Amiodarone, rivaroxaban, and gastrointestinal haemorrhage – a drug interaction signal

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Summary

A signal regarding the interaction between amiodarone and rivaroxaban resulting in gastrointestinal haemorrhage was detected during a screening of VigiBase, the WHO global database of individual case safety reports (ICSRs) in autumn 2020. Up to 6 December 2020 VigiBase contained 24 unique reports of gastrointestinal haemorrhage resulting from the concomitant use of amiodarone and rivaroxaban. Most patients were elderly with a median age of 74 years (range 34 to 91 years). In five cases (20.8%) reduced renal function was reported, potentially influencing rivaroxaban's exposure.

The antiarrhythmic drug amiodarone and its active metabolite act as moderate inhibitors for a series of CYP enzymes as well as P-glycoprotein (P-gp) and therefore have the potential for pharmacokinetic (PK) interactions with various drugs. The oral factor Xa inhibitor rivaroxaban is metabolised hepatically via the cytochrome P450 (CYP) enzymes 3A4 and 2J2 and is eliminated renally, via P-gp-mediated secretion. Its PK profile carries the risk for the development of dose-dependent toxicity when administered to patients suffering from hepatic or renal impairment, or to patients receiving CYP enzyme inhibiting drugs concomitantly.

Substances that are strong inhibitors of both CYP3A4 and P-gp may increase rivaroxaban plasma concentrations to a clinically significant degree resulting in an increased risk for bleeding, but advice on the use of weak to moderate inhibitors, such as amiodarone, is lacking. Cases in VigiBase and literature findings suggest that concomitant treatment of patients with multiple drugs potentially increasing the risk for haemorrhagic events via PK and/or PD interactions with rivaroxaban and amiodarone constitutes a concern for their concurrent use in clinical practice. Caution should be advised when attempting concomitant use of amiodarone and rivaroxaban, and benefit/risk exploration recommended on an individual patient basis, particularly in vulnerable patients.

Introduction

Amiodarone is an antiarrhythmic drug used for the conversion and prevention of supraventricular arrhythmias, such as atrial fibrillation (AF)[1,2]. Its antiarrhythmic effect is based on a prolongation of the heart's action potential by inhibition of voltage-gated potassium and calcium channels. Amiodarone is poorly bioavailable after oral administration. After intravenous injection it is strongly protein-bound with an extremely long plasma half-life (20-100 days). Amiodarone undergoes extensive hepatic metabolism, mainly via the cytochrome P450 (CYP) enzyme 3A4 and several others. In vitro experiments have shown that amiodarone and its active metabolite are moderate inhibitors for a series of CYP enzymes as well as P-glycoprotein (P-gp) and therefore carry the potential for pharmacokinetic (PK) interactions with various drugs[2,3].

Rivaroxaban is an orally bioavailable, highly selective factor Xa inhibitor, blocking the intrinsic as well as the extrinsic pathway of the blood coagulation cascade. It is indicated for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults[3]. After oral administration, rivaroxaban reaches maximal serum concentrations (t_{max}) after two to four hours. Elimination of rivaroxaban occurs through a dual pathway: two thirds of the administered dose undergo hepatic metabolism via the CYP enzymes 3A4 and 2J2. The remaining third is eliminated renally via P-gp-mediated secretion[1,3]. Elimination half-time ($t_{1/2}$) is seven to eleven hours[3,4]. The summary of product characteristics (SmPC) advises the cautious use of rivaroxaban in patients suffering from renal impairment as well as in patients receiving comedications inhibiting both CYP3A4 and P-gp because of potential PK interactions[4]. Due to its pharmacodynamic (PD) properties, the risk for all kinds of haemorrhages is increased under rivaroxaban therapy[4].

Reports from VigiBase

The preliminary signal "amiodarone – interaction with rivaroxaban causing gastrointestinal (GI) haemorrhage" was identified during a screening of VigiBase in the autumn of 2020 focussing on drugs reported as suspected or concomitant in the period of the pandemic novel coronavirus disease, COVID-19, where a disproportionate reporting for the combination amiodarone and gastrointestinal haemorrhage (IC_{025}=1.68) was observed (observed 18 and expected 3 cases), and in 15 of the 18 cases rivaroxaban was co-reported. Despite the analysed setting none of the patients included in the case series was reported to have COVID-19.

