Update overview 2019 of reports on direct oral anticoagulants (DOACs) and the antidote idarucizumab

Introduction

Lareb previously published yearly overviews of reports (most recently in 2018) in consultation with the Medicines Evaluation Board CBG-MEB, concerning the direct oral anticoagulants (DOACs) dabigatran Pradaxa®, registered in the Netherlands in 2008 [1], rivaroxaban Xarelto®, registered in 2008 [2], apixaban Eliquis®, registered in 2011 [3] and edoxaban (Lixiana®), registered in 2015 [4-9]. The current overview provides a new yearly update of the reports received by Lareb for these DOACs. Furthermore, reports received by Lareb for the antidote idarucizumab are described in this overview. Idarucizumab is a specific antidote for dabigatran and was registered in the Netherlands in 2015 [10]. For this overview, data from the national ADR database were used. These data include reports with serious outcome from the Lareb Intensive Monitoring System (LIM). The DOACs have been monitored with the LIM methodology since September 2012.

Prescription data

The number of patients using DOACs in the Netherlands according to the GIP database is shown in table 1 [11]. These data are based on extramurally provided medication included in the Dutch health insurance package.
Because the antidote idarucizumab is administered in the hospital and not reimbursed directly via the healthcare insurance, these data are not available for this drug.
The number of reports received by the Netherlands Pharmacovigilance Centre Lareb per year since 2013 for each DOAC, is also shown in table 1. Furthermore, table 1 shows the calculated number of these reports per 1.000 users according to the GIP database. As noted before, the data from the GIP database represent reimbursed medicines and these may differ from actually prescribed medicines.

The age distributions concerning patients using DOACs in the Netherlands for 2017, are shown in table 2 for males and table 3 for females [11].

Table 1. Number of patients using DOACs in the Netherlands between 2013 and 2017 according to the GIP database [11], the number of received reports per year, and the calculated number of reports per 1.000 users.

Number of patients using DOACs in in the Netherlands between 2013 and 2017 according to the GIP database [11].

Drug	2013	2014	2015	2016	2017
Dabigatran	13,053	18,902	26,912	40,027	53,383
Rivaroxaban	12,718	20,620	35,337	57,602	84,216
Apixaban	730	4,766	15,403	31,397	54,486
Edoxaban	.	.	58	2,084	10,755

Number of reports received by the Netherlands Pharmacovigilance Centre Lareb per year

Drug	2013	2014	2015	2016	2017
Dabigatran	138	110	116	131	156
Rivaroxaban	73	138	190	151	216
Apixaban	1	33	53	75	137
Edoxaban	.	.	.	8	62

Calculated number of reports per 1.000 users according to the GIP database

Drug	2013	2014	2015	2016	2017

Dabigatran	10.6	5.8	4.3	3.3	2.9
Rivaroxaban	5.7	6.7	5.4	2.6	2.6
Apixaban	1,4	6.9	3.4	2.4	2.5
Edoxaban	.	.	.	3.8	5.8

Table 2. Age distribution concerning males using DOACs in the Netherlands for 2017 according to the GIP database [11].

Males	Age groups (years)					
Drug	**5-14**	**15-24**	**25-44**	**45-64**	**65-74**	**75+**
Dabigatran	.	20	368	6,338	11,579	12,043
Rivaroxaban	.	118	1,409	12,475	17,107	14,769
Apixaban	.	43	522	6,487	10,933	11,629
Edoxaban	.	9	130	1,539	2,306	2,192

Table 3. Age distribution concerning females using DOACs in the Netherlands for 2017 according to the GIP database [11].

Females	Age groups (years)					
Drug	**5-14**	**15-24**	**25-44**	**45-64**	**65-74**	**75+**
Dabigatran	.	33	255	3,218	7,534	11,973
Rivaroxaban	1	257	1,510	7,882	12,533	16,139
Apixaban	.	92	541	3,494	7,542	13,184
Edoxaban	.	16	109	764	1,493	2,191

Reports for the DOACs

On 4th February 2019 the Netherlands Pharmacovigilance Centre Lareb had received 2,694 reports, concerning 4,933 ADRs, in the national reporting database for the DOACs. These reports include reports with serious outcome from our prospective LIM cohort, that were exported to the national ADR database.
Compared to the previous overview in 2018 (in the overview in 2018 Lareb had received 2,083 reports, concerning 3,828 ADRs), this is an addition of 611 reports.

From start of the monitoring in September 2012 up till 19th February 2019, 2633 patients were included in our prospective LIM cohort. From the LIM cohort, Lareb received 22 reports with a serious outcome.

There were 1070 reports with a serious outcome (compared to 910 reports in the previous overview), including the 22 reports originating from LIM. In 134 reports a fatal outcome was reported (compared to 121 reports in the previous overview). Additional information is provided in table 4.

