ABSTRACT

Introduction: Non-valvular atrial fibrillation (NVAF) is often accompanied by multiple comorbid conditions, which increase the associated risks and complexity of patient management. This study evaluated the risk of stroke/systemic embolism (SE) and major bleeding (MB) among multimorbid patients with NVAF who were prescribed non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

Methods: A retrospective study of patients with NVAF and high multimorbidity who initiated apixaban, dabigatran, rivaroxaban, or warfarin from 1 January 2013 to 30 September 2015 was conducted using five insurance claims databases. Multimorbidity was defined as six or more comorbid conditions, and 1:1 propensity score matching (PSM) was conducted between the NOAC-warfarin and NOAC-NOAC cohorts. Cox proportional hazard models were used to evaluate the hazard ratios of stroke/SE and MB.
Results: Of the NVAF population (*n* = 466,991), 33.4% (*n* = 155,959) had multimorbidity, including 36,921 apixaban, 10,248 dabigatran, 45,509 rivaroxaban, and 63,281 warfarin patients. Compared to warfarin, apixaban and rivaroxaban were associated with a lower risk of stroke/SE (hazard ratio [HR] 0.63, 95% CI 0.54–0.74; HR 0.70, 95% CI 0.64–0.77, respectively). Apixaban and dabigatran were associated with a lower risk of MB (HR 0.61, 95% CI 0.56–0.67; HR 0.75, 95% CI 0.66–0.86, respectively) and rivaroxaban was associated with a higher risk of MB (HR 1.06, 95% CI 1.01–1.12) compared to warfarin.

Conclusions: Among patients with NVAF and six or more comorbid conditions, NOACs were associated with varying risks of stroke/SE and MB compared to warfarin and to each other. Rather than a “one drug fits all” approach, our results may be useful for appropriate OAC treatment for multimorbid patients.

Keywords: Anticoagulation; Bleeding; Multimorbidity; Outcomes; Stroke

**Key Summary Points**

**Why carry out this study?**

The presence of multiple comorbid conditions increases the risk of adverse clinical outcomes in patients with AF.

This study evaluates the safety and effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin among patients with AF and multiple comorbid conditions.

**What was learned from the study?**

In this multimorbid subgroup of patients with AF, NOACs were associated with varying risks of stroke/SE and major bleeding compared to warfarin.

These results may help inform treatment selection in this high-risk subgroup of patients with AF by allowing clinicians to choose the safest and most effective treatment according to the patient comorbidity burden.

**INTRODUCTION**

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia, affecting 2–3% of the population in North America [1]. Previously, vitamin K antagonists, such as warfarin, were the most commonly prescribed therapeutic agents for AF. However, the needs for periodic patient monitoring and frequent dose adjustment increase the patient burden of treatment [2]. Non-vitamin K antagonist oral anticoagulants (NOACs: apixaban, dabigatran, edoxaban, and rivaroxaban) offer a non-inferior, safe, effective treatment choice for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) without the restrictions of conventional therapy [3, 4].

Multimorbidity, often defined as the coexistence of two or more comorbid conditions, may provide a proxy for identifying chronic disease burden and functional status and may influence treatment selection [5]. More than two-thirds of Medicare patients have two or more comorbidities; the median number is six, with AF being the 11th most common [6]. Multimorbidity is associated with an increased risk of AF, cerebrovascular events, and mortality, with the risk increasing in accordance with the number of long-term conditions [7, 8]. Furthermore, patients with multimorbidity receiving oral anticoagulation therapy are associated with an increased risk of stroke relative to patients without multimorbidity who receive anticoagulation therapy [6]. Indeed, ad hoc results from the ARISTOTLE trial found that the risk of major bleeding (MB) rises by approximately 15% for each singular comorbidity [9]. However, despite the need for a safe treatment in this patient population, anticoagulants are generally underused—fewer than half of older adults with AF, who are generally multimorbid, receive
anticoagulants even without contraindications [6]. There have been very few observational studies comparing NOACs and warfarin among patients with NVAF and multimorbidity. This ARISTOPHANES (Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients; NCT03087487) sub-study compared the risk of stroke/SE and MB among multimorbid patients with NVAF who were newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin.

METHODS

Data Sources

This retrospective observational analysis utilized Medicare fee-for-service data from the US Centers for Medicare & Medicaid Services (CMS) and data from four US commercial claims databases: the IBM MarketScan® Commercial Claims and Encounter Database, the IQVIA PharMetrics Plus™ Database, the Optum Clininformatics™ Data Mart, and the Humana Research Database. Previously published articles include detailed descriptions of the datasets, the rationale for the pooling process, and the approaches to minimizing potential patient record duplicates across data sources [10, 11]. To avoid potential duplicates, patients with Medicare supplemental plans in MarketScan and PharMetrics data were excluded from the study because those patients may also have Medicare Part A and Part B coverage. For Optum and Humana, beneficiaries aged 65 years or more are enrolled in Medicare Advantage plans but are not covered in Medicare data. There is a possibility that employer-based commercial claims datasets may contain duplicate patient records when pooled together; however, the number of duplicates is likely to be small at an estimated 0.5%.

Patient Selection

For this study, multimorbidity was defined as the presence of six or more comorbid conditions, not including AF, among the 17 conditions listed in Tables 1 and 2 [9], based on both the distribution of comorbidities as well as the ARISTOTLE multimorbidity subgroup analysis, the only prior published analysis based on a phase 3 randomized controlled trial (RCT) for NOACs in a multimorbid population [9]. The present study utilized the same count for high multimorbidity as seen in the ARISTOTLE subgroup analysis. Patients with NVAF and multimorbidity were selected if they had at least one pharmacy claim for apixaban, dabigatran, rivaroxaban, or warfarin between 1 January 2013 to 30 September 2015 (identification period). Edoxaban was not included in the final analysis because of the small sample size. For patients with a NOAC claim during the identification period, the first NOAC prescription date was designated as the index date; for patients with no NOAC claim during the identification period, the first warfarin prescription date was designated as the index date. Patients were required to have an AF diagnosis before the index date and have continuous medical and pharmacy health plan enrollment for at least 12 months pre-index date.

