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Risk Levels and Adverse Clinical Outcomes Among Patients With Nonvalvular Atrial Fibrillation Receiving Oral Anticoagulants

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Abstract

IMPORTANCE The CHA₂DS₂-VASc score (calculated as congestive heart failure, hypertension, age 75 years and older, diabetes, stroke or TIA, vascular disease, age 65 to 74 years, and sex category) is the standard for assessing risk of stroke and systemic embolism and includes age and thromboembolic history. To our knowledge, no studies have comprehensively evaluated safety and effectiveness outcomes among patients with nonvalvular atrial fibrillation receiving oral anticoagulants according to independent, categorical risk strata.

OBJECTIVE To evaluate the incidence of key adverse outcomes among patients with nonvalvular atrial fibrillation receiving oral anticoagulants by CHA₂DS₂-VASc risk score range, thromboembolic event history, and age group.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was a retrospective claims data analysis using combined data sets from 5 large health claims databases. Eligible participants were adult patients with nonvalvular atrial fibrillation who initiated oral anticoagulants. Data were analyzed between January 2012 and June 2019.

EXPOSURE Initiation of oral anticoagulants.

MAIN OUTCOMES AND MEASURES We observed clinical outcomes (including stroke or systemic embolism, major bleeding, and a composite outcome) on treatment through study end, censoring for discontinuation of oral anticoagulants, death, and insurance disenrollment. The population was stratified by CHA₂DS₂-VASc risk score; history of stroke, systemic embolism, or transient ischemic attack; and age groups. We calculated time to event, incidence rates, and cumulative incidence for outcomes.

RESULTS We identified 1 141 097 patients with nonvalvular atrial fibrillation; the mean (SD) age was 75.0 (10.5) years, 608 127 patients (53.3%) were men, and over 1 million were placed in the 2 highest risk categories (high risk 1, 327 766 participants; high risk 2, 688 449 participants). Deyo-Charlson Comorbidity Index scores ranged progressively alongside CHA₂DS₂-VASc risk score strata (mean [SD] scores: low risk, 0.4 [1.0]; high risk 2, 4.1 [2.9]). The crude incidence of stroke and systemic embolism generally progressed alongside risk score strata (low risk, 0.25 events per 100 person-years [95% CI, 0.18-0.34 events]; high risk 2, 3.43 events per 100 person-years [95% CI, 3.06-4.20 events]); patients at the second-highest risk strata with thromboembolic event history had higher stroke incidence vs patients at the highest risk score strata without event history (2.06 events per 100 person-years [95% CI, 2.00-3.12 events] vs 1.18 events per 100 person-years [95% CI, 1.14-1.30 events]). Major bleeding and composite incidence also increased progressively alongside risk score strata (major bleeding: low risk, 0.68 events per 100 person-years [95% CI, 0.56-0.82 events]; high risk 2, 6.29 events per 100 person-years [95% CI, 6.21-6.62 events]; composite incidence: 1.22

(continued)

Key Points

Question What are the relative safety and effectiveness outcomes among patients with nonvalvular atrial fibrillation receiving anticoagulants by CHA₂DS₂-VASc risk score range, thromboembolic event history, and age group?

Findings In this cohort study including data from more than 1 million patients, the observed incidence of stroke, systemic embolism, and major bleeding events generally conformed to an expected increasing incidence by risk score.

Meaning These results suggest that the assessment of individual baseline risk profiles can better inform clinical decision-making, research, and policy for this patient population.

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Abstract (continued)

events per 100 person-years [95% CI, 1.06-1.41 events]; high risk 2, 10.67 events per 100 person-years [95% CI, 10.26-11.48 events]). The 12-month cumulative incidence proportions for stroke and systemic embolism, major bleeding, and composite outcomes progressed alongside risk score strata (stroke or systemic embolism, 0.30%-1.85%; major bleeding, 0.55%-5.55%; composite, 1.05%-8.23%). Age subgroup analysis followed similar trends.

CONCLUSIONS AND RELEVANCE The observed incidence of stroke or systemic embolism and major bleeding events generally conformed to an expected increasing incidence by risk score, adding insight into the importance of specific risk score range, thromboembolic event history, and age group strata. These results can help inform clinical decision-making, research, and policy.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the US, currently estimated to affect up to 6 million people and a projected 12 million by 2030.^{1,2} The risk of AF rises with age, with a sharp increase at ages 60 to 69 years and progressive increases for ages 70 to 79 and 80 to 89 years.¹⁻³

