Medicines Adverse Reactions Committee

Meeting date	7/12/2023	Agenda item	3.2.1
Title	**Direct-acting oral anticoagulants (DOACs) and anticoagulant-related nephropathy (ARN)**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Dabigatran Rivaroxaban Apixaban	**Product name** See Table 1	**Sponsor**	
PHARMAC funding	Dabigatran and rivaroxaban are funded in the community and in hospitals. See Table 1 for details.		
Previous MARC meetings	Dabigatran • 176th meeting (6 December 2018) - Dose reductions for Pradaxa (dabigatran etexilate): DVT/PE indications • 175th meeting (13 September 2018) - Dabigatran and gout, gout aggravation and gout-like symptoms • 170th meeting (8 June 2017) - The risk of haemorrhage from concomitant use of statins and dabigatran • 148th meeting (8 December 2011) - Update on the safety profile of dabigatran (Pradaxa) • 147th meeting (8 September 2011) - Dabigatran safety profile Rivaroxaban • 149th meeting (8 March 2012) - Risk management plan: rivaroxaban (Xarelto) Dabigatran, rivaroxaban and apixaban • 180th meeting (5 December 2019) – Direct-acting oral anticoagulants and risk of recurrent thrombotic events		
International action	• Australia – TGA identified an association between ARN and oral anticoagulants as a class, and requested updates to product information • Europe – EMA PRAC investigated oral anticoagulants separately, and requested updates to dabigatran and rivaroxaban prescribing information • US – FDA currently investigating ARN as a form of acute kidney injury		
Prescriber Update	Dabigatran - is there a bleeding problem? – Sep 2011 Dabigatran etexilate (Pradaxa): Summary of reports to CARM – Dec 2011 Antithrombotic Medicines - Still Causing Bleeding – Mar 2012 Acute kidney injury – dangerous to continue some medicines – Mar 2014 Monitor renal function in elderly patients taking dabigatran – Dec 2015 Update: Oral anticoagulants and gastrointestinal bleeding – June 2016 Spotlight on rivaroxaban (Xarelto) – Mar 2019 Direct-acting oral anticoagulants may not be the best choice for patients with antiphospholipid syndrome – Sep 2019 Discuss possible effects on uterine bleeding in people taking oral anticoagulant therapy – Dec 2023		
Classification	Prescription medicine		

Usage data	See section 2.1.5

Advice sought	**The Committee is asked to advise:**
	• Whether there is evidence for an association between anticoagulant-related nephropathy and direct-acting oral anticoagulants as a class (dabigatran, rivaroxaban and apixaban)?
	  ○ If yes, are data sheet updates required (for example, to align with the recent updates requested by the TGA)?
	• If there is no evidence for the class, is there evidence for an association between anticoagulant-related nephropathy and particular direct-acting oral anticoagulants, and if so, which ones?
	  ○ Are data sheet updates required for the specified anticoagulants?
	• Does the topic require further communication, other than MARC's remarks in *Prescriber Update*?

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1 PURPOSE

Oral anticoagulants include warfarin, a vitamin K antagonist, and dabigatran etexilate, rivaroxaban and apixaban, which are direct-acting oral anticoagulants (DOACs).

Anticoagulant-related nephropathy (ARN), a form of acute kidney injury, has been identified as an adverse reaction associated with warfarin, and prescribing information in New Zealand and internationally reflects this risk. More recently, international regulators have reviewed the potential association of ARN with DOACs. The European Medicines Agency reviewed the risk with dabigatran and rivaroxaban (separate reviews) and requested updates to the prescribing information. The Australian Therapeutic Goods Administration (TGA) identified a class effect for all oral anticoagulants (warfarin + DOACs) and requested updates to the prescribing information. The United States Food and Drug Administration is currently reviewing the risk of acute kidney injury with DOACs.

In New Zealand, the Xarelto (rivaroxaban) data sheet was updated in May 2023 to include ARN. The current dabigatran and apixaban data sheets do not include ARN. Therefore, the purpose of this review is to consider whether ARN is a class effect for DOACs or for specific DOACs, and whether the data sheets should be updated.

2 BACKGROUND

2.1 Direct-acting oral anticoagulants (DOACs)

2.1.1 Approved products

Dabigatran etexilate, rivaroxaban and apixaban are the DOACs available in NZ. See Table 1 for the specific products and their funding status.

Table 1: Direct oral anticoagulants approved in New Zealand, as of 20 November 2023

Product name, form and dose	Sponsor	TT50	Community Funded	Hospital funded
Dabigatran etexilate (Direct thrombin inhibitor, ATC code: B01AE07)				
Pradaxa capsule, 75mg, 110mg, 150mg	Boehringer Ingelheim (NZ) Ltd	7557/1, 7557/1a, 7557/1b	Yes[a]	Yes[a]
Dabigatran etexilate (Teva)[b] capsule, 75mg, 110mg, 150mg	Teva Pharma (New Zealand) Limited	11070, 11070a, 11070b	No	No
Dabigatran etexilate Sandoz capsule, 75mg, 110mg, 150mg	Sandoz New Zealand Limited	10937, 10937a, 10937b	No	No
Rivaroxaban (Direct factor Xa inhibitor, ATC code: B01AF01)				
Rivaroxaban (Clinect)[c] film coated tablet, 10mg, 15mg, 20mg	Clinect NZ Pty Limited	10128, 10128a, 10128b	No	No
Rivaroxaban Sandoz[c] film coated tablet, 10mg, 15mg, 20mg	Novartis New Zealand Ltd	10722, 10722a, 10722b	No	No
Rivaroxaban Viatris[c] film coated tablet, 10mg, 15mg, 20mg	Viatris Limited	11058, 11058a, 11058b	No	No
Xarelto film coated tablet, 2.5mg, 10mg, 15mg, 20mg	Bayer New Zealand Limited	8275c, 8275, 8275a, 8275b	10mg, 15mg, 20mg	10mg, 15mg, 20mg
Apixaban (Direct factor Xa inhibitor, ATC code: B01AF02)				
Eliquis film coated tablet, 2.5mg, 5mg	Pfizer New Zealand Limited	9119, 9119a	No	No

Notes:

a. Pradaxa is the currently funded brand, but PHARMAC are consulting on a potential brand change for dabigatran capsules.

b. Dabigatran etexilate (Teva) is an approved generic, but it is not available, and the data sheet is not published. Pradaxa is the reference product.

c. Rivaroxaban (Clinect), Rivaroxaban Sandoz and Rivaroxaban Viatris are approved generics, but they are not available, and the data sheets are not published. Xarelto is the reference product.

Sources:

Medsafe. *Product/Application search*. URL: https://www.medsafe.govt.nz/regulatory/dbsearch.asp (accessed 20 November 2023).
PHARMAC. *Community Schedule March 2023*. URL: https://schedule.pharmac.govt.nz/ScheduleOnline.php (accessed 20 November 2023).
PHARMAC. *Hospital Medicines (HML) March 2023*. URL: https://schedule.pharmac.govt.nz/HMLOnline.php (accessed 20 November 2023).

2.1.2 Mechanism of action

The coagulation pathway is a cascade of events that leads to haemostasis. The intricate pathway allows for rapid healing and prevention of spontaneous bleeding. Two paths, intrinsic and extrinsic, originate separately but converge at a specific point, leading to fibrin activation. The purpose is to ultimately stabilise the platelet plug with a fibrin mesh [1].

All anticoagulant agents work by inhibiting the activity of thrombin. Thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, therefore its inhibition prevents the development of thrombus (Figure 1) [2].

The anticoagulatory effect of warfarin is due to inhibition of several components of the coagulation pathway including vitamin K-dependent factors II, VII, IX and X, and proteins C and S, therefore indirectly inhibiting thrombin. In contrast, dabigatran selectively and directly inhibits thrombin, and rivaroxaban and apixaban selectively and directly inhibit factor Xa (Figure 1) [2].

Figure 1: Coagulation cascade, showing site of action of warfarin, dabigatran, rivaroxaban and apixaban

2.1.3 Indications and dosing

The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. Anticoagulants are of less use in preventing thrombus formation in arteries, as in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin [3].

DOACs are indicated for prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation in adults with at least one identified risk factor, 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 [3].

Tables 2 to 4 show the approved standard dosing by indication for dabigatran [4], rivaroxaban [5] and apixaban [6]. See Annex 1 for additional prescribing information – with a focus on warnings and precautions, undesirable effects and overdose (ie, excessive anticoagulation).

Table 2: Dabigatran (Pradaxa) standard dosing by indication

Indication	Dose
SPAF	150mg twice daily Treatment should be continued life-long
pVTEp orthopaedic surgery	110mg initially then 110mg twice daily Knee replacement: Treat for 10 days Hip replacement: treat for 28-35 days
DVT/PE treatment	150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days Treat for 6 months
DVT/PE prevention	150mg twice daily Treatment should be continued life-long

SPAF: stroke prevention in atrial fibrillation; pVTEp: primary prevention of venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.

Source: Boehringer Ingelheim (NZ) Limited. 2020. *Pradaxa New Zealand Data Sheet* 11 March 2020. URL: https://www.medsafe.govt.nz/profs/Datasheet/p/Pradaxacap.pdf (accessed 27 August 2023).

Table 3: Rivaroxaban (Xarelto) standard dosing by indication

Indication	Dose
SPAF	20mg once daily Continue long-term on a risk-benefit basis
VTE prevention orthopaedic surgery	10mg taken once daily. Knee replacement: treat for 2 weeks Hip replacement: treat for 5 weeks
DVT/PE treatment and prevention of recurrent DVT/PE	15mg twice daily for initial DVT/PE treatment for 3 weeks Continue on 20mg once daily for prevention of recurrent DVT/PE, for as long as risk persists. After 6-12 months, consider dose reduction to 10mg once daily
CAD/PAD	2.5mg twice daily in combination with 100mg aspirin Continue treatment on risk-benefit basis

SPAF: stroke prevention in atrial fibrillation; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CAD: coronary artery disease; PAD: peripheral artery disease.

Source: Bayer New Zealand Limited. 2022. *Xarelto New Zealand Data Sheet* 29 May 2023. URL: https://www.medsafe.govt.nz/profs/Datasheet/x/Xareltotab.pdf (accessed 27 August 2023).

Table 4: Apixaban (Eliquis) standard dosing by indication

Indication	Dose
SPAF	5mg twice daily
VTE prevention orthopaedic surgery	2.5mg twice daily Knee replacement: treat for 10-14 days Hip replacement: treat for 32-38 days
DVT/PE treatment	2.5mg twice daily for 7 days, then 5mg twice daily
Prevention recurrent DVT/PE	2.5mg twice daily for at least 6 months

SPAF: stroke prevention in atrial fibrillation; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.
Source: Pfizer New Zealand Limited. 2019. Eliquis New Zealand Data Sheet 30 August 2019. URL: https://www.medsafe.govt.nz/profs/Datasheet/e/eliquistab.pdf (accessed 27 August 2023).

2.1.3.1 Renal function

Renal function should be assessed prior to initiation of a DOAC. Dose adjustments are required in those with reduced renal impairment, and use should be avoided with significant renal impairment. Dabigatran is predominately renally cleared (approximately 85%); the factor Xa inhibitors, rivaroxaban and apixaban, have lower renal clearance (approximately 25-35%) [3].

The New Zealand Formulary and the Best Practice Advocacy Centre (bpac^{NZ}) recommend that all individuals taking DOACs should have their renal function assessed at least annually, or more frequently if clinically indicated, for example in progressive kidney disease, hypovolaemia, dehydration or if nephrotoxic drugs are initiated, and in patients with co-morbidities or risk factors associated with CKD (eg, Māori or Pacific ethnicity, diabetes or hypertension) [3, 7].

The Xarelto (rivaroxaban) and Pradaxa (dabigatran) data sheets recommend that renal function should be assessed prior to initiation of treatment [4, 5], and the Pradaxa data sheet also recommends assessing renal function during treatment in certain clinical situations when renal function could decline or deteriorate (such as hypovolemia, dehydration and with certain co-medications) [4]. The Eliquis (apixaban) data sheet states that use is contraindicated in those with renal impairment with a creatinine clearance <25 mL/min, but there are no explicit recommendations for renal function monitoring [6].

2.1.3.2 Liver function

Apixaban and rivaroxaban are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment [5, 6]. No treatment experience is available for use of dabigatran in patients with liver enzymes >2 times the upper limit of normal, and use is not recommended in this population [4].

2.1.4 DOACs versus vitamin K antagonists (warfarin)

For most individuals, in the absence of contraindications, DOACs are preferred to treatment with warfarin. Routine International Normalised Ratio (INR) monitoring is not required during treatment with a DOAC, and they have fewer medicine and food interactions compared with warfarin [3, 7]. Table 5 is the New Zealand Formulary's comparison of the properties of warfarin and DOACs.

Table 5: Comparison of properties of warfarin and direct-acting oral anticoagulants*

Ongoing management of the patient taking on anticoagulant therapy should always consider modifiable risk factors for bleeding, treatment adherence and monitoring for adverse effects [7].

