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POSTER ABSTRACTS

904.OUTCOMES RESEARCH-NON-MALIGNANT CONDITIONS

Outcomes of Oral Anticoagulation with Concomitant NSAID Use: A Registry Based Cohort Study

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), available without a prescription, are some of the most commonly used drugs in the United States. For patients on oral anticoagulation (OAC), concomitant NSAID use can increase the risk of bleeding. Patients are often advised to avoid this drug combination, or else consider adding a proton pump inhibitor (PPI) or H2 receptor antagonists (H2RA) for gastroprotection when both NSAIDs and OAC are used. However, there are limited data on how NSAID use impacts thrombotic and hemorrhagic outcomes. Available data may be biased due to selection bias, confounding, misclassification, and variable NSAID exposure. We sought to determine the frequency of NSAID use among patients on OAC, the impact on clinical outcomes, and if gastroprotection may mitigate bleeding risk. We hypothesized that NSAIDs would increase bleeding risk without impacting thrombotic risk. We did not anticipate gastroprotection would mitigate this risk.

Methods

We conducted a retrospective registry-based cohort study of adults starting a direct oral anticoagulant (DOAC) or warfarin therapy for the indications of venous thromboembolism and/or non-valvular atrial fibrillation between June 2011 and June 2023. As part of the Michigan Anticoagulation Quality Improvement Initiative (MAQI^2), warfarin-treated patients were followed by six anticoagulation clinics, and four of the six clinics contributed data for patients on DOACs. Patients were excluded if they had a history of valvular AF, less than 3 months of follow-up, or on more than one antiplatelet drug. Two propensity matched cohorts (OAC alone vs. OAC+NSAID) of patients were analyzed based on NSAID use at the time of study enrollment, using a 4:1 matching ratio. Both prescribed and over the counter NSAIDs were included, potentially with the former being more frequently captured in the study registry. The primary outcome was any new bleeding event. Secondary outcomes included new episodes of arterial or venous thrombosis, bleeding event type (major, fatal, life threatening, central nervous system, and non-major bleeding), emergency room visits, hospitalizations, transfusions, and death. Random chart audits were done to confirm the accuracy of the abstracted data. Event rates were compared using Poisson regression.

Results

Of 12,083 patients on OAC, 449 (3.7%) were on concomitant NSAIDs. After propensity matching, we compared 1,796 patients on OAC to 449 patients on OAC+NSAIDs. Patient demographics, co-morbidities, indication for anticoagulation, history of bleeding or clotting, medications, and duration of follow-up were well-balanced after matching. Patients were followed for an

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average of 30 months (standard deviation 34.2 months). For patients on OAC alone vs. OAC+NSAIDs, bleeding event rates were similar: 25.1 (95% confidence interval [CI] 23.7-26.6) versus 24.3 (95% CI 21.4-27.3) bleeds per 100 patient years (*P*=0.56). Rates of non-major, major, life-threatening, central nervous system, and fatal bleeding were also similar. Furthermore, rates of thrombosis, emergency room visits, hospitalizations, transfusion, and death were similar. A pre-defined subgroup analysis comparing patients on OAC+NSAIDs with gastrointestinal prophylaxis (PPIs or H2RAs, N=179) to patients on OAC+NSAIDs without gastrointestinal prophylaxis (N=270) also showed similar rates of bleeding and healthcare utilization.

Conclusions

Nearly 4% of patients were taking NSAIDs with OAC and outcomes were similar to patients on OAC alone. Study limitations include NSAIDs and gastroprotection were only reliably known at time of enrollment. In addition, the potential for unmeasured or unadjusted confounding inherent to observational studies. Further research is needed to determine if there is a "safe" level of NSAID use for patients on OAC and to better define the role of gastrointestinal prophylaxis.

Disclosures Kaatz: *AC Forum:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Honoraria; *Gilead:* Honoraria; *PhaseBio:* Honoraria; *Pfizer:* Honoraria; *Bristol Myers Squibb:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding; *Osmosis Research:* Research Funding; *National Blood Clot Alliance:* Membership on an entity's Board of Directors or advisory committees; *PERT Consortium:* Membership on an entity's Board of Directors or advisory committees. **Froehlich:** *Pfizer:* Honoraria; *Merck:* Honoraria; *Janssen:* Honoraria; *Novartis:* Honoraria; *Boehringer Ingelheim:* Honoraria. **Barnes:** *National Certification Board of Anticoagulation Providers:* Membership on an entity's Board of Directors or advisory committees; *AC Forum:* Membership on an entity's Board of Directors or advisory committees; *Connected Health:* Honoraria; *Boston Scientific:* Honoraria; *Abbott Vascular:* Honoraria; *Acelis:* Honoraria; *Janssen:* Honoraria; *Pfizer:* Honoraria; *Bristol Myers Squibb:* Honoraria.

