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Complementary Use of U.S. FDA's Adverse Event Reporting System and Sentinel System to Characterize Direct Oral Anticoagulants-Associated Cutaneous Small Vessel Vasculitis

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Abstract

Background—Cutaneous small vessel vasculitis (CSVV) has been reported after exposure to direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban.

Objective—We used the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) to describe clinical characteristics associated with CSVV among DOAC-exposed patients. Furthermore, we characterized this signal in the Sentinel System to relate the clinical data from the individual FAERS cases to population-based electronic healthcare data.

Methods—We queried FAERS for all cases of CSVV associated with DOACs from U.S. approval date of each DOAC through March 16, 2018. Within the Sentinel System, we identified incident CSVV cases using ICD-9 and ICD-10 diagnosis codes among adults aged ≥ 30 years who received a DOAC in the prior 90 days between January 1, 2010, and June 30, 2018. We excluded patients with evidence of select autoimmune diagnoses in the 183 days prior to their CSVV diagnoses and reported patient characteristics in the 183-day period prior to CSVV diagnoses.

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Prior Presentation: Preliminary findings were presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) in Philadelphia, PA August 24–28, 2019.

Results—In FAERS, we identified 50 cases of CSVV reported with rivaroxaban (n=26), apixaban (n=14), dabigatran (n=9), and edoxaban (n=1). Approximately 50% of the cases reported time to onset within 10 days after DOAC exposure. When specified, the predominant type of CSVV reported was leukocytoclastic vasculitis (n=31), followed by Henoch-Schonlein purpura (n=4). Hospitalization occurred in most of the cases (n=37). Switching of the offending agent after the development of CSVV was reported (n=26). Three rivaroxaban (n=3) cases and one dabigatran case (n=1) reported positive rechallenge. In the Sentinel system, we identified 3659 CSVV cases with prior DOAC exposure, with 85% of events occurring within 10 days.

Conclusions—The assessment of FAERS cases, combined with the temporal clustering of the Sentinel System cases suggest a possible causal relationship of DOACs and CSVV. Future efforts should characterize the risk of CSVV among the various DOAC users.

Keywords

vitamin K antagonist oral anticoagulants; cutaneous small vessel vasculitis; leukocytoclastic vasculitis; Henoch-Schonlein purpura; adverse drug reaction

Cutaneous small vessel vasculitis (CSVV) is a single organ, skin-isolated small vessel vasculitis, often leukocytoclastic vasculitis (LCV), without apparent systemic vasculitis or extracutaneous involvement.[1–3] CSVV can be triggered by infections, medications, autoimmune disease, or malignancy. It also can be idiopathic when there is no evidence of an inciting factor.[1,4] Various terms are used interchangeably in the medical literature to describe CSVV, including drug-induced vasculitis, LCV, hypersensitivity vasculitis, hypersensitivity angiitis, cutaneous leukocytoclastic angiitis, and allergic vasculitis.[3,5] The incidence of CSVV is not well known; however, available studies estimate it to be between 15 and 45 cases per million adults per year.[6–8]

Classically, CSVV presents as a symmetric palpable purpura of the lower extremities but can sometimes involve skin on the trunk and upper extremities.[3,5] Clinical presentation such as urticarial lesions and ulcerative vesicles or nodules may be indicative of deeper or medium vessel involvement.[3] Confirmation of CSVV diagnosis is by skin biopsy, ideally taken from a lesion present for 18 to 48 hours to avoid non-specific results.[1,4] Histologically, CSVV presents with inflammatory infiltrate composed of neutrophils, primarily affecting postcapillary venules, with fibrin deposits around the vessel wall, endothelial swelling, and extravasation of red blood cells.[1,4]

By definition, CSVV primarily is limited to the skin; however, an organ-threatening systemic vasculitis can occur later in the disease course.[1,2] Therefore, CSVV is considered a symptom that requires excluding potential systemic involvement that can affect management and prognosis.[1,2] For example, Henoch-Schonlein purpura (HSP), a subset of CSVV is characterized by cutaneous, gastrointestinal, joint, and/or kidney involvement that has the same initial presentation as CSVV; however, its management and prognosis are different.[1,2] Additionally, patients initially diagnosed with CSVV can later develop systemic forms of small vessel vasculitides (e.g., antineutrophil cytoplasmic antibody–associated vasculitis).[2]

The association of drugs with the development of CSVV is documented with various therapeutic agents.[9] Symptoms usually occur 7 to 10 days after drug initiation; however, shorter and longer periods of drug exposure have been reported with various agents.[9,10] In most cases, discontinuation of the offending agent can resolve drug-induced CSVV with good prognosis.[4] Treatment with corticosteroids and immunosuppressive agents has been used in some cases.[11] Although not completely understood, the mechanism of drug-induced CSVV is thought to be mediated by the deposition of immune complexes in small vessels.