Up to 6 December 2020, VigiBase contained 24 unique ICSRs with the MedDRA preferred term (PT) "gastrointestinal haemorrhage" in patients receiving rivaroxaban and amiodarone as suspected and/or interacting drugs and these were subjected to in-depth assessment. All cases were classified as serious; in three cases (12.5%) a fatal outcome was reported. Reports were from five different countries (United States of America (USA), Switzerland, France, Canada, and Belgium), with most of them (n = 18; 75%) from the USA. Information on the daily dose for amiodarone and rivaroxaban was available in 19 and 12 cases, respectively. Patients received on average 19.0 mg rivaroxaban (range 15-20 mg/d) and 233.3 mg amiodarone (range 200-400 mg/d) daily. This is in line with the therapeutic doses recommended in the SmPCs (2,4). Information on the time-to-onset (TTO) between therapy start with rivaroxaban and amiodarone and the occurrence of the reported GI haemorrhage was available in 17 cases. In seven cases this information was given only for rivaroxaban. Median TTO was observed to be eight weeks, ranging from five days to two years. Table 1 gives an overview of the 24 assessed case reports.

Table 1. Overview of case details

Among the 24 cases, 12 patients were female and nine male with a median age of 74 years (range 34 – 91 years); in three cases information on patients' sex and age was missing. In five cases (21%) the MedDRA PT "Drug interaction" was specifically co-reported. In eight cases (33%) rivaroxaban and amiodarone were the only two reported drugs (including one case with concomitant hepatic and renal impairment, and one case with underlying haemophilia). In five cases (21%) reduced renal function was reported, potentially influencing rivaroxaban's plasma concentrations (see Table 1, p8).

Patients received a median of three suspected/interacting drugs (range two to 15). Fourteen reports included co-medications that, in addition to

rivaroxaban, had anticoagulant or antiplatelet activity. Acetylsalicylic acid was listed in all fourteen reports and in five of these one or more other antiplatelet agents (clopidogrel, ticagrelor) or anticoagulants (warfarin, enoxaparin, apixaban, dabigatran) were also listed as shown in Table 1.

Analysing the concomitant drugs, 12 substances had PD interaction potential, another four substances had PK interaction potential, and one substance (ticagrelor) had PK as well as PD interaction potential with rivaroxaban[5,6]. A data-driven exploration of the reports pinpointing features using vigiPoint[8] revealed an unexpectedly frequent reporting of nicotinic acid as a concomitantly administered drug (13% (three ICSRs)) in cases reporting GI haemorrhage with rivaroxaban and amiodarone in combinations (foreground) vs 0.3% in cases reporting GI haemorrhage with rivaroxaban (background 1) and 0.0% in cases reporting GI haemorrhage with amiodarone (background 2)).

An overview of the 17 substances (reported in 16 different cases) that showed the potential to interact with rivaroxaban on a PD and/or PK level as labelled in the Flockhart table and in DrugBank, is given in Table 2.

Table 2. Potentially interacting co-medication in the 24 assessed ICSRs

In one case (Table 1, case 16) it was noted that the plasma concentrations of rivaroxaban were elevated (500 ng/mL, ref. ≤ 249 ng/mL) at admission in a patient suffering from a mild to moderate renal insufficiency who was concomitantly treated with clopidogrel and acetylsalicylic acid. For another patient, 13 suspected drugs were reported, resulting

Table 2. Potentially interacting co-medication in the 24 assessed individual case safety reports (ICSRs)

