1.1. Update overview 2017 of reports on direct oral anticoagulants (DOACs)

Introduction

Lareb previously published overviews of reports (most recently in 2016) concerning the direct oral anticoagulants (DOACs) dabigatran Pradaxa®, registered in 2008 (1), rivaroxaban Xarelto®, registered in 2008 (2) and apixaban Eliquis®, registered in 2011(3) (4-6). With the current overview, Lareb provides a short update of the reports received for these DOACs with addition of the newest DOAC edoxaban (Lixiana®), which was registered in June 2015 (7).
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 and in the Netherlands is shown in table 1 (8). These data of the antidotum idarucizumab are not yet available, because this drug was only registered in November 2015 (9).

Table 1. Number of patients using DOACs in the Netherlands between 2011 and 2015 (8).

Drug	2011	2012	2013	2014	2015
Dabigatran	2,066	4,678	13,065	18,896	27,305
Rivaroxaban	7,035	9,850	12,720	20,618	34,938
Apixaban	.	3	730	4,765	15,632
Edoxaban	.	.	.	.	6,172

Reports

On January 18, 2017 the Netherlands Pharmacovigilance Centre Lareb had received 1389 reports (with 2418 ADRs) in the national reporting database. Compared to the previous overview in 2016, this is an addition of 277 reports.
In our prospective LIM cohort, 1621 patients were included, of which 604 (37%) reported at least 1 ADR. In total 1058 ADRs were reported in LIM for the DOACs.

There were 662 reports with a serious outcome, including 17* reports originating from LIM that were exported to the national ADR database. In 81 reports a fatal outcome was reported (compared to 66 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	578	642	161	8	1390
Number of serious reports	284 (49%)	316 (49%)	58 (36%)	4 (50%)	663 (48%)
Total number of ADRs*	948	1177	280	13	2418
Reports with a fatal outcome#	34	35	10	2	81

* 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 reports		
	Total	Serious (%)	Non-serious (%)
Dabigatran	387	3* (1%)	384 (99%)
Rivaroxaban	479	5* (1%)	474 (99%)
Apixaban	174	9* (5%)	165 (95%)
Edoxaban	18	0 (0%)	18 (100%)

* 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 outcomes are presented in table 4. These data show that haemorrhages are the most frequently reported ADRs, followed by pulmonary embolism. In the usage of DOACs, reports of thrombo-embolism indicate lack of therapeutic effect. Additionally, ten reports mention the MedDRA term 'Death' as an ADR with no other reported 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.

There were three reports with fatal outcome of rivaroxaban and drug interaction. One report concerned a possible interaction of rivaroxaban and venlafaxine with intracranial haemorrhage as reaction. One report concerned a possible interaction with citalopram, with cerebral haemorrhage as reaction. Venlafaxine and citalopram are not reported in the SmPC of rivaroxaban as interacting drugs. The SmPC describes though that care is required when patients are treated with drugs that influence haemostasis (2). One report was based on a scientific publication and concerned interaction with rifampicine resulting in a subtherapeutic level of rivaroxaban with pulmonary embolism as reaction (10). The interaction between rivaroxaban and rifampicine is described in the SmPC of rivaroxaban (2).

It should be noted that the numbers reported in table 3 do not necessarily represent distinct reports, since one report can contain multiple ADRs.

Table 4. Most frequently reported ADRs* (with a minimum of two) in reports with a fatal outcome

Dabigatran		Rivaroxaban		Apixaban		Endoxaban	
Death[#]	10	Cerebral haemorrhage	10	Cerebral haemorrhage	2	Subdural haematoma	2
Haemorrhage intracranial	3	Pulmonary embolism	6	Haemorrhage intracranial	2	-	
Haemorrhage	3	Drug interaction	3	-		-	

* Several ADRs can originate from a single report

[#] The majority of cases (9 of 10) with 'death' coded as an ADR represent reports from MAHs

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 (excl 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. For the readability of this overview, the indications and the used doses of the drugs are separately described in an addendum.