According to current guidelines direct oral anticoagulants (DOACs), also known as non–vitamin K oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, apixaban and edoxaban, are now the preferred treatment for reducing the risk of stroke in atrial fibrillation (AFib) and in the prevention and treatment of venous thromboembolism (VTE).[12,13] Betrixaban, the newest approved DOAC, was not included in this study due to its limited market uptake. Mechanistically, DOACs directly target the enzymatic activity of thrombin or factor Xa. In the postmarket setting, DOACs appear to be most frequently associated with type III and type IV delayed drug hypersensitivity reactions both mild and severe in nature.[14] Additionally, all DOACs are labeled for hypersensitivity reactions ranging from skin rash to anaphylactic reactions, suggesting that these drugs may induce an immune response in some patients. Research exploring the pathogenesis of DOAC-associated CSVV is lacking. However, CSVV associated with warfarin and heparin has been described and attributed to immune-complex deposition.[15,16]

In the pivotal DOAC trials, vasculitis adverse events including CSVV were reported in patients treated with DOACs. For example, in the ROCKET-AF trial (7111 patients treated with rivaroxaban) the incidence of cutaneous vasculitis in the rivaroxaban arm was low (0.01%).[17,18] Similarly, vasculitis adverse events including CSVV were reported in all premarketing trial data supporting the approval of all DOACs, but the incidence of these adverse events was low[19–21] and similar to the comparator (i.e., warfarin or placebo). Notably, warfarin already is labeled for vasculitis in the Adverse Reactions section of the prescribing information.[22]

During routine postmarketing surveillance, the U.S. Food and Drug Administration (FDA) Division of Pharmacovigilance identified postmarketing cases of CSVV reported after DOAC exposure.[23–26] This prompted a review of all CSVV cases submitted to the U.S. FDA Adverse Event Reporting System (FAERS) database and published in the medical literature. Furthermore, we characterized this signal in the Sentinel System to relate the clinical data from the individual FAERS cases to population-based electronic healthcare data. This evaluation provides a complementary assessment of DOAC-associated CSVV using two different data sources available to the FDA in the postmarket setting.

Methods

FAERS and Literature Case Series Data

We conducted a postmarketing case series analysis to identify and describe all potential cases of CSVV reported with DOACs. We queried the FAERS database from the U.S. approval date of each DOAC for postmarketing cases of CSVV reported with DOACs

received by FDA through March 16, 2018. FAERS is a computerized spontaneous reporting system that encompasses> 14 million adverse event reports submitted voluntarily by health care professionals, consumers, and mandatorily by manufacturers. The FAERS database is designed to support the FDA's postmarking safety surveillance program for drug and therapeutic biologic products.[27] Adverse events are coded using the *Medical Dictionary for Regulatory Activities (MedDRA*) terminology. MedDRA is the international medical terminology developed by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.[28]

To identify cases of CSVV, we searched the FAERS database using the Standardized MedDRA Query (SMQ) "Vasculitis" (*narrow search*). SMQs are validated, pre-determined sets of MedDRA terms grouped together after extensive review, testing, analysis, and expert discussion.[28] We included cases that met the following case definition: clinical diagnosis of CSVV with or without histological confirmation by skin biopsy. Cases that met the case definition were assessed for a causal association with DOACs using published FDA guidance.[29] A case had a probable causal association if there was a plausible temporal sequence to a DOAC along with skin biopsy findings consistent with CSVV and absence of factors with a contributory or confounding role (i.e., unknown or negative dechallenge, concomitant drugs frequently associated with CSVV[9] or active diseases associated with CSVV including malignancies, infectious, autoimmune disease). Possible cases had a plausible temporal sequence to a DOAC administration that included clinical descriptions of CSVV (i.e., palpable purpura) documented by a physician (e.g., dermatologist), but lacked specific skin biopsy findings. PubMed and Embase were searched for additional cases published in the literature but not submitted to FAERS. The search terms consisted of ("dabigatran" OR " rivaroxaban" OR "apixaban" OR "edoxaban") AND ("vasculitis" OR "leukocytoclastic vasculitis") through September 20, 2019. All literature case reports obtained were reviewed using the same case definition and causal assessment used in the FAERS search.

