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Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the ARISTOPHANES study

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Abstract. Lip GYH, Keshishian AV, Kang AL, Dhamane AD, Luo X, Li X, Balachander N, Rosenblatt L, Mardekian J, Pan X, Di Fusco M, Garcia Reeves AB, Yuce H, Deitelzweig S (University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; Aalborg University, Aalborg, Denmark; STATinMED Research, Ann Arbor, MI; New York City College of Technology (CUNY), New York, NY; Bristol-Myers Squibb Company, Lawrenceville, NJ; Pfizer, Inc., Groton, CT; Pfizer, Inc., New York, NY; University of North Carolina, Chapel Hill, NC; Ochsner Clinic Foundation, New Orleans, LA; The University of Queensland School of Medicine, New Orleans, LA, USA). Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the ARISTOPHANES study. *J Intern Med* 2021;**289**: 42–52. https://doi.org/10.1111/joim.13140

Background. Patient frailty amongst patients with nonvalvular atrial fibrillation (NVAF) is associated with adverse health outcomes and increased risk of mortality. Additional evidence is needed to evaluate effective and safe NVAF treatment in this patient population.

Objectives. This subgroup analysis of the ARISTOPHANES study compared the risk of stroke/systemic embolism (S/SE) and major bleeding (MB) amongst frail NVAF patients prescribed nonvitamin K antagonist oral anticoagulants (NOACs) or warfarin.

Methods. This comparative retrospective observational study of frail, older NVAF patients who initiated apixaban, dabigatran, rivaroxaban or warfarin from 01JAN2013-30SEP2015 was conducted using Medicare and 3 US commercial claims databases. To compare each drug, 6 propensity score-matched (PSM) cohorts were created. Patient cohorts were pooled from 4 databases after PSM. Cox models were used to estimate hazard ratios (HR) of S/SE and MB.

Results. Amongst NVAF patients, 34% (N = 150 487) met frailty criteria. Apixaban and rivaroxaban were associated with a lower risk of S/SE vs warfarin (apixaban: HR: 0.61, 95% CI: 0.55–0.69; rivaroxaban: HR: 0.79, 95% CI: 0.72–0.87). For MB, apixaban (HR: 0.62, 95% CI: 0.57–0.66) and dabigatran (HR: 0.79, 95% CI: 0.70–0.89) were associated with a lower risk and rivaroxaban (HR: 1.14, 95% CI: 1.08–1.21) was associated with a higher risk vs warfarin.

Conclusion. Amongst this cohort of frail NVAF patients, NOACs were associated with varying rates of stroke/SE and MB compared with warfarin. Due to the lack of real-world data regarding OAC treatment in frail patients, these results may inform clinical practice in the treatment of this patient population.

Keywords: anticoagulation treatment, atrial fibrillation, cardiology, stroke, warfarin.

Abbreviations: AF, atrial fibrillation; ARISTOPHANES, Anticoagulants for Reduction In STroke: Observational Pooled analysis on Health outcomes ANd Experience of patientS; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age, Diabetes, and Stroke—Vascular disease, Age, Sex category; HAS-BLED, Hypertension, Abnormal liver function, Stroke, Bleeding, Labile international normalized ratio (unstable/high), Elderly, Drugs or alcohol; MB, major bleeding; NOAC, non-VKA oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; PSM, propensity score matching; S/SE, stroke/systemic embolism; VKA, vitamin K antagonist.

Introduction

Frailty is a clinical state characterized by loss of biological reserves, failure of homoeostatic mechanisms and increased vulnerability to negative health-related outcomes [1, 2]. Frailty prevalence increases steadily with age, from ~4% at 65–69 years to nearly 26% at ≥85 years [3]. Atrial fibrillation (AF) is the most common arrhythmia amongst older patients and is associated with high frailty risk [4, 5]. Moreover, the odds of a frail classification are 4 times higher for nonvalvular AF (NVAF) patients vs non-NVAF patients [6].

Since AF is an independent risk factor for stroke, oral anticoagulants (OACs)—including nonvitamin K antagonists (VKAs) and non-VKA OACs (NOACs)—are recommended for stroke prevention amongst AF patients [7]. Amongst AF patients, in addition to older age, frailty is associated with increased stroke incidence, mortality, symptom severity and length of hospital stay [1, 8-10]. The European Society of Cardiology guidelines for AF management specifies that frail and older patients are more likely to benefit from OAC than younger patients, and all available evidences show NOACs are noninferior to VKA treatment for cardiovascular risk [11]. However, despite high AF prevalence amongst frail older patients, a few receive OACs compared with nonfrail patients [12, 13].

