Medicines Adverse Reactions Committee

Meeting date	5/12/2024	Agenda item	3.2.1
Title	**Direct-acting oral anticoagulants and the possible risk of cutaneous small vessel vasculitis**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	
Dabigatran	Pradaxa	Boehringer Ingelheim (NZ) Limited	
	Dabigatran etexilate Sandoz*	Sandoz New Zealand Limited	
	Dabigatran etexilate*	Teva Pharma (New Zealand) Limited	
Rivaroxaban	Xarelto	Bayer New Zealand Limited	
	Rivaroxaban Dr. Reddy's*	Dr Reddy's New Zealand Limited	
	Rivaroxaban (Clinect)*	Clinect NZ Pty Limited	
	Rivaroxaban Sandoz*	Sandoz New Zealand Limited	
	Rivaroxaban Viatris*	Viatris Limited	
Apixaban	Eliquis	Pfizer New Zealand Limited	
	*No published data sheet		
PHARMAC funding	Dabigatran (Pradaxa) and rivaroxaban (Xarelto) are fully funded. Apixaban is not funded.		
Previous MARC meetings	None.		
International action	None.		
Prescriber Update	None.		
Classification	Prescription medicine		
Usage data	Number of funded community dispensings in 2023: • Dabigatran 75 mg: 7,018 • Dabigatran 110 mg: 130,660 • Dabigatran 150mg: 117,331 • Rivaroxaban 10 mg: 23,239 • Rivaroxaban 15 mg: 82,537 • Rivaroxaban 20mg: 139,319 No usage data is available for apixaban as this is not a funded medicine.		
Advice sought	**The Committee is asked to advise:** • Whether the data sheets for direct-acting oral anticoagulants (dabigatran, rivaroxaban and apixaban) should be updated to list cutaneous vasculitis as an adverse reaction.		

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1 PURPOSE

This report reviews a signal of cutaneous vasculitis with direct-acting oral anticoagulants (DOACs). The review was triggered by local spontaneous reports of cutaneous vasculitis (including leukocytoclastic vasculitis) associated with rivaroxaban and dabigatran.

In 2019, Medsafe published a Monitoring Communication highlighting a possible risk of vasculitis with the use of dabigatran. During the monitoring period (14 November 2019 to 14 May 2020), there were no further reports received and no further action was taken. Since that time, further reports of vasculitis have been received, highlighting the need for a further review.

2 BACKGROUND

2.1 Direct-acting oral anticoagulants

Mechanism of action

Dabigatran, rivaroxaban and apixaban are direct-acting oral anticoagulants (DOACs), which directly inhibit components of the coagulation cascade. Dabigatran inhibits thrombin while apixaban and rivaroxaban inhibit factor Xa (Figure 1) [1]. Edoxaban is another factor Xa inhibitor that is not currently approved in New Zealand.

Figure 1: The effects of direct oral anticoagulants (DOACs) on the coagulation cascade.

Source: Van Gorp RH and Schurgers LJ. 2015. New Insights into the Pros and Cons of the Clinical Use of Vitamin K Antagonists (VKAs) Versus Direct Oral Anticoagulants (DOACs). Nutrients 7(11): 9538-9557. URL: https://www.mdpi.com/2072-6643/7/11/5479 (accessed 13 November 2024).

Indications

DOACs are indicated for prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation (AF) in adults with at least one identified risk factor. Risk factors include congestive heart failure, hypertension, age ≥65 years, diabetes mellitus, and prior stroke, transient ischaemic attack or systemic embolism [2, 3].

DOACs are also indicated for treatment of deep-vein thrombosis (DVT) or pulmonary embolism (PE), prevention of recurrent DVT or PE, and prophylaxis of venous thromboembolism (VTE) in adults undergoing major orthopaedic surgery [2]. Rivaroxaban has an additional indication for the prevention of major cardiovascular events in patients with coronary artery disease or peripheral artery disease (in combination with aspirin) [4].

Place in therapy

DOACs are generally preferred to warfarin for anticoagulation as they have significantly fewer monitoring requirements and interactions, and a rapid onset of action. However, anticoagulant selection must be based on patient characteristics and comorbidities, such as bleeding risk, renal function and adherence [5].

Warfarin may be preferred in moderate-to-severe mitral stenosis, severe liver or renal dysfunction, gastrointestinal disease, antiphospholipid syndrome or when thrombosis has occurred despite DOAC treatment. DOACs are contraindicated in patients with mechanical heart valves [5].

In AF, the need for anticoagulation is determined by balancing the risk of stroke against the risk of bleeding. In patients with AF this can be assessed using the CHA_2DS_2-VASc and HAS-BLED assessment tools. Treatment decisions should be made in accordance with local clinical guidelines [2, 3].

Initiation and monitoring

Prior to initiation, assessment and management of bleeding risk factors is needed (eg, medicines that increase bleeding risk such as NSAIDs, hypertension, alcohol use). Investigations should be undertaken to assess for contraindications or risk factors. Investigations include:

- full blood count to assess for thrombocytopaenia or anaemia
- coagulation screen to rule out clotting disorders and establish baseline
- renal function, which may influence selection and dosage
- liver function, as severe liver dysfunction may impact clearance.

Renal function should be established at baseline and checked at least annually in patients treated with DOACs [5].

Adverse reactions

DOACs carry an increased risk of bleeding from any anatomical site, which can be fatal. Patients should be monitored throughout treatment for signs of bleeding. Haemorrhage may present as weakness, paleness, dizziness, headache, dyspnoea or unexplained swelling. Anaemia may present with chest pain. Risk factors for bleeding include increasing age, renal impairment, concomitant strong P-gp inhibitors, concomitant antiplatelet medicines and history of gastrointestinal bleeding. Any unexplained fall in blood pressure or haemoglobin should prompt investigation for bleeding.

Anticoagulant-related nephropathy has also been reported.

GI disorders such as dyspepsia, nausea, vomiting, diarrhoea and constipation are common.

Hypersensitivity reactions, including skin rash and serious skin reactions, have been reported with DOACs [4, 6].

2.2 Medicine-induced cutaneous small vessel vasculitis

The term vasculitis encompasses a large, diverse group of conditions with overlapping presentations. Vasculitis is classified according to the size of the vessels affected, organs affected, and association with systemic disease or other aetiology [7].

This review uses the broad term cutaneous small vessel vasculitis (CSVV) to refer to vasculitis events of interest. The term leukocytoclastic vasculitis (LCV) is also used and describes the histological findings of CSVV.