Table 5. Number and percentages (of total number of reported ADRs in the national reporting database) related to thromboembolic events

Drug	Thromboembolic events			
	Arterial	Venous	Mixed / unspecified	Total
Apixaban	5 (1.2%)	0 (0%)	6 (2.1%)	11 (3.9%)
Dabigatran	56 (5.9%)	9 (0.9%)	54 (6.0%)	119 (12.6%)
Rivaroxaban	15 (1.3%)	36 (3.1%)	20 (1.7%)	71 (6.0%)
Edoxaban	1(7.7%)	0 (0%)	0 (0%)	1 (7.7%)

Table 6. Number and percentages (of total number of reported ADRs in the national reporting database) related to haemorrhages*

Drug	Haemorrhages		
	CNS	Gastrointestinal	Total
Apixaban	14 (5.0%)	6 (2.1%)	68 (24.3%)
Dabigatran	64 (6.8%)	60 (6.3%)	308 (32.5%)
Rivaroxaban	41 (3.5%)	77 (6.5%)	461 (39.2%)
Edoxaban	3 (23.1%)	1 (7.7%)	8 (61.5%)

* 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 patient 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). Recently an extensive overview of the studies on haemorrhages and thromboembolic events for the DOACs and the various indications was published in the "Geneesmiddelenbulletin" (11).

Other associations concerning DOACs under special attention of Lareb

The following associations are especially notable. The reports of Lareb supply not enough evidence to give rise to a signal at the moment, but the associations are under close attention of Lareb. For each association relevant information from the scientific literature is described.

DOACs associated with alopecia: nine reports for rivaroxaban, two reports for dabigatran and four reports for apixaban

Lareb received fifteen cases of DOAC's associated with alopecia. Of none of the DOACs alopecia is labelled.
The fifteen reports concerned nine reports of rivaroxaban, two of dabigatran and four of apixaban. There were twelve females and three males. Ages varied between 42 and 82 years, mean 67 years, median 69 years. Latencies were less than a week (two reports), between one and four weeks (nine reports), longer than four weeks (two reports) or unknown (two reports). There were two positive dechallenges. There were also two reports where the patients recovered from the reaction despite continuing the DOAC.
Although in the reports from Lareb latencies were rather short and the underlying disorder might have caused the reaction is well, this association is under close attention of Lareb.

Literature: Reports of the WHO of alopecia associated with DOACs were investigated, and although suspicion raised, a causal relationship could not be established (16).

DOACs associated with pancreatitis: three reports for rivaroxaban and one report for dabigatran

Lareb received four reports of pancreatitis associated with DOAC's. Although elevated lipase and amylase are labeled adverse drug reaction in the SmPC of rivaroxaban, pancreatitis is not reported as adverse drug reaction (2). In the SmPC of dabigatran neither elevated lipase and amylase, nor pancreatitis is reported as adverse drug reactions (1).

The three cases of rivaroxaban (A: 179730, B: 218564, C: 217844) concerned one male and two females with ages between 67 and 70 years. Latencies were two weeks, about five weeks and unknown in one case. There was one positive dechallenge (case A), one patient recovered after withdrawal of the suspect drugs and treatment of the reaction (case C), and in one case outcome was

not reported (case B). In case A rifampicine was another suspect in causing the reaction, where of rifampicine pancreatitis is a labeled adverse drug reaction with unknown frequency of occurrence (17), and gallstones was also another possible cause of the reaction. Case B was very limited documented. In case C pantoprazole and metoprolol were also suspect drugs; in neither of these drugs pancreatitis is a labeled adverse drug reaction (18;19).
The one case of dabigatran (D: 152228) concerned a male, aged 61-70 years, with acute pancreatitis three weeks after starting dabigatran. Dabigatran was withdrawn and the patient recovered after treatment. No other causes of pancreatitis were reported in this case.

Literature: Pancreatitis associated with DOACs has not been described in the scientific literature.