Various frailty measures have been developed, and whilst there is no operational consensus on defining frailty amongst older patients, the frailty phenotype proposed by Fried et al. has gained widespread acceptance [14]. It measures frailty by ≥3 of the following criteria: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity [14]. Based on the Fried phenotype, Segal et al. developed a claims-based frailty indicator to identify frail individuals using only administrative data [15].

Given the increased risk of both stroke and bleeding in this population, careful evaluation of optimal treatment strategies is necessary. This analysis of older (aged ≥ 65 years) frail patients in the ARISTOPHANES (Anticoagulants for Reduction In STroke: Observational Pooled analysis on Health outcomes ANd Experience of patientS; NCT03087487) study aimed to provide complementary evidence regarding this poorly studied population by evaluating and comparing the rates of stroke/systemic embolism (SE), major bleeding (MB) and all-cause mortality (US Centers for Medicare & Medicaid Services [CMS] Medicare population only) amongst NVAF patients newly prescribed apixaban, dabigatran, rivaroxaban or warfarin.

Materials and methods

Data sources and patient selection

This study was conducted amongst older frail NVAF patients newly treated with apixaban, dabigatran, rivaroxaban or warfarin, as a subgroup analysis of the ARISTOPHANES study [16]. Data were pooled from the US CMS Medicare database and 3 US commercial claims databases: the commercial section of the IQVIA PharMetrics Plus™ Database ('PharMetrics'), the Optum Clinformatics™ Data Mart ('Optum') and the Humana Research Database ('Humana'). Collectively, the 4 datasets cover >123 million beneficiaries annually, accounting for ~38% of the US population. The IBM Watson MarketScan® Commercial Claims and Encounter database population, which was assessed in the ARISTOPHANES study, was not included in this analysis, as all patients were <65 years of age [16]. The ARISTOPHANES data description details and pooling process have been published previously [16, 17]. Patients prescribed edoxaban were not included in this study given the insufficient sample size.

Amongst patients included in the ARISTOPHANES study, older frail patients were further selected for this analysis, including AF patients with an OAC pharmacy claim between 1 January 2013 and 30 September 2015 (identification period). 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 [18]. Patient demographics and clinical characteristics in the 12 months prior to or on the index date were examined (baseline period).

Patients were excluded from the study if they had one of the following: (a) an OAC prescription within 12 months before the index date; (b) evidence of valvular heart disease, venous thromboembolism (VTE), transient AF (pericarditis, hyperthyroidism, thyrotoxicosis) or heart valve replacement/transplant during the baseline period; (c) pregnancy during the study period; (d) hip or knee

replacement surgery within 6 weeks prior to the index date; (e) >1 OAC on the index date; (f) ICD-10 code during the study period; and/or (g) follow-up time of zero days (Fig. 1).

Frailty was defined with an algorithm defined by Segal et al. (based on the most commonly used Fried phenotype for frailty), wherein 44 conditions were considered and evaluated during a 6-month period [15]. In the final model, 21 variables were included in the predicted probability of frailty (range: 0–1). This study measured the 21 variables (Table S1) during the 12-month baseline period and used a predicted probability cut-off of 0.20 to classify individuals as frail, with sensitivity of 35% and specificity of 91% [15]. Instead of a cut-off of 0.12, which would yield the maximized sensitivity of 66% and specificity of 73% and a larger sample size, the more restrictive cut-off of 0.20 was chosen to assure the accuracy of frail patient identification.

Outcome measures

Primary outcomes were stroke/SE, stratified by ischaemic stroke, haemorrhagic stroke and SE. The primary safety outcome was MB, stratified by gastrointestinal (GI) bleeding, intracranial haemorrhage and MB in other key sites (Table S2) [19, 20]. The primary outcomes were identified using inpatient claims with stroke/SE or MB as the principal (Medicare and Optum) or first-listed (Humana and PharMetrics) diagnosis. The secondary outcome was all-cause mortality in the Medicare population (these data provide reliable and validated death information from the Social Security Administration).

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

Statistical analysis

Descriptive analysis was conducted for each treatment cohort. Means and standard deviations were calculated for continuous variables; numbers and percentages were reported for categorical variables. To control for different patient characteristics, propensity score matching (PSM) was used to compare NOAC vs warfarin (apixaban vs warfarin, dabigatran vs warfarin, and rivaroxaban vs warfarin) and NOAC vs NOAC (apixaban vs dabigatran, apixaban vs rivaroxaban, and dabigatran vs rivaroxaban). PSM was conducted in each database using 2 comparative cohorts before pooling the datasets. Patients were matched 1:1 by propensity scores generated using multivariable logistic regressions for baseline characteristics, including demographic and clinical characteristics (see Table S3 for complete covariate list). Further details on PSM methodology appear in the literature [16, 17]. The PSM-adjusted baseline variables were compared based on standardized differences, with a threshold of 10% [21].