Aetiology and pathogenesis [8]

Aetiologies of CSVV include infection, autoimmune conditions, malignancy and medicines.

Medicines are thought to cause around 10-15% of cases of LCV. Medicines that are known to cause CSVV include granulocyte colony stimulating factor, allopurinol, sulphonamides, propylthiouracil, penicillins, carbamazepine and diltiazem. However, this list is far from exhaustive, and many medicines have been reported in the literature as suspected of causing vasculitis.

Medicine-induced CSVV is believed to be a type III immune complex reaction, involving abnormal immune complex formation and deposition, activation of the complement and inflammatory cascade, endothelial activation and altered gene expression. Post-capillary venules have increased susceptibility to immune complex deposition due to slow blood flow and low oxygen content.

Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis is another umbrella term for systemic vasculitides that may present with skin involvement [9]. ANCA-associated vasculitis is thought to be a type II antibody-mediated cytolytic/cytotoxic reaction. It has been reported less frequently in association with medicines.

Presentation [8]

Medicine-induced CSVV involves inflammation and necrosis of the superficial post-capillary dermal venules presenting as palpable, non-blanching purpuric papules. This may range from punctate small petechiae to large confluent purpuric patches (Figure 2). More severe inflammation resulting in ischaemia may present as bullous, pustular or ulcerated papules or plaques.

Figure 2: Cutaneous vasculitis

Source: Dermnet. URL: https://dermnetnz.org/imagedetail/18941-vasculitis and https://dermnetnz.org/imagedetail/9533-cutaneous-vasculitis (accessed 19 November 2024).

Lesions commonly affect dependent areas such as the legs and ankles, but can also affect the trunk, arms, palms, soles and face. Areas of friction and pressure such as the buttocks and back may be affected, especially in immobile patients.

The rash may be painful, burning or itching and accompanied by fever, arthralgia and myalgia. Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) may be elevated.

The onset time of skin rash in medicine-induced CSVV is typically 7 to 10 days after exposure to the causative medicine. However, delayed onset medicine-induced CSVV has also been reported, for example, with tumour necrosis factor alpha (TNF-alpha) inhibitors.

Medicine-induced CSVV is often mild, limited to the skin and resolves upon stopping the offending medicine. However, in severe cases, complications can include necrosis and infection. Systemic involvement (eg, renal, gastrointestinal) has also been reported.

Henoch-Schönlein purpura, now referred to as IgA vasculitis, is usually seen in children but can occur in adults. It has also been associated with medicines. It is a leukocytoclastic vasculitis caused by IgA immune complex deposition of in small vessels, which presents with non-thrombocytopaenic palpable purpura, abdominal pain and arthralgia, and renal involvement in a subset of patients [10].

Urticarial vasculitis is a rare presentation that is reported in section 3.2: Literature case reports. It presents with urticarial lesions with histological features of LCV.

Diagnosis [8]

A clinical presentation of CSVV is ideally confirmed by skin biopsy taken 24-48 hours after lesions have developed. The histological characteristics of CSVV are fibrinoid necrosis of the vessel wall, red blood cell extravasation and a neutrophilic infiltrate with leukocytoclastic. Perivascular nuclear dust and epidermal changes may also be seen. Direct immunofluorescence may be negative in medicine-induced CSVV.

A diagnosis of medicine-induced CSVV may be considered where there is a plausible temporal association between starting the medicine and onset of symptoms, and alternative aetiologies such an infection, autoimmune disease or malignancy have been excluded.

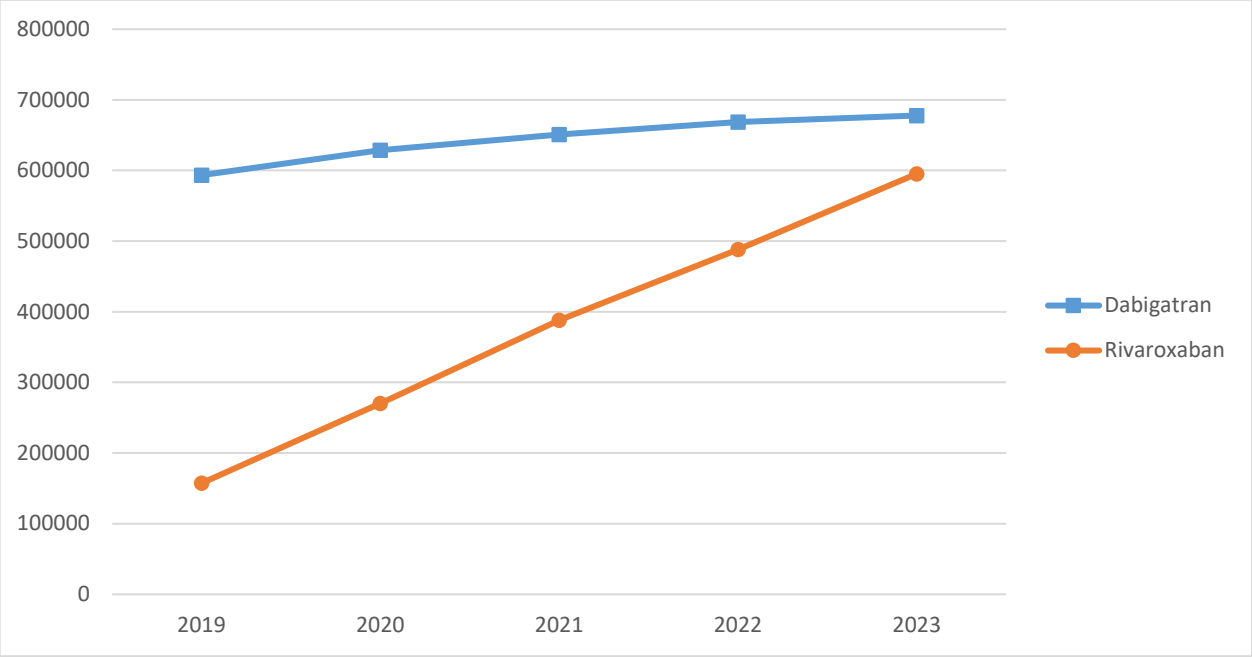
Treatment

Uncomplicated medicine-induced CSVV usually resolves spontaneously with withdrawal of the causative medicine. In some cases, treatment with systemic corticosteroids may be warranted.

2.3 Usage

The total number of funded community dispensings of dabigatran and rivaroxaban are shown in Figure 1. Dispensing data is not available for apixaban as this is not a funded medicine.