Patients treated with an OAC within 12 months pre-index date were excluded. Patients were also excluded if they had evidence of valvular heart disease, venous thromboembolism, transient AF, heart valve replacement/transplant during the baseline period, pregnancy during the study period, or hip or knee replacement surgery within 6 weeks pre-index date. Additional exclusion criteria are shown in Fig. 1.

Outcome Measures

The primary outcomes measured were time to first stroke/SE and time to first MB. Stroke/SE was stratified by ischemic stroke, hemorrhagic stroke, and systemic embolism (SE). MB was stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage, and bleeding at other key sites (Supplementary Table S1) [12, 13]. Outcomes were based on hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis. The follow-up period ranged from
|                      | Apixaban cohort | Warfarin cohort | Dabigatran cohort | Warfarin cohort | Rivaroxaban cohort | Warfarin cohort |
|----------------------|-----------------|-----------------|-------------------|-----------------|-------------------|----------------|
| Sample size          | 34,658 100%     | 34,658 100%     | 10,027 100%       | 10,027 100%     | 40,601 100%       | 40,601 100%     |
| Age                  | 78.68 8.50      | 78.57 8.45      | 77.07 8.31        | 77.20 8.51      | 77.89 8.45        | 77.99 8.53      |
| 18–54                | 205 0.59%       | 201 0.58%       | 76 0.76%          | 80 0.80%        | 275 0.68%         | 289 0.71%       |
| 55–64                | 974 2.81%       | 956 2.76%       | 408 4.07%         | 407 4.06%       | 1342 3.31%        | 1329 3.27%      |
| 65–74                | 10,055 29.01%   | 10,113 29.18%   | 3435 34.26%       | 3462 34.53%     | 12,866 31.69%     | 12,703 31.29%   |
| ≥75                  | 23,424 67.59%   | 23,388 67.48%   | 6108 60.92%       | 6078 60.62%     | 26,118 64.33%     | 26,280 64.73%   |
| Gender               | Male            | Female          | Male              | Female          | Male              | Female          |
|                      | 16,281 46.98%   | 18,377 53.02%   | 16,303 47.04%     | 18,355 52.96%   | 4918 49.05%       | 5109 50.95%     |
|                      | 4918 49.05%     | 5109 50.95%     | 4999 48.86%       | 5128 51.14%     | 19,479 47.98%     | 21,122 52.02%   |
|                      | 19,479 48.86%   | 21,122 52.02%   | 19,493 48.01%     | 21,108 51.99%   | 19,493 48.01%     | 21,108 51.99%   |
| Baseline comorbidity |                 |                 |                   |                 |                   |                 |
| Deyo-Charlson Comorbidity Index | 5.21 2.65 | 5.22 2.64 | 4.94 2.58 | 4.95 2.56 | 5.13 2.62 | 5.12 2.61 |
| CHA2DS2-VASc Score | 5.00 1.45 | 5.00 1.42 | 4.87 1.45 | 4.87 1.43 | 4.93 1.44 | 4.93 1.42 |
| 0                    |                 |                 |                   |                 |                   |                 |
| 1                    | 75 0.22%        | 76 0.22%        | 39 0.39%          | 26 0.26%        | 114 0.28%         | 105 0.26%       |
| 2                    | 968 2.79%       | 805 2.32%       | 330 3.29%         | 327 3.26%       | 1214 2.99%        | 1098 2.70%      |
| 3                    | 3964 11.44%     | 3878 11.19%     | 1345 13.41%       | 1311 13.07%     | 5031 12.39%       | 4825 11.88%     |
| 4+                   | 29,647 85.54%   | 29,894 86.25%   | 8312 82.90%       | 8361 83.38%     | 34,235 84.32%     | 34,563 85.13%   |
| HAS-BLED Score       | 4.05 1.14       | 4.04 1.15       | 3.91 1.15         | 3.90 1.14       | 4.00 1.14         | 3.99 1.15       |
| 0                    | 190 0.55%       | 181 0.52%       | 84 0.84%          | 71 0.71%        | 250 0.62%         | 263 0.65%       |
| 1                    |                 |                 |                   |                 |                   |                 |
| Comorbidities for multimorbidity definition | Apixaban cohort | Warfarin cohort | Dabigatran cohort | Warfarin cohort | Rivaroxaban cohort | Warfarin cohort |
|-------------------------------------------|----------------|----------------|------------------|----------------|--------------------|----------------|
|                                           | N/mean | %/SD | N/mean | %/SD | N/mean | %/SD | N/mean | %/SD | N/mean | %/SD | N/mean | %/SD |
| Bleeding history                          | 10,857 | 31.33% | 10,844 | 31.29% | 2966 | 29.58% | 2979 | 29.71% | 13,076 | 32.21% | 13,087 | 32.23% |
| Stroke/SE                                 | 7683   | 22.17% | 7687   | 22.18% | 2117 | 21.11% | 2146 | 21.40% | 8781   | 21.63% | 8819   | 21.72% |

