Complementary Use of US FDA's Adverse Event Reporting System and Sentinel Distributed Database to Characterize Non-Vitamin K Oral Anticoagulant-Associated Cutaneous Small Vessel Vasculitis

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BACKGROUND

- Non-vitamin K oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban are increasingly being used as an alternative to Vitamin K antagonist (VKAs) such as warfarin in the prevention of stroke in atrial fibrillation (AFib) and in the prevention and treatment of venous thromboembolism (VTE).
- In the pre- and post-market setting, cutaneous small vessel vasculitis (CSVV) has been reported after new exposure to NOACs.

OBJECTIVE

- To describe the temporal association and select clinical characteristics between NOACs and CSVV using both the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database and the Sentinel Distributed Database (SDD) (https://www.sentinelinitiative.org)

METHODS

Data Sources:

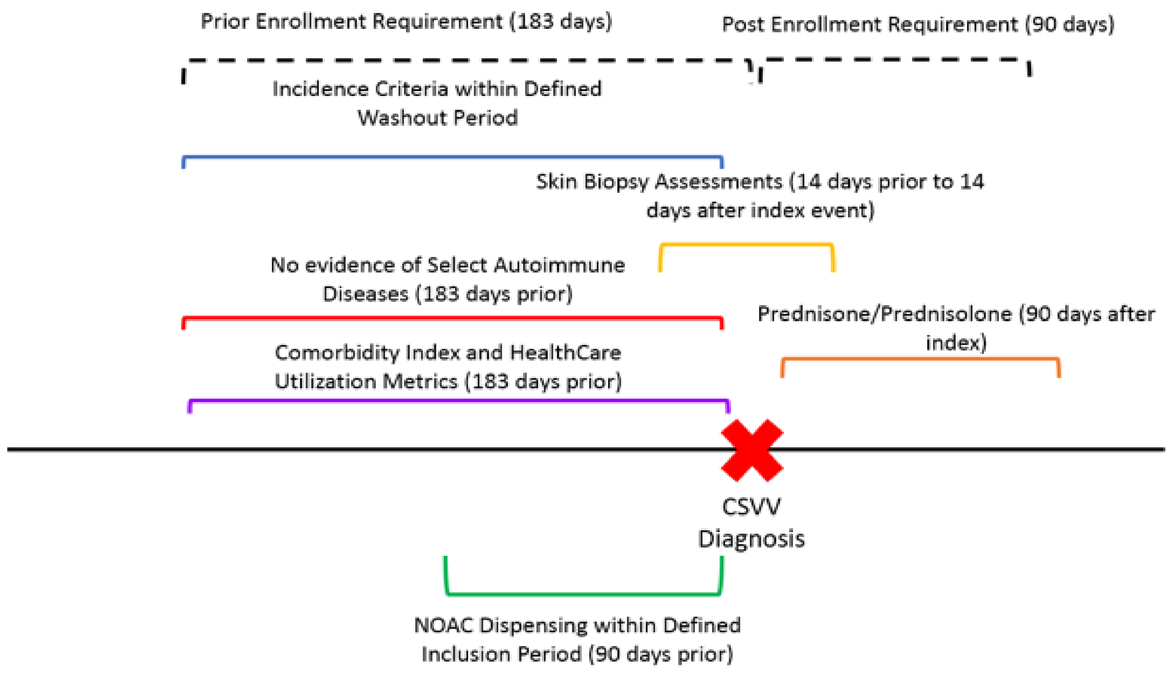
FAERS

- Spontaneous reporting surveillance system managed by FDA containing >14 million postmarketing adverse event reports for drugs and therapeutic biologics.
- We queried FAERS for all reports of CSVV associated with NOACs from US approval date of each NOAC through March 16, 2018 using the Standardized MedDRA Query (SMQ) "Vasculitis" (narrow).
- We included FAERS reports that showed a temporal relationship between NOACs and CSVV with a confirmed clinical diagnosis (i.e., skin biopsy and/or by dermatologist/physician).
- Reports were excluded if the report included an alternative cause of CSVV, uncertain diagnosis of CSVV, evidence of CSVV prior to NOAC initiation or unknown/ negative dechallenge information.

Sentinel System

- National distributed data network of electronic healthcare databases.
- We evaluated claims data from 17 Data Partners in the SDD, consisting of both U.S. commercial and public health insurers.
- We identified the incident CSVV cases amongst adults aged ≥30 who received a NOAC in the prior 90 days with no evidence of select autoimmune diseases in the 183 days prior to their CSVV diagnosis, between January 1, 2010 and June 30, 2018.
- We used NDCs and ICD-9-CM/ICD-10-CM codes to define inclusion and exclusion criteria.
- We identified the recorded history of skin biopsy 14 days before and after CSVV diagnosis and corticosteroid treatment in the 90 days after CSVV diagnosis. **(Figure 1)**

Figure 1. SDD Patient Diagram for Inclusion in the CSVV and Prior NOAC Exposure Cohort



RESULTS

- In FAERS, we identified 363 potential cases of NOAC-induced CSVV of which 47(13%) met our case selection criteria (**Table1**).