Figure 3: Total number of funded community dispensings of dabigatran and rivaroxaban, 2019 to 2023



Source: Pharmaceutical Data web tool version 12 September 2024 (data extracted from the Pharmaceutical Collection on 23 July 2024). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (Accessed 24 October 2024).

Note: The Pharmaceutical Data web tool includes summary data about dispensings that were dispensed in the community and funded by the New Zealand Government. The number of dispensings includes the following formulations: dabigatran 75 mg, 110 mg and 150 mg and rivaroxaban 10 mg, 15 mg and 20 mg.

2.4 New Zealand data sheets and international product information

The New Zealand data sheets for dabigatran (Pradaxa), rivaroxaban (Xarelto) and apixaban (Eliquis) do not list vasculitis as an adverse reaction.

The EU SmPC and UK SPC for apixaban (Eliquis) list cutaneous vasculitis with an unknown frequency in section 4.8.

Except as noted above, vasculitis is not listed as an adverse reaction in any other product information for dabigatran, apixaban or rivaroxaban in the United States, Canada, Europe, United Kingdom or Australia.

3 SCIENTIFIC INFORMATION

3.1 New Zealand case reports

The New Zealand pharmacovigilance database was searched for cases reporting PTs under the SMQ 'vasculitis', where dabigatran, rivaroxaban or apixaban were suspect medicines. The search returned 12 cases. One case was excluded as the reported PT was arteritis and was therefore considered out of scope of this review. The 11 included cases are summarised in table 1.

Five cases [redacted] related to dabigatran. The reported PTs were vasculitic rash (2), vasculitis (1), leukocytoclastic vasculitis (1), and vasculitis allergic (1). [redacted] One case reported concomitant allopurinol treatment, which is a possible alternative aetiology.

The remaining 6 cases [redacted] related to rivaroxaban. The reported PTs were vasculitic rash (2), vasculitis (2), leukocytoclastic vasculitis (1), and chillblains (1). [redacted] One case reported concomitant allopurinol treatment, which is a possible alternative aetiology.

Table 1: Spontaneous reports in the New Zealand pharmacovigilance database describing vasculitis with direct-acting oral anticoagulants.

Report ID	Report date	Age and sex	Suspect medicine	Concomitant medicines	[redacted]	[redacted]	[redacted]	PTs	[redacted]
Dabigatran									
100884	[redacted]/04/12	83 F	Dabigatran	None reported	[redacted]	[redacted]	[redacted]	Vasculitic rash	[redacted]
117107	[redacted]/07/15	78 F	Dabigatran	Digoxin Sotalol Diltiazem Metoprolol	[redacted]	[redacted]	[redacted]	Acute kidney injury Pulmonary haemorrhage Vasculitis	[redacted]
126181	[redacted]/10/17	82 F	Dabigatran	Insulin Hydroxyurea Gliclazide Metformin Candesartan Aspirin Furosemide Bisoprolol Atorvastatin	[redacted]	[redacted]	[redacted]	Vasculitic rash	[redacted]
127024	[redacted]/01/18	60 M	Dabigatran	Allopurinol Atorvastatin Cilazapril + hydrochlorthiazide Omeprazole	[redacted]	[redacted]	[redacted]	Leukocytoclastic vasculitis	[redacted]
NZ-Medsafe-153769	[redacted]/11/23	66 F	Dabigatran	None reported	[redacted]	[redacted]	[redacted]	Vasculitis allergic Impaired renal function Hypersensation skin Cough	[redacted]

Report ID	Report date	Age and sex	Suspect medicine	Concomitant medicines	[redacted]	[redacted]	[redacted]	PTs	[redacted]
Rivaroxaban									
134994	[redacted]/11/19	81 M	Rivaroxaban	Clopidogrel Metoclopramide Allopurinol Atorvastatin	[redacted]	[redacted]	[redacted]	Atheroembolism Skin necrosis Vasculitis	[redacted]
137112	[redacted]/05/20	81 F	Rivaroxaban	None reported	[redacted]	[redacted]	[redacted]	Dermatitis Vasculitic rash	[redacted]
145469	[redacted]/10/22	70 F	Rivaroxaban [redacted]	Dexamethasone Ibuprofen Mupirocin Omeprazole Paracetamol	[redacted]	[redacted]	[redacted]	Vasculitis	[redacted]
146508	[redacted]/02/23	73 M	Rivaroxaban [redacted]	Colecalciferol	[redacted]	[redacted]	[redacted]	Chillblains	[redacted]
NZ-Medsafe-153646	[redacted]/11/23	69 F	Rivaroxaban [redacted]	Metoprolol Losartan Bendroflumethiazide Atorvastatin Lansoprazole Metformin Mometasone cream	[redacted]	[redacted]	[redacted]	Leukocytoclastic vasculitis Nausea Diarrhoea Acute kidney injury Decreased appetite	[redacted]

Report ID	Report date	Age and sex	Suspect medicine	Concomitant medicines	[redacted]	[redacted]	[redacted]	PTs	[redacted]
NZ-Medsafe-154325	[redacted]/01/24	F	Rivaroxaban [redacted]	None reported	[redacted]	[redacted]	[redacted]	Vasculitic rash Skin burning sensation Cough Impaired renal function	[redacted]

3.2 Literature case reports

A literature search of Embase and PubMed was carried out with the search terms 'dabigatran' or 'rivaroxaban' or 'apixaban' or 'edoxaban' AND 'vasculitis'. In the Embase search, the 'vasculitis' term was modified with the disease subheading 'side effect'.

The following exclusion criteria were applied to the case reports:

- No clinical description or definitive diagnosis of CSVV
- Concomitant treatment with medicines associated with CSVV (eg, propylthiouracil, allopurinol, granulocyte-colony stimulating factor)
- Concomitant active infection, rheumatologic condition or malignancy
- Unknown or negative dechallenge outcome
- Lack of clear temporal association between DOAC treatment and CSVV.

A total of 28 literature case reports were identified that reported vasculitis associated with a DOAC. 10 reports were excluded for the following reasons:

- Outcome of DOAC dechallenge not explicitly stated.
- Limited clinical description of CSVV and differential diagnosis, or lack of definitive diagnosis.
- Limited discussion of exclusion of alternative aetiologies or confounders.
- Unclear information on temporal relationship.
- Concomitant allopurinol.
- Comorbid infection or malignancy.

The 18 included case reports are summarised in Table 2 and Table 3. See Annex 1 for the literature references. In each report, reasonable steps to exclude alternative aetiologies such as infection, autoimmune conditions, malignancy, or concomitant medicines were documented. All but one of the cases were confirmed by skin biopsy. The remaining case was diagnosed via tele-health consultation with a dermatologist.