CAD (CAD, prior MI, PCI/CABG)   | 24,926 | 71.92% | 24,786 | 71.52% | 7181  | 71.62% | 7028  | 70.09% | 28,723 | 70.74% | 28,752 | 70.82% |
Congestive heart failure          | 18,813 | 54.28% | 18721  | 54.02% | 5278  | 52.64% | 5296  | 52.82% | 21,662 | 53.35% | 21,656 | 53.34% |
Valvular disease                  | 10,306 | 29.74% | 10,044 | 28.98% | 2682  | 26.75% | 2820  | 28.12% | 11,445 | 28.19% |
Hypertension                      | 34,038 | 98.21% | 34,051 | 98.25% | 9822  | 97.96% | 9835  | 98.09% | 39,783 | 97.99% | 39,736 | 97.87% |
PVD (PAD or aortic aneurysm)      | 15,136 | 43.67% | 15,695  | 45.29% | 4218  | 42.07% | 4486  | 44.74% | 17,859 | 43.99% | 18,237 | 44.92% |
CVD (carotid stenosis, TIA, stroke) | 13,555 | 39.11% | 13,374 | 38.59% | 3745  | 37.35% | 3704  | 36.94% | 15,474 | 38.11% | 15,378 | 37.88% |
Depression or dementia            | 17,870 | 51.56% | 18,040  | 52.05% | 5237  | 52.23% | 5159  | 51.45% | 21,432 | 52.79% | 21,150 | 52.09% |
Pulmonary (COPD, asthma)          | 12,090 | 34.88% | 12,136 | 35.02% | 3608  | 35.98% | 3591  | 35.81% | 14,972 | 36.88% | 14,450 | 35.59% |
Sleep apnea                       | 8462   | 24.42% | 7769   | 22.42% | 2602  | 25.95% | 2433  | 24.26% | 9507   | 23.42% | 9359   | 23.05% |
GI disorder (dyspepsia, GERD, PUD) | 21,461 | 61.92% | 21,401 | 61.75% | 6116  | 61.00% | 6126  | 61.10% | 25,176 | 60.01% | 24,899 | 61.33% |
Chronic liver disease             | 1687   | 4.87%  | 1652   | 4.77%  | 539   | 5.38%  | 491   | 4.90%  | 2180   | 5.37%  | 2073   | 5.11%  |
Hypo- or hyperthyroidism          | 13,889 | 40.07% | 13017  | 37.56% | 3925  | 39.14% | 3790  | 37.80% | 15,870 | 39.09% | 15,161 | 37.34% |
Diabetes                          | 19,763 | 57.02% | 19,868 | 57.33% | 5953  | 59.37% | 5985  | 59.69% | 23,569 | 58.05% | 23,456 | 57.77% |
Musculoskeletal (falls, osteoporosis) | 9206   | 26.56% | 9023   | 26.03% | 2489  | 24.82% | 2465  | 24.58% | 10,957 | 26.99% | 10,497 | 25.85% |
Renal disease (CKD or CrCl < 50 ml/ min) | 17,980 | 51.88% | 17,724 | 51.14% | 4852  | 48.39% | 4877  | 48.64% | 20,386 | 50.21% | 20,193 | 49.74% |
|                      | Apixaban cohort | Warfarin cohort | Dabigatran cohort | Warfarin cohort | Rivaroxaban cohort | Warfarin cohort |
|----------------------|-----------------|-----------------|-------------------|-----------------|--------------------|-----------------|
|                      | N/mean %/SD     | N/mean %/SD     | N/mean %/SD       | N/mean %/SD     | N/mean %/SD       | N/mean %/SD     |
| Anemia               | 18,603 53.68%   | 18,168 52.42%   | 5033 50.19%       | 4965 49.52%     | 21,440 52.81%     | 21,141 52.07%   |
| Malignancy           | 8425 24.31%     | 8021 23.14%     | 2241 22.35%       | 2283 22.77%     | 9926 24.45%       | 9484 23.36%     |

Dose of the index prescription

|                      |                 |                 |                  |                 |                   |                 |
|----------------------|-----------------|-----------------|------------------|-----------------|-------------------|-----------------|
| Standard dose\(^b\) | 22,624 65.28%   |                 | 7338 73.18%      |                 | 24,092 59.34%     |                 |
| Low dose\(^c\)      | 12,034 34.72%   |                 | 2689 26.82%      |                 | 16,509 40.66%     |                 |

\(^a\) Cells with values < 11 are not reported
\(^b\) 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban
\(^c\) 25 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 3035 and 13,474 patients received 10 mg and 15 mg rivaroxaban, respectively, in the rivaroxaban-warfarin matched cohort

\(CAD\) coronary artery disease, \(CHA_2DS_2-VASc\) congestive heart failure, hypertension, aged \(\geq 75\) years, diabetes mellitus, prior stroke or transient ischemic attack, or thromboembolism, \(CKD\) chronic kidney disease, \(COPD\) chronic obstructive pulmonary disease, \(CrCl\) creatinine clearance, \(CVD\) cardiovascular disease, \(GERD\) gastroesophageal reflux disease, \(GI\) gastrointestinal, \(HAS-BLED\) hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol, \(MI\) myocardial infarction, \(NOAC\) non-vitamin K antagonist oral anticoagulants, \(NVAF\) non-valvular atrial fibrillation, \(PAD\) peripheral artery disease, \(PCI/CABG\) percutaneous coronary intervention/coronary artery bypass grafting, \(PUD\) peptic ulcer disease, \(PVD\) peripheral vascular disease, \(SD\) standard deviation, \(SE\) systemic embolism, \(TIA\) transient ischemic attack
Table 2: Baseline characteristics among multimorbid patients with NVAF after propensity score matching among NOACs vs NOACs

