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ORAL ABSTRACTS

904.OUTCOMES RESEARCH-NON-MALIGNANT CONDITIONS

A Comparison of Bleeding Events Among Patients on Apixaban, Rivaroxaban, and Warfarin for Atrial Fibrillation and/or Venous Thromboembolism

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Introduction

Apixaban and rivaroxaban are the most commonly used direct oral anticoagulants (DOACs) for atrial fibrillation (AF) and venous thromboembolism (VTE). Both have been compared to warfarin in landmark clinical trials. However, there are limited comparative efficacy data between these drugs in a real-world setting. We sought to assess patient characteristics and outcomes of apixaban, rivaroxaban, and warfarin in a non-trial based study cohort.

Methods

Retrospective registry-based cohort of adults starting apixaban, rivaroxaban, or warfarin therapy or switching between these anticoagulants for the indications of VTE and/or non-valvular AF. Through the Michigan Anticoagulation Quality Improvement Initiative (MAQI [2]) collaborative of six anticoagulation clinics, warfarin treated patients were followed from January 2009 to June 2023. Four of these clinics contributed DOAC patient data from June 2011 to June 2023. Patients treated with other anticoagulants, with valvular AF, or with less than 3 months of follow-up were excluded.

Propensity matched cohorts (apixaban versus warfarin [1:1], rivaroxaban versus warfarin [1:3], and apixaban versus rivaroxaban [1:1]) of patients were analyzed based on DOAC use at study enrollment, using 1:1-3:1 matching ratios. Patients were matched based on demographics, social history, comorbidities, medications, bleeding/thrombotic history, indication for anticoagulation, and follow-up. The primary outcome was any new bleeding event. Secondary outcomes included new episodes of thrombosis, bleeding event type (major, fatal, life threatening, central nervous system, and non-major bleeding), emergency room (ER) visits, hospitalizations, and death. Random chart audits were done to confirm the accuracy of the abstracted data. Event rates were compared using Poisson regression.

Results

Of 13,435 patients on OAC who met the study inclusion criteria (3,536 on apixaban, 1,395 on rivaroxaban, and 8,504 on warfarin), the average age was 66.7 years (standard deviation [SD] 14.9 years), 51.1% identified as male, most (58.0%) were on anticoagulation for AF, and the average follow-up was 28.2 months (SD 30.7 months). After propensity matching, 3,527 patients on apixaban were compared to 3,527 patients on warfarin. Any bleeding was similar between groups, but major bleeding was higher with warfarin (3.4 versus 4.7 events/100 patient years, $p<0.001$). Thrombotic event rates were higher with apixaban (2.6 versus 2.1 events/100 patient years, $p=0.026$), including the thrombotic subtype of other thrombosis (1.0 versus 0.5 events/100 patient years, $p<0.001$). Rates of ER visits and hospitalizations for bleeding were higher with warfarin. Mortality was higher with warfarin (3.7 versus 4.4 deaths/100 patient years, $p=0.027$).

After propensity matching, 1,395 patients on rivaroxaban were compared to 4,185 patients on warfarin. Any bleeding and major bleeding were higher with rivaroxaban (37.9 versus 24.9 events/100 patient years, $p<0.001$; 4.7 versus 3.6 events/100 patient years, $p=0.041$ respectively). Thrombotic event rates were similar, aside from a higher rate of the thrombotic subtype of

other thrombosis with rivaroxaban (1.0 versus 0.3 events/100 patient years, p=0.002). ER visits, hospitalizations, and mortality were similar between rivaroxaban and warfarin.

After propensity matching, 1,395 patients on apixaban were compared to 1,395 patients on rivaroxaban. Any bleeding and major bleeding were higher with rivaroxaban (37.9 versus 25.7 events/100 patient years, p<0.001; 4.7 versus 2.6 events/100 patient years, p<0.001). Thrombotic event rates were similar. ER visits occurred more frequently on rivaroxaban (12.8 versus 10.1 events/100 patient years, p=0.003) as did patient mortality (3.5 versus 2.6 deaths/100 patient years, p=0.047).

Conclusions

For patients on oral anticoagulation for AF and/or VTE we observed that bleeding was highest with rivaroxaban, followed by warfarin, and then apixaban. Rates of thrombosis were higher with apixaban compared to warfarin, seemingly largely driven by "other" thrombotic events. Thrombotic event rates were otherwise similar between apixaban, rivaroxaban, and warfarin. We observed apixaban to be associated with lower mortality than rivaroxaban and warfarin. While these findings should be confirmed with randomized studies, they may have implications for anticoagulant selection.