Patients with AF are nearly 5 times more likely to experience stroke or systemic embolism (SE) as compared with the general population, and stroke or SE is associated with considerable morbidity, mortality, and health care costs among people living with AF—especially those aged 65 years or older.^{4,5} Other potentially debilitating conditions associated with AF include transient ischemic attack (TIA), myocardial infarction (MI), and retinal vascular occlusion (RVO).^{6,7} As with AF, risk for these conditions increases with age.⁸⁻¹⁰ TIA and MI are also independent risk factors for stroke among patients with AF.¹¹ The CHA₂DS₂-VASc score is currently the most common thromboembolism risk categorization method used for patients with AF.^{12,13} CHA₂DS₂-VASc scoring includes congestive heart failure or left ventricular dysfunction, hypertension, age 75 years or older (double-weighted), diabetes, stroke or TIA (double-weighted), vascular disease (including MI), age 65 to 74 years, and sex category (women).¹¹

Oral anticoagulants (OACs) are used for stroke prevention among patients with AF; warfarin was the standard of care until circa 2010, but newer direct OACs (DOACs) have similar effectiveness and safety profiles ranging from noninferior to superior as compared with warfarin and are now recommended for most patients.¹² All OAC therapy is complicated by some risk of major bleeding (MB), which increases at advanced ages.¹⁴ However, some clinicians may overestimate MB risk; subsequently, they may be reluctant to prescribe OACs to eligible older patients who could be exposed to unnecessary stroke risk as a result.¹⁵ Thus, it is important to monitor changes in bleeding risk as the OAC landscape continues to evolve; this is particularly true of older patients as well as those at greater risk of stroke per other CHA₂DS₂-VASc criteria.¹⁴

Several network meta-analyses and studies have evaluated safety and effectiveness among subgroups of patients with clinically relevant comorbidities. The ARISTOPHANES study also stratified results by age category and CHA₂DS₂-VASc score.¹⁶ However, CHA₂DS₂-VASc treatment guidelines for male vs female patients have since changed,¹² and there remains a dearth of data that comprehensively evaluate risk across stroke risk score ranges, thromboembolic event history, or categorical age ranges. It is unclear if the presence of multiple factors (in CHA₂DS₂-VASc risk score), other than prior stroke, would present the same estimate of future stroke risk as a prior stroke—especially for younger individuals. An estimate of differences in risk of future stroke risk by such risk stratifications may aid clinicians and policy makers in identifying more specific at-risk subgroups.

Thus, we undertook this retrospective analysis of a large data set from combined commercial and federal data sources to evaluate the incidence of key adverse events among patients with NVA

who initiated OACs. We categorized all included patients by CHA₂DS₂-VASc risk score ranges and further stratified results by prior stroke, SE, or TIA and age group.

Methods

Data Sources

We conducted this retrospective analysis with combined data sets from the Optum Insight Research Database (January 2012 through March 2019), Humana (January 2012 through March 2019), IQVIA LifeLink Health Plan Claims Data set (January 2012 through March 2019), IBM Watson MarketScan (January 2012 through June 2019), and US Centers for Medicare & Medicaid Services (CMS) Medicare (January 2012 through December 2017). Of note, patients with Medicare supplemental plans in MarketScan and IQVIA data were not included in the study to avoid potential duplicates with Medicare Part A and Part B. More details on the data sets have been published in previous articles.¹⁶

Both the data sets and the security of the offices where analysis was completed (and where the data sets are kept) met the requirements of the Health Insurance Portability and Accountability Act of 1996. Solutions IRB determined this study to be exempt from the Office for Human Research Protections Regulations for the Protection of Human Subjects (45 CFR 46) under 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. The HIPAA Authorization Waiver was granted in accordance with the specifications of 45 CFR 164.512(i). This project was conducted in full accordance with all applicable laws and regulations, and adhered to the project plan that was reviewed by Solutions IRB. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

We identified all medical claims with *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*, and *ICD-10 Procedural Coding System* diagnosis and procedure codes as well as Health Care Common Procedure Coding System and *Current Procedural Terminology* codes.

Patient Selection

We included adult patients (as of the index date) with 1 or more claims for an OAC prescription (warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban) during the identification period (January 2013 through June 2019). The first OAC prescription during the identification period was defined as the index date. We further required patients who had 1 or more claims with an AF diagnosis (*ICD-9* code, 427.31; *ICD-10*, I480-I482, I4891) prior to or on the index date. To evaluate baseline demographic and clinical characteristics, we also required patients to have 12 or more months of health plan enrollment with medical and pharmacy benefits prior to the index date (baseline period). We excluded patients with evidence of rheumatic mitral valvular heart disease, heart valve replacement or transplantation, venous thromboembolism, or transient AF (within 12 months prior to or on the index date); hip or knee replacement or transplantation (within 6 weeks prior to the index date); pregnancy during the study period; or 1 or more previous OAC prescriptions during the 12 months prior to the index date. Patients with a follow-up time of zero days and those with more than 1 OAC prescription claim on the index date were also excluded. To isolate time on treatment, we observed patients from the day after the index date through the earliest of OAC discontinuation, death, disenrollment, or study end (eTable 1 in the [Supplement](#)).