Substance (WHODrug AI)	No. of ICSRs	PK/PD interaction*	Comment**
Acetylsalicylic acid	15	PD	Haemorrhagic risk
Clopidogrel	4	PD	Haemorrhagic risk
Enoxaparin	4	PD	Haemorrhagic risk
Nicotinic acid	4	PD	Dose-dependent risk for coagulopathy
Diltiazem	3	PK	Moderate CYP3A4 inhibitor
Apixaban	2	PD	Haemorrhagic risk
Dabigatran	2	PD	Haemorrhagic risk
Fluconazole	2	PK	Moderate CYP3A4 inhibitor
Ibrutinib	2	PD	Haemorrhagic risk
Ibuprofen	2	PD	Haemorrhagic risk
Ticagrelor	2	PK/PD	Weak CYP3A4 inhibitor Weak P-gp inhibitor Haemorrhagic potential
Verapamil	2	PK	Moderate CYP3A4 inhibitor P-gp inhibitor
Warfarin	2	PD	Haemorrhagic risk
Venlafaxin	2	PD	Haemorrhagic risk
Carvedilol	1	PK	P-gp inhibitor
Ketorolac	1	PD	Haemorrhagic risk
Sertralin	1	PD	Haemorrhagic risk

AI = Active Ingredient; PK = pharmacokinetic; PD = pharmacodynamic

* CYP-/P-gp interaction as labelled in the Flockhart table/DrugBank

** Haemorrhagic risk as labelled in substance's SmPC

in both GI and cerebral haemorrhages (Table 1, case 3). In 11 cases, there were at least four co-existing risk factors present increasing the bleeding risk with rivaroxaban, including concomitant drugs and/or organ diseases or dysfunction (Table 1, cases 3, 5, 7, 8, 11, 13, 14, 16, 17, 18, and 23). These findings suggest that the reasons for the occurrence of GI haemorrhage with rivaroxaban could be multifactorial, for example increased pharmacological effect through PK and/or PD mechanisms, or increased susceptibility through underlying diseases (e.g. previous GI haemorrhage, and haemophilia A).

Labelling and literature

Labelling

Rivaroxaban

According to the SmPC of Xarelto® (rivaroxaban), limited clinical data suggest that rivaroxaban plasma concentrations are significantly increased (approximately 44-64%) in patients suffering from severe renal impairment (creatinine clearance 15-29 mL/min), resulting in increased therapeutic effects[3,8]. The FDA's SmPC of rivaroxaban therefore advises prescribers to regularly assess patients' renal function and possibly to adjust the dose accordingly[9]. Furthermore, a formal contraindication for the use of rivaroxaban in patients suffering from hepatic disease is stated, as it has been associated with a clinically relevant bleeding risk[4].

The SmPC also advises against the use of rivaroxaban in patients being concomitantly treated with azole-antimycotics or HIV protease inhibitors, since substances that are strong inhibitors of both CYP3A4 and P-gp may increase rivaroxaban plasma concentrations to a clinically significant degree, resulting in an increased risk of bleeding. Inhibitors of only one of the rivaroxaban elimination pathways – either CYP3A4 or P-gp – are expected to increase rivaroxaban plasma concentrations to a lesser extent. Advice on the use of weak to moderate inhibitors of CYP3A4 and P-gp, such as amiodarone, is absent. The SmPC warns, however, specifically against co-treatment with dronedarone, a less lipophilic successor substance of amiodarone, in patients receiving rivaroxaban therapy, due to limited available clinical data[4].

The SmPC labels bleeding as the most reported adverse reaction in patients treated with rivaroxaban. Amongst bleeding events, gastrointestinal tract haemorrhages were observed most frequently, occurring in 3.8% of cases in one study[9]. Due to its pharmacological properties, rivaroxaban can cause an increased risk of occult or overt bleeding from any tissue or organ[4].

Amiodarone

Amiodarone and its active metabolite, desethylamiodarone, act as moderate inhibitors of various CYP enzymes as well as the P-gp, potentially resulting in increased exposure to their substrates[1,2]. Though only a limited number of in vivo drug-drug interactions (DDIs) have been reported, a potential for other interactions should be anticipated in relation to amiodarone[11]. Important to consider is amiodarone's long half-life, and that effects resulting from PK interactions may be observed months after discontinuation of amiodarone therapy[1].