|                      | Apixaban cohort | Dabigatran cohort | Apixaban cohort | Rivaroxaban cohort | Dabigatran cohort | Rivaroxaban cohort |
|----------------------|-----------------|-------------------|-----------------|--------------------|-------------------|--------------------|
|                      | N/ mean %/SD    | N/ mean %/SD      | N/ mean %/SD    | N/ mean %/SD       | N/ mean %/SD      | N/ mean %/SD       |
| Sample size          | 9962 100%       | 9962 100%         | 35,126 100%     | 35,126 100%        | 10,156 100%       | 10,156 100%        |
| Age                  | 77.27 8.59      | 77.06 8.39        | 78.33 8.67      | 78.16 8.58         | 76.84 8.53        | 76.96 8.66         |
| 18–54                | 96 0.96%        | 97 0.97%          | 298 0.85%       | 299 0.85%          | 111 1.09%         | 110 1.08%          |
| 55–64                | 397 3.99%       | 386 3.87%         | 1196 3.40%      | 1198 3.41%         | 474 4.67%         | 459 4.52%          |
| 65–74                | 3364 33.77%     | 3406 34.19%       | 10,340 29.44%   | 10,392 29.58%      | 3468 34.15%       | 3502 34.48%        |
| ≥ 75                 | 6105 61.28%     | 6073 60.96%       | 23,292 66.31%   | 23,237 66.15%      | 6103 60.09%       | 6085 59.92%        |
| Gender               |                 |                   |                 |                    |                   |                    |
| Male                 | 4837 48.55%     | 4863 48.82%       | 16,475 46.90%   | 16,430 46.77%      | 5004 49.27%       | 4976 49.00%        |
| Female               | 5125 51.45%     | 5099 51.18%       | 18,651 53.10%   | 18,696 53.23%      | 5152 50.73%       | 5180 51.00%        |
| Baseline comorbidity |                 |                   |                 |                    |                   |                    |
| Deyo-Charlson Comorbidity Index | 4.95 2.64 | 4.92 2.59 | 5.08 2.64 | 5.07 2.61 | 4.91 2.58 | 4.89 2.59 |
| CHA²DS²-VASc score⁴ | 4.86 1.45 | 4.86 1.46 | 4.94 1.45 | 4.94 1.45 | 4.84 1.48 | 4.83 1.46 |
| 0                    | 39 0.39%        | 41 0.41%          | 105 0.30%       | 128 0.36%          | 49 0.48%          | 58 0.57%           |
| 1                    | 354 3.55%       | 347 3.48%         | 1120 3.19%      | 1057 3.01%         | 393 3.87%         | 366 3.60%          |
| 2                    | 1307 13.12%     | 1326 13.31%       | 4283 12.19%     | 4316 12.29%        | 1385 13.64%       | 1420 13.98%        |
| 3                    | 8261 82.93%     | 8246 82.77%       | 29,611 84.30%   | 29,617 84.32%      | 8325 81.97%       | 8312 81.84%        |
| 4+                   |                 |                   |                 |                    |                   |                    |
| HAS-BLED score⁴      | 3.92 1.15       | 3.91 1.15         | 4.01 1.15       | 4.01 1.14          | 3.89 1.16         | 3.89 1.15          |
| 0                    | 93 0.93%        | 90 0.90%          | 249 0.7%        | 234 0.7%           | 104 1.02%         | 104 1.02%          |
| 1                    |                 |                   |                 |                    |                   |                    |
### Table 2 continued

|                          | Apixaban cohort | Dabigatran cohort | Apixaban cohort | Rivaroxaban cohort | Dabigatran cohort | Rivaroxaban cohort |
|--------------------------|-----------------|-------------------|-----------------|--------------------|-------------------|--------------------|
|                          | N/mean | %/SD    | N/mean | %/SD    | N/mean | %/SD    | N/mean | %/SD    | N/mean | %/SD    |
|                          |        |         |        |         |        |         |        |         |        |         |
| 2                        |        |         |        |         |        |         |        |         |        |         |
|                          | 959    | 9.63%   | 967    | 9.71%   | 2970   | 8.5%    | 2921   | 8.3%    | 1025   | 10.09%  |
|                          | 8909   | 89.43%  | 8904   | 89.38%  | 31,904 | 90.8%   | 31,963 | 91.0%   | 9026   | 88.87%  |
|                          |         |         |        |         |        |         |        |         |        |         |
|                            | 2923   | 29.34%  | 2922   | 29.33%  | 10,718 | 30.51%  | 10,740 | 30.58%  | 2970   | 29.24%  |
|                            | 2082   | 20.90%  | 2085   | 20.93%  | 7493   | 21.33%  | 7443   | 21.19%  | 2108   | 20.76%  |
|                            |         |         |        |         |        |         |        |         |        |         |
| **Comorbidities for multimorbidity definition** |        |         |        |         |        |         |        |         |        |         |
| CAD (CAD, prior MI, PCI/CABG) | 7122   | 71.49%  | 7121   | 71.48%  | 25,146 | 71.59%  | 24,877 | 70.82%  | 7254   | 71.43%  |
| Congestive heart failure   | 5259   | 52.79%  | 5215   | 52.35%  | 18,408 | 52.41%  | 18,428 | 52.46%  | 5299   | 52.18%  |
| Valvular disease           | 2878   | 28.89%  | 2682   | 26.92%  | 10,368 | 29.52%  | 9643   | 27.45%  | 2709   | 26.67%  |
| Hypertension               | 9756   | 97.93%  | 9760   | 97.97%  | 34,504 | 98.23%  | 34,500 | 98.22%  | 9948   | 97.95%  |
| PVD (PAD or aortic aneurysm) | 4189   | 42.05%  | 4193   | 42.09%  | 15,174 | 43.20%  | 15,469 | 44.04%  | 4244   | 41.79%  |
| CVD (carotid stenosis, TIA, stroke) | 3791   | 38.05%  | 3717   | 37.31%  | 13,582 | 38.67%  | 13,489 | 38.40%  | 3759   | 37.01%  |
| Depression (diagnosis or antidepressants) or dementia | 5125   | 51.45%  | 5217   | 52.37%  | 18,182 | 51.76%  | 18,675 | 53.17%  | 5314   | 52.32%  |
| Pulmonary (COPD, asthma)  | 3479   | 34.92%  | 3572   | 35.86%  | 12,224 | 34.80%  | 12,771 | 36.36%  | 3644   | 35.88%  |
| Sleep apnea               | 2689   | 26.99%  | 2599   | 26.09%  | 8800   | 25.05%  | 8066   | 22.96%  | 2694   | 26.53%  |
| GI disorder (dyspepsia, GERD, PUD) | 6143   | 61.66%  | 6090   | 61.13%  | 21,900 | 62.35%  | 21,921 | 62.41%  | 6208   | 61.13%  |
| Chronic liver disease     | 549    | 5.51%   | 538    | 5.40%   | 1759   | 5.01%   | 1827   | 5.20%   | 558    | 5.49%   |
| Hypo- or hyperthyroidism  | 4011   | 40.26%  | 3924   | 39.39%  | 14,091 | 40.12%  | 13,924 | 39.64%  | 3976   | 39.15%  |
| Diabetes                  | 5871   | 58.93%  | 5902   | 59.25%  | 19,871 | 56.57%  | 19,910 | 56.68%  | 6040   | 59.47%  |
| Musculoskeletal (falls, osteoporosis) | 2478   | 24.87%  | 2482   | 24.91%  | 9281   | 26.42%  | 9581   | 27.28%  | 2499   | 24.61%  |