Baseline Characteristics

We evaluated baseline demographic and clinical characteristics for the overall sample and for risk strata defined by mean CHA₂DS₂-VASc score on the index date as follows: low risk (men, 0; women,

1); moderate risk (men, 1; women, 2); high risk 1 (men, 2 to 3; women, 3); and high risk 2 (men and women, 4 or more). The CHA₂DS₂-VASc risk scores were calculated based on the presence (or absence) of individual components during the 12 months prior to and on the index date. Within risk groups, we further stratified results by age group (18 to 54, 55 to 64, 65 to 74, and 75 years or older); baseline stroke, SE, or TIA history (those with an event history vs no event history, which may also be viewed as secondary vs primary prevention strategy); sex (men, women); and baseline stroke, SE, or TIA history. We captured age, sex, and Deyo-Charlson comorbidity index (CCI) score on the index date as well as key comorbidities and baseline medications of interest during the 12 months prior to and on the index date (eTable 2 in the [Supplement](#)).

Outcomes

For the overall sample and within each strata of interest, we reported crude incidence rates for stroke or SE, MB, TIA, RVO, MI, and a composite of all outcomes. We also reported cumulative incidence for stroke or SE, MB, and composite outcomes. The outcomes were defined by hospitalization with a primary diagnosis of the respective outcomes (eTable 3 in the [Supplement](#)).

Statistical Analysis

We described baseline demographic and clinical characteristics with standard summary statistics, with numbers and percentages reported for categorical variables and means, medians, standard deviations (SDs) and with interquartile ranges reported for continuous variables. Because not all of the databases have race included as a variable, race and ethnicity were not a part of the study. We evaluated cohort differences in categorical and binary variables using the χ^2 test or Fisher exact test and compared continuous variables using the Student *t* test or Wilcoxon rank sum test. We presented clinical outcome incidence rates per 100 person-years (PY) overall and within risk score, age, and event history strata—calculated as the number of patients with events of interest divided by time at risk for developing the event (multiplied by 100). Unadjusted Kaplan-Meier survival curves were generated to evaluate the cumulative incidence of the outcomes. The a priori significance level of 2-sided *P* < .05 was used to perform the analysis. All analysis was conducted with statistical software SAS version 9.4 (SAS Institute Inc).

Results

After applying the inclusion and exclusion criteria, we included 1 141 097 patients with NVAf who initiated an OAC. Among the overall study population, we categorized 29 298 (2.6%) as low risk, 95 584 (8.4%) as moderate risk, 327 766 (28.7%) as high risk 1, and 688 449 (60.3%) as high risk 2 ([Figure 1](#)).