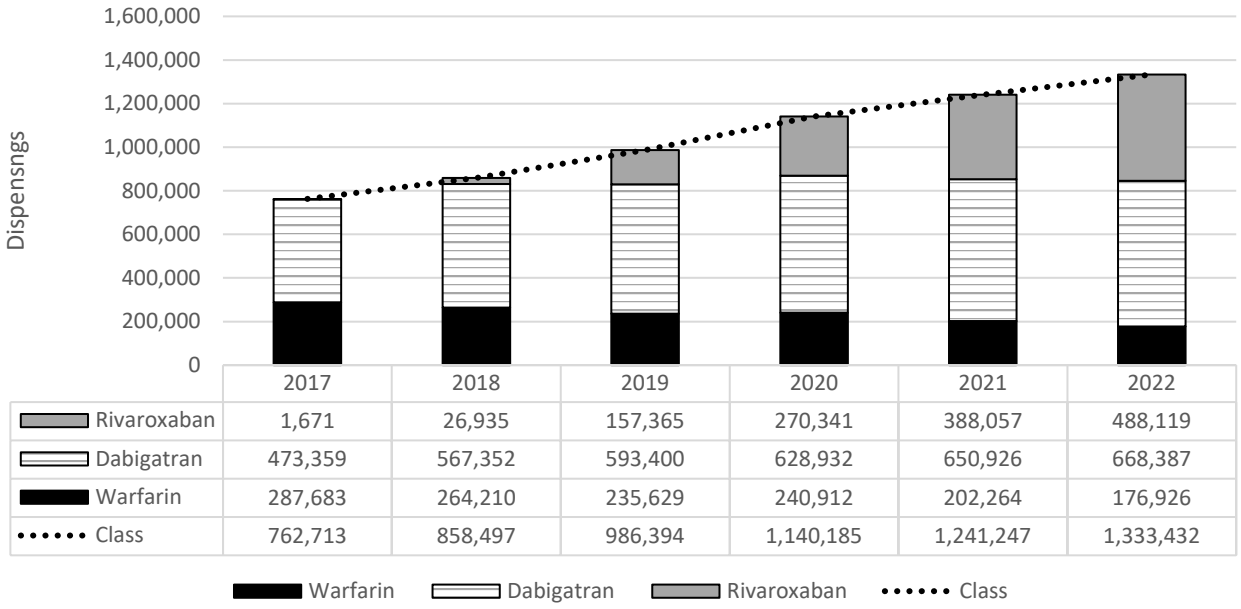
2.1.5 Usage data

The data below includes warfarin, to show how usage has changed since the widening of access to rivaroxaban and dabigatran. Apixaban is not funded in the community, so there is no dispensing data.

Figure 2 shows oral anticoagulant usage data by the number of dispensings (a) and the number of people (b) from 2017 to 2022. As a class, oral anticoagulant use is increasing. Dabigatran has the greatest use per year, but rivaroxaban has seen the largest overall increase since 2017. Warfarin use has decreased.

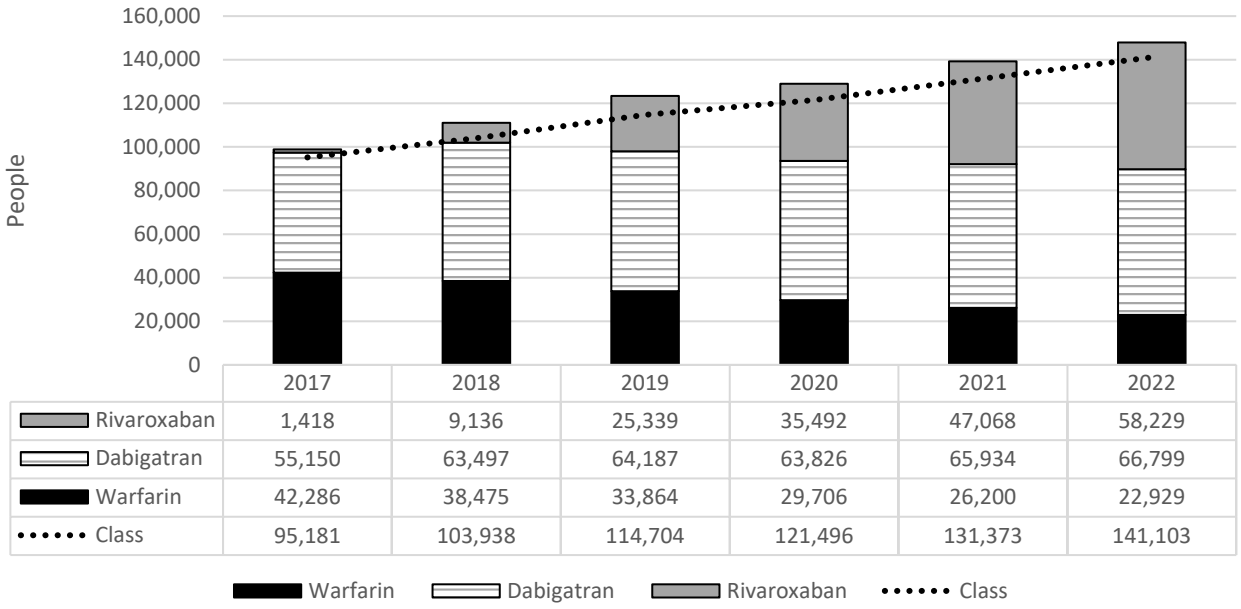
Figure 2: Oral anticoagulant usage data[a], by chemical, 2017 to 2022

a: Number of dispensings[b]



	2017	2018	2019	2020	2021	2022
Rivaroxaban	1,671	26,935	157,365	270,341	388,057	488,119
Dabigatran	473,359	567,352	593,400	628,932	650,926	668,387
Warfarin	287,683	264,210	235,629	240,912	202,264	176,926
Class	762,713	858,497	986,394	1,140,185	1,241,247	1,333,432

b: Number of people[c]



	2017	2018	2019	2020	2021	2022
Rivaroxaban	1,418	9,136	25,339	35,492	47,068	58,229
Dabigatran	55,150	63,497	64,187	63,826	65,934	66,799
Warfarin	42,286	38,475	33,864	29,706	26,200	22,929
Class	95,181	103,938	114,704	121,496	131,373	141,103

Notes:

a. Oral anticoagulant data includes warfarin (1, 2, 3 and 5mg tablets), dabigatran(75, 110 and 150mg capsules) and rivaroxaban (10, 15 and 20mg tablets). The Class data is equal to the sum of the individual anticoagulants for dispensings but not for people.

b. Dispensings: Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.

c. People: Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Sources:

Te Whatu Ora. 2022. *Pharmaceutical Data web tool version* 07 November 2022 (data extracted from the Pharmaceutical Collection on 10 August 2022). URL: https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool/ (Accessed 14 June 2023). [2017 data only]

Te Whatu Ora. 2023. *Pharmaceutical Data web tool* version 24 August 2023 (data extracted from the Pharmaceutical Collection on 08 June 2023). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (Accessed 6 November 2023).

2.2 Anticoagulant-related nephropathy (ARN)

2.2.1 Description

Anticoagulant-related nephropathy is a complication associated with the use of anticoagulants that has been reported in recent years [8]. It was initially termed 'warfarin-related nephropathy', but the ARN has become the preferred term as it has been reported with anticoagulants other than warfarin [9].

This condition is frequently underdiagnosed and is characterised by the following criteria, which may not occur together [8]:

- excessive anticoagulation (INR >3 in most studies)
- haematuria
- acute renal failure unexplained by other causes (worsening of baseline creatinine by >0.3 mg/dL).

ARN has been associated with irreversible kidney injury in some patients and with increased risk of mortality [9].

2.2.2 ARN is a type of acute kidney injury (AKI)

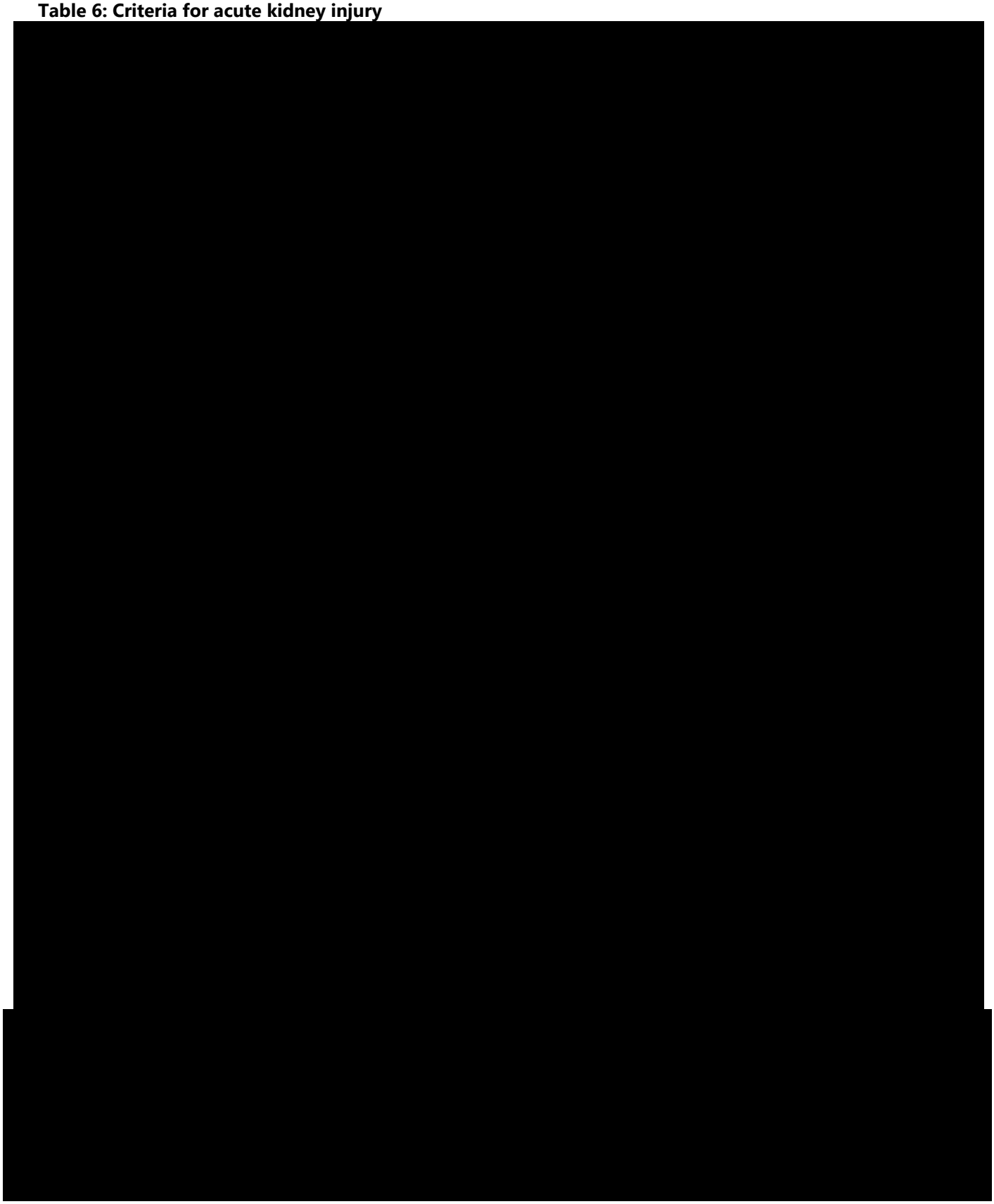
ARN is a type of AKI that may be caused by excessive anticoagulation with warfarin and anticoagulants [9].

AKI is an abrupt and usually reversible decline in the glomerular filtration rate (GFR). This results in an elevation of serum blood urea nitrogen (BUN), creatinine, and other metabolic waste products that are normally excreted by the kidney. In addition, if urine output is also diminished, fluid retention and volume overload may result [10].

The term AKI has replaced acute renal failure (ARF), reflecting the recognition that smaller decrements in kidney function are associated with increased morbidity and mortality [11].

The Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging system is the most recent and preferred definition for AKI. Other criteria include the RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) and a subsequent modification proposed by the Acute Kidney Injury Network (AKIN) and others [11]. The KDIGO, RIFLE and AKIN criteria are shown in Table 6.