The incidence rates of stroke/SE, MB and all-cause death (Medicare only) in the matched population were calculated using the number of events divided by total person-years at risk and multiplied by 100, with Kaplan–Meier curves to illustrate cumulative rates. Cox proportional hazard models with robust sandwich estimates were also applied to the PSM population within the pooled dataset to evaluate the comparative risks [22]. OAC treatment was included as the independent variable in the Cox models because all the matched confounders were similar after PSM between the 2 comparative arms. *P*-values of 0.05 were used as the threshold for statistical significance.

Subgroup analysis

For the NOAC cohorts, standard-dose (apixaban 5 mg twice a day (BID), dabigatran 150 mg BID, rivaroxaban 20 mg once a day (QD)) and lower-dose (apixaban 2.5 mg BID, dabigatran 75 mg BID, rivaroxaban 15 mg/10 mg QD) patients were examined separately based on index prescription dosage (dabigatran 110 mg is not approved in the United States). Warfarin cohort patients were matched to NOAC patients with either dosage. The statistical methods of the main analysis were used, wherein 1:1 PSM patients in each dataset were pooled and compared.

Role of the funding source

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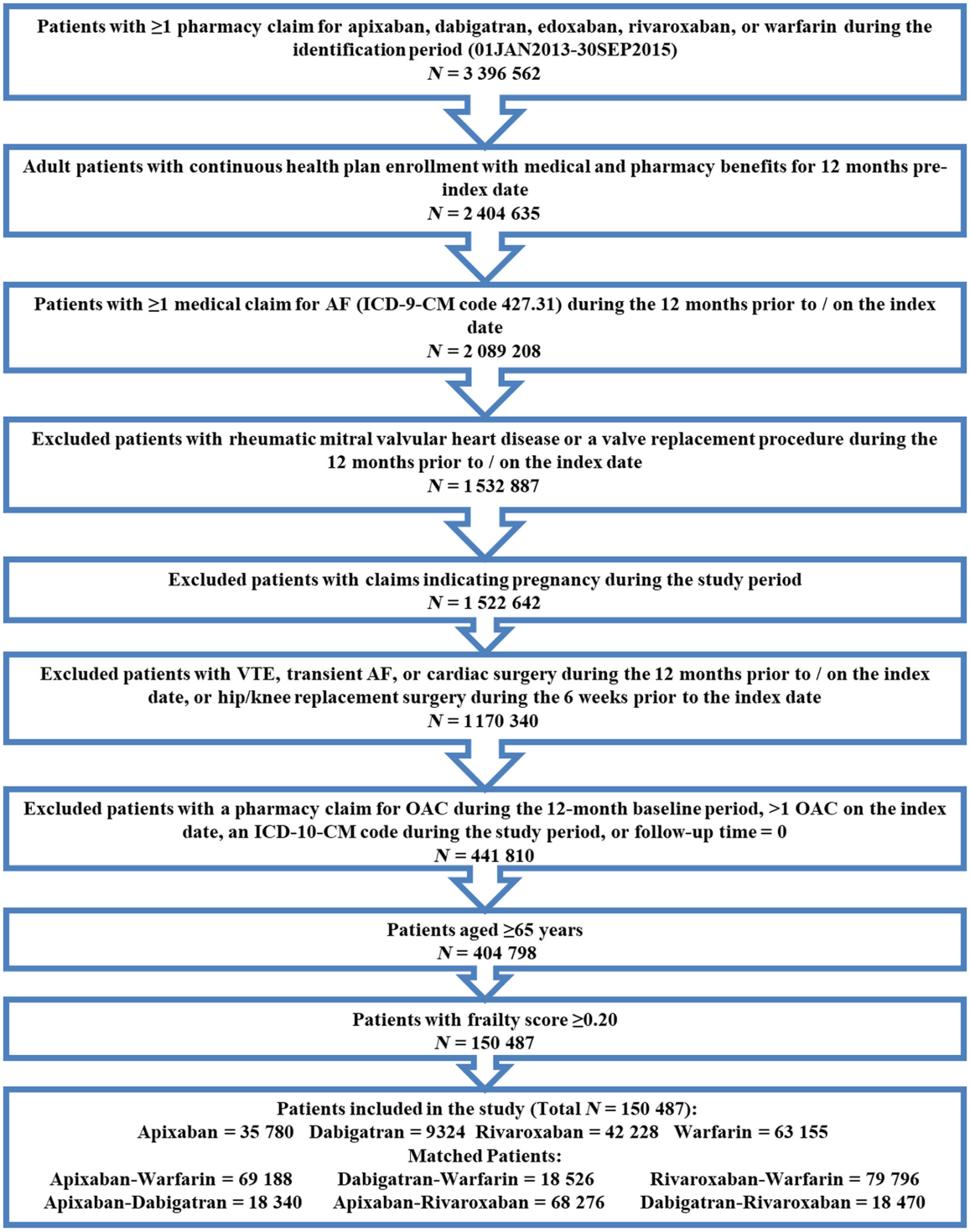