The assessment of cases included patient demographics, DOAC reported reason for use, time to onset of CSVV, CSVV adverse event characteristics (e.g., biopsy confirmed, type of CSVV, dechallenge/rechallenge and treatment information, and serious adverse drug experiences). The regulatory definition of serious adverse drug experiences includes outcomes of death, life-threatening events, hospitalizations, disability, congenital anomalies, and other important medical events. Only descriptive statistics were used to characterize results.

Investigation of CSVV in Sentinel System

The Sentinel System is a distributed data network of electronic healthcare databases used by FDA for active surveillance of medical product safety. The Sentinel System includes large national insurers, integrated delivery care networks, and the 100% Medicare fee-for-service plan. Currently, the Sentinel System has a cumulative 310.8 million patient identifiers from 2000 to 2018. Each Data Partner maintains information on their enrollees and periodically formats quality checked data into a Common Data Model.[30,31] This facilitates quick and systematic querying of the data in response to safety questions. The data include medical

and pharmacy claims, including inpatient and outpatient diagnosis, procedures, retail, and outpatient dispensing. After the specifications are agreed on with FDA staff, the Sentinel Operation Center distributes an analytic program that can be executed against the Common Data Model to the various Data Partners. The analytic programs are run locally, and summary-level statistics are returned to the Sentinel Operation Center for aggregation.

We used data from the Sentinel System, provided by 17 Data Partners from January 1, 2010, to June 30, 2018. The cohort included patients who received a DOAC (defined using National Drug Codes) (Appendix S1) in the 90 days prior to the index date (Figure 1). Index date was defined as first diagnosis of CSVV (defined using ICD-9 and ICD-10 codes) within 183 days (washout period) (Appendix S2). Because most of the CSVV cases identified in FAERS were in adults over ≥ 30 years, we limited the analysis to that population. We required continuous enrollment in health plans with both medical and pharmacy coverage of at least 183 days prior to CSVV diagnosis and 90 days post index date. Gaps in coverage of 45 days were allowed since they usually represent administrative gaps and not actual disenrollment. Given the association of CSVV with autoimmune disease, we excluded patients with autoimmune disease (defined using ICD-9 and ICD-10 codes) (Appendix S3) in the 183 days prior to index date. Among patients with diagnosis of CSVV, we examined the proportion of patients with a recorded history of skin biopsy and prednisone/prednisolone treatment within 14 and 90 days post index date, respectively. We reported patient characteristics in the 183-day period prior to CSVV diagnoses (e.g., patient demographics, any DOAC dispensing up to 10 days prior to CSVV diagnosis and CSVV coding on day of diagnosis). Only descriptive statistics were used to characterize the results.

Results

FAERS and Literature Case Series Data

The FAERS search retrieved 50 cases that met the case definition and plausible causal association to a DOAC. Thirteen of the fifty cases from FAERS were also reported in the literature. We did not identify any additional cases in the literature search. Rivaroxaban accounted for the largest number of cases (n=26), followed by apixaban (n=14), dabigatran (n=9), and edoxaban (n=1). The mean age was 70 years and the median age was 68 years (range 28–90 years); 26 (52%) were males and 24 (48%) were females. AFib was the most common indication for all DOACs (n=33, 66%), followed by VTE (n=15, 30%). All 50 cases reported a serious outcome per regulatory definition, mostly specifying hospitalization (n=37, 74%). The descriptive characteristics of all 50 cases are presented in Table 1.

Approximately 50% of the cases reported time to onset within 10 days post DOAC exposure (range 1–547 days). When specified, the predominant type of CSVV reported was LCV (n=31, 62%), followed by HSP (n=4, 8%) with the remaining cases describing non-specific types of CSVV including necrotic and ulcerative vasculitis (n=15, 30%). A positive dechallenge was reported in all 50 cases. Additionally, three rivaroxaban cases and one dabigatran case reported a positive rechallenge. Switching of the offending DOAC after the development of CSVV was reported in 26 (52%) cases. This switch included 10 (20%) cases reporting a switch to another DOAC, followed by vitamin K antagonists (VKAs) (n=8, 16%) and low molecular weight heparins (LMWHs) (n=8, 16%). Corticosteroids were

the most frequently reported treatment after the development of CSVV (n=26, 52%). The 50 cases included 33 (66%) skin biopsy confirmed cases and 17 (34%) physician and or dermatologist diagnosed cases.

