bijwerkingen centrumlareb

Update overview 2018 of reports on direct oral anticoagulants (DOACs) and the antidote idarucizumab

Introduction

Lareb previously published yearly overviews of reports (most recently in 2017) 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 (4-8). 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 (9). For this overview, data from both the national ADR database, and the Lareb Intensive Monitoring System (LIM) were used. The DOACs have been monitored with the LIM methodology since September 2012.

Prescription data

The number of patients using DOACs in the Netherlands is shown in table 1 (10). 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.

Table 1. Number of patients using DOACs in the Netherlands between 2012 and 2016 (10).

Drug	2012	2013	2014	2015	2016
Dabigatran	6,326	13,053	18,902	26,487	39,562
Rivaroxaban	10,608	12,718	20,620	34,751	56,914
Apixaban	3	730	4,766	15,155	31,087
Edoxaban	.	.	.	6,172	.

Reports for the DOACs

On April 13, 2018 the Netherlands Pharmacovigilance Centre Lareb had received 2,083 reports (concerning 3,828 ADRs) in the national reporting database for the DOACs. Compared to the previous overview in 2017, this is an addition of 694 reports.

On February 8, 2018, in our prospective LIM cohort, 1748 patients were included, of which 661 reported at least one ADR. 15 reports concerned reports with a serious outcome. In total 1179 ADRs were reported in LIM for the DOACs.

There were 910 reports with a serious outcome, including the reports originating from LIM that were exported to the national ADR database. In 121 reports a fatal outcome was reported (compared to 81 reports in the previous overview). Additional information is provided in table 2 and 3.

Table 2. Numbers of reports received by Lareb in the national reporting database for the DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Total
Total number of reports	762	911	330	80	2083
Number of serious reports	346	429	108	27	910
Total number of ADRs*	1305	1691	683	149	3828
Reports with a fatal outcome#	42	55	21	3	121

* 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.

Table 3. Number of patients using DOACs who reported at least one ADR in Lareb Intensive Monitoring (LIM)

Active substance	Number of patients with ADR(s)	Number of ADRs	Number of reports with serious outcome
Dabigatran	225	401	2*

Rivaroxaban	289	534	8*
Apixaban	122	192	5*
Edoxaban	25	52	0*
Total	**661**	**1179**	**15***

* Serious ADRs reported in LIM are also exported to the Lareb reporting database, which means that they are counted in both datasets.

Reports with fatal outcome

The most frequently reported ADRs with fatal outcome are presented in table 4.
The numbers reported in table 4 do not necessarily represent distinct reports, since one report can contain multiple ADRs.

Table 4. Most frequently reported ADRs* with a fatal outcome and number of times reported, for each DOAC

Dabigatran		Rivaroxaban		Apixaban		Endoxaban	
Death	13	Cerebral haemorrhage	13	Cerebral haemorrhage	3	Subdural haematoma	2
Haemorrhage	4	Pulmonary embolism	8	Haemorrhage intracranial	3	Haematemesis	1
Haemorrhage intracranial	3	Drug interaction	5	Haemorrhage	3	Drug interaction	1

* 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. In the usage of DOACs, reports of thrombo-embolism indicate lack of therapeutic effect. Additionally, thirteen 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 request on further details by Lareb is 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 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 5 and 6. The indications and the used doses of the drugs are separately described in an addendum.

For table 5, 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 5. Number of reported ADRs related to thromboembolic events

Drug	Thromboembolic events		
	Sub-SMQ Arterial	Sub-SMQ Venous	Sub-SMQ Mixed / unspecified
Apixaban	21	5	11
Dabigatran	66	15	65
Rivaroxaban	27	52	27
Edoxaban	3	1	2
Total	**117**	**73**	**105**

Table 6. 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	25	12	98
Dabigatran	78	78	269
Rivaroxaban	58	101	458
Edoxaban	5	10	27
Total	**166**	**201**	**852**

* It should be noted that the sub-SMQ 'Haemorrhagic central nervous system vascular conditions' also contains the PT 'Cerebrovascular accident'.