Fig. 1 *Patient Selection Criteria. The study population selected frail NVAF patients who initiated an OAC of interest, resulting in 6 PSM cohorts ranging from 18 340 to 79 796 matched patients. AF: atrial fibrillation; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; OAC: oral anticoagulant; VTE: venous thromboembolism.*

IRB approval

Since 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 150 487 frail patients (of the total elderly NVAF patients) with NVAF were identified, including 35 780 (23.8%) taking apixaban, 9324 (6.2%) dabigatran, 42 228 (28.1%) rivaroxaban, and 63 155 (42.0%) warfarin patients (Fig. 1). Amongst the identified frail patients, the mean frailty score was 0.4 (maximum of 1.0); details on the frailty indicator appear in Tables S1 and S3. Over 90% of the patients had CHA_2DS_2-VASc scores ≥ 4, and over 80% had HAS-BLED scores ≥ 3, indicating a high risk of stroke and bleeding. For apixaban, dabigatran and rivaroxaban patients, 50%, 37% and 51% had lower dosage regimens, respectively (Table S3).

The unadjusted incidence rate of stroke/SE—including ischaemic stroke, haemorrhagic stroke and SE—was 2.2 (apixaban), 2.6 (dabigatran), 2.6 (rivaroxaban) and 3.3 (warfarin) per 100 person-years. The unadjusted incidence rate of MB—including GI bleeding, ICH and other MB—was 6.1 (apixaban), 7.0 (dabigatran), 10.2 (rivaroxaban) and 9.4 (warfarin) per 100 person-years, respectively (Table S3).

After 1:1 PSM, a total of 34 594 apixaban-warfarin, 9263 dabigatran–warfarin, 39 898 rivaroxaban–warfarin, 9170 apixaban–dabigatran, 34 138 apixaban–rivaroxaban, and 9235 dabigatran–rivaroxaban PSM pairs were matched. The mean age was 83–84 years for the matched cohorts, and the mean follow-up time was 6–8 months. All baseline variables included in the PSM logistic models were balanced with standardized differences <10% (Tables S4 and S5).

NOAC–warfarin comparisons

Amongst elderly frail NVAF patients, apixaban (hazard ratio [HR]: 0.61, 95% CI: 0.55–0.69), and rivaroxaban use (HR: 0.79, 95% CI: 0.72–0.87) were associated with a lower risk of stroke/SE compared with warfarin. Ischaemic stroke was the most prevalent type of stroke/SE, with a lower risk in apixaban and rivaroxaban patients compared with warfarin patients. Apixaban, dabigatran and rivaroxaban were associated with a lower risk of haemorrhagic stroke vs warfarin (Fig. 2a).

Regarding MB, apixaban (HR: 0.62, 95% CI: 0.57–0.66) and dabigatran (HR: 0.79, 95% CI: 0.70–0.89) were associated with a lower risk compared with warfarin. Rivaroxaban (HR: 1.14, 95% CI: 1.08–1.21) was associated with a higher risk of MB compared with warfarin. Likewise, apixaban was associated with a lower risk, and rivaroxaban was associated with a higher risk of GI bleeding (the most prevalent type of MB) compared with warfarin. All NOACs were associated with a lower risk of intracranial haemorrhage vs warfarin (Fig. 2a).

NOAC-NOAC comparisons

Apixaban patients had a similar risk of stroke/SE (HR: 0.83, 95% CI: 0.66-1.06) compared to dabigatran patients and a lower risk of stroke/SE compared to rivaroxaban (HR: 0.80, 95% CI: 0.70–0.90). Dabigatran patients were associated with a similar risk of stroke/SE compared to rivaroxaban (HR: 1.03, 95% CI: 0.83–1.28; Fig. 2b).

Compared to dabigatran (HR: 0.73, 95% CI: 0.63–0.85) and rivaroxaban (HR: 0.53, 95% CI: 0.50–0.57), apixaban was associated with a lower risk of MB and GI bleeding (HR: 0.61, 95% CI: 0.50–0.76 and HR: 0.46, 95% CI: 0.42–0.50, respectively). Compared to rivaroxaban, dabigatran was associated with a lower risk of MB and GI bleeding (HR: 0.71, 95% CI: 0.63–0.80 and HR: 0.77, 95% CI: 0.66–0.89; Fig. 2b).