We assessed 33 (66%) cases as probable from a causal association perspective considering the plausible temporal sequence to a DOAC, the histopathologic confirmation of CSVV via skin biopsy and the lack of known predisposing factors such as other concomitant medications and/or underlying diseases known to be associated with CSVV. We assessed the remaining 17 (34%) cases as having a possible causal association with a DOAC due to reasonable although less plausible temporal sequence, the lack of skin biopsy findings to confirm the diagnosis of CSVV as well as other predisposing factors.

Sentinel System Data

We identified 3659 CSVV cases with evidence of DOAC dispensing at least 90 days before the case date. Approximately 85% of patients had a DOAC dispensing at least 10 days before the CSVV diagnosis. Similar to the FAERS data, the demographic characteristics among patients with a CSVV diagnosis in the Sentinel System showed a 1:1 male:female ratio with the number of CSVV cases increasing with age. The mean age (75.2 years) of patients with CSVV diagnosis post DOAC exposure in the Sentinel System was approximately similar to those in FAERS (Table 2). Similar to the FAERS data, atrioventricular fibrillation diagnosis was present in a majority of patients (n=2876, 78.6%). Skin biopsy up to 14 days before or after the CSVV diagnosis occurred in 704 patients (19.2%). Corticosteroid treatment within 90 days after CSVV diagnosis occurred in 1123 patients (30.7%). Similar to the FAERS cases, the most common CSVV diagnosis in the Sentinel System was vascular disorders of the skin (1040 patients, 28.4%), followed by HSP (752 patients, 20.6%).

Discussion

To our knowledge, the 50 cases identified in FAERS and the literature represents the largest published case series of DOAC-associated CSVV. Consistent with U.S. utilization patterns, rivaroxaban accounted for the largest number of cases followed by apixaban, dabigatran, and edoxaban.[32] Approximately 50% and 85% of events occurred within 10 days of DOAC exposure in FAERS and Sentinel System, respectively. This finding in FAERS and the Sentinel System suggests that DOAC-associated CSVV may be an acute event. This is generally consistent with drug-induced CSVV that typically appears within 7 to 10 days after exposure to a drug but may range from 2 days to years.[9] Moreover, this finding represents an adequate time to allow for a sufficient quantity of antibody to produce an antibody-antigen complex.[9] Furthermore, in the FAERS case series and in the Sentinel System, CSVV cases had a similar mean age and were equally reported in both males and females, consistent with the epidemiology of CSVV[2] and the patient population typically exposed to DOACs.

We identified three rivaroxaban-associated CSVV cases with a positive rechallenge. In two cases, rivaroxaban was restarted because rivaroxaban-associated CSVV was not frequently reported in the medical literature.[33,34] Similarly, we identified a dabigatran rechallenge case

where the DOAC was restarted because the physician was unaware of the patient's previous history of dabigatran-associated CSVV and it recurred within 10 days.

The predominant reported type of CSVV in the case series was LCV, followed by HSP. The LCV cases reported a palpable purpura, characterized by small skin lesions suggesting only small vessel involvement. The HSP cases reported cutaneous and kidney involvement.[35] Several cases reported urticarial lesions, ulcerative vesicles, or nodules suggestive of small and medium vessel involvement.[1] In one HSP case, the initial diagnosis of rivaroxaban-associated LCV lesions began to resolve five days after switching to apixaban. However, on follow-up, persistent proteinuria prompted a kidney biopsy that showed HSP.[36] This highlights the importance of follow-up post-CSVV diagnosis because the initial presentation of HSP can be indistinguishable from other types of CSVV; however, its management and prognosis are different.[2] Similar to the FAERS cases, the most common CSVV diagnosis in the Sentinel System was vascular disorders of the skin followed by HSP. However, we are unable to determine which patients in the cohort had CSVV and then subsequently developed HSP.

