Evaluation of Effectiveness and Safety for Non-Valvular Atrial Fibrillation Patients Who Switched from Warfarin to Direct Oral Anticoagulants from Multiple Health Care Claims Databases

Poster 132

Gregory Y. H. Lip[1], Virginia Noxon[2], Amiee Kang[3], Xuemei Luo[4], Nipun Atreja[3], Stella Han[3], Dong Cheng[3], Jenny Jiang[3], Lisa Abramovitz[2], Steven Deitelzweig[5]

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; and the Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [2]STATinMED LLC, Dallas, Texas, USA; [3]Bristol Myers Squibb Company, New York, New York, USA; [4]Pfizer Inc., New York, New York, USA ; [5]Ochsner Clinic Foundation, Department of Hospital Medicine, New Orleans, Louisiana, USA

Introduction

- Warfarin has been shown to decrease the risk of stroke in patients with non-valvular atrial fibrillation (NVAF), but concerns remain regarding adherence and long-term safety, such as risk of bleeding[1,2]
- Direct oral anticoagulants (DOACs) provide a convenient and tolerable alternative to warfarin[3] Therefore, NVAF patients that were previously prescribed warfarin may switch to a DOAC over the course of their treatment
- There is a paucity of real-world studies examining stroke/systemic embolism and major bleeding risks among NVAF patients who switched from warfarin to a direct oral anticoagulant

Objective

- Compare the clinical effectiveness and safety outcomes (i.e., stroke/systemic embolism and major bleeding) between patients who switched from warfarin to a DOAC

Methods

Study Design/Data Source

- This pooled study was an observational retrospective cohort analysis using data from four United States 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

Patient Population

- The study population included adult NVAF patients that were initially treated with warfarin and switched to a DOAC (apixaban, dabigatran, rivaroxaban, or edoxaban [sample size too small for further analysis]) within 90 days of their warfarin prescription ending
- Full inclusion and exclusion criteria are shown in Figure 1

Study Outcomes

Stroke/Systemic Embolism (SE)

- Identified during follow-up period using hospital claims that included an ICD-9/10-CM diagnosis code for stroke/SE in the primary position
- The first stroke/SE event was further classified as ischemic stroke, hemorrhagic stroke, or SE

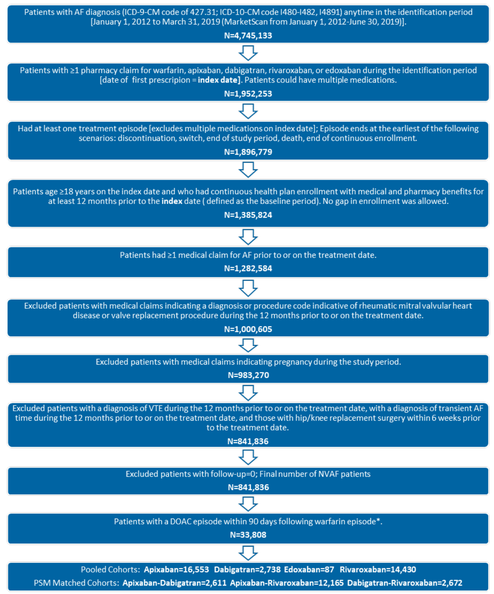
Major Bleeding

- Identified during follow-up period using hospital claims that included an ICD-9/10-CM diagnosis code for major bleeding in the primary position
- The first major bleeding event was further classified as gastrointestinal hemorrhage, intracranial hemorrhage, or major bleeding at other sites

Statistical Analysis

- Patients were matched 1:1 between DOACs (apixaban vs dabigatran, apixaban vs rivaroxaban and dabigatran vs rivaroxaban) in each database using propensity scores and then pooled for the final analysis
- Cox proportional hazards models were used to compare the risk of major bleeding and stroke between apixaban vs dabigatran, apixaban vs rivaroxaban, and dabigatran vs rivaroxaban cohorts

Figure 1. Patient Selection Criteria



AF: atrial fibrillation; DOAC: direct oral anticoagulant; OAC: oral anticoagulant; NVAF: non-valvular atrial fibrillation; PSM: propensity score matching; VTE: venous thromboembolism
* Patients were followed from the day after their index date until the earliest of switch or discontinuation of DOAC, end of enrollment, death or end of study period