Literature: As mentioned in our previous overviews, 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 (11). 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). In 2016 an extensive overview of the studies on haemorrhages and thromboembolic events for the DOACs and the various indications was published in the “Geneesmiddelenbulletin” (11).

Signals concerning DOACs published by Lareb

Since the previous overview in 2017, Lareb published two signals concerning the DOACs. One signal concerned DOACs and cholesterol crystal embolisms (16) and one signal concerned DOACs and paraesthesia (17).

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 (9). Lareb received a very limited number of reports on idarucizumab and the reports received by Lareb concerning idarucizumab so far gave no rise to a Signal.

Discussion and conclusion

Previously, Lareb published overviews of the DOACs, most recently in 2017. 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 outcome and reports of haemorrhage 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

(1) Dutch SmPC dabigatran Pradaxa, 75 mg harde capsules. (version date 2013 January 17, access date 2018 Feb 21) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf;
(2) Dutch SmPC rivaroxaban Xarelto, 2,5 mg filmomhulde tabletten. (version date 2013 May 22, access date 2018 Feb 21) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf;
(3) Dutch SmPC apixaban Eliquis, 2,5 mg filmomhulde tabletten. (version date 2016 Jan 14, access date 2018 Feb 21) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf;
(4) Dutch SmPC edoxaban Lixiana, 15 mg filmomhulde tabletten. (version date 2015 June 19, access date 2018 Feb 21) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf;
(5) Overview of reports on novel anticoagulants. Lareb Quarterly Report 2014/1. https://databankws.lareb.nl/Downloads/KWB_2014_1_DOACs.pdf;
(6) Overview of reports on direct oral anticoagulants (DOACs). Lareb Quarterly Report 2015/1. http://www.lareb.nl/Signalen/KWB_2015_1_DOAC;
(7) Overview of reports on novel anticoagulants. Lareb Signal 2016/06/14. https://databankws.lareb.nl/Downloads/Signals_2016_NOACs_update_overview.pdf;
(8) Update overview 2017 of reports on direct oral anticoagulants. Lareb Signal 2017/04/03. https://databankws.lareb.nl/Downloads/Signals_2017_DOACs_update_overview%202017_with_addendum.pdf;
(9) Dutch SmPC idarucizumab Praxbind, 2,5 g/50 ml oplossing voor injectie. (version date 2015 November 20, access date 2018 Feb 21) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/003986/WC500197462.pdf;
(10) College voor Zorgverzekeringen. GIP Databank. (version date 2018, access date 2018 Feb 21) http://www.gipdatabank.nl/;
(11) Directwerkende orale anticoagulantia. Geneesmiddelenbulletin 2016 Apr 28;4(50):41-50;
(12) Connolly SJ, Ezekowitz MD et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361(12):1139-51;
(13) Schulman S, Kaeron C et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009 Dec 10;361(24):2342-52;
(14) Schulman S, Kaeron C et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013 Feb 21;368(8):709-18;
(15) Patel MR, Mahaffey KW et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-891. N Engl J Med 2011;365:883-91;
(16) Direct oral anticoagulants (DOACs) and cholesterol crystal embolisms. Lareb Signal 2018/08/28. https://databankws.lareb.nl/Downloads/Signals_2017_DOACs%20and%20cholesterol%20crystal%20embolisms.pdf;
(17) Direct oral anticoagulants and paraesthesia. Lareb Signal 2018/04/09. https://databankws.lareb.nl/Downloads/Signals_2018_DOACs%20and%20paraesthesia.pdf.

This signal has been raised on July 5, 2018. 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

Addendum - Update overview 2018 of reports on direct oral anticoagulants (DOACs) and the antidote idarucizumab

This addendum to the Update overview 2018 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. These data are based on the number of reported indications, where it must be noted that 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.

