS2 score         | 2.9                  | 1.4                  | 2.8                    | 1.5                    |
| CHA2DS2-VASc score   | 4.7                  | 1.7                  | 4.6                    | 1.8                    |
| HAS-BLED scoreb      | 3.3                  | 1.3                  | 3.4                    | 1.3                    |
| Baseline prior bleed | 24.780               | 30.4%                | 11,807                 | 30.7%                  |
| Baseline prior stroke| 12,496               | 15.3%                | 5280                   | 13.7%                  |
| Congestive heart failure | 29,326              | 36.0%                | 12,064                 | 31.4%                  |
| Diabetes             | 32,705               | 40.2%                | 13,602                 | 35.4%                  |
| Hypertension         | 71,416               | 87.7%                | 34,649                 | 90.1%                  |
| Renal disease        | 21,021               | 25.8%                | 8599                   | 22.4%                  |
| Myocardial infarction | 12,021              | 14.8%                | 5040                   | 13.1%                  |
| Dyspepsia or stomach discomfort | 17,317          | 21.3%                | 8699                   | 22.6%                  |
| Peripheral vascular disease | 46,697         | 57.4%                | 22,742                 | 59.1%                  |
| Peripheral artery disease | 20,131         | 24.7%                | 8932                   | 23.2%                  |
| Transient ischemic attack | 6411            | 7.9%                 | 3528                   | 9.2%                   |
| Coronary artery disease | 40,079             | 49.2%                | 19,962                 | 51.9%                  |
| **Baseline medication use** |              |                      |                        |                        |
| Angiotensin converting enzyme inhibitor | 30,102     | 37.0%                | 13,194                 | 34.3%                  |
| Amiodarone           | 5612                 | 6.9%                 | 4300                   | 11.2%                  |
| Angiotensin receptor blocker | 17,030          | 20.9%                | 10,056                 | 26.1%                  |
| Beta blockers        | 42,053               | 51.7%                | 22,070                 | 57.4%                  |
| H2-receptor antagonist | 5699             | 7.0%                 | 2282                   | 7.4%                   |
| Proton pump inhibitor | 24,020             | 29.5%                | 13,008                 | 33.8%                  |
| Anti-platelets       | 15,589               | 19.1%                | 9235                   | 24.0%                  |
| Statins              | 45,149               | 55.5%                | 23,492                 | 61.1%                  |
| Inpatient admission  | 36,572               | 44.9%                | 15,168                 | 39.4%                  |

Std Difference greater than 10 is considered significant is given in bolditalic

CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs, and alcohol; PSM: propensity score matching; SD: standard deviation

a Std Difference = 100*|actual std diff|

b As the INR value was not available in the data, a modified HAS-BLED score was calculated using a range of 0 to 8

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Table 2  Baseline descriptive and mean follow-up time table after PSM between warfarin and DOACs