Table 2: Descriptive characteristics of literature case reports of cutaneous small vessel vasculitis associated with DOACs.

	Dabigatran (n=3)	**Rivaroxaban (n=5)**	**Apixaban (n=9)**	**Edoxaban (n=1)**	**All (n=18)**
Sex					
Male	1	2	6	1	10
Female	2	3	3		8
Median age (range) in years	70 (57-74)	45 (28-76)	62 (45-95)	69	64.5 (28-95)
Indication					
AF	2	2	5	1	10
DVT/PE	1	3	4		8
Median time to onset (range) in days	4 (3-7)	7 (4-730)	10 (1-30)	14	7 (1-730)
Diagnosis					
Skin biopsy confirmed	3	4	7	1	15
(or) Physician diagnosed		1	2		3

	Dabigatran (n=3)	Rivaroxaban (n=5)	Apixaban (n=9)	Edoxaban (n=1)	All (n=18)
Dechallenge/rechallenge					
Positive dechallenge	3	5	9	1	18
Positive rechallenge		1			1
Type of vasculitis					
LCV	2	3	9	1	15
Henoch-Schönlein		1			1
Other*	1	1			2
Clinical intervention					
Discontinuation of suspect DOAC	3	5	9	1	18
Treatment with corticosteroids	3	2	9		14
Treatment with other agents**	1	1			2
Substituted anticoagulant					
Another DOAC	1	2	4	1	8
Warfarin	2	1	4		7
LMWH		2	1		3
Seriousness					
Serious	3	5	4		12
Not serious			5	1	6

*Other reported types of vasculitis were urticarial vasculitis and ANCA-associated vasculitis (AAV).
** Other reported treatments were hydroxychloroquine and rituximab.

Table 3: Summary of literature case reports describing cutaneous vasculitis associated with DOAC treatment.

Author (year published)	Age and sex	Suspect medicine (indication)	Type of vasculitis	Description	Time to onset	Diagnosis by	Dechallenge /rechallenge	Substituted medicine
Apixaban								
Nasir et al (2018) [11]	60 M	Apixaban (AF)	LCV	Within 10 days of starting apixaban, the patient presented with burning, pruritic, petechial rash on the lower extremities. Punch biopsy and direct immunofluorescence studies were consistent with immune-mediated leukocytoclastic small-vessel vasculitis. The patient was switched to rivaroxaban and treated with prednisone with gradual resolution of symptoms.	10 days	Skin biopsy	Positive dechallenge	Rivaroxaban
Daul et al (2020) [12]	74 F	Apixaban (DVT)	LCV	One week after starting apixaban, the patient noted a small red rash on lower extremities. Two weeks later, the patient presented with worsened petechial, non-pruritic, non-blanching rash on both lower legs and reported occasional mild paraesthesia. LCV was diagnosed by tele-dermatology consultation. The patient was switched to rivaroxaban and treated with a topical corticosteroid with significant improvement over the following months.	1 week	Physician	Positive dechallenge	Rivaroxaban
Esbech et al (2020) [13]	62 M	Apixaban (AF)	LCV	One hour after the first dose of apixaban, the patient had tingling and burning sensations in the legs which rapidly evolved into haematomas and later ecchymosis. It was decided to continue the treatment. After 8 days of treatment, the patient was readmitted due to worsening of symptoms. Apixaban was discontinued and treatment with LMWH was initiated. In the following days, the haematomas increased in size and spread all over the body. Skin biopsy was consistent with LCV. The patient was treated with prednisone and a topical steroid with improvement of LCV over 8 weeks.	<1-8 days	Skin biopsy	Positive dechallenge	LMWH
Khan et al (2020) [14]	68 F	Apixaban (AF)	LCV	One month after starting apixaban, the patient developed diffuse palpable tender non-blanching violaceous coalescent macules and patches with purple bullae on thighs, calves and feet. Punch biopsy and direct immunofluorescence confirmed pandermal LCV with no medium vessel involvement. The patient was switched to warfarin and treated with prednisone with resolution over 4 months.	1 month	Skin biopsy	Positive dechallenge	Warfarin

Author (year published)	Age and sex	Suspect medicine (indication)	Type of vasculitis	Description	Time to onset	Diagnosis by	Dechallenge /rechallenge	Substituted medicine
Spears et al (2020) [15]	95 M	Apixaban (AF)	LCV	The patient presented with a 1-day history of diffuse, mildly tender but nonpruritic palpable purpura of his feet, ankles, and lower legs, with onset 11 days after changing from warfarin to apixaban. Blood tests showed thrombocytopenia, low complement, positive ANA and positive rheumatoid factor. Infectious and autoimmune laboratory tests were otherwise negative. Skin biopsy was consistent with LCV. Prednisone was started with rapid improvement of rash and platelet count. Apixaban was replaced with warfarin with no recurrence of vasculitis.	11 days	Skin biopsy	Positive dechallenge	Warfarin
Yang et al (2021) [16]	86 M	Apixaban (AF)	Drug-induced lupus with LCV	On day 15 after starting apixaban, the patient noted nonpruritic petechial rash on his feet, followed by weakness and dyspnoea on exertion leading to hospital admission. The rash later spread to the arms and legs with associated myalgia. Skin biopsy showed LCV. Drug-induced lupus was diagnosed on the basis of strong positive anti-histone antibody titre, systemic symptoms, temporal relationship between starting apixaban and onset of symptoms, and rapid resolution after discontinuation of apixaban and initiation of prednisone.	15 days	Skin biopsy	Positive dechallenge	Warfarin
El-Sabbagh et al (2023) [17]	45 M	Apixaban (DVT)	LCV	One week after starting apixaban, the patient developed a diffuse petechial rash and a non-blanching palpable purpura on the lower extremities, including palms and soles, some of which had coalesced, blistered, and ulcerated. Prior to this, he had been taking rivaroxaban for an unstated period. The rash had been present for one month and had persisted despite discontinuation of apixaban. Medical evaluation found atrioventricular dissociation accompanied by bradycardia, renal insufficiency with elevated serum creatinine, proteinuria, and haematuria, and leg oedema. Skin biopsy was consistent with cutaneous LCV. Kidney biopsy was not taken, and it is unknown whether the renal findings represented systemic involvement. The LCV resolved with discontinuation of apixaban and treatment with a steroid.	1 week	Skin biopsy	Positive dechallenge	Warfarin