According to the SmPC of amiodarone, thrombocytopenia, potentially increasing the risk of haemorrhagic events, is labelled as a very rare adverse reaction[2].

Literature

A series of four published case reports describes patients experiencing abnormal anticoagulation parameters and/or haemorrhagic events after co-treatment with rivaroxaban and amiodarone, in one case even weeks after amiodarone cessation[1].

The four case reports describe three male patients and one female, aged 71 to 88 years old, who were admitted to hospital due to experiencing haemorrhagic events (pulmonary haemorrhage, intracerebral mass bleeding, and cardiac tamponade)[12-14] or elevated INR[1]. In two cases the adverse reactions resolved after withdrawal of rivaroxaban[1,12], in one case rivaroxaban as well as amiodarone were withdrawn and the patient recovered[14], and in one case the patient's death was reported as the outcome[13]. In one case the patient's renal function was reported to be impaired (eGFR = 50 mL/min)[1].

Discussion

In the 24 assessed ICSRs reporting GI haemorrhage in combination with amiodarone and rivaroxaban as suspected or interacting drugs, amongst the 79

reported concomitant drugs, 17 substances were found to have PK and/or PD interaction potential[6]. VigiBase data characteristics and their limitations should be kept in mind when analysing concomitant medication. Due to missing therapy dates for concomitant medication in many cases, it cannot be excluded that concomitant drugs were paused or even suspended at the time of the reported event. The potential DDI between amiodarone and rivaroxaban was indicated by the reporter in only five cases. Possible reasons for this might be lack of awareness or mis-labelling. Furthermore, amiodarone's long half-life might impede recognition of the potential DDI.

Nicotinic acid was co-reported with an unexpected frequency in cases of GI haemorrhage following concomitant use of amiodarone and rivaroxaban. In the SmPC of nicotinic acid, as well as in published case reports, the potential to cause decreased platelet counts and coagulopathy are discussed, noting that the exact mechanism of action of nicotinic acid is not yet explored[15-20].

In 15 cases patients received additional substances with antithrombotic activity. Most were "elderly patients" (≥ 65 years old). Advanced age is a known risk factor for bleeding events associated with anticoagulation. Furthermore, it is known that renal function decreases with advancing age. For five patients impaired renal function was specifically reported. A series of four published literature case reports indicates that the DDI potential for rivaroxaban and amiodarone in real-world clinical practice warrants attention[1,12-14].

According to the European Public Assessment Report (EPAR) Risk Management Plan (RMP) from 2018[21], potential risks of rivaroxaban treatment of patients with severe renal impairment (creatinine clearance < 30 mL/min) as well as patients being co-treated with systemic inhibitors of CYP3A4 or P-gp – other than azole antimycotics and HIV-protease inhibitors – were identified as "missing information". In 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updating the European SmPC of rivaroxaban in the sections "Contraindications" and "Interactions"[22]. This would have been to include a series of potential DDIs, amongst them amiodarone, to be mentioned for cautious concomitant use.

Based on preclinical and clinical data that did not show a significantly increased clinical risk, the Market Muthorization Holder did not consider including amiodarone in section 4.5.

Haemorrhage being a known risk associated with rivaroxaban, the identification of a possible interaction with another medicine, such as amiodarone, resulting in an increased risk of haemorrhagic events, is inevitably confounded. However, although several of the assessed cases as well as the published case reports include confounding factors, such as the use of concomitant medications and underlying organ dysfunctions, the case series supports the hypothesis of a clinically relevant potential interaction between amiodarone and rivaroxaban, and suggests particular caution for co-prescription in patients predisposed to rivaroxaban-related haemorrhage through age, co-morbidities and other medicines that also increase the risk through PK or PD mechanisms. The decision to consider co-prescribing amiodarone and rivaroxaban is an opportunity to review the patient's medicines, especially where multiple antithrombotic medicines are being prescribed. There are clinical indications for dual antiplatelet/anticoagulant therapy, but de-prescribing of an unnecessary antiplatelet medicine may be appropriate in some cases[23].