DOACs associated with tubulointerstitial nephritis: three reports for rivaroxaban

Lareb received three reports of tubulointerstitial nephritis associated with DOAC's, all three concerning rivaroxaban. Tubulointerstitial nephritis is not reported as adverse drug reaction in the SmPC of rivaroxaban. The SmPC of rivaroxaban does describe renal impairment including increased blood creatinine, as adverse drug reaction.(2).

The three cases (E: 107424, F: 206349, G: 217118) concerned all three males aged 71 years and older. Latencies were two weeks in two reports and not reported in one report. In one report use of NSAID and flucloxacillin was another possible cause of the reaction (case E). Case F reported there was granulomatous tubulointerstitial nephritis, but contained very little other information. In case G the results from renal biopsy were described, which showed extensive interstitial nephritis. In this case, rivaroxaban was withdrawn and the reaction was treated with prednisone and dialysis. Action of the drug and outcome were unknown in cases E and F. In case G at the moment of reporting the patient had not recovered.

Concerning other renal ADRs, reports received by Lareb included totally twenty reports of DOACs with renal impairment as reported ADR. Ten of these reports concerned rivaroxaban. In many cases renal impairment was reported in combination with an ADR concerning heamorrhage. The haemorrhage itself might have resulted in the renal impairment due to hypovolaemia and together with the limited specificity of the term renal impairment, makes the possible direct role of the DOAC is the reaction uncertain.

Literature: Tubulointerstitial nephritis associated with DOACs has not been described in the scientific literature.

DOACs associated with interstitial lung disease: one report of interstitial pneumonitis for apixaban and one report of eosinophilic pneumonia for dabigatran

Lareb received one report of interstitial pneumonitis associated with the use of apixaban and one report of chronic eosinophilic pneumonitis associated with dabigatran. There were no reports of these reactions associated with other DOACs. Interstitial pneumonitis and eosinophilic pneumonia are not reported as adverse drug reaction in the SmPC of apixaban and dabigatran respectively (1;3).

The case (H: 222856) of interstitial pneumonitis associated with apixaban concerned a female, age 71 years and older, with interstitial pneumonitis following administration of apixaban for atrial fibrillation with a latency of three days after start. The drug apixaban was withdrawn. The reaction was treated with steroids and mechanical ventilation. The patient died due to respiratory failure twenty days after the onset of the reaction.

The case (I: 184871) of chronic eosinophilic pneumonitis associated with dabigatran concerned a male, age 51-60 years, who developed the reaction about eight weeks after starting dabigatran. CT-thorax showed interstitial abnormalities. After a bronchoalveolar lavage, anatomic pathology investigations were compatible with eosinophilic pneumonia. Dabigatran was withdrawn and the reaction was treated with high dose prednisone. The patient was recovering at the moment of reporting. The patient had asthma bronchiale, which was another factor which might have caused or aggravated the reaction.

Literature: Reports of interstitial lung disease associated with apixaban were received in Japan and the Japanese phamacovigilance center requested to add precautions concerning this topic to the package insert (11;20). In Europe, this condition is not reported as an adverse drug reaction in the SmPC op apixaban (3).

DOACs associated with auto-immune hepatitis: one report for dabigatran

Lareb received one report of auto-immune hepatitis associated with dabigatran. There were no reports of this reaction associated with other DOACs. Auto-immune hepatitis is not reported as adverse drug reaction in the SmPC of dabigatran. Abnormal hepatic function is reported as often occurring adverse drug reaction (1).

The one case (J: 166668) concerned a female, age 61-70 years, with auto-immune hepatitis following administration of dabigatran for atrial fibrillation with a latency of ten months after start. Virus serology was negative. There were no auto-antibodies except anti-smooth muscle cell antibodies. Liver biopsy was compatible with auto-immune hepatitis. Dabigatran was withdrawn and the reaction was treated with budesonide. The patient is recovering.

Literature: Hepatic toxicity of rivaroxaban was described in the literature (21;22), but could not be confirmed by the pharmacovigilance center of Canada in 2015 (23).