Table 6: Criteria for acute kidney injury



The AKI definition does not distinguish between the multiple aetiologies that can cause AKI. Other limitations include the use of urine output as a sole criterion for AKI, which has not been conclusively validated, and

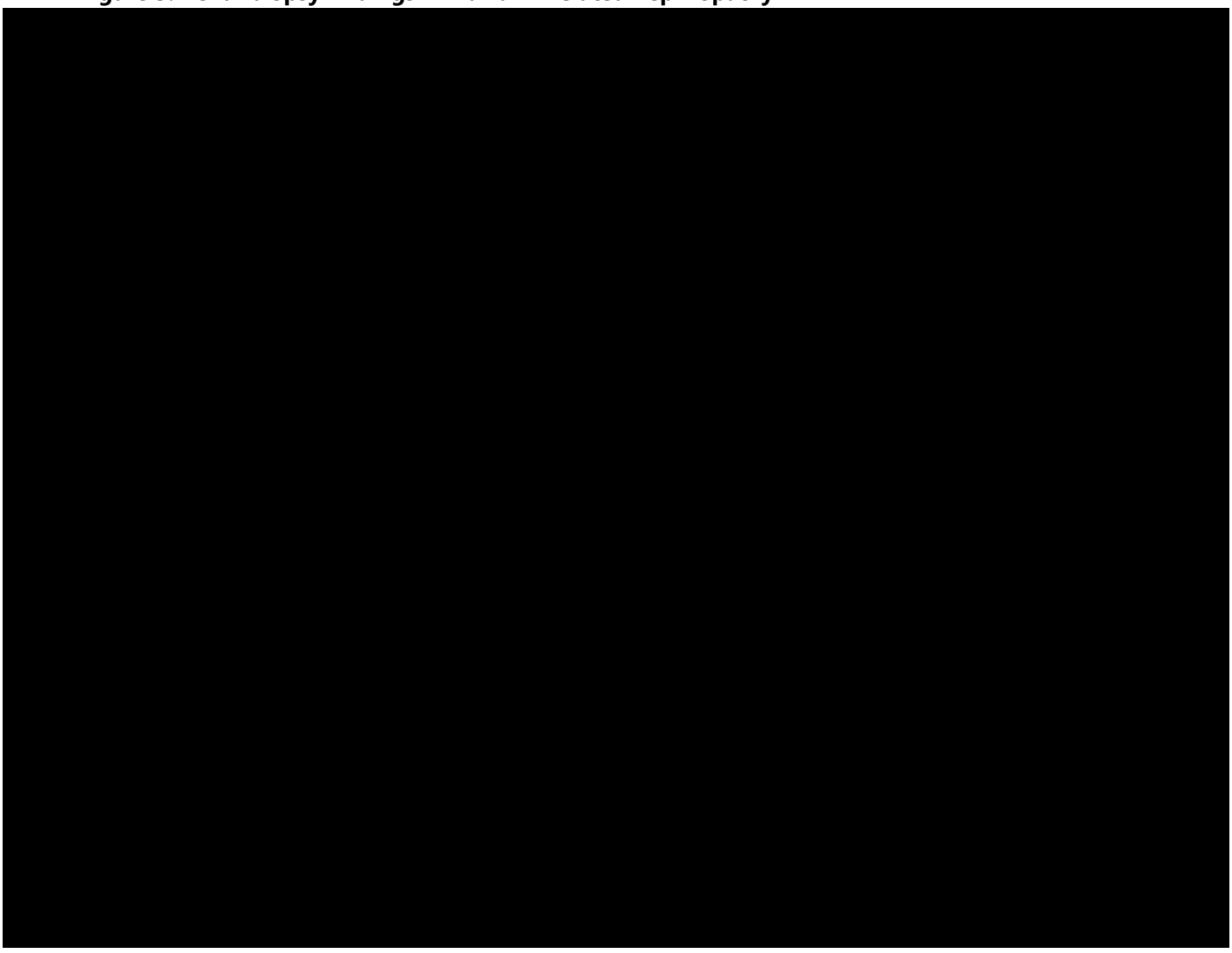
difficulty determining baseline kidney function among patients who have not had recent creatinine measurement [11].

2.2.3 Pathophysiology and proposed mechanisms

The macroscopic pathophysiology of ARN is well understood. Disruption of the glomerular filtration barrier leads to haemorrhage into Bowman's space and renal tubules. RBC casts form in the renal tubules, causing obstruction, ischemia and eventual obliteration – resulting in AKI [12].

The first reports of ARN involved two unrelated cases in which the patients experienced unexplained AKI and gross haematuria while receiving warfarin. After reversal of their international normalized ratio (INR), which was in the INR=6–9 range at presentation, the patients underwent renal biopsy, which showed unexplained profuse glomerular haemorrhage. Specifically, there were numerous renal tubules containing red cells and red cell casts (Figure 3) [13]. The glomeruli showed little or no abnormalities by light, immunofluorescence, or electron microscopy [9]. The recognition of this characteristic histologic lesion that was associated with the clinical presentation of otherwise unexplained AKI in the setting of over-anticoagulation led to the term "anticoagulant-related nephropathy" [9].

Figure 3: Renal biopsy findings in warfarin-related nephropathy



Initially, the molecular mechanism for ARN was thought to be due to warfarin-induced thrombin depletion that may also lead to increases in endothelial pressure that leads to renal damage. More recent studies suggest an alternative mechanisms involving a reduction in protein C and abnormal endothelial protein C receptor signalling [14].

2.2.4 ARN epidemiology

The true incidence of ARN is not known as there are no prospective studies, however retrospective studies have estimated the prevalence to range from 16% to 37% of patients being treated with warfarin [14].

Studies that have examined incidence have relied upon a presumptive diagnosis of ARN (defined by an elevation in the serum creatinine within several days of an abnormally elevated INR) rather than a more definitive diagnosis (defined by biopsy) [9].

In the absence of biopsy data, epidemiologic studies probably overestimated the incidence of ARN. Incidence was also overestimated by ascertainment bias since the detection of AKI was dependent upon having the serum creatinine measured within one week of the elevated INR; sicker patients are more likely to have creatinine measured and are also more likely to develop ARN [9].

However, in practice, ARN may be underdiagnosed for two main reasons [9].

- Doctors are reluctant to perform kidney biopsy in patients who need therapeutic anticoagulation. This is because of concerns related to the risk of thrombosis/thromboembolism while systemic anticoagulation is held and to the risk of haemorrhage from the kidney biopsy site after the systemic anticoagulants are restarted.
- The possibility of ARN may be overlooked because it is most common among patients who have multiple risk factors for AKI from any cause, and AKI may be attributed to other causes.

Also, the prevalence of ARN may be low even though the incidence is high [9]. Most of the cases of potential ARN with warfarin occurred in the first eight weeks after starting treatment [15, 16]. Approximately 30% of patients with CKD and ARN died within approximately one month after the onset of ARN, thus reducing the prevalence [15].

2.2.5 Risk factors

The major risk factor for ARN is moderate or severe anticoagulation induced by warfarin or other anticoagulants. The risk appears to increase at International Normalized Ratio (INR) >4. Other risk factors include underlying chronic kidney disease (CKD), diabetes mellitus, age (>65 years), heart failure, hypertension, and glomerulonephritis, particularly with nephrotic syndrome [9, 14].

2.2.6 Management, prognosis and prevention

There are no prospective studies or definitive guidelines for managing ARN, and the role of kidney biopsy in patients with presumptive ARN remains to be determined [9].

Though the optimal management of ARN is not well defined, correction of the coagulopathy either by holding the agent or with active reversal may be necessary depending on bleed severity or degree of INR elevation (in the case of warfarin). If the patient develops ARN while on warfarin, it may be appropriate to switch to a DOAC; if a patient is already on a DOAC, dose-reduction or potentially switching to an alternative DOAC may be appropriate [9, 13, 17].

In most patients, kidney function was reported to resolve spontaneously [14]. However, in an early warfarin study, the 5-year Kaplan-Meier survival rate was significantly lower in patients with ARN than those without ARN (58% vs. 73%, P<0.001), with 1-year survival of 68.9% in ARN vs. 81.1% in no-ARN group, P=0.049 [16].

Brodsky et al state that the most important measure to prevent ARN is proper adjustment of the anticoagulant dose [9]. Wheeler recommends frequent renal monitoring at the initiation of therapy, based on warfarin data indicating that ARN is most likely to occur within the first 6–8 weeks of therapy (Table 7) [12]. Ongoing monitoring should occur annually, but more frequently in those with CKD.

Table 7: Recommended frequency of renal monitoring for patients receiving anticoagulation

[redacted]

2.3 Product information – anticoagulant-related nephropathy

2.3.1 New Zealand data sheets

The pivotal clinical trials for DOACs all reported renal adverse effects and bleeding, and this information is reflected in the data sheets. They describe the risk of excessive anticoagulation and haemorrhage, along with acute renal failure/AKI, urogenital haemorrhage and haematuria (see Annex 1).

Xarelto (rivaroxaban) is the only NZ DOAC data sheet that describes ARN. [redacted]

The Xarelto wording is shown below.

> **4.4 Special warnings and precautions for use**
>
> Anticoagulant-related nephropathy
>
> There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following anticoagulant use, presenting as acute kidney injury. In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and haematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic).
>
> **4.8 Undesirable effects**
>
> Postmarketing observations
>
> Renal and urinary disorders, Frequency: Not known, Anticoagulant-related nephropathy (see section 4.4)

2.3.2 International prescribing information

Table 8 shows the dabigatran, rivaroxaban and apixaban prescribing information from Australia, the UK, Europe, the US and Canada, and whether or not ARN is listed. See section 3.2 for information about international regulatory action.

Comments

Prescribing information varies by jurisdiction and active ingredient. Only Australia has ARN in the prescribing information for all DOACs, [redacted]

Table 8: International prescribing information for direct-acting oral anticoagulants – ARN wording

Substance	Country/Region				
	Australia	**UK**	**Europe**	**US**	**Canada**
Dabigatran	Pradaxa (5/5/23) **4.4 Special warnings and precautions for use** Anticoagulant-related nephropathy There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following anticoagulant use, presenting as acute kidney injury. In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and haematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic). **4.8 Undesirable effects/Postmarketing** Renal and urinary disorders, Frequency: Not known, Anticoagulant-related nephropathy (see Section 4.4 Special warnings and precautions for use), haematuria.	Pradaxa coated granules (6/9/22) **4.8 Undesirable effects** Description of selected adverse reactions *Bleeding reactions* [2nd paragraph]: Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.	Pradaxa (25/7/22) **4.8 Undesirable effects** Description of selected adverse reactions *Bleeding reactions* [2nd paragraph]: Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. For adult patients, a specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).	Pradaxa (14/11/2023) **6.2 Postmarketing experience** Renal and urinary disorders: Anticoagulant-related nephropathy	Pradaxa (23/3/20) Not listed
Rivaroxaban	Xarelto (5/5/23) Yes. As per Pradaxa above (excluding haematuria in section 4.8, but it is in treatment-emergent adverse reaction data, Tables 7 and 8)	Xarelto (24/1/23) Not listed	Xarelto (2/8/23) **4.8 Undesirable effects** Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use* and in two phase II and two phase III studies in paediatric patients *Renal and urinary disorders:* Anticoagulant-related nephropathy (frequency unknown) Description of selected adverse reactions Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion, or anticoagulant-related nephropathy have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.	Xarelto (8/2/23) **6.2 Postmarketing experience** *Renal disorders:* Anticoagulant-related nephropathy	Xarelto (17/4/23) Not listed
Apixaban	Eliquis (15/5/23) Yes. As per Pradaxa above	Eliquis (27/4/22) Not listed	Eliquis (23/6/23) Not listed	Eliquis (12/10/21) Not listed	Eliquis (7/10/19) Not listed

Sources (access dates: 27 August 2023 and 17 November 2023): Australia: TGA – Information about therapeutic goods in Australia; UK: MHRA Products; Europe: HPRA and EMA Medicines; US: Drugs@FDA: FDA-Approved Drugs, DailyMed and Drug Safety-related Labeling Changes; Canada: Health Canada Drug Product Database online query

3 SCIENTIFIC INFORMATION

3.1 Published literature

Recently published literature (ie, within the past 10 years) is provided below. This is not a full literature review. The studies were included because they focus on ARN as a specific condition rather than being a form of AKI. Most of the retrieved studies were case reports or case series, and they are described in section 3.3.1, by DOAC. Section 3.1.2 contains other relevant studies.

3.1.1 Case reports + case series

3.1.1.1 Dabigatran

Escoli et al [18] present the case of a 69-year-old female with biopsy-proven ARN related to dabigatran. The patient had a history of hypertension and was prescribed dabigatran for new onset AF (baseline serum creatinine 1.5mg/dL, corresponding to eGFR of 32.5mL/min/1.73m^2). Two weeks later she presented developed AKI with haematuria (serum creatinine at admission 8mg/dL). Due to oliguric acute renal failure she started haemodialysis. Kidney biopsy showed ARN and IgA nephropathy. She was treated with 3 units of RBC and IV fluids. Renal function improved within 2 weeks (serum creatinine 1.9mg/dL at last evaluation).

Awesat et al [19] (abstract only) report a clinical case of an 80-year-old patient recently started on dabigatran for new onset atrial fibrillation. She presented with AKI and haematuria, urine specimen showed RBC casts, and a working diagnosis of anticoagulant nephropathy due to dabigatran was made. During hospitalisation she was treated with idarucizumab with a full recovery of renal function.

Ikeda et al [20] present the case of a 67-year-old female was referred to hospital with persistent macrohematuria and AKI. At the age of 62, she started dabigatran (150 mg twice daily) for deep vein thrombosis. Her other routine medications comprised amlodipine, imidapril, metformin, and teneligliptin with normal pre-existing renal function. Her creatinine level increased from 0.5 to 2.16 mg/dL over 10 days, and she was admitted for the assessment of AKI. After stopping dabigatran, a percutaneous renal biopsy was performed and ARN with co-existing nonactive IgA nephropathy was diagnosed. After dabigatran withdrawal, her macrohematuria and renal function improved.