The Kaplan–Meier curves for cumulative incidence of stroke/SE and MB in the matched populations appear in Fig. 3a and b.

All-cause mortality in the CMS population

In the CMS Medicare population, all NOACs were associated with a lower risk of all-cause mortality compared with warfarin: apixaban (HR: 0.69, 95% CI: 0.65-0.73), dabigatran (HR: 0.70, 95% CI: 0.63-0.78) and rivaroxaban (HR: 0.84, 95% CI: 0.80-0.89). Apixaban was associated with a lower risk of

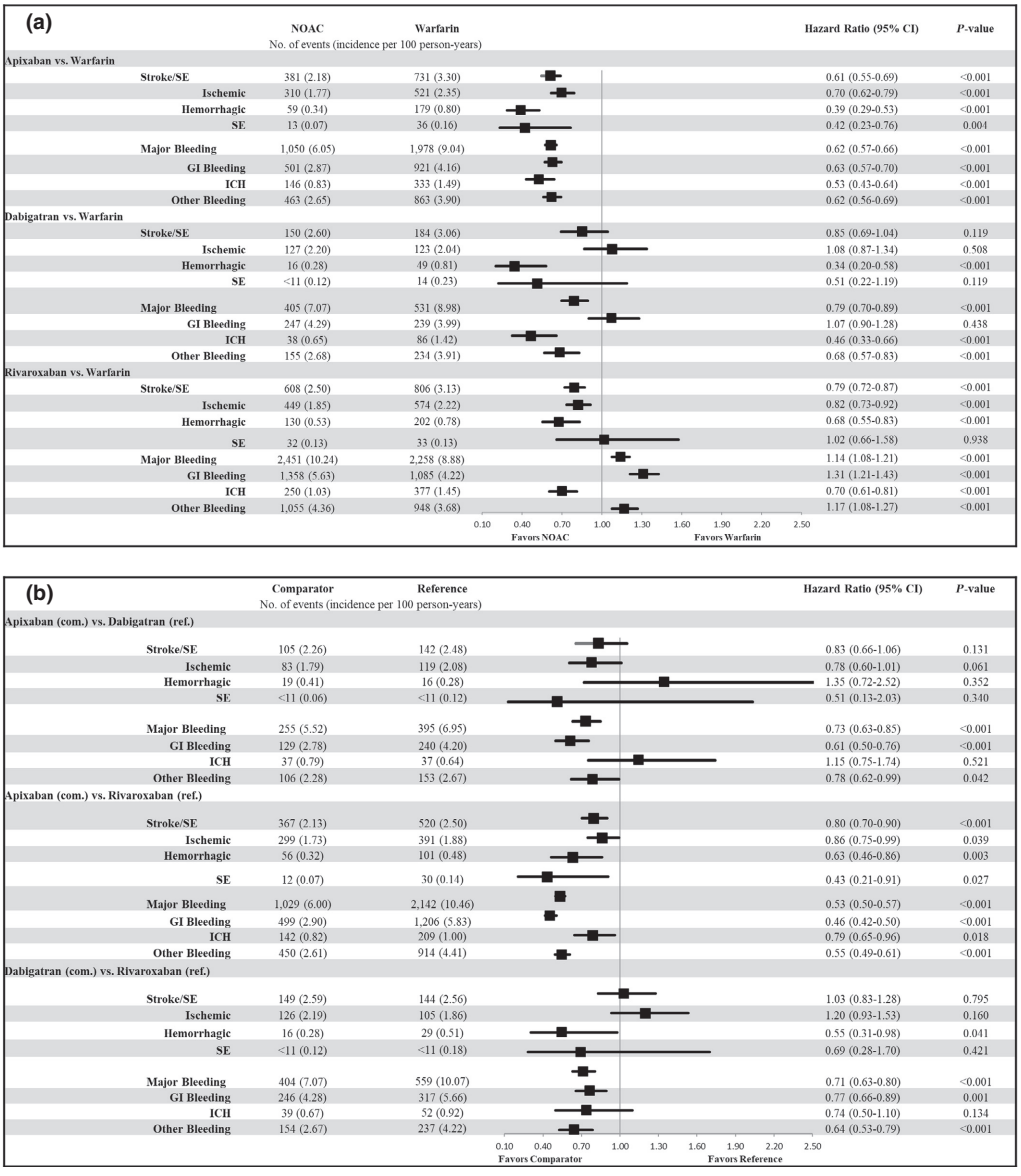

Fig. 2 *(a) Propensity Score-Matched Incidence Rates and Hazard Ratios of Stroke/SE and Major Bleeding for NOAC versus Warfarin. Cox proportional hazard models with robust sandwich estimates were used to evaluate the risk of stroke/SE and major bleeding. Apixaban and rivaroxaban were associated with a lower risk of stroke/SE compared with warfarin. Apixaban and dabigatran were associated with a lower risk of major bleeding, and rivaroxaban was associated with a higher risk of major bleeding compared with warfarin. CI: confidence interval; GI: gastrointestinal; ICH: intracranial haemorrhage; NOAC: nonvitamin K antagonist oral anticoagulant; SE: systemic embolism. (b) Propensity Score-Matched Incidence Rates and Hazard Ratios of Stroke/SE and Major Bleeding for NOAC Comparisons. Cox proportional hazard models with robust sandwich estimates were used to evaluate the risk of stroke/SE and major bleeding and demonstrated that apixaban has a lower risk of stroke/SE compared with rivaroxaban and both dabigatran and apixaban have a lower risk of major bleeding compared with rivaroxaban. In addition, apixaban had a lower risk of major bleeding compared with dabigatran. CI: confidence interval; GI: gastrointestinal; ICH: intracranial haemorrhage; NOAC: nonvitamin K antagonist oral anticoagulant; SE: systemic embolism.*

all-cause mortality compared with rivaroxaban (HR: 0.82, 95% CI: 0.78-0.87). There was no significant difference between apixaban vs dabigatran and dabigatran vs rivaroxaban for all-cause mortality (Figure S1).

Dose subgroup analysis

Results from the subgroup analysis by dose showed generally consistent trends with the main results for standard and low doses (Figure S2).

Discussion

This subgroup analysis of ARISTOPHANES study showed that amongst frail NVAF patients, apixaban and rivaroxaban use were associated with lower risk of stroke/SE when compared with warfarin use. Further, apixaban and dabigatran were associated with a lower risk of MB, and rivaroxaban was associated with a higher risk compared with warfarin. In the elderly frail CMS Medicare population, all NOACs were associated with a lower risk of all-cause mortality compared with warfarin.