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Table 1: Patient Characteristics Before Matching[a]			
Anticoagulant	Apixaban N=3,536	Rivaroxaban N=1,395	Warfarin N=8,504
DOAC dose[b]			
Reduced dose	648 (18.3)	139 (10.0)	/
Standard dose	2888 (81.7)	1257 (90.0)	/
Aspirin (%)	1185 (33.5)	410 (29.4)	3315 (39.0)
Demographics			
Age, y mean (sd)	70.5 (13.2)	64.8 (15.1)	65.4 (15.4)
Male	1767 (50.0)	696 (49.9)	4404 (51.8)
BMI > 30 kg/m2	1740 (49.2)	701 (50.3)	4124 (48.5)
Alcohol or drug use	215 (6.1)	100 (7.2)	417 (4.9)
Current tobacco use	256 (7.2)	129 (9.3)	676 (8.0)
Former tobacco use	1332 (37.7)	490 (35.1)	2731 (32.1)
Indication n (%)			
AF/Aflutter	2509 (71.0)	682 (48.9)	4598 (54.1)
DVT/PE	1056 (29.9)	730 (52.3)	4026 (47.3)
Both	29 (0.8)	17 (1.2)	120 (1.4)
TTR (warfarin) mean (sd)	/	/	0.6 (0.2)
Co-Morbidities n (%)			
CAD	1028 (29.1)	260 (18.6)	2153 (25.3)
Cancer	940 (26.6)	320 (22.9)	1805 (21.2)
CHF	736 (20.8)	181 (13)	1615 (19.0)
Chronic liver disease	163 (4.6)	72 (5.2)	214 (2.5)
CKD	848 (24.0)	205 (14.7)	2572 (30.2)
Diabetes mellitus	1019 (28.8)	314 (22.5)	2248 (26.4)
History of falls	287 (8.1)	75 (5.4)	353 (4.2)
Hypercoagulable state/History of APS	43 (1.2)	34 (2.4)	311 (3.7)
OSA	659 (18.6)	260 (18.6)	1112 (13.1)
HTN	2373 (67.1)	773 (55.4)	5627 (66.2)
PAD	227 (6.4)	54 (3.9)	472 (5.6)
Prior PCI/CABG	478 (13.5)	115 (8.2)	972 (11.4)
Prior CVA/TIA	479 (13.6)	120 (8.6)	982 (11.6)
Prior DVT/PE	262 (7.4)	146 (10.5)	1502 (17.7)
History of MI	328 (9.3)	96 (6.9)	776 (9.1)
Recent bleeding (<30 days)	149 (4.2)	43 (3.1)	247 (2.9)
Remote bleeding (>30 days)	195 (5.5)	77 (5.5)	290 (3.4)
Bleeding diathesis	8 (0.2)	0 (0.0)	46 (0.5)
Medications n (%)			
NSAID	94 (2.7)	60 (4.3)	336 (4.0)
Aspirin <100 mg	1108 (31.3)	373 (26.7)	2875 (33.8)
Aspirin >100 mg	78 (2.2)	38 (2.7)	443 (5.2)
Non-ASA antiplatelet	187 (5.3)	29 (2.1)	497 (5.8)
PPI/ H2RA	1248 (35.3)	456 (32.7)	3129 (36.8)
Estrogen or progesterone	71 (2.0)	45 (3.2)	87 (1.0)
Other mean (sd)			
Follow-up Months	27 (24.1)	26.5 (27.1)	28.9 (33.6)
Modified HAS-BLED[c]	2.7 (1.4)	2.2 (1.4)	2.5 (1.4)
CCI	4.8 (2.1)	4.0 (2.2)	4.5 (2.5)

[a]Values are n (%) unless otherwise specified.
[b]Reduced dose defined as a total daily dose of apixaban <10 mg, rivaroxaban <20 mg. Standard dose is considered a total daily dose of apixaban ≥10 mg, rivaroxaban ≥20 mg.
[c]HAS-BLED modified to exclude labile INR.
Abbreviations: AF, atrial fibrillation; APS, antiphospholipid syndrome; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; Coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ER, emergency room; H2RA, H2 receptor antagonist; HAS-BLED, hypertension abnormal renal/liver function stroke, bleeding history or predisposition, labile INR, eldery, drugs/alcohol concomitantly; HTN, hypertension; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnea; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PPI, proton pump inhibitor; SD, standard deviation; TIA, transient ischemic attack; TTR, time in the therapeutic range.