The authors describe three other known cases of ARN reported in association with dabigatran (Table 9). All patients, including the one in the present study, were aged greater than 65 years, and none had a severe renal impairment at the baseline. Three of four patients had hypertension, and the period between initiating dabigatran and the AKI onset varied from a few weeks to several years. All patients, except for one, presented with macrohematuria. At the onset of ARN, APTT was prolonged in three patients and PT-INR was prolonged in all patients. APTT and PT-INR returned to normal rapidly in three and two patients after discontinuing dabigatran, respectively. While one patient needed temporary haemodialysis, all patients had nearly complete recovery to their baseline renal function by discontinuing dabigatran. Underlying IgA nephropathy could be a risk factor for ARN. Excessive anticoagulation with dabigatran may accelerate macrohematuria due to IgA nephropathy and aggravate the tubular injury associated with macrohematuria.

Table 9: Case reports of histologically confirmed, anticoagulant-related, dabigatran-induced nephropathy – Ikeda et al

Zeni et al [21] describe a case of ARN in a 71-year-old male patient admitted to their nephrology unit with a strong suspicion of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis due to gross haematuria and haemoptysis. Eight months earlier he was diagnosed with AF and started on 150mg of dabigatran twice a day. His medical history included hypertension, chronic obstructive pulmonary disease, obesity, heavy smoking, obstructive sleep apnoea, and hypercholesterolemia. Renal biopsy excluded ANCA-associated vasculitis and diagnosed a red blood cell cast nephropathy superimposed to an underlying IgA nephropathy. A combination of reversal of coagulopathy (ie, withdrawal of dabigatran and infusion of its specific antidote) along with administration of fluids, sodium bicarbonate, steroids, and mannitol resulted in conservative management of AKI and fast recovery of renal function.

Alsamarrai et al [22] describe the case of a 78-year-old New Zealand European male with a background history of atrial fibrillation, mitral valve prolapse and fusion of the lower lumbar vertebral bodies and was usually on dabigatran 110mg twice daily, flecainide and cilazapril. He developed macroscopic haematuria and acute kidney injury 2 weeks after mitral valve repair, reaching a peak creatinine of 415 mmol/L from a normal baseline. He did not undergo renal biopsy due to risk of procedural complications (ie, recent administration of dabigatran). Medical history identified an episode of macroscopic haematuria 6 years earlier when on warfarin – for which no cause was found. A presumptive diagnosis of ARN due to dabigatran was made and 5 g of Idarucizumab was administered. After 2 days there was an improvement in his serum creatinine to 265 mmol/L, with subsequent improvement to a new baseline of 120 mmol/L over 5 days. There was also the immediate resolution of the macroscopic haematuria, although there was a polyuric phase in the recovery. He

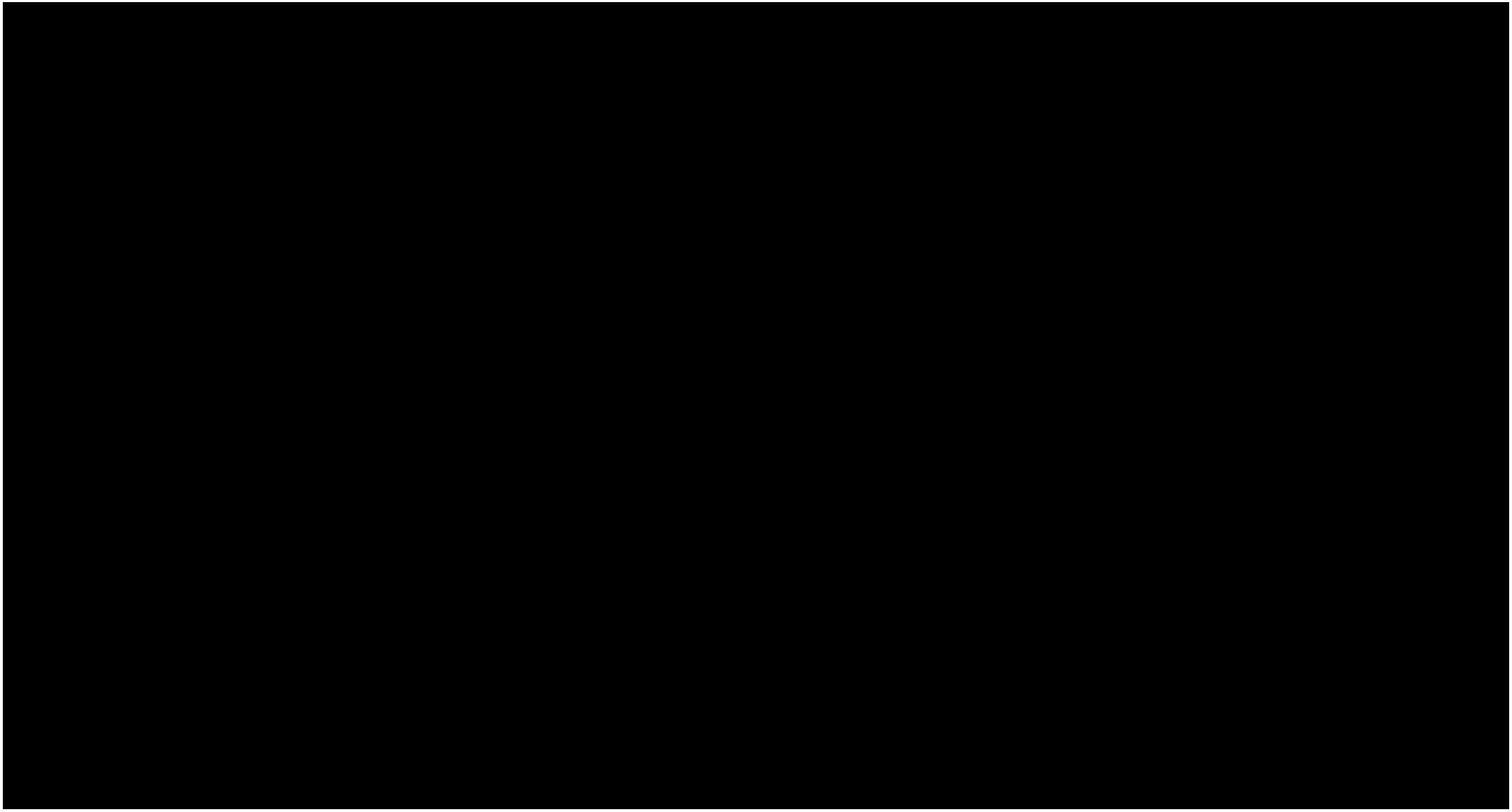
was successfully discharged home 1 month after the operation and the serum creatinine returned to normal after 2 months. The authors noted that as renal biopsy was not undertaken in this case, the diagnosis of ARN was empiric and they cannot exclude that spontaneous recovery of renal function occurred. The authors noted that while there is no specific treatment for ARN, anticoagulant reversal agents have provided a novel therapeutic option (Table 10).

Table 10: List of common oral anticoagulants and their reversal agents

Mikič et al [23] present the case of an 82-year-old Slovenian woman with a history of arterial hypertension, insulin-dependent diabetes mellitus type 2, hypothyroidism, cognitive decline, and CKD with a creatinine baseline value of 124 µmol/L and microscopic haematuria was admitted to the nephrology department because of AKI. Her daily medication included levothyroxine, memantine, bisoprolol, rosuvastatin, and insulin. Eighteen days previously, dabigatran had been introduced at a dose of 110 mg bd due to a new onset of atrial fibrillation and a transient ischemic attack in her medical history. The serum concentration of dabigatran was highly elevated (650 µg/L). Dabigatran was discontinued and dialysis started. Kidney biopsy showed signs of ARN together with mild IgA nephropathy. Following three weeks of dialysis, methylprednisone was introduced and the patient was discharged. Four weeks after discharge, methylprednisone was tapered down and she was started on warfarin due to advanced CKD and stroke risk. Six months later she was readmitted with decreased kidney function, gross haematuria, supratherapeutic INR and subscapular haematoma at the site of the kidney biopsy and required urgent embolization of a segmental artery. Her condition worsened, with infection of the subscapular haematoma and septic shock, leading to death.

The authors then reviewed cases of ARN at a national level – by reviewing 1960 kidney biopsies between 2014 and 2020. They identified 13 cases of ARN (including the case described above), 5 of which were taking DOACs and the other taking coumarins (warfarin or adenocoumarol). The DOAC cases are presented in Table 11 below. Four of the five DOAC cases also had IgA nephropathy, and one had thin glomerular basement membrane disease with latent IgA deposits. The authors concluded that anticoagulant therapy together with pre-existing glomerular injury may lead to ARN.

Table 11: Clinical and demographic data in a Slovenian cohort of patients with anticoagulant-related nephropathy: DOAC patients only



3.1.1.2 Rivaroxaban

Oliveira et al [24] describe the case of an 82-year-old woman suffering from atrial fibrillation under rivaroxaban treatment with previous normal renal function, who was admitted to their hospital with gross haematuria and acute kidney injury. A renal biopsy revealed typical features of anticoagulant-related nephropathy superimposed on chronic interstitial nephritis and hypertensive nephroangiosclerosis. There was no recovery of renal function despite withdrawal of rivaroxaban and the patient started on chronic haemodialysis three months after initial episode.

Fujino et al [25] report the case of a 75-year-old man with IgA vasculitis and atrial fibrillation treated with rivaroxaban, who presented with macroscopic haematuria and an acute decline in renal function (an elevated serum creatinine level (4.12 mg/dL). Medical history included hypertension and diabetes, plus percutaneous coronary intervention of the left circumflex artery 8 years previously and cerebral infarction, which had occurred 3 years previously. He was treated with verapamil (40 mg, two times per day), metformin (500 mg, daily), and pilsicainide (50 mg, two times per day). He had also been treated with rivaroxaban (10 mg) for more than 3 years for AF. Two months before referral, he noted palpable purpuric lesions and was diagnosed with IgA vasculitis based on skin biopsy findings; the skin lesion disappeared following treatment with a steroid external preparation. Renal biopsy revealed glomerular haemorrhage and red blood cell casts. Although rivaroxaban was withdrawn, his kidney function worsened, and he was started on haemodialysis. His renal function did not recover.

3.1.1.3 Apixaban

Brodsky et al [26] report the case of an 82-year-old Caucasian female with a history of hypertension, pre-existing stage 3 chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), coronary artery disease and congestive heart failure presented with COPD exacerbation and AKI. She then developed new-onset atrial fibrillation and was started on apixaban, plus steroids for the COPD exacerbation. A few days after apixaban therapy, she presented with oligoanuria and further elevations in serum creatinine, and haemodialysis was initiated. She also received methylprednisolone for suspected ANCA-related vasculitis. She did not have overt haemorrhage, but urinalysis revealed microscopic haematuria (20-50 RBCs per high power field). Apixaban was stopped and a kidney biopsy performed. The patient remained on dialysis 4 months later.

Saling et al [27] report the case of a 68-year-old male with a history of uncontrolled systemic lupus erythematosus (SLE) and persistent atrial fibrillation of apixaban who presented with acute kidney injury. The patient had kidney biopsy due to concern for lupus nephritis. He was found to have renal tubules with RBCs consistent with ARN with some features of lupus nephritis. Apixaban was discontinued and a prednisone burst was initiated, then the patient was discharged home. The patient returned with new onset lower extremity oedema, ascites, and shortness of breath. The patient was found to have an elevated INR, a creatinine 3 times greater than baseline, and a low albumin. The patient was found to have cirrhosis. The patient had a positive anti ds-DNA and antismooth muscle antibody. A liver biopsy was performed and was consistent with lupoid hepatitis.

3.1.1.4 All DOACs

Chen et al. 2023. Anticoagulant-related nephropathy induced by direct-acting oral anticoagulants: Clinical characteristics, treatments and outcome [28]

This paper is included as it summarises many of the case reports described above [18-22, 24-26].

Methods

The authors performed a literature review on DOAC-induced ARN to 1 October 2022, without language restrictions for retrospective analysis. They identified 20 patients in 16 articles involving 15 case reports and one case series.

Results

Table 12 provides the characteristics of the 20 ARN patients. There were 9 men and 11 women, with a medium age of 75 years old (61–82 years old). The anticoagulants were dabigatran in 14 cases, rivaroxaban in 4 cases,

apixaban in one case and edoxaban in one case, most of which were prescribed for atrial fibrillation (17 patients). The most common comorbidities were CKD (17/20) and hypertension (13/20).

Table 12: Characteristics of the 20 included patients with ARN induced by DOACs

Table 13 summarises the clinical characteristics of ARN. The time-to-onset varied from seven days to several years, with a medium period of 28 days. All patients developed haematuria. At ARN diagnosis, all patients had reduced eGFR, including 16 with an eGFR<15 mL/min/1.73 m^2.

Table 13: Clinical features of ARN induced by DOACs

Biopsy results were available for 14/20 patients, with 13/14 showing occlusive intratubular RBC casts. Ten patients had acute tubular injury of varying intensity. Eight patients had extensive changes in interstitial compartment with interstitial haemorrhage, interstitial fibrosis or interstitial inflammation. Eight biopsies were suggestive for a latent IgA nephropathy without clinical manifestations.

Treatment was mainly supportive, and all DOACs were discontinued in all patients (Table 14). Twelve patients did not recover renal function.

Table 14: Treatments and outcomes of ARN induced by DOACs

[redacted]

Comments
Cases of biopsy-proven and presumptive ARN have been reported with all DOACs, some of which reported positive dechallenge once the DOAC was withdrawn. Many cases were confounded by comorbid conditions.

