Non-persistence to Oral Anticoagulation Treatment in Nonvalvular Atrial Fibrillation Patients in the United States

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Disclosures

This study was sponsored by Bristol-Myers Squibb and Pfizer.

Conflicts of Interest: Amol Dhamane and Mauricio Ferri are paid employees of Bristol-Myers Squibb; Manuela Di Fusco, Cristina Russ and Birol Emir are paid employees of Pfizer Inc. Allison Keshishian, Cynthia Gutierrez and Wan-Lun Tsai are paid employees of STATinMED Research, which is a paid consultant to Pfizer and Bristol-Myers Squibb.

Background and Objectives

- Atrial fibrillation (AF) is a known independent risk factor for stroke.[1] Oral anticoagulants (OACs) are recommended to reduce the risk of stroke and all-cause mortality.[1]

- Randomized controlled trials and real-world studies have previously shown that direct oral anticoagulants (DOACs) were associated with similar or lower risks of stroke/systemic embolism (SE) and variable comparative risks of major bleeding (MB) versus warfarin.[2,3]

- Studies have shown that nonvalvular AF (NVAF) patients who discontinue DOACs have higher rates of thromboembolic events (5.6 vs. 2.5; $p<0.001$), major (6.1 vs. 3.7; $p=0.004$) bleeds and minor (21.2 vs. 11.1; $p<0.001$) bleeds, and continue to have higher risk of all-cause mortality (HR: 1.30; 1.02-1.67).[4]

- Previous studies have found gradual declines in persistence after the initial prescriptions, with some studies reporting a wide range of persistence from 55% to 69% after 12 months*.[5,6]

- This analysis used US commercial claims data to compare the risk of non-persistence of OACs among NVAF patients.

*Generally, non-persistence has been defined as patients either discontinuing, stopping, or switching from their OAC treatment.[5]

Methods

Data Source

- IMS PharMetrics Plus™ Database ("PharMetrics"), a US commercial claims database, covering ~40 million lives in all 50 states. The study period was 01JAN2012-31MAR2019.

Eligible Patient Criteria

- ≥1 pharmacy claim for warfarin, apixaban, dabigatran, or rivaroxaban 01JAN2013-31MAR2019.
- Aged ≥18 years with AF (ICD-9-CM: 427.31; ICD-10-CM code I480-I482) and ≥12 months continuous health plan enrollment pre-index date
- Excluded: Patients with any OAC treatment within 12 months pre-index date, evidence of valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity) or heart valve replacement/transplant during baseline period, pregnancy during study period, or hip/knee replacement surgery ≤6 weeks pre-index date, more than one OAC prescription on the index date, and less than 60 days of follow-up.

Note: Edoxaban was not included in the study given the recent FDA approval in 2015, and the hence small sample size (N = 276).

AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM: International Classification of Diseases, 9th Revision, Clinical Modification.

Methods

Statistical Methods

- Non-persistence was defined as either discontinuation or switch of index therapy during the follow-up. Follow-up was defined as time from patients' index therapy to health plan disenrollment or study end.
- The rate of non-persistence among OAC-naïve NVAF patients who initiated an OAC during the study period was calculated during the follow-up period overall and at 12 months post-index date.
- Unadjusted Kaplan-Meier survival curves were generated to illustrate time-to-non-persistence along with cumulative incidences of non-persistence.
- Cox proportional models with robust sandwich estimates were developed to evaluate non-persistence risk and predictors of non-persistence.
- Time-varying covariates (e.g., major bleeding, stroke) were included in the Cox proportional hazards models and were used to evaluate non-persistence risk.

AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant.