Results

Patient Population

Figure 1

- After applying the selection criteria, 33,721 NVAF patients who switched from warfarin to a DOAC were retained. Of these patients, most switched to apixaban [16,553 (49.09%)] followed by rivaroxaban [14,430 (42.79%)] and dabigatran [2,738 (8.12%)]
- After applying propensity score matching, there were 2,611 apixaban-dabigatran, 12,165 apixaban-rivaroxaban, and 2,672 dabigatran-rivaroxaban pairs

Table 1

- The mean age of patients was between 70 (dabigatran-rivaroxaban) and 72 (apixaban-rivaroxaban) and patients were generally male (>55% for all cohorts)
- The mean Deyo-Charlson Comorbidity Index score ranged from 2.8 (apixaban-dabigatran and dabigatran-rivaroxaban) to 3.2 (apixaban-rivaroxaban)
- The mean CHA_2DS_2-VASc score was ~4 for all cohorts and the mean HAS-BLED score was ~2.9 for all cohorts
- Patients generally initiated DOAC within 9 days of discontinuing warfarin

Table 1. Baseline Characteristics for the PSM DOAC Comparison Cohorts

	Apixaban [N=2,611]	Dabigatran (Reference) [N=2,611]	STD	Apixaban [N=12,165]	Rivaroxaban (Reference) [N=12,165]	STD	Dabigatran [N=2,672]	Rivaroxaban (Reference) [N=2,672]	STD
Age (Mean, SD)	70.6 (12.5)	71.1 (12.5)	3.81	72.2 (12.1)	72.2 (12.2)	0.06	70.8 (12.6)	70.4 (12.2)	3.4
Gender (N, %)									
Male	1,542 (59.1%)	1,558 (59.7%)	1.25	6,904 (56.8%)	6,913 (56.8%)	0.15	1,597 (59.8%)	1,557 (58.3%)	3.04
Female	1,069 (40.9%)	1,053 (40.3%)	1.25	5,261 (43.2%)	5,252 (43.2%)	0.15	1,075 (40.2%)	1,115 (41.7%)	3.04
Baseline Scores (Mean, SD)									
Deyo-Charlson Comorbidity Index	2.8 (2.6)	2.8 (2.7)	0.10	3.2 (2.7)	3.2 (2.8)	0.37	2.8 (2.6)	2.8 (2.6)	0.37
CHA_2DS_2-VASc Score	3.8 (1.9)	3.9 (1.9)	3.58	4.0 (1.9)	4.0 (1.9)	1.91	3.8 (1.9)	3.8 (1.9)	2.65
HAS-BLED Score	2.9 (1.4)	2.8 (1.4)	0.97	2.9 (1.3)	3.0 (1.4)	0.73	2.8 (1.4)	2.8 (1.4)	0.24
Baseline Comorbidity (N, %)									
Bleeding History	669 (25.6%)	640 (24.5%)	2.56	3,051 (25.1%)	3,041 (25.0%)	0.19	644 (24.1%)	649 (24.3%)	0.44
Congestive Heart Failure (CHF)	856 (32.8%)	850 (32.6%)	0.49	4,255 (35.0%)	4,244 (34.9%)	0.19	855 (32.0%)	843 (31.5%)	0.96
Diabetes Mellitus	1,048 (40.1%)	1,064 (40.8%)	1.25	5,005 (41.1%)	5,054 (41.5%)	0.82	1,093 (40.9%)	1,102 (41.2%)	0.68
Hypertension	2,322 (88.9%)	2,306 (88.3%)	1.93	10,837 (89.1%)	10,812 (88.9%)	0.66	2,351 (88.0%)	2,344 (87.7%)	0.80
Renal Disease	618 (23.7%)	615 (23.6%)	0.27	3,236 (26.6%)	3,277 (26.9%)	0.76	605 (22.6%)	585 (21.9%)	1.80
Non-stroke/ SE Peripheral Vascular Disease	592 (22.7%)	607 (23.2%)	1.37	3,184 (26.2%)	3,177 (26.1%)	0.13	603 (22.6%)	603 (22.6%)	0.00
Anemia and Coagulation Defects	832 (31.9%)	766 (29.3%)	5.49	4,159 (34.2%)	3,970 (32.6%)	3.29	767 (28.7%)	807 (30.2%)	3.28
Peripheral Artery Disease	552 (21.1%)	599 (22.9%)	4.34	2,996 (24.6%)	3,066 (25.2%)	1.33	596 (22.3%)	583 (21.8%)	1.17
Coronary Artery Disease	1,117 (42.8%)	1,113 (42.6%)	0.31	5,301 (43.6%)	5,231 (43.0%)	1.16	1,116 (41.8%)	1,102 (41.2%)	1.06
Events During the Baseline (N, %)									
Stroke/SE Hospitalization	165 (6.3%)	168 (6.4%)	0.47	652 (5.4%)	640 (5.3%)	0.44	165 (6.2%)	150 (5.6%)	2.38
Major Bleed Hospitalization	112 (4.3%)	116 (4.4%)	0.75	489 (4.0%)	461 (3.8%)	1.19	112 (4.2%)	114 (4.3%)	0.37
Baseline Warfarin (Mean, SD)									
Days Between Warfarin Discontinuation and DOAC Initiation	8.7 (17.6)	7.4 (16.9)	7.48	8.9 (17.9)	7.5 (16.6)	7.83	7.3 (16.8)	6.9 (15.7)	2.35
Length of Warfarin Therapy	179.1 (209.0)	180.1 (210.2)	0.45	229.6 (264.6)	227.3 (266.2)	0.86	176.1 (204.6)	175.8 (200.4)	0.16