3.1.2 Other

de Aquino Moura KB, et al. 2019. Anticoagulant-related nephropathy: systematic review and meta-analysis [8]

Aim

To report the prevalence and mortality associated with ARN through a systematic review of the literature.

Methods

The authors conducted electronic searches in the Medline and EMBASE databases and performed manual searches in the reference lists of the identified studies. There was no start date, and the end date was November 2017. The studies were selected by two independent researchers, first by evaluating the titles and abstracts and then by reading the complete texts of the identified studies. Observational studies and case series with five or more participants with data on the rate of ARN and clinical characteristics of patients undergoing anticoagulant therapy by any indication were included. Case reports or case series with four or fewer participants, in vitro studies or animal studies were excluded.

The primary outcome to be analysed was the prevalence of ARN. The secondary outcomes evaluated included mortality, progression to end-stage kidney disease, and clinical and sociodemographic characteristics related to the development of ARN.

The methodological quality was assessed using the Newcastle–Ottawa scale (maximum possible score of 9, with 7 being the threshold for high quality).

Meta-analyses of the prevalence of ARN and 5-year mortality using the random effects model were performed when possible. Heterogeneity was assessed using the I^2 statistic.

Results

Five studies were included, all of which involved warfarin, and none involved novel oral anticoagulants (NOACs; eg, direct thrombin inhibitors and factor Xa inhibitors) – see Table 15.

Table 15: Characteristics of the included studies

Prevalence of ARN ranged from 19% to 63% among the four included cohort studies. Meta-analysis of these resulted in high heterogeneity [I^2 96%, summary effect 31%; 95% CI: 22–42%]. Subgroup meta-analysis yielded an ARN prevalence of 20% among studies that included patients with fewer comorbidities (I2 12%; 95% CI: 19–22%). In a direct comparison, meta-analysis of the 5-year mortality rate between anticoagulated patients who had experienced ARN and anticoagulated patients without ARN, patients with ARN were 91% more likely to die (risk ratio = 1.91; 95% CI: 1.22–3; I^2 87%).

Risk factors for ARN that were reported in the literature included initial excessive anticoagulation, chronic kidney disease, age, diabetes, hypertension, cardiovascular disease and heart failure. In addition, there are factors related to warfarin anticoagulation in other contexts, including excessive anticoagulation at the onset of warfarin use, excessive anticoagulation (INR >3) in the presence of hypoalbuminaemia and increased AST after an increase in INR, anticoagulation in patients with underlying glomerulopathies such as immunoglobulin A nephropathy [18] and thin glomerular basement membrane disease, and genetic polymorphisms such as a variant of the CYP2C9*3 gene associated with increased risk of bleeding. However, all of the possible risk factors for ARN that were reported in the included studies are themselves causes of acute kidney injury, and there was insufficient adjusting for confounding.

Limitations

The very high heterogeneity and the lack of sufficient information to permit confounder-adjusted comparative mortality risk meta-analyses precludes the use of the estimated summary effects for practical applications. The impossibility of performing a meta-analysis of the possible risk factors of ARN. The impossibility of excluding the occurrence of publication bias because of the small number of studies included and the limited understanding of the nature of this type of bias in systematic reviews of observational studies.

Conclusions

ARN studies are scarce and heterogeneous, and present significant methodological limitations. The high prevalence of ARN reported herein suggests that this entity is underdiagnosed in clinical practice. Mortality in patients with ARN seems to be high compared with patients without this condition in observational studies.

There are no clinical–epidemiological studies on NOAC-related nephropathy, and the presence of this association is unknown.

Comment

The authors found no studies for ARN with dabigatran, rivaroxaban or apixaban. However, this paper was published in 2019, prior to the new MedDRA PT for ARN, so the absence of studies may reflect under diagnosis of the condition rather than an absence of the condition.

Marcelino G, et al. 2020. Acute renal failure in a patient with rivaroxaban-induced hypersensitivity syndrome: a case report with a review of the literature and of pharmacovigilance registries [29]

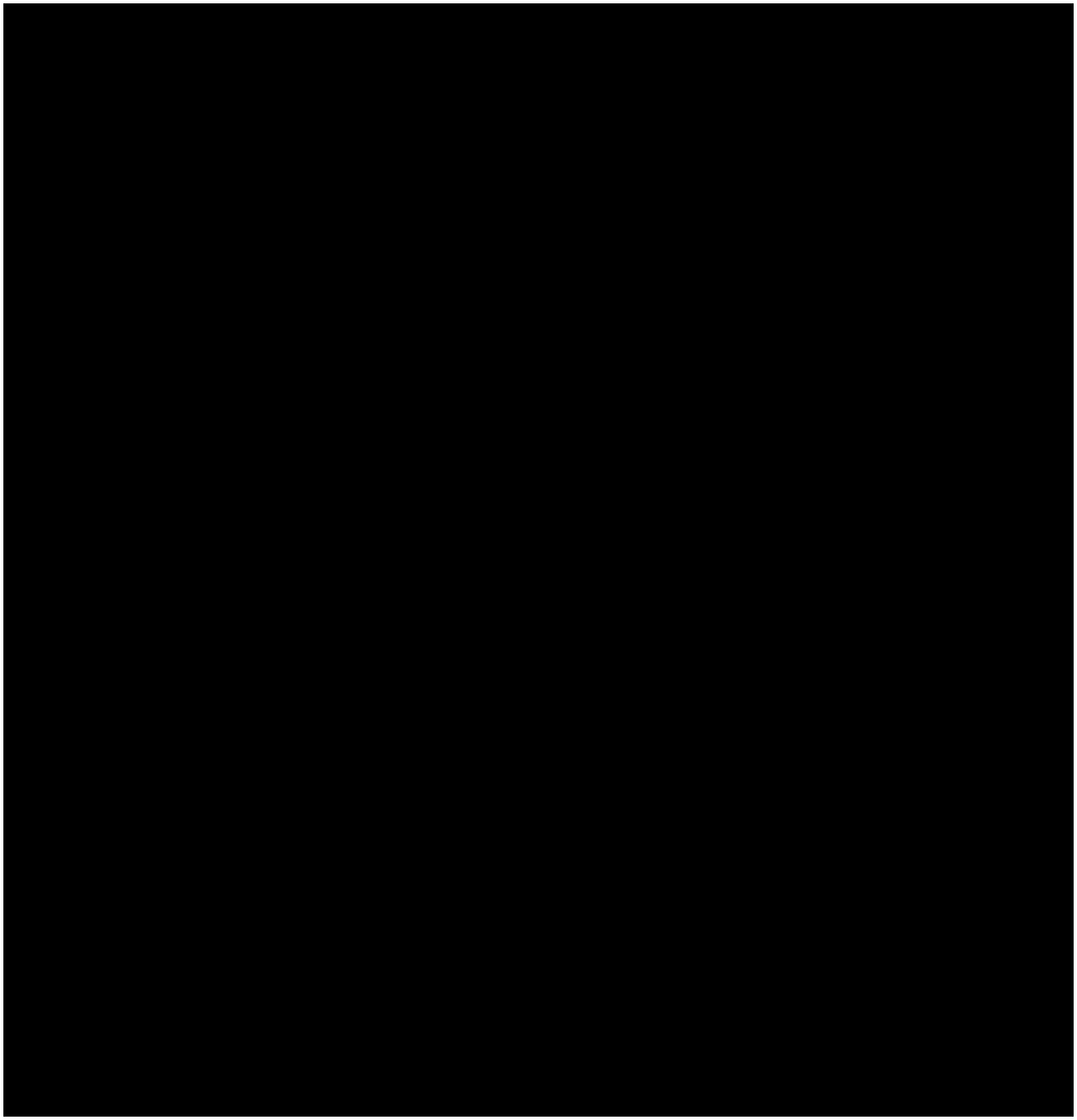
Aim

This article presents a case report of drug-induced hypersensitivity syndrome with rivaroxaban (not further described below), plus a literature review of rivaroxaban-related acute renal failure (ARF) and data from the WHO's VigiAccess database.

Literature review

The authors identified five cases in the literature reporting an association between rivaroxaban and ARF (Table 16). ARF developed within two days to two months after the prescription of rivaroxaban in all these cases, with one exception. Renal histology showed tubulointerstitial nephritis (TIN) in two patients, anticoagulant-related nephropathy in two others, and IgA nephropathy in the last one. Renal function improved in two of the cases (who had TIN at renal biopsy and who had received low-dose corticotherapy), while two of the three others had to undergo chronic dialysis. Overall, when considering all these case reports, including the one presented here, four of the cases involved men, with a median age of 76 years; two had pre-existing chronic kidney disease, and five of the six cases exhibited several cardiovascular risk factors.

Table 16: Clinical characteristics of the full-published case reports of rivaroxaban-associated acute renal failure



VigiAccess data

The authors were surprised by the small number of ARF cases retrieved from the literature, "which is in contrast to the alarming tone of some recent articles associating anticoagulation with ARF". They questioned whether renal injury associated with anticoagulants might be greatly underdiagnosed and/or underreported. Therefore, they consulted VigiAccess, an international pharmacovigilance database that collects data from 134 countries that are members of the World Health Organization Program for International Drug Monitoring.

Rivaroxaban data was retrieved from VigiAccess for the period 2006 to April 2019. There were 121,038 reports for rivaroxaban, and of these, 4323 (3.5%) were for kidney-related adverse events. Renal side effects were the 8th most frequent type of ADR reported for rivaroxaban and were equally distributed among genders and were more frequent in patients >65 years. The authors state that dabigatran and rivaroxaban are the drugs for

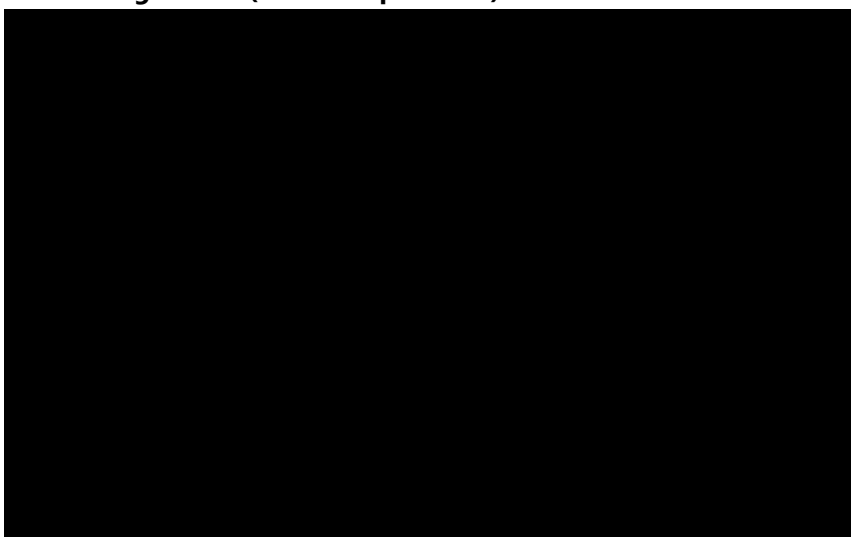
which the proportion of kidney-related adverse events is higher: 4.6% and 3.5%, respectively, compared to only 2.0% for apixaban and 1.7% for edoxaban [search terms and date ranges not provided].

Rivaroxaban data from 2006 to 2019 is presented in Table 17. It shows that the clinical presentation was ARF (54.3%) in the majority of the cases reported for rivaroxaban, with only a small number developing CKD or ESRD (2.1%). Also, these data suggest that the mechanism of renal injury most frequently associated with rivaroxaban seems to be anticoagulant-related nephropathy (as it is characteristically associated with renal haemorrhage, which occurred in 363 cases), rather than tubulointerstitial nephritis with only 24 cases reported.

Table 17: Number and type of renal side effects reported for rivaroxaban retrieved from VigiAccess (until 27 April 2019)

DOACs versus vitamin K antagonists (ie, including warfarin) reporting data is presented in Table 18. It shows that the reported annual rate of renal adverse events is almost ten times higher for DOACs (7,725 cases in 15 years) than for AVKs (2,145 cases reported in 50 years). The authors comment that this difference may be related to bias in diagnosing and/or reporting the side effects for these different classes of anticoagulants. And that the data from the pharmacovigilance registries reported above may suggest that anticoagulation-related nephropathy, although probably sometimes underdiagnosed, was probably a rare complication in the era of antivitamin K drugs, but that this may no longer be the case in the DOACs era.

Table 18: Number and type of renal side effects for DOACs and vitamin K antagonists (AVK) retrieved from VigiAccess (until 27 April 2019)



Conclusion

This analysis suggests that the frequency of renal adverse events associated with rivaroxaban and other DOACs may be appreciably higher than what one might currently consider based only on the small number of fully published cases. Systematic screening of the renal function is required in patients taking DOACs and that regular monitoring of renal function should be performed in all patients receiving therapeutic anticoagulation.

Comments

The article was included due to the review of the pharmacovigilance database data. However, higher reporting rates identified with DOACs than warfarin may reflect higher usage and changes in reporting patterns over time. The authors also presumed that renal haemorrhage was ARN but did not provide further information as to why they categorised these cases as ARN. In addition, ARN was only added as a MedDRA term in 2020, so the VigiAccess data would not have reported on ARN cases at the time of the authors' search.