Baseline Patient Characteristics

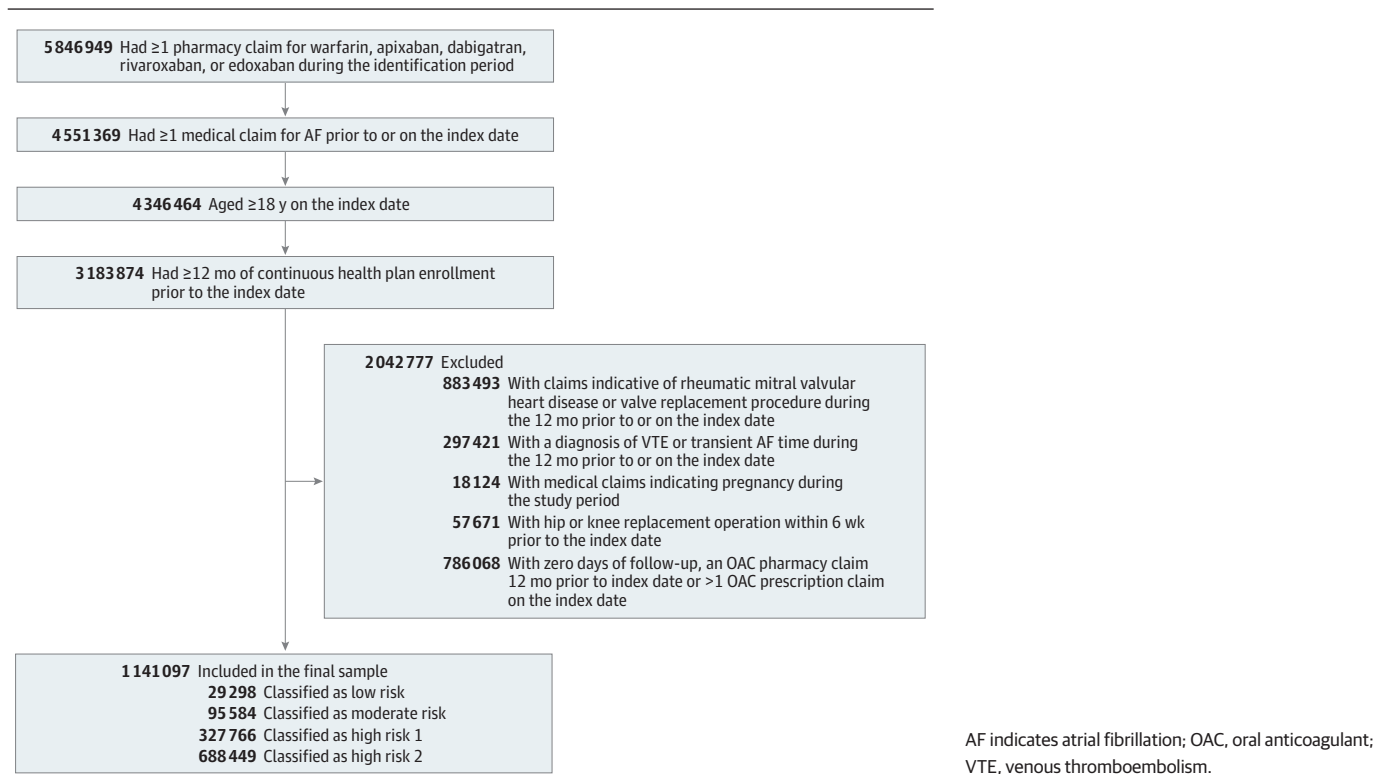
The mean (SD) age in the overall sample was 75.0 (10.5) years, with a notable divergence between the low risk (53.9 [8.8] years) and moderate risk (53.9 [8.5] years) vs high risk 1 (71.9 [9.1] years) and high risk 2 (79.0 [8.3] years) cohorts. The majority (608 127 [53.3%]) of patients in the overall sample were men; trends generally aligned among risk cohorts, with the exception of the high risk 2 cohort, which was majority women (408 895 [59.4%]). The overall mean (SD) Deyo-CCI score was 1.6 (1.9); cohort scores ranged progressively from low risk (0.4 [1.0]) to high risk 2 (4.1 [2.9]). The most common comorbidity overall was hypertension (964 137 [84.5%]), followed by coronary artery disease (487 047 [42.7%]), diabetes (410 617 [36.0%]), anemia and coagulation defects (330 848 [29.0%]), and congestive heart failure (328 219 [28.8%]); proportions increased progressively with stroke risk ranges across all comorbidities ([Table 1](#)). DOAC treatment was more common than warfarin (794 670 [69.7%] vs 346 427 [30.3%]), but warfarin proportions increased progressively with risk score range (low risk, 4088 of 29 298 [14.0%] to high risk 2, 235 145 of 688 449 [34.2%]). Trends among patients with and without prior stroke or TIA within the high risk 1 and high risk 2

cohorts followed generally similar trends, but the high risk 2 cohort with prior stroke, SE, or TIA had a higher comorbidity burden (eTable 4 in the Supplement).

Event Incident Rates

The incidence rates for stroke and SE among the overall population were 1.31 events per 100 PY (95% CI, 1.29-1.34 events) and ranged from 0.25 events per 100 PY (95% CI, 0.18-0.34) for individuals with low risk and no stroke, SE, or TIA event history to 3.43 per 100 PY (95% CI, 3.06-4.20) for individuals in the high risk 2 group with thromboembolic event history. MB incidence rates among the overall population were 4.08 events per 100 PY (95% CI, 4.04-4.12) and ranged from 0.68 per 100 PY (95% CI, 0.56-0.82) for individuals in the low risk group with no stroke, SE, or TIA event history to 6.29 per 100 PY (95% CI, 6.21-6.62) for individuals in the high risk 2 group with event history. Composite incidence rates among the overall population were 6.15 events per 100 PY (95% CI, 6.10-6.20) and ranged from 1.22 per 100 PY (95% CI, 1.06-1.41) for individuals with low risk and no stroke, SE, or TIA event history to 10.67 per 100 PY (95% CI, 10.26-11.48) for individuals in the high risk 2 group with event history. Rates for TIA, RVO, and MI followed similar predominantly progressive trends (Table 2). Incidence rates among age groups followed similar, predominantly progressive increasing trends by risk score, but incidence rates tended to peak with patients aged 55 to 64 years for the majority of end points. Notable exceptions were stroke incidence among patients in the high risk 1 group with event history, which peaked with patients aged 18 to 54 years (4.19 per 100 PY; 95% CI, 2.89-6.06 per 100 PY), and MB incidence among patients in the high risk 2 group with event history, which peaked with patients aged 75 years or older (6.89 per 100 PY; 95% CI, 6.70-7.09 per 100 PY) (eTable 5 in the Supplement). Stroke incidence rates stratified by gender also followed progressively increasing trends by risk score. Men with low and high risk 1 scores had higher incidence rates compared with women. Among patients with high risk 2 scores, women had higher incidence rates compared with men (eTable 6 in the Supplement).