Variables

- ***Baseline Predictors***: Predictors of non-persistence measured at baseline.
  - Age
  - Deyo-Charlson Comorbidity Index Score
  - CHA_2DS_2-VASc Score
  - HAS-BLED Score
  - Bleeding history
  - Renal disease
  - Stroke/SE history

- ***Time-varying Predictors:*** Time-dependent predictors of non-persistence were evaluated daily during the follow-up period and included in the Cox proportional hazard ratio models.
  - Stroke/SE Hospitalization
  - Major Bleeding Hospitalization
  - New Acute Renal Failure Diagnosis
  - New Chronic Renal Failure Diagnosis
  - New Cancer Diagnosis
  - Cardioversions and Catheter Ablations

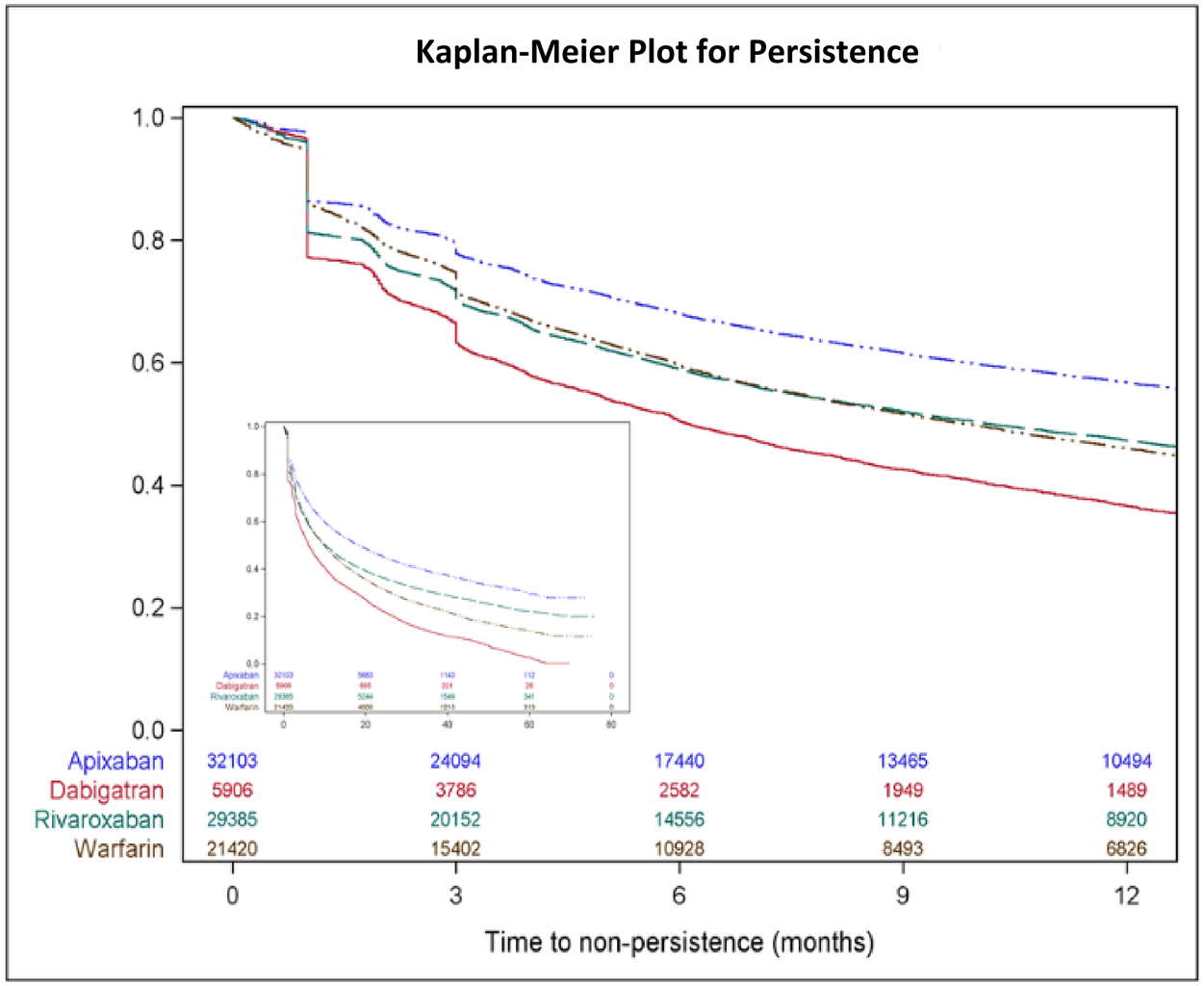
AF: atrial fibrillation; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs, and alcohol; SE: systemic embolism.