DOACs associated with otosclerosis: one report for rivaroxaban.

Lareb received one report (K: 223154) of otosclerosis following administration of rivaroxaban for cardiac arrhythmia with a latency of 10 months after start. Rivaroxaban was withdrawn. The patient had not recovered at the moment of reporting. The medical history indicated hearing impairment wherefore several surgical procedures. This report was also described as case-report in the literature (24). The authors state that a causal relationship in the patient is not absolutely sure, but they still plead to be reservedly to start rivaroxaban in patients with pre-existing otosclerosis until more conclusive information becomes available.
Lareb received no others reports of otosclerosis associated with DOACs. In the WHO database there were also no other cases of otosclerosis associated with rivaroxaban, apixaban, edoxaban or dabigatran (25).

Other reports concerning the ear, received by Lareb included several report of tinnitus, that is six for rivaroxaban, four for dabigatran and one for apixaban.

Literature: Besides the report received by Lareb (case K), which was also reported in the literature (24), no other case reports concerning otosclerosis were described in the literature.

DOACs associated with changed odour of the body / skin / sweat / urine or changed odour from the mouth: five reports for dabigatran, three reports for rivaroxaban and one report for apixaban.

Lareb received nine reports of changed odour associated with dabigatran, rivaroxaban or apixaban. The odours were mostly described as strong, unpleasant or altered. Three ADRs concerned odour of the body, three the skin, one the sweat, three the urine and two ADRs concerned abnormal smell from the mouth. Some patients experienced more than one of these ADRs at the same time. These reactions are not mentioned as adverse drug reactions in the SmPCs of these DOACs.
The nine reports concerned seven males and two females. Ages varied between 21 and 81 years, with a mean of 57 years and a median of 64 years. Latencies were one to five days in three reports, four week in two reports, six months in one report and unknown in three reports. There were three reports with positive dechallenges.

Literature: An association with DOACs has not described been in the literature.

Reports concerning DOACs antidotum idarucizumab

Idarucizumab (Praxbind®) is up till now the only registered antidotum for the DOACs. Idarucizumab is an antidotum for dabigatran and was granted marketing authorization in the Netherlands in November 2015 (9). Lareb received four reports concerning idarucizumab. One report concerned hypotension and bradycardia, with the indication rectal bleeding, where the reporting professional reported that the rectal bleeding could also have cause or aggraved the reaction. The other three reports were received through the MAH and concerned haemorrhage with concomitant use of dabigatran, implying lack of effect of idarucizumab. In one of these reports it was reported that 24-48 hours after administration APTT increased mildly again, using the standard dosage 2.5 g twice daily. Creatinine clearance was 30 ml/min and BMI was 52 kg/m^2.
No other reports concerning idarucizumab were received 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 2016. The aim of this report was to give an update on the reports of ADRs associated with the use of 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 associations under special attention of Lareb were described in this overvieuw. These associations concerned DOACs and alopecia, pancreatitis, tubulointerstitial nephritis, interstitial lung disease, auto-immune hepatitis, otosclerosis and changed odour of urine, sweat and breath. The reports of Lareb concerning these associations do not supply enough evidence to support signals at the moment.
Finally attention was given to idarucizumab, the so far only registered antidotum for the DOACs.
In conclusion, this overview resulting from the ongoing pharmacovigilance activities for the DOACs did not reveal any new safety concerns.