Figure 1. Patient Selection Criteria



Cumulative Incidence

From OAC initiation, the 12-month cumulative incidence of stroke or SE ranged from 0.30% (low risk) to 1.85% (high risk 2). The 12-month cumulative incidence of MB ranged from 0.55% (low risk) to 5.55% (high risk 2). The 12-month cumulative incidence composite outcomes ranged from 1.05% (low risk) to 8.23% (high risk 2) (Figure 2). The cumulative incidence of TIA, MI, and the composite outcome for the high risk 1 and high risk 2 cohorts stratified by prior stroke, SE, and TIA is illustrated in the eFigure in the Supplement.

MB incidence rates among the patients in the high risk 1 group without stroke, SE, or TIA event history were higher than patients in that group with event history (2.17 per 100 PY vs 1.63 per 100 PY), and MI incidence followed directionally with a more pronounced relative difference (0.51 per 100 PY vs 0.27 per 100 PY). Given that mean Deyo-CCI scores were similar between the subgroups, these findings may be attributable to difference in mean ages and age group distribution (no history: mean [SD] age, 72.1 [9.0] years with 275 161 patients [85.4%] aged 65 years and older vs with history: mean [SD] 59.8 [8.4] years with 1299 patients [22.9%] aged 65 to 74 years and no patients older

Table 1. Demographics and Clinical Characteristics of OAC-Treated Patients With NVAf, by Risk Cohort

| Baseline characteristics | Patients, No. (%) | | | | |
|---|-------------------------|-------------------------------|------------------------------------|--|--|
| | Overall (N = 1 141 097) | Low (n = 29 298) ^a | Moderate (n = 95 584) ^a | High risk 1 (n = 327 766) ^a | High risk 2 (n = 688 449) ^a |
| Age, y | | | | | |
| Mean (SD) | 75.0 (10.5) | 53.9 (8.8) | 53.9 (8.5) | 71.9 (9.1) | 79.0 (8.3) |
| 18-54 | 43 326 (3.8) | 12 338 (42.1) | 15 451 (16.2) | 12 507 (3.8) | 3030 (0.4) |
| 55-64 | 107469 (9.4) | 16 960 (57.9) | 38 313 (40.1) | 38 799 (11.8) | 13 397 (2.0) |
| 65-74 | 379 288 (33.2) | 0 | 41 820 (43.8) | 164 998 (50.3) | 172 470 (25.1) |
| ≥75 | 611 014 (53.5) | 0 | 0 | 111 462 (34.0) | 499 552 (72.6) |
| Sex | | | | | |
| Men | 608 127 (53.3) | 21 873 (74.7) | 61 421 (64.3) | 245 279 (74.8) | 279 554 (40.6) |
| Women | 532 970 (46.7) | 7425 (25.3) | 34 163 (35.7) | 82 487(25.2) | 408 895 (59.4) |
| Deyo-Charlson Comorbidity Index, mean (SD) | 1.6 (1.9) | 0.4 (1.0) | 0.6 (1.3) | 1.6 (1.9) | 4.1 (2.9) |
| CHA ₂ DS ₂ -VASc score, mean (SD) | 4.1 (1.9) | 0.3 (0.4) | 1.4 (0.5) | 2.7 (0.5) | 5.3 (1.26) |
| HAS-BLED score, mean (SD) | 3.0 (1.4) | 0.4 (0.6) | 1.5 (0.8) | 2.5 (1.0) | 3.6 (1.2) |
| Baseline comorbidities^b | | | | | |
| Bleeding history | 216 640 (19.0) | 2020 (6.9) | 8078 (8.5) | 44 424 (13.6) | 162 118 (23.6) |
| Stroke history | 143 792 (12.6) | NA | NA | 3859 (1.2) | 139 933 (20.3) |
| Congestive heart failure | 328 219 (28.8) | NA | 2632 (2.8) | 32 607 (10.0) | 292 980 (42.6) |
| Diabetes | 410 617 (36.0) | NA | 2789 (2.9) | 68 109 (20.8) | 339 719 (49.4) |
| Hypertension | 964 137 (84.5) | NA | 46 623 (48.8) | 252 619 (77.1) | 664 895 (96.6) |
| Renal disease | 268 867 (23.6) | 434 (1.5) | 3555 (3.7) | 40 409 (12.3) | 224 469 (32.6) |
| Liver disease | 62 643 (5.5) | 760 (2.6) | 3404 (3.6) | 15 506 (4.7) | 42 973 (6.2) |
| Myocardial infarction | 149 478 (13.1) | NA | 729 (0.8) | 15 607 (4.8) | 133 142 (19.3) |
| Dyspepsia or stomach discomfort | 216 485 (19.0) | 2904 (9.9) | 10 371 (10.9) | 44 582 (13.6) | 158 628 (23.0) |
| Nonstroke or SE peripheral vascular disease | 266 533 (23.4) | NA | 896 (0.9) | 22 838 (7.0) | 242 799 (35.3) |
| TIA | 147 586 (12.9) | NA | NA | 3762 (1.2) | 143 824 (20.9) |
| Anemia and coagulation defects | 330 848 (29.0) | 1646 (5.6) | 8001 (8.4) | 57 358 (17.5) | 263 843 (38.3) |
| Alcoholism | 20 920 (1.8) | 754 (2.6) | 2500 (2.6) | 7154 (2.2) | 10 512 (1.5) |
| Peripheral artery disease | 268 438 (23.5) | NA | 896 (0.9) | 22 885 (7.0) | 244 657 (35.5) |
| Coronary artery disease | 487 047 (42.7) | 2227 (7.6) | 13 324 (13.9) | 102 552 (31.3) | 368 944 (53.6) |
| Index treatment | | | | | |
| Warfarin | 346 427 (30.3) | 4088 (14.0) | 18 505 (19.4) | 88 689 (27.1) | 235 145 (34.2) |
| DOAC ^c | 794 670 (69.7) | 25 210 (86.0) | 77 079 (80.6) | 239 077 (72.9) | 453 304 (65.8) |