Author (year published)	Age and sex	Suspect medicine (indication)	Type of vasculitis	Description	Time to onset	Diagnosis by	Dechallenge /rechallenge	Substituted medicine
Famularo and Casorati (2023) [18]	59 F	Apixaban (PE)	LCV	Two days after starting apixaban, the patient developed painful, swollen, warm knees and palpable and painful purpura on the lower legs. Investigations were normal, aside from elevated CRP. Patient declined skin biopsy. Apixaban was switched to enoxaparin followed by transition to dabigatran. Prednisone was initiated with improvement of rash over a few weeks. There was no relapse at 2-month follow-up.	2 days	Physician	Positive dechallenge	Dabigatran
Adebayo et al (2024) [19]	55 M	Apixaban (DVT)	LCV	The patient developed widespread, mildly tender, non-itchy palpable purpura on his lower extremities, such as feet, legs, and thighs 17 days after changing from warfarin to apixaban. Skin biopsy was consistent with LCV. Apixaban was changed to dabigatran and prednisone was initiated with rapid improvement of the rash.	17 days	Skin biopsy	Positive dechallenge	Dabigatran
Dabigatran								
Cakmak et al (2014) [20]	74 F	Dabigatran (AF)	LCV	One week after starting dabigatran, the patient developed a raised, purpuric macular rash on the trunk and upper limbs. Skin biopsy was consistent with LCV. Dabigatran was switched to warfarin. The LCV was treated with prednisolone and the lesions resolved within 72 hours.	1 week	Skin biopsy	Positive dechallenge	Warfarin
An et al (2017) [21]	57 M	Dabigatran (DVT)	LCV	The patient was switched from warfarin to dabigatran. Three days later, the patient developed palpable purpura and petechiae from the feet to lower abdomen and lower arms, and lower leg oedema. Punch biopsy was consistent with LCV and direct immunofluorescence was negative. LCV was diagnosed in accordance with American College of Rheumatology criteria. Dabigatran was switched to enoxaparin followed by transition to rivaroxaban. The LCV was treated with prednisone and a topical steroid with gradual resolution.	3 days	Skin biopsy	Positive dechallenge	Rivaroxaban

Author (year published)	Age and sex	Suspect medicine (indication)	Type of vasculitis	Description	Time to onset	Diagnosis by	Dechallenge /rechallenge	Substituted medicine
Macedo Brás et al (2024) [22]	70 F	Dabigatran (AF)	Urticarial vasculitis	The patient presented with a 7-day history of worsening painful, pruritic rash that started 4 days after initiating dabigatran. She had a history of skin eruptions with rivaroxaban and apixaban that were less severe and resolved with discontinuation. Examination revealed a papular rash with geographic patterns, a pale centre surrounded by violaceous lesions, and an erythematous annular pattern on the trunk, back, and proximal limbs. Skin biopsy was consistent with a clinical picture of LCV, however direct immunofluorescence was negative. A diagnosis of normocomplementaemic urticarial vasculitis was established. Dabigatran was switched to warfarin. The patient was treated with antihistamines, prednisolone and hydroxychloroquine with improvement over the following month.	4 days	Skin biopsy	Positive dechallenge	Warfarin
Rivaroxaban								
Coppola et al (2017) [23]	67 F	Rivaroxaban (AF)	LCV	The patient was hospitalised with lower extremity purpura and nonspecific abdominal pain one week after changing from warfarin to rivaroxaban. Blood tests showed a slight leukocytosis and elevated CRP and ESR. Abdominal ultrasound and CT scan revealed thickening of the intestinal wall and oedema with the lumen filled with fluid and prominent engorgement of mesenteric vessels. Skin biopsy was consistent with LCV. Rivaroxaban was switched to enoxaparin. LCV was treated with prednisone with gradual resolution of symptoms and skin lesions at 2 weeks after admission. Resolution of the mural thickening was observed within 1 week. She continued warfarin therapy.	1 week	Skin biopsy	Positive dechallenge	Enoxaparin

Author (year published)	Age and sex	Suspect medicine (indication)	Type of vasculitis	Description	Time to onset	Diagnosis by	Dechallenge /rechallenge	Substituted medicine
Dean et al (2017) [24]	38 F	Rivaroxaban (DVT)	LCV	The patient presented to the emergency department with pain and swelling of the lower leg and was treated rivaroxaban for DVT and metformin for type 2 diabetes. The patient later represented to the emergency department with a diffuse purpuric skin eruption that started 4 days after starting rivaroxaban. The lesions appeared sterile and there were no systemic symptoms. Rivaroxaban was discontinued and the patient was discharged. One week later the patient represented with secondary infection of the existing skin lesions on the lower leg. The rash had otherwise improved on other areas of the body. Physical examination showed purpuric papules from the waist down in the areas of childhood thermal injuries, and there were urticarial-appearing plaques on the arms. Laboratory investigations were normal, aside from elevated ESR and CRP. Punch biopsies were consistent with leukocytoclastic vasculitis. The infection resolved with empirical antibiotic treatment. The DVT was treated with heparin bridging to warfarin and metformin was continued, with no recurrence of vasculitis at the 12-week follow-up appointment.	4 days	Skin biopsy	Positive dechallenge	Warfarin
Hasbal et al (2017) [25]	28 M	Rivaroxaban (DVT)	LCV	The patient, who was being treated for IgA nephropathy was hospitalised with non-blanching palpable purpura on lower legs that occurred 10 days following the addition of rivaroxaban for acute DVT. Rivaroxaban was replaced with enoxaparin and the skin lesions resolved within 1 week. Two weeks later, the patient was prescribed rivaroxaban again. Lower leg purpura reoccurred within 3 days of retreatment and a skin biopsy was consistent with LCV. Rivaroxaban was switched to enoxaparin and the skin lesions resolved. The patient was in a clinically steady state for IgA nephropathy during the two episodes of vasculitis.	10 days	Skin biopsy	Positive rechallenge	Enoxaparin