Table 4. Numbers of reports received by Lareb in the national reporting database for the DOACs (in parentheses are the number of reports in the previous report in 2018)

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Total**
Total number of reports	944 (762)	1093 (911)	486 (330)	171 (80)	2694 (2083)
Number of serious reports	381 (346)	472 (429)	166 (108)	51 (27)	1070 (910)
Total number of ADRs*	1614 (1305)	2019 (1691)	1011 (683)	289 (149)	4933 (3828)
Reports with a fatal outcome[#]	44 (42)	56 (55)	29 (21)	5 (3)	134

* One report can contain multiple ADRs.
[#] The causal relation between the death of a patient and the use of the drug in question is not always clear.

Age distribution of the ADRs

The age distributions of the reported ADRs are presented for the serious ADRs in figure 1, and for the non-serious ADRs in figure 2.

There were 2 reports in figure 2 concerning patients with very young ages. These reports concerned a neonate who did not experience any abnormalities after exposure to rivaroxaban via breast milk, and a report of a young child who accidentally took 1 or 2 tablets apixaban 5 mg without experiencing side effects.

Figure 1. Age distribution of the serious ADRs concerning all four DOACs

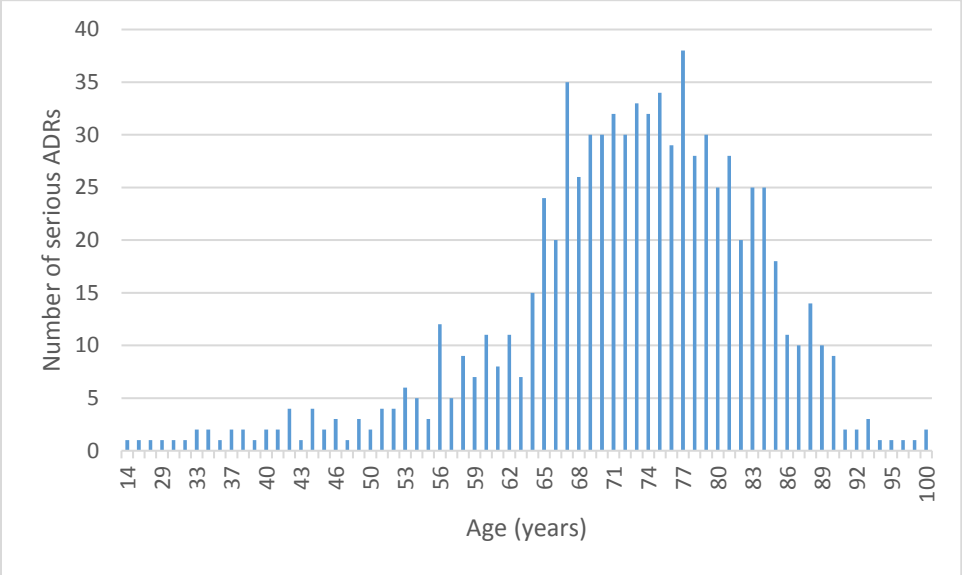
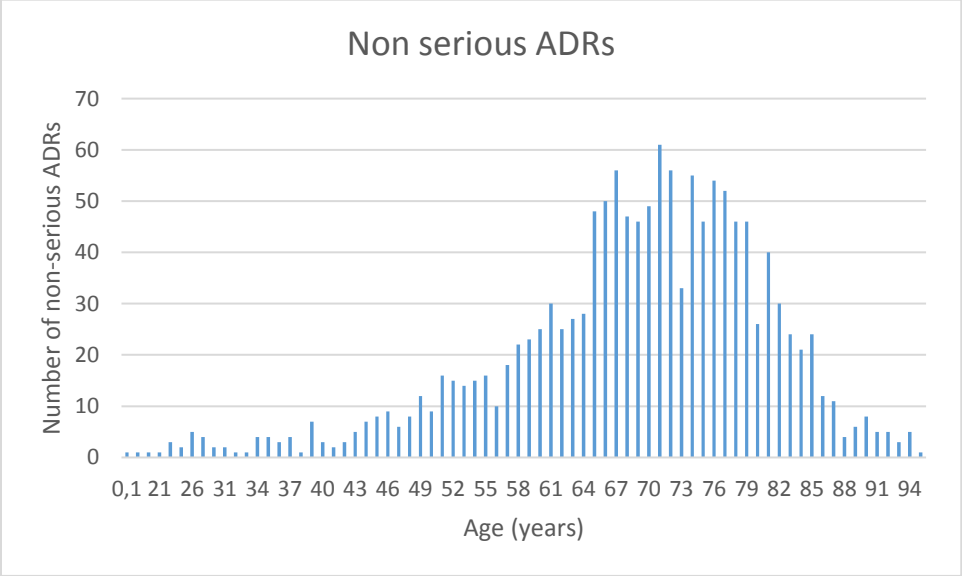


Figure 2. Age distribution of the non-serious ADRs concerning all four DOACs



Reports with fatal outcome

The most frequently reported ADRs with fatal outcome are presented in table 5.