N/mean: Number of cases; %/SD: Percentage and standard deviation.
| Condition                        | Apixaban cohort | Dabigatran cohort | Apixaban cohort | Rivaroxaban cohort | Dabigatran cohort | Rivaroxaban cohort |
|---------------------------------|-----------------|-------------------|-----------------|-------------------|-------------------|-------------------|
|                                 | N/mean %/SD     | N/mean %/SD       | N/mean %/SD     | N/mean %/SD       | N/mean %/SD       | N/mean %/SD       |
| Renal disease (CKD or CrCl < 50 ml/min) | 4858 48.77%     | 4800 48.18%       | 17,882 50.91%   | 17,719 50.44%      | 4892 48.17%       | 4880 48.05%       |
| Anemia                          | 4944 49.63%     | 4967 49.86%       | 18,250 51.96%   | 18,260 51.98%      | 5043 49.66%       | 5060 49.82%       |
| Malignancy                      | 2364 23.73%     | 2210 22.18%       | 8532 24.29%     | 8447 24.05%        | 2256 22.21%       | 2411 23.74%       |

Dose of the index prescription

|                      | Apixaban cohort | Dabigatran cohort | Apixaban cohort | Rivaroxaban cohort | Dabigatran cohort | Rivaroxaban cohort |
|----------------------|-----------------|-------------------|-----------------|-------------------|-------------------|-------------------|
| Standard dose<sup>b</sup> | 7017 70.44%     | 7288 73.16%       | 23,378 66.55%   | 20,504 58.37%      | 7462 73.47%       | 6336 62.39%       |
| Low dose<sup>c</sup>  | 2945 29.56%     | 2674 26.84%       | 11,748 33.45%   | 14,622 41.63%      | 2694 26.53%       | 3820 37.61%       |

<sup>a</sup> Cells with values < 11 are not reported
<sup>b</sup> 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban
<sup>c</sup> 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban. 2615 and 12,007 patients received 10 mg and 15 mg rivaroxaban, respectively, in the apixaban-rivaroxaban matched cohort and 704 and 3116 patients received 10 mg and 15 mg rivaroxaban, respectively, in the dabigatran-rivaroxaban matched cohort.
Adult patients with ≥1 pharmacy claim for warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban during the identification period (01JAN2013-30SEP2015)
N = 3,327,019

≥12 months continuous medical and pharmacy health plan enrollment pre-index date
N = 2,493,649

≥1 medical claim for AF prior to or on the index date
N = 2,165,113

Excluded patients with rheumatic mitral valvular heart disease, valve replacement procedure, diagnosis of VTE, transient AF, and those who had cardiac surgery in the 12 months prior to or on the index date or medical claims indicating pregnancy during the study period
N=1,258,915

Excluded individuals with hip/knee replacement surgery within 6 weeks prior to the index date
N=1,218,587

Excluded patients with more than one OAC treatment on the index date or had a pharmacy claim for an OAC during the baseline
N=468,845

Excluded patients with ICD-10 codes or with no follow-up period
N=467,461

Total Patients
N= 466,991

Multimorbid Patients
N= 155,959

All Patients included in the study
Apixaban Cohort N= 36,921  Dabigatran Cohort N=10,248
Rivaroxaban Cohort N=45,509  Warfarin Cohort N=63,281

Matched Patients
Apixaban-Warfarin  Dabigatran-Warfarin  Rivaroxaban-Warfarin
N= 34,658  N= 34,658  N= 10,027  N=10,027  N=40,601  N=40,601

Apixaban-Dabigatran  Apixaban-Rivaroxaban  Dabigatran-Rivaroxaban
N= 9,962  N= 9,962  N=35,126  N=35,126  N=10,156  N=10,156
1 day post-index date to the first of 30 days after discontinuation, switch date, death, end of continuous medical or pharmacy plan enrollment, or end of study.

**Statistical Methods**

Propensity score matching (PSM) was conducted between NOAC and warfarin cohorts and between the NOAC cohorts. Patients were matched 1:1 in each dataset based on the propensity scores generated by logistic regression using demographics, Charlson Comorbidity Index (CCI) scores [14], comorbidities that were documented risk factors for stroke/SE or MB, and baseline co-medications. Patients were matched by nearest neighbor matching without replacement using a caliper of 0.01. Covariate balance was checked through standardized differences, with a threshold of 10% [15]. Patients from the five matched datasets were pooled for the final analysis.

Risk of stroke/SE and risk of MB were evaluated using Cox proportional hazard models, with robust sandwich estimates ($\alpha = 0.05$) [16]. OAC treatment was included as the independent variable; no other covariates were included as the cohorts were balanced.

All statistical analyses were performed using SAS version 9.4.

**Subgroup Analyses**

An interaction analysis was conducted between treatment and comorbidity level among patients with 6–8 comorbidities vs patients with 9+ comorbidities. The statistical significance ($p < 0.10$) of the interaction between treatment and comorbidity level was evaluated. Further, PSM and Cox proportional hazard models were separately completed for patients prescribed standard dose NOACs (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) and low dose NOACs (apixaban 2.5 mg, dabigatran 75 mg, rivaroxaban 10 or 15 mg).