Author (year published)	Age and sex	Suspect medicine (indication)	Type of vasculitis	Description	Time to onset	Diagnosis by	Dechallenge /rechallenge	Substituted medicine
Chung et al (2018) [26]	45 M	Rivaroxaban (DVT/PE)	Henoch-Schönlein	Seven days after starting rivaroxaban for PE/DVT, the patient developed a non-blanching purpuric rash from ankles to abdomen. Night sweats, myalgias, arthralgias, pitting lower limb oedema, nausea and bilateral flank pain developed over the next week. Skin biopsy confirmed leukocytoclastic vasculitis. Investigations showed nephrotic-range proteinuria, microscopic haematuria, red cell casts and normal renal function. Other screens were negative. Rivaroxaban was changed to apixaban with subsequent improvement after 5 days and resolution after weeks. A few months later, persistent proteinuria and urinary sediment activity prompted kidney biopsy which confirmed IgA nephropathy. Ramipril was commenced with improvement in proteinuria.	1 week	Skin biopsy	Positive dechallenge	Apixaban
Argawal et al (2023) [27]	76 F	Rivaroxaban (AF)	AAV	The patient presented to ED with fatigue, bilateral lower extremity purpura, and a 24-hour history of haemoptysis. Physical examination also showed joint swelling in hand. She had been taking rivaroxaban for two years and was also taking levothyroxine and losartan. Cytoplasmic-ANCA titre and anti-myeloperoxidase antibody were positive. CT and bronchoscopy confirmed diffuse alveolar haemorrhage. Lung biopsy findings showed capillaritis suggestive of drug-associated ANCA-associated vasculitis (AAV). The combination of positive ANCA, purpuric lesions, and lung biopsy findings led to a diagnosis or drug-associated AAV. Rivaroxaban was thought to be the cause as it and other Factor X inhibitors have been previously associated with diffuse alveolar haemorrhage. Rivaroxaban was switched to dabigatran and she was treated with methylprednisolone and rituximab.	2 years	Physician/ lung biopsy	Positive dechallenge	Dabigatran
Edoxaban								
Celik et al (2024) [28]	69 M	Edoxaban (AF)	LCV	The patient presented with non-blanching erythematous palpable petechiae and purpura in the glutaeal region and lower extremities two weeks after starting edoxaban. Skin biopsy showed LCV. Edoxaban was switched to dabigatran with resolution of rash within two weeks.	2 weeks	Skin biopsy	Positive dechallenge	Dabigatran

LCV = leukocytoclastic vasculitis; AAV = Anti-neutrophil cytoplasm antibodies (ANCA) associated vasculitis; AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism

3.3 Other literature

3.3.1 Mohamoud et al (2020). Complementary use of US FDA's adverse event reporting system and sentinel system to characterize direct oral anticoagulants-associated cutaneous small vessel vasculitis. [29]

Objective

To use the US Food and Drug Administration Adverse Event Reporting System (FAERS) to describe clinical characteristics associated with CSVV among DOAC-exposed patients and further characterise this signal in the Sentinel System to relate the clinical data from the individual FAERS cases to population-based electronic healthcare data.

Methods

FAERS was searched for all cases of CSVV associated with DOACs from the US approval date of each DOAC to 16 March 2018, using the Standardised MedDRA Query (SMQ) 'vasculitis (narrow)'. Cases were included if they had a clinical diagnosis of CSVV, with or without confirmation by skin biopsy.

The cases were considered to have a probable causal association if there was:

- a plausible temporal sequence
- diagnosis by skin biopsy
- positive dechallenge and
- absence of known confounders (concomitant drugs frequently associated with CSVV or active malignancy, infection or autoimmune disease).

The cases were considered to have a possible causal association if there was:

- a plausible temporal sequence
- clinical description of CSVV documented by a physician, without skin biopsy.

A supplementary literature search was conducted. The cases were summarised by descriptive characteristics.

Using the Sentinel System, incident CSVV cases were identified using ICD-9 and ICD-10 diagnosis codes among adults aged ≥ 30 years who received a DOAC in the 90 days prior to CSVV diagnosis and between 1 January 2010 and 30 June 2018. Continuous medical and pharmacy coverage of at least 183 days prior to CSVV diagnosis and 90 days post index date was required. Patients with evidence of selected autoimmune diagnoses in the 183 days prior to their CSVV diagnoses were excluded. Patient characteristics in the 183-day period prior to CSVV diagnoses were summarised using descriptive statistics.

Results

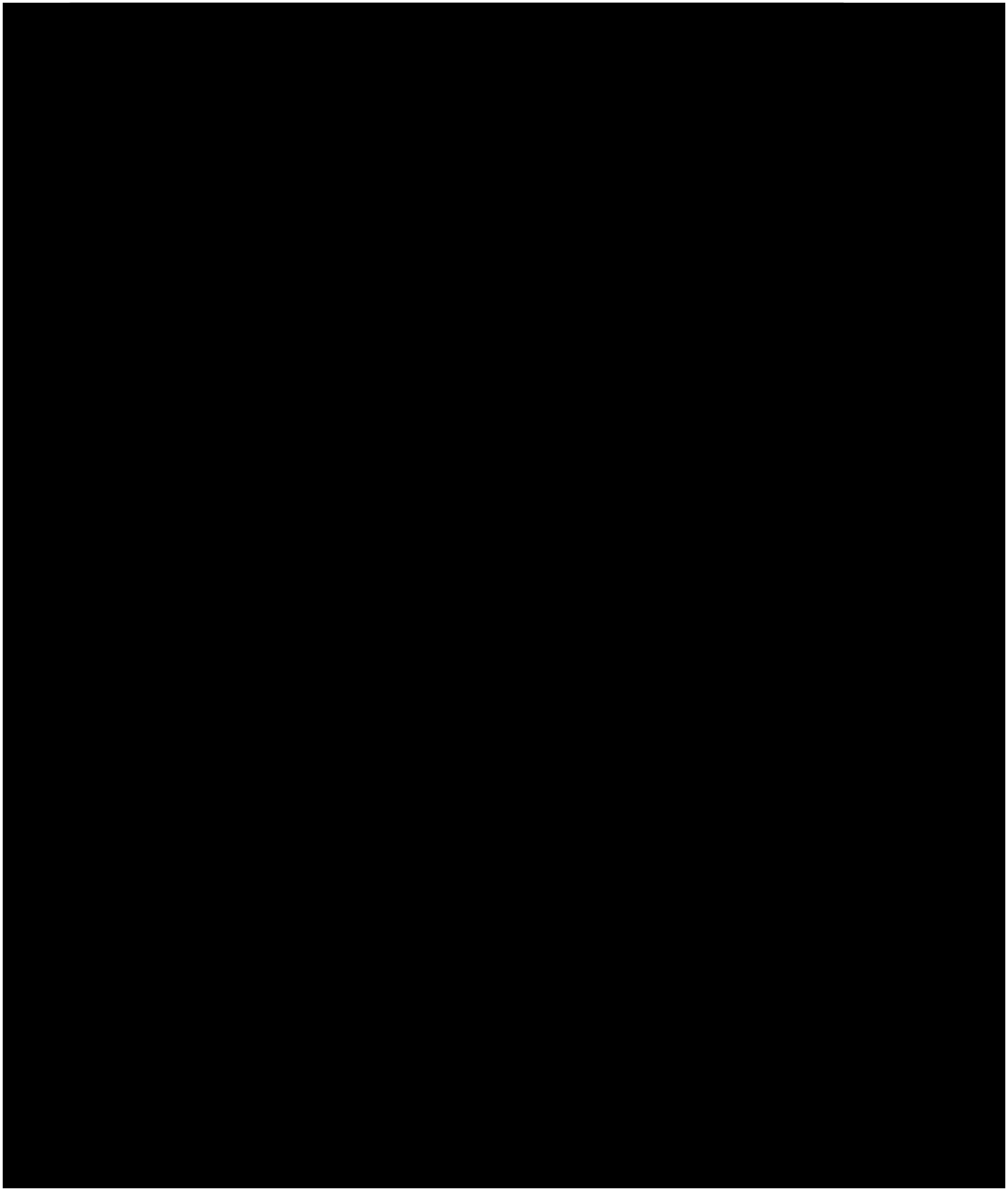
The FAERS search retrieved 50 cases. Thirteen of the fifty cases from FAERS were also reported in the literature, with no additional cases identified in the literature search. Rivaroxaban had the most cases (n=26), followed by apixaban (n=14), dabigatran (n=9), and edoxaban (n=1). The median age was 68 years (range 28–90 years). AF was the most common indication (n=33, 66%), followed by VTE (n=15, 30%). All 50 cases reported a serious outcome, with 74% reporting hospitalisation.