The treatment of drug-induced CSVV involves discontinuation of the suspected agent, usually with good prognosis. Typically, corticosteroids and immunosuppressive agents are reserved for extensive disease.[1,4] Fifty percent of the patients in the FAERS case series were treated with corticosteroids after discontinuation of the suspected DOAC. Furthermore, 31% of the Sentinel System cohort showed evidence of prednisone and/or prednisolone treatment, up to 90 days after CSVV diagnosis. This may suggest that some patients did not require treatments with corticosteroids, although topical and other injectable corticosteroids may have been used to treat these patients, which was not captured in the Sentinel System analysis. In FAERS, some patients improved after the suspected switching to other anticoagulants. Researchers reported a similar finding of switching patients that experienced hypersensitivity reactions with DOACs to VKAs and LMWH.[14] The FAERS case series also highlights the ability to switch to other DOACs after experiencing CSVV. They reported a similar finding in which patients who developed a reaction to rivaroxaban tolerated other DOACs and vice versa.[14] The successful switch to another DOAC after developing DOAC-associated CSVV in the case series supports a lack of cross-reactivity between these agents, although additional studies are necessary to elucidate this finding.[14]

Historically, numerous terms have been used interchangeably to describe CSVV. The American College of Rheumatology (ACR) criteria of 1990 refers to CSVV as "hypersensitivity vasculitis."[5] However, the Chapel Hill Consensus Conference (CHCC) revised 2012 nomenclature system refers to CSVV as "cutaneous leukocytoclastic angiitis."[3] The use of multiple terms to describe CSVV may account for the variability in MedDRA preferred terms used to identify vasculitis adverse events in FAERS and for the variability of diagnostic codes observed in the Sentinel System when attempting to capture CSVV events as an outcome.

The study is not without limitations. The limitations of the FAERS data are well-known and have been described elsewhere.[29,37] In this feasibility assessment in the Sentinel System, we did not exclude alternative causes of CSVV except autoimmune disease; the history of

active infection or active malignancy was difficult to ascertain. Additionally, we did not differentiate incident from prevalent DOAC exposure or adjust for potential confounders. Additional limitations include the lack of validation for the codes used to identify CSVV events and skin biopsy. Therefore, the positive predictive value of the procedures and outcome codes used in this analysis are unknown. Moreover, we did not account for the presence of other drugs that may be associated with CSVV in the Sentinel System analysis.

Given the high use of DOACs and the underreporting of adverse events in the postmarketing setting, we cannot calculate true incidence of CSVV as a denominator is not available.[37] CSVV represents a relatively rare adverse event associated with DOACs in susceptible individuals that may result in systemic involvement and hospitalization.[11] Additional observational studies should be planned to further characterize the risk of CSVV among DOAC users and to evaluate if there is differential risk by individual DOAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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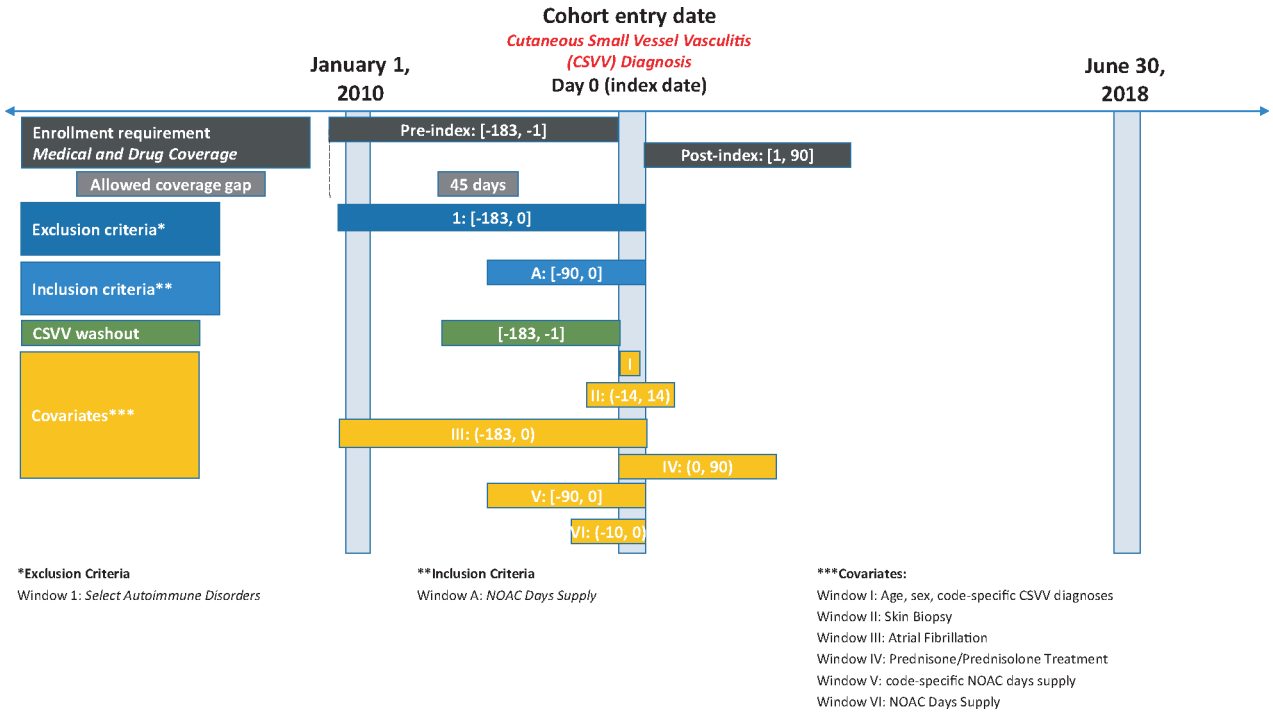