**Compliance with Ethics Guidelines**

Since the core study described herein did not involve the collection, use, or transmittal of individual identifiable data, institutional review board (IRB) approval to conduct this study was not required. The security of the data meets the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study protocol was reviewed and determined to be exempt from the Office for Human Research Protections (OHRP’s) Regulations for the Protection of Human Subjects (45 CFR 46) under the following category: Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

**RESULTS**

After applying the selection criteria, 33.4% ($n = 155,959$) of the NVAF population newly initiated on OACs ($n = 466,991$) had multimorbidity; 36,921 (23.7%) initiated apixaban, 10,248 (6.6%) dabigatran, 45,509 (29.2%) rivaroxaban, and 63,281 (40.6%) warfarin (Fig. 1). The mean number of comorbidities ranged from 7.5 to 7.8 across the drug cohorts.

Before PSM, apixaban patients were older and warfarin patients had higher CCI, CHA2DS2-VASc, and HAS-BLED scores compared to NOAC patients (Supplementary Table S2).

The unadjusted incidence rates of stroke/SE per 100 person-years were 3.7 (warfarin), 2.4 (apixaban), 2.8 (dabigatran), and 2.4 (rivaroxaban). The unadjusted rates for MB per 100 person-years were 11.5 (warfarin), 6.9 (apixaban), 7.2 (dabigatran), and 10.5 (rivaroxaban) (Supplementary Table S3).

After PSM, 34,658 apixaban-warfarin, 10,027 dabigatran-warfarin, and 40,601 rivaroxaban-warfarin patient pairs were studied. Matching

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△ Adis
for NOAC comparisons included 9962 patient pairs for the apixaban-dabigatran, 35,126 pairs for the apixaban-rivaroxaban, and 10,156 pairs for the dabigatran-rivaroxaban cohorts (Fig. 1). Coronary artery disease, hypertension, and GI disorders were among some of the most prevalent comorbid conditions. The baseline characteristics of the matched populations are shown in Tables 1 and 2.

**NOAC vs Warfarin Comparisons**

Compared to warfarin, apixaban and rivaroxaban were associated with a lower risk of stroke/SE (apixaban: hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.54–0.74; rivaroxaban: HR 0.70, 95% CI 0.64–0.77). Dabigatran was associated with a similar risk of stroke/SE (HR 0.91, 95% CI 0.75–1.10) compared to warfarin. Apixaban and dabigatran were associated with a lower risk of MB compared to warfarin (HR 0.61, 95% CI 0.56–0.67; HR 0.75, 95% CI 0.66–0.86, respectively) while rivaroxaban patients had a higher risk of MB (HR 1.06, 95% CI 1.01–1.12; Fig. 2a).

**NOAC vs NOAC Comparisons**

Compared to dabigatran, apixaban was associated with a lower risk of stroke/SE (HR 0.81, 95% CI 0.65–1.00) and MB (HR 0.82, 95% CI 0.69–0.98). Dabigatran was associated with a higher risk of stroke/SE versus rivaroxaban (HR 1.29, 95% CI 1.02–1.62). Apixaban and dabigatran were associated with lower risks of MB versus rivaroxaban (HR 0.57, 95% CI 0.52–0.63; HR 0.72, 95% CI 0.64–0.81, respectively) (Fig. 2b). The Kaplan–Meier curves for cumulative incidence rates of stroke/SE and MB in the matched populations are shown in Supplementary Figs. S1A–S1L.

**Subgroup Analyses**

Significant interactions were observed for treatment and number of comorbidities among some of the analyses for stroke/SE and MB. For apixaban vs warfarin and apixaban vs rivaroxaban, patients with 6–8 comorbidities experienced a greater relative magnitude of reduction in the risk of MB compared to patients with 9+ comorbidities (Tables 3 and 4). A significant interaction was also found for apixaban vs rivaroxaban for stroke/SE ($p = 0.064$) where apixaban patients with 6–8 comorbidities had a similar risk of stroke/SE, but apixaban patients with 9+ comorbidities trended towards a lower risk of stroke/SE compared with rivaroxaban patients (Table 4). The results of the dose analyses were generally consistent with the main analysis. In the standard dose comparison, all NOACs demonstrated a lower risk of stroke/SE compared to warfarin (Supplementary Figs. S2 and S3).

**DISCUSSION**

This ARISTOPHANES subgroup analysis is the largest study to date that evaluates the effectiveness and safety of OAC treatment in a multimorbid (at least six comorbidities) patient population with NVAF. Overall, NOACs were found to be associated with varying risk of stroke/SE and MB compared to warfarin and differential risk of stroke/SE and MB was also observed between NOACs. Further analyses in key subgroups, including NOAC low- and standard-dose populations and patients with 6–8 vs 9+ comorbidities, showed generally consistent findings.

Multimorbidity is common in patients with NVAF, and proportionally becoming more prevalent in recent years [17]. The presence of multimorbidity is associated with an increased risk of stroke, bleeding, and death [17]. The results of the present study are similar to the findings from related post hoc analyses of the ARISTOTLE trial. Therein, patients were included on the basis of the number of comorbidities and classified as no multimorbidity (0–2
### Table A

#### a) Apixaban vs Warfarin

| Comparator | Incidence per 100 person-years | Hazard Ratio (95% CI) | P-value |
|------------|---------------------------------|------------------------|---------|
| Stroke / SE | 2.40                            | 0.63 (0.54-0.74)       | <0.001  |
| Ischemic   | 1.95                            | 0.70 (0.63-0.79)       | <0.001  |
| Hemorrhagic| 0.37                            | 0.43 (0.27-0.67)       | <0.001  |
| Systemic Embolism | 0.10 | 0.54 (0.32-0.93)       | 0.021   |
| Major Bleeding | 7.06 | 0.81 (0.56-1.19)       | <0.001  |
| GI Bleeding | 4.43                            | 0.63 (0.66-1.31)       | <0.001  |
| Intracranial Hemorrhage | 0.82 | 0.55 (0.43-0.72)       | <0.001  |
| Other sites | 3.12                            | 0.60 (0.54-0.66)       | <0.001  |