The numbers reported in table 5 do not necessarily represent distinct reports, since one report can contain multiple ADRs.

Table 5. Most frequently reported ADRs* (and reported more than once) with a fatal outcome and number of times reported, for each DOAC

Dabigatran		Rivaroxaban		Apixaban		Endoxaban	
Death	11	Cerebral haemorrhage	14	Cerebral haemorrhage	4	Subdural haematoma	2
Haemorrhage	4	Pulmonary embolism	7	Haemorrhage intracranial	3		
Cerebral haemorrhage	3	Cerebral infarction	4	Haemorrhage	2		
Haemorrhage intracranial	3	Drug interaction	4	Rectal haemorrhage	2		

* Several ADRs can originate from a single report.

These data show that haemorrhages are the most frequently reported ADRs with fatal outcome, followed by pulmonary embolism and cerebral infarction. In the usage of DOACs, reports of thrombo-embolism or cerebral infarction may indicate lack of therapeutic effect. Additionally, eleven reports for dabigatran mention the MedDRA term 'Death' as an ADR. These reports were mainly sent to Lareb through the Marketing Authorization Holders (MAH), so follow-up requests on further details by Lareb are not possible. In one of these reports pulmonary embolism was also reported as reaction with fatal outcome and in one report gastrointestinal complaints.
The reports with fatal outcome of drug interaction as reported ADR, were heterogeneous and did not give rise to a signal from Lareb in addition to the information that is already reported in the SmPCs.

Details on reports concerning haemorrhage and thromboembolic events
Since reports of haemorrhages and thromboembolic events (as indication of a possible lack of therapeutic effect for the DOACs) associated with the use of DOACs are of particular interest, reports containing these types of ADRs were analysed in further detail. The selection of relevant preferred terms (PTs) was based on the following Standardised MedDRA Queries (SMQs):

1) 'Embolic and thrombotic events' (with sub-SMQs 'arterial, venous and mixed / unspecified')
2) 'Gastrointestinal haemorrhage' (level 2 sub-SMQ from SMQ 'Gastrointestinal perforation, ulceration, haemorrhage or obstruction')
3) 'Haemorrhagic central nervous system vascular conditions' (level 3 sub-SMQ from SMQ 'Central nervous system vascular disorders')
4) 'Haemorrhage terms' (excluding 'laboratory terms') (level 2 sub-SMQ from SMQ 'Haemorrhages')

For all SMQs the narrow scope approach was used, implying that only PTs that are highly likely to represent the condition of interest were selected. The number of reports of thromboembolic events and haemorrhages are presented in table 6 and 7. The indications and the used doses of the drugs are separately described in an addendum.

For table 6, it should be noted that in three times, the same ADR is mentioned in two different columns. The reason for this, is that the reported ADRs concern PTs that are grouped under two sub-SMQs: The reported ADRs 'Angioplasty' and 'Embolism' are part of both the sub-SMQ Arterial and the sub-SMQ Mixed / unspecified, so as a consequence the same single reported ADRs 'Angioplasty' (reported once) and 'Embolism' (reported twice), are mentioned in both the column Arterial and the column Mixed / unspecified.

Table 6. Number of reported ADRs related to thromboembolic events

Drug	Thromboembolic events		
	Sub-SMQ Arterial	Sub-SMQ Venous	Sub-SMQ Mixed / unspecified
Apixaban	33	7	14
Dabigatran	72	17	84
Rivaroxaban	41	73	45
Edoxaban	4	1	3
Total	**150**	**98**	**146**

Table 7. Number of reported ADRs related to haemorrhages*

Drug	Haemorrhages		
	Sub-SMQ Central nervous system	Sub-SMQ Gastrointestinal	All kinds of hemorrhage together **(including central nervous system and gastrointestinal)**
Apixaban	28	36	232
Dabigatran	94	96	483
Rivaroxaban	75	174	932
Edoxaban	7	17	81
Total	**204**	**323**	**1728**

* It should be noted that the sub-SMQ 'Haemorrhagic central nervous system vascular conditions' also contains the PT 'Cerebrovascular accident' (this reaction concerned 52 ADRs in the sub-SMQ Central nervous system).