Frail NVAF patients are more susceptible to stroke/SE and MB due to multimorbidity, polypharmacy and low weight [1]. The frailty index, a prognostic tool increasingly recognized by physicians, can be created using diagnosis and procedure codes from claims data [23]. There are 2 commonly used frailty indices: the Frailty Phenotype (Fried) and Frailty Index (accumulation of deficits; Mitnitski and Rockwood) [14, 24, 25]. As mentioned, the Fried model is based on 5 conditions, and the Rockwood Index is based on a cumulative deficit of items and presented as a proportion. The Fried model and the Rockwood Index have been shown to have common characteristics, and both accurately predict adverse outcomes [26-28]. The Johns Hopkins Claims-based Frailty Indicator used in this study was developed by Segal et al. based on the Fried model, which has been vigorously validated and is the most widely used frailty instrument [15].

Frailty status is positively associated with CHA_2DS_2-VASc and HAS-BLED scores, which suggest that frail patients are likely to receive a greater benefit from stroke prevention but potential higher risk of bleeding by taking anticoagulants [29]. However, the data support the use of OACs amongst frail elderly NVAF patients, as the benefits outweigh the risks [11]. Compared to nonfrail patients, frail AF patients were found to have higher incidence of stroke and death but not MB [30-32]. However, despite the increased risk of stroke and death, frailty is amongst the most common reasons to withhold OAC therapy [8, 33]. Frail AF patients were reported to be significantly less likely to use warfarin than nonfrail patients upon hospital admission and discharge across geriatric medicine, general medicine and cardiology services [8]. Several challenges have been recognized in the administration of warfarin amongst frail patients, for example required monitoring of time in therapeutic range, reduced mobility and risk of falls [34]. NOACs, conversely, are favourable treatment alternatives to warfarin, due to fixed dosing, steady pharmacokinetics and no requirement for coagulation monitoring [34]. Moreover, clinical trials have demonstrated NOACs have noninferior rates of stroke/SE and MB compared with warfarin [35-37], and these trends are consistent amongst older (≥75 years) NVAF patients [38-40]. However, no clinical trials comparing NOACs vs warfarin have been conducted specifically amongst frail NVAF patients, who are also under-represented in clinical trials.