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Addendum - Update overview 2017 of reports on direct oral anticoagulants (DOACs)

This addendum to the Update overview 2017 of reports on direct oral anticoagulants (DOACs) 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. Indications (and percentage of total) for apixaban of the reports of thromboembolic events

Drug apixaban Indication (sorted by frequency with most often first)	Number of times reported
Atrial fibrillation (including paroxysmal)	5 (38.5%)
Cerebrovacular accident (CVA) prophylaxis	4 (30.8%)
Unknown indication	4 (30.8%)
Total	**13 (100%)**

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 5 mg	10 (76.9%)
Unknown dose	3 (23.1%)
Total	**13 (100%)**

Apixaban and haemorrhage

Table C. Indications (and percentage of total) for apixaban of the reports of haemorrhage

Drug apixaban Indication (sorted by frequency with most often first)	Number of times reported
Atrial fibrillation (including paroxysmal)	39 (55.7%)
CVA prophylaxis	16 (22.9%)
Cardiac pacemaker insertion	2 (2.9%)
Thrombosis prophylaxis	2 (2.9%)
Coronairy artery bypass	1 (1.4%)
Cardiac fibrillation	1 (1.4%)
Prophylaxis	1 (1.4%)
Unknown indication	5 (7.1%)
Total	**70 (100%)**

Table D. Doses for apixaban of the reports of haemorrhage

Drug apixaban Dose (sorted by dose from low to high)	Number of times reported
Once daily 2.5 mg	1 (1.4%)
Twice daily 2.5 mg	11 (15.7%)
Twice daily 5 mg	40 (57.1%)

Unknown dose	18 (25.7%)
Total	**70 (100%)**

Dabigatran

Dabigatran and thromboembolic events

Table E. Indications (and percentage of total) for dabigatran of the reports of thromboembolic events

Drug dabigatran Indication (sorted by frequency with most often first)	Number of times reported
Atrial fibrillation (including paroxysmal)	70 (57.4%)
Unknown indication	44 (36.1%)
Deep venous thrombosis (DVT)	2 (1.6%)
Pulmonary embolism	2 (1.6%)
Atrial flutter	1 (0.8%)
Cerebral haemorrhage*	1 (0.8%)
Knee operation	1 (0.8%)
Prophylaxis	1 (0.8%)
Total	**122 (100%)**

*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
Once daily 110 mg	2 (1.6%)
Once daily 150 mg	1 (0.8%)
Twice daily 75 mg	2 (1.6%)
Twice daily 110 mg	34 (27.9%)
Once daily 300 mg	2 (1.6%)
Twice daily 150 mg	35 (28.7%)
Four times daily 150 mg	1(0.8%)
Unknown dose	45 (36.9%)
Total	**122 (100%)**

Dabigatran and haemorrhage

Table G. Indications (and percentage of total) for dabigatran of the reports of haemorrhage

Drug dabigatran Indication (sorted by frequency with most often first)	Number of times reported
Atrial fibrillation (including paroxysmal)	178 (54.9%)
CVA	9 (2.8%)
(Cardiac) arrhythmia	8 (2.5%)
Thrombosis prophylaxis	8 (2.5%)
Atrial flutter	3 (0.9%)
Hip surgery	3 (0.9%)
Prophylaxis	3 (0.9%)
Stroke	4 (1.2%)
Clotting disorder	2 (0.6%)

Cardiovascular event prophylaxis	1 (0.3%)
Vascular disorder	1 (0.3%)
Unknown indication	104 (32.1%)
Total	**324 (100%)**

Table H. Doses for dabigatran of the reports of haemorrhage

Drug dabigatran Dose (sorted by dose from low to high)	Number of times reported
Once daily 75 mg	2 (0.6%)
Once daily 110 mg	7 (2.2%)
Twice daily 75 mg	7 (2.2%)
Once daily 220 mg	24 (7.4%)
Twice daily 110 mg	101 (31.2%)
Once daily 300 mg	9 (2.8%)
Twice daily 150 mg	71 (21.9%)
Once daily 1590 mg**	1 (0.3%)
Unknown dose	102 (31.5%)
Total	**324 (100%)**

** As was reported in the database

Rivaroxaban

Rivaroxaban and thromboembolic events

Table I. Indications (and percentage of total) for rivaroxaban of the reports of thromboembolic events