DOAC: direct oral anticoagulant; SD: standard deviation; SE: systemic embolism; STD: standardized difference

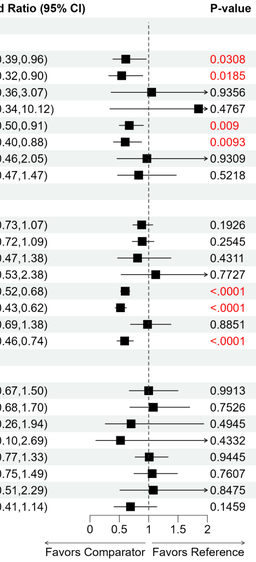
Study Outcomes

Figure 2

- Apixaban (vs dabigatran) was associated with a lower risk of stroke/SE (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.39-0.96) and major bleeding (HR: 0.67; 95% CI: 0.50-0.91)
- Apixaban (vs rivaroxaban) was associated with a similar risk of stroke/SE (HR: 0.88; 95% CI: 0.73-1.07) and lower risk of major bleeding (HR: 0.60; 95% CI: 0.52-0.68)
- There were no significant differences in risk of stroke/SE and major bleeding between dabigatran and rivaroxaban

Figure 2. Hazard Ratio of Stroke/SE and Major Bleeding for PSM Patients

PSM Matched Cohorts	Comparator*	Reference*	Hazard Ratio (95% CI)	P-value
Apixaban vs. Dabigatran (ref)				
(N=2,611 vs. N=2,611)				
Stroke/SE	1.31	2.17	0.61 (0.39,0.96)	0.0308
Ischemic Stroke	0.94	1.79	0.54 (0.32,0.90)	0.0185
Hemorrhagic Stroke	0.32	0.28	1.05 (0.36,3.07)	0.9356
Systemic Embolism	0.16	0.09	1.85 (0.34,10.12)	0.4767
Major Bleeding	3.14	4.73	0.67 (0.50,0.91)	0.009
Gastrointestinal Bleeding	1.75	2.97	0.60 (0.40,0.88)	0.0093
Intracranial Hemorrhage	0.61	0.61	0.97 (0.46,2.05)	0.9309
Other Sites	0.94	1.17	0.83 (0.47,1.47)	0.5218
Apixaban vs. Rivaroxaban (ref)				
(N=12,165 vs. N=12,165)				
Stroke/SE	1.8	2.03	0.88 (0.73,1.07)	0.1926
Ischemic Stroke	1.5	1.69	0.89 (0.72,1.09)	0.2545
Hemorrhagic Stroke	0.21	0.27	0.81 (0.47,1.38)	0.4311
Systemic Embolism	0.13	0.11	1.12 (0.53,2.38)	0.7727
Major Bleeding	3.04	5.03	0.60 (0.52,0.68)	<.0001
Gastrointestinal Bleeding	1.62	3.07	0.52 (0.43,0.62)	<.0001
Intracranial Hemorrhage	0.55	0.56	0.98 (0.69,1.38)	0.8851
Other Sites	0.99	1.65	0.59 (0.46,0.74)	<.0001
Dabigatran vs. Rivaroxaban (ref)				
(N=2,672 vs. N=2,672)				
Stroke/SE	1.99	1.99	1.00 (0.67,1.50)	0.9913
Ischemic Stroke	1.62	1.49	1.08 (0.68,1.70)	0.7526
Hemorrhagic Stroke	0.28	0.38	0.70 (0.26,1.94)	0.4945
Systemic Embolism	0.09	0.19	0.52 (0.10,2.69)	0.4332
Major Bleeding	4.55	4.31	1.01 (0.77,1.33)	0.9445
Gastrointestinal Bleeding	2.86	2.6	1.06 (0.75,1.49)	0.7607
Intracranial Hemorrhage	0.6	0.53	1.08 (0.51,2.29)	0.8475
Other Sites	1.1	1.53	0.69 (0.41,1.14)	0.1459



* incidence per 100 person-years; red p-value indicates significant at p<0.05
CI: confidence interval; PSM: propensity score matching; SE: systemic embolism

Limitations

- As with other retrospective observational studies, causal relationships cannot be determined between the exposures and outcomes of interest