A few real-world studies have examined the comparative effectiveness and safety outcomes of NOACs and warfarin use amongst the frail NVAF population [41, 42]. Martinez et al. conducted a retrospective claims study using the US IBM Watson MarketScan data from November 2011 through December 2016. This study examined the risks of stroke/SE and MB between each NOAC (apixaban $n = 1392$; dabigatran $n = 1{,}350$; rivaroxaban $n = 2635$) and warfarin amongst frail NVAF patients based on the Johns Hopkins Claims-based Frailty Indicator [41]. With a follow-up of ≤2 years, compared to warfarin, apixaban and dabigatran were associated with similar risk of stroke/SE and MB. Compared with warfarin, rivaroxaban was associated with a lower risk of stroke/SE and a similar risk of MB. Another study of 122 AF patients with self-rated frailty conditions showed that NOACs had similar cumulative rates of bleeding events and stroke/SE vs warfarin [42]. Using pooled claims data and the entire follow-up period, the present study provided a larger sample size, hence statistical power, to compare effectiveness and safety between NOACs and warfarin amongst frail NVAF patients. Moreover, it conducted dose subgroup analyses. To the best of the study authors' knowledge, this report to date

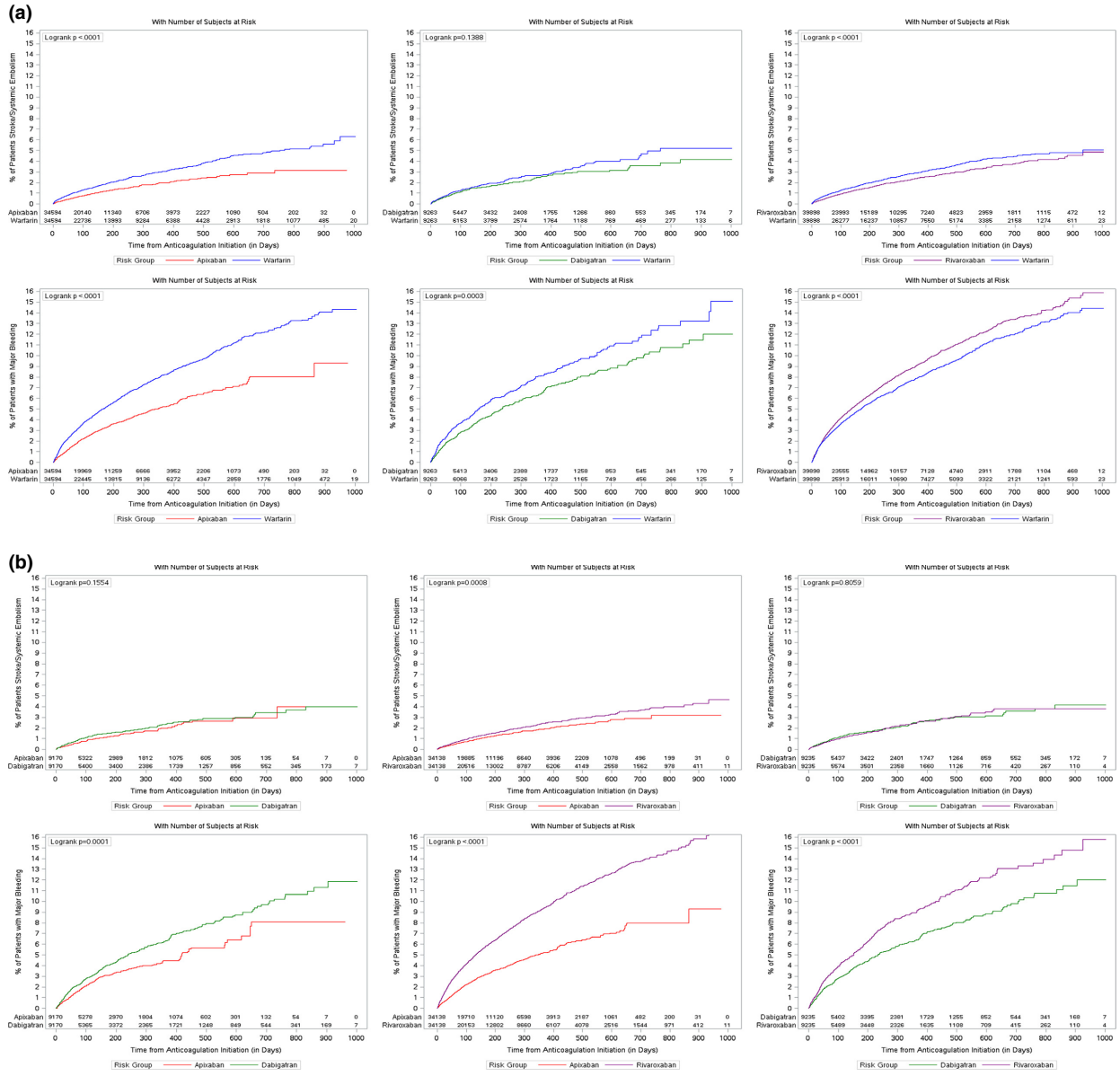

Fig. 3 *(a) Cumulative Incidence of Stroke/SE and Major Bleeding in NOAC–Warfarin Propensity Score-Matched Cohorts. Kaplan–Meier curves were used to compare the cumulative incidence of stroke/SE and major bleeding between NOACs and warfarin. (b) Cumulative Incidence of Stroke/SE and Major Bleeding in NOAC-NOAC Propensity Score-Matched Cohorts. Kaplan–Meier curves were used to compare the cumulative incidence of stroke/SE and major bleeding between NOACs.*