Conclusion

Concomitant use of rivaroxaban and substances acting as strong inhibitors of CYP3A4 and P-gp is clearly to be advised against. Information on its concomitant use with moderate or weak inhibitors – such as amiodarone – however, does not exist. Due to their overlapping indication field and their clinical significance, amiodarone and rivaroxaban could commonly be used concomitantly or close in time in clinical practice. Cases in VigiBase and literature findings suggest that concomitant treatment of patients with multiple drugs potentially increasing the risk for haemorrhagic events via PK and/or PD interactions with rivaroxaban and amiodarone constitutes a concern for their concomitant use in real-world clinical practice. Caution when attempting concomitant use of amiodarone and rivaroxaban should be advised, recommending benefit/risk exploration on an individual patient basis, particularly in vulnerable patients.

References

1. Skov K, Falskov B, Jensen EA, Dorff MH. Supratheraputic rivaroxaban levels: A persistent drug-drug interaction after discontinuation of amiodarone. Basic Clin Pharmacol Toxicol. 2020 Oct 1;127(4):351-3.

2. Electronic Medicines Compendium: Summary of Product Characteristics for amiodarone. Available from: https://www.medicines.org.uk/emc/product/6019/smpc#INDICATIONS. Accessed on 21 December 2020.

3. Jobson MD. Cytochrome P450 3A (including 3A4) inhibitors and inducers. Available at: https://www.uptodate.com. Accessed on 03/02/2021.

4. Electronic Medicines Compendium: Summary of Product Characteristics for rivaroxaban (Xarelto®). Available from: https://www.medicines.org.uk/emc/product/6402/smpc#PHARMACOLOGICAL_PROPS. Accessed on 21 December 2020.

5. Kreutz R. Pharmacodynamic and pharmacokinetic basics of rivaroxaban. Fundam Clin Pharmacol. 2012;26(1):27-32.

6. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). Available from: https://drug-interactions.medicine.iu.edu. Accessed on 12 January 2021.

7. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 Jan 1;34(Database issue):D668-672.

8. Juhlin K, Star K, Norén GN. A method for data-driven exploration to pinpoint key features in medical data and facilitate expert review. Pharmacoepidemiol Drug Saf. 2017 Oct;26(10):1256-65.

9. Food and Drug Administration: Summary of Product Characteristics for rivaroxaban (Xarelto®). Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022406. Accessed on 12 January 2021.

10. Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, et al. Outcomes After Cardioversion and Atrial Fibrillation Ablation in Patients Treated With Rivaroxaban and Warfarin in the ROCKET AF Trial. J Am Coll Cardiol. 2013 May;61(19):1998-2006.

11. Food and Drug Administration: Summary of Product Characteristics for amiodarone (Cordarone®). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018972s054lbl.pdf Accessed on 12 January 2021.

12. Wong A, Koutsogiannis Z, Greene SL. Pulmonary haemorrhage from therapeutic rivaroxaban use: Chest radiograph consolidation is not always infection! Emerg Med Australas. 2014 Jun;26(3):318-9.

13. Stöllberger C, Bastovansky A, Finsterer J. Fatal intracerebral bleeding under rivaroxaban. Int J Cardiol. 2015 Dec;201:110-2.

14. Oladiran O, Segal J, Nwosu I, Nazir S. A Rare Case of Spontaneous Cardiac Tamponade Induced by Concomitant Use of Rivaroxaban and Amiodarone. Case Rep Cardiol. 2018 Aug 12;2018:1-4.

15. Abbvie: Summary of Product Characteristics for Niaspan. Available from: https://www.rxabbvie.com/pdf/niaspan.pdf. Accessed on 19 January 2021.

16. Fayyaz B, Rehman, Hafiz J, Upreti, Sunita. Beating the urine drug test – a case report on niacin toxicity. J Community Hosp Intern Med Perspect. 2018;8(2):73-5.

17. Chesney CM, Elam MB, Herd JA, Davis KB, Garg R, Hunninghake D, et al. Effect of niacin, warfarin, and antioxidant therapy on coagulation parameters in patients with peripheral arterial disease in the Arterial Disease Multiple Intervention Trial (ADMIT). Am Heart J. 2000 Oct;140(4):631–6.