Half the cases reported a time to onset within 10 days on DOAC initiation. Most cases reported LCV (n=31, 62%). There were 33 cases (66%) confirmed by skin biopsy and the remainder were physician diagnosed. All but one of the cases reported positive dechallenge and four cases reported positive rechallenge.

The authors assessed 33 cases (66%) as meeting the criteria for a probable causal relationship, as they reported a plausible temporal sequence, diagnosis of CSVV by skin biopsy, and a lack of known predisposing factors.

The descriptive characteristics of the cases are presented in Table 4.

Table 4: 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]



[redacted]

The Sentinel System data identified 3659 CSVV cases with evidence of DOAC dispensing in the 90 days before the case date. Approximately 85% of patients had a DOAC dispensing up to 10 days before the CSVV diagnosis. Approximately 20% of patients had a skin biopsy within 2 weeks of CSVV diagnosis and 30% received corticosteroid treatment in the 3 months following diagnosis.

Table 5: Clinical characteristics of CSVV cases associated with DOACs in the Sentinel System.

[redacted]

Discussion

The FAERS search identified 50 cases of CSVV associated with DOACs. Rivaroxaban had the highest number of cases, followed by apixaban, dabigatran, then edoxaban. This was consistent with usage patterns at the time of analysis. Approximately 50% of cases had a time to onset within 10 days of DOAC initiation, which is consistent with a typical time to onset for drug-induced CSVV.

There were four cases reporting positive rechallenge. In two cases, rivaroxaban was restarted as it was not frequently reported in the literature as associated with CSVV. In another case, dabigatran was prescribed as the physician was unaware of the previous reaction, and CSVV recurred within 10 days.

The limitations of the Sentinel System data include lack of differentiation between incident and prevalent DOAC exposure, not excluding possible alternative causes such as malignancy, infection or other medicine, and lack of validation of outcome codes used in the analysis.

Comments

The cases reported in the literature are not identified, but it is likely that these are included in section 3.2 Literature case reports.

The Sentinel System data counts people taking a DOAC when they received a CSVV diagnosis, without taking into account length of exposure or whether they were new users. It also doesn't exclude known confounders such as malignancy, infection or other medicines associated with vasculitis. The Ajao et al paper below uses the Sentinel System data to estimate and compare the risk of CSVV among new users of DOACs and warfarin for AF.

3.3.2 Ajao et al (2022). A cohort study to assess risk of cutaneous small vessel vasculitis among users of different oral anticoagulants. [30]

Objective

The objective of this study was to assess the adjusted comparative risk of CSVV among patients with atrial fibrillation (AF) who newly initiated a DOAC (dabigatran, rivaroxaban, or apixaban) or warfarin in the Sentinel Distributed Database (SDD) to determine if CSVV risk is differential across oral anticoagulants using a cohort design.

Methods

Data source: The SDD is a United States database containing health data for 16 participating health plans (data partners) at the time of the study and 354 million patient identifiers. SDD combines analytic datasets meeting quality standards with standard SAS programs which may be customized for each analysis. The US FDA uses the SDD for evaluation of safety signals.

Study design: This is a retrospective new-user cohort study which identified patients who were new users of dabigatran, apixaban, or warfarin. Patients were aged ≥21 years, had at least six months of continuous medical and drug coverage prior to the first index dispensing between 19 October 2010 and 29 February 2020, and had a diagnosis of AF within the 183 days prior to the index dispensing date. Excluded patients were those with any of the following during the 183 days prior to the index dispensing date:

- evidence of institutional stay or dispensing of another study drug
- CSVV diagnosis or treatment
- diagnosis or treatment of selected autoimmune diseases (rheumatoid arthritis, lupus, Crohn's disease, Sjogren's syndrome, dermatomyositis, polymyositis, and cryoglobulinemia)
- cancer diagnosis or treatment
- kidney dialysis or transplant
- other anticoagulant indications (DVT, PE, joint replacement surgery prophylaxis).

Patients were followed from the index date until censoring which occurred when:

- a gap in anticoagulant days of supply exceeded three days
- patients initiated any other DOAC or warfarin
- study outcome occurred
- patients were disenrolled, died, or data were no longer available.

Outcome: CSVV was defined as a diagnosis of hypersensitivity angiitis, vasculitis of the skin, or allergic purpura in the ambulatory visit, other ambulatory visit, or emergency department care settings and a dispensing of an oral or topical steroid within 90 days of the diagnosis date. The Sentinel Patient Episode Profile Retrieval (PEPR) analytic tool was used to randomly generate an individual level line listing for 90 patients with a CSVV diagnosis. These cases were reviewed to ensure they likely represented DOAC-induced CSVV. The review was used to further define the study outcome. The outcome date was defined as the date of CSVV diagnosis.