Reports of DOACs associated with vaginal bleeding

Lareb received 47 ADRs associated with vaginal bleeding for the DOACs. The ADRs concerned menorrhagia 27 times, vaginal haemorrhage 19 times, metrorrhagia 1 time, and postmenopausal haemorrhage 1 time, in association with a DOAC. Of these ADRs, 34 ADRs concerned rivaroxaban, 7 ADRs concerned dabigatran, 5 ADRs concerned apixaban, and 2 ADRs concerned edoxaban.
The SmPCs of all DOACs mention vaginal bleeding as adverse drug reaction. The SmPC of dabigatran mentions urogenital bleeding as adverse reaction, the SmPC of rivaroxaban mentions urogenital hemorrage (including hematuria and menorragia), the SmPC of apixaban mentions abnormal vaginal bleedings and urogenital bleeding, and the SmPC of edoxaban mentions vaginal bleeding [1-4].

Reports with ADRs related to haemorrhages and / or thromboembolic events with more than one antithrombotic drug

All reports with a DOAC as suspect drug and ADRs related to haemorrhages and / or thromboembolic events, were screened for another antithrombotic drug as reported co-suspected of concomitant drug. The antithrombotic drugs that were included for this screening, are reported in the addendum in table Q.
There were 74 reports with ADRs related to haemorrhages with a DOAC as suspect drug, where another antithrombotic drug than a DOAC was coded as co-suspect of concomitant drug. Of these 74 reports, in 12 reports fatal outcomes were reported. Details of the reports with fatal outcomes are shown in table 8.
There were 14 reports with ADRs related to thromboembolic events with a DOAC as suspect drug, where another antithrombotic drug than a DOAC was coded as co-suspect of concomitant drug. In 5 of these reports, also ADRs related to haemorrhages were reported. Of the 14 reports, in 4 reports fatal outcomes were reported. In 2 of these reports also ADRs related to haemorrhages were reported, and these were described as report c and f in table 6. Details of the other 2 reports with fatal outcomes are shown in table 9.

Table 8. Reports with ADRs related to haemorrhages with fatal outcomes, where a DOAC was a suspect drug and also another antithrombotic drug than a DOAC was coded as co-suspect of concomitant drug

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug	Remarks
a: NL-BAYER-2014-063226, M, 51-60, Physician This report concerns a study report received through the MAH	rivaroxaban, dose unknown Cerebrovascular accident prophylaxis, atrial fibrillation and thrombosis prophylaxis	nadroparin, dose unknown, omeprazol, salbutamol, fluticason, tiotropium, insulin aspart, calciumcarbonate, noradrenalin, doxazosin, telmisartan, prednisolone, prednisolone, hydrocortisone, amoxicillin, cefotaxim, cefotaxim, erytromycine, metronidazol, caspofungine, sufentanil, sufentanil, morphin, pregabaline	Gastrointestinal necrosis, Hypovolaemic shock, Ileus, Intestinal ischaemia (reported as ischaemic coecum), Intestinal ischaemia (reported as ischemic colon ascendens), Large intestine perforation, Multiple organ dysfunction syndrome, Rectal haemorrhage, Sepsis, Sepsis (reported as worsening of sepsis)	122 days Not applicable	The drug nadroparin was started 2 days after start of the reaction rectal bleeding.
b: NL-BAYER-2015-411137, F, 71 years and older, Physician from another country This report was received through the MAH	rivaroxaban, varying dose Cerebrovascular accident prophylaxis and atrial fibrillation	dalteparine, dose unknown, calcium carbonate / colecalciferole, lisinopril / hydrochlorothiazide, etoricoxib, non specified drugs	Diarrhoea, Loss of consciousness, Lower gastrointestinal haemorrhage, Malaise, Nausea, Rectal haemorrhage, Vomiting	12 hours for nausea, vomiting, diarrhea, rectal bleeding and malaise. 12 days for loss of consciousnes s. Not applicable	The drug dalteparine was withdrawn 3 months before start of rivaroxaban.
c: NL-BAYER-2015-453820, Unknown gender, 71 years and older, Physician This report was received through the MAH	rivaroxaban, dose unknown Total knee replacement and thrombosis prophylaxis clopidogrel, dose unknown Indication unknown	unspecified antidiabetics and heart medication	Haemorrhagic stroke, Hemiplegia, Vomiting	25 days for rivaroxaban, unknown for clopidogrel Not applicable	