- Potential residual confounders, such as over-the-counter aspirin use, serum creatinine/creatinine clearance, and laboratory values, were unavailable in our data and potentially could have resulted in bias
- Medications were based on pharmacy fills and we were unable to determine if a patient took their medication as prescribed
- Since ICD, current procedural terminology, and healthcare common procedure coding system codes were used to identify the diagnoses and procedures, there is the potential of human data entry errors

Conclusion

- **Risk of stroke/SE and major bleeding varied depending on which DOAC a NVAF patient switched to after initially being prescribed warfarin**
- **Apixaban had lower or similar risk of stroke/SE and lower risk of major bleeding compared to other DOACs**
- **These results may be useful in helping clinicians make informed decisions on which DOAC to prescribe if a NVAF patient was previously using warfarin, but further research is needed before providing any treatment specific recommendations**

References

1. Skeppholm M, Friberg L. Adherence to warfarin treatment among patients with atrial fibrillation. *Clin Res Cardiol*. 2014;103(12):998-1005. doi: 10.1007/s00392-014-0742-y. PMID: 25080281.
2. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: A prevalent adverse effect resulting in regulatory action. *Arch Intern Med*. 2007;167(13):1414-9. doi: 10.1001/archinte.167.13.1414. PMID: 17620536.
3. Amin A, Keshishian A, Hines DM, et al. Risk of stroke/systemic embolism, major bleeding, and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran, or rivaroxaban compared with warfarin in the United States Medicare population: updated analysis. *Curr Med Res Opin*. 2022;38(12):2131-2140. doi: 10.1080/03007995.2022.2115772. PMID: 35993487.

Disclosures

This study was sponsored by Pfizer and Bristol Myers Squibb. GYHL is a consultant and speaker for Bristol Myers Squibb/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. AK, NA, SH. DC and JJ are paid employees of Bristol Myers Squibb. XL is a paid employee of Pfizer. VN and LA are paid employees of STATinMED, which is a paid consultant to Pfizer and Bristol Myers Squibb in connection with the development of this poster. SD is a consultant for Bristol Myers Squibb/Pfizer, Daiichi-Sankyo, Portola, and Boehringer Ingelheim, and has been on the speakers' bureau for Bristol Myers Squibb/Pfizer, and Boehringer Ingelheim.

Poster presented at the *American College of Cardiology's ACC.23 Annual Scientific Session & Expo 2023*: March 4-6, 2023, New Orleans, LA