No Differential Risk of Cutaneous Small Vessel Vasculitis with Oral Anticoagulant Use Among Patients with Atrial Fibrillation

Presented at ICPE 2021 All Access

Adebola Ajao[1], Austin Cosgrove[2], Efe Eworuke[1], Mohamed Mohamoud[1], Rongmei Zhang[1], Oren Shapira[2], Joy Kolonoski[2], John Connolly[2]

[1]U.S. Food and Drug Administration, Silver Spring, MD, [2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

BACKGROUND

- Cutaneous small vessel vasculitis (CSVV) was identified as a safety signal through the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) among patients treated with Direct Oral Anticoagulants (DOACs)
- CSVV is a form of vasculitis defined as a single organ, skin isolated leukocytoclastic vasculitis or angiitis often without apparent systemic vasculitis or glomerulonephritis

OBJECTIVE

- To determine if CSVV risk differed among patients with atrial fibrillation (Afib) who newly initiated warfarin, dabigatran, rivaroxaban, or apixaban

METHODS

- We identified patients aged 21+ years diagnosed with Afib, with at least six months of continuous medical and drug coverage in the Sentinel Distributed Database between October 19, 2010 and February 29, 2020
- We selected patients who newly initiated rivaroxaban, dabigatran, apixaban, or warfarin during the study period and did not have evidence of the following in the 183 days prior to initiating treatment: CSVV diagnosis, dispensing of other study drugs, select autoimmune diseases or autoimmune medications, cancer diagnoses or chemotherapeutic treatment, kidney dialysis or transplant, or alternative anticoagulation indications; we also excluded an institutional stay (skilled nursing facility, hospice care, etc.) on the treatment initiation date (index date). Eligible patients were followed from the index date until CSVV outcome or pre-specified censoring.
- We conducted 1:1 unconditional propensity score (PS) matching for six comparisons: 1) rivaroxaban vs. warfarin; 2) dabigatran vs. warfarin; 3) apixaban vs. warfarin; 4) rivaroxaban vs. dabigatran; 5) rivaroxaban vs. apixaban; and 6) dabigatran vs. apixaban. This analysis was designed on Sentinel Query Request Package (QRP) version 9.6.0, with Propensity Score Analysis module.

RESULTS

- In our study population of Afib patients, warfarin was the most commonly used anticoagulant, followed by apixaban, rivaroxaban, and dabigatran
- Prior to PS matching, we identified 328,249 rivaroxaban new users (mean age ± standard deviation (SD): 73.3 ± 9.6 years), 142,328 dabigatran new users (72.7 ± 9.9 years), 532,973 apixaban new users (75.5 ± 9.6 years), and over 617,000 warfarin new users (75.4 ± 9.8 years) across all three warfarin pairwise comparisons
- Prior to PS matching, warfarin users were generally older, more likely to be Caucasian and have comorbidities, take cardiovascular and diuretic drugs, and more likely to utilize healthcare compared to rivaroxaban, dabigatran, and apixaban users. Rivaroxaban and dabigatran users were generally similar with regards to their baseline demographic and clinical characteristics. Apixaban users were slightly older, more likely to have comorbidities and utilize healthcare services than new users of rivaroxaban and dabigatran
- After PS matching, the matched cohorts were balanced on measured covariates
- CSVV incidence rates for DOACs and warfarin ranged from 3.3 to 5.6 per 10,000 person-years in our matched Afib population
- No statistically significant difference in CSVV risk was observed among all pairwise comparisons. The adjusted CSVV hazard ratio (HR) and 95% confidence interval (CI) was 0.94 (0.64, 1.39) for rivaroxaban vs. warfarin; 1.17 (0.67, 2.06) for dabigatran vs. warfarin; 0.85 (0.62, 1.16) for apixaban vs. warfarin; 0.86 (0.49, 1.50) for rivaroxaban vs. dabigatran; 0.99 (0.68, 1.45) for rivaroxaban vs. apixaban; and 1.70 (0.90, 3.21) for dabigatran vs. apixaban (Table 1)
- There was a non-significant increased risk of CSVV for dabigatran compared to warfarin, apixaban, and rivaroxaban

TABLE OF RESULTS

Propensity Score Matched Analysis of the Incidence of CSVV by DOACs and Warfarin

	Number of New Users	Number of events	Incidence Rate per 10,000 Person Years	Hazard Ratio (95% CI)	P-Value
Rivaroxaban	320,363	53	4.1	0.94 (0.64, 1.39)	0.765
Warfarin	320,363	51	4.5		
Dabigatran	142,197	26	5.1	1.17 (0.67, 2.06)	0.576
Warfarin	142,197	23	4.6		
Apixaban	503,885	75	3.8	0.85 (0.62, 1.16)	0.298
Warfarin	503,885	82	4.6		
Rivaroxaban	125,338	25	4.9	0.86 (0.49, 1.50)	0.586
Dabigatran	125,338	24	5.6		
Rivaroxaban	331,796	55	4.1	0.99 (0.68, 1.45)	0.977
Apixaban	331,796	54	4.2		
Dabigatran	125,718	24	5.6	1.70 (0.90, 3.21)	0.099
Apixaban	125,718	16	3.3		

CONCLUSION

- We did not find statistically significant evidence of differential CSVV risk in pair-wise comparisons of DOACs and warfarin. However, we observed a non-significant increased risk of CSVV for dabigatran compared to warfarin, apixaban, and rivaroxaban that deserves further evaluation

LIMITATIONS

- Due to the rarity of CSVV, our study may be underpowered to identify a significant differential association for specific DOACs like dabigatran despite our large cohort sizes
- CSVV was not validated in our study, therefore, the positive predictive value and sensitivity of the procedure and outcome codes are unknown. However, our study outcome required a CSVV diagnosis to be followed by an oral or topical dispensing of steroid treatment within 90 days of the qualifying CSVV diagnosis date and was based on a review of chronological claims of 90 CSVV cases

The authors have no conflicts of interest to disclose. The views expressed in this poster represent those of the presenters and do not necessarily represent the official views of the U.S. FDA. Many thanks are due to the Data Partners who provided data used in the analysis. This project was supported by Task Order HHSF22301012T under Master Agreement HHSF223201400030I from the US Food and Drug Administration (FDA).