Statistical methods: The risk of CSVV was compared for: 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. For each of the six comparisons, a logistic regression model was fitted within each data partner to estimate the probability of exposure, or propensity score, based on the following potential confounders: age (continuous variable), sex, autoimmune diseases, haematological blood disorders, viral infections, bacterial infections, anti-infectives, nonsteroidal anti-inflammatory drugs, psychoactive drugs, cardiovascular and diuretic drugs, beta-adrenergic receptor agonists, and anticonvulsants. For each comparison, the authors 1:1 matched exposed patients and their comparators within each Data Partner based on their propensity score using a nearest neighbour matching algorithm with a caliper of 0.05. Cox proportional hazard regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) in the matched cohort after aggregation across data partners. The Cox model was stratified by data partner, which allowed the baseline hazard function to be different across data partners; however, the HRs were assumed to be the same across data partners.

Results

The study population of AF patients included 328,249 rivaroxaban new users, 142,328 dabigatran new users, 532,973 apixaban new users and over 617,000 warfarin new users. Prior to matching, warfarin users were more likely to be Caucasian, have comorbidities such as haematological blood disorders, take cardiovascular and diuretic medicines and utilise healthcare compared to DOAC users. Dabigatran and rivaroxaban users had similar baseline characteristics, while apixaban users were slightly older, and more likely to have comorbidities and utilise healthcare. After propensity score matching, the matched cohorts were balanced on all measured covariates.

The CSVV crude incidence rates for the DOACs and warfarin ranged from 3.3 to 5.6 per 10,000-person years. The adjusted CSVV HRs and 95% CI for each comparison are shown in Table 6. There was no statistically significant difference in the risk of CSVV for any of the comparisons.

Table 6: Propensity score matched unconditional analysis of incidence of CSVV by DOACs and warfarin.

[redacted]

Discussion

The authors did not find a statistically significant increase in CSVV risk for any propensity score matched comparisons between DOACs and warfarin, or between DOACs. There was a non-significant increased risk of CSVV for dabigatran compared to warfarin, apixaban, and rivaroxaban.

The incidence rates of CSVV among DOACs and warfarin initiators with AF were low and ranged from 3.3 to 5.6 per 10,000-person years. The background rate of CSVV is unclear. However, the incidence of biopsy-proven LCV has been reported in the literature as 45 per million person-years and 7.5 cases per million patients. The estimated incidence rates in this study population are much higher than this. However, the use of biopsy to confirm LCV may mean that the background rate was underestimated.

Several study limitations were noted.

- CSVV is rare and the study may have been underpowered to detect a difference in the risk between anticoagulants.
- The study definition of CSVV was not validated and outcome misclassification may have resulted in bias of the risk estimates towards the null.
- Drug-induced CSVV is expected to occur shortly after initiation whereas the study included all events during exposure. This may have resulted in inclusion of cases unrelated to anticoagulant use and biased the estimates towards the null. This decision was made due to the possibility of delayed hypersensitivity reactions.
- This work was completed in a regulatory setting, with limitations around the sentinel system and a need to rapidly assess the safety signal. This meant that sensitivity analyses were not carried out, such as assessing a risk window or limiting the study period to when the compared medicines were both available. However, these analyses may have been underpowered due to rarity of CSVV.
- Residual confounding by unmeasured variables or variables not included in the propensity score (eg, calendar year) may have biased the study results.

The authors considered that despite the apparent lack of differential CSVV risk between anticoagulants, a potential association between oral anticoagulants and CSVV cannot be completely ruled out. Early recognition of drug-induced CSVV is important as prompt discontinuation of the offending medicine usually results in rapid improvement. Overall, the risk is likely to be low and the benefit-risk profile of DOACs remains favourable for the intended indications.

3.4 VigiLyze data

[redacted]

4 DISCUSSION AND CONCLUSIONS

This report presents a review of local case reports and literature case reports of CSVV associated with DOACs. Cutaneous vasculitis is not currently listed in the New Zealand data sheet for any DOAC. However, the EU SmPC and UK SPC list cutaneous vasculitis as a post-market adverse event for apixaban.

There have been 11 local case reports, of which 5 related to dabigatran and 6 related to rivaroxaban. [redacted] In some cases, the reported time to onset was approximate, or it was uncertain whether it was calculated from time of presentation or first symptoms. None of the reported onset times were consistent with the typical onset of medicine-induced CSVV of 7 to 10 days. However, delayed onset of medicine-induced CSVV has been reported. Two cases reported concomitant allopurinol, which were not identified as suspect medicines but are possible alternative aetiologies in those cases.

A review of the literature identified 18 case reports with a plausible relationship between DOACs and CSVV. There were 9 reports for apixaban, 5 reports for rivaroxaban, 3 reports for dabigatran and 1 report for edoxaban. All but one of the cases were confirmed by skin biopsy. The remaining case was diagnosed via tele-health consultation with a dermatologist. In each case, reasonable steps were documented to exclude

alternative aetiologies such as infection, autoimmune conditions, malignancy, or concomitant medicines. All cases reported improvement of CSVV after stopping the suspect DOAC and one case reported positive rechallenge.

The time to onset was consistent with the typical timeframe of 7 to 10 days in 8 of the cases. A further 4 cases had an onset time of 2 to 4 weeks. 5 cases reported a short time to onset of less than a week. One case reported a time to onset of 2 years.

The literature review identified a further two publications affiliated with the US FDA. A publication by Mohamoud et al describes the characteristics of reports of CSVV with DOACs in FAERS up to March 2018. The search retrieved 50 cases, of which 13 were also reported in the literature and are likely among those described in section 3.2. Most of the cases related to rivaroxaban (n=26), followed by apixaban (n=14) and dabigatran (n=9).

Two thirds of the cases met the defined criteria of a probable causal association, with a plausible temporal sequence, diagnosis by skin biopsy, positive dechallenge and absence of alternative aetiology. The remaining one third of the cases had a plausible temporal sequence and a clinical description of CSVV documented by a physician. Overall, half the cases reported a time to onset within 10 days of DOAC initiation. All but one of the cases reported positive dechallenge and four cases reported positive rechallenge.

A 2022 publication by Ajao et al, also affiliated with the US FDA, used the Sentinel Distributed Database (SDD) to estimate the adjusted comparative risk of CSVV among patients with atrial fibrillation (AF) who newly initiated a DOAC (dabigatran, rivaroxaban, or apixaban) or warfarin. The authors did not find a statistically significant difference in CSVV risk between DOACs and warfarin, or between DOACs. It should be noted that warfarin has also been associated with CSVV. As this is a rare outcome it is uncertain whether the study was powered to detect any difference in risk.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the data sheets for direct-acting oral anticoagulants (dabigatran, rivaroxaban and apixaban) should be updated to list cutaneous vasculitis as an adverse reaction.

6 ANNEXES

Annex 1 – Case report literature references

Annex 2 – Mohamoud et al

Annex 3 – Ajao et al

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