Abbreviations: DOAC, direct oral anticoagulant; NA, not applicable; NVAf, nonvalvular atrial fibrillation; OAC, oral anticoagulant; SE, systemic embolism; TIA, transient ischemic attack.

^a Patients were stratified by CHA₂DS₂-VASc score on index: low (0 for men and 1 for women), moderate (1 for men and 2 for women), high risk 1 (2-3 for men and 3 for women), and high risk 2 (≥4 for men and women).

^b Comorbidities were defined using diagnosis codes in any claim position.

^c Including apixaban, dabigatran, rivaroxaban, or edoxaban.

than 75 years). Age is a well-established independent risk factor for MB as well as MI,^{9,17-21} and the average age for first MI is 65.6 years old for men and 72.0 years old for women.²²

Discussion

Our study used large, nationally representative commercial and federal data sets to comprehensively evaluate stroke and SE, MB, and other key adverse events among highly specific groups of patients with NVAf who initiated anticoagulation. Results revealed an older, mostly male study population with considerable comorbidity among those at the highest risk of stroke, which is consistent with reported general AF population characteristics and correlations between increasing age, CHA₂DS₂-VASc scores, and overall comorbidity.^{23,24} Overall crude incidence ranges across key outcomes (stroke and SE, MB) were generally consistent with unadjusted results in the preponderance of similar studies.^{16,25,26} The progressive increase of proportions of patients treated with OAC, in line with general CHA₂DS₂-VASc score ranges, was also consistent with the ARISTOPHANES study.¹⁶ Novel findings included incidence and cumulative incidence of stroke and SE, MB, and composite outcomes that predominantly increased in line with CHA₂DS₂-VASc risk score ranges, with pronounced increases in cumulative incidence across outcomes observed among the high risk 2 cohort.

Notable results included stroke and SE incidence among high risk 1 patients with stroke, SE, or TIA event history (2.06 per 100 PY), which was nearly twice that of patients in the high risk 2 group event history (1.18 per 100 PY) despite lower overall CHA₂DS₂-VASc and Deyo-CCI scores (1.9 vs 3.8) among the former group. These data suggest that prior stroke, SE, or TIA is a significant factor in adverse event outcomes independent of the overall CHA₂DS₂-VASc score and overall comorbidity. Although our combination of descriptive end points and highly specific subgroups preclude direct comparison at this time, these findings align directionally with data on independent risk for prior stroke and SE, which has been reported to increase the relative risk of subsequent stroke by 2.5 times as compared with no prior stroke, SE, or TIA and has remained stable over time (between 1994 and 2019).²⁷⁻²⁹

Among age group strata, overall incidence of adverse events generally tended to peak with the 55-to-64-year-old subgroup and progressively decrease at older strata. Notably, MB incidence peaked with this age group in all risk score event history strata except patients in the low risk group without event history (who had higher incidence in the age 18 to 54 years subgroup) and patients in the high risk 2 group with event history (who had the highest incidence among the age 75 years and older subgroup). This finding appears to be contrary to the abovementioned hypothesis of age distribution in MB incidence among history vs no history subgroups and is inconsistent with age cutoffs for bleeding risk in most risk assessment tools.¹⁷⁻²¹ To the best of our knowledge, there is currently no comparable clinical data that stratifies risk across the same range of age groups;