Mitsuboshi M, et al. 2020. Differences in risk factors for anticoagulant-related nephropathy between warfarin and direct oral anticoagulants: Analysis of the Japanese adverse drug event report database [30]

Aim

To investigate kidney injury (KI), as a surrogate marker for ARN, in patients administered warfarin or DOACs to clarify risk factors for ARN.

Methods

This observational study used anonymized patient data recorded in the open-access Japanese Adverse Drug Event Report (JADER) database. Data recorded from April 2004 to November 2019 were downloaded from the Pharmaceuticals and Medical Devices Agency website on 25 March 2020. The authors collected data about sex, age, body weight, presence of CKD (glomerular filtration rate <60 mL/min/1.73 m^2), use of drugs (in particular CYP3A4 inhibitors) and adverse events related to kidney injury. Inclusion criteria were all warfarin and DOAC users regardless of whether the data reporter suspected a possible adverse event. Exclusion criteria were use of both warfarin and a DOAC and missing data on sex, age or body weight. Nonsteroidal anti-inflammatory drug users were also excluded because they are a common cause of KI and were likely to be major confounders.

To evaluate potential cases of ARN, all cases of KI were included in the analysis. KI was defined as reported KI (reduction in creatinine clearance ≤60 mL/min), reported acute KI (elevated serum creatinine ≥0.5 mg/dL) or elevated serum creatinine level.

Statistical analysis included Fisher's exact test to compare KI frequency and multiple logistic regression analysis to identify KI risk factors.

Results

There were 148,688 reports including 6,066 cases of KI. Table 19 shows KI events according to each anticoagulant drug. Warfarin users were included as controls for DOAC users, and DOAC users were included as controls for warfarin users. Use of warfarin (OR, 1.20; 95% CI, 1.08–1.32; P < .01)] was associated with a significantly increased risk of KI.

Table 19: Proportion of KI cases according to anticoagulant drug

[redacted]

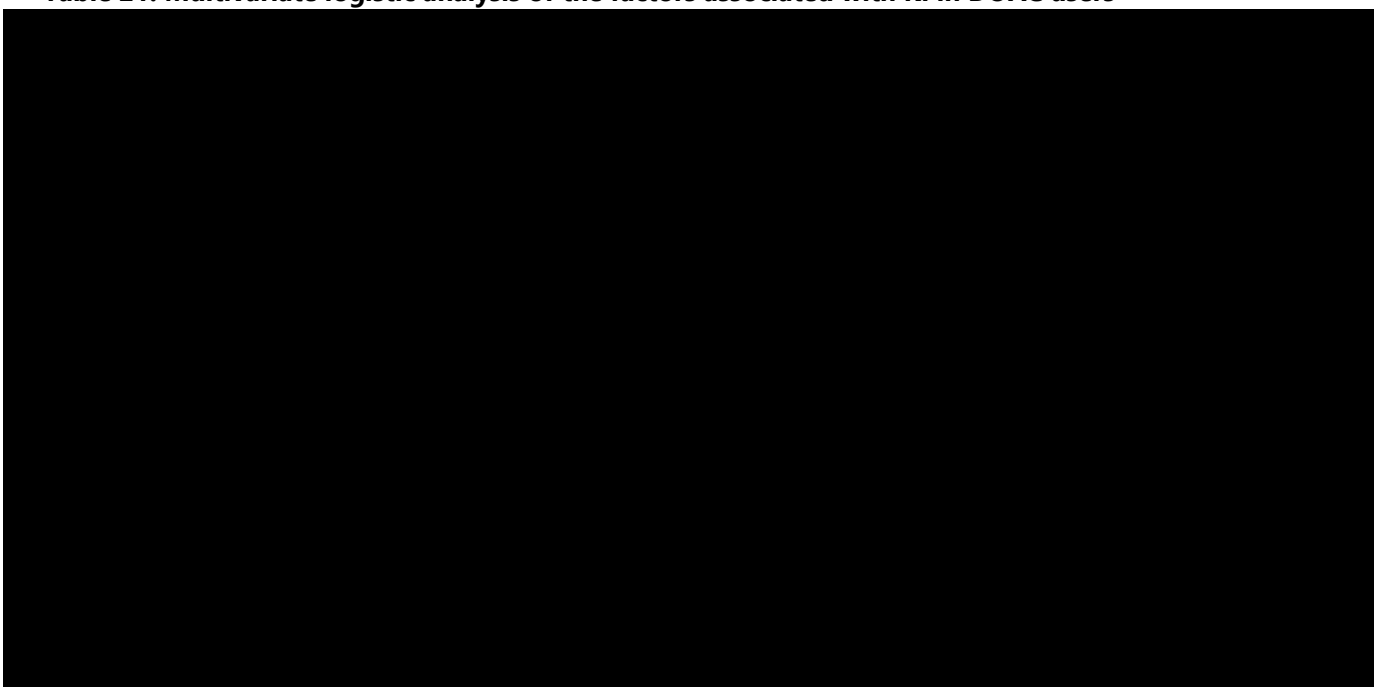
Tables 20 and 21 show the multivariate logistic analysis of factors associated with KI in patients administered warfarin or DOACs.

- KI risk in warfarin users was associated with male sex, age ≥80 years and use of CYP3A4 inhibitors.
- KI risk in DOAC users was associated with body weight ≥80 kg, comorbidity of CKD, use of CYP3A4 inhibitors and use of dabigatran.

Table 20: Multivariate logistic analysis of the factors associated with KI in warfarin users

[redacted]

Table 21: Multivariate logistic analysis of the factors associated with KI in DOAC users



Considerations and limitations

- The ORs do not definitively indicate an increased risk of KI, and the results showed increased frequencies of only certain factors because this study analysed an adverse events database.
- The relationship between anticoagulant therapy and KI is complex. For example, atrial fibrillation and KI are bidirectional. An anticoagulant may protect against KI but may also lead to acute KI and chronic worsening of the kidney. This means the results may include KI caused by atrial fibrillation or other underlying diseases.
- The definition of ARN remains to be clarified. Although ARN is usually defined as an international normalised ratio >3, haematuria and worsening of baseline creatinine by >0.3 mg/dL, these may not occur together. In this study, KI was a surrogate marker for ARN but the methods and criteria for diagnosing KI may not be consistent.
- Data from the adverse events database may be affected by reporting bias and differences in patient backgrounds, including underlying diseases, among warfarin and DOAC users.
- Patients with KI but without ARN will have been included in the analysis.
- No information on DOAC or warfarin dose, length of treatment, or other factors that may influence kidney outcomes.

Conclusion

The authors stated that their findings suggest that the risk factors for ARN differ between warfarin and DOACs, and these risk factors may be associated with bleeding risk.

Comments

This study uses spontaneous report data, so the usual limitations apply – including under-reporting, no denominator and incomplete information on diagnosis and history of the patient.

3.2 International regulatory action

3.2.1 Europe

3.2.1.1 Dabigatran

At their September 2021 meeting, the Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the dabigatran (Pradaxa) PBRER for the period covering 18 March 2020 to 18 March 2021. Following this review,

the PRAC recommended an update to the product information to add ARN as an undesirable effect part of the bleeding reactions [31]. This was endorsed by the Committee for Medicinal Products for Human Use (CHMP) in October 2021 [32].

See section 2.3.2 for the European product information wording for dabigatran.

3.2.1.2 Rivaroxaban

At their May 2023 meeting, the PRAC reviewed the rivaroxaban (Xarelto) PSUR for the period covering 15 September 2020 to 15 September 2022 [33]. Following this review, the PRAC recommended updating section 4.8 of the SmPC to include ARN as an undesirable effect of unknown frequency. The CHMP agreed with the PRAC's recommendation [34].

See section 2.3.2 for the European product information wording for rivaroxaban.

3.2.2 Australia

The TGA assessed the risk of ARN for anticoagulants as a class in mid-2022.

The TGA investigation of oral anticoagulants and the risk of ARN concluded there to be sufficient evidence to warrant updating the product information (PI) for vitamin K antagonists and direct thrombin inhibitors to warn clinicians of the risk of ARN. This issue was referred to the TGA's Advisory Committee on Medicines (ACM) in August 2022. While the ACM was not asked to provide specific advice regarding vitamin K antagonists and direct thrombin inhibitors, the committee supported the TGA in this position [35].

The ACM was asked to consider the current evidence pertaining to the risk of ARN with factor Xa inhibitors (rivaroxaban and apixaban) for which the ACM advised is also sufficient to warrant updating the PI in line with the proposed updates for vitamin K antagonists and direct thrombin inhibitors [35].

The ACM highlighted that ARN is a rare, but serious event that is likely underdiagnosed and requires prescriber education around its presentation (as acute kidney injury) and management. Additionally, the ACM advised that the term 'anticoagulant-related nephropathy' should be included in the PI as an adverse event, distinct from 'haematuria or genitourinary haemorrhage' and 'acute kidney injury' [35].

The TGA requested updates to the apixaban, dabigatran and rivaroxaban PI. Similar warnings were included in the prescribing information for warfarin. However, close monitoring is specifically advised in patients with a supratherapeutic INR and haematuria (including microscopic) [36].

See section 2.3.2 for the Australian product information wording.

In June 2023, the TGA published safety alerts for healthcare professionals [36] and for consumers [37].

- Oral anticoagulants can cause serious kidney damage in rare circumstances
- Risk of kidney damage with oral anticoagulants