#### b) Dabigatran vs Warfarin

| Comparator | Incidence per 100 person-years | Hazard Ratio (95% CI) | P-value |
|------------|---------------------------------|------------------------|---------|
| Stroke / SE | 2.79                            | 0.91 (0.75-1.10)       | 0.329   |
| Ischemic   | 2.34                            | 1.03 (0.83-1.28)       | 0.787   |
| Hemorrhagic| 0.33                            | 0.45 (0.28-0.73)       | 0.001   |
| Systemic Embolism | 0.12 | 1.14 (0.56-2.31)       | 0.417   |
| Major Bleeding | 7.27 | 0.75 (0.66-0.86)       | <0.001  |
| GI Bleeding | 4.40                            | 0.99 (0.85-1.15)       | 0.876   |
| Intracranial Hemorrhage | 0.74 | 0.57 (0.43-0.78)       | <0.001  |
| Other sites | 2.59                            | 0.58 (0.48-0.70)       | <0.001  |

### Table B

#### Apixaban vs Dabigatran (ref.)

| Comparator | Incidence per 100 person-years | Hazard Ratio (95% CI) | P-value |
|------------|---------------------------------|------------------------|---------|
| Stroke / SE | 2.51                            | 0.81 (0.65-1.00)       | 0.049   |
| Ischemic   | 2.04                            | 0.78 (0.63-0.97)       | 0.025   |
| Hemorrhagic| 0.32                            | 0.96 (0.44-2.09)       | 0.918   |
| Systemic Embolism | 0.16 | 1.06 (0.48-2.56)       | 0.877   |
| Major Bleeding | 6.50 | 0.82 (0.69-0.98)       | 0.032   |
| GI Bleeding | 3.14                            | 0.66 (0.53-0.82)       | <0.001  |
| Intracranial Hemorrhage | 0.75 | 0.98 (0.63-1.53)       | 0.910   |
| Other sites | 2.90                            | 1.00 (0.80-1.25)       | 0.991   |

#### Apixaban vs Rivaroxaban (ref.)

| Comparator | Incidence per 100 person-years | Hazard Ratio (95% CI) | P-value |
|------------|---------------------------------|------------------------|---------|
| Stroke / SE | 2.28                            | 0.87 (0.74-1.02)       | 0.095   |
| Ischemic   | 1.85                            | 0.94 (0.63-1.71)       | 0.346   |
| Hemorrhagic| 0.34                            | 0.70 (0.43-1.17)       | 0.173   |
| Systemic Embolism | 0.10 | 0.59 (0.35-0.99)       | 0.045   |
| Major Bleeding | 6.75 | 0.57 (0.52-0.63)       | <0.001  |
| GI Bleeding | 3.24                            | 0.49 (0.44-0.55)       | <0.001  |
| Intracranial Hemorrhage | 0.77 | 0.87 (0.66-1.40)       | 0.300   |
| Other sites | 3.08                            | 0.58 (0.53-0.65)       | <0.001  |

#### Dabigatran vs Rivaroxaban (ref.)

| Comparator | Incidence per 100 person-years | Hazard Ratio (95% CI) | P-value |
|------------|---------------------------------|------------------------|---------|
| Stroke / SE | 2.79                            | 1.29 (1.02-1.62)       | 0.054   |
| Ischemic   | 2.33                            | 1.56 (1.07-2.22)       | 0.018   |
| Hemorrhagic| 0.33                            | 0.91 (0.53-1.57)       | 0.748   |
| Systemic Embolism | 0.13 | 1.01 (0.38-2.88)       | 0.984   |
| Major Bleeding | 7.13 | 0.72 (0.44-1.18)       | <0.001  |
| GI Bleeding | 4.33                            | 0.79 (0.68-0.92)       | 0.002   |
| Intracranial Hemorrhage | 0.72 | 1.02 (0.69-1.50)       | 0.923   |
| Other sites | 2.57                            | 0.56 (0.47-0.67)       | <0.001  |
| 6–8 Comorbidities | Incidence per 100 person-years | Hazard ratio (95% CI) | 9+ Comorbidities | Incidence per 100 person-years | Hazard ratio (95% CI) | Interaction p value |
|-------------------|-------------------------------|-----------------------|-------------------|-------------------------------|-----------------------|--------------------|
| Stroke/SE         | Apixaban 2.25, Warfarin 3.24  | 0.63 (0.52, 0.77)     | Stroke/SE         | Apixaban 2.85, Warfarin 4.24  | 0.62 (0.51, 0.76)     | 0.870              |
|                   | MB 5.55, Warfarin 8.97        | 0.57 (0.52, 0.62)     | MB 11.72          | 15.99                         | 0.68 (0.58, 0.79)     | 0.023              |
|                   | Dabigatran 2.68, Warfarin 2.82| 0.94 (0.74, 1.21)     | Dabigatran         | 3.18                          | 4.06                  | 0.496              |
|                   | MB 5.93, Warfarin 8.35        | 0.71 (0.59, 0.84)     | MB 12.06          | 15.03                         | 0.83 (0.68, 1.01)     | 0.285              |
|                   | Rivaroxaban 2.08, Warfarin 3.14| 0.65 (0.59, 0.73)     | Rivaroxaban        | 3.13                          | 3.73                  | 0.020              |
|                   | MB 9.49, Warfarin 8.73        | 1.07 (1.01, 1.14)     | MB 15.68          | 15.42                         | 1.01 (0.92, 1.11)     | 0.333              |