Table 1. Clinical Characteristics of NOAC Cases Associated with CSVV* in FAERS

Selected Characteristics	Dabigatran (n=7)	Rivaroxaban (n=25)	Apixaban (n=14)	Edoxaban (n=1)
FDA approval date	10/19/2010	07/11/2011	12/28/2012	01/08/2015
Age (years)¥	n=6	n=24	n=14	
Mean	67	65	73	
Median age, years (range)	70 (54-78)	68 (28-87)	76 (49-90)	
Sex				
Male	5	10	9	1
Reported Indication				
Atrial fibrillation	5	13	10	1
Venous thromboembolism	1	10	4	-
Not reported	1	2	-	-
Time-to-onset (days)				
Median (range)	7 (2-23)	11 (1-120)	10 (1-547)	7
Biopsy confirmed, n (%)	6 (86)	18 (72)	7 (50)	1 (100)
Physician diagnosed	1	7	7	-
Dechallenge/Rechallenge				
Positive dechallenge	7	25	13	1
Rechallenge	1	2	-	-
Not reported	-	-	1	-
Type of CSVV, n (%)				
Leukocytoclastic	6 (86)	14 (56)	8 (57)	-
Henoch-Schonlein	-	4 (16)	-	-
Other†	1 (14)	7 (28)	6 (43)	1 (100)
Clinical Intervention, n (%) §				
Discontinuation of offending NOAC	7 (100)	25 (100)	13 (93)	1 (100)
Treatment with corticosteroids	5 (71)	17 (68)	3 (21)	1 (100)
Offending anticoagulant substitution§				
Another NOAC	3	2	2	1
Vitamin K antagonist	1	5	1	-
Low molecular weight heparin	1	5	2	-
Not reported	2	13	9	-
Serious Outcomes§				
Death	-	1	1	-
Hospitalization	6	18	9	1
Life threatening	-	1	1	-
Other serious	1	7	12	-

*As of March 16, 2018
¥ Refers to the number of cases in which the specific demographic data were provided; balance of the total had incomplete data
†Other includes non-specific types of CSVV (e.g., urticarial/ulcerative/necrotic vasculitis)
§More than one clinical intervention, outcome, or NOAC may have been reported per case

- In SDD, we identified 3,659 CSVV cases with prior NOAC exposure, with 85% of events occurring within 10 days**. (Table 2)**

Table 2. Clinical Characteristics of NOAC Cases Associated with CSVV in SDD

Patient Characteristic		
	N	%
Number of unique patients	3,659	
Demographics		
Mean Age, (SD)	75.2	(10.3)
Age		
30-39	33	0.9
40-49	71	1.9
50-59	223	6.1
60-69	642	17.5
70+	2,690	73.5
Gender		
Male	1,793	49.0
Any NOAC dispensing, up to 10 days prior to CSVV diagnosis	3,112	85.1
Clinical Characteristics		
Atrial Fibrillation, up to 183 days before CSVV diagnosis	2,876	78.6
Skin biopsy, up to 14 days before or after CSVV diagnosis	704	19.2
Prednisone and/or Prednisolone treatment, up to 90 days after CSVV diagnosis	1,123	30.7
Prednisone and/or Prednisolone treatment, up to 90 days after CSVV diagnosis AND skin biopsy, up to 14 days before or after CSVV diagnosis	244	6.7
Cutaneous Small Vessel Vasculitis Coding on day of Diagnosis*		
Vascular disorders of skin	1,040	28.4
Henoch-Schonlein allergic purpura	752	20.6
Vasculitis limited to the skin, unspecified	598	16.3
Allergic purpura	378	10.3
Other specified hypersensitivity angiitis	368	10.1
Other vasculitis limited to the skin, specified NEC	265	7.2
Hypersensitivity angiitis	225	6.1
Hypersensitivity angiitis, unspecified	138	3.8
* Counts may sum to greater than the total number of unique patients due to patients with multiple valid index-defining codes on their index date		

DISCUSSION & CONCLUSIONS

- Consistent with US utilization patterns *(results not shown),* our FAERS case series indicates that rivaroxaban accounted for the largest number of cases (n=25), followed by apixaban (n=14), dabigatran (n=7), and edoxaban (n=1).
- In both FAERS and SDD, the majority of CSVV cases occurred within 10 days of NOAC exposure, suggesting a possible temporal association between NOACs and CSVV. CSVV occurred primarily in patients 70 years and older.
- In the pre-marketing phase 3 trials, the incidence of vasculitis adverse events was (0.1 to 0.2%) among all NOACs and was similar to that of the comparator (i.e., warfarin, which is labeled for vasculitis in the Warnings and Precautions Section).
- Rapid assessments of electronic health information data in SDD are important tools in pharmacovigilance and help bridge the gap between spontaneous reports and observational studies.
- Future efforts will characterize the risk of CSVV among warfarin and NOAC users in SDD using subsequent inferential analysis.

LIMITATIONS

- FAERS limitations include underreporting, variable reporting quality, selective or delayed reporting and the lack of event adjudication.
- SDD analysis limitations include unknown positive predictive value for ICD-9-CM/ICD-10-CM diagnosis codes used to define CSVV.

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