Figure 1.

Sentinel system patient diagram for inclusion in the CSVV and prior DOAC exposure cohort.

Table 1.

Descriptive Characteristics of Cases Reporting CSVV Associated with DOACs in FAERS or Published Literature from Approval of each DOAC through March 16, 2018 (n=50)[a,b]

Selected Characteristics	Dabigatran (n=9)	Rivaroxaban (n=26)	Apixaban (n=14)	Edoxaban (n=1)
FDA approval date	10/19/2010	07/11/2011	12/28/2012	01/08/2015
Age (years)[c]	n=8	n=25	n=14	
Mean	69	65	73	-
Median age, years (range)	70 (54–78)	68 (28–87)	76 (49–90)	-
Sex				
Male	6	10	9	1
Female	3	16	5	-
Reported reason for use				
Atrial fibrillation	8	14	10	1
Venous thromboembolism	1	10	4	-
Not reported	-	2	-	-
Time-to-onset (days)				
Median (range)	10 (2–23)	12 (1–120)	10 (1–547)	7
Biopsy confirmed	7	18	7	1
Physician diagnosed	2	8	7	-
Dechallenge/Rechallenge				
Positive dechallenge	9	26	13	1
Rechallenge	1	3	-	-
Not reported	-	-	1	-
Type of CSVV				
Leukocytoclastic	8	15	8	-
Henoch-Schonlein	-	4	-	-
Not specified[d]	1	7	6	1
Clinical Intervention[e]				
Discontinuation of offending DOAC	9	25	13	1
Treatment with corticosteroids	6	17	3	1

Selected Characteristics	Dabigatran (n=9)	Rivaroxaban (n=26)	Apixaban (n=14)	Edoxaban (n=1)
Offending anticoagulant substitution[e]				
Another DOAC	4	3	2	1
Vitamin K antagonist	2	5	1	-
Low molecular weight heparin	1	5	2	-
Not reported	2	13	9	-
Serious Outcomes[e,f]				
Hospitalization	8	19	9	1
Life threatening	-	1	1	-
Other serious	1	11	12	-
Causality Assessment				
Probable	7	18	7	1
Possible	2	8	7	-

[a] Literature search was conducted through September 20, 2019.

[b] Betrixaban the newest approved DOAC was not included in this study due to its limited market uptake.

[c] Refers to the cases in which age information was reported.

[d] Include non-specific types of CSVV (e.g., vasculitis/ulcerative/necrotic vasculitis).

[e] More than one clinical intervention, outcome, or DOAC may have been reported per case.

[f] Per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, and other serious important medical events.

Table 2.

Clinical Characteristics of DOAC Cases Associated with CSVV in Sentinel System

Patient Characteristic	N	%
Number of unique patients	3659	
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+	2690	73.5
Sex		
Male	1793	49.0
Female	1865	51.0
Any DOAC dispensing, up to 10 days prior to CSVV diagnosis	3112	85.1
Clinical Characteristics		
Atrial Fibrillation, up to 183 days before CSVV diagnosis	2876	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	1123	30.7
Prednisone and/or Prednisolone treatment, up to 90 days after CSVV biopsy, up to 14 days before or after CSVV diagnosis	244	6.7
Cutaneous Small Vessel Vasculitis Coding on day of Diagnosis[a]		
Vascular disorders of skin	1040	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

[a]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.