CI confidence interval, MB major bleeding, NOAC non-vitamin K antagonist oral anticoagulant, SE systemic embolism
| 6–8 Comorbidities | Incidence per 100 person-years | Hazard ratio (95% CI) | 9+ Comorbidities | Incidence per 100 person-years | Hazard ratio (95% CI) | Interaction p value |
|-------------------|--------------------------------|-----------------------|-------------------|--------------------------------|-----------------------|---------------------|
| Stroke/SE         | 2.38                           | 2.75                  | 0.80 (0.60, 1.05)  | Stroke/SE                      | 2.95                  | 3.20                | 0.84 (0.56, 1.27)  | 0.853              |
| MB                | 5.18                           | 5.84                  | 0.81 (0.64, 1.02)  | MB                             | 10.99                 | 12.11               | 0.82 (0.66, 1.02)  | 0.951              |
|                   | Apixaban                       | Dabigatran            |                   | Apixaban                       | Dabigatran            |                     |                     |                    |
| Stroke/SE         | 2.13                           | 2.11                  | 0.93 (0.79, 1.11)  | Stroke/SE                      | 2.74                  | 3.44                | 0.74 (0.59, 0.93)  | 0.064              |
| MB                | 5.40                           | 9.47                  | 0.53 (0.48, 0.58)  | MB                             | 11.15                 | 15.62               | 0.66 (0.57, 0.77)  | 0.002              |
|                   | Apixaban                       | Rivaroxaban           |                   | Apixaban                       | Rivaroxaban           |                     |                     |                    |
| Stroke/SE         | 2.71                           | 2.06                  | 1.32 (1.02, 1.71)  | Stroke/SE                      | 3.11                  | 2.66                | 1.19 (0.79, 1.79)  | 0.636              |
| MB                | 5.78                           | 8.68                  | 0.67 (0.58, 0.77)  | MB                             | 12.14                 | 14.70               | 0.84 (0.66, 1.07)  | 0.134              |

CI confidence interval, MB major bleeding, NOAC non-vitamin K antagonist oral anticoagulant, SE systemic embolism
comorbidities), moderate multimorbidity (3–5 comorbidities), and high multimorbidity (at least 6 comorbidities), and the risks of stroke/SE and MB were elevated for patients in the high and moderate multimorbidity groups compared with the no multimorbidity group [9]. The ARISTOTLE post hoc analysis also found that multimorbid apixaban patients trended toward a lower risk of stroke/SE and MB compared to warfarin, which is consistent with both the main trial results and the present study [9].

Few real-world retrospective studies have evaluated the impact of OAC treatment in patients with AF and multimorbidity. One study done by Mentias et al. assessed the effectiveness of dabigatran, rivaroxaban, and warfarin among Medicare patients with AF where multimorbidity was indicated by CHA2DS2-VASc, HAS-BLED, and Gagne comorbidity scores rather than number of comorbid conditions at baseline [18]. Across the three comorbidity scores, the authors found that standard-dose dabigatran patients did not have a significantly different risk of stroke or MB compared to warfarin. This is inconsistent with the results of both the standard-dose subgroup analysis of this study and results from the RE-LY trial, which showed that dabigatran had a significantly lower risk of stroke/SE and MB compared to warfarin [19]. Mentias et al. (2018) found that standard-dose rivaroxaban patients had a higher risk of MB compared to dabigatran patients across all three scores, which is consistent with results of our main analysis and standard-dose subgroup analysis [18]. The discrepancy in trends may be due to the difference in defining multimorbidity.

Compared to previous studies, this ARISTOPHANES subgroup analysis provides a larger sample of patients with NVAF and multimorbidity from a more representative population, including both Medicare and commercially insured patients. The results are consistent with available RCT literature in showing that NOACs are associated with favorable benefit/risk profile when compared to warfarin.

**Limitations**

For this retrospective observational study, only statistical associations could be concluded, not causal relationships. Although cohorts were matched through PSM, there were potential residual confounders. As a result of the nature of claims studies, outcome measures could only be based on International Classification of Diseases—Ninth Revision—Clinical Modification (ICD-9-CM) codes without further adjustment with precise clinical criteria. In addition, laboratory values, such as hemoglobin or international normalized ratio (INR) measurements, are not available in the dataset so time in therapeutic range for patients prescribed warfarin was indeterminable. Nonetheless, the inclusion of patients with potentially poorer quality control of warfarin therapy in everyday clinical practice may enable the study findings to better reflect real-world situations. Additionally, previously verified mortality information was only available for Medicare patients, and although 62% of stroke deaths occur outside of an acute hospital setting, it is unlikely that the proportion of deaths would differ by cohort [20, 21].

This study used both the distribution of comorbidities at baseline and previously published ARISTOTLE trial subgroup analyses to define multimorbidity, but definition of multimorbidity differs from some other studies and presents a challenge to compare our findings with those of other studies. While all patients were required to have at least six comorbidities, the severity of conditions remained unknown and may not be equal among patients. Moreover, unobserved heterogeneity may exist across the five data sources. Although some of the datasets contain information from different insurance plans that do not overlap at the plan level, others are employer-based claims datasets which may contain duplicate patient records when pooled together. However, the number of such duplicates is likely to be low—on the basis of a published estimate of 0.5%—and therefore unlikely to have any significant effect on the results [22]. Finally, the results may not reflect the overall multimorbid NVAF population in the USA because the study did not include...
uninsured patients and those solely covered by other public health insurance plans.

CONCLUSIONS

In the largest observational study of patients with NVAF and multimorbidity, we show that among patients with NVAF and six or more comorbid conditions, NOACs were associated with varying risk of stroke/SE and MB compared to warfarin and to each other. Rather than a "one drug fits all" approach, our results may be useful for selecting appropriate OAC treatment for multimorbid patients.

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Compliance with Ethics Guidelines. Since the core study described herein did not involve the collection, use, or transmittal of individual identifiable data, institutional review board (IRB) approval to conduct this study was not required. The security of the data meets the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study protocol was reviewed and determined to be exempt from the Office for Human Research Protections (OHRP’s) Regulations for the Protection of Human Subjects (45 CFR 46) under the following category: Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The raw data on which these analyses were based were obtained from the Centers for Medicare & Medicaid Services (CMS) and four US 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. These data are available from the respective organizations upon request.

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