Baseline Characteristics & Outcomes

	Warfarin (N = 21,420)		Apixaban (N = 32,103)		Dabigatran (N = 5,906)		Rivaroxaban (N = 29,385)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Age	66.5	10.8	62.6	10.5	61.6	10.0	61.0	10.2
Sex								
Female	7,596	35.5%	10,397	32.4%	1,606	27.2%	8,379	28.5%
Baseline Comorbidity								
Deyo-Charlson Comorbidity Index	2.2	2.4	1.8	2.1	1.5	2.0	1.5	1.9
CHA_2DS_2-VASc Score	3.1	1.8	2.5	1.7	2.3	1.6	2.2	1.6
HAS-BLED Score	2.3	1.4	2.1	1.3	1.9	1.2	1.9	1.2
Bleeding History	3,399	15.9%	3,718	11.6%	647	11.0%	3,175	10.8%
Renal Disease	3,417	16.0%	3,840	12.0%	430	7.3%	2,185	7.4%
Acute Renal Failure	2,031	9.5%	2,095	6.5%	249	4.2%	1,286	4.4%
Chronic Renal Failure	1,516	7.1%	1,216	3.8%	138	2.3%	719	2.4%
Stroke/SE History	2,235	10.4%	2,326	7.2%	379	6.4%	1,523	5.2%
Follow-up Time (days)	770.0	614.0	523.3	445.3	805.5	613.8	683.4	557.1
Number of Prescriptions								
Patients with >1 Index OAC Prescription	18,528	86.5%	28,180	87.8%	4,596	77.8%	24,366	82.9%

CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs, and alcohol; SD: standard deviation; SE: systemic embolism.

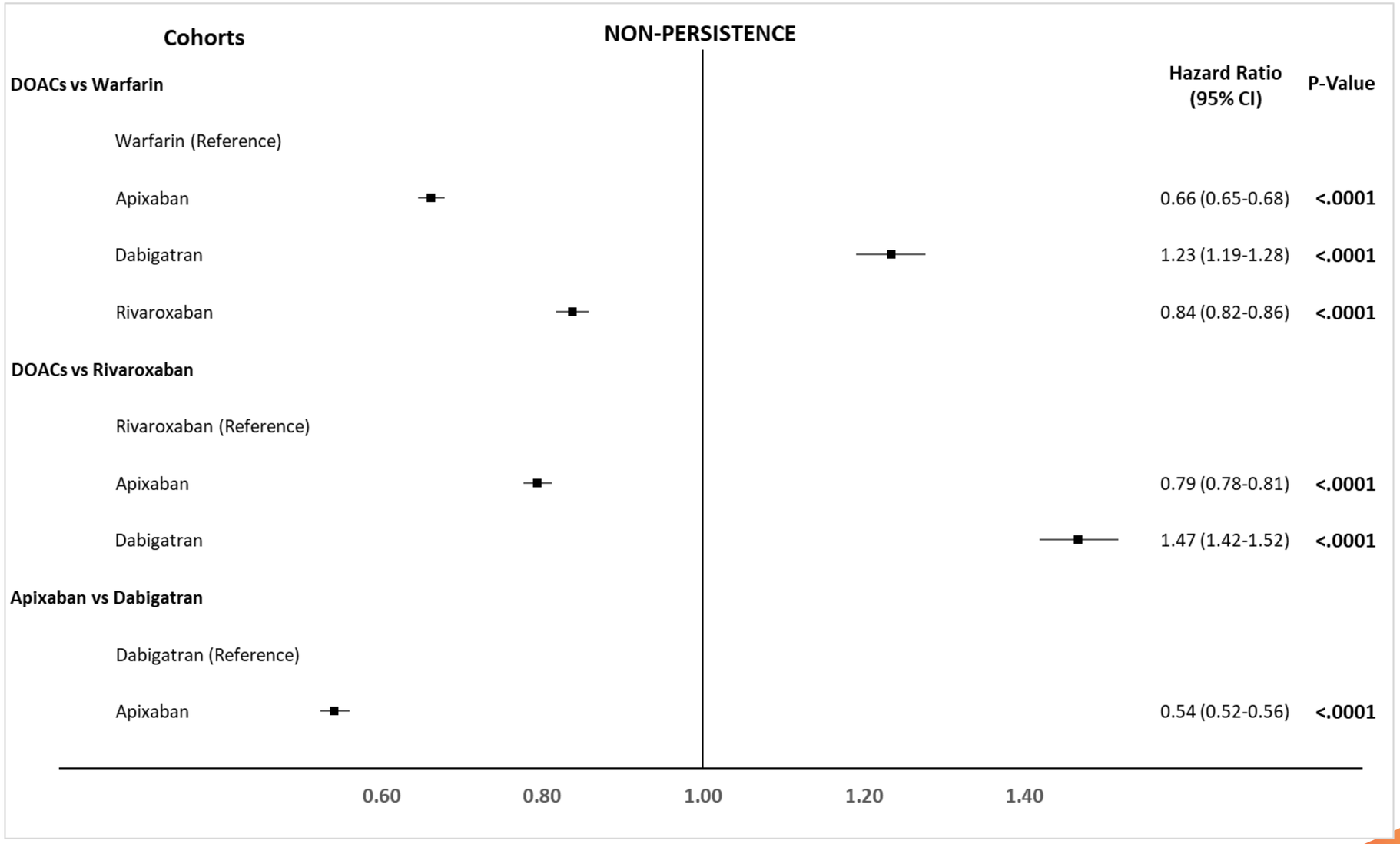
*Unadjusted Cumulative Incidence of Non-Persistence**