Table 2. Incidence Rates per 100 Person-Years by Risk Group and Prior Stroke, SE, or TIA

| Event | Incidence rate per 100 PY (95% CI) | | | | | | | | |
|------------------------|------------------------------------|------------------|-------|------------------|-------|------------------|-----------------------|------------------|---------------------|
| | All | Low | | Moderate | | High 1 | | High 2 | |
| | | No prior | Prior | No prior | Prior | No prior | Prior | No prior | Prior |
| Stroke | 1.31 (1.29-1.34) | 0.25 (0.18-0.34) | NA | 0.31 (0.27-0.35) | NA | 0.56 (0.54-0.60) | 2.06 (2.00-3.12) | 1.18 (1.14-1.30) | 3.43 (3.06-4.20) |
| MB | 4.08 (4.04-4.12) | 0.68 (0.56-0.82) | | 0.94 (0.87-1.02) | | 2.17 (2.11-2.22) | 1.63 (1.34-2.24) | 5.26 (5.20-5.40) | 6.29 (6.21-6.62) |
| TIA | 0.36 (0.35-0.37) | 0.10 (0.07-0.17) | | 0.11 (0.08-0.13) | | 0.15 (0.14-0.17) | 0.60 (0.41-0.96) | 0.30 (0.26-0.38) | 1.07 (1.01-1.14) |
| RVO ^a | 0.01 (0.00-0.01) | 0.01 (0.00-0.04) | | 0.00 (0.00-0.01) | | 0.00 (0.00-0.01) | 0.00 (0) ^b | 0.01 (0-0.01) | 0.01 (0-0.01) |
| MI | 0.92 (0.90-0.94) | 0.25 (0.18-0.34) | | 0.26 (0.22-0.30) | | 0.51 (0.49-0.54) | 0.27 (0.10-0.44) | 1.19 (1.16-1.24) | 1.34 (1.25-1.38) |
| Composite ^c | 6.15 (6.10-6.20) | 1.22 (1.06-1.41) | | 1.48 (1.39-1.57) | | 3.14 (3.07-3.20) | 3.97 (3.75-5.19) | 7.41 (7.31-7.72) | 10.67 (10.26-11.48) |

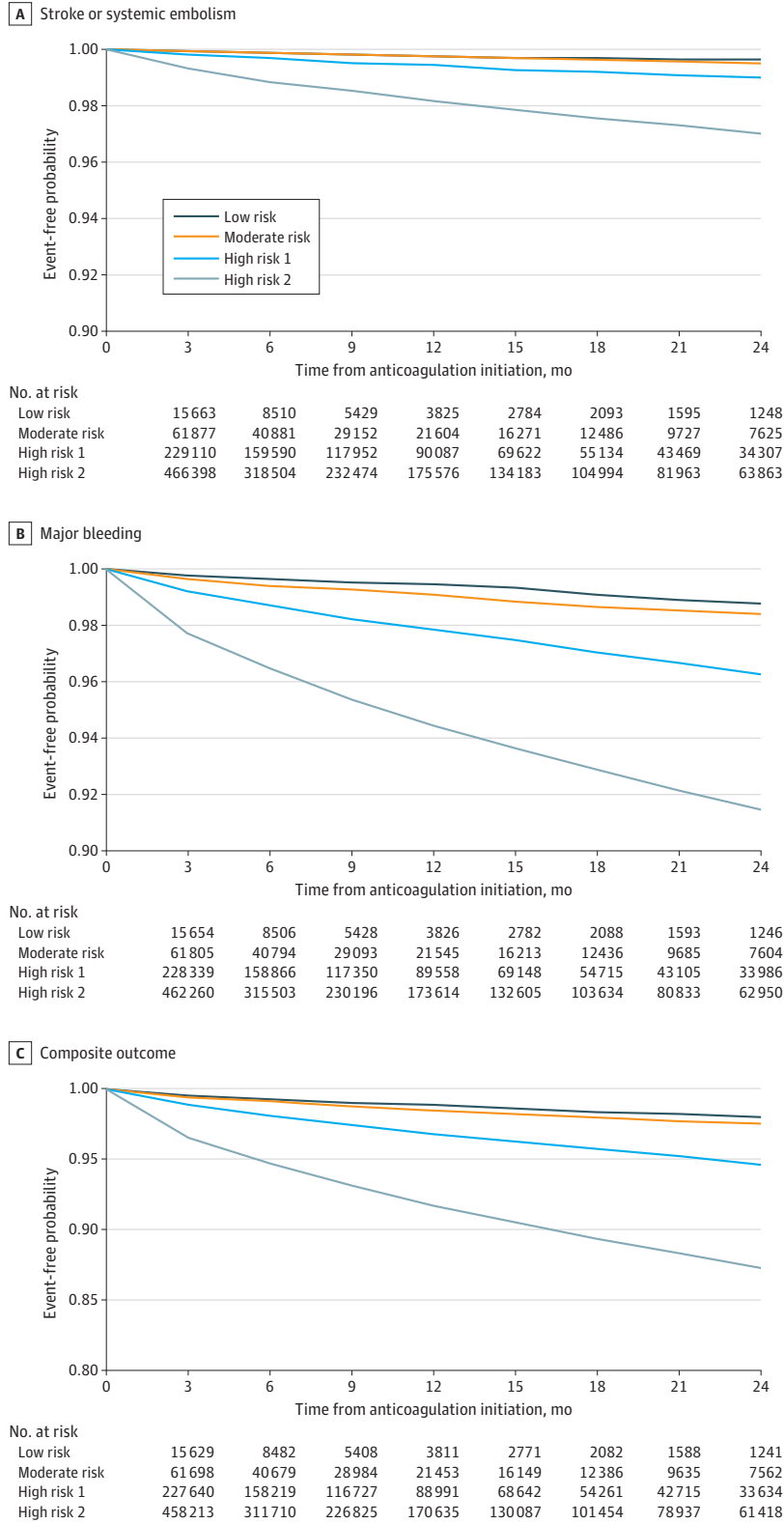
Abbreviations: MB, major bleeding; MI, myocardial infarction; PY, person-years; RVO, retinal vascular occlusion; SE, systemic embolism; TIA, transient ischemic attack.

