Incidence of Cutaneous Small Vessel Vasculitis Associated with Oral Anticoagulant Use

Adebola Ajao[1], Oren Shapira[2], Efe Eworuke[1], Mohamed Mohamoud[1], Rongmei Zhang[1], 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 among patients treated with Non-Vitamin K Oral Anticoagulants (NOACs).
- CSVV is a form of vasculitis defined as a single organ, skin isolated small vessel vasculitis or angiitis often leukocytoclastic vasculitis without apparent systemic vasculitis or glomerulonephritis.

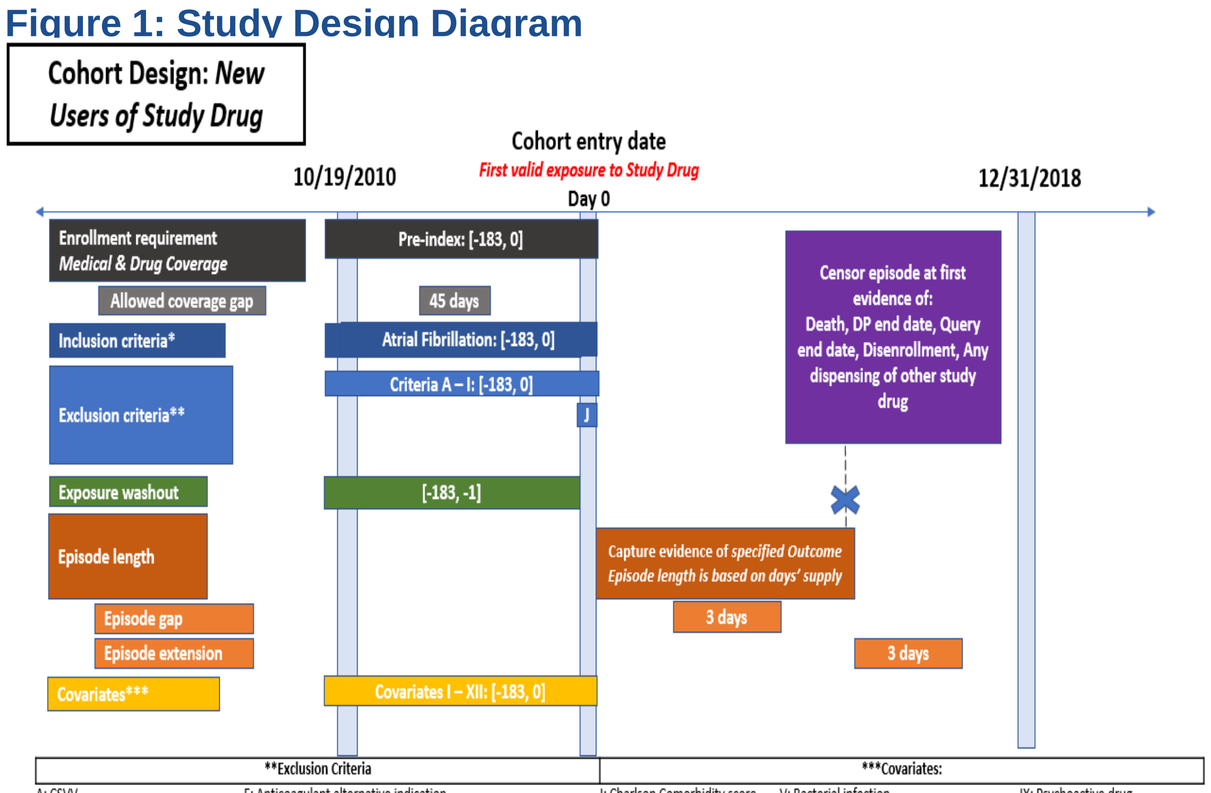
OBJECTIVE

- To determine the crude incidence rate of CSVV among new users of a NOAC, warfarin, or allopurinol (both labeled for vasculitis) among patients with Atrial Fibrillation (Afib) in the Sentinel System (https://www.sentinelinitiative.org).