|                          | Apixaban–warfarin cohort | Dabigatran–warfarin cohort | Rivaroxaban–warfarin cohort |
|--------------------------|--------------------------|-----------------------------|-----------------------------|
|                          | Apixaban                  | Warfarin                    | Dabigatran                  | Warfarin                    | Rivaroxaban                | Warfarin                  |
|                          | (N = 37,525)              | (N = 37,525)                | (N = 18,131)                | (N = 18,131)                | (N = 55,359)               | (N = 55,359)               |
| **Age**                  |                          |                             |                             |                             |                             |                             |
| 65–74                    | 78.4 7.5                 | 78.4 7.4                    | 77.1 7.0                    | 77.3 7.1                    | 77.9 7.3                   | 78.0 7.3                   |
| 75–84                    | 15,164 41.6%             | 15,698 41.8%                | 7606 42.0%                  | 7602 41.9%                  | 23,651 42.7%               | 23,685 42.8%               |
| ≥ 85                     | 8775 23.4%               | 8623 23.0%                  | 3076 17.0%                  | 3057 16.9%                  | 11,488 20.8%               | 11,472 20.7%               |
| **Sex**                  |                          |                             |                             |                             |                             |                             |
| Male                     | 18,176 48.4%             | 18,112 48.3%                | 9313 51.4%                  | 9268 51.1%                  | 27,463 49.6%               | 27,494 49.7%               |
| Female                   | 19,349 51.6%             | 19,413 51.7%                | 8818 48.6%                  | 8863 48.9%                  | 27,896 50.4%               | 27,865 50.3%               |
| **Race**                 |                          |                             |                             |                             |                             |                             |
| White                    | 34,436 91.8%             | 34,369 91.6%                | 16,288 89.8%                | 16,308 89.9%                | 50,418 91.1%               | 50,373 91.0%               |
| Black                    | 1424 3.8%                | 1451 3.9%                   | 785 4.3%                    | 816 4.5%                    | 2282 4.1%                  | 2309 4.2%                  |
| Hispanic                 | 412 1.1%                 | 427 1.1%                    | 288 1.6%                    | 269 1.5%                    | 788 1.4%                   | 797 1.4%                   |
| Other                    | 1253 3.3%                | 1278 3.4%                   | 770 4.2%                    | 738 4.1%                    | 1871 3.4%                  | 1880 3.4%                  |
| **Geographic region**    |                          |                             |                             |                             |                             |                             |
| Northeast                | 6486 17.3%               | 6530 17.4%                  | 3606 19.9%                  | 3559 19.6%                  | 10,234 18.5%               | 10,215 18.5%               |
| North central            | 7906 21.1%               | 7897 21.0%                  | 4184 23.1%                  | 4135 22.8%                  | 13,233 23.9%               | 13,260 24.0%               |
| South                    | 16,433 43.8%             | 16,467 43.9%                | 6932 38.2%                  | 7161 39.5%                  | 21,568 39.0%               | 21,515 38.9%               |
| West                     | 6679 17.8%               | 6615 17.6%                  | 3379 18.6%                  | 3245 17.9%                  | 10,241 18.5%               | 10,292 18.6%               |
| Other                    | 21 0.1%                  | 16 0.0%                     | 30 0.2%                     | 31 0.2%                     | 83 0.1%                    | 77 0.1%                    |
| Medicaid dual-eligibility| 7399 19.7%               | 7509 20.0%                  | 4257 23.5%                  | 4230 23.3%                  | 12,157 22.0%               | 12,053 21.8%               |
| Part D low-income subsidy| 8454 22.5%               | 8584 22.9%                  | 4801 26.5%                  | 4782 26.4%                  | 13,697 24.7%               | 13,620 24.6%               |
| **Baseline comorbidity** |                          |                             |                             |                             |                             |                             |
| Deyo-Charlson comorbidity index | 2.9 2.6 | 2.9 2.7 | 2.5 2.4 | 2.5 2.4 | 2.7 2.5 | 2.7 2.6 |
| CHADS2 score             | 2.8 1.5                  | 2.8 1.4                     | 2.6 1.4                     | 2.6 1.4                     | 2.7 1.4                    | 2.7 1.4                    |
| CHA2DS2-VASc score       | 4.6 1.8                  | 4.7 1.7                     | 4.4 1.7                     | 4.4 1.7                     | 4.5 1.7                    | 4.5 1.7                    |