Cumulative Incidence of Non-Persistence	3 months	6 months	9 months	12 months
Apixaban	22.2%	32.0%	38.5%	43.2%
Dabigatran	36.8%	49.6%	57.5%	63.4%
Rivaroxaban	29.9%	41.1%	48.0%	52.7%
Warfarin	28.7%	40.5%	48.4%	54.0%

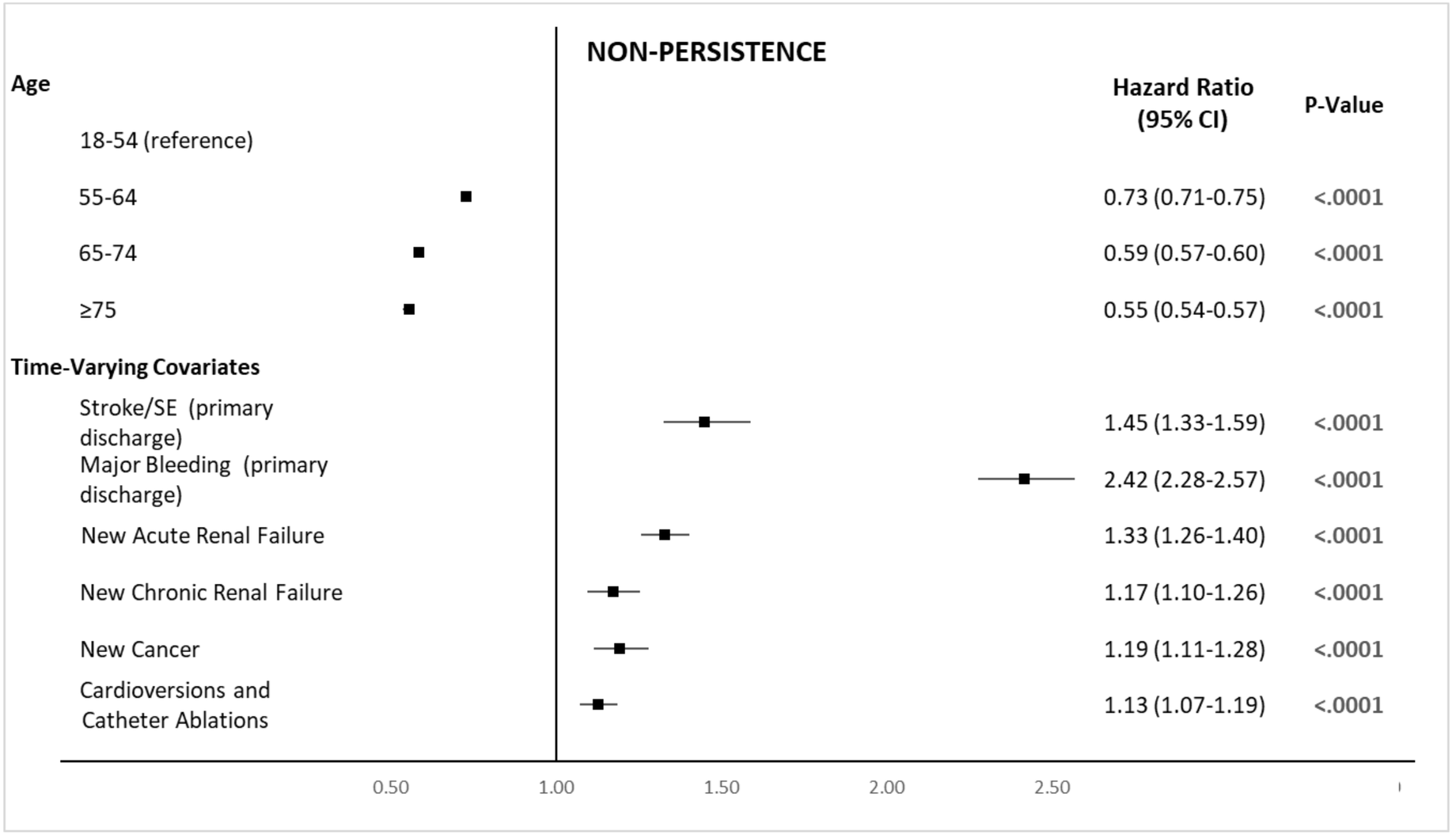
*Inset KM curve is for persistence over the entire follow-up