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Table 1: Patient Characteristics After Matching[a]			
Patient Characteristics			
	OAC alone N=1,796	OAC+NSAID N=449	Standardized Difference
DOAC	486 (27.1)	126 (28.1)	-0.022
Apixaban	352 (19.6)	76 (16.9)	0.067
Dabigatran	1 (0.1)	1 (0.2)	-0.038
Edoxaban	0 (0.0)	0 (0.0)	-
Rivaroxaban	133 (7.4)	49 (10.9)	-0.118
Warfarin TTR mean (sd)	0.6 (0.2)	0.6 (0.2)	
DOAC dose[b]			
Reduced dose	25 (5.2)	6 (4.8)	-
Standard dose	460 (94.9)	120 (95.2)	-
Demographics			
Age, years mean (sd)	63.7 (15.1)	64.3 (14.4)	0.039
Gender (% male)	896 (49.9)	224 (49.9)	0.000
Indication n (%)			
AF/Aflutter	850 (47.3)	219 (48.8)	-0.029
DVT/PE	884 (49.2)	230 (51.2)	0.040
Both	219 (12.2)	63 (14)	0.053
Co-Morbidities n (%)			
CAD	286 (15.9)	74 (16.5)	-0.014
Cancer	351 (19.5)	92 (20.5)	-0.023
CHF	158 (8.8)	41 (9.1)	-0.010
OSA	252 (14)	65 (14.5)	-0.013
Chronic liver disease	32 (1.8)	9 (2)	-0.014
CKD	256 (14.3)	74 (16.5)	-0.054
Diabetes mellitus	429 (23.9)	110 (24.5)	-0.014
Heart valve replacement	17 (1)	5 (1.1)	-0.011
History of falls	93 (5.2)	23 (5.1)	0.003
Hypercoagulable state	49 (2.7)	9 (2)	0.047
HTN	1,116 (62.1)	284 (63.3)	-0.023
PAD	80 (4.5)	25 (5.6)	-0.050
Prior PCI/CABG	133 (7.4)	33 (7.4)	0.002
History of Bleeding or Thrombosis n (%)			
Bleeding (≤30 days)	59 (3.3)	15 (3.3)	-0.003
Bleeding (>30 days)	61 (3.4)	16 (3.6)	-0.009
Bleeding diathesis	6 (0.3)	1 (0.2)	0.020
History of embolism (not DTE/PE)	15 (0.8)	3 (0.7)	0.018
Prior CVA/TIA	147 (8.2)	38 (8.5)	-0.009
Prior DVT/PE	147 (8.2)	38 (8.5)	-0.011
Prior GIB	95 (5.3)	22 (4.9)	0.017
Recent MI (<6 months)	23 (1.3)	5 (1.1)	0.012
Remote MI (>6 months)	112 (6.2)	26 (5.8)	0.019
Medications n (%)			
Aspirin ≤ 100 mg	544 (30.3)	141 (31.4)	-0.024
Aspirin >100 mg	53 (3)	23 (5.1)	0.105
Estrogen/progesterone	40 (2.2)	10 (2.2)	0.000
Non-ASA antiplatelet	17 (1)	3 (0.7)	0.025
Chemotherapy	42 (2.3)	11 (2.5)	-0.007
PPI/H2RA	726 (40.4)	179 (39.9)	0.012
Other (mean ± sd, median)			
Months of follow-up mean (sd)	30 (34.3)	29.6 (33.9)	-0.013
Modified HAS-BLED[c]	2.1 (1.3)	2.1 (1.3)	0.033
Charlson Comorbidity Index	3.8 (2.1)	3.9 (2.2)	0.055

[a]Values are n(%) unless otherwise specified
[b]Standard dose is considered a total daily dose of dabigatrain ≥ 300 mg, apixaban ≥10 mg, rivaroxaban ≥20 mg, and edoxaban ≥60 mg. Other doses are considered reduced dose.
[c]HAS-BLED modified to exclude labile INR.
Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid or aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ER, emergency room; GIB, gastrointestinal bleed; HAS-BLED, hypertension abnormal renal/liver function stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; HTN, hypertension; MI, myocardial infarction; 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: Patient Outcomes			
Events per 100 patient years (95% confidence interval)	OAC alone N=1,796	OAC+NSAID N=449	p-value
Thrombosis	1.9 (1.5, 2.3)	1.7 (1.0, 2.7)	0.78
Ischemic/Embolic Stroke	0.42 (0.25, 0.66)	0.54 (0.20, 1.18)	0.74
TIA	0.24 (0.12, 0.44)	0.09 (0.00, 0.50)	0.39
PE	0.18 (0.08, 0.35)	0.45 (0.15, 1.06)	0.28
DVT	0.53 (0.34, 0.80)	0.27 (0.06, 0.79)	0.31
Bleeding	25.1 (23.7, 26.6)	24.3 (21.4, 27.3)	0.56
Non-major	21.5 (20.1, 22.9)	20.4 (17.8, 23.2)	0.46
Major	3.3 (2.8, 3.9)	3.4 (2.4, 4.7)	0.84
Fatal	1.05 (0.77, 1.39)	0.54 (0.20, 1.18)	0.20
Life Threatening	0.58 (0.38, 0.85)	0.54 (0.20, 1.18)	0.95
Intracranial or intraspinal	0.04 (0.01, 0.16)	0.18 (0.02, 0.65)	0.36
ER Visit	10.5 (9.6, 11.5)	10.9 (9.0, 13.0)	0.81
Hospitalization	6.8 (6.1, 7.6)	6.9 (5.4, 8.6)	0.96
For bleeding	5.4 (4.8, 6.2)	5.9 (4.5, 7.5)	0.67
For clotting	1.43 (1.10, 1.82)	1.27 (0.69, 2.13)	0.73
Blood Transfusion	2.3 (1.9, 2.8)	2.1 (1.3, 3.1)	0.68
Death	2.4 (2.0, 2.9)	2.1 (1.4, 3.2)	0.60

Figure 1

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