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	16
Cerebrovacular accident (CVA) prophylaxis	12
Unknown indication	9
Deep vein thrombosis	2
Pulmonary embolism	2
Ischaemic cerebral infarction	1
Transient ischaemic attack	1
Total	**43**

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	1
5 mg per day	2
Twice daily 5 mg	7
10 mg per day	27
20 mg per day	1
Unknown dose	5
Total	**43**

Apixaban and haemorrhage

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

Drug apixaban	
Reported indication	Number of times reported
Atrial fibrillation	72
Unknown indication	31
CVA prophylaxis	29
Pulmonary embolism	3
Cardiac pacemaker insertion	2
Cerebral infarction	2
Thrombosis prophylaxis	2
Cerebrovascular accident	1

Coronairy artery bypass	1
Coronary artery disease	1
Cardiac fibrillation	1
Prophylaxis	1
Venous thrombosis	1
Arrhythmia	1
Total	**148**

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	1
5 mg per day	23
Twice daily 5 mg	14
10 mg per day	86
Unknown dose	23
Total	**148**

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	89
Unknown indication	50
Deep vein thrombosis	4
Pulmonary embolism	3
Atrial septal defect	2
Cerebrovascular accident	2
Electrocardiogram ambulatory	2
Supraventricular tachycardia	2
Prophylaxis	2
Atrial flutter	1
Cerebral haemorrhage*	1
Knee operation	1
Myocardial infarction	1
Total	**160**

* 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	2
150 mg per day	4
Twice daily 110 mg	2
220 mg per day	41

Twice daily 150 mg	6
300 mg per day	44
600 mg per day	2
Unknown dose	59
Total	**160**

Dabigatran and haemorrhage

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

Drug dabigatran	
Reported indication	Number of times reported
Atrial fibrillation	245
Unknown indication	119
Cerebrovascular accident	14
Arrhythmia	8
Thrombosis prophylaxis	8
Atrial flutter	3
Hip surgery	3
Prophylaxis	3
Pulmonary embolism	3
Aortic valve replacement	2
Cardiovascular event prophylaxis	2
Coagulopathy	2
Prophylactic chemotherapy*	2
Angiopathy	1
Hip arthroplasty	1
Total	**416**

* 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	10
150 mg per day	8
Twice daily 110 mg	11
220 mg per day	159
Twice daily 150 mg	3
300 mg per day	109
Once daily 1590 mg*	1
Unknown dose	113
Total	**416**

* 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 (including paroxysmal)	36
Thrombosis prophylaxis	24
Unknown indication	22
Cerebrovascular accident prophylaxis	14
Knee arthroplasty	13
Deep vein thrombosis	11
Embolism venous	7
Pulmonary embolism	6
Prophylaxis	4
Hip arthroplasty	3
Surgery	3
Knee operation	2
Anticoagulation therapy	1
Arrhytmia	1
Hip surgery	1
Venous thrombosis	1
Total	**149**

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	25
15 mg per day	5
20 mg per day	45
30 mg per day	3
Unknown dose	71
Total	**149**

Rivaroxaban and haemorrhage

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

Drug rivaroxaban	
Reported indication	Number of times reported
Atrial fibrillation	311
Cerebrovascular accident prophylaxis	132
Unknown indication	123
Thrombosis prophylaxis	86
Deep vein thrombosis	29
Pulmonary embolism	28
Hip arthroplasty	23
Knee arthroplasty	22
Prophylaxis	21
Thrombosis	16
Arrhythmia	15
Embolism venous	9

Cardiac disorder	4
Hip surgery	4
Anticoagulant therapy	3
Cardiac valve disease	2
Knee operation	2
Transient ischaemic attack	2
Vena cava thrombosis	2
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	**843**

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	68
15 mg per day	55
20 mg per day	342
Twice daily 15 mg	3
30 mg per day	21
40 mg per day	2
60 mg per day	2
Unknown dose	347
Total	**843**

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	4
Coronairy disease	1
Pulmonary embolism	1
Unknown indication	1
Total	**7**

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	4
Total	**7**

Edoxaban and haemorrhage

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

Drug edoxaban	
Reported indication	Number of times reported
Atrial fibrillation	30
Unknown indication	7
Prophylaxis	2
Angina unstable	1
Anticoagulant therapy	1
Pulmonary embolism	1
Thrombosis prophylaxis	1
Total	**43**

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	8
Twice daily 30 mg	1
60 mg per day	25
Unknown dose	9
Total	**43**