Cox Proportional Non-Persistence Hazard Ratios*



CI: confidence interval.
*Model adjusted for age, sex, region, AF index year, Deyo-CCI, bleeding history, history of congestive heart failure, diabetes mellitus, hypertension, renal disease, liver disease, cancer, myocardial infarction, cardioversion and catheter ablations, dyspepsia or stomach discomfort, non-stroke/SE peripheral vascular disease, stroke/SE, transient ischemic attack, anemia and coagulation defects, alcoholism, peripheral artery disease, coronary artery disease, baseline medication use, and time-varying covariates during the follow-up.

*Other Key Predictors of Non-Persistence**



CI: confidence interval; SE: systemic embolism.
*Model adjusted for age, sex, region, AF index year, Deyo-CCI, bleeding history, history of congestive heart failure, diabetes mellitus, hypertension, renal disease, liver disease, cancer, myocardial infarction, cardioversion and catheter ablations, dyspepsia or stomach discomfort, non-stroke/SE peripheral vascular disease, stroke/SE, transient ischemic attack, anemia and coagulation defects, alcoholism, peripheral artery disease, coronary artery disease, baseline medication use, and time-varying covariates during the follow-up.

Limitations

- Only associations could be concluded from this retrospective observational study.
- Given the nature of claims data, laboratory test results and biomarkers were not available. Diagnoses and drug prescriptions were identified using claims. Missing values, coding errors, and lack of clinical accuracy may have introduced bias into the study.
- This analysis evaluated demographics and clinical characteristics, not predictors related to cost or access. The results may in fact be driven by nonmedical reasons, including out-of-pocket costs, formulary changes, physician preferences, and access issues, which we are unable to capture.

Conclusion

- In this group of NVAF patients, at the end of the first 12 months of follow-up, over half of dabigatran, rivaroxaban, and warfarin patients had discontinued or switched from their index therapy

- Apixaban was associated with a significantly lower risk of non-persistence compared to warfarin, rivaroxaban, and dabigatran. Rivaroxaban was associated with a lower risk of non-persistence compared to warfarin and dabigatran.

- Age at baseline and clinical time-varying covariates were significant predictors of non-persistence, specifically older age at baseline was a significant predictor of persistence and patients with a hospitalization for a stroke or major bleeding after treatment initiation were more likely to be non-persistent.

- Such differences are critical as persistence with OACs is essential to prevent thromboembolic complications associated with NVAF.

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THANK YOU!