represents the largest cohort of frail patients treated with NOACs.

Limitations

This study does have several limitations. Given the nature of retrospective observational studies, no causal relationships can be examined. In addition, the datasets engender certain specific limitations. For example, potential residual confounders such as over-the-counter aspirin use, serum creatinine/creatinine clearance and laboratory values are unavailable and therefore may introduce bias. Moreover, age is top-coded in several datasets:

the maximum age in PharMetrics is 84 years, and the maximum age in Optum and Humana is 89 years. Patients older than these thresholds are set to the maximum age due to privacy concerns; this may have led to underestimation of age and, hence, the frailty score. Besides age, complete mortality information is only available in the CMS data; for the commercial datasets, only inpatient deaths can be assessed. With CMS data contributing to the majority of the study patient population, potential, but minimal, bias may have been introduced into our analysis. Further, since International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes were used to identify the diagnoses and procedures, some variables in the datasets may lack clinical accuracy. Additionally, although dose monitoring for warfarin and a lower dose for NOACs is available, the lack of information on weight and laboratory data (e.g. time in therapeutic range and renal function) precluded evaluation of anticoagulation quality or label-adherent dosing. Nevertheless, by including patients with potentially poor-quality OAC treatment, especially for warfarin, this study may reflect real-world clinical practice [43]. Future studies may investigate the impact of inappropriate OAC dosing on clinical outcomes to further inform clinical practice. Also, the definition and cut-off for frailty used in this study (developed by Segal et al.) were reported to provide a sensitivity of 35% and a specificity of 91%, which whilst accurate, still has potential for some misclassification of frail patients [15]. Reversal agents were not available at the time of the study; therefore, the impact of licensed antidotes for patients with life-threatening bleeding or requiring urgent surgery was not evaluated. Whilst our study represents a comprehensive real-world retrospective claims study amongst older frail NVAF patients comparing NOACs and warfarin, as well as each NOAC to each other, more studies are needed to better comprehend anticoagulant efficacy and safety in specific subpopulations.

Conclusion

Amongst elderly frail NVAF patients, apixaban and rivaroxaban were associated with lower risk of stroke/SE and NOACs were associated with varying comparative risks of major bleeding compared with warfarin. We also found that apixaban was associated with a lower risk of stroke/SE compared with rivaroxaban. Apixaban was associated with a lower risk of MB compared with dabigatran and rivaroxaban, and dabigatran had a lower risk of MB compared with rivaroxaban. This is one of the first real-world studies to compare NOACs in the elderly frail NVAF population; the results may facilitate decision-making regarding OACs in frail patients.

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Conflict of interest

GYHL is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi Sankyo, and Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim and Daiichi Sankyo. No fees are directly received personally. **AVK** is an employee of STATinMED Research (a paid consultant to Pfizer and Bristol-Myers Squibb Company). **AK, XL, AD, NB, LR, XP** and **ABGR** are employees of Bristol-Myers Squibb Company. **XL, MDF** and **JM** are employees of Pfizer Inc. **SD** consults for Bristol-Myers Squibb Company/Pfizer Inc., Daiichi Sankyo, Portola and Boehringer Ingelheim, and has been on the speakers' bureau for Bristol-Myers Squibb Company/Pfizer Inc., and Boehringer Ingelheim. All authors fully meet ICMJE criteria for authorship and take full responsibility for this paper.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Frailty Indicator Score.

Table S2. ICD-9-CM Codes for stroke/systemic embolism and major bleeding.

Table S3. Baseline characteristics and outcomes for pre-matched apixaban, dabigatran, rivaroxaban, and warfarin patients.

Table S4. PSM-adjusted baseline characteristics (Warfarin as the Reference).

Table S5. PSM-adjusted baseline characteristics (NOAC Comparisons).

Figure S1. Propensity score-matched incidence rates and hazard ratios of all-cause mortality in the CMS population.

Figure S2. Propensity score-matched incidence rates and hazard ratios of stroke/SE and major bleeding for dose subgroup analysis.