18. Daul AM, Beuhler MC. Niacin Toxicity Resulting From Urine Drug Test Evasion Scheme. J Emerg Med. 2010 Feb;S073646790900955X.

19. Dearing BD, Lavie CJ, Lohmann TP, Genton E. Niacin-induced clotting factor synthesis deficiency with coagulopathy. Arch Intern Med. 1992 Apr;152(4):861–3.

20. Guyton JR, Bays HE. Safety Considerations with Niacin Therapy. Am J Cardiol. 2007 Mar;99(6):S22–31.

21. European Medicines Agency: European Public Assessment Report - EU Risk Management Plan Xarelto® Available at: xarelto-epar-risk-management-plan-summary_en.pdf. Accessed on 12 January 2021.

22. Europena Medicines Agency: European Public Assessment Report - Xarelto® 2013. Available at: xarelto-h-c-944-ii-0023-epar-assessment-report-variation_en.pdf. Accessed on 12 January 2021.

23. Floyd CN, Ferro A. Indications for anticoagulant and antiplatelet combined therapy. BMJ. 2017 Oct 5;j3782.

Table 1. Overview of case details

Case	Age/Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
1	63/F	**Amiodarone (S)** **Rivaroxaban (I)**	Gastrointestinal haemorrhage Drug interaction	Unknown Unknown	
2	71/F	**Amiodarone (S)** **Rivaroxaban (I)** Acetylsalicylic acid (I)	Gastrointestinal haemorrhage Drug interaction	Unknown Unknown	
3	-/-	**Amiodarone (S)** **Rivaroxaban (S)** Ibrutinib (S) Acetylsalicylic acid (S) Fluconazole (S) Warfarin (S) Enoxaparin (S) Diltiazem (S) Fish oil (S) Verapamil (S) Tocopherol (S) Apixaban (S) Nicotinic acid (S) Clopidogrel (S) Ticagrelor (S)	Gastrointestinal haemorrhage Contusion Cerebral haemorrhage Haematoma Epistaxis	Unknown Unknown	
4	-/-	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal bleeding	Approx. 10 days Approx. 10 days	
5	66/M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Tamsulosin, Hydromorphone, Prednisone, Methocarbamole, Metoprolol, Salbutamol, Furosemide, Oxycodone, Simvastatin, Tiotropium, Lorazepam, Fluticasone/Salmeterol, Gabapentin, Clonazepam, Lisinopril (C)	Gastrointestinal haemorrhage	Approx. 2 months Approx. 2 months	

Case	Age/Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
6	91/F	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal haemorrhage Rectal haemorrhage Melaena Drug interaction Anemia	5 days 5 days	
7	85/M	**Amiodarone (S)** **Rivaroxaban (S)** Dabigatran (S) Acetylsalicylic acid (S) Enoxaparin (S) Furosemide, Pantoprazole, Metoprolol, Zolmitriptan (C)	Gastrointestinal haemorrhage Haematuria Fall Acute kidney injury Haemorrhage intracranial	Unknown 2 years	
8	62/M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S)	Blood loss anemia Gastrointestinal haemorrhage	Unknown 6 months	Predisposing factors: liver cirrhosis Removal of benign colon polyp (10/12/2015)
9	73/F	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal Haemorrhage Swelling (amiodarone) Weight increase (amiodarone)	Unknown 2 weeks	
10	83/F	**Amiodarone (S)** **Rivaroxaban (S)** Sertraline (S) Nadolol, Pantoprazole, Vitamin D nos, Vitamins nos, Febofibrate, Furosemide, Alprazolam, Cyanocobalamin, Fluticasone (C)	Dyspnoea Gastrointestinal haemorrhage Melaena Gastritis Haematemesis Vomiting	1 year 3 years	Predisposing factors: Solitary kidney
11	74/F	**Amiodarone (S)** **Rivaroxaban (S)** Enoxaparin (S) Dabigatran (S) Acetylsalicylic acid (S) Prednisolone, Hydrochlorothiazide, Nicotinic acid, Multivitamin, Lisinopril, Ketorolac, Atenolol, Ibuprofen (C)	Gastrointestinal haemorrhage	Unknown 20 days	