Table 2: Comparative Outcomes of Oral Anticoagulants			
Outcomes of Apixaban versus Warfarin			
Events/100 patient years (95% CI)	**Apixaban N=3,527**	**Warfarin N=3,527**	**p-value**
New Bleed	28.6 (27.4, 29.8)	27.6 (26.5, 28.8)	0.26
Fatal	0.08 (0.03, 0.16)	0.21 (0.12, 0.33)	0.033
Life Threatening	0.90 (0.70, 1.13)	1.49 (1.23, 1.78)	<0.001
Major	3.4 (3.0, 3.8)	4.7 (4.2, 5.2)	<0.001
Non-major	24.3 (23.2, 25.4)	22.8 (21.7, 23.9)	0.059
Intracranial or intraspinal	0.38 (0.26, 0.54)	0.92 (0.72, 1.16)	<0.001
New Thrombosis	2.6 (2.3, 3.0)	2.1 (1.8, 2.4)	0.026
ER Visit	11.5 (10.8, 12.3)	13.4 (12.6, 14.3)	<0.001
Hospitalization	7.7 (7.1, 8.4)	8.6 (8.0, 9.3)	0.058
For bleeding	6.2 (5.7, 6.8)	7.4 (6.8, 8.0)	0.005
For clotting	1.5 (1.3, 1.8)	1.4 (1.1, 1.7)	0.51
Death	3.7 (3.3, 4.2)	4.4 (4.0, 4.9)	0.027
Outcomes of Rivaroxaban versus Warfarin			
Events/100 patient years (95% CI)	**Rivaroxaban N=1,395**	**Warfarin N=4,185**	**p-value**
New Bleed	37.9 (35.7, 40.1)	24.9 (23.9, 25.9)	<0.001
Fatal	0.10 (0.02, 0.28)	0.12 (0.06, 0.21)	0.80
Life Threatening	1.07 (0.74, 1.51)	1.12 (0.91, 1.35)	0.87
Major	4.7 (3.9, 5.5)	3.6 (3.2, 4.0)	0.041
Non-major	32.1 (30.2, 34.2)	21.1 (20.2, 22.1)	<0.001
Intracranial or intraspinal	0.29 (0.13, 0.56)	0.65 (0.5, 0.84)	0.047
New Thrombosis	2.8 (2.2, 3.5)	2.1 (1.8, 2.4)	0.089
ER Visit	12.8 (11.5, 14.1)	10.9 (10.2, 11.6)	0.45
Hospitalization	7.1 (6.1, 8.1)	7.3 (6.8, 7.9)	0.70
For bleeding	5.8 (5.0, 6.7)	6.1 (5.6, 6.6)	0.69
For clotting	1.23 (0.87, 1.69)	1.35 (1.13, 1.61)	0.68
Death	3.5 (2.9, 4.3)	3.0 (2.7, 3.4)	0.24
Outcomes of Apixaban versus Rivaroxaban			
Events/100 patient years (95% CI)	**Apixaban N=1,395**	**Rivaroxaban N=1,395**	**p-value**
New Bleed	25.7 (23.9, 27.6)	37.9 (35.7, 40.1)	<0.001
Fatal	0.07 (0.01, 0.25)	0.10 (0.02, 0.28)	1.0
Life Threatening	0.71 (0.44, 1.09)	1.27 (0.74, 1.51)	0.17
Major	2.6 (2.0, 3.2)	4.7 (3.9, 5.5)	<0.001
Non-major	22.1 (20.5, 23.9)	32.1 (30.2, 34.2)	<0.001
Intracranial or intraspinal	0.27 (0.12, 0.54)	0.29 (0.13, 0.56)	1.0
New Thrombosis	2.6 (2.0, 3.2)	2.8 (2.2, 3.5)	0.58
ER Visit	10.1 (9.0, 11.3)	12.8 (11.5, 14.1)	0.003
Hospitalization	6.7 (5.8, 7.7)	7.1 (6.1, 8.1)	0.63
For bleeding	5.7 (4.8, 6.6)	5.8 (5.0, 6.7)	0.83
For clotting	1.39 (1.00, 1.89)	1.23 (0.87, 1.69)	0.65
Death	2.6 (2.1, 3.3)	3.5 (2.9, 4.3)	0.047

Figure 1

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