| HAS-BLED score           | 3.4 1.3                  | 3.4 1.3                     | 3.2 1.2                     | 3.2 1.2                     | 3.3 1.3                    | 3.3 1.3                    |
| Baseline prior bleed     | 11,495 30.6%             | 11,455 30.5%                | 4726 26.1%                  | 4748 26.2%                  | 16,013 28.9%               | 16,128 29.1%               |
| Baseline prior stroke    | 5202 13.9%               | 5221 13.9%                  | 2159 11.9%                  | 2226 12.3%                  | 7131 12.9%                 | 7146 12.9%                 |
| Congestive heart failure | 11,897 31.7%             | 12,028 32.1%                | 5114 28.2%                  | 5177 28.6%                  | 16,729 30.2%               | 16,615 30.0%               |
| Diabetes                 | 13,442 35.8%             | 13,565 36.1%                | 6731 37.1%                  | 6753 37.2%                  | 20,370 36.8%               | 20,298 36.7%               |
| Hypertension             | 33,730 89.9%             | 33,816 90.1%                | 15,934 87.9%                | 15,991 88.2%                | 48,716 88.0%               | 48,780 88.1%               |
| Renal disease            | 8,479 22.6%              | 8,508 22.7%                 | 2892 16.0%                  | 2984 16.5%                  | 10,376 18.7%               | 10,392 18.8%               |
| Myocardial infarction    | 4941 13.2%               | 4990 13.3%                  | 1940 10.7%                  | 2040 11.3%                  | 6890 12.4%                 | 6877 12.4%                 |
| Dyspepsia or stomach discomfort | 8427 22.5% | 8411 22.4% | 3597 19.8% | 3691 20.4% | 11,843 21.4% | 11,852 21.4% |
|                                | Apixaban–warfarin cohort | Warfarin (N = 37,525) | Dabigatran–warfarin cohort | Warfarin (N = 18,131) | Rivaroxaban–warfarin cohort | Warfarin (N = 55,359) |
|--------------------------------|--------------------------|-----------------------|---------------------------|------------------------|---------------------------|------------------------|
|                                | N/mean %/SD              | N/mean %/SD           | N/mean %/SD               | N/mean %/SD            | N/mean %/SD               | N/mean %/SD            |
| Peripheral vascular disease    | 22,042 58.7%             | 22,245 59.3%          | 9669 53.3%                | 9867 54.4%             | 30,815 55.7%              | 30,831 55.7%           |
| Peripheral artery disease      | 8717 23.2%               | 9076 24.2%            | 3633 20.0%                | 3707 20.4%             | 12,412 22.4%              | 12,567 22.7%           |
| Transient ischemic attack      | 3384 9.0%                | 3395 9.0%             | 1338 7.4%                 | 1344 7.4%              | 4342 7.8%                 | 4373 7.9%              |
| Coronary artery disease        | 19,294 51.4%             | 19,501 52.0%          | 8347 46.0%                | 8582 47.3%             | 26,481 47.8%              | 26,523 47.9%           |
| Baseline medication use        |                          |                       |                           |                        |                           |                        |
| Angiotensin converting enzyme inhibitor | 12,998 34.6% | 13,084 34.9% | 6859 37.8% | 6841 37.7% | 19,972 36.1% | 20,044 36.2% |
| Amiodarone                      | 3867 10.3%               | 3801 10.1%            | 1614 8.9%                 | 1637 9.0%              | 4355 7.9%                 | 4360 7.9%              |
| Angiotensin receptor blocker    | 9532 25.4%               | 9538 25.4%            | 4478 24.7%                | 4603 25.4%             | 13,103 23.7%              | 13,042 23.6%           |
| Beta blockers                   | 21,347 56.9%             | 21,379 57.0%          | 9731 53.7%                | 9777 53.9%             | 29,724 53.7%              | 29,670 53.6%           |
| H2-receptor antagonist          | 2728 7.3%                | 2797 7.5%             | 1208 6.7%                 | 1232 6.8%              | 3800 6.9%                 | 3822 6.9%              |
| Proton pump inhibitor           | 12,520 33.4%             | 12,521 33.4%          | 5347 29.5%                | 5553 30.6%             | 17,089 30.9%              | 17,116 30.9%           |
| Anti-platelets                  | 8722 23.2%               | 8814 23.5%            | 3436 19.0%                | 3510 19.4%             | 11,334 20.5%              | 11,404 20.6%           |
| Statins                         | 22,711 60.5%             | 22,960 61.2%          | 10,449 57.6%              | 10,589 58.4%           | 31,640 57.2%              | 31,568 57.0%           |
| Inpatient admission            | 14,935 39.8%             | 15,081 40.2%          | 6819 37.6%                | 6986 38.5%             | 23,133 41.8%              | 23,214 41.9%           |
| Patients on standard dose DOAC | 26,628 71.0%             | 26,926 71.5%          | 14,496 80.0%              | 14,566 80.6%           | 36,656 66.2%              | 36,656 66.2%           |
| Mean follow-up time (in days)  | 230.3 211.3              | 281.3 260.0           | 257.0 265.9               | 285.6 264.7            | 275.8 265.7               | 284.0 262.7            |

CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs, and alcohol; PSM: propensity score matching; SD: standard deviation

*As the INR value was not available in the data, a modified HAS-BLED score was calculated using a range of 0 to 8*
among elderly patients, apixaban was associated with similar risk for ischemic stroke and MI, a lower risk for stroke and similar risk for MB; and a higher major GI bleeding risk. Our results are generally consistent with previous literature. However, more studies are needed to better understand effectiveness and safety profiles in elderly populations. Moreover, as DOAC use increases, further research will be necessary to assist in decision-making for such populations [33].

Despite growing evidence of improved safety with DOACs, warfarin is still widely used in high-risk NVAF populations [34]. Our study provides a current and comprehensive analysis comparing DOACs and warfarin regarding the risk of stroke/SE, MB, NCOs, and MACE among elderly US Medicare NVAF patients. Given the distinct clinical characteristics of the elderly NVAF population, the study results may add useful information to the literature to assist in disease management decision making.

This study has several limitations. Given its observational nature, confounding factors may have impacted the results. To control for potential confounders, a comprehensive list of baseline covariates was included in the PSM, including patient demographics and clinical characteristics. However, variables such as over-the-counter use of aspirin, serum creatinine/creatinine clearance, and laboratory test result values are not captured in the Medicare data. As claims data analysis, the study may also be subject to coding errors and inaccurate or incomplete clinical information. For example, treatments recorded based on prescription claims include no

| Apixaban vs Warfarin | DOAC | Warfarin | Hazard Ratio (95% CI) | P-value |
|----------------------|------|----------|----------------------|---------|
| Stroke/SE            | 261 (1.11) | 426 (1.52) | 0.69 (0.59 – 0.81) | <0.001 |
| Ischemic             | 218 (0.92) | 315 (1.10) | 0.79 (0.66 – 0.94) | 0.007 |
| Hemorrhagic          | 32 (0.14)  | 101 (0.35) | 0.38 (0.26 – 0.57) | <0.001 |
| Major Bleeding       | 11 (0.05)  | 29 (0.07)  | 0.65 (0.31 – 1.35) | 0.245 |
| GI Bleeding          | 868 (2.70) | 1,611 (5.66) | 0.61 (0.57 – 0.67) | <0.001 |
| ICH                  | 416 (1.76) | 787 (2.74) | 0.60 (0.55 – 0.67) | <0.001 |
| Other Bleeding       | 121 (0.51) | 243 (0.84) | 0.60 (0.48 – 0.75) | <0.001 |
|                      | 375 (1.59) | 688 (2.40) | 0.62 (0.55 – 0.71) | <0.001 |

| Dabigatran vs Warfarin | Stroke/SE | 176 (1.39) | 217 (1.54) | 0.88 (0.72 – 1.07) | 0.206 |
|                       | Ischemic  | 155 (1.22) | 160 (1.13) | 1.05 (0.84 – 1.31) | 0.685 |
|                       | Hemorrhagic | 15 (0.12)  | 47 (0.33)  | 0.35 (0.20 – 0.64) | <0.001 |
|                       | SE        | 6 (0.05)  | 19 (0.07)  | 0.64 (0.23 – 1.75) | 0.381 |
|                       | Major Bleeding | 516 (4.08) | 709 (5.07) | 0.79 (0.71 – 0.89) | <0.001 |
|                       | GI Bleeding | 323 (2.54) | 331 (2.15) | 1.06 (0.91 – 1.23) | 0.460 |
|                       | ICH       | 52 (0.41) | 113 (0.80) | 0.51 (0.37 – 0.71) | <0.001 |
|                       | Other Bleeding | 187 (1.47) | 301 (2.14) | 0.68 (0.57 – 0.81) | <0.001 |

| Rivaroxaban vs Warfarin | Stroke/SE | 567 (1.36) | 714 (1.67) | 0.82 (0.73 – 0.91) | <0.001 |
|                        | Ischemic  | 413 (0.99) | 507 (1.38) | 0.84 (0.75 – 0.93) | 0.007 |
|                        | Hemorrhagic | 125 (0.30) | 171 (0.40) | 0.76 (0.60 – 0.95) | 0.017 |
|                        | SE        | 29 (0.07)  | 36 (0.08)  | 0.83 (0.51 – 1.35) | 0.444 |
|                        | Major Bleeding | 2,506 (6.08) | 2,384 (5.63) | 1.08 (1.02 – 1.14) | 0.006 |
|                        | GI Bleeding | 1,367 (2.9) | 1,126 (2.64) | 1.25 (1.16 – 1.35) | <0.001 |
|                        | ICH       | 277 (0.66) | 400 (0.93) | 0.71 (0.61 – 0.83) | <0.001 |
|                        | Other Bleeding | 1,056 (2.54) | 1,015 (2.38) | 1.07 (0.98 – 1.17) | 0.121 |

Fig. 2  Incidence rate and hazard ratio of stroke/SE and major bleeding for propensity score-matched patients
evidence of drug adherence. Moreover, since international normalized ratio values were not obtained, the quality of warfarin treatment could not be evaluated and the calculation for HAS-BLED score was modified. Moreover, proper dosage for DOACs based on age, renal function, and weight could not be assessed.

In summary, in the elderly Medicare population with NVAF, compared to warfarin, the DOACs were associated with a lower to similar risk of stroke/SE and MACE, but with varying comparative risks for MB and NCO.

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Compliance with ethical standards

Conflict of interest Amin is an employee of the University of California, Irvine and was a paid consultant to Bristol-Myers Squibb in connection with this study and the development of this manuscript. Keshishian is an employee of STATinMED Research, a paid consultant to Pfizer and Bristol-Myers Squibb in connection with this study and the development of this manuscript. Dina, Carda, Russ, Mardekian, and Baker are employees of Pfizer Inc., with ownership of stocks in Pfizer Inc. Dhamane, Nadkarni, and Rosenblatt are employees of Bristol-Myers Squibb Company, with ownership of stocks in Bristol-Myers Squibb Company. Yuce has no conflicts of interest.

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