Case	Age/Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
12	63/M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S)	Gastrointestinal haemorrhage Off label use Pulse absent Acute respiratory distress syndrome Product use issue	Unknown Unknown	
13	74/F	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Valsartan, Diltiazem, Pravastatin (C)	Gastrointestinal haemorrhage Myocardial infarction Haemorrhagic stroke Haemoptysis Epistaxis	Unknown 5 days	
14	85/M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Allopurinol, Lorazepam, Insulin, Furosemide, Ibuprofen, Acetaminophen/Hydrocodon, Nortryptilin, Omeprazole, Potassium, Sennosoid (C)	Acute kidney injury Blood blister Haemorrhage Gastrointestinal haemorrhage Petechiae Haematuria	Unknown 2 months	
15	60/M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S)	Anaemia Gastrointestinal haemorrhage	Unknown 2 months	
16	75/F	**Amiodarone (I)** **Rivaroxaban (I)** Clopidogrel (I) Acetylsalicylic acid (I)	Overdose Gastrointestinal haemorrhage Ecchymosis	2 months 2 months	Predisponen factors: Pyelonephritis secondary to diabetes mellitus II Elevated rivaroxaban plasma concentrations at admission (500 ng/mL) Light to moderate renal insufficiency (age-dependent) (61 mL/min CKD-EPI)
17	74/M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Macrogol 3350, Carvedilol, Simvastatin, Ramipril (C)	Gastrointestinal haemorrhage Blood loss anaemia	Unknown Unknown	

Case	Age/Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
18	89/M	**Amiodarone (S)** **Rivaroxaban (S)** Clopidogrel (S) Acetylsalicylic acid (S) Vitamin D, Iron, Finasterid, Nicotinic acid, Ramipril, Rosuvastatin, Tamdulosin, Trimetoprim/Sulfamethoxazole, Lycopene (C)	Gastrointestinal haemorrhage Iron defficiency anaemia Diverticulum Small intestinal haemorrhage	Unknown Unknown	
19	-/-	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal haemorrhage Errosive oesophagitis	Unknown Unknown	
20	87/F	**Amiodarone (I)** **Rivaroxaban (I)** Torasemide, Enalapril, Ipratropium, Salbutamol, Spironolactone, Pramipexole, Insulin degludec, Pantoprazole (C)	Gastrointestinal haemorrhage Melaena Drug interaction	30 days 15 days	Predisposing factors: hepatic cirrhosis, renal insufficiency (GFR ca. 40 mL/min)
21	77/F	**Amiodarone (S)** **Rivaroxaban (S)** Venlafaxine (S) Oxazepam, Atrovastatin, Spironolactone, Zolpidem, Rimenidine, Furosemide, Olmesartan, Nicardipine, Macrogol 3350/Potassium/Sodium bicarbonate/Sodium sulfate (C)	Gastrointestinal haemorrhage Shock haemorrhagic	9 days 9 days	Initial creatinine clearance (52 mL/min), decreased dramatically within 10 days (21 mL/min)
22	34/F	**Amiodarone (I)** **Rivaroxaban (S)**	Gastrointestinal haemorrhage Gingival bleeding	16 days 16 days	Predisposing factors: Haemophilia A
23	72/M	**Amiodarone (I)** **Rivaroxaban (I)** Acetylsalicylic acid (I) Metoprolol, Rosuvastatin, Loperamide, Pantoprazole, Diphenhydramine/Lorazepam (C)	Gastrointestinal haemorrhage Melaena Dyspnoea Asthenia Blood loss anemia	2 years 3 months	Predisposing factors: GI haemorrhage 6 years before event onset, chronic renal insufficiency grad III secondary to diabetes mellitus type II
24	78/F	**Amiodarone (S)** **Rivaroxaban (S)**	Optic atrophy Atrial fibrillation Haemoglobin decreased Gastrointestinal haemorrhage	1 year 2 months	

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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