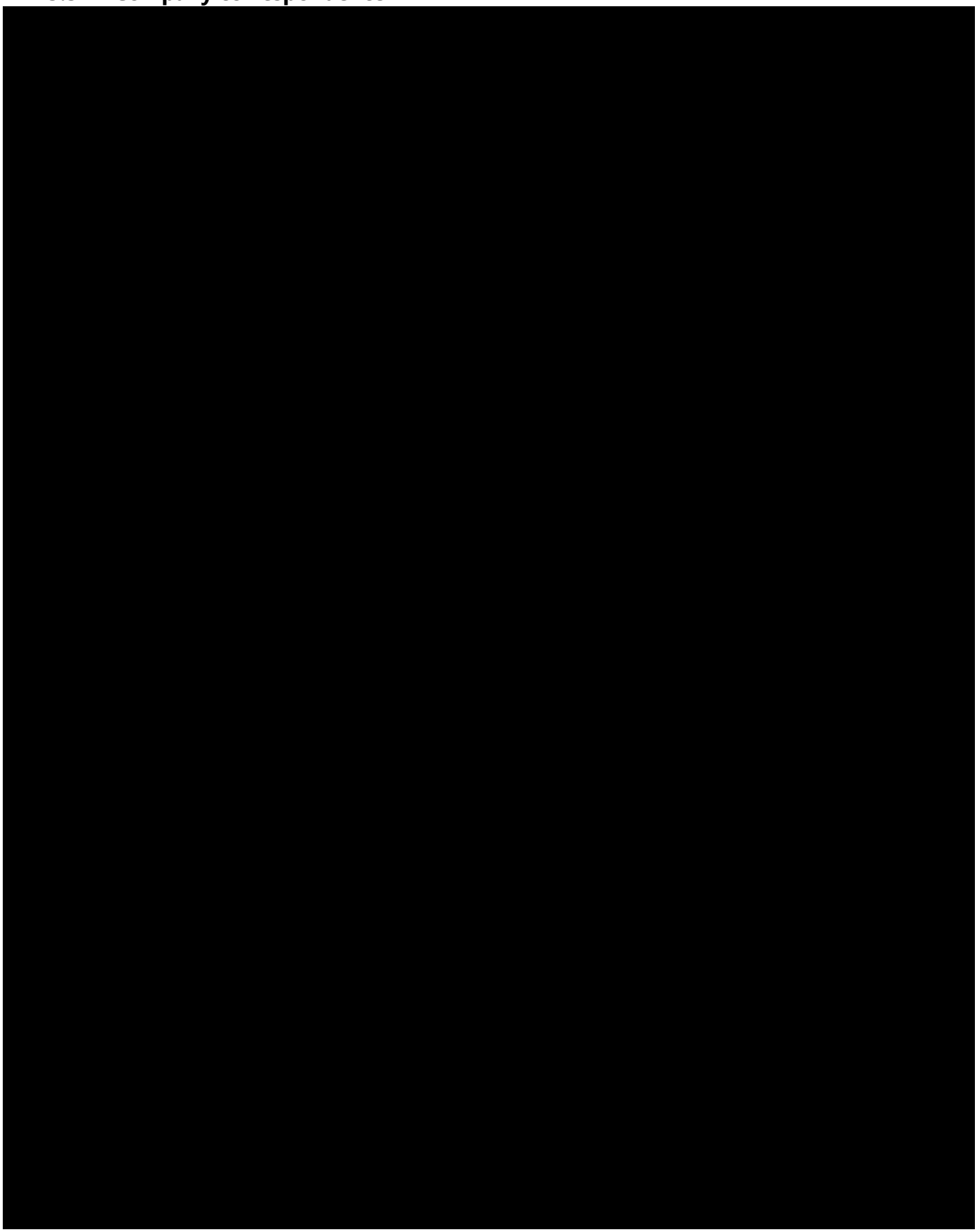
3.2.3 United States

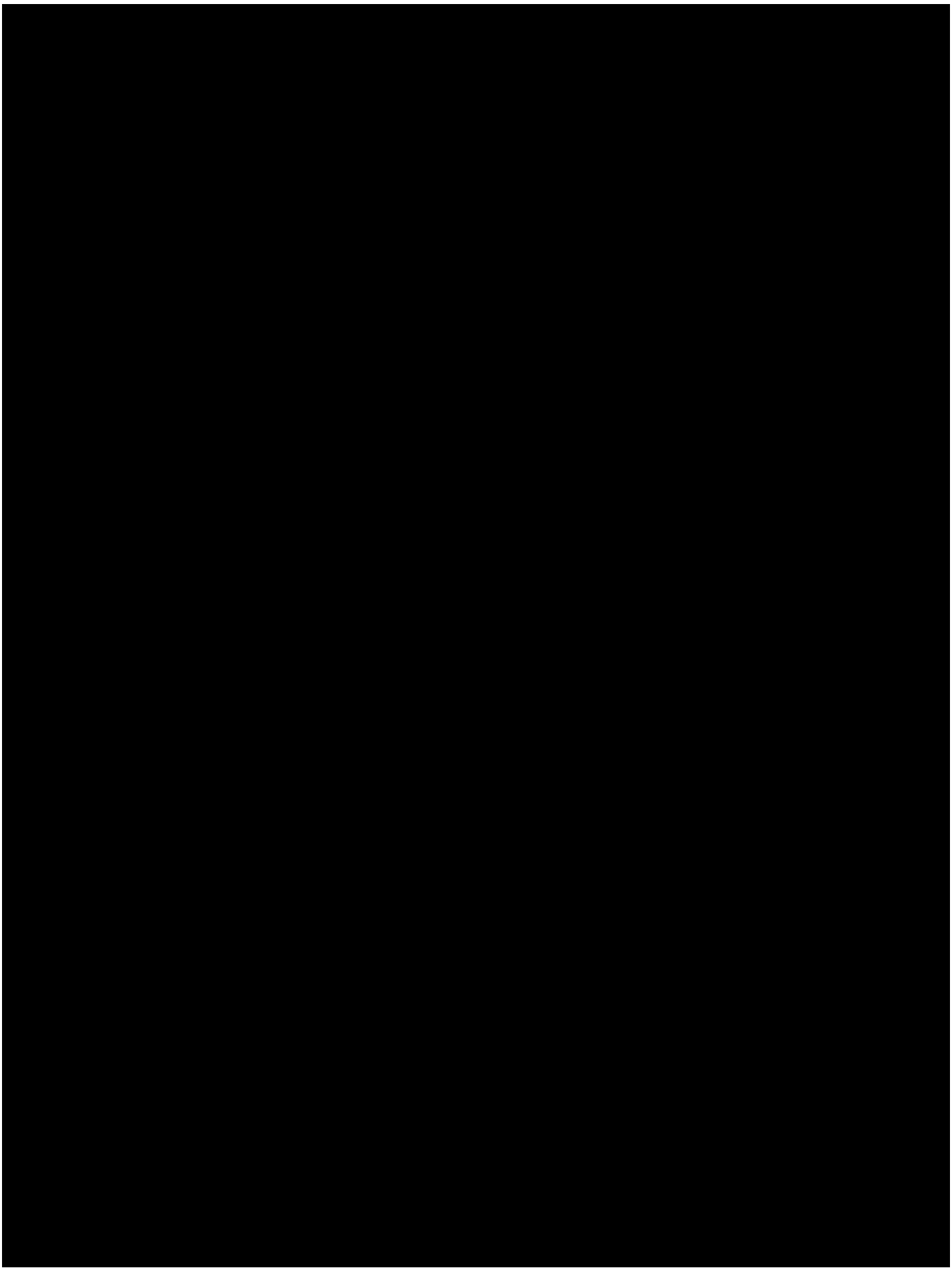
In late 2022, the US FDA began evaluating a safety signal for acute kidney injury in association with apixaban, edoxaban, dabigatran and rivaroxaban. [redacted]

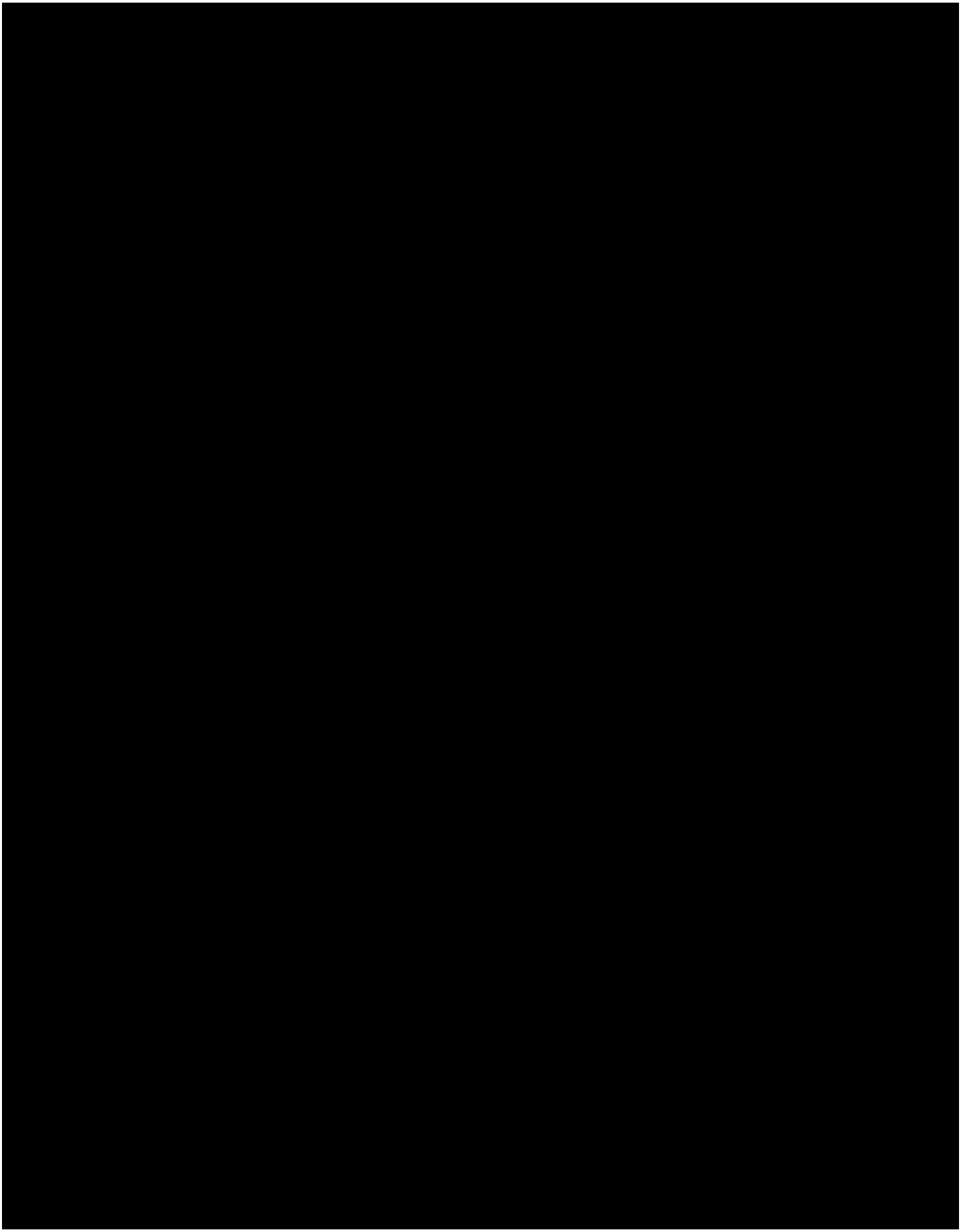
The outcome of the review is not yet available.

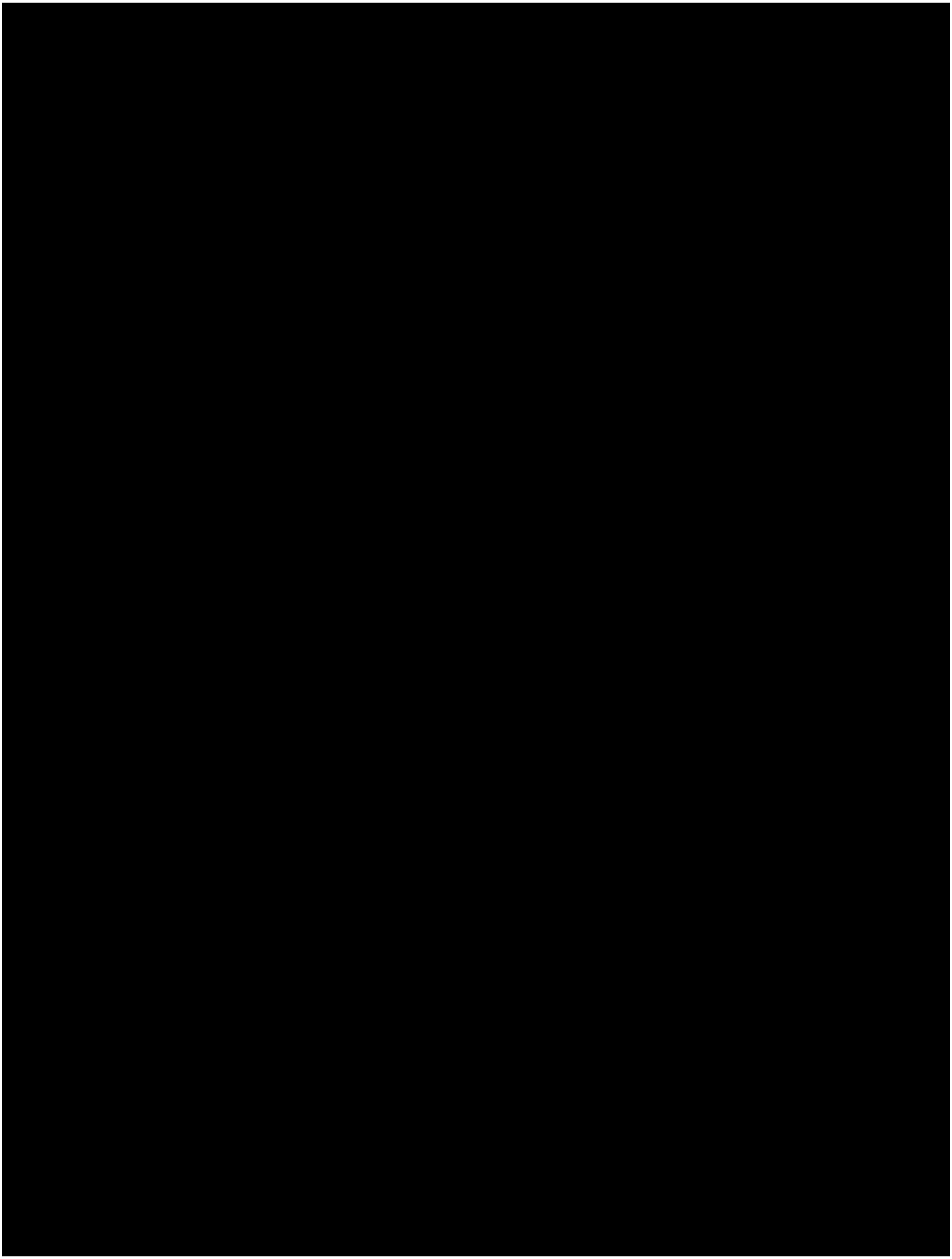
See section 2.3.2 for the US product information wording.