^c The composite score was defined as having any of the events of interest (Stroke/SE, MB, TIA, RVO, or MI).

^b Could not be estimated as there were not enough events to estimate a standard error.

^c P values were significant (P < .05) for all events except RVO.

Figure 2. Cumulative Incidence for Stroke and Systemic Embolism, Major Bleeding, and Composite Events



continued research that compares risk across similarly broad age strata may be useful to clinicians considering OAC treatment for patients at advanced ages. Other unexpected results included stroke incidence among high risk 1 with event history and high risk 2 without event history, which peaked with the 18-to-54-year-old subgroup. This may be attributable to relatively low sample size among the 18-to-54-year-old high risk 1 and 2 subgroups. However, it may also suggest, apart from risk score, age, and event history, influencing factors such as dyslipidemia and tobacco use, or different weighting of factors included in the risk score, which warrants continued investigation.³⁰

In concert, these data add validation to the use of the CHA₂DS₂-VASc score for stroke risk assessment in routine practice as well as more granular data on specific score ranges. Moreover, the data suggest value in considering age and stroke, SE, and TIA history independent of—and in tandem with—stroke and bleeding risk assessment tools, which may aid more precise overall risk assessment for individual patients.

Strengths and Limitations

In addition to this novel granular approach to risk assessment, a key strength of this study is the large and comprehensive sample of patients pooled from diverse and complimentary national commercial and federal data sets. However, the data should be interpreted in the context of several limitations. As with all retrospective designs, the present study was limited to the observation of associations as opposed to inference of causality. While claims data are extremely valuable to augment randomized controlled trial results with observation of real clinical practice, all claims databases also have certain inherent limitations because claims are collected for administrative purposes and not research. For example, the presence of a claim for a filled prescription does not indicate that the medication was taken as prescribed or at all, and the presence of a diagnosis code on a medical claim does not indicate the positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease.

Limitations specific to this study include the differences between databases regarding information on concomitant use of over-the-counter medications such as aspirin or medication provided as samples. In addition, limited laboratory data availability precluded longitudinal evaluation of specific international normalized ratio values among patients treated with warfarin as well as other laboratory values such as creatinine clearance. Results should be interpreted with respect to these limitations.

Conclusions

The findings of this study for incidence of stroke or SE and MB by CHA₂DS₂-VASc risk score categories generally confirm expected increasing incidence by risk score, with more comprehensive insight into the importance of specific clinical risk factors among patients with NVAF receiving anticoagulants. These data can aid in the assessment of individual baseline risk profiles and thereby better inform clinical decision-making, research, and policy for this patient population.

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SUPPLEMENT.**eTable 1.** Inclusion and Exclusion Criteria Codes**eTable 2.** CHA₂DS₂-VASC Score Codes**eTable 3.** Clinical Outcome Diagnostic Codes**eTable 4.** Baseline Characteristics for High Risk 1 and 2 Cohorts**eTable 5.** Incidence Rates of Clinical Outcomes per 100 Person-years Stratified by Age and Risk Level**eTable 6.** Incidence Rates of Clinical Outcomes per 100 Person-years Stratified by Gender and Risk Level**eFigure.** Kaplan-Meier Plot for Primary vs. Secondary Prevention for High Risk 1 and High Risk 2 Groups