Drug rivaroxaban Indication (sorted by frequency with most often first)	Number of times reported
Atrial fibrillation (including paroxysmal)	22 (19.8%)
CVA prophylaxis	15 (13.5%)
Thrombo(embolism) prophylaxis	16 (14.4%)
DVT (including recurrent)	6 (5.4%)
Venous thrombosis/ thromboembolism	8 (7.2%)
Prophylaxis	3 (2.7%)
Anticoagulation therapy	1 (0.9%)
Cardiac arrhytmia	1 (0.9%)
Knee surgery	12 (10.8%)
Hip surgery	3 (2.7%)
Pulmonary embolism (including recurrent)	2 (1.8%)
Surgery	3 (2.7%)
Unknown indication	19 (17.1%)
Total	**111 (100%)**

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
Once daily 10 mg	12 (10.8%)
Once daily 15 mg	4 (3.6%)
Once daily 20 mg	17 (15.3%)

Twice daily 10 mg	1 (0.9%)
Twice daily 15 mg	2 (1.8%)
Unknown dose	75 (67.6%)
Total	**111 (100%)**

Rivaroxaban and haemorrhage

Table K. Indications (and percentage of total) for rivaroxaban of the reports of haemorrhage

Drug rivaroxaban Indication (sorted by frequency with most often first)	Number of times reported
Atrial fibrillation (including paroxysmal)	220 (32,5%)
CVA prophylaxis	131 (19.4%)
Thrombo(embolism) prophylaxis	84 (12.4%)
Hip surgery	27 (4.0%)
Knee surgery	24 (3.5%)
DVT	20 (3.0%)
Prophylaxis	17 (2.5%)
Pulmonary embolism (including recurrent)	17 (2.5%)
(Cardiac) arrhythmia	12 (1.8%)
Venous thromboembolism	6 (0.9%)
Thrombosis leg	5 (0.7%)
Thrombosis	4 (0.6%)
Anticoagulant therapy	3 (0.4%)
Cardiac valvulopathy	2 (0.3%)
Transient ischaemic attack (TIA)	2 (0.3%)
Coronary disease	1 (0.1%)
Cardiac fibrillation	1 (0.1%)
Orthopedic procedure	1 (0.1%)
Supraventricular tachycardia	1 (0.1%)
Surgery	1 (0.1%)
Thromboembolism	1 (0.1%)
Vena cava thrombosis	1 (0.1%)
Venous thrombosis	1 (0.1%)
Unknown indication	95 (14%)
Total	**677 (100%)**

Table L. Doses for rivaroxaban of the reports of haemorrhage

Drug rivaroxaban Dose (sorted by dose from low to high)	Number of times reported
Once daily 2.5 mg	3 (0.4%)
Once daily 10 mg	54 (8.0%)
Once daily 15 mg	19 (2.8%)
Once daily 20 mg	190 (28.1%)
Once daily 30 mg	1 (0.1%)
Twice daily 10 mg	1 (0.1%)
Twice daily 15 mg	8 (1.2%)
Twice daily 20 mg	2 (0.3%)
Twice daily 30 mg	2 (0.3%)

Unknown dose	397 (58.6%)
Total	**677 (100%)**

Edoxaban

Edoxaban and thromboembolic events

Table M. Indications (and percentage of total) for edoxaban of the reports of thromboembolic events

Drug edoxaban	
Indication	Number of times reported
Coronairy disease	1 (100%)
Total	**1 (100%)**

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

Drug edoxaban	
Dose	Number of times reported
Once daily 30 mg	1 (100%)
Total	**1 (100%)**

Edoxaban and haemorrhage

Table O. Indications (and percentage of total) for edoxaban of the reports of haemorrhage

Drug edoxaban	
Indication	Number of times reported
Atrial fibrillation	8 (100%)
Total	**8 (100%)**

Table P. Doses for edoxaban of the reports of haemorrhage

Drug edoxaban	
Dose (sorted by dose from low to high)	Number of times reported
Once daily 30 mg	4 (50%)
Once daily 260 mg	2 (25%)
Unknown dose	2 (25%)
Total	**8 (100%)**