METHODS

- We identified patients 21+ years diagnosed with Afib, with at least six months of continuous medical and drug coverage between October 19, 2010 and December 31, 2018.
- Of these, patients were eligible if they newly initiated NOACs, warfarin, or allopurinol, and did not have any of the following in the 183 days prior to initiating treatment (index date): prior CSVV diagnosis, a dispensing of the other study drugs, select autoimmune disease or autoimmune medications, any cancer diagnoses or treatment, kidney dialysis or transplant, alternative anticoagulation indications, or an institutional (skilled nursing home, hospice, hospital) stay. **(Figure 1)**
- New users were followed from the day after treatment initiation until a CSVV outcome, death, disenrollment, end of study period, end of exposure period, or dispensing of the other study drugs. Study outcome was defined as outpatient CSVV diagnoses followed by a dispensing of oral or topical prednisone, prednisolone, or select oral or topical steroid treatments within 90 days.

Figure 1: Study Design Diagram



Patients were eligible if they newly initiated NOACs, warfarin, or allopurinol, and did not have any of the exclusion criteria in the 183 days prior to initiating treatment.

RESULTS

- We identified 824,515 NOAC new users (mean age ± SD: 74.2 ± 9.7 years), 679,363 warfarin new users (mean age ± SD: 75.6 ± 9.8 years), and 59,369 allopurinol new users (mean age ± SD: 75.9 ± 9.6 years). **(Table 1)**
- Baseline patient characteristics were similar in the NOAC and warfarin new user groups while allopurinol new users had a slightly higher prevalence of autoimmune diseases, hematologic blood disorders, and cardiovascular medications. **(Table 1)**
- The crude CSVV incidence rate (events per 10,000 person-years at risk) for NOAC, warfarin, and allopurinol new users were 4.05, 3.23, 5.24 respectively. **(Table 2)**

Table 1. Baseline Characteristics of Study Cohort

	NOAC New Users	Warfarin New Users	Allopurinol New Users
Number of unique patients	824,515	679,363	59,369
Demographics:			
Mean Age (Years)	74.2	75.6	75.9
21-64 years	15.3%	12.2%	13.6%
65-74 years	36.1%	32.6%	31.8%
75-84 years	32.9%	36.8%	32.6%
85+ years	15.6%	18.4%	22.1%
Gender			
Female	48.4%	48.8%	37.3%
Male	51.6%	51.2%	62.7%
Race			
White	74.5%	78.9%	71.4%
Asian	1.5%	1.7%	3.1%
Black or African American	4.7%	4.8%	10.2%
Native Hawaiian or Other Pacific Islander	0.1%	0.2%	0.4%
Recorded History of:			
Charlson/Elixhauser Combined Comorbidity Score	2.6	2.8	4.1
Autoimmune diseases	5.2%	6.0%	8.9%
Hematological blood disorders	19.1%	24.6%	38.0%
Cardiovascular medications and diuretics	61.7%	67.2%	70.9%
Beta-adrenergic receptor agonists	0.0%	0.0%	0.0%
Anticonvulsants	0.6%	0.9%	0.7%

Table 2. Incidence of CSVV Among New Users of NOAC, Warfarin, and Allopurinol

	Number of New Users	Number of Years at Risk	Number of CSVV Events	CSVV Event per 10,000 Years at Risk
NOAC	824,515	313,754.5	127	4.05
Warfarin	679,363	244,445.3	79	3.23
Allopurinol	59,369	21,007.3	11	5.24

DISCUSSION & CONCLUSIONS

- In the Sentinel System, crude incidence rate of CSVV among new users of NOACs was comparable to the crude incidence rate of CSVV in new users of warfarin and allopurinol, both of which are labeled for vasculitis.
- Adjusted studies are ongoing to further characterize the risk of CSVV among NOAC users and to evaluate if there is differential risk by individual NOACs.

LIMITATIONS

- We report crude CSVV incidence rates and not adjusted rates.
- Low number of CSVV events over the study period may underpower planned adjusted analyses for NOAC vs. NOAC comparisons, likely making it more difficult to assess differential risk by individual NOACs.

The authors have no conflicts of interest to disclose. The opinions expressed in this poster are those of the authors and not necessarily 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 contract HHSF223201400030I from the US Food and Drug Administration (FDA).