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug	Remarks
d: NL-Boehringer Ingelheim GmbH, Germany-2015-BI-44980NL, M, unknown, Pharmacist This report was received through the MAH	dabigatran, 1 dd 220 mg Atrial fibrillation	clopidogrel, dose unknown carbasalate calcium, dose unknown	Neoplasma malignant, Haemorrhage	Unknown Unknown	It was reported that the patient had a relapse carcinoma operation.
e: NL-LRB-00265545, M, 61-70, Physician	apixaban, 2 dd 2.5 mg Atrial fibrillation	clopidogrel, dose unknown	Pulmonary haemorrhage	About 6 months	The medical history indicated placement of a drug eluting stent about 6 months before the reaction.
f: NL-LRB-00274677, F, 71 years and older, Physician	apixaban, 2 dd 5 mg Atrial fibrillation	clopidogrel, 1 dd 75 mg, pantoprazol, formoterol / beclometason, metformine, bisoprolol, telmisartan, solifenacin, prednisolone, alendronic acid / colecalciferol, paracetamol, haloperidol, oxazepam, nortriptyline	Cerebrovascular accident (reported as a possible cerebrovascular accident), Epistaxis	12 days Action unknown	Clopidogrel was withdrawn on the day apixaban was started. The medical history indicated squamous cell carcinoma of lung, impaired renal function, hypertension, diabetes mellitus, transient ischaemic attack.
g: NL-LRB-00301125, M, 71 years and older, Physician	edoxaban, 1 dd 60 mg Atrial fibrillation acetylsalicylic acid, dose unknown Atrial fibrillation dalteparin, dose unknown Atrial fibrillation	isosorbidedinitrate, hydrochlorothiazide, propranolol, diltiazem, simvastatin, levothyroxine	Cerebral haemorrhage (reported as: CVA most likely haemorrhagic; no imaging was performed)	Edoxaban: 5 hours Drug withdrawn Acetylsalicylic acid: 7 days after start and 1 day after withdrawal Dalteparin: 7 days after start and 1 day after withdrawal	Acetylsalicylic acid and dalteparin were replaced by edoxaban. The medical history indicated nonspecified cardiovascular disorder and one week before the reaction acetabulum fracture.

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug	Remarks
h: NL-LRB-178277, M, 71 years and older, Pharmacist and physician	apixaban, 2 dd 5 mg Atrial fibrillation	carbasalate calcium, 1 dd 100 mg, pantoprazole, metoclopramide, ondansetron, verapamil, telmisartan, tramadol, paracetamol, levetiracetam, haloperidol, diazepam, oxazepam, paroxetine	Haemorrhage intracranial	3 Months Drug withdrawn	The medical history indicated polycytemia vera and a possible TIA after atrial fibrillation. The reaction haemorrhage intracranial was treated with platelet concentrate and four coagulantia factors. The patient died 1 day later.
i: NL-LRB-208367, F, 51-60, Physician	rivaroxaban, 1 dd 20 mg Vena cava thrombosis	acetylsalicylic acid, dose unknown	Gastric haemorrhage	2 Months Not applicable	At times of the reaction the general condition was indicated as poor. The medical history indicated metastatic colorectal cancer.
j: NL-LRB-238883, F, 71 years and older, Physician	rivaroxaban, 1 dd 20 mg Atrial fibrillation nadroparin, dose unknown acenocoumarol, dose unknown	digoxin, bisoprolol, perindopril	Mouth haemorrhage, Acquired haemophilia, Subcutaneous haematoma	Rivaroxaban: 7 months after start for mouth haemorrhage and 7 months after start and 2 months after stop for acquired haemophilia A. Nadroparine and acenocoumarol were started after withdrawal of rivaroxaban. Nadroparin withdrawn Acenocoumarol unknown	The reaction was treated with prednisone and cyclophosphamide. Outcome of the reactions: Recovered for mouth haemorrhage and subcutaneous haematoma Fatal for acquired haemophilia. The patient died about 6 months after start of the reactions. The reported cause of death was bilateral pneumonia, right sided cardiac failure and multiorgan failure in sepsis.
k: NL-LRB-244839, F, 71 years and older, Physician	apixaban, 2 dd 2.5mg Atrial fibrillation clopidogrel, 1 dd 75mg Cerebral infarct	pantoprazol, digoxin, verapamil, rosuvastatin, amitriptyline	Subdural haematoma	8 Months Not applicable	The reaction subdural haematoma occurred after a fall.

Table 9. Reports that were not reported in table 8, with ADRs related to thromboembolic events with fatal outcomes, where a DOAC was a suspect drug and also another antithrombotic drug than a DOAC was coded as co-suspect of concomitant drug

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug	Remarks
l: NL-Boehringer Ingelheim GmbH, Germany-2013-BI-30853NL M, age unknown, Physician This report was received through the MAH	dabigatran, dose unknown Embolism lung	fenprocoumon, dose unknown	Pulmonary embolism, Death	Unknown Unknown	The specific cause of death was not reported. Concomitant diseases included cancer. It was reported that the patient was put on dabigatran as a last resort. Even with the use of fenproumon and other unspecified medications, the patient had repeated lung embolisms.
m: NL-LRB-110525, F, 71 years and older, Physician	dabigatran, 1 dd 150 mg Prophylaxis after total knee prothesis	nadroparin, 1 dd 9500 IE, pantoprazole, ferrous fumarate, simvastatin, diclofenac	Thrombocytopenia, Cerebral infarction	11 days Drug withdrawn	11 days after start of dabigatran thrombocytopenia occurred; because of the thrombocytopenia dabigatran was withdrawn, and was replaced by nadroparin. 2 days after start of nadroparin the patient was hospitalized with a large cerebral vascular accident, which transformed into haemorrhagic stroke.