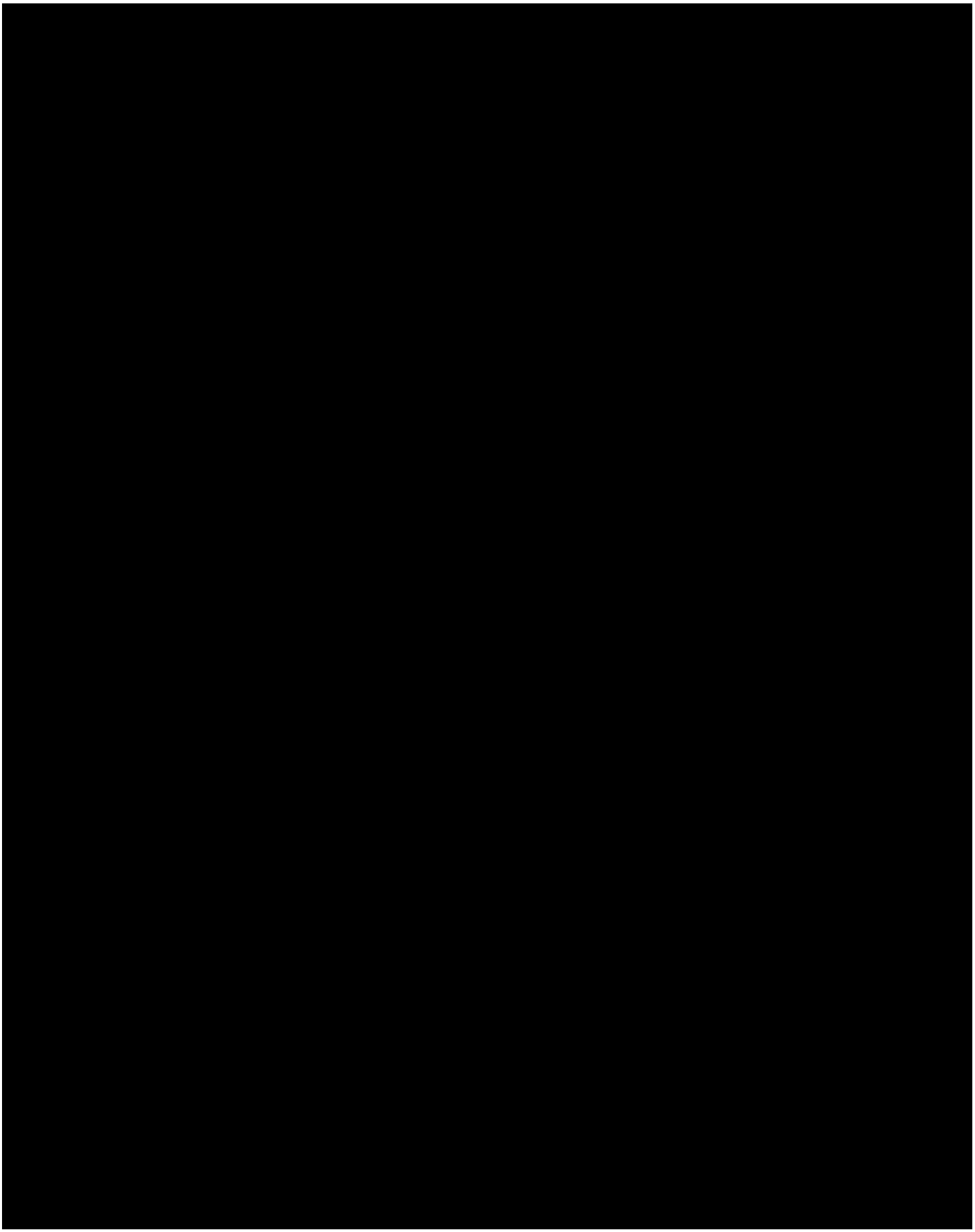
3.3 Company correspondence

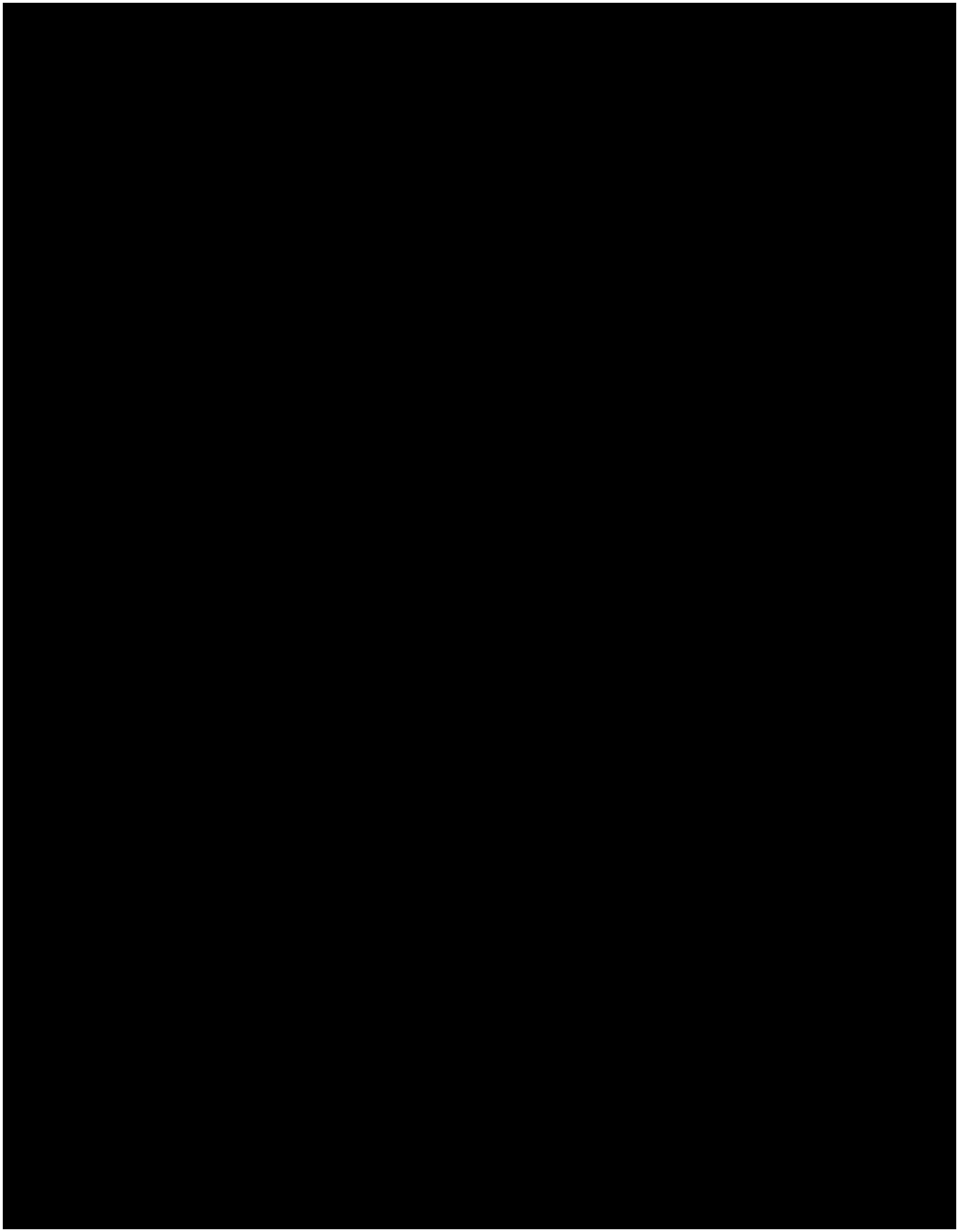


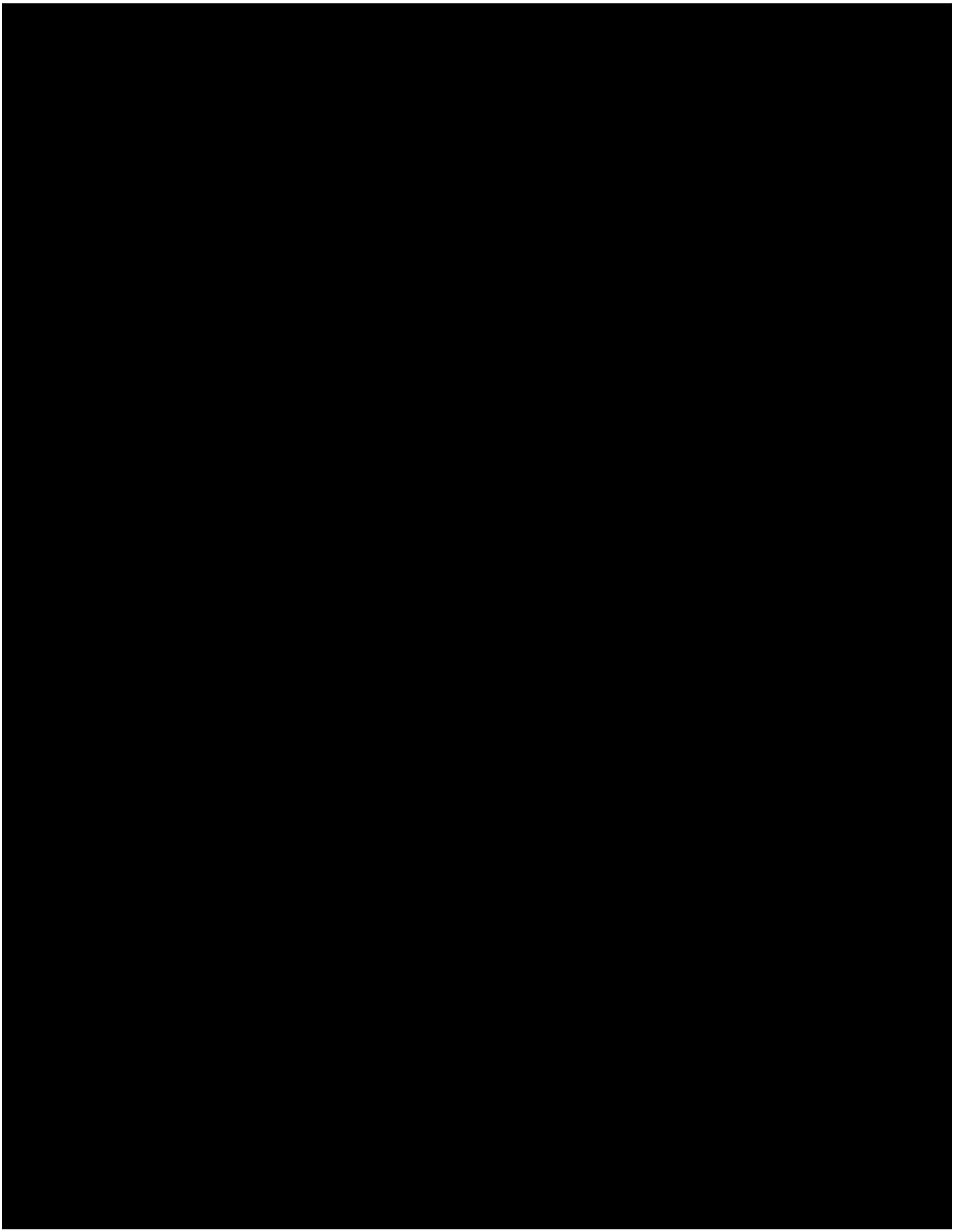












[redacted]

3.4 Spontaneous reports

3.4.1 New Zealand

Table 23 shows the number of case reports received by CARM where a DOAC was the suspect medicine, plus the number of reports containing urinary or renal terms. Although there are numerous reports with renal involvement, there is only case of ARN, reported in association with dabigatran [redacted]

Table 23: Direct-acting oral anticoagulant case reports received by CARM, total reports and those with urinary or renal terms, to 30 June 2023

	Dabigatran	Rivaroxaban	Apixaban
Total	1039	153	42
Urinary System Disorder	101	6	3
Renal involvement[a]	42	3	2
Renal failure[b]	26	3	1
Nephritis/nephropathy[c]	2	0	0

a. Renal involvement: Renal failure acute, renal failure hypotensive, renal failure ischaemic, renal failure aggravated, renal failure chronic, renal failure chronic aggravated, renal failure NOS, renal function abnormal, renal impairment, renal impairment aggravated. Creatinine blood increased, creatinine clearance decreased. Nephritis, nephritis interstitial, nephropathy NOS, nephropathy toxic, nephrosis, nephrotic syndrome.

b. Renal failure: renal failure acute, renal failure aggravated, renal failure chronic, renal failure chronic aggravated, renal failure NOS.

c. Nephritis/nephropathy: nephritis, nephritis interstitial, nephropathy NOS, nephropathy toxic, nephrosis, nephrotic syndrome.

[redacted]

3.4.2 International

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) reported with the use of oral anticoagulants in recent years, especially in cases involving warfarin-related nephropathy.

The pathogenesis of ARN is thought to be multifactorial, and includes glomerular haemorrhage, obstruction to renal tubules by red blood cells, and tubular epithelial cell injury. It may be underdiagnosed in clinical practice because of the requirement for kidney biopsy to confirm the diagnosis, and because people who develop ARN have multiple risk factors that may provide an alternative explanation for this type of AKI.

ARN has been reported in the medical literature with all types of direct acting oral anticoagulants (DOACs), and in spontaneous adverse event case reports. Some of the cases reported a positive dechallenge upon withdrawal of the DOAC. However, many cases were confounded by pre-existing conditions. As yet, there are no prospective clinical trials reporting ARN. However, the pivotal clinical trials for DOACs all reported renal adverse effects and bleeding, and this information is reflected in the data sheets.

International regulators have reviewed the risk of ARN with individual DOACs and for the class. The TGA identified a class effect and recommended that the product information for all DOACs include information about ARN. The dabigatran prescribing information in the UK, Europe and the US includes information about ARN, as does the rivaroxaban prescribing information in Europe and the US.

Currently, only the New Zealand Xarelto (rivaroxaban) data sheet includes information about ARN. However, all data sheets include information about bleeding, acute renal failure/AKI, urogenital haemorrhage and/or haematuria. The Xarelto and Pradaxa (dabigatran) recommend assessment of renal function prior to starting treatment, and the Pradaxa data sheet recommends assessing renal function during therapy in clinical situations that could lead to renal function decline.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether there is evidence for an association between anticoagulant-related nephropathy and direct-acting oral anticoagulants as a class (dabigatran, rivaroxaban and apixaban)?
  - If yes, are data sheet updates required (for example, to align with the recent updates requested by the TGA)?
- If there is no evidence for the class, is there evidence for an association between anticoagulant-related nephropathy and particular direct-acting oral anticoagulants, and if so, which ones?
  - Are data sheet updates required for the specified anticoagulants?
- Does the topic require further communication, other than MARC's remarks in *Prescriber Update*?

6 ANNEXES

A1 – Direct oral anticoagulant prescribing information – New Zealand

[redacted]

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