Reports concerning DOACs antidote idarucizumab

Idarucizumab (Praxbind®) is up till now the only registered antidote for the DOACs. Idarucizumab is an antidote for dabigatran and was granted marketing authorization in the Netherlands in November 2015 [10]. Lareb received a very limited number of reports on idarucizumab, Lareb received no additional reports compared to the previous overview, and the reports received by Lareb concerning idarucizumab so far gave no rise to a Signal.

Literature

A large amount of studies and meta-analyses evaluating the non-inferiority and the bleeding risk profiles of the DOACs (mainly in comparison with warfarin) has been published in recent years. The DOACs dabigatran, rivaroxaban, apixaban and edoxaban were non-inferior compared to warfarin for the indications prevention of cerebrovascular accidents in atrial fibrillation and treatment of venous thromboembolisms. There appears to be a lower risk of intracranial haemorrhages and fatal bleeding for the DOACs and a slight increase in gastrointestinal haemorrhage. In 14,264 patients with atrial fibrillation major bleeding from a gastrointestinal site was more common in the rivaroxaban group, with 224 bleeding events (3.2%), as compared with 154 events in the warfarin group (2.2%, $p<0.001$) [12-15]. The EMA recently started a review of an observational study “Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU”, commissioned by EMA, assessing the risk of major bleedings with these medicines when used to prevent blood clotting in patients with non-valvular atrial fibrillation, in comparison with other oral anticoagulants [16,17].

Signal concerning DOACs published by the Uppsala Monitoring Centre in Sweden, in collaboration with the Netherlands Pharmacovigilance Centre Lareb

The Uppsala Monitoring Centre in Sweden, in collaboration with Lareb, published a signal on DOACs associated with haematospermia based on reports in the worldwide database VigiBase, concerning factor Xa inhibitors and haematospermia [18]. At time of the analyses, there were 39 cases of haematospermia is association with rivaroxaban and apixaban in VigiBase.
The Dutch SmPCs of rivaroxaban and apixaban mention urogenital hemorrhage or urogenital bleeding as adverse drug reactions [2,3].
On February 4, 2019. Pharmacovigilance center Lareb, received 1 report of haematospermia in association with rivaroxaban.

Discussion and conclusion

Previously, Lareb published overviews of the DOACs, most recently in 2018. The aim of this report was to give an update on the reports received by Lareb concerning the DOACs, with special focus on reports with fatal outcomes and reports of haemorrhages and thromboembolic events. Due to the nature of spontaneous reporting, no direct comparisons between drugs can be made in terms of frequencies for any ADR. Therefore, the occurrence of haemorrhages and thromboembolic events between the DOACs should only be compared with great caution.
Furthermore, attention was given to the antidote for dabigatran idarucizumab. Idarucizumab is the so far only registered antidote for the DOACs.
In conclusion, this overview resulting from the ongoing pharmacovigilance activities for the DOACs and the antidote idarucizumab, did not reveal any new additional safety concerns.

Reference List

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Addendum - Update overview 2019 of reports on direct oral anticoagulants (DOACs) and the antidote idarucizumab

This addendum to the Update overview 2019 of reports on direct oral anticoagulants (DOACs) and the antidote idarucizumab, provides more details on indications and the doses of the DOACs with the reactions thromboembolic events and haemorrhages. For table A t/m P, it must be noted that these data are based on the number of reported indications, where several indications can originate from a single report and the number of indications also don't always respond with the number of ADRs in a report.
Table Q reports the antithrombotic drugs that were included in the screening for other antithrombotic drugs as co-suspect or concomitant use, in the reports with a DOAC as suspect drug and ADRs related to haemorrhages and / or thromboembolic events.

Apixaban

Apixaban and thromboembolic events

Table A. Reported indications for apixaban of the reports of thromboembolic events

Drug apixaban	
Reported indication	Number of times reported
Atrial fibrillation	27
Cerebrovacular accident (CVA) prophylaxis	11
Unknown indication	7
Deep vein thrombosis	3
Cerebral ischaemia	2
Pulmonary embolism	2
Ischaemic cerebral infarction	1
Transient ischaemic attack	1
Total	**54**

Table B. Doses for apixaban of the reports of thromboembolic events

Drug apixaban	
Dose (sorted by dose from low to high)	Number of times reported
Twice daily 2.5 mg	5
5 mg per day	2
Twice daily 5 mg	17
10 mg per day	24
Unknown dose	6
Total	**54**

Apixaban and haemorrhage

Table C. Reported indications for apixaban of the reports of haemorrhage

Drug apixaban	
Reported indication	Number of times reported
Atrial fibrillation	103
Unknown indication	48
Cerebrovascular accident prophylaxis	50
Pulmonary embolism	6
Arrhythmia	3

Cardiovascular event prophylaxis	3
Cerebrovascular accident	3
Cardiac pacemaker insertion	2
Cerebral infarction	2
Deep vein thrombosis	2
Thrombosis prophylaxis	2
Coronairy artery bypass	1
Coronary artery disease	1
Cardiac fibrillation	1
Embolism venous	1
Myocardial infarction	1
Prophylaxis	1
Thrombosis	1
Venous thrombosis	1
Total	**232**

Table D. Doses for apixaban of the reports of haemorrhage

Drug apixaban	
Dose (sorted by dose from low to high)	Number of times reported
2.5 mg per day	1
Twice daily 2.5 mg	7
4 mg per day	8
5 mg per day	25
Twice daily 5 mg	43
10 mg per day	111
Unknown dose	37
Total	**232**

Dabigatran

Dabigatran and thromboembolic events

Table E. Reported indications for dabigatran of the reports of thromboembolic events

Drug dabigatran	
Reported indication	Number of times reported
Atrial fibrillation	94
Unknown indication	56
Deep vein thrombosis	4
Pulmonary embolism	3
Atrial septal defect	2
Cerebrovascular accident	2
Electrocardiogram ambulatory	2
Supraventricular tachycardia	2
Anticoagulant therapy	2
Atrial flutter	1
Cardiovascular event prophylaxis	1
Cerebral haemorrhage*	1
Knee operation	1

Myocardial infarction	1
Prophylaxis	1
Total	**173**

* As was reported in the database.

Table F. Doses for dabigatran of the reports of thromboembolic events

Drug dabigatran	
Dose (sorted by dose from low to high)	Number of times reported
110 mg per day	3
150 mg per day	3
Twice daily 110 mg	3
220 mg per day	41
Twice daily 150 mg	9
300 mg per day	46
600 mg per day	1
Unknown dose	67
Total	**173**

Dabigatran and haemorrhage

Table G. Reported indications for dabigatran of the reports of haemorrhage

Drug dabigatran	
Reported indication	Number of times reported
Atrial fibrillation	258
Unknown indication	165
Cerebrovascular accident	13
Arrhythmia	9
Thrombosis prophylaxis	8
Atrial flutter	3
Hip surgery	3
Prophylaxis	3
Pulmonary embolism	4
Anticoagulant therapy	2
Aortic valve replacement	2
Cardiovascular event prophylaxis	6
Coagulopathy	2
Prophylactic chemotherapy*	2
Angiopathy	1
Cardiac fibrillation	1
Hip arthroplasty	1
Total	**483**

* As was reported in the database.

Table H. Doses for dabigatran of the reports of haemorrhage

Drug dabigatran	
Dose (sorted by dose from low to high)	Number of times reported
75 mg per day	2
110 mg per day	11
150 mg per day	10

Twice daily 110 mg	19
220 mg per day	167
Twice daily 150 mg	20
300 mg per day	115
Unknown dose	139
Total	**483**

* As was reported in the database.

Rivaroxaban

Rivaroxaban and thromboembolic events

Table I. Reported indications for rivaroxaban of the reports of thromboembolic events

Drug rivaroxaban	
Reported indication	Number of times reported
Atrial fibrillation	42
Unknown indication	22
Thrombosis prophylaxis	20
Deep vein thrombosis	15
Cerebrovascular accident prophylaxis	14
Pulmonary embolism	12
Knee arthroplasty	10
Embolism venous	7
Prophylaxis	4
Arrhytmia	2
Hip arthroplasty	2
Knee operation	2
Surgery	2
Acute coronary syndrome	1
Anticoagulation therapy	1
Hip surgery	1
Thrombosis	1
Venous thrombosis	1
Total	**159**

Table J. Doses for rivaroxaban of the reports of thromboembolic events

Drug rivaroxaban	
Dose (sorted by dose from low to high)	Number of times reported
10 mg per day	18
15 mg per day	9
20 mg per day	55
Twice daily 15 mg	2
30 mg per day	6
Unknown dose	69
Total	**159**

Rivaroxaban and haemorrhage

Table K. Reported indications for rivaroxaban of the reports of haemorrhage

Drug rivaroxaban	
Reported indication	Number of times reported
Atrial fibrillation	350
Cerebrovascular accident prophylaxis	130
Unknown indication	144
Thrombosis prophylaxis	88
Deep vein thrombosis	36
Pulmonary embolism	36
Hip arthroplasty	19
Knee arthroplasty	21
Prophylaxis	21
Thrombosis	18
Arrhythmia	16
Embolism venous	14
Cardiac disorder	2
Hip surgery	4
Anticoagulant therapy	7
Aortic aneurysm repair	2
Cardiac valve disease	2
Ischaemic cerebral infarction	2
Knee operation	2
Segmented hyalinising vasculitis	2
Transient ischaemic attack	4
Vena cava thrombosis	2
Acute coronary syndrome	1
Cardiac fibrillation	1
Cardiomyopathy	1
Coagulopathy	1
Coronary artery disease	1
Embolism	1
Orthopedic procedure	1
Supraventricular tachycardia	1
Surgery	1
Venous thrombosis	1
Total	**932**

Table L. Doses for rivaroxaban of the reports of haemorrhage

Drug rivaroxaban	
Dose (sorted by dose from low to high)	Number of times reported
2.5 mg per day	3
10 mg per day	66
15 mg per day	68
20 mg per day	367
Twice daily 15 mg	3
30 mg per day	21
40 mg per day	2
60 mg per day	2

Unknown dose	400
Total	**932**

Edoxaban

Edoxaban and thromboembolic events

Table M. Reported indications for edoxaban of the reports of thromboembolic events

Drug edoxaban	
Reported indication	Number of times reported
Atrial fibrillation	5
Coronairy artery disease	1
Pulmonary embolism	1
Unknown indication	1
Total	**8**

Table N. Doses for edoxaban of the reports of thromboembolic events

Drug edoxaban	
Dose (sorted by dose from low to high)	Number of times reported
30 mg per day	3
60 mg per day	5
Total	**8**

Edoxaban and haemorrhage

Table O. Reported indications for edoxaban of the reports of haemorrhage

Drug edoxaban	
Reported indication	Number of times reported
Atrial fibrillation	58
Unknown indication	11
Embolism venous	3
Prophylaxis	2
Thrombosis	2
Angina unstable	1
Anticoagulant therapy	1
Arrhythmia	1
Pulmonary embolism	1
Thrombosis prophylaxis	1
Total	**81**

Table P. Doses for edoxaban of the reports of haemorrhage

Drug edoxaban	
Dose (sorted by dose from low to high)	Number of times reported
30 mg per day	16
Twice daily 30 mg	1
60 mg per day	51
Unknown dose	13
Total	**81**

Reports with ADRs related to haemorrhages and / or thromboembolic events with more than one antithrombotic drug

All reports with ADRs related to haemorrhages and / or thromboembolic events with a DOAC as suspect drug, were screened for another antithrombotic drug as reported co-suspected of concomitant drug. The included antithrombotic drug are reported in the addendum in table Q. The screening occurred for reports where the ATCs, the substances and / or the manufacturers / brands as mentioned in table Q, were reported as co-suspect or concomitant drugs.

Table Q. Antithrombotic drug that were included in the screening for other antithrombotic drugs as co-suspect or concomitant use.

ATC code	Substance	Manufacturers / brands
B01AA07	acenocoumarol	acenocoumarol diverse fabrikanten
B01AA04	fenprocoumon	Marcoumar, fenprocoumon diverse fabrikanten
B01AB04	dalteparine	Fragmin
B01AB05	enoxaparine	Clexane, Inhixa
B01AB06	nadroparine	Fraxiparine, Fraxodi
B01AB10	tinzaparine	Innohep
B01AB09	danaparoïde	Orgaran
B01AX05	fondaparinux	Arixtra
B01AB01	heparine	Heparine Leo
B01AE03	argatroban	Arganova
B01AE06	bivalirudine	Angiox, bivalirudine diverse fabrikanten
B01AC06	acetylsalicylzuur	Acetylsalicylzuur Cardio, Acetylsalicylzuur Neuro, Aspirine Protect
N02BA01	acetylsalicylzuur	Alka-Seltzer, Aspégic, Aspirine, Aspro, acetylsalicylzuur diverse fabrikanten
B01AC08	carbasalaatcalcium	Ascal '38', Ascal Cardio (Neuro), carbasalaatcalcium Cardio diverse fabrikanten
B01AC07	dipyridamol	Persantin, dipyridamol diverse fabrikanten
B01AC25	cangrelor	Kengrexal
B01AC04	clopidogrel	Grepid, Iscover, Plavix, clopidogrel diverse fabrikanten
B01AC22	prasugrel	Efient
B01AC24	ticagrelor	Brilique
B01AC30	dipyridamol/ acetylsalicylzuur	Asasantin, dipyridamol/acetylsalicylzuur diverse fabrikanten
B01AC30	clopidogrel/ acetylsalicylzuur	Duoplavin
B01AD02	alteplase	Actilyse
B01AD11	tenecteplase	Metalyse
B01AD04	urokinase	Medacinase
C05BA01	heparinoiden	Hirudoïd
N02BA51	acetylsalicylzuur/ ascorbinezuur	Aspirine C
N02BA51	acetylsalicylzuur/ metoclopramide	Migrafin

N02BE51	acetylsalicylzuur/ paracetamol/coffeïne	APC, Excedrin